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Basic and Clinical Immunology by Names

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"Rise before an elderly person and stand before a wise man."
Torah, Parshas Kedoshim, 19:32.

"The memory of the righteous is a blessing, but the name of the wicked will rot."
Bible, Proverbs 10:7.

"And do not pursue that of which you have no knowledge."
Quran, 17.36.

Preface

We have been working on this book for almost 20 years and are happy to share what we have learned about people who deserved being remembered in the history of science, medicine, and immunology. We also realize that some important facts, events, biographies, dates, and subjects can be missed or inaccurate and, therefore, we very much appreciate correspondence and notes from all readers that allow us to improve the content of this book.

We dedicate this book to our parents and grandparents who inspired our love of history and biology and taught us to celebrate life and remember our ancestors.

We want to acknowledge our relatives, friends, and colleagues who support our life and work with love, friendship, and inspiration.

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Introduction

What is an eponym? Why do we use it? Webster's dictionary defines eponym as one for whom or which something is named. An eponym is the addition of a (person's) name(s) to the description of an object, a phenomenon, a fact, or even a miracle, e.g., Bode's Galaxy, Achilles heel, Luer lock, Petri dish or Gaucher cells.

Eponyms are broadly used in our life and the tradition of eponyms in research fields and especially in medical terminology has a long history. It is estimated that about 15% of all medical terms are eponyms, and their number is suggested to range from a few thousands up to 30,000 (Kucharz 2015, 2017). Interestingly, many myths and legends have had a deep inspiration in modern medical language and terminology and this extends to all specialties as part of their culture and the history of medicine (Karenberg 2017; Donoso et al. 2019).

The word "eponym" came from the Greek words "*epi*" meaning "upon" or "in addition" and "*onyma,*" meaning "name." (In Greek, έπονομαζω means to name something after.) In the English language this is done in the form of the Anglo-Saxon genitive, in other languages in grammatically corresponding ways. Remarkably, in standard anatomical terminology, the use of eponyms in the macroscopic anatomical terms is not allowed (Bujalkova 1999). However, in clinical terminology, the use of eponyms is rather common (Thomas 2016). Some people consider this practice inappropriate and confusing, because using the names of real or imaginary persons (eponyms) may reflect either inspiration or power instead of the real authorship of findings or invention, or when the same name is attached to different disorders (Cogan 1978; Karenberg 2017). On the other hand, others consider the use of eponyms functional because they are part of a scientific tradition used to name syndromes or diseases or tests/methods (Goic 2009). It is quite possible that "Eponyms will remain a cornerstone in medical education and communication moving forward" (Zheng and Gold 2020). Usefulness of eponyms is demonstrated by facts that they simplify interactions between peers, prove the significance or historical relevance of the discovery, and are also a tribute to the clinical intelligence and observational skills of their originators. Furthermore, the awareness of the biography and historical background of discoverers of signs, syndromes,

or diseases provides us with a historical perception of medicine and adds interest to the past and modern knowledge and practice of medicine (Goic 2009). Another point is that the eponymic approach in some cases is one of the most accurate ways of avoiding unnecessary synonyms and multiplicity of terms. From the teaching and remembering point of view, many signs and syndromes, although they fascinate residents, are difficult to remember, may complicate the pronunciations of diagnosis, and often place residents in a confused state (Jindal et al. 2014, 2015). Finally, "in modern times, when social values are often exclusively centered on economical profit, eponyms are the least we can offer to those who altruistically committed their personal time and effort to medicine" (Fernandez-Flores 2012).

At the same time, the use of eponyms, in rare cases, may be misleading. An interesting example is the utilization of "St. Anthony's fire," associated with St. Anthony of Egypt (251–356 AD), who was involved in a number of healings and exorcisms during his permanence in the desert (Cervellin et al. 2020). It was commonly believed that St. Anthony had cured people with numerous skin diseases using pork fat, which was helpful in alleviating inflammation and itching. The term "St. Anthony's fire" became widespread and was applied to several different diseases that share the so-called "burning skin" sensation. At least three diseases – ergotism, erysipelas, and herpes zoster have been called, at different times and in different countries, the same eponym term "St. Anthony's fire" (Cervellin et al. 2020).

Understanding and familiarization with common and uncommon eponyms in clinical immunology also have several important and interesting aspects. First of all, a fascinating historical aspect is that eponyms bring a human aspect to a disease, molecule, or cell and in many instances an associated intriguing story behind the origin of the eponym. Second, an educational and scientific aspect, because new eponyms come into use these days that might have a strong, stimulating effect on young and new clinical scientists and researchers. Third, an ethical aspect is when discussions often arise, especially since the involvement of the protagonists in the National Socialist regime, which led to great controversies (e.g., Clara, Stieve, Reiter, Wegener). They are a component of cultural specialist memories and contribute to the conciseness of the nomenclature (Moll et al. 2015). For instance, Reiter's name has been universally accepted as the eponym for the syndrome of reactive arthritis associated with urethritis and conjunctivitis. From 1977 onward, international appeals have been made to use the descriptive term "reactive arthritis" instead of the eponym "Reiter" in the medical literature. However, contrary to English-language publications the Dutch-language medical literature does not show any obvious decline in the use of this eponym (Harper 1996; Zegers 2014). Awareness of using this eponym is still lacking, even in Israel, where it is still used in most medical textbooks (Keynan and Rimar 2008).

In 2000, Daniel J. Wallace and Michael Weisman from Cedar Sinai Medical Center in Los Angeles undertook a review of Hans Reiter's background (Wallace and Weisman 2000, 2003). The documents relating to charges against Reiter and their investigation during the Nuremberg Trials between 1945 and 1947 were obtained, translated from German, and published. During the Nazi era, physicians were responsible for over 200,000 cases of involuntary sterilization and 170,000

cases of euthanasia. Millions of prisoners died in the concentration camps under the supervision of physicians, where at least 60 different medical investigations were undertaken. Among the charges leveled at Reiter are active participation in experiments related to involuntary sterilization, euthanasia, and experimental vaccination against typhus, resulting in hundreds of deaths in the Buchenwald Concentration Camp.

Another important aspect of eponym use is related to the national pride and honor of a person or a group of clinicians and researchers. Numerous eponyms in clinical immunology originated in nineteenth and twentieth centuries in France and Germany, suggesting the high level of clinical practice and medical research in these countries. However, some areas in Germany at that time are today in Poland and some of the names behind the eponyms can be considered Polish names. Another concern raised is the common use of the term "an American" pathologist or physician or surgeon, which may lead to the overestimation or over-honoring of "the USA" eponyms. Many of those known as "American" doctors emigrated from various European or Asian countries and their native countries deserve to be mentioned at least. The same is partly true for other countries, and a well-known example is a famous "French" immunologist, "Father of natural immunity," and the Nobel laureate Elie Metchnikoff.

A related issue is a non-intentional or purposeful omission of information related to the Jewish heritage of person(s) associated with an eponym. During the modern rise of antisemitism in certain countries, the lack of these facts does not support the equal and trustful evaluation of the input of various nations into modern medical knowledge and medical practice in different countries. This fact is quite visible when investigating stories behind many "American–German" and "German" physicians, who gave rise to several eponyms in the middle of the nineteenth century. There are many sad stories about the fate of Jewish physicians in Nazi Germany. In 1933, there were about 525,000 Jews living in Germany, accounting for about 0.75% of the population. Approximately 16% of physicians were Jewish. Because many larger medical disciplines, such as surgery, internal medicine, and gynecology, were almost closed to Jews, dermatology became a favored specialty, with more than 25% of the practitioners being Jewish (Burgdorf et al. 2014a). In 1933, there were 569 registered Jewish dermatologists. From the known life of many individuals, almost 50% were forced to emigrate (to the USA, British Palestine, and other countries), 10% were killed in concentration camps, and 2% chose suicide (Scholz and Eppinger 1999). One must fear that many of those listed as unknown also perished, making the statistics even more depressing (Burgdorf et al. 2014b). Overall, approximately 9000 physicians were uprooted for so-called "racial" or "political" reasons by the Nazi regime and 6000 fled Germany. The last aspect that it is important to notice is an enormous, well-documented contribution of Jewish clinicians to medicine in the USA and European countries after the exodus during the Third Reich (Scholz and Burgdorf 2005), as well as at other times (Dubovsky 1989a, b, c).

Commonly used or forgotten eponyms in clinical immunology reflect the development of the field during the last two to three centuries, but do not necessarily create a pantheon for pioneers of immunology, because chance had played a significant role in eponymy. Some persons whose names are well-known added only small contributions to understanding of a particular disease or syndrome, whereas those whose studies proved or supported a real breakthrough may be forgotten or under some circumstances, even unknown. One known example is Carl Wilhelm von Kupffer who, in his own estimation, made major contributions to embryology, especially in the field of comparative neuroanatomy. For this well-regarded work, the noble "von" was conferred on his name, but not for the description of Kupffer cells in the liver. This is yet another example of the irony of history, wherein a name is perpetuated for what the author himself would have considered a mere footnote among his accomplishments. Knowing the history of eponymic discoveries will help us not only to better remember many diseases and satisfy our curiosity but may even help somebody to create or introduce a new eponym into the field.

Acknowledgements

The following internet sites were used in preparation of this book:

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http://www.deutsche-biographie.de
http://www.nlm.nih.gov/hmd/manuscripts
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Memorial Book for the victims of National Socialism at the University of Vienna in 1938.
https://gedenkbuch.univie.ac.at/index.php?id=433&L=2
NIH/US National Library of Medicine/History of Medicine/Archives and Modern Manuscripts > Oral History Collections > Online Oral Histories
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Abbreviations

AAE	Acquired angioedema
aCL	Anticardiolipin antibodies
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AIDS	Acquired immunodeficiency syndrome
AIRE	Autoimmune regulator
ALL	Acute lymphocytic leukemia
ALPS	Autoimmune lymphoproliferative syndrome
ALS	Amyotrophic lateral sclerosis
AMAN	Acute motor axonal neuropathy
AML	Acute myeloid leukemia
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
aPL	Antiphospholipid antibodies
APS	Antiphospholipid antibody syndrome
APS-1	Autoimmune polyendocrine syndrome type 1
AQP4	Aquaporin 4
ATM	Ataxia-telangiectasia mutated
BBB	Blood–brain barrier
BBE	Bickerstaff's brainstem encephalitis
BCG	Bacillus Calmette–Guérin
BLOC	Biogenesis of lysosome-related organelles complex
BNP	Brain natriuretic peptide
BTK	Bruton tyrosine kinase
C1-INH	C1 inhibitor
CAPS	Cryopyrin-associated periodic syndromes
CASPR-2	Contactin-associated protein-2
CC10	Clara Cell-Specific 10 kD Protein
CC16	Clara cell secretory protein 16KDa
CCSP	Clara cell secretory protein
CD	Cluster of differentiation

CHS	Chédiak–Higashi syndrome
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
CSF-R	Granulocyte colony-stimulating factor receptor
CTLA-4	Cytotoxic T lymphocyte antigen-4
CVID	Common variable immune deficiency
DAMP	Damage-associated molecular pattern
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
EBV	Epstein–Barr virus
ELISA	Enzyme-linked immunosorbent assays
ENA	Extractable nuclear antigen(s)
ET-1	Endothelin-1
FDA	United States Food and Drug Administration
GBM	Glomerular basement membrane
GBS	Guillain–Barré syndrome
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage-stimulating factor
GWS	Gulf War syndrome
HAE	Hereditary angioedema
HCD	Heavy chain diseases
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPS	Hermansky–Pudlak syndrome
HPV	Human papillomavirus
HSP	Heat-shock protein(s)
HSV	Herpes simplex virus
IAP	International Academy of Pathology
IBD	Inflammatory bowel disease
ICA	Islet cell antibodies
IDO	Indoleamine 2,3-dioxygenase
IEI	Inborn error of immunity
Ig	Immunoglobulin
IL	Interleukin
IPH	Idiopathic pulmonary hemorrhage
IPPA	International Pediatric Pathology Association
ISG	Interferon stimulated gene(s)
ITP	Idiopathic thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
KSHV	Kaposi sarcoma-associated herpesvirus
LBR	Lamin B receptor
LE	Lupus erythematosus cell
LEP	Lupus erythematosus profundus
LYST	Lysosomal trafficking regulator
MALT	Mucosa-associated lymphoid tissue

MFS	Miller Fisher syndrome
MHC	Major histocompatibility complex
MICA	MHC class I-related chain A
MMP	Matrix metalloproteinase
NF-1	Neurofibromatosis type 1
NIH	The National Institutes of Health
NK	Natural killer (cell)
NKG2D	Natural-killer group 2 member D
NKT	Natural killer T (cell)
NLR	NOD-like receptor
NMO	Neuromyelitis optica
PAMP	Pathogen-associated molecular patterns
PGA	Polyglandular autoimmune syndrome
PHA	Phytohemagglutinin
PIRD	Primary immuno-regulatory disorders
PM	Polymyositis
PMN	Polymorphonuclear leukocyte(s)
PPD	Purified protein derivative
PRR	Pathogen recognition receptor
PTX3	Pentraxin 3
RF	Rheumatoid factor
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
ROS	Reactive oxygen species
RT-PCR	Reverse transcription polymerase chain reaction
SAP	SLAM-associated protein
SCID	Severe combined immunodeficiency
SDF1	Stromal cell-derived factor 1
SLAM	Signaling lymphocyte activation molecule
SLE	Systemic lupus erythematosus
SOD	Superoxide dismutase
T3	Triiodothyronine
T4	Thyroxine
TB	Tuberculosis
TEC	Thymic epithelial cells
TGF	Transforming growth factor
Th	T helper (cell)
TLR	Toll-like receptor(s)
TNF-α	Tumor necrosis factor-α
TPO	Thyroid peroxidase
TSLP	Thymic stromal lymphopoietin
TTP	Thrombotic thrombocytopenic purpura
UG	Uteroglobin
UGL	Uteroglobin-like antigen
VEGF	Vascular endothelial growth factor

VGKC	Voltage-gated potassium channels
vWf	Von Willebrand factor
VWFCP	Von Willebrand factor-cleaving protease
WAS	Wiskott–Aldrich syndrome
WHIM	Warts, hypogammaglobulinemia, infections, and myelokathexis
WHO	World Health Organization
w/v	Weight/volume
XLA	X-linked agammaglobulinemia

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Letter A



Abrami's syndrome see **Hayem-Widal syndrome**

Abt-Letterer-Siwe disease (**Letterer-Siwe disease**) is an acute differentiated progressive histiocytosis, one of histiocytic disorders defined as disorders caused by an abnormal accumulation of cells of the mononuclear phagocytic system, consisting of dendritic cells, macrophages, and granulocytes. They include a wide range of various conditions that affect both children and adults. Basically, this is an old name for Langerhans cell histiocytosis. See also **Langerhans cell histiocytosis** and **Hand-Schuller-Christian disease**. Histiocytosis X encompasses three entities known as eosinophilic granuloma, **Hand-Schuller-Christian disease,** and **Letterer-Siwe** disease characterized by the accumulation of histiocytes. Physicians commonly do not diagnose Letterer-Siwe disease as a distinct one anymore, but commonly diagnose Langerhans cell histiocytosis.

Erich Letterer*,** in 1924, while working as an assistant at the Institute of Pathology of the University of Wurzburg, described a 6-month-old infant with fulminant nonleukemic reticuloendothelial system disorder. Nine years later, the Swedish physician ***Sture Siwe described similar symptoms in a 1.5-year-old child. His work provided a literature overview and defined the disease as a separate entity. Siwe described marked splenomegaly, hepatomegaly, lymphadenopathy, localized bone tumors, bleeding, anemia, and secondary generalized hyperplasia of macrophages in various organs. In 1936, ***Arthur Abt*** and Denenholc Edward published a paper showing 9 patients and first adopted the term **Letterer-Siwe disease**.

In 1940, two similar works appeared that described bone lesions. The first paper from Sadao Otani and Ehrlich Josef named the disease as solitary granuloma of the bone. The second paper, by Louis Lichtenstein and Henry Jaffe, called the disease eosinophilic granuloma. Farber and Green in 1942 reported bone lesions composed of aggregates of phagocytic cells admixed with eosinophils, thus eosinophilic granuloma. In 1953, Liechtenstein introduced the term histiocytosis X, bringing under

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the same heading eosinophilic granuloma, Hand-Schüller-Christian, and Letterer-Siwe disease, indicating that they are the same clinical entity with a similar pathophysiological mechanism of origin.

Christian Nezelof, a pathologist, in 1973 introduced the name **Langerhans Cell Histiocytosis**. He also became a founding member and the first president of the International Histiocyte Society established in 1985 in Philadelphia.

Erich Gustav Hermann Karl Letterer (Jan 30, 1895–May 26, 1982) was a German pathologist. He was one of the most renowned German pathologists of the twentieth century and a pioneer in the field of immunopathology. He was born in Nuremberg, the only child in the Protestant merchant family. He studied medicine and natural sciences at the University of Freiburg. In 1916, he was inducted into the army medical service with the primary task of caring for the war wounded in field hospitals and clinics. In 1919, he was discharged and started his medical internship at the Institute of Pathology in Würzburg. In 1920, Letterer got his medical license and continued to work at the same institution. Then he worked at the Dresden-Friedrichstadt hospital; however, in 1939, Letterer was appointed full Professor of Pathology and Director of the Institute of Pathology at Tübingen University. In 1943, Letterer began his service in the Wehrmacht as "military district pathologist" and medical advisor of district V. As an adviser, he participated in only a couple of operations in France and Russia as a medical officer. In spite of the difficulties of the denazification process, after World War II, Letterer adopted "denazification," which allowed him to stay on his career track as a full professor.

Letterer published about 200 clinical research articles in the fields of immunopathology, antigen-antibody interactions, and allergic inflammation. In the postwar period, Letterer accepted numerous invitations from scientific societies and received numerous international positions, awards, and honors. Less well known is how Letterer achieved the decisive career step in the Third Reich. He was a member of various Nazi organizations, including Schutzstaffel (SS), "NS-Ärztebund" (National Socialist German Doctors' League), and applied for membership in the NSDAP in 1942. It seems that Letterer was loyal during the Nazi era and that he enjoyed political support. Although it is unlikely that Letterer was in the group of university professors who accelerated their careers during the Third Reich because of political motives. Letterer was a well-known pathologist and recognized researcher who was politically honest even at thps critical step of his career.

Sture August Siwe (Jan 23, 1897–Apr 24, 1966) was a Swedish physician/pediatrician. He was born in Karlskrona, Blekinge County, Sweden, and obtained his medical doctorate from the University of Lund in 1927, specialized in pediatrics, and became a Professor of Pediatrics in 1937.

Arthur Frederick Abt (Sept 7, 1898–Mar 25, 1974), a US pediatrician, was the son of Isaac Arthur Abt, also a US pediatrician, and Lena Abt (born Rosenberg). He was born in Chicago, Illinois. He was a recipient of a 50-year medal from the University of Chicago in 1968.

Christian Nezelof see **Nezelof's syndrome**

(**Publ**.: Letterer E. Aleukamische Retikulose: Ein Beitrag zu den proliferativen Erkrankungen des Retikuloendothelialapparates. *Frank Z Pathol* 1924; 30:377–394.

Siwe SA. Die Retikuloendotheliose: Ein neues Krankheitsbild unter den Hepatosplenomegalien. *Z Kinderheilkd* 1933; 55:212–247.

Abt AF, Denenholz EJ. Letterer-Siwe's disease: Splenohepatomegaly associated with widespread hyperplasia of nonlipoid-storing macrophages-discussion of the so-called reticuloendothelioses. *Am J Dis Child* 1936; 51:499–522.)

Aicardi-Goutières syndrome is a rare genetic syndrome caused by multiple genetic defects that affect the brain, skin, and immune system. It develops in young patients and is characterized by encephalopathy and cutaneous involvement. Antinuclear antibodies (ANA) and autoantibodies recognize endothelial cells and astrocytes in the brain, as well as gliadin and components of basement membrane, are commonly detected in these patients. Elevated levels of type I interferon (IFN) in serum and cerebral spinal fluid (CSF) suggest that genetic abnormalities, causing insufficient DNA and/or RNA clearance, are associated with upregulated expression of IFN and interferon-stimulated gene (ISG) factors, which next lead to autoimmune reactions. Consequently, **Aicardi-Goutières syndrome** also can be considered as forms of monogenic lupus or lupus-like syndromes and classified as interferonopathy.

Approximately 25% of patients have a *TREX1* mutation and 60% of them develop some autoimmune markers, like ANA—that is, anti-dsDNA antibodies or antibodies to extractable nuclear antigens (ENA)—and autoimmune reactions (e.g., arthritis, thrombocytopenia, oral ulceration, leukopenia, or skin lesions). The *TREX1* gene, located on chromosome 3, encodes an IFN-inducible protein the exonuclease activity of which causes degradation of genomic DNA after DNA damage. Consequently, it has a regulatory role in the development of immune responses to single-stranded (ss)-DNA and dsDNA and preserving immune tolerance to cytosolic DNA. When TREX1 protein is absent or not fully functional, the cytosolic DNA cannot be completely degraded and starts working as a damage-associated molecular pattern (DAMP) agent. This upregulates IFN expression and IFN-associated responses leading to systemic inflammation, and it triggers autoimmunity through the accumulation of self-DNA in the cytosol.

Gain-of-function mutations of other genes—for example, *IFIH1* (interferon induced with helicase C domain 1), *SAMHD1* (SAM domain and HD domain-containing protein 1), *RNASEH2A, RNASEH2B, RNASEH2C,* and *ADAR1* (adenosine deaminase, RNA specific) genes—also might be involved in the pathogenic mechanisms of Aicardi-Goutières syndrome. Most cases are inherited in an autosomal-recessive pattern, although rare autosomal-dominant cases have been reported.

Aicardi-Goutières syndrome was first described in 1984 in 8 children from 5 families who presented with an early-onset progressive encephalopathy, characterized by basal ganglia calcifications, white matter abnormalities, and chronic CSF lymphocytosis. In 1988, the disorder was listed as Aicardi-Goutières syndrome, an autosomal recessive disorder. The eponym "Aicardi-Goutières syndrome" was used for the first time in 1992 (Bönnemann and Meinecke, 1992). Aicardi and Goutières wrote more than 60 papers together between 1966 and 2007.

Jean François Marie Aicardi (Nov 8, 1926–Aug 3, 2015) was a French neurologist. He was born in Rambouillet, France, 50 km from Paris, the seventh of 9 children. After earning his MD from the Faculté de Médecine in Paris in 1955, he was further trained at the Hospital des Enfants Malades. With no defined training program, he found a path forward through many obstacles, including the lack of formal support for physicians who wished to enter the field of child neurology. Later, he was Director of Research for INSERM until his mandatory retirement at age 65, but official retirement did not stop his life's mission to help children with neurological problems. He continued his work well into his 70s at Miami Children's Hospital and at the Institute of Child Health in London. From 1992 to 1998, he was Honorary Professor of Child Neurology at the Institute of Child Health in London, UK.

Aicardi authored more than 400 articles and was the founding Editor-in-Chief of *Epileptic Disorders*. He mentored many who are now national and international leaders in child neurology. Aicardi was awarded the Cornelia de Lange Medallion from the Dutch Society of Child Neurology in 1985 and the Hower Award from the American Child Neurology Society in 1986. In 1995, he received the Epilepsy Research Award from the American Epilepsy Society.

Francoise Goutieres is a French pediatric neurologist. She got her MD degree in 1968 and worked at Neuropediatric Unit, Hospital des Enfants Malades in Paris and Hospital Saint Vincent de Paul.

(**Publ**.: Aicardi J, Goutieres F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. *Ann Neurol* 1984; 15:49–54.

Goutières F. Aicardi-Goutières syndrome**.** *Brain Dev* 2005; 27(3):201–206.)

Albarran-Ormond syndrome see **Ormond's disease**

Alder-Reilly anomaly (**Alder constitutional granulation anomaly**) is an autosomal dominant or recessive condition with disturbance of the polysaccharid metabolism, in which leukocytes contain coarse azurophil granules called **Alder-Reilly bodies.** It is often associated with gargoylism and disturbance of skeletal growth, and particularly with the mucopolysaccharidoses—for example, Hurler's, Hunter's, or Maroteaux-Lamy syndromes.

[Hurler syndrome, also known as mucopolysaccharidosis type I, is a genetic disorder that results in the buildup of glycosaminoglycans (formerly known as mucopolysaccharides) because of a deficiency of alpha-L iduronidase—an enzyme responsible for the degradation of mucopolysaccharides in lysosomes. Hunter syndrome, or mucopolysaccharidosis II, is a X-linked recessive lysosomal storage disease caused by accumulated heparan sulfate and dermatan sulfate because of a deficient enzyme (i.e., iduronate-2-sulfatase). Maroteaux–Lamy syndrome, also known as mucopolysaccharidosis type VI, is a form of mucopolysaccharidosis caused by a deficiency in arylsulfatase B, or N-acetylgalactosamine 4-sulfatase.]

Alder-Reilly bodies are coarse azurophil granules found in leukocytes in the **Alder-Reilly anomaly**. They stain a dark color with **Giemsa** and react metachromatically

with toluidine blue. Neutrophil granulocytes, or also monocytes and lymphocytes, contain conspicuous, dark or reddish-colored granules. The appearance resembles "toxic granulation" seen in sepsis.

Albert von Alder (1888–1951) was a Swiss hematologist.

William Anthony Reilly (1901–1963) was a US pediatrician.

(**Publ**.: Reilly W.A. The granules in the leukocytes in gargoylism. Am J Dis Child. 1941; 62(3): 489-491.)

Aldrich-McClure test see **McClure-Aldrich test**

Alibert-Bazin syndrome (**Auspitz syndrome**, **Auspitz dermatosis**). Mucosis fungoides (also known as granuloma fungoides) is the prevalent form of cutaneous T-cell lymphoma, which, however, in addition to the skin also can develop internally. Symptoms of **Alibert-Bazin syndrome** may consist of rash and itchy skin lesions and tumors. Most cases of mucosis fungoides were described in individuals older than 20, more often in men than women with no genetic or hereditary predisposition. Because the course of this disease remains unclear, treatment approaches involve exposure to ultraviolet light and sunlight, local steroids, irradiation, and chemotherapy.

In 1832, ***Jean-Louis Alibert*** (***Jean-Louis-Marc Alibert***) (May 2, 1768–Nov 4, 1837) while in Paris introduced the term *mycosis fungoides*. Alibert was born in Villefranche-de-Rouergue, a small town in Southwest France. In Villefranche and then in Toulouse in schools of the Fathers of Christian Doctrine, Alibert studied mainly philosophy, literature, Greek, Latin, and theology and even might have begun a religious career as a novice. But the Revolution intervened, and the religious teaching orders were suppressed. Alibert moved to Paris but did not begin studying medicine until he was 26 years old. In 1801, he got an assistant physician position to work with patients with skin diseases, leprosy, and syphilis at the Hospital Saint-Louis (then the Hospice du Nord). After the Monarchy was restored in France, Alibert was a personal physician of Louis XVIII and then personal physician of Charles X. He also was awarded the title of "Baron." Alibert was known for his first classification of skin diseases, which was based on skin lesion presence. In addition, the diseases were subdivided into "families, genera, and species." Alibert expressed his classification concept in pictures as the "Tree of Dermatoses."

Alibert was also a prodigious writer. While still a medical student, Alibert started writing medical papers, as well as many philosophical and medico-literary works. His books were very popular as they were presented in a new way: they were written in French, not Latin, and they explained many dermatological diseases and conditions; they were brilliantly illustrated with a lot of painted figures in a large format. Therefore, these books were quite expensive. The rumor said that Alibert, who married his publisher's daughter, spent her dowry to publish his books. Interestingly, because his books were too costly for students, Alibert had to prepare and print less expensive, smaller, and less-illustrated books as well. In 1806, he was the first to describe mycosis fungoides, initially called Pian fungoides, only in one patient named Lucas. The disease was formerly referred to as **Alibert-Bazin syndrome**. In 1818, he was the first to describe a patient with psoriatic arthritis.

Alibert created many special terms using Greek- and Latin-origin words. Although most of them were confusing and worthless, at least two became famous and useful—**dermatoses** and syphilides. The name of Alibert is also closely associated with the discovery of the etiology of scabies. Others, however, suggest that Italian biologist Diacinto Cestoni described the mite, now called *Sarcoptes scabiei*, variety *hominis*, as the cause of scabies.

Pierre-Antoine-Ernest Bazin (Feb 20, 1807–Dec 14, 1878) was a French physician and dermatologist born in Saint-Brice-sous-Forêt to Pierre-Elisabeth Bazin, doctor of medicine, appointed a member of the municipal council, and Anne Rose Gault. In 1828, he started to work as a hospital intern, earning his doctorate in Paris in 1834. In 1836, he became *médecin des hôpitaux*, later working at the Hospital Lourcine from 1841 to 1844, followed by three years at Hospital Saint-Antoine. From 1847 on, he was a departmental head at Hospital Saint-Louis. He died in Paris and was buried in the Carnot cemetery in Suresnes.

Heinrich Auspitz (***Carl Heinrich Auspitz***) (Sept 2, 1835–May 22, 1886) was a Jewish Austrian dermatologist. He was born in Nikolsburg (Mikulov), Moravia (Czechoslovakia) and was a son of Jewish surgeon Moritz Auspitz. In 1840, Moritz accepted a job at a Jewish hospital in Vienna to obtain a better education for his sons. Trained at the University of Vienna, Heinrich specialized in dermatology and syphilis. From 1863, he worked as Privatdozent of dermatology and syphilis; and from 1875, he was Extraordinary Professor at the University of Vienna, where he was a Director of the General Policlinic from 1872. From 1869, Auspitz edited and published the quarterly journal *Vierteljahresschrift für Dermatologie und Syphilis* (Wien). In 1885, he published a paper introducing **Mycosis fungoides**. Being a well-known expert in tissue pathology, Auspitz defined the pinpoint bleeding after removal of psoriasis lesions and rupturing blood capillaries beneath the skin surface. This phenomenon bears his name: **Auspitz's sign**. From 1884, he was a Clinical Unit Chief in Vienna. But two years later, at age of 50, he died of heart complications. From 2005 onward, the "Heinrich Auspitz Award" was established by the Wyeth and Pfizer Incorporation in Austria to endorse research and clinical studies in the field of dermatology.

(**Publ**.: Alibert JL. Monographie des dermatoses ou précis théorique et pratique des maladies de la peau. *G. Baillie're Paris*. 1832; 2:414–427.

Bazin A. Affections cutanées artificielles. Paris, 1852.

Auspitz H. Ein Fall von Granuloma fungoides (Mycosis fungoides Alibert). *Vierteljahresschrift für Dermatologie und Syphilis*, Wien, 1885; 12:123–143.)

Alsever's (**Alsever's**, **Alsevers**, **Alserver solution** or **buffer**). Anticoagulant for storing red blood cells, erythrocytes. Consists of 0.42% (w/v) NaCl, 0.8% (w/v) trisodium citrate dihydrate, 2.05% (w/v) dextrose, and pH 6.4 adjusted with citric acid (~0.055%). A modified **Alsever solution** formula is used to conserve red blood cells in American commercial blood solutions. The solution received its name from US hematologist ***John B. Alsever*** who devised a solution to preserve blood for transfusion. John B. Alsever described it together with Dr. Ainslie.

John Bellows Alsever (Nov 24, 1908–Feb 22, 1978) was a US hematologist. He was a son of William Dewey Alsever and Clara Bradner Bellows Alsever. After receiving medical education, he was an instructor in Pathology at the Syracuse University College of Medicine in New York, prior to being assigned to the medical division of the Office of Civilian Defense as technical director of its blood and plasma service by the Surgeon General of the US Public Health Service when The Office of Civilian Defense established Blood and Plasma Banks in 1942. Later, he was a Senior Surgeon in the US Public Health Service. He was appointed the first full-time medical director of Southwest Blood Banks, Inc., with headquarters in Phoenix. He also was a Secretary of the American Association of Blood Banks. John Alsever died in 1978 of metastatic carcinoma in Arizona.

(**Publ**.: Alsever JB, Ainslie RB. A new method for the preparation of dilute blood plasma and the operation of a complete transfusion service. *NY State J Med* 1941; 41:126–135.)

Altmann-Schridde granules (**Schridde's granules**). Characteristic, tiny fuchsinophilic granulations occurring in lymphocytes near the nucleus. ***Altmann*** first reported that the glandular cells of tested vertebrates comprise well-defined granules and these organelles can be precisely visualized using acid fuchsin. The distribution and quantity of these granules can vary and correlate with cell activity and cell type. These cell inclusions are generally termed **Altmann's granules**, but also can be called "fuchsinophil granules" or "plasmosomes." Smaller but generally similar granules were identified in lymphocytes and plasma cells by ***Schridde***.

Richard Altmann (Mar 12, 1852–Dec 7, 1900) was a German pathologist. He was born in Deutsch-Eylau, Germany (now Poland) and studied in Greifswald, Königsberg, Marburg, and Giessen, where he was granted a Doctor of Medicine in 1877. He became an Assistant and Prosector in Leipzig and lived there in 1882, and in 1887 he became extraordinary Professor of Anatomy. Altmann concerned himself with the problems of organic structural doctrines and presented his granule theory in 1890. He coined the term **nucleic acid**. He died of a nervous disorder in 1900 after 6 years of illness.

Hermann Robert August Schridde (Jul 20, 1875–Jan 19, 1946) was a German pathologist. He was born in Derneburg, Hannover and studied at Marburg, Jena, Greifswald, and Erlangen, receiving his doctorate in 1902. In 1905, he joined the Institute of Pathology in Marburg for the training in pathological anatomy. From 1906, he worked in Freiburg becoming Titular Professor in 1911, and from 1912 he was a Director of the Institute of Pathology and the Research Institute for Occupational and Accident-Related Diseases in Dortmund.

His name is also associated with Schridde's cancer hair, Schridde's sign, and Schridde's syndrome.

(**Publ**.: Altmann R. Die Elementarorganismen und ihre Beziehungen zu den Zellen. Leipzig, Veit & Comp, 2nd ed. 1890, p. 28 and 145; 1894.

Schridde H. In: Anatomische Hefte, Berlin; 1905; 28:1.)

Amato bodies see **Döhle bodies**

Anichkov (or **Anitschkow**) **cells** (cardiac histiocyte, also called caterpillar cells) are often associated with rheumatic heart disease. Anitschkow cells are enlarged macrophages found within granulomas (called **Aschoff bodies**) related with the disease.

Nikolay Nikolaevich Anichkov (often spelled ***Anitschkow*** in German literature) (Nov 3, 1885–Dec 7, 1964) was a Russian pathologist. His father, Nikolay M. Anichkov, as a part of Russian nobility, was a Vice-Minister of Education of the Russian Empire. His grandfather on his mother side, L. I. Vasiliyeva, was a priest and founder of the Alexander Nevsky Orthodox Church built in Paris. In 1903, Anichkov started his studies in the Imperial Military Medical Academy in St. Petersburg, Russia. When he graduated, Anichkov did his doctoral thesis on the inflammatory changes in myocardium; he was the first to describe the specific heart macrophages that today bear his name. Anichkov worked on an experimental model of atherosclerosis. In 1912, he moved to Freiburg, Germany, and explained macrophage-derived "cholesterinesterphagozyten," known now as foam cells. By using histological evaluation of atherosclerotic plaque, Anichkov recognized that the smooth muscle cells, macrophages, and lymphocytes all participate in the formation of atherosclerotic lesions. He also delineated the crucial role of cholesterol in the process.

During World War I, Anichkov joined the Russian Army Medical Corps and was a physician-in-charge. In 1920, he became a Professor at the Military Medical Academy, Department of Pathophysiology, and had this position until 1939. Despite the fact that he was not a member of the USSR's Communist Party and was a descendant of ancient Russian nobility, he led the Academy's Department of Pathology as a research institute. From 1939 to 1946 as a lieutenant-general of Medical Corps, Anichkov headed the Military Medical Academy's Department of Pathological Anatomy. Then he led the Academy of Medical Sciences from 1946 until 1953 as President. Overall, Anichkov played an important role in building several research institutes and establishing research journals. He died of a myocardial infarction.

(**Publ**.: Anitschkow N. Ober die Histogenese der Myokardveranderungen bei einigen Intoxikationen. *Virchow Arch Path Anat* 1913; 211:193–237.)

Arakwa-Highashi syndrome is an uracil–uric refractory anemia with peroxidase-negative neutrophils and megaloblastic bone marrow. The peroxidase reaction of leukocytes generally is considered to be of the same biological significance as the oxidase reaction. In 1922, the negative peroxidase reaction of all the myeloid leukocytes of blood in acute encephalitis was described, even though they remained normally oxidase-positive. The "Striatal Blood Syndrome" was then recommended. Currently, the name **Arakawa-Higashi's syndrome** is suggested for simplicity instead of "Uracil–uric Refractory Anemia with Peroxidase-Negative Neutrophils" (Arakawa, 1965).

Tsuneo Arakawa (1949–2003), a Japanese physician, who was associated with the Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan.

Otokata Higashi see **Chediak-Hegashi syndrome**

(**Publ**.: Arakawa T, Tamura T, Higashi O, Ohara K, Tanno K. Formiminotransferase deficiency syndrome associated with megaloblastic anemia responsive to pyridoxine or folic acid. *Tohoku J Exp Med* 1968; 94(1):3–16.

Higashi O. [Arakawa-Higashi syndrome]. *Nihon Rinsho* 1977; 35(Suppl 1):922–923.)

Arndt-Gottron syndrome (scleromyxedema) is a generalized lichen myxedematosus with diffuse thickening of the skin underlying the papules. It is believed to be caused by paraproteinemia and the accumulation of mucinous material in the dermis. Systemic manifestations are common and may include gastrointestinal symptoms, pulmonary disease causing exertional dyspnea, and proximal myopathy. Less common are central nervous system (CNS) concerns, arthritis and arthralgias, and urinary tract involvement. In approximately 80% of cases, the disease is associated with a gammopathy, usually IgG-λ. Many authors propose that the paraproteins could be autoantibodies that stimulate fibroblast proliferation and dermal mucin deposition. Others speculate that the paraprotein represents a clone (or several clones) of B lymphocytes to the deposition of acidic mucin in the skin.

Scleromyxedema was originally described by Dubreuilh in 1906 and Reitmann in 1908 (Dubreuilh, 1906; Reitmann, 1908). The name scleromyxoedema or **Arndt-Gottron** was first coined by Gottron in 1954, with reference to the generalized papulous lichen myxedematosus, where the tegumen presents sclerodermiform infiltration. This signified the generalized lichenoid papular eruption.

Georg Arndt (Sept 2, 1874–Aug 9, 1929) was a German dermatologist. He was born in Berlin, received medical education in surgery, and served as a ship's physician. He then was trained in dermatology in Geneva, Paris, and Bern. He worked at the Charité Clinic in Berlin starting in 1906 and moved to Strassburg as a professor in 1916. In 1919, he returned to Berlin, his home city, to continue his clinical research on scarred alopecia, lichen nitidus, and lymphadenosis of the skin. His descriptions of sporotrichosis were one of the first published in medical literature.

(**Publ**.: Gottron HA. Slderomyxoedem (Eine eigenartige Erscheinungsform yon Myxothesaurodermie). *Arch Dermatol Syph* 1954; 199:71–91.

Arndt G.: XXII. Beiträge zur Kenntnis des Lichen nitidus. *Dermatol Z* 1909; 16:551–570.)

Heinrich Adolf Gottron see **Gottron's papules**

Arneth count or **Arneth index** describes the nucleus of a type of neutrophil in an attempt to detect disease. Neutrophils typically have 2 or 3 lobes, and, usually, older neutrophils have more lobes than younger neutrophils. In 1904, Joseph Arneth

divided the polymorphonuclear leucocytes into 5 classes according to the number of divisions or lobules in the nucleus. On this basis, he attempted to draw certain conclusions of diagnostic importance. In the first class, he placed myelocytes and neutrophils with indented- or horseshoe-shaped nuclei; in the second, were neutrophils with bilobed nuclei; in the third were those with trilobed nuclei; in the fourth were those with 4-lobed nuclei; the fifth contained those with 5 or more lobes in the nuclei. Under normal conditions, the proportions of the various types ran as follows: 5%, 35%, 41%, 17%, and 2% for Classes I, II, III, IV, and V, respectively. In health, the proportions given for the separate classes remain constant. Arneth found that in toxic conditions there were fewer cells in Classes IV and V so that the neutrophil blood picture manifests a dislocation to the left. He believed that this left-sided shift indicates the existence of active tuberculosis, and where it occurs in other infections.

The **Arneth count** is not commonly used in modern medicine but is a frequent medical choice question (MCQ) in PG (postgraduate) entrance exams. Basically, the Arneth count is calculated as the percentage of neutrophils with 1, 2, 3, 4, 5, and more than 5 lobes. People with a higher percentage of cells with fewer lobes have a so-called left shift, often associated with malignant tumors, infection, myocardial infarction, hemolytic crises, acidosis, and other diseases. People having a higher percentage of neutrophils with a high number of lobes, or a so-called right shift, frequently suffer from vitamin B_{12} or folate deficiency, liver disease, chronic uremia, and other conditions. The Arneth index is named for ***Josef Arneth***.

Josef Arneth (Oct 13, 1873–1955) was a German physician and hematologist. He was born in Burgkunstadt, Upper Franconia. He was a medical student in Munich, Heidelberg, and Würzburg universities and obtained his MD degree in Würzburg in 1897. He then worked at the Department of Medicine serving in the syphilis clinic, and in 1904, Arneth obtained a position of Privatdozent (university lecturer) of Internal Medicine. In 1907, he went to a position of Director of the Municipal Hospital in Münster and an Honorary Professor of Medicine and worked until 1944. Arneth's research focused mostly on hematology and pulmonary tuberculosis, and he published several books on these subjects. He is, however, considered one of the pioneers of German hematology.

(**Publ**.: Arneth J. *Die neutrophilen weissen Blutkärperchen bei Infektions-Krankheiten.* Habilitation paper, Jena 1903; *Deut Med Wchnschr* 1904; 30:54.)

Arthus reaction is a type of local type III hypersensitivity reaction. It involves the in situ formation of antigen–antibody complexes after the intradermal injection of an antigen in a previously sensitized host which should have a circulating antibody. The Arthus reaction owing to deposition of IgG-formed immune complexes in blood vessels in the skin occurs as local vasculitis. Activation of classic complement cascade and formation of C5a and C3a fragments results in attraction of polymorphonuclear leukocytes, while binding of the immune complexes to FcγRIII causes degranulation of mast cells, altogether augmenting an inflammatory response.

In 1903, the **Arthus reaction** was first described by ***Nicolas Maurice Arthus*** when he repetitively injected horse serum into rabbit skin. He observed a slow

absorption of the serum and formation of edema after 4 doses. Additional serum innoculations led to gangrene.

Nicolas Maurice Arthus (Jan 9, 1862–Feb 24, 1945) was a French immunologist and physiologist. He was born in Angers, France. He studied medicine in Paris receiving his MD degree in 1886. From 1896, he was a Professor of Physiology at the University of Fribourg in Switzerland. In 1900, he received an invitation from the Pasteur Institute and returned to France. Later, he was a lecturer at the L'Ecole de Médecine de Marseille (now the University of the Mediterranean). He was a chair of the Department of Physiology at the University of Lausanne, Switzerland, from 1907 and remained there for 25 years. He passed away in Fribourg.

Apart from the reaction named after him, Arthus made numerous contributions to the understanding of the immune and allergic mechanisms of serum. He also studied snake venom and the role of calcium in the coagulation of blood. His final years were devoted to the study of the physiological effects of the products of microorganisms.

(**Publ**.: Arthus NM. Injections répétées de serum du cheval chez le lapin, *Comptes rendus des séances de la Société de biologie et de ses filiales*, Paris. 1903; 55:817–820.)

Aschoff body also **Aschoff's bodies** or **nodules** are granulomatous lesions believed to be pathognomonic of rheumatic fever. An Aschoff body is a small granulomatous lesion composed of macrophages, lymphocytes, and multinucleated giant cells that surround pale eosinophilic collagenous material, classically seen in rheumatic fever-related myocarditis. Aschoff nodules can be globular, elliptic, or fusiform microscopic structures. These usually are located in the interstitial tissue of the heart, especially in the myocardium and the endocardium, often close to small blood vessels. Occasionally, they are present in the pericardium.

Karl Albert Ludwig Aschoff see **Aschoff cells**

Aschoff cells (**Aschoff giant cells**) are often associated with rheumatic heart disease. The Aschoff cell is a large component of rheumatic nodules in the myocardium with a characteristic nucleus and relatively little cytoplasm. The cells are found in **Aschoff bodies** surrounding centers of fibrinoid necrosis. In comparison with **Anitschkow cells**, their cytoplasm is more basophilic and can contain up to 4 nuclei, although the Anitschkow and Aschoff cells are stained prominently with macrophage markers.

Aschoff cells were named after the German physician and pathologist ***Ludwig Aschoff***. He believed that these giant cells were some type of connective or endothelial tissue. Currently, the general thought is that Aschoff cells are derivatives of cardiac myocytes instead of connective tissue cells. The importance of Aschoff's discoveries was in his identification of a granuloma specific for rheumatic carditis and in acknowledgement that the myocardium damage could be secondary to the specific connective tissue injury.

The **Aschoff nodules** can be classified into 3 stages based on their immunohistochemically characterization in rheumatic fever and comparative morphology analysis: (1) Aschoff nodules without admixed lymphocytes, (2) Aschoff nodules with a small number of T cells, and (3) Aschoff nodules comprised of many T and B lymphocytes. It has been assumed that the lesions' progress from stage 1 with only visible macrophages, to stage 2 with the appearance of T cells, and to stage 3 with additional homing B lymphocytes.

The etiology of the **Aschoff body** still is not completely understood. The general assumption is that alterations in primary collagen fibers lead to the formation of Aschoff cells. Another concept states that Aschoff bodies can be created as an evolution of primary injured muscle cells in the heart. There is a suggestion, however, that the Aschoff bodies could be developed from abnormal lymphatic vessels with propagating endothelial cells giving rise to the Aschoff cells. Finally, there is an opinion that Aschoff bodies are derived from nerves because a close anatomic relationship between nerves and Aschoff bodies has been observed.

Karl Albert Ludwig Aschoff (Jan 10, 1866–Jun 24, 1942) was a German pathologist. He was born in Berlin, Prussia, and studied medicine at the universities of Bonn, Strasbourg, and Würzburg. He received his medical degree at the University in Bonn in 1889. After additional training and a final qualification in 1894, he received the title of Professor of Pathology at the University of Göttingen in 1901; he relocated to the University of Marburg in 1903 as a chair of the Department of Pathological Anatomy. He next took a position at the University of Freiburg in 1906, where he remained until his last days.

In Freiburg, he established the Institute of Pathology that attracted students from all over the world. His professional trips to England, Canada, Japan, and the US established numerous research collaborations and contacts, with his trips to Japan being particularly important. Aschoff's popularity in the medical field in Japan came from his journey there in 1924 and his work with his friend and colleague—doctor Tawara. At the beginning of the twentieth century, 23 out of 26 pathology institutes in Japan were supervised by Aschoff's students.

Aschoff was known for his clinical studies in various fields, including thrombosis, appendicitis, scurvy, jaundice, and gallstones. He also provided classic histomorphological characterizations for rheumatic conditions. Nevertheless, Aschoff's name is associated with his identification of cellular phagocytic activity in various tissues and the introduction of the term, **the reticuloendothelial system,** in 1924. In addition, he investigated racial differences in his pathologo-anatomical analyses; and he created the term "pathology of constitution," which later was transformed into a special focus on research about the National Socialist (Nazi) doctors under the title of "military pathology." One of Aschoff's sons, Jürgen Aschoff, became one of the founders of the field of chronobiology.

Several conditions named after him are: Aschoff cells, Aschoff's organ, Aschoff-Geipel bodies, Rokitansky-Aschoff sinuses.

(**Publ**.: Aschoff L. Zur Myocarditisfrage.*Verh Dtsch Path Ges* 1904; 8:46–51.

Aschoff L, Tawara S. Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzchwache. Fischer, Jena; 1906.)

"**Asherson's syndrome** (catastrophic antiphospholipid antibodies) is a rare autoimmune disorder which clinically progresses as blood clots affecting multiple organ systems and rapidly develops within hours or days. It is considered as a deviation of another autoimmune disease—that is, antiphospholipid syndrome (APS)—which is when blood clots happen because of the antiphospholipid antibodies that bind to phospholipids on cell surfaces. Clinical signs can vary and depend on the involved tissue or specific cells. **Asherson's syndrome** could cause a rapidly progressive life-threatening multiorgan malfunction.

The syndrome is particularly common among patients with APS who have previously experienced a simple episode of it. Conditions (e.g., infections, immunizations, and wounds) initiated as a result of physical trauma and failure in the body's anticoagulation mechanism usually act as "triggers." Asherson's syndrome also can occur in individuals who have primary or secondary APS or in individuals with lupus or other autoimmune disorders. The exact cause of Asherson's syndrome is unknown. This condition was first described by ***Ronald Asherson*** in 1992, giving his name to it.

Ronald A. "Ron" Asherson (Dec 19, 1934–May 6, 2008) was a South African physician. He was born in Cape Town, South Africa, to the Jewish family of Milly Gelb and Asher Asherson. He qualified in medicine in South Africa in 1957 and held various positions at several hospitals before joining the Hammersmith Hospital in the early 1980s. He developed an interest in systemic autoimmune diseases and antiphospholipid antibodies. He worked at the Division of Immunology, School of Pathology, University of the Witwatersrand, Johannesburg, South Africa. He pioneered much of the published work related to the antiphospholipid syndrome.

Asherson was a productive scientist, and his profile includes more than 500 papers and more than 100 textbook chapters. He edited quite a few books and belonged to many professional societies. He was invited to speak at numerous scientific meetings, universities, and hospitals and served on the organizing committee of various congresses. Asherson worked very hard until his last days, visiting his patients, preparing manuscripts and books, and working on many projects. He spent his life in South Africa and died in Johannesburg at the age of 73.

(**Publ**.: Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome in 2004—a review. *Autoimmun Rev* 2005; 4(1):48–54.

Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome. *Autoimmun Rev* 2006; 6(2):64–67.)

Auer rods (**McCrae-Auer rods**) are needle-shaped azurophilic intracytoplasmic inclusion bodies. They are 0.1–2 μm wide and 3–6 μm long and are formed by fusion of lysosomes. They contain peroxidase and lysosomal enzymes. They are seen in acute leukemia (i.e., myeloblastic, promyelocytic, monomyelocytic, and monocytic), myelodysplastic syndromes, and chronic monomyeloid leukemia. These cytoplasmic inclusions are named for ***John Auer***, who described them in a 21-year-old patient suffering from a nosebleed and a sore throat. They were, however, first described in 1905 by a Canadian physician, ***Thomas McCrae,*** one year before Auer, as acknowledged in Auer's article. McCrae in his paper mentioned the

forthcoming more detailed description by Auer. Both McCrae and Auer mistakenly thought that the cells containing the rods were lymphoblasts.

John Auer (Mar 30, 1875–Apr 30, 1948) was a US physiologist and pharmacologist. He was born in Rochester, NY. In 1902, he graduated from Johns Hopkins University Medical School. His father-in-law was physiologist Samuel James Meltzer, with whom he worked for a long time at the Rockefeller Institute for Medical Research. While working at Rockefeller, Auer met Clara Meltzer, a fellow researcher in the laboratory. They were married in 1903 and had three children. Between 1906 and 1907, he was sent to Harvard Medical School as an Instructor in Physiology, and then became an Assistant in Physiology at the Rockefeller Institute in New York. He was promoted to Associate Member in Physiology and Pharmacology, holding that position until 1921. During World War I, the Rockefeller Institute worked as the US Army's Auxiliary Laboratory. While working on the projects associated with the war's needs, Auer developed an intravenous solution of magnesium sulfate as a medication to treat convulsions caused by tetanus. In 1921, he became a Professor of Pharmacology and later the Chair of the Department at the St. Louis University School of Medicine. Auer also worked as a pharmacologist at the St. Mary's Hospital in St. Louis, keeping this job until his death.

Auer conducted experiments with his father-in-law focused on the correlation between bronchial asthma and foreign substances, as well as the mechanisms of anaphylaxis in guinea pigs. He first detected xylene-induced allergic inflammations in rabbits, which is now known as **Auer's phenomena**. He also is credited with the method of intratracheal intubation without respiratory lung movement for constant respiration of patients. It is used for lung ventilation with anesthesia during open thorax surgery. He published nearly 150 papers during his career. John Auer died in St. Louis from a cardiac infarction.

Thomas McCrae (Dec 16, 1870–Jun 30, 1935) is often quoted for his remark: "more is missed by not looking than not knowing." He was born in Guelph, Ontario, Canada, to Lieutenant-Colonel David McCrae and Janet Simpson Eckford McCrae. McCrae trained in medicine at the University of Toronto, obtaining his Doctorate of Medicine in 1903. He became an assistant resident at Johns Hopkins Hospital in 1895. In 1912, he became Professor of Medicine at Jefferson Medical College in Philadelphia. McCrae died in 1935 in Philadelphia; he is buried at Grove Cemetery in Dundas, Ontario.

(**Publ**.: Auer J. Some hitherto undescribed structures found in the large lymphocytes of a case of acute leukaemia. *Amer J Med Sciences* 1906; 131(6):1002–1015.

McCrae T. Acute lymphatic leukaemia with a report of five cases. *British Med J* 1905; 2304(1):404–408.)

Auspitz dermatosis see **Alibert-Bazin syndrome**

Auspitz syndrome see **Alibert-Bazin syndrome**

Letter B



Baader's syndrome see **Stevens-Johnson syndrome**

Baader-Fiessinger-Stevens-Johnson syndrome see **Stevens-Johnson syndrome**

Bacillus Calmette-Guérin (referred as *Bacille de Calmette et Guérin* or **BCG**) is a vaccine against tuberculosis that is prepared from a strain of the attenuated live bovine tuberculosis bacillus, *Mycobacterium bovis*. BCG vaccination is used widely in many countries with a high incidence of tuberculosis to prevent childhood tuberculosis. BCG administration, however, is not normally recommended in the US because of its low efficiency in preventing pulmonary tuberculosis in adults, which is associated with the low risk of *Mycobacterium tuberculosis* infection and documented interference with a popular tuberculin skin test. With this test, previous vaccination with BCG can cause a false-positive response and thus interfere with judgments about further treatment. Furthermore, the positive extent of this test in vaccinated people does not predict protection against tuberculosis infection and cannot distinquish between latent infection and prior BCG vaccination. But common blood tests for diagnosing tuberculosis infection (e.g., Quantiferon assays) are not impacted by prior vaccination with BCG and provide much less false-positive reactions because they use different *Mycobacterium* antigens.

Currently, BCG is a live attenuated strain of *Mycobacterium bovis* and is the only agent approved by the US Food and Drug Administration as the primary therapy of carcinoma in situ of the bladder.

In 1882, ***Robert Koch,*** the famous German microbiologist, was first to refer to *Mycobacterium tuberculosis* as a pathogenic agent. In 1906, ***Camille Guérin***, a French veterinarian and immunologist, reported that antituberculosis immunity was linked to the tubercle bacilli living in the blood. ***Albert Calmette*** also worked on the immune responses induced after administration of bovine bacilli in experimental animals, and together with ***Guérin***—his laboratory assistant and later friend and colleague—working at the Pasteur Institute in Paris from 1908, they investigated

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several virulent strains of the tubercle bacillus and verified a number of useful culture conditions and media. To attenuate various strains, they used the idea of Kristian Feyer Andvord, a Norwegian researcher, and cultures of bacteria in a bile-containing substrate. They observed that a glycerin-bile-potato mixture grew bacilli that were less virulent and started to test whether repeated subculturing would produce a strain that was attenuated enough to be considered for use as a vaccine. The BCG strain was isolated after subculturing 239 times during 13 years from a virulent strain on a glycerin-potato medium. These studies continued throughout World War I until 1919, when the now avirulent bacilli were unable to cause tuberculosis disease in research animals. This preparation received the name of its two innovators (**Bacillum Calmette-Guérin**, or BCG). The BCG vaccine was first used in humans in 1921. In 1924, vaccination of newborn infants with BCG began in France and has spread worldwide.

Léon Charles Albert Calmette (Jul 12, 1863–Oct 29, 1933) was a French physician, bacteriologist, and immunologist. He was born in Nice, France. His father was secretary to the prefecture. In 1881, he joined the School of Naval Physicians at Brest and started to serve in 1883 in the Naval Medical Corps in Hong Kong. He completed his medical degree on the subject of filariasis. He was then assigned to Saint-Pierre and Miquelon and afterward served in West Africa, Gabon, and the French Congo, where he researched malaria, sleeping sickness, and pellagra.

When he returned to France in 1890, Calmette met Louis Pasteur and was charged by Pasteur to found and direct a branch of the Pasteur Institute at Saigon (French Indochina) in 1891. There, he dedicated himself to toxicology and immunology and worked on snake and bee venom, plant poisons, and curare. He prearranged the manufacture of anti-smallpox and anti-rabies vaccines, studied cholera infections, and described fermentation of opium and rice. On his return to France in 1894, he prepared his first anti-venom against snake bites using blood from vaccinated horses and called it Calmette's serum. This methodology was successfully continued at the Instituto Butantan in São Paulo, Brazil, by physician and scientist Vital Brazil, who established many anti-venom formulations against snake, scorpion, and spider bites. Together with Alexandre Yersin, the discoverer of the bubonic plague (i.e., black pest) pathogenic agent, *Yersinia pestis*, Calmette worked on the preparation of the first immune serum against this infection. He even travelled to Portugal to work on and save people from the bubonic plague epidemic at Oporto.

In 1895, Calmette became the Director of the Institut Pasteur de Lille, serving there for the next 25 years. In 1901, he created the Antituberculosis Dispensary in Lille named after Emile Roux. He also started the "Ligue du Nord contre la Tuberculose" (Northern Antituberculosis League) in 1904 that is still running today. In 1909, Calmette participated in creating a branch of the Paster Institute in Algeria. Starting in 1918, he was an Assistant Director of the Institute in Paris and from 1919 was a member of the French Académie de Médecine.

Calmette was well-known worldwide for his efforts in initiating the vaccination programs after BCG's discovery. Still, the programs were not always successful. In

1930, in Lübeck, Germany, 72 kids got tuberculosis after vaccination. Although it was determined that some batches were contaminated, and vaccination was restored in all countries after 1932 with the introduction of a novel and safely manufactured vaccine. Calmette was shocked and distressed by the accident and passed away in Paris one year later.

Importantly, Calmette's name remains one of a few French names in Vietnam's Ho Chi Minh City (Saigon) streets these days; other names are Yersin, Rhodes, and Pasteur. In 2009, a new bridge was completed and also named "Calmette." In Cambodia, one of the major hospitals is named Calmette Hospital.

Jean-Marie Camille Guérin (Dec 22, 1872–Jun 9, 1961) was a French veterinarian, bacteriologist, and immunologist. He was born in Poitiers, France. His father, as well as his wife, died of tuberculosis. He studied veterinary medicine at the École Nationale Vétérinaire d'Alfort from 1892 to 1896, working as an assistant to pathologists while a student. In 1897, Guwéin joined the Institut Pasteur de Lille in France and started to work with its director ***Albert Calmette***. He started as a technician in charge of preparing Calmette's serum (anti-venom against snake bites) and the vaccine against smallpox. He improved considerably the production techniques of the latter by using rabbits as intermediate hosts, and also he developed a method to quantify the remaining virulence of these vaccines.

At Lille, Guwéin was promoted to Head of Laboratory in 1900. Thereafter, from 1905 to 1915 and from 1918 to 1928, he devoted himself to research on a vaccine against tuberculosis, in close association with Calmette, until Calmette's death in 1933.

In 1919, he was promoted again to Head of Services. In 1928, Guwéin accepted a position as Director of Tuberculosis Service at the Pasteur Institute in Paris, becoming a Vice-President of the "Comité National de Défense contre la Tuberculose" (*National Defense Committee against Tuberculosis*) in 1939. In 1948, Guérin chaired the First International BCG Congress. His positions also included the presidency of the Veterinary Academy of France (1949) and the Academy of Medicine (1951). The French Academy of Sciences presented him the Scientific Grand Prix in 1955. Guérin died at 89 in the Hospital Pasteur in Paris.

(**Publ**.: Calmette A. Un nouveau système de pulvérisation des liquides. *Archives de médecine navale et coloniale* 1883; 40:378–386.

Calmette A. The treatment of animals poisened with snake venom by the injection of anti-venomous serum. *Lancet* 1896, 2:449–450.

Calmette A. La levure chinoise, ferment de l'amidon. *Annales de l'Institut Pasteur*, Paris, 1892; 6:604–620.

Calmette LCA, Guerin C, Weill-Halle B. Essai d'immunisation contre infection tuberculeuse. *Bull*

Acad Med (Paris) 1924; 91:787–796.

Calmette LCA, Gudrin C, Negre L, Bouquet A. Sur la vaccination preventive des enfants nouveau-nes contre la tuberculose par le BCG. *Ann Inst Pasteur* 1927; 41:201–232.)

Balo disease (**Baló's disease**, **Balo concentric sclerosis**, **Balò's concentric sclerosis**) is an uncommon demyelinating disease of the central nervous system (CNS) with primary inflammatory etiology. Symptoms include gradual paralysis, headache, involuntary muscle spasms, seizures, and cognitive loss. It may involve the cerebellum, brainstem, cerebral hemispheres, and spinal cord where peculiar patterns of varying rings of myelin preservation, demyelination, and remyelination can be seen after pathomorphological examination. Although the disease usually is seen in adults, several cases have been reported in children. **Balo disease** differs from multiple sclerosis, where demyelination can wane and slow down. Balo disease is usually characterized by symptoms that can progress rapidly over several weeks or more slowly over 2–3 years.

The exact cause of Balo disease is not known, but there is a strong evidence that a specific herpes virus infection is a factor in developing this autoimmune disorder. It is presently considered as a borderline form of multiple sclerosis.

The disease was clearly described by ***Joszef Balo*** who called it "leukoencephalitis periaxialis concentrica." Even though the disease carries his name, it was discovered by ***Otto Marburg*** in 1906 (see **Marburg disease**). In 1928, Balo studied and treated a Hungarian patient with the encephalitis periaxialis concentrica and discovered signs of demyelination of the peripheral nervous system.

József Mátyás Baló (Nov 10, 1895–Oct 9, 1979) was a Hungarian physician. He was born in Transylvania (formerly Austrian–Hungarian Empire; today Romania), the son of a minor noble, and graduated from Pázmány Péter Catholic University Medical School in Budapest in 1919. In 1922, after receiving a Rockefeller Fellowship, he spent 2 years at the Johns Hopkins University in Baltimore and in the Hygiene Institute in Boston where he began work on virology.

Baló accepted a position of Professor of Medicine in the Pázmány Péter University in 1926 but became the chairman of the Pathological Institute at the Ferencz József University of Szeged in 1928. After the war, Baló led the Institute of Forensic Pathology, then the Institute of Pathology at the Pázmány Péter University, staying there until 1967 when he retired. He successfully accomplished his objective of reestablishing the institute that was seriously destroyed during the war. He also built the Cancer Research Institute where he continued his research and lectured after his retirement and until his death.

Baló discovered the pancreas elastase enzyme with his wife, Ilona Banga. He was the first in Hungary who confirmed the role of viruses in the pathogenesis of cancer. Baló did internationally respected work on the pathology of lung cancer. His publication record includes more than 350 research articles and book chapters. He was a member of many European scientific societies, including the Royal Society, Deutsche Gesellschaft für Pathologie, Deutsche Akademie der Naturforscher-Leopoldina, and Pathology Society of Russia.

(**Publ**.: Balo J. Encephalitis periaxialis concentrica. *Arch Neurol Psychiatry* 1928; 19:242–244.)

Bannister syndrome see **Quincke's oedema**

Banti's disease (**Banti's syndrome**) is a clinical syndrome characterized by congestive splenomegaly, leukopenia, anemia, thrombocytopenia, gastrointestinal hemorrhages, obstruction of splenic, portal and/or intrahepatic veins, and liver cirrhosis eventually. It affects both genders and occurs at all ages but commonly is seen in females under 35 years of age with insidious or sudden onset. See also **Korovnokov's syndrome**, a special form of Banti's disease characterized by splenomegaly with subthrombocytosis and gastrointestinal hemorrhage.

There is some discrepancy in using the terms Banti's disease and Banti's syndrome. ***Guido Banti*** defined splenic anemia, or **Banti's disease** in 1882 and 1883. In 1894, he described hepatic cirrhosis as the consequence of prior splenomegalic anemia—named **Banti's syndrome**. It is an obsolete term coined by Emilio Cavazzani in 1896.

Guido Banti (Jun 8, 1852–Jan 8, 1925) was one of the most eminent Italian pathologists of the early twentieth century. He was born in Montebicchieri, a typical village in Tuscany in the lower valley of the Arno River, to Scipione Banti, a physician, and Virginia Bruni. He was a medical student for 4 years in Pisa and 2 years in Florence prior to his graduation. With his MD degree, he acquired an assistant's position at the Institute of Pathological Anatomy in Florence. When he was 35, he became a Lecturer in Pathology in the medical school and after 3 years was appointed as a Director of the Institute.

Banti was a perspicacious clinician, excellent histologist, and talented bacteriologist who published the first Italian textbook of bacteriological techniques. Banti said that clinical observations, anatomical reports, and laboratory examinations are three links in the same chain. As a bacteriologist, Banti integrated bacteriology with the pathogenesis of infectious diseases. In 1890, he declared that acute pneumonia had the hematogenic pathogenesis. His research studies focusing on the bacterial death greatly contributed to the development of the Metchnikoff's concept of phagocytosis as a defense pathway from bacterial infection. As a histologist, Banti illustrated several forms of endocarditis and described arteriosclerosis of the kidney. As an anatomist, he contributed to the understanding of aphasia. Banti's name is associated with his contributions to the pathophysiology of leukemia and spleen function. In 1913, he defined the term *leukemia* and proved the involvement of the spleen to hemolysis in vivo. He claimed that splenectomy should interrupt the hemolytic path, and the **first splenectomy** for hemolytic jaundice was conducted under his authorization and supervision in Florence on February 20, 1903.

Biographers have described Banti as a very shy and diffident person, who was not referred to by his colleagues as a prominent scientist. He was a highly educated person who spoke and read in 4 languages. His lectures were always popular as they clearly reflected his unlimited enthusiasm for research studies combined with original and unique thinking. His contribution to Florentine medicine was significant and important.

(**Publ**.: Banti G. Dell'Anemia Splenica (Ital), Firenze, C. Le Monnier, 1882.
Banti G. Splenomegaly with cirrhosis of the liver (Ital), *Sperimentale* 1894; 48:407–432.)

Basedow's syndrome, **Basedow's disease** see **Graves' disease**

Bechterew's disease (**Bechterew disease**, **Bekhterev disease**, **Marie-Strümpell disease**, ankylosing spondylitis) is a chronic autoimmune inflammatory disease that predominantly involves the axial skeleton, tendon insertions and joints. Ankylosing spondylitis often affects men between 15–30 years old, although it is possible that females may be underdiagnosed. Patients suffer from stiffness and pain in the lower back and buttock region, as well as strong stooping curvature of the spine. Stiffness in the chest could impact breathing. There is an accompanying enhanced risk of developing osteoporosis. Thirty percent of people with Bechterew disease have an inflammation of the eye's iris.

The disease has a clear genetic predisposition because 90% of patients display a HLA-B27 genotype. Other potentially promoting genes include *ERAP-1*, *IL23R,* and TNF-associated ones. Although genes appear to play an important role, the exact origin of ankylosing spondylitis is not known. Even though specific autoantigens have not been identified yet, it is likely that a bacterial infection can trigger the disease in people who are already predisposed. Bechterew's disease is not curable.

The disease evidently was distinguished from rheumatoid arthritis by Galen in the second century AD. The first description of pathologic changes to the skeleton, probably related to ankylosing spondylitis, was published in 1691 by Bernard Connor, an Irish physician and historian. Skeletons with ankylosing (crooked) spondylitis are found in Egyptian mummies. A joint inflammation of the vertebral column was first described by ***Vladimir Bechterew*** in 1892, as well as by ***Adolph Strümpell*** in Germany in 1897 and ***Pierre Marie*** in France in 1898.

Vladimir Mikhailovich Bechterew (***Bekhterev***) (Jan 20, 1857–Dec 24, 1927) was a Russian neurologist and psychiatrist. He was born in Sorali, a village between the Volga River and the Ural Mountains in the Russian Empire. His father, Mikhail Pavlovich, was a district police officer, and his mother, Maria Mikhailovna, was a daughter of a titular councilor. Vladimir and two of his brothers received an excellent education. Bekhterev graduated from the Military Medical Academy in St. Petersburg in 1873 and continued his medical education in St. Petersburg Medicosurgical (Medical and Surgery) Academy, where he developed an interest in neuropathology and psychiatry. He then worked at the Psychiatric Clinic in St. Petersburg and focused on the anatomy and physiology of the brain.

From 1885 until 1893, Bekhterev was the Chair of the Psychiatry Department at the University of Kazan, where he established the first laboratory of experimental psychology in Russia to focus on the nervous system and the brain and made some of his largest contributions in neurology. In 1893, Bekhterev returned to the St. Petersburg Military Medical Academy to lead the Department of Nervous and Mental Diseases, where he organized the first Russian neurosurgical operating room. He founded *Neurology Bulletin*, *Archives of Psychiatry, Neurology and*

Experimental Psychology, and the *Bulletin of Psychology, Criminal Anthropology and Hypnotism*, published 20–25 papers per year (~600 scientific papers total), and wrote many books such as *Pathways of Brain and Bone Marrow*, *Mind and Life*, *Foundations for Brain Functions Theory*, and *Suggestion and Its Role in Social Life*.

After the Socialist Revolution in Russia, Bekhterev continued his clinical and scientific work holding various positions. But his death was mystic and sudden. In December 1927, in Moscow, he was a president of the First All-Russian Congress of Neurologists and Psychiatrists when he was called to go to the Kremlin to examine Joseph Stalin. A few hours later after returning to the meeting, he said to his colleagues: "I have just examined a paranoiac with a short, dry hand." The next day, Bekhterev unexpectedly died, and the rumor was that he was poisoned by Stalin as revenge for the diagnosis.

Ernst Adolf Gustav Gottfried Strümpell (Jun 29, 1853–Jan 10, 1925) was born in Neu-Autz in Kurland, a Baltic province of Russia (presently Latvia) and spent time in Dorpat, Estonia, where his father, Ludwig Strümpell (Braunschweiger) was a Professor of Philosophy. He received his medical degree from the University of Leipzig in 1875, where he continued to work as a clinician and scientist. Then, he was a full professor at the Universities of Erlangen, Breslau, Vienna, and Leipzig. In 1884, he prepared a textbook on internal medicine, which was published in more than 30 editions and translated into many languages. Adolf von Strümpell was known as an optimistic and thoughtful person who loved music and was an excellent violinist.

Pierre Marie (Sept 9, 1853–Apr 13, 1940) was a French neurologist and political journalist. He was born in Paris and received his medical degree in 1883 with a graduate thesis on **Basedow's disease**. In 1907, he was appointed the Chair of Pathological Anatomy at the Department of Medicine at the University of Paris, and in 1917 the Chair of Neurology, a position he held until 1925. From 1928 on, Marie changed his career from the medical academy to political journalism and wrote for the Socialist Party's daily newspaper.

Marie's name is associated with the eponymous Charcot-Marie-Tooth disease, Bamberger-Marie disease, Marie-Léri syndrome, Marie-Foix-Alajouanine syndrome, and Marie-Strümpell disease.

(**Publ**.: Bechterew W. Steifigkeit der Wirbelsaule und ihre Verkrummung als besondere Erkrankungsform. *Neurol Centralbl* 1893; 12:426–434.

Strumpell A. Bemerkung uber die chronische ankylosirende Entzundung der Wirbelsaule und der Huftgelenke. *Dtsch Z Nervenheilkd* 1897; 11(3–4): 338–342.

Marie P. Sur la spondylose rhizomelique. *Rev Med* 1898; 18:285–315.

Begbie's disease see **Graves' disease**

Beguez-Cesar's syndrome see **Chediak-Higashi syndrome**

Beguez-Chediak-Higashi syndrome see **Chediak-Higashi syndrome**

Behçet's disease (**Behçet's syndrome**, **Morbus Behçet**, **Behçet-Adamantiades syndrome**, **Silk Road disease**) is a chronic systemic inflammatory disorder at the crossroads between autoimmune and autoinflammatory syndromes. It is a rare immune-mediated, small-vessel systemic vasculitis that often presents with mucous membrane ulceration and ocular problems. The oral lesions are similar to those found in inflammatory bowel disease and can relapse as a systemic disease; it also can involve visceral organs (e.g., the gastrointestinal tract, pulmonary, musculoskeletal, cardiovascular, and neurological systems).

The primary cause of Behçet's disease is not well known, but the primary mechanism of the damage is autoimmune. The involvement of Th17 cells might to be important. Many serological studies show a linkage between the disease and HLA-B51, which is more frequently found from the Middle East to Southeastern Siberia. Certain strains of *Streptococcus sanguinis* have been found to have a homologous antigenicity. The syndrome is rare in the US but is common in the areas surrounding the old silk trading routes in the Middle East and Asia. Thus, it is sometimes known as **Silk Road disease**.

Behçet's disease was named in 1937 after the Turkish dermatologist ***Hulusi Behçet***, who described three patients with oral and genital ulcerations and hypopyon uveitis. Yet, during the annual meeting of the Medical Association of Athens on November 15, 1930, ***Benediktos Adamantiades*** presented a lecture entitled "A case of relapsing iritis with hypopyon"; it described a 20-y-old male patient with 3 cardinal signs of the disease. Adamantiades took the genital ulcers, the arthritis, and the ocular signs as signs of a single disease. Behçet appreciated Adamantiades' contribution and included his description in his reference list.

In 1941, Jensen used the term "Behçet's syndrome" based on Behçet's work but was not aware of Adamantiades description. He used this term to characterize clinical signs of a patient with the triple symptom complex and ulcerous hemorrhagic colitis (Jensen, 1941). Interestingly, given the Feigenbaum paper, the very first report of the disease was neither by Adamantiades nor by Behçet. Hippocrates of Kos (460–377 BC) in his third "Epidemion" book, case 7, defined an illness with clinical signs similar to the fundamental signs of **Adamantiades-Behçet's disease** (Feigenbaum, 1956).

Hulusi (Hulsi) ***Behçet*** (Feb 20, 1889–Mar 8, 1948) was born in Istanbul to Turkish parents because his father was an official in the Ottoman Empire; they immigrated to Damascus and he spent his early childhood there after he lost his mother to illness. Behçet received his primary education in Damascus; learned French, Latin, and German; and graduated from Gülhane Military Medical Academy in Istanbul at age 21. He subsequently specialized in dermatology and venereal diseases. During World War I, he was assigned to assist the director of the military hospital in Edirne, serving as an expert in dermatology and venereal diseases. After the war, he studied in Budapest and Berlin to advance his medical skills. After returning back to Turkey, Behçet started a private practice, but in 1923 was selected as the Chief Physician at the Hasköy Venereal Diseases Hospital at Golden Horn in Istanbul. Then, he relocated to Guraba Hospital (now the School of Medicine,

Istanbul University) as the Professor and Chair of the Department of Dermatology and Syphilology. He also maintained his private practice. In 1937, at the meeting of the Dermatological Association of Istanbul, together with Professor Braun, Director of the Institute of Microbiology, Behçet presented a study of a 34-year-old female patient suffering for 7 years from recurrent oral aphthous ulcers, genital ulcers, and ocular lesions. This and other clinical cases were published by Behçet in 1937.

Behçet was a shy and silent man who had good relationships with his colleagues. He was very attracted by the arts and predominantly literature. His health was feeble, and he suffered from spastic colitis, chronic insomnia, and heart failure. As a heavy smoker, he experienced angina pectoris and respiratory failure and died of myocardial infarction at 59.

Benediktos Adamantiades (1875–Oct 27, 1962) was a Greek ophthalmologist. He was born in Prousa, Asia Minor (now Bursa, Turkey) to a father who was a teacher; his mother died when he was a child. Thanks to the financial support of his uncle, Adamantiades was able to attend the illustrious School of the Nation in Constantinople, which was well-known at that time for excellent Greek teachers. He studied at the Medical School of the University of Athens and specialized in ophthalmology in Paris. After being a Director of the Ophthalmology Department of Hippocration Hospital in Athens, he developed significant scientific activities. In addition to **Adamantiades-Behçet's disease**, Adamantiades described the interstitial keratitis in trichromatic patients to be a bacterial infection and classified the epidemic idiopathic hemeralopia. His pioneer works were on marginal corneal degeneration, the posterior vitreous detachment, the measurement of the optic fundi, and of the ocular pressure, as well as investigations on trachoma and the pathogenesis of glaucoma. Adamantiades published more than 150 scientific papers. He died in Athens.

(**Publ**.: Behçet H. Über rezidivierende, aphthöse, durch ein Virus verursachte Geschwüre im Mund, am Auge und an den Genitalien. *Dermatol Wochenschr* 1937; 105:1152–1157.

Behçet H. Considerations sur le lésions aphteuses de la bouche et des parties génitales ainsi que sur les manifestations oculaires d'origine probablement parasitaire et observations concernant leur foyer d'infection. *Bull Soc Fr Dermatol Syph* 1938; 45:420–433.)

Adamantiades B. A case of relapsing iritis with hypopyon (in Greek). *Archia Iatrikis Etairias, (Proceedings od the Medical Society of Athens)* Athens. 1930; 586–593.

Adamantiades B. Sur un cas d'iritis à hypopion récidivant. *Ann Ocul (Paris)* 1931; 168:271–278.)

Bell's palsy is a form of temporary facial paralysis resulting from damage or trauma to the facial nerves (i.e., seventh cranial nerve), which is not related to stroke. Clinically, it is described by the sudden initiation of facial weakness or even paralysis. It might be associated with a stiff neck, pain behind the ear, weakness on one side of the face, and a fever. Facial paralysis may be caused by ischemia and

compression of the seventh cranial nerve. However, the nature of **Bell's palsy** is not understood. It is possible that a viral infection (e.g., viral meningitis) or the common cold sore virus—*herpes simplex*—could cause the disorder. The facial nerve swells and becomes inflamed in reaction to the infection, causing pressure within the Fallopian canal and leading to ischemia. Some other immune-mediated disorders (e.g., myasthenia gravis and **Lyme disease**) frequently are implicated as a cause for this disease.

Bell's palsy is named for Sir ***Charles Bell***, a Scottish surgeon who described the facial nerve and its connection to the condition in 1821. He is noted for discovering the difference between sensory nerves and motor nerves in the spinal cord.

Charles Bell (Nov 12, 1774–Apr 28, 1842) was a Scottish surgeon, anatomist, neurologist, and philosophical theologian. He was born and grew up in Edinburgh and attended Edinburgh University, where he acquired his medical degree in 1798. He conducted his surgical training as assistant to his elder brother, John Bell. Shortly after his graduation, Bell was admitted to the Royal College of Surgeons in Edinburgh, where he operated and taught anatomy. In 1804, he arrived in London to establish a private service as a surgeon and opened an anatomical school. From 1812 to 1825, Bell and his brother operated the Great Windmill Street School of Anatomy. Bell also worked as a military surgeon. Interestingly, his service was documented at the Royal Hospital Haslar. He participated at Waterloo in 1815, where the anatomist Robert Knox quite negatively mentioned Bell's surgical capabilities: the mortality rate of amputations conducted by Bell reached 90%.

Bell participated in the formation of the Middlesex Hospital Medical School. He was the first Professor of Anatomy and Surgery at the College of Surgeons in London. He was asked to serve as the first Professor of Physiology at the new King's College London but quickly resigned from that position. In 1836, he moved back to Scotland as Professor of Surgery at the University of Edinburgh. Bell is remembered as a pioneering physicians who linked his clinical practice with neuroanatomy research and teaching. He prepared a lot of wax models of various tissues and used them for comprehensive surgical and anatomical illustrations in his books. In addition, he was a productive author with many scientific, artistic, and writing talents. Bell died of coronary thrombosis at Hallow Park near Worcester in the Midlands, while travelling from Edinburgh to London.

(**Publ**.: Bell C. On the nerves: Giving an account of some experiments on their structure and functions, which lead to a new arrangement of the system. *Phil Trans R Soc Lond* 1821; 111:398–424.)

Bence Jones protein(**s**) is a monoclonal globulin protein or the "light chain" portion of immunoglobulin protein (antibody) with a molecular weight of 22–24 kDa (kappa and lambda chains), which can be seen in the blood (serum) and urine in patients with multiple myeloma (plasma cell malignancy) or **Waldenström's macroglobulinemia**.

Bence Jones proteinuria is the presence of Bence Jones proteins in the urine, usually indicative of multiple myeloma, amyloidosis, or **Waldenström's**

macroglobulinemia. The renal manifestations of diseases associated with the production of monoclonal light chains (e.g., myeloma nephropathy, light-chain deposition disease, and amyloidosis) result from the deposition of certain Bence Jones proteins as tubular casts, basement-membrane precipitates, or fibrils, respectively.

The **Bence Jones protein** was described by the English physician ***Henry Bence Jones*** in 1847 and published in 1848. Bence Jones was not the first to describe the characteristics of the protein, but he recognized its place in the diagnosis of myeloma.

Although immunoglobulin free light chains are synonymous with Bence Jones proteins, history may have been more generous to others involved in their discovery. On Friday, October 30, 1845, William MacIntyre, physician to the Western General Dispensary, St. Marylebone, London, was called to see Thomas Alexander McBean, a highly respectable grocer who had severe bone pain and fractures. On examination, MacIntyre noticed edema; verifying the risk of nephrosis, he also examined albumin in the urine. He found precipitated protein after urine warming, which could be redissolved when heated to 75°C. All urine samples were sent to a chemical pathologist at St. George's Hospital for consultations. Later, Bence Jones reported his findings in 2, single-author papers; one manuscript was published in *Lancet* in 1847. He described the protein as an "hydrated deutoxide of albumen."

Henry Bence Jones reported his clinical findings in more than 40 papers and was elected to receive a fellowship from The Royal Society at the age of 33. He became rich and notable because he was "the best chemical doctor in London" and his clinical practice and lecturing. Amazingly, there was no indication of his work on the Bence Jones protein in his obituary, and the eponym was not introduced until after his death.

Bence Jones proteins were shown to originate in the plasma cells in bone marrow and were first identified by Waldeyer in 1875. By 1909, more than 40 cases of Bence Jones proteinuria had been identified, and in 1922, Bayne-Jones and Wilson reported two types of **Bence Jones protein** by detecting precipitation with antisera harvested from rabbits, immunizing with urine specimens obtained from several patients. But only in 1956, using the **Ouchterlony technique**, ***Korngold*** and ***Lapiri*** demonstrated that tested antisera also reacted with myeloma proteins. To honor their discovery, the two types of Bence Jones protein were designated kappa and lambda (κ and λ) based on the first letters of their surnames. In 1962, Edelman and Gally consequently demonstrated that immunoglobulin-free light chains made from monoclonal IgG proteins were identical to Bence Jones protein. Thus, it took 117 years to determine the nature of Bence Jones proteins.

Henry Bence Jones (Dec 31, 1813–Apr 20, 1873) was an English physician and chemist. He was born in Suffolk, the son of Lieutenant Colonel William Jones and Matilda Bence. He went to school at Hingham, Norfolk, and a private school in Putney. He entered Harrow in 1827 and then went to Trinity College, Cambridge, obtaining his degree in 1836. He started working for a pharmacy but soon switched, first, to study medicine at St George's Hospital and, then in 1839, chemistry at University College London. In 1841, he moved to Giessen, Germany, to improve his

knowledge of chemistry. After this training, he returned to St George's Hospital as an assistant physician and then a full physician. Because of some health issues, he retired in 1862.

Jones began his laboratory work each day at 6:00 am and arrived at the hospital at about 1:00 pm for ward rounds. Students did not like a clerkship with Dr. Jones because of his "scandalous unpunctuality." He was a sceptic with regard to therapeutics and, as a biochemist, believed in nothing that he could not separate, test, and measure. He scorned empirical experience, tradition, and authority and concentrated on "medical facts."

Jones was a fellow and senior censor of the Royal College of Physicians, a fellow of the Royal Society, and secretary to the Royal Institute. He wrote, in addition to several scientific books and several papers in scientific periodicals, *The Life and Letters of Faraday* (1870). He married his second cousin, Lady Millicent Acheson, in 1842. They had 7 children. He died in London as a result of congestive heart failure.

Leonhard Korngold (Jun 21, 1921–Oct. 17, 2010) was a US clinical scientist. He was born in 1921 in the former Czechoslovakia and spent his childhood in the Netherlands. He immigrated to the US during his teenage years, enlisted in the US Army in 1942, and received the Bronze Star for his military service in World War II, landing in Normandy shortly after D-Day and serving in the European Theater until his troup met up with the Russians. After the war, Korngold completed his BA at Brooklyn College and received his PhD in bacteriology from Ohio State University. He then did immunology research at Memorial Hospital in New York (later to become Memorial Sloan-Kettering) for many years where he met his wife, Grace. Korngold moved on to the Hospital for Special Surgery (part of New York Hospital) nearby for the immunological study of multiple myeloma proteins; a strand of an immunoglobulin molecule is named for him.

In 1981, Len and his wife retired to Eastham, MA, where he enjoyed engaging in his photography hobby both during extensive world travel and in the nooks and crannies of the Cape which he enjoyed so much as an avid hiker and nature lover. Len Korngold passed away in 2010 at Cape Cod Hospital after a brief illness.

Rose Lipari (?) worked as a technician with Dr. Korngold in their study of the Bence Jones protein.

(**Publ**.: Bence Jones H. Chemical pathology. *Lancet* 1847; 2:88–92.

Bence Jones H. On the new substance occurring in the urine of a patient with mollities ossium. *Philos Trans R Soc London, Ser B: Biol Sci* 1848; 138:55–62.

Korngold L, Lipari R. Multiple-myeloma proteins. III. The antigenic relationship of Bence Jones proteins to normal gammaglobulin and multiple-myeloma serum proteins. *Cancer* 1956; 9(2):262–272.)

Berger's disease (IgA nephropathy) is the most common form of glomerulonephritis, which is characterized by accumulation of the IgA antibodies in the glomerulus and presents with a characteristic purpuric skin rash, arthritis, episodic hematuria,

and abdominal pain. Glomerular IgA deposits can be seen in several diseases; for instance, in well-known **Henoch-Schönlein purpura**, which is a systemic IgA nephropathy. At the same time, the mechanisms of specific deposition and accumulation of IgA are not clear. There are no known kidney antigens for IgA formation, although there is a possibility that exogenous antigens could be cleared prior to the disease manifestation. One possibility is that IgA may serve as the antigen.

Based on the finding that IgA can reappear after renal transplantation, one can speculate that the dysfunction of the immune system, but not some kidney function problems, may induce the disease. Interestingly, kidney deposition of the IgA1 may not result from the mucosa-associated lymphoid tissue (MALT), known as the place of common upper respiratory tract infections. It probably originates in the bone marrow. This supports the view that the pathogenesis of the disease is associated with immune dysregulation rather than with exogenous factors.

Berger's disease was first introduced in 1801 by Heberden who described a 5-year-old child suffering from hematuria, hematochezia, abdominal pain, and purpura of the legs. In 1837, ***Johann Schönlein*** reported a few cases of purpura linked to urinary precipitates and joint pain in children. ***Eduard Henoch***, a student of Schönlein, also connected the disease with renal abnormalities and abdominal pain. In 1968 for the first time, ***Jean Berger*** and Hinglais detected IgA deposition in this type of glomerulonephritis. Nicole Hinglais oversaw both light and electron microscopy in the Department of Pathology of Nephrology Clinic. Later, she defined specific glomerular basement membranes in ultrastructural lesions in Alport syndrome. In 1967, Berger reported a specter of immunofluorescence patterns of renal lesions during his presentation at the Actualités Néphrologiques de l'Hospital Necker meeting. He identified IgA accumulations in the kidney of patients with chronic glomerulonephritis and patients with **Henoch-Schönlein purpura**. In 1968, Berger also presented his findings in Paris at the meeting of the Société de Néphrologie, and the summary of his talk was published in French as a less than one page long abstract.

Jean Berger (Sept 17, 1930–May 22, 2011) was born in Valdoie (Territoire de Belfort). He was a medical student in Paris and a resident in the Department of Nephrology. He became an *Interne des Hôpitaux de Paris* (the equivalent of residency) in 1954. While working at the Department of Nephrology at the Necker-Enfants Malades Hospital in Paris, he became interested in pathology. He qualified as a specialist in medicine in 1960, writing a thesis entitled "Contribution of the renal biopsy to the pathological knowledge of the kidney diseases."

In 1970, he was promoted to Professor of Pathology at the Paul Brousse Hospital-Villejuif (University of Paris) in France. In 1979, he became a Director of the Pathology Department in Laennec Hospital Paris V University. He is well known for his powerful attempt to use electron and fluorescent techniques for renal biopsy analysis as a groundbreaking investigative tool in kidney disease. Berger was helped by Professor Bernard Antoine, an immunologist working at Necker-Enfants Malades Hospital, who developed the methodology for immunofluorescence. They tested commercial sera and labeled them with fluorescein; anti-IgA specificity was

confirmed with an anti-IgA serum produced by Professor Maxime Seligmann, who had first described anti-DNA antibodies. After this discovery, Berger did not make many further significant contributions. He was a complex, original, and unusual man. Outside renal pathology, Berger was passionately fond of music, painting, and travel. He was invited to numerous meetings, and with his French accent, he was very popular because of his humor and skepticism.

(**Publ**.: Berger J, Hinglais N. Les depots intercapillaires d'IgA-IgG. *J Urol Nephrol* 1968; 74:694–695.

Berger J. IgA glomerular deposits in renal disease. *Transplant Proc* 1969; 1:939–944.)

Bernard-Soulier syndrome is a rare autosomal recessive coagulopathy (i.e., bleeding disorder) caused by abnormal platelets and subsequent abnormal clotting. The molecular basis is because of a defect in the platelet glycoprotein complex 1b-IX-V (GpIb), an adhesion complex and the receptor for von Willebrand factor—an important glycoprotein involved in hemostasis. The glycoprotein Ib-IX-V complex has two important roles in platelet function that explain the often severe bleeding observed in Bernard-Soulier syndrome: (1) it mediates adhesion to the blood vessel wall at sites of injury by binding von Willebrand factor, and (2) it facilitates the ability of thrombin at low concentrations to activate platelets.

This syndrome was originally described in 1948 by ***Bernard*** and ***Soulier*** who treated a young male patient with a severe bleeding disorder that was characterized by a prolonged bleeding time, thrombocytopenia, and extremely large platelets. They termed the disorder "la dystrophie thrombocytaire-hémorragipare congénitale."

Jean Bernard (May 26, 1907–Apr 17, 2006) was a French physician and hematologist. He was born in Paris, and after graduating in medicine in Paris in 1926, he commenced his laboratory training at the Pasteur Institute. During the German occupation of France, Bernard was active in the French resistance. Later, he was a Professor of Hematology and Director of the Institute for Leukemia at the University of Paris. Bernard published 14 textbooks and several monographs on hematology. In 1932, Bernard gave the first description of the use of high-dosage radiotherapy in the treatment of Hodgkin's disease. His research ranged from the demonstration of neoplastic nature of leukemia to the formulation of methods of treatment.

Jean Pierre Soulier see **Soulier-Boffa syndrome**

(**Publ**.: Bernard J, Soulier JP. Sur une nouvelle variété de dystrophie thrombocytaire hémorragipare congénitale. *Semaine des Hôpitaux de Paris* (in French) 1948; 24:3217–3223.)

Besnier-Boeck disease see **Besnier-Boeck-Schaumann disease**

Besnier-Boeck-Schaumann disease (**Boeck's sarcoid**, **Besnier-Boeck disease**, **Schaumann syndrome/sarcoidosis**) is a chronic granulomatous, probably

immune-mediated disease of unknown etiology. Sarcoidosis may somewhat resemble true tubercles, but show small or no necrosis, affecting the lymph nodes, skin, liver, spleen, heart, skeletal muscles, lungs, bones in distal parts of the extremities, and other structures; and sometimes by hyperglobulinemia, cutaneous anergy, and hypercalcinuria. The list of signs and symptoms mentioned in various sources for **Besnier-Boeck-Schaumann disease** includes 28 symptoms. **Besnier's disease** is often referred as a severe form of dermatitis characterized by atopy.

It was first described in 1877, by dermatologist Jonathan Hutchinson, as a condition causing red, raised rashes on the face, arms, and hands. Later from 1888–1889, it was described as a skin disease by the French dermatologist ***Ernest Besnier*** and the Norwegian dermatologist ***Cæsar Boeck***. Sarcoidosis was first studied as a systemic disease by the Swedish dermatologist ***Jörgen Schaumann*** in the first quarter of the twentieth century. During the first US sarcoidosis conference in 1961 in Washington, DC, the disease was called **Besnier-Boeck disease** or Besnier-Boeck-Schaumann disease.

Ernest Henri Besnier (Apr 21, 1831–May 15, 1909) was born in Honfleur, department Calvados, Basse-Normandie, the son of a French customs official who moved from Givet to Marseille and then to Orléans. After conspicuously successful study in Paris under Jean Baptiste Barth and ***Pierre Antoine Ernest Bazin***, he received his doctorate in 1857. Besnier became a practicing physician in 1863 and worked in several hospitals in Paris; in 1873, he succeeded Bazin as the dermatologist at the Hospital St. Louis, of which he became a director. He built histopathology and parasitology laboratories at the St. Louis Hospital and introduced the term and technique of **biopsy**. With Pierre Adolphe Adrien Doyon, he founded the journal *Annales de Dermatologie et de Syphiligraphie*. In addition to dermatology, Besnier worked on other medical fields—for example, rheumatology and he introduced the term *lupus pernio* as "une variété de lupus érythémateux à forme d'érythème pernio ou d'asphyx locale." In 1881, he was elected a member of the Academy of Medicine as a hygienist because of his contributions to epidemiology. Besnier died in Paris in 1909.

Cæsar Peter Møller Boeck (Sept 28, 1845–Mar 17, 1917) was a Norwegian dermatologist born in Lier, outside the city of Drammen, Norway. He was the son of a ship's captain Cæsar Boeck and Elen Holter, and a nephew to dermatologist Professor Carl Wilhelm Boeck and zoologist Christian Peder Bianco Boeck. The family originally came from Flanders (Bocken). His grandfather went to Norway toward the end of the eighteenth century, acquired substantial forest properties, and established a trade in wood. In 1871, Cæsar graduated with top marks in 1871 from the Christiania Medical School (now Oslo) and did postgraduate work in Vienna. In 1889, he was appointed a Chief of Dermatology at Rikshospitalet, Christiania, later becoming an Associate Professor (1895) and Full Professor of Medicine (1896).

Boeck is remembered for the comprehensive characterization of granulomatous diseases affecting the lymph nodes and other lymphoid and nonlymphoid tissues. In 1899, being an outstanding histologist, he reported massive skin changes in the face and scalp, back, and lower extremities and lymph node obliteration associated with

a chronic granulomatous in a 36-year-old policeman. The condition was later named Boeck's sarcoidosis and is sometimes referred to as Besnier-Boeck-Schaumann disease. Boeck reported the disease characteristics in a paper entitled "Multiple benign sarcoid of the skin."

Boeck was fluent in many languages, including French, German, and English, and travelled a lot during his professional career. He also was devoted to art and literature and liked visiting numerous art museums. In 1917, he even published his investigation of Rembrandt's life titled "Rembrandt of Saskia i Deres Hjem" (Rembrandt and Saskia in Their Home). In his will, Boeck donated his beautiful and unique art collection to the city museum in Drammen. He retired in 1915 and died suddenly of angina pectoris in 1917.

Jörgen Nilsen Schaumann (Jun 3, 1879–1953), a Swedish dermatologist, was the son of a garden director. He studied medicine at the University of Lund and graduated with his MD degree in 1907 in Stockholm. Then he worked as a dermatologist in St. Göran's Hospital in Stockholm and from 1912 onward was a physician in the Finsen Institute in Copenhagen. In 1939, he was awarded a position as a full Professor. He held this position until 1946 when he retired.

Schaumann's name is linked to the Besnier-Boeck-Schaumann disease. In 1917, he published a paper describing this disease and suggesting its systemic nature. Schaumann's name also is associated with Schaumann bodies—calcium-containing cytoplasmic inclusions seen in giant cells during progression of sarcoidosis and berylliosis. Schaumann is remembered as a modest and quiet person with a very strong interest in art, music, and religion. He was an art collector and talented painter and sculptor. His beautiful paintings were exhibited in the Skin Clinic, Karolinska University Hospital and the Lung Clinic of the Huddinge Hospital. Several of his sculptures were displayed in the offices of the Svenska Läkaresällskapet (The Swedish Society of Physicians). Schaumann retired in 1946 but continued to work for 7 more years, investigating unresolved problems of the benign lymphogranulomatosis until his last working days. He died of a heart attack at the age of 74.

(**Publ**.: Besnier E. Lupus pernio of the face (Fr). *Ann Derm Syph* 1889; 10:333–336.

Boeck C. Multiple benign sarkoid of the skin (Nor), *Norsk Mag Laegevidensk* 1899; 14:1321–1334.

Schaumann JN. Recherches sur le lupus pernio et ses relations avec les sarcoides cutanées et sous-cutanées (paper on Boeck's sarcoid). *Nordiskt medicinskt Arkiv*, Stockholm, 1917; II(17):1–81.

Schaumann JN. Study of lupus pernio and its association with sarcoidosis and tuberculosis (Fr). *Ann Derm Syph* 1916–1917; 6:357–373.)

Besredka's anaphylaxis (**Besredka's desensitization**, **Besredka's method**) is a method suggested by ***Besredka*** for avoiding anaphylactic shock in the practice of serotherapy. The discovery of anaphylaxis in 1902 presented a remarkable challenge to clinical researchers trying to understand the phenomena of immunity in terms of the body's defense response. The term **anaphylaxis** was coined by the

French physiologist ***Charles Richet*** to describe a biological phenomenon contrary to **phylaxis**, which indicated protection through immunization. Shortly after the phenomenon of immunity was described, it became clear that the activation of immune mechanisms could have adverse and hazardous effects. Anaphylaxis, especially one induced by serotherapy, was seen as a major applied problem, as well as a key theoretical question.

During his early work on anaphylaxis, Besredka wanted to increase the safety of the injection of therapeutic antisera. His starting point was the discovery that the onset of anaphylactic sensitivity was markedly delayed in animals that received a second injection of the sensitizing ingredient before the complete period for the progress of anaphylactic sensitivity. Besredka reported that even animals with established anaphylactic sensitivity could be "desensitized" with intradermal administration of low doses of the sensitizing serum. The site and the timing of the second injection dictated the reaction: anaphylactic shock or desensitization. The latter, he claimed, was not a new immunization, because it followed quickly on the desensitizing injection. Therefore, Besredka proposed desensitizing patients by an introductory injection of a small amount of the antiserum—a method he called "subintirant injection."

Besredka's concept about anaphylaxis formed the basis for his overall theory of immunity. All immune reactions, including allergy and anaphylaxis and natural and acquired immunity, are various forms of a basic physiological mechanism: "natura non facit saltus." The specificity of anaphylactic or immune reactions is not predominantly addressed by the chemistry of humoral antibodies and is reflected in the receptivity of target cells to pathogenic germs or their ability to react to toxins. Given his belief that immunity had its origin in the desensitization of cells, Besredka developed an "antivirus" therapy, which used filtered supernatants of bacterial cultures for vaccines and for the treatment of chronic infections.

Alexandre (Oleksandr) Mykhaylovych Bezredko (Mar 29, 1870–Feb 28, 1940) was an Ukrainian/Russian-French serologist. He was born in Odessa and the son of a Professor of Foreign Languages. From 1888 to 1892, he studied biology in Odessa, where ***Ilya Ilich Mechnikov*** (***Metchnikoff***) had been teaching, and graduated with his thesis for Doctor of Sciences: "Evolution de la Conception Stéréochimique."

In 1893, Bezredko left Russia for Paris and began working with Mechnikov at the Pasteur Institute, until completing his medical education in 1897. From 1905 to 1914, he was head of a laboratory at the Pasteur Institute and focused on immunology, cellular mechanisms of self-defense, and phagocytosis; he collaborated with Mechnikov in the experimental study of typhoid fever on chimpanzees. Bezredko became a French citizen in 1910 when he was appointed a Professor at the Pasteur Institute. His research work was interrupted by the outbreak of World War I in 1914, when Besredko was mobilized as a medical officer and directed the bacteriology laboratory of the Citadel of Verdun and then Bar-le-Duc.

In 1919, after returning from the war, he succeeded Mechnikov, who had died in 1916, as Head of Services. He remained at this position until 1940. From that time on, Bezredko's studies focused on the immune reactivity of intestinal infections

(e.g., cholera, typhoid fever, and dysentery). The development of this field forced him to reexamine Mechnikov's cellular theory of the immunity and to validate an idea of a "local immunity." He stated, "Each virus has its body and each body its immunity."

Besredko is remembered for his important and innovative research on anaphylaxis and for his crucial involvement in developing vaccines against serious infectious diseases, including cholera, dysentery, pests, anthrax, typhus, and paratyphus. He is particularly remembered for his 1907 work on anaphylaxis and antianaphylaxis. He introduced the term **antivirus** in 1923. **Besredko's antivirus** is the filtered and heated broth cultures of bacteria used by him to produce local immunity. His findings were crucial for developing techniques for preventing and curing many diseases that are still in use today.

Bezredko also is remembered as an active, prominent participant in the Association for the Protection of Jewish Public Health (Obschestvo zdravookhranenya evreev (Russian), O.Z.E.). He created "preventive medicine service for infants" for Jewish emigrant families in Paris. He also arranged acceptance and treatment for the first 300 Austrian, German, and Czech children assigned to the O.Z.E. after the "Night of Broken Glass" in 1938—the November *pogroms* against Jews organized by the Nazi Party's Sturmabteilung (SA) paramilitary forces. Bezredko died in Paris just a few months before German forces occupied France.

(**Publ**.: Bezredko AM. Anaphylaxie et antianaphylaxie Paris; 1918.

Bezredko AM. Le chic anaphylactique et le principe de la desensibilisation. Paris; 1930.

Bezredko AM. Antivirusthérapie Paris, Masson; 1930.)

Bickerstaff's encephalitis is a rare inflammatory disorder of the CNS, first described by ***Edwin Bickerstaff*** in 1951. It also can affect the peripheral nervous system and has features in common with both **Miller Fisher syndrome** and **Guillain-Barré syndrome**. The clinical features and course of the condition, the associated autoantibodies against relevant antigens, and the response to treatment, all suggest that Bickerstaff's encephalitis is an autoimmune disease. Still, each of these criteria fails to take in a substantial percentage of patients, and there is no single test or feature that is diagnostic of Bickerstaff's encephalitis. **Bickerstaff's brainstem encephalitis** (BBE) together with **Miller Fisher syndrome** (MFS) and **Guillain-Barré syndrome** (GBS) were considered to form a continuous clinical spectrum. Common autoantibody (anti-GQ1b IgG) suggests that a generic autoimmune mechanism functions in the pathogenesis of these illnesses. Other studies, however, have found a positive anti-GM1 instead of anti-GQ1b antibody. There is a report of a case of Bickerstaff's brainstem encephalitis associated with IgM antibodies to GM1b and GalNAc-GD1a subsequent to *Campylobacter jejuni* enteritis. Therefore, the nosological relationship of BBE to FS or GBS remains controversial, and it is not clear whether BBE is a distinct disease entity or a variant of FS or GBS. The immunological profile common to BBE and MFS lends supports to a common pathogenesis, but it does not provide the answer to the question of whether these syndromes are separate entities.

In 1951, Bickerstaff and Cloake published a few clinical cases of patients suffering from drowsiness, ophthalmoplegia, and ataxia and called them "mesencephalitis and rhombencephalitis." They suggested that the midbrain lesions caused those clinical symptoms. In 1956, ***C. Miller Fisher*** reported another three cases of ophthalmoplegia, areflexia, and ataxia, and he speculated that this disorder should be considered a variant of Guillain-Barré syndrome based on the existence of areflexia and CSF albuminocytological dissociation. Then Bickerstaff described 8 patients with drowsiness and extensor plantar responses, or loss of hemisensory associated with ataxia, and acute ophthalmoplegia. These symptoms were termed Bickerstaff's brainstem encephalitis. Analysis of autopsy materials from BBE patients revealed glial nodules and perivascular lymphocytic infiltration with edema—for example, signs of distinct inflammatory changes in the brainstem. Many patients with BBE also have axonal **Guillain-Barré syndrome**, which suggests that these related disorders may form a continuous spectrum.

Edwin Robert Bickerstaff (Nov 20, 1920–Nov 23, 2007) was born at Aberystwyth (Wales). His father was a High Sheriff of Cardiganshire and a Governor of the University College of Wales. Soon the whole family had to move to Birmingham, and young Dwin joined the King Edward's School in Edgbaston. As a teenager, he surprised everybody with his excellent bass voice, but he did not want a major career in music. Instead, he selected medicine, and after graduation in 1943, Dwin joined the Royal Air Force's medical branch in Europe. He participated in the D-Day landings as a chief of the Royal Air Force's medical service for patients with tuberculosis. This experience helped him prepare his MD thesis in 1947. Dwin Bickerstaff married Claire Woodhall in 1943, and they had a son and a daughter. After obtaining his medical license, he was trained in neurology. In 1952, Bickerstaff entered a fellowship program and worked for a year in Boston at the Massachusetts General Hospital. He also received an honorary research associate position at Harvard.

When he returned home, Bickerstaff worked as a consultant neurologist and leading clinician in the neurological service of Midlands Centre for Neurosurgery and Neurology, Smethwick. In addition to unlimited clinical duties, he spent a lot of time with medical students and postgraduates and was an author of many clinical papers and several textbooks. For instance, Bickerstaff's *Neurological Examination in Clinical Practice* textbook is known for its six editions over 25 years, and his short book, *Textbook of Neurology,* had four editions between 1965 and 1987.

Bickerstaff's reputation as a prominent physician and scientist gave him a council member position and a trustee of the Association of British Neurologists. He was also a section President of Neuroscience at the Royal Society of Medicine and an honorary member of the French Neurological Society. In addition, he was known for his love of music and another great passion: golf. After his first divorce, Bickerstaff married Sara Bramall, the daughter of Field Marshal Lord Bramall, in 1987. His wife took outstanding care of him during his prolonged terminal illness—a major stroke.

(**Publ**.: Bickerstaff ER, Cloake PCP. Mesencephalitis and rhombencephalitis. *Br Med J* 1951; 2:77–81.

Bickerstaff ER. Brain-stem encephalitis: Further observations on a grave syndrome with benign prognosis. *Br Med J* 1957; 1:1384–1387.)

Billroth's cords (**cords of Billroth**, splenic cords, or red pulp cords) consist of fibrils and cells of the connective tissues with a large proportion of monocytes and macrophages. They can be seen in the spleen's red pulp between the sinusoids. The cords hold almost 50% of monocytes in humans in storage. These reserve monocytes are used after tissue injury, functioning as important cells during wound healing. Red blood cells pass through the **cords of Billroth** before entering the sinusoids and should be flexible to pass into the sinusoids because cords might work as a bottleneck. Diseases associated with abnormality of red blood cell flexibility or shape, such as hereditary spherocytosis (**Minkowski-Chauffard disease**), result in erythrocyte failure to pass through the cords and lead to extravascular hemolysis and erythrocyte phagocytosis. Splenic cords are named for ***Theodor Billroth***.

Christian Albert Theodor Billroth (Apr 26, 1829–Feb 6, 1894) was a Prussian-born Austrian surgeon and amateur musician. He was born in Bergen, on the island of Rügen, Prussia, and was the first of 5 sons of Carl Theodor Billroth, a Diaconus priest of the Lutheran church and Johanna Christina, born Nagel, the daughter of a Berlin Kammerrat (Chamber Council). Christian was musically oriented, was not a good pupil, and needed home tutoring. He was not great in languages and mathematics, was not quick-witted, and spoke slowly. His mother encouraged Billroth to become a doctor for financial reasons. He studied medicine at the University of Greifswald, University of Göttingen, and University of Berlin.

Billroth worked as a doctor at the Charité in Berlin. In 1856, he was shortlisted for the Chair of Pathologic Anatomy in Berlin with Robert Remak and ***Rudof Virchow***. The former had lost support because he was a Jew, and Virchow had publicly expressed strong political views favoring democracy and freedom. Eventually, Virchow got a position even as Billroth was the second candidate. In Berlin in 1858, he married Christine, a daughter of the court physician, Heinrich Sabatier Michaelis and Karoline Eunike. They had 4 daughters and a son but only 3 daughters survived.

From 1860, Billroth was a Professor at the University of Zurich and Director of the Surgical Hospital and Clinic in Zurich. While in Zurich, Billroth published his classic textbook, *General Surgical Pathology and Therapy* (1863). He also introduced the concept of audits and publishing brought both good and bad results, which automatically caused truthful discussions on morbidity, mortality, and clinical techniques. He was appointed a Professor of Surgery at the University of Vienna in 1867 and practiced surgery as a Chief of the Second Surgical Clinic at the Vienna General Hospital. In 1870, Billroth volunteered for the Franco-Prussian War, working in field hospitals at Weissenburg and Mannheim.

Billroth introduced several important surgical procedures, including the first esophagectomy (1871); the first laryngectomy (1873); and, most famously, the first successful, after many ill-fated attempts, gastrectomy (1881) for gastric cancer. He was the first surgeon in the world to achieve success against stomach cancer by removing a part of it. He published numerous works on the pathology of cystoid

tumors in the testis, blood vessel development, and comparative anatomy of the spleen.

In addition to his exceptional love of music, Billroth was a very talented artist by nature: intuitive, gentle, and imaginative. His Vienna house was a well-known and attractive musical center, and he played second violin and viola. During the 1860s, Billroth met Brahms, a composer and a highflier of the Viennese musical society. They became good friends, sharing musical visions and priorities. Brahms often presented his novel compositions to get Billroth's opinion before official presentations. As a musician, Billroth frequently contributed to the trial preparations for Brahms' chamber works prior to their first appearances in open concerts. Brahms devoted his first two string quartets, Opus 51, to Billroth. He died in Opatija, Austria-Hungary (Primorsko-Goranska, Croatia) of a heart attack.

(**Publ**.: Billroth T. Neue Beobachtungen über die feinere structur pathologisch veränderter Lymphdrüsen. *Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, Berlin, 1861; 21:423–443.)

Billroth's disease II is a malignant lymphoma, which are a heterogeneous group of diseases with variable clinical presentations and prognoses. These diseases are linked only by their common lymphoid origin. ***Billroth*** was the first to use the **term Malignant lymphomas** in 1871. **Hodgkin's disease** is the most well-defined lymphoma with the presence of **Reid Sternberg cells**; the remainders are known as non-Hodgkin's lymphomas.

Christian Albert Theodor Billroth see **Billroth's cords**

Billroth-von Winiwarter disease see **Buerger's disease**

Bing-Neel syndrome is an extremely rare neurologic complication of **Waldenström macroglobulinemia** and is the result of the CNS infiltration by malignant lymphoplasmacytic cells and IgM accumulation seen in approximately 1% patients. Clinically, it appears as headaches, nausea, vomiting, visual disturbances, hearing loss, cranial neuropathies, and psychiatric abnormalities. Malignant lymphoplasmacytic cells can be isolated from the cerebrospinal fluid (CSF), the meninges, or the cerebral parenchyma. Rarely, the peripheral nervous system also could be involved. A histological biopsy of the cerebrum or meninges usually reveals a lymphoplasmacytic lymphoma with small lymphocytes having morphological evidence of plasma cell differentiation. Immunochemistry usually confirms monotypic B cells expressing the pan B cell antigens CD19, CD20, CD79a, and CD79b, and the memory B cell marker CD27, as well as CD52. Monotypic plasma cells also could be seen, expressing CD138 and IgM. MYD88L265P and CXCR4 mutations are common.

The syndrome is named after two Danish physicians working in Copenhagen—***Jens Bing*** and ***Axel Neel***; they first reported on 2 patients with hyperglobulinemia and neurological symptoms in 1936. It is of interest that this original report was published 8 years earlier than the seminal report of the cases of myelomatosis associated with anemia, macroglobulinemia, and coagulopathy by ***Jan Waldenström***.

Eighty years later, at the Eighth International Workshop on Waldenstrom macroglobulinemia, diagnostic criteria for Bing-Neel syndrome were finally formulated.

Jens Bing (1906–1980) was a Danish clinician. He worked at the Copenhagen Municipal Hospital; at the Institute of Medical Physiology, Copenhagen; at the Department of General Pathology, University of Copenhagen, Department of Experimental Medicine, Institute of General Pathology, University of Copenhagen; and at the Research Department of "Ferrosan," Copenhagen, Denmark.

Axel Valdemar von Neel (May 15, 1878–Jan 24, 1952) was a Danish clinician. He was born in Ejby, Vends Herred, Denmark, to Peter Nielsen and Ane Madsen. He graduated in 1897 from Odense and obtained his medical degree in 1903. Neel's medical education was interrupted by 2 long trips to East Asia and Australia, but it was finalized with a specialty in neurology. In 1911, he practiced in Paris, and from 1913 on began to work at the psychiatric laboratory of the University of Copenhagen, first as Assistant Professor and then Professor of Psychiatry until 1941, when he selected an amanuensis position. Neel also practiced as a neurologist, leading the unit associated with the Department of Clinical Psychiatry. His main research focused on the understanding of the anatomical basis of nerve-mental disorders. Neel did a lot of research on CSF, and in 1939, he published "The Content of Cells and Proteins in the Normal Cerebrospinal Fluid." He died in Aarhus, Denmark.

(**Publ**.: Bing J, von Neel A. Two cases of hyperglobulinaemia with affection of the central nervous system on a toxiinfectious basis. *Acta Med Scand* 1936; 88:492–506.)

Birbeck bodies see **Birbeck granules**

Birbeck granules (**Birbeck bodies**) are rod-shaped or "tennis-racket" shaped cytoplasmic organelles with a central linear density and a striated appearance. They are a characteristic microscopic finding in **Langerhans cell histiocytosis** (Histiocytosis X), which is one of a group of rare conditions collectively known as histiocytosis. Birbeck granules are unusual rod-shaped structures specific to epidermal Langerhans cells, the origin and function of which remain undetermined. It has been suggested that Birbeck granules are not endocytic structures, rather they are subdomains of the endosomal recycling compartment that form where Langerin accumulates. **Birbeck granules** were described by ***Michael Birbek***, a British scientist and electron microscopist, who worked at the Chester Beatty Cancer Research Institute or Institute of Cancer Research, London, from 1950 until 1981. Interestingly, BG deficiency resulting from mutation in the CD207 gene (chromosome 2p13) has been described; no deficiency in Langerhans cells have been seen because they were CD1A and HLA Class II positive.

Michael Stanley Clive Birbeck (***Clive Stanley Michael Birbeck***) (1925–2005). He was a British scientist and electron microscopist who worked at the Chester Beatty Cancer Research Institute or Institute of Cancer Research, London, from 1950 until 1981.

(**Publ**.: Birbeck MS, Breathnach AS, Everall JD. An electron microscope study of basal melanocytes and high-level clear cells (Langerhans cells) in vitiligo. *J Invest Dermatol* 1961; 37:51–63.)

Blackfan-Diamond syndrome (congenital hypoplastic anemia, inherited erythroblastopenia) in its classic form is characterized by a profound isolated normochromic and macrocytic anemia with normal leukocytes and platelets, congenital malformations in 50%, and growth retardation in 30% of affected individuals. Hematologic complications occur in 90% of impacted persons during the first year of life. The phenotypic spectrum ranges from a mild form to a severe form of fetal anemia, resulting in nonimmune hydrops fetalis. Blackfan-Diamond syndrome is associated with an increased risk for acute myelogenous leukemia, myelodysplastic syndrome, and solid tumors including osteogenic sarcoma. **Blackfan-Diamond syndrome** has been associated with mutations in 11 genes that encode ribosomal proteins (i.e., *RPS19, RPL5, RPL11, RPL35A, RPS24, RPS17, RPS7, RPS10, RPS26, RPL26,* or *RPL15)* and in *GATA1*.

Diamond and ***Blackfan*** described congenital hypoplastic anemia in 1938. In 1961, Diamond and colleagues presented longitudinal data on 30 patients and noted an association with skeletal abnormalities. In 1997, a region on chromosome 19 was determined to carry a gene mutated in Blackfan-Diamond syndrome. Later, additional mutations have been detected.

Louis Klein Diamond (May 11, 1902–Jun 14, 1999) was a US pediatrician, known as the "father of pediatric hematology," Diamond was born near Kishinev, Bessarabia, at the time part of the Russian Empire (now the Republic of Moldova). He immigrated to the US with his parents at the age of 2 and grew up in New York City. He joined Harvard College (1919–1923) and afterward graduated from Harvard Medical School in 1927. Still being a student, he successfully diagnosed a child with mononucleosis—the first case recognized at Boston Children's Hospital. After medical school, Diamond studied pediatrics in Boston Children's Hospital, mentored by ***Kenneth Blackfan***.

Diamond established one of the first pediatric hematology research and clinical centers in the US in a hospital for children. Concentrating on child anemia diagnosis and therapy, in 1930 he successfully identified thalassemia. In 1932, along with Blackfan, he identified erythroblastosis fetalis, later called Hemolytic disease of the newborn. He also discovered the blood diseases Gardner-Diamond syndrome, a painful bruising disorder, and Shwachman-Diamond syndrome, a rare genetic disorder that affects many different organs. Diamond rose through the academic ranks, being Chief of Hematology at Children's and later the Chair of Pediatrics. Except for the years 1948 to 1950, when he served as Medical Director of the American Red Cross's new National Blood Program, he remained in Boston until he resigned in 1968, receiving emeritus status.

After retirement from Harvard in 1968 at the age of 66, Diamond moved to the University of California at San Francisco, as an adjunct Professor of Pediatrics, to set up a pediatric hematology lab. When he retired from UCSF in 1987 at the age of

85, he moved to UCLA Medical School, where he remained professionally active until his 90s. In Los Angeles, he continued to follow patients with Diamond-Blackfan syndrome whom he had begun treating at their birth several decades previously. Diamond died at his home in Los Angeles at the age of 97. In December 1998, his wife of 69 years, Flora Kaplan Diamond, died half a year before him. He was survived by their son Jared and daughter Susan.

Kenneth Daniel Blackfan (Sept 9, 1883–Nov 1941) was a US pediatrician. He was born in Cambridge, MA. Blackfan began his medical studies at the Albany Medical School of Union University, New York, graduating at the age of only 22. Initially, he returned home to join his father in general practice. Four years later, however, he returned to Albany seeking academic challenges. He then did some pediatric training in the Founding Hospital in Philadelphia. He did a residency at Washington University in St. Louis, and in 1913, moved to Johns Hopkins Hospital in Baltimore. Working with Walter Edward Dandy (who described the Dandy-Walker syndrome), Blackfan discovered where cerebrospinal fluid originated by tracking dye injected into the cerebral ventricle of a dog.

Blackfan later showed dehydration to be the most important problem in infant diarrhea. In 1918, he was the first in the US literature to mention intraperitoneal injections of saline solutions. Soon he moved to a position of Associate Professor of Pediatrics at Johns Hopkins Hospital. Then he went to Cincinnati Children's Hospital Medical Center and finally to Harvard University, where he was a director of clinical services at Children's Hospital and a Professor of Pediatrics. He remained in this position until his death.

Blackfan's clinical research focused on nutrition and hematology when in Harvard. He was a mentor for ***Louis K Diamond***, and together they prepared the first set of microscopic photographs of the blood specimens in childhood diseases (i.e., *Atlas of the Blood in Childhood*). In 1938, they published a study of the characteristics of Diamond-Blackfan syndrome. Blackfan also mentored Sidney Farber, now known as the father of modern cancer chemotherapy. Blackfan died of lung cancer in 1941 at age 58, being on the top of his professional career. Children's Hospital in Boston is on Blackfan Street, named after Kenneth Daniel Blackfan.

(**Publ**.: Diamond LK, Blackfan KD. Hypoplastic anemia. *Am J Dis Child* 1938; 56:464–467.)

Blau syndrome (**Blau's syndrome**, **Jabs syndrome**, **Jabs-Blaus syndrome**, Arthrocutaneouveal granulomatosis) is an inflammatory disorder that primarily affects the skin, joints, and eyes (e.g., granulomatous dermatitis, arthritis, and uveitis). It is a disease of early childhood, which usually begins with a spontaneously resolving rash. Eye involvement can lead to blindness without prompt treatment. Patients are generally negative for antinuclear antibodies, rheumatoid factors, and HLA-B27. Pathologic investigation of organs reveals the presence of noncaseating epithelioid and giant-cell granulomas in affected tissues—one of the most interesting aspects of **Blau syndrome**. Blau syndrome is the prototypic autoinflammatory granulomatous disease and is the only autoinflammatory disease associated with a gain-of-function mutation to show granulomatous inflammation.

In 1985, ***Edward Blau***, a pediatrician in Marshfield, Wisconsin, described one family with granulomatous inflammation of the skin, eyes, and joints that had these signs over 4 generations. The disease was transmitted in an autosomal dominant manner. At the same time, **Jabs** et al. reported a family that had granulomatous synovitis, uveitis, and cranial neuropathies over 2 generations. Here too, the disease was transmitted in an autosomal dominant fashion. In 1990, Pastores et al. reported a group of related individuals who displayed a phenotype similar to the one reported by Blau. They also recommended terming this "Blau syndrome" (Pastores *et al*., 1990). In 2001, Miceli-Richard et al. revealed that the defect in Blau syndrome is in the nucleotide-binding domain of CARD15/NOD2 that had also been found in **Crohn's disease** (2001). Over time, the number of different NOD2 mutations associated with Blau has expanded greatly. These genetic defects seem to lead to overexpression and poor control of the inflammatory response leading to widespread granulomatous inflammation and tissue damage.

NOD2 is a member of the NOD-like receptor (NLR) family of pattern-recognition receptors, which are involved in inflammation and innate immune defense against invading pathogens. Consequent activation of the key downstream signaling molecules, NF-κB and MAP kinase, ultimately results in production of inflammatory cytokines (e.g., IL-1β, IL-6, IL-8, TNF-α) and a variety of other cytokines, chemokines, and adhesion molecules. The hypothesis is that NOD2 mutations in Blau syndrome act in a gain-of-function manner. Interestingly, Blau NOD2 mutations occur in amino acid positions homologous to known gain-of-function mutations occurring in the related pattern-recognitions receptor NLRP3, which leads to spontaneous IL-1β production in the autoinflammatory Cryopyrin-associated periodic syndromes (see **Mackle-Wells syndrome**).

Edward Bernard Blau (Nov 29, 1938–) is a US pediatrician. He was born in Minnesota and graduated from Saint Louis University School of Medicine in 1964. He did his internship in pediatrics (1964–1965), residency in pediatrics (1965–1967), and fellowship in nephrology (1967–1971)—all at the University of Minnesota Medical School. Later, he worked at the Department of Pediatrics, Marshfield Clinic in Wisconsin and was a director of a pediatric clinic in Marshfield and has more than 45 years of experience and practice in pediatrics and pediatric nephrology.

Douglas A. Jabs (Oct 2, 1951–) is a US ophthalmologist. He was born in Elmire, New York, and graduated with a degree in chemistry from Dartmouth College in 1973. He obtained his medical degree from Johns Hopkins University School of Medicine in 1977. He attended residencies and internships in medicine at New York Hospital–Cornell Medical Center, The Johns Hopkins Hospital and Wilmer Eye Institute, and a rheumatology fellowship at Johns Hopkins.

In 1984, Jabs moved to the Johns Hopkins School of Medicine as an Assistant, then Associate Professor. In 1993, he was appointed Professor of Ophthalmology and Medicine. In 2007, he became a chair of Ophthalmology at the Mount Sinai School of Medicine. He is currently the Chief Executive Officer of Mount Sinai Faculty Practice Associates. Jabs is also a Dean for Clinical Affairs, Professor and Chair of the Department of Ophthalmology, and Professor of Medicine at Mount Sinai School of Medicine in New York City. Additionally, he is adjunct Professor of

Epidemiology at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland.

Jabs is affiliated with several scientific societies. He has received many scientific awards. His publication record includes more than 230 journal articles, 45 books chapters, and 86 published abstracts.

(**Publ**.: Blau EB. Familial granulomatous arthritis, iritis, and rash. *J Pediatr* 1985; 107:689–693.

Blau EB. Autosomal dominant granulomatous disease of childhood: the naming of things. *J Pediatr* 1998; 133:322–323.

Jabs DA, Houk JL, Bias WB, Arnett FC. Familial granulomatous synovitis, uveitis, and cranial neuropathies. *Am J Med* 1985; 78:801–804.)

Boder-Sedgwick syndrome see **Louis-Bar syndrome**

Bouillaud-Sokolsky disease (**Bouillaud's disease**, **Bouillaud-Sokolski rheumatism**) is an immunopathological illness caused by group A Streptococcus, following a tonsillitis process. It is a systemic inflammatory disease characterized by acute attacks of fever separated by remissions, the incidence of acute joint disorder, endocarditis, and pericarditis. Other signs include chorea (i.e., rapid, unpredictable, involuntary body movements), subacute nodules (i.e., large fibroid areas), and erythema marginatum (i.e., rounded skin rash on the trunk and limbs). Onset often follows scarlet fever (scarlatina), streptococcal sore throat, and tonsillitis. Infection with the group A streptococci is considered the principal etiological factor. Serious clinical problems can involve cardiac lesions characterized by **Aschoff bodies**, fibrosis, and valvulitis with fibrous scarring and stenosis. Subcutaneous nodules and scarring of the synovia, joint capsules, tendons, and muscle sheaths, as well as acute inflammatory exudative changes in the blood vessels; and pneumonia also may be associated with rheumatic fever.

Its pathogenesis combines immune-complex hypersensitivity reactions, which involves endothelium, and autoimmune responses, which is because of molecular mimicry of streptococcal M5 protein peptides and some self-antigens. The *streptococcus pyogenes* cell wall is comprised of branched polymers that sometimes contain M protein, a virulence factor that is very antigenic. Antibodies recognizing the M protein can cross-react with heart muscle cells and smooth muscle cells of arteries.

Tissue damage is facilitated by attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages. Two weeks after the streptococcal infection, the children experience migratory polyarthritis and sometimes endocarditis, with less often involvement of other cardiac layers. Rheumatic valvular lesions also may include a cell-mediated immunity reaction because these lesions mainly include T-helper cells and macrophages. The bigger macrophages may become **Anitschkow cells**. Some manifestations can have a late onset, such as erythema migrans (an expanding rash), and **Sydenham's chorea**.

The first medical descriptions of the disease were made by a French physician ***Jean-Baptiste Bouillaud*** (in 1832, as a joint disease) and a Russian physician ***Grigory I. Sokolski*** (in 1838, as a heart disease). Although not the first to notice the cardiac manifestations of acute rheumatism, Bouillaud was the earliest to report the frequency and significance of heart disease coincident with acute articular rheumatism. He stressed that endocarditis and pericarditis were coincidental occurrences in acute articular rheumatism but noncoincidental occurrences when coupled with chronic articular rheumatism.

Bouillaud disease is an obsolete term that formerly dignified the combination of pericarditis, endocarditis, and the joint involvement in rheumatic fever or an acute rheumatic fever with endocarditis.

Jean-Baptiste Bouillaud (Sept 16, 1796–Oct 29, 1881) was a French physician. He was born in Bragette near Angoulème, the capital of the Department of Charente, France. He was encouraged to study medicine by his uncle, Jean Bouillaud, who was a surgeon-major in the army under Napoleon I. At the age of 18, Bouillaud moved to Paris to start his studies. After completion of his medical education, he got his doctorate degree in Paris in 1823, and his dissertation thesis focused on diseases of the heart. Specifically, it described the diagnosis of aortic aneurysm, especially by auscultation. In 1924, when the textbook on heart disease, prepared together with his teacher R. Bertin, was published and made Bouillaud famous in Paris, he tried to habilitate. But he was rejected for "moral, political, and religious" reasons. He then joined a Masonic-like secret society. Because of the negotiations of a Dominican priest, he was given another chance in 1826 and gave his inaugural lecture (in Latin) on the topic: "Are asthma and angina pectoris symptoms or independent diseases?"

In 1831, he became the Professor and Chair of clinical medicine at the Charité Hospital in Paris, and soon acquired the reputation of an outstanding clinician. His patients included celebrities and royalty including Napoleon III. He was a member of the University Senate and was elected dean and chair of the Department of Medicine from 1842–1846. Yet, he resigned the position because of many conflicts with the administration. In 1862, Bouillaud was elected president of the Academy of Medicine. He was a member of the Academy of Sciences from 1868 onward.

Bouillaud was interested in various medical problems and published on various forms of fever, cancer, hermaphroditism, cholera, heart disease, encephalitis, and other topics. Nevertheless, his major accomplishment was in the field of rheumatology. Bouillaud was the first to describe the endocardium and its inflammation, endocarditis. He correctly recognized and first reported the cartilaginous and synovial lesions of endocarditis. Both the terms *endocardium* and *endocarditis* come from him. Acute rheumatoid endocarditis is still commonly called Bouillaud's disease in French medical publications and dictionaries.

The prerequisite for his cardiological investigations was that Bouillaud used the stethoscope, which he significantly improved. The first correct methods of weighing and measuring the heart are the result of Bouillaud's studies. He is credited with introducing the topographical anatomy of the heart. He recognized the importance

of auscultation in diagnosing heart diseases and was among the first clinicians to recognize the importance of physics and chemistry to medicine.

Almost nothing is known about Bouillaud's private life. He married Angélique-Anaïs in 1824, and she helped him a lot with his animal experiments on brain characterization. When she died in 1870, Bouillaud dropped almost everything and traveled through the Mediterranean and Switzerland. Returning from that journey, he died at the age of 85. A bronze statue was commissioned in his honor in 1885 at Angouleme on Place Bouillaud, one of the most beautiful squares directly at the town hall. When in 1940, during the World War II, the French government law required all metallic statues and monuments to be melted for the making of weapons, a cast of the head was immediately made; it is preserved in the Musée des Beaux Arts (Museum of Fine Arts) in Paris.

Grigory Ivanovich Sokolsky (***Sokolski***, ***Sokol'skiy***) (Mar 12 (24), 1807–Feb 28 (Mar 12), 1886) was a Russian physician. He was born in Moscow to a priest's family and graduated from Theological College. In 1828, he completed his medical course at the University of Moscow as physician first class. ***Nikolay Pirogov*** was his closest friend at the University. Sokolsky was not allowed to continue his medical education in Moscow because of a reputation as an intransigent person who does not respect his superiors. He was sent to Dorpat (now Tartu, Estonia) to take a course at the Professorial Institute at the University of Dorpat. He obtained his medical doctorate in 1832. Sokolsky continued his medical training in Vienna in 1833 and Berlin in 1834. Although he was appointed professor of clinical medicine at the University of Kazan in 1835, he was called to Moscow to teach at the University of Moscow. He was a Clinical Professor and taught pathology, internal diseases, and psychiatry.

Sokolsky gained international recognition for his work "On Rheumatism of Heart Muscle Tissue" (1836), which brought new light to our understanding of the pathophysiology of rheumatism by forming a link between joint injuries and the heart. He also published several books and a lot of casuistical reports. Contemporaries highly appreciated the lecturing abilities of Sokolsky, noted his originality, sharpness, and courage in judgment, and also appreciated him as a popular Moscow doctor. Sokolsky retired in 1848 and lived in Moscow at his home in the Arbat district for the rest of his life. He continued to work as a private physician but died soon.

(**Publ**.: Bouillaud JB. Traité clinique du rheumatisme articulaire. Paris; 1832.

Bouillaud JB. Traité théorique, pratique et staistique du choléra-morbus de Paris; 1832.

Sokolskii GI. O revmatizme myschecnoi tkani serdtsa (rheumatismus cordis). *Uchen Zap Imp Mossk Univ* 1838; 12:568.

Сокольский ГИ. Учение о грудных болезнях. 1838; Москва.

Сокольский ГИ. Исследование патологических свойств воспаления легочной и соседних ее тканей, с приложением к диагностике и терапевтике. 1838; Москва.)

Bruton's agammaglobulinemia (X-linked agammaglobulinemia (XLA), **Bruton's disease**, **Bruton-Gitlin syndrome**) is an inherited immunodeficiency disease caused by mutations in the gene coding for **Bruton tyrosine kinase** (BTK). BTK is critical to the maturation of pre-B cells to differentiating mature B cells. The *Btk* gene defect has been mapped to the long arm of the X chromosome at band Xq21.3 to Xq22, spanning 37.5 kb with 19 exons forming 659 amino acids to complete the BTK cytosolic tyrosine kinase.

Children with XLA are usually healthy for the first several months of life because they are protected by antibodies acquired before birth from their mothers. After this time, the affected child begins to develop recurrent infections. The most common bacterial illnesses that occur in people with XLA are lung infections (i.e., pneumonia and bronchitis), ear infections (otitis), pink eye (conjunctivitis), and sinus infections (sinusitis). Infections that cause chronic diarrhea are also common. People with XLA can develop severe, life-threatening bacterial infections; however, affected individuals are not particularly vulnerable to infections caused by viruses. With treatment to replace antibodies, infections usually can be prevented, improving the quality of life for people with XLA.

The disease was first discovered by ***Ogden C. Bruton*** in 1952, for whom the disease and the gene associated with this defect, *Btk* (Bruton's tyrosine kinase) is named. While at Walter Reed Army Hospital in Washington, DC, Bruton, the chief of Pediatric Ward 17, observed Joseph S. Holtoner, Jr., an 8-year-old boy, who suffered from recurrent lung infections and who lacked gamma globulin (e.g., antibodies) in his serum. This agammaglobulinemia was later termed Bruton's syndrome or X-linked agammaglobulinemia. Bruton's results were published in the journal *Pediatrics* in 1952. He also is remembered as the first physician who offered a specific immunotherapeutic approach for this disease—that is, intramuscular injections of IgG immunoglobulin as a replacement therapy. A milder form of X-linked congenital Swiss-type agammaglobulinemia, known as **Bruton-Gitlin syndrome**, also has been reported. The disease is categorized by lower levels of serum gammaglobulin and cellular functional deficiencies. A defect in the *Btk* gene also is present.

Ogden Carr Bruton (Jun 14, 1908–Jan 20, 2003) was a US pediatrician. He was born in Mount Gilead, North Carolina, graduated from Trinity College (Duke University) in 1929, and then Vanderbilt University School of Medicine in 1933 with honors. He remained at a pediatric residency at Duke, and continued at Vanderbilt as a faculty member. Here he entered the Army as a reserve officer and served a year in 1940. But this turned out to be his first step in his subsequent 21-year military career. In 1944, he married Melda Kathryn (Kay) Dove, and they had a daughter, Kathryn Jo, and a son, Odgen Carr, Jr.

Bruton worked at Walter Reed Hospital, first as a consultant to the Army Surgeon General's Office. He received a regular Army commission and went to Europe on an assignment to improve the health conditions of immigrating war brides and their children. Thereafter, he returned to Walter Reed to develop the Army's first pediatric training program. At the same time, he became a clinical Professor of Pediatrics at

Georgetown University School of Medicine. He also served as a consultant at the Children's Hospital in Washington, DC. He retired in 1961.

In 1992, Bruton was awarded the Department of Defense Distinguished Civilian Service Award, the highest Department of Defense award given to civilians requiring the approval of the Secretary of Defense.

David Gitlin (Aug 7, 1921–Jan 4, 2010) was a US pediatrician and protein chemist. He was born in Bronx, attended the College of the City of New York, and received his medical degree in 1947 from the New York University School of Medicine. In 1944, he married Geraldine Mary Wadsworth and they had a daughter, Susan, and a son, Jonathan. After an internship in Morrisania City Hospital, NY, he finished residency and research fellowships at Boston Children's Hospital and obtained a faculty position at Harvard Medical School to carry out clinical and fundamental studies and teaching. In 1963, Gitlin joined the Department of Pediatrics at the University of Pittsburgh School of Medicine as a full Professor. He retainedt the title of emeritus Professor until his death. He was a chair of the postgraduate education committee (1971–1973) and a member of the Pittsburgh Pediatric Society.

In 1953, while working at Harvard Medical School, Gitlin reported on an inherited disease affecting children with recurrent and serious infections and characterized by agammaglobulinemia (e.g., the absence of antibody generation). Gitlin also investigated the metabolism of plasma protein in children with kidney disease, described the mechanism of intestinal iron absorption, and revealed that ceruloplasmin deficiency may serve as a marker of Wilson's disease. His clinical chemistry research on protein synthesis proved that alpha fetoprotein is a key marker of possible life-threatening birth defects in the developing baby. This biomarker is still in use.

For his findings on protein chemistry, Gitlin received many awards including the 1956 E. Mead Johnson Award from the Society for Pediatric Research, the 1963 Borden Award for Pediatric Research from the American Academy of Pediatrics, the 1967 Medal of the University of Helsinki, and the 1968 Federico Gomez Award from the Hospital Infantil de Mexico. Gitlin died in Islamorada, FL, of gastrointestinal cancer. (One can see a very interesting description of David Gitlin's research at http://pittmed.health.pitt.edu/Fall_2010/bricks.pdf.)

(**Publ**.: Bruton OC. Agammaglobulinemia. *Pediatrics* 1952; 9(6):722–728.

Gitlin D, Craig JM. The thymus and other lymphoid tissues in congenital agammaglobulinemia. *Pediatrics* 1963; 32:517–530.)

Bruton's disease see **Bruton's agammaglobulinemia**

Bruton-Gitlin syndrome see **Bruton's agammaglobulinemia**

Buckley syndrome see **Job syndrome**

Buehler test (**Buehler assay**) is an in vivo test for hazard identification of chemical substances that cause human skin sensitization (e.g., allergens). It is a nonadjuvant

test where Guinea pigs are exposed to a high dose of the substance and are then given a challenge dose, which is the highest dose that does not cause irritation. Three Buehler tests are used for a 6-h duration topical induction patches (one patch per week). Two weeks after induction, the animals are challenged by closed-patch tests to the flanks for 6 h. All tests in the **Buehler assay** are performed on restrained animals.

The predictive allergenicity testing of chemicals was first proposed by ***Edwin V. Buehler*** in 1965 and further optimized in 1980. The test has been largely superseded by the murine local lymph node assay developed in 1989 (Kimber et al., 1989). In this assay, the test material is applied to the ears of mice inducing sensitization and proliferation of lymphocytes in the lymph nodes draining the site of application, which is detected by radio- or bioluminescent or immunoassay of intraperitoneally injected and incorporated into lymphocytes tracers such as ^{3}H-Methylthymidine or Bromodeoxyuridine (5-bromo-2′-deoxyuridine, BrdU).

Edwin Vernon Buehler (Sept 23, 1929–Oct 8, 2017) was an US scientist working on immunotoxicology testing. After graduation, he received his PhD degree and worked for various companies, including Procter & Gamble Company; Miami Valley Laboratories, Cincinnati, OH (1964–1986); Biolabs, Inc., Cincinnati, OH (1990); and Hill Top Research, Inc./Hill Top Biolabs, Inc., Cincinnati, OH (1990–1996). He also worked for the International Research and Development Corporation, Bethesda, MD, in 1972. Buehler was an active member of the Society of Toxicology and served as the president of the Academy of Toxicological Sciences in 1993–1994. He had 13 grandchildren and 21 great-grandchildren and died at age 88 in his house in Lebanon, OH.

(**Publ**.: Buehler EV. Delayed contact hypersensitivity in the guinea pig. *Arch Dermatol* 1965; 91:171.

Ritz HL, Buehler EV. Procedure for conducting the guinea pig assay. In: Drill, V.A. and Lazar, P. (eds.). Current Concepts in Dermatology. New York: Academic Press; 1980; pp. 25–40.)

Buerger's disease (**Buerger disease**, Thromboangiitis obliterans, **Billroth-von Winiwarter disease**, **Winiwarter-Buerger syndrome**) is a recurring progressive inflammation and thrombosis of the small and medium arteries and veins of the hands and feet. The mechanisms are still largely unknown but smoking and tobacco consumption are major risk factors. It is possible that the tobacco triggers an immune response in susceptible persons or unmasks a clotting defect causing an inflammatory reaction of the vessel wall. Some data suggest the existence of an immunologic phenomenon leading to vasodysfunction and inflammatory thrombi. Patients with **Buerger's disease** exhibit hypersensitivity to intradermally injected tobacco extracts, increased cellular sensitivity to collagen types I and III, elevated serum antiendothelial cell antibody titers, and impaired peripheral endothelium-dependent vasorelaxation. They also show a higher prevalence of HLA-A9, HLA-A54, and HLA-B5, suggesting a genetic component to the disease. A possible role for *Rickettsia* in Buerger's disease also has been proposed.

Buerger's disease was first reported by ***Felix von Winiwarter*** in 1878–1879 in Austria. He reported a clinical case of a 57-year-old patient with unusual obliteration of the veins and arteries of his legs. Buerger suggested that this disease, which he called the "endarteritis obliterans" is the result of new tissue growth from the intima. But its first accurate pathological description was given in 1908 by ***Leo Buerger*** at Mount Sinai Hospital in New York City. He described a young Jewish patient with an unusual pattern of occlusion of small arteries in his feet and hands. The blockage of arteries caused chronic sores and required amputations. Buerger investigated the removed tissues and noticed an intense inflammation around small- and medium-sized blood vessels. In addition, the walls of arteries were not damaged as is commonly observed in atherosclerosis or true arteritis. Buerger called it "presenile spontaneous gangrene" and "Thromboangiitis Obliterans" after studying amputations from 11 patients.

Leo Buerger (Sept 13, 1879–Oct 6, 1943) was an Austrian-American pathologist, surgeon, and urologist. He was born in Vienna to a Jewish family, but they immigrated to the US when he was a year old, and he attended several elementary schools in New York, Chicago, and Philadelphia. He graduated from the New York City College and received an MD degree from the College of Physicians and Surgeons, Columbia University, in 1901. Initially, Buerger practiced at the Lenox Hill Hospital, then at the Mount Sinai Hospital. In 1905, he returned to Europe where he served as a voluntary assistant at the surgical department in Breslau, Germany, with study visits to Vienna and Paris. Then he returned to private practice in New York where he worked as a pathologist and surgeon. Buerger was very much interested in radiology and was able to establish a radium therapy for the treatment of malignant tumors of the bladder. He is remembered for the development a **cystoscope**, which was done in collaboration with F. Tilder Brown. It was known as the Brown-Buerger cystoscope, although the rumor was that he tried to change that name to Buerger's cystoscope. Being a surgeon, Buerger worked in various hospitals in New York, including Beth David Hospital, Bronx Hospital, and Wyckoff Heights Hospital in Brooklyn. In 1917, he obtained a professorship position at the Medical Urology Outpatient Clinic in New York, where he practiced until 1930.

Buerger was extremely unpopular among his colleagues, maybe because of his unusual and overreaching success in several fields. He was described as a short, dapper, immaculately groomed man. His talent in music also exceeded an amateur rank. Buerguer's wife was a concert pianist, and he could have made a living as a concert violinist if he had wanted. In 1929, Buerger was divorced from his first wife because of some financial difficulties. He remarried and moved to Los Angeles, where he was appointed Professor of Urology at the College of Medical Evangelists (Loma Linda University). Buerger did not ingratiate himself with his colleagues; when at a dinner at the Alexandria Hotel, he publicly announced that he had come to Los Angeles to teach the local urologists how to practice urology. Furthermore, his desire for fast cars and assorted accoutrements probably did not impress a minister and administrator of the College.

In 1934, Buerger returned to New York but was not allowed back on the staff at the Mount Sinai Hospital and was forced into relative obscurity, working at smaller private hospitals. He died in New York in 1943. Buerger alone or in collaboration with others wrote more than 160 articles in various scientific journals on a variety of subjects, including infectious diseases, shock, osteogenic sarcoma, and early transfusion experiences.

Felix von Winiwarter (Feb 28, 1852–Jul 10, 1931) was an Austrian physician. He was born in Vienna to Joseph Max Ritter von Winiwarter and Helene von Winiwarter. He attended the University of Vienna and received his doctorate in 1876. Felix von Winiwarter was the brother of Alexander von Winiwarter, and both of them studied surgery under ***Christian Albert Theodor Billroth***. From 1881 on, he was the director of a hospital in Hollabrunn, Nieder-Österreich and died there.

Christian Albert Theodor Billroth see **Billroth's cords**

(**Publ**.: von Winiwarter F. Ueber eine eigenthumliche form von endarteriitis und endophlebitis mit gangran des fusses. *Arch Klin Chir* 1879; 23:202–226.

Buerger L. Thrombo-angiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene. *Am J Med Sci* 1908; 136:567–580.)

Burkitt lymphoma (**Burkitt's lymphoma**) is an aggressive form of lymphoma that affects the B lymphocytes. Lymphoma is the most common blood cancer. The two main forms of lymphoma are **Hodgkin lymphoma** and non-Hodgkin lymphoma. Non-Hodgkin lymphoma is broadly categorized as B-cell lymphoma (85% of all non-Hodgkin lymphoma) or T-cell lymphoma (15%). Burkitt lymphoma is a rare but highly aggressive B-cell non-Hodgkin lymphoma that occurs most often in children and young adults. The disease could affect the jaw, central nervous system, bowel, kidneys, ovaries, or other organs. There are 3 main types of **Burkitt lymphoma**: endemic, sporadic, and immunodeficiency-related. Sporadic Burkitt lymphoma occurs throughout the world, and endemic Burkitt lymphoma occurs in Africa. Immunodeficiency-related Burkitt lymphoma is most often seen in AIDS patients. It is named after ***Burkitt***, a surgeon who first described the disease in 1958 while working in equatorial Africa.

Denis Parsons Burkitt (Feb 28, 1911–Mar 23, 1993) was a surgeon. He was born in Enniskillen, County Fermanagh, Ireland. Denis's father, James Parsons Burkitt, the second son of a Presbyterian minister, was a civil engineer and county surveyor in Fermanagh and was considered one of the pioneers of modern ornithology. Denis's mother, Gwendoline Hill, one of 12 children, was from Cork.

At age 11, following a fracas between two groups of boys where stones were thrown, Denis's glasses were broken, and he lost sight in his right eye. He was then sent to schools in Wales and England. Burkitt enrolled in the School of Engineering at Trinity College in Dublin in 1929. It was during his first year at college when a life-changing event happened—Burkitt joined an evangelical group, where he was totally convinced to "abandon an engineering career and take up medicine." The following year, he moved on to study at the Medical Faculty.

After graduating, Burkitt secured house jobs in Chester, Dublin, and Preston before becoming a Senior Resident Surgical Officer. In 1938, he spent 5 months as a ship's surgeon on a cargo ship that traveled between Britain and northeast China. After returning to England, he practiced as a Resident Surgical Officer at the Prince of Wales Hospital in Plymouth, even though he hoped to combine his wish to be a surgeon with his interest in being a missionary and to serve at the Colonial Service in West Africa. Soon he met Olive Mary Rogers, a nurse trainee who shared his religious faith, and they planned to marry in 1943. During World War II, Burkitt worked for the Royal Army Medical Corps in England, Kenya, and Somaliland. After the war, Burkitt made a decision to offer his medical knowledge to developing countries and moved to Uganda. After working in a few places, he finally settled in Kampala, where he worked until 1964.

Burkitt is remembered for 2 important contributions to the medical field associated with his medical practice in Africa, and his remarkable experimental and diagnostic skills. First, he was able to recognize and offer an effective medication for a childhood cancer now known as Burkitt lymphoma. Second, after returning to England, he compared the disease patterns he observed in African hospitals with common Western diseases. Burkitt came to the conclusion that many diseases seen in Western hospitals are rare in Africa and that this could be because of specific diets and lifestyles. He published a book entitled *Don't Forget Fibre in Your Diet*, which became an international bestseller. In various papers and books, Burkitt also described his belief that the "natural squatting position" habit for defecation, as normally seen in Africa and Asia, protects native people from many gastrointestinal diseases.

Burkitt was widely honored all over the world for his clinical and research achievements. He was awarded 19 major prizes and medals, 13 honorary degrees and fellowships, 4 honorary memberships in various research and clinical societies, and the Companion of the Order of St. Michael and St. George. In January 1993, he received the Bower Award and Prize for achievements in science—the oldest US science and technology awards program and one of the most admired awards in North America. A few weeks after accepting this prestigious award, he suffered a stroke at his home in Bisley, Gloucestershire. He died shortly after in Gloucester Royal Hospital and was buried in Bisley, England.

(**Publ**.: Burkitt D. A sarcoma involving the jaws in African children. *Br J Surg* 1958; 46(197):218–223.)

Letter C



Cabot rings (**Cabot-Schleip rings**, **Cabot's ring bodies**) are thin, red or purple with a Wright's stain, threadlike strands in the shape of a ring or loop-shaped structure found on rare occasions in red blood cells. They are believed to be microtubules that are remnants from a mitotic spindle. They have been observed in a handful of cases in patients with pernicious anemia, lead poisoning, and other disorders of erythropoiesis. The Cabot ring contains arginine-rich histone and nonhemoglobin iron. Structures that can represent precursors of Cabot rings have been found in stippled late-intermediate marrow megaloblasts. The **Cabot ring** could result in part from abnormalities in metabolism of both iron and arginine-rich histone known to occur in pernicious anemia. They were first described in 1903 by a US physician ***Richard Clarke Cabot***.

Richard Clarke Cabot (May 21, 1868–May 7, 1939) was born in Brookline, MA. He was the fifth son of James Elliot and Elizabeth (Dwight) Cabot. He attended the Nobel and Greenough School after which he studied philosophy at Harvard University before switching to medicine. He finished his studies in 1892 and began to work at the outpatient department of Massachusetts General Hospital, refusing a more prestigious position of the first bacteriologist. He thought that social, economic, and psychological circumstances caused many clinical conditions presented in patients in the outpatient clinic, where a lot of people who could not afford inpatient treatment or people with incurable chronic conditions (e.g., tuberculosis or diabetes) were commonly seen. Cabot believed that social work should advance the medical practice by offering a critical perspective in an organizational setting. In 1905, he organized one of the first positions of professional social employee in the world. Because the hospital declined any hiring support for social workers, Cabot paid their salaries himself. Only in 1919, when he received the chair position at the Department of Social Ethics at Harvard, did the hospital approve the regular payment of social workers, even though Cabot had to cover the salaries of 13 social workers during the last 12 years.

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Cabot also worked as a consultant for the Westboro School for Boys, the Lancaster School for Girls, and the New England Hospital for Women and Children. He worked as an army doctor on a hospital ship during the Spanish-American War, as well as at a hospital in France during World War I. From 1935 to 1939, he was Professor of Natural Theology at the Andover-Newton Theological School. He died in Cambridge, MA.

Karl Friedrich Wilhelm Schleip (Dec 22, 1872–?) was a German physician, born in Freiburg im Breisgau, and attended the university of his native town in Kiel; he obtained his doctorate at Freiburg in 1898. Then he spent his internship and a period as assistant during 1898–1909 in Kiel as well as in Hamburg. He was habilitated for internal medicine at Freiburg in 1903. In 1909–1919, he was a chief physician at the German hospital in Constantinople and later lived in Freiburg.

(**Publ**.: Cabot RC. Ring bodies (nuclear remnants?) in anaemic blood. *J Med Res* 1903; 9:15–19.

Schleip KFW. *Hematological atlas, with a description of the technic of blood examination*.1908. New York: Rebman Company.

Schleip KFW. *Atlas der Blutkrankheiten nebst einer Technik der Blutuntersuchung*. Munich: Urban & Schwarzenberg, 1907.)

Cabot-Schleip rings see **Cabot rings**

Cajal bodies (coiled body, nucleolar bodies, nuclear dots) are spherical nuclear bodies of 0.2–2.0 μm in diameter, detected in the nucleus of some proliferative or metabolically active cells. They are distinctive subnuclear domains rich in small nuclear ribonucleoprotein particles (RNP) and thus could be involved in RNA metabolism and RNP biogenesis in transcription, splicing, ribosome biogenesis, and telomere maintenance. In clinical immunology, the term "Cajal bodies" is used for reflecting the presence of antibodies and recognizing Cajal bodies during antinuclear antibody (ANA) testing.

A specific ANA-staining pattern (AC-7)—a "few nuclear dots"—can be seen on Hep-2 cell substrate fluorescent staining as countable discrete speckles with 1–6 nuclear dots per cell in most visible ones. The staining pattern on the ANA/Hep-2 test is a critical parameter for discriminating ANA-positive healthy individuals and patients with autoimmune rheumatic diseases. Clinical diagnosis of patients with anti-Cajal body autoantibodies is heterogeneous, including Sjögren syndrome, primary biliary cirrhosis, a milder form of linear scleroderma (i.e., systemic sclerosis), systemic lupus erythematosus (SLE), and other autoimmune connective tissue diseases. An autoantibody to a Cajal body represents an uncommon specificity of SLE but may be associated with extensive mucous ulceration.

The autoantibodies to Cajal bodies are usually of the IgG class and demonstrate reactivity against an 80 kDa protein associated with **Sm antigen** (or Sm protein). Thus, p80 coilin is a nuclear autoantigen that effectively accumulates in Cajal bodies and is widely considered as a marker and essential component of Cajal bodies. Although the p80-coilin protein is the most concentrated protein in coiled bodies,

the proteome of Cajal bodies has been significantly expanded since discovery of coilin and now comprises tens of structurally and functionally diverse components. For instance, survival of motor neuron (SMN) complex has been identified as an additional autoantigen in the nuclear dots structure Cajal body.

Cajal bodies were originally discovered by Spanish neurobiologist ***Santiago Ramón y Cajal*** in 1903 as small spots in the nuclei of silver-stained neuronal cells and were called "nucleolar accessory bodies." He and his Italian colleague, Camillo Golgi, shared the Nobel Prize in 1906 for Physiology or medicine "in recognition of their work on the structure of the nervous system." They demonstrated that nerve fibers are not extracellular constructions, as was originally thought, but are expansions of cell bodies located in the brain and spinal cord.

Santiago Ramón y Cajal (May 1, 1852–Oct 17, 1934) was a Spanish pathologist and histologist considered to be the founder of modern neurobiology. He was born in Petilla de Aragón, Navarre, Spain. He had to change schools many times because of poor behavior and an anti-authoritarian attitude. He studied medicine at the University of Zaragoza, where his father was an anatomy teacher. He graduated in 1873 and then served as a medical officer in the Spanish Army, participating in an expedition to Cuba in 1874–1875, where he caught malaria and tuberculosis. Cajal took his final MD examination in Madrid in 1877 and worked as the director of the Zaragoza Museum at the University of Zaragoza. He married Silveria Fañanás García, and they had 5 sons and 7 daughters. In 1883, he moved to the University of Valencia as an anatomy professor.

In 1887, Cajal moved to Barcelona focusing his research on the cells of the central nervous system (CNS). Having a natural painting talent, he prepared very detailed drawings of neural specimens obtained from various species and several regions of the brain. In 1892, he moved as a professor to Madrid, where he became the director of the National Institute of Hygiene in 1899, and he established the Laboratory of Biological Investigations in 1922 under the order of King Alfonso XIII of Spain, which was later renamed the Cajal Institute. He published more than 100 scientific papers and many books on nervous structure in Spanish, German, and French. Cajal received a lot of awards, prizes, distinctions, and professional societal memberships during his very successful scientific career. He died in Madrid at the age of 82, working even on his deathbed.

(**Publ**.: Cajal SR. Un sencillo metodo de coloracion seletiva del reticulo protoplasmatico y sus efectos en los diversos organos nerviosos de vertebrados e invertebrados. *Trab Lab Invest Biol (Madrid)* 1903; 2:129–221.)

Canale-Smith syndrome, also known as an **autoimmune lymphoproliferative syndrome** (ALPS), is a form of a lymphoproliferative disorder. It is a RASopathy—that is a developmental syndromes caused by germlike mutations in genes that alter the RAS subfamily and mitogen-activated protein kinases, including these syndromes: Costello, Legius, LEOPARD, cardiofaciocutaneous, Noonan, and others. ALPS is a rare disorder of abnormal lymphocyte survival caused by defective

FAS-mediated apoptosis, leading to chronic nonmalignant lymphoproliferation, autoimmune disease, and secondary cancers.

Canale-Smith syndrome type Ia is associated with mutations in the *APT1* (TNFRSF6) gene-encoding FAS (CD95/Apo-1). The increased proliferation of lymphoid cells can cause an increase in the size of lymphoid organs (e.g., the lymphadenopathy and the splenomegaly) present in, respectively, more than 90% and more than 80% of patients. This condition is usually caused by mutations in the FAS gene. Rarely cases because of mutations in other genes, including the FAS-ligand gene, have been reported. Mutations in the *Fas*-ligand gene (TNFSF6) possess ALPS type Ib. Cases with mutations in caspase 10 and caspase 8 are termed ALPS type Iia and Iib, respectively; and those without defined mutations are termed ALPS type III. The second most common clinical manifestation is autoimmune diseases—that is, autoimmune cytopenias (e.g., autoimmune hemolytic anemia, autoimmune neutropenia, and autoimmune thrombocytopenia), autoimmune cerebellar ataxia, Guillain-Barre syndrome, autoimmune esophagitis, gastritis, colitis, hepatitis, pancreatitis, and autoimmune glomerulonephritis. Patients have elevated peripheral blood TCRα/β $CD3^+CD4^-CD8^-$ T cells, polyclonal hypergammaglobulinemia, elevated serum FASL, and elevated plasma IL-10 and/or IL-18. Autoantibodies are usually nonspecific, including antibodies to blood cells (i.e., DAT, antineutrophil, antiplatelet), antinuclear antibodies (ANA), rheumatoid factor (RF), and antineutrophil cytoplasmic antibodies (ANCA).

The disease was described in 1967 by US hematologists ***Virginia C. Canale*** and ***Carl H. Smith***, but it was named for the first time in 1995.

Virginia Claire Canale (Sep 20, 1936–Jan 17, 2005) was a US hematologist. She was born Brooklyn, New York. In 1961, she graduated medicine from the Woman's Medical College of Pennsylvania. After Pediatric residency in New York Hospital, she worked at the Department of Pediatrics, Division of Pediatric Hematology, New York Hospital-Cornell Medical Center (now Weill Medical College of Cornell University). In 1978, she emigrated to Italy following her Italian husband and worked at the Division of Oncology and Radiotherapy, Ospedale Civile di Pordenone, Italy. She died in Udine, Italy.

Carl Henry Smith (Jul 14, 1895–Apr 23, 1971) was a US physician. He graduated from City College in 1915, received an MA degree from Columbia in 1916, and obtained his medical degree from Cornell in 1922. Smith worked in various hospitals during his professional career, including Memorial Hospital, Beekman Downtown Hospital, Staten Island Hospital, Misericordia Hospital, Roosevelt Hospital, St. Joseph's Hospital, Lenox Hill Hospital, and New York Infirmary. In 1941, he first reported the infectious lymphocytosis disease.

Smith was known for his deep personal affection for his young patients and their families. He always explained and discussed their medical problems in an open and honest manner but stayed within what they could generally understand. He had a tradition of giving the children pennies and frequently appeared as Santa Claus at Beekman Hospital parties.

After World War II, Smith participated in physician organizations supporting the Committee for Displaced European Children. In 1952, he founded the Children's Blood Foundation and served as Director Emeritus until his death. He was awarded the Townsend Harris Medal from City College and the Order of Merit from the Italian government. In 1968, a special clinical hematology session was conducted in his honor at New York Hospital. He died at New York Hospital at 75.

(**Publ**.: Canale VC, Smith CH. Chronic lymphadenopathy simulating malignant lymphoma. *J Pediatr* 1967; 70:891–899.)

Caplan's syndrome (**Caplan syndrome** or Rheumatoid pneumoconiosis) is a mixture of rheumatoid arthritis with pneumoconiosis, which is revealed as nodules in the lungs. Clinically, it appears as a cough and shortness of breath in combination with specific signs of rheumatoid arthritis, including morning stiffness and painful joints. Caplan syndrome is a nodular illness of the lung occurring in people exposed to dust and having a history of rheumatoid arthritis or development of rheumatoid arthritis within the subsequent 5–10 years. Nodules in the lung classically develop quickly, frequently in several weeks. On a histological examination, nodules have a peripheral inflammatory zone infiltrated by macrophages and neutrophils and a necrotic center with plasma cells and other lymphocytes around it. **Caplan syndrome** arises only in patients who have both rheumatoid arthritis and pneumoconiosis associated with mining dust exposure (e.g., asbestos, coal, silica), particularly in people working in anthracite coal mines. It has been suggested that rheumatoid arthritis conditions may modify the immune system response to foreign materials—dust from coal. If people with rheumatoid arthritis are exposed to unusual aggressive agents, risk of emerging pneumoconiosis is increased significantly.

The syndrome was named after ***Anthony Caplan***, a physician who identified the assemblage of clinical signs as a discrete entity. In 1952, at a meeting of the Thoracic Society of Great Britain, attention was first drawn to an association of coal miners in South Wales with rheumatoid arthritis and certain unusual radiological appearances in chest radiograms. Epidemiological studies of rheumatoid arthritis in a community of coal miners in South Wales were carried out by the Pneumoconiosis Research Unit to investigate this syndrome.

Anthony Caplan (1907–1976) was a British physician associated with the Cardiff Pneumoconiosis Panel.

(**Publ**.: Caplan A. Certain unusual radiological appearances in the chest of coalminers suffering from rheumatoid arthritis. *Thorax* 1953; 8(1):29–37.)

Carrington-Liebow syndrome see **Wegener's granulomatosis**

Castleman disease (**Castleman's lymphadenopathy**, **Castleman's tumor**, giant or angiofollicular lymph node hyperplasia, lymphoid hamartoma, angiofollicular lymph node hyperplasia) describes a group of uncommon lymphoproliferative disorders that share common lymph-node histological features that may be localized to a single lymph node or occur systemically. The clinical manifestations are heterogeneous, ranging from asymptomatic discrete lymphadenopathy to recurrent episodes of diffuse

lymphadenopathy with severe systemic symptoms. This disease is named after ***Benjamin Castleman***.

Benjamin Castleman (May 17, 1906–Jun 29, 1982) was a US physician and pathologist. He was born in Everett, MA, received his BA degree from Harvard University in 1927, and his MD degree from Yale University in 1931. In December 1935, he married Anna Segal and they had 3 children. He worked for many years at the Massachusetts General Hospital in Boston, serving as a chief of the Division of Anatomic Pathology and was Professor of Pathology at the Harvard Medical School. Castleman was an editor of the clinicopathological case presentation series in the *New England Journal of Medicine*. He undertook clinicopathologic investigations of parathyroid disease and wrote several important papers on diseases of the thymus and mediastinum. He authored or coauthored more than 100 publications on a variety of disorders. Castleman died of lymphoma in June 1982 in Boston.

The Benjamin Castleman Award has been given annually since 1982 to the first author of an English-language research article that is considered the worthiest in the field of human pathology. It is administered by the US and Canadian Academy of Pathology.

(**Publ**.: Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. *Cancer* 1956; 9(4):822–830.)

Ceelen-Gellerstedt syndrome (idiopathic pulmonary hemosiderosis) is a rare, generally fatal disease of unknown cause, typically affecting small children and is more prevalent in boys. It is characterized by infiltration of pulmonary system with hemosiderin-containing macrophages progressing to diffuse pulmonary fibrosis.

Clinical features include recurrent pulmonary hemorrhages, anemia, dyspnea, and cardiorespiratory failure. Recurrent cough, dyspnea, and hemoptysis (i.e., expectoration of blood from the lungs or airways) are a result of focal fibrosiderosis and lung hemorrhages. The condition is considered to be autoimmune derangement and is associated with the **Goodpasture**, **Wegener**, and **Churg-Strauss syndromes**. Idiopathic pulmonary hemosiderosis can occur either as a primary lung disorder or as the sequela to other pulmonary, cardiovascular, or immune system disorders. It may involve either circulating antiglomerular basement membrane (anti-GBM, **Goodpasture disease**) antibodies or the immune complex disease (e.g., systemic lupus erythematosus). An elevated serum IgA level seems to be a common finding in idiopathic pulmonary hemosiderosis.

The condition was first described as "brown lung induration" by ***Rudolf Virchow*** in 1864 in patients after their death. ***Ceelen*** first mentioned the disease's image at a meeting of the Pathological Society in 1921. The term "Ceelen-Gellerstedt" was introduced in 1944 by P. Selander.

Wilhelm Ceelen (Aug 21,1883–1964) was a German pathologist. He was born in Frankfurt am Main and studied medicine in Freiburg, Munich, and Berlin and received his medical doctorate in 1910. He then worked at the Berlin Pathological Institute, finished his training in 1913, and moved to a position of Extraordinary Professor in 1917. In 1925, he became the chair of the Pathological Anatomy in Greifswald and

then in 1926 went to Bonn. In his clinical studies, he focused on heart diseases and infectious diseases, including typhus, spotted fever, and lymphogranulomatosis.

Nils Gellerstedt (Aug 14, 1896–Jul 7, 1954) was a Swedish pathologist. He was born in Piteå, Sweden, to Karl August Gellerstedt and Ida Katarina Aurora Gellerstedt. He worked in Läkare as a medical doctor and was a Professor at Uppsala University. Gellerstedt was known as an excellent clinical pathologist and had quite wide interests in many different medical conditions.

(**Publ**.: Ceelen W. *Die Kreislaufstörungen der Lungen.* In: Henke, F and Lubarsch, O. (eds.).*Handbuch der Speziellen Pathologischen Anatomie und Histologie*, vol 3. Berlin: Springer, 1931; p. 10.

Gellerstedt N. Über die "essentielle" anämisierende form der braunen lungeninduration. *Acta Pathol Microbiol Scand*, Copenhagen. 1939; 16:386–400.)

Chediak-Higashi syndrome (**Chediak-Steinbrinck-Higashi syndrome**, **Begnez Cesar's syndrome/disease**, **Beguez-Chediak-Higashi syndrome**, **Béguez-Steinbrinck-Higashi syndrome**) is an autosomal recessive immunodeficiency disorder characterized by abnormal intracellular protein transport, abnormal function of phagocytes, and impaired cytotoxic lymphocyte function, mainly that of NK cells. The Chédiak-Higashi syndrome gene was described in 1996 as the lysosomal trafficking regulator (LYST) or *CHS1* gene and is localized to bands 1q42–43. The **Chédiak-Higashi syndrome** protein is expressed in the cytoplasm of cells in various tissues and reflects an abnormal intracellular protein trafficking. The Chédiak-Higashi syndrome gene affects the synthesis and/or maintenance of storage/secretory granules in various cell populations. In fact, azurophilic granules of neutrophils, lysosomes of leukocytes and fibroblasts, dense bodies of platelets, and melanosomes of melanocytes are generally larger in size and irregular in morphology, indicating that a common pathway in the synthesis of organelles responsible for storage is affected. **Dohle bodies** in neutrophils also are seen in this syndrome. Poor bactericidal function of neutrophils leads to susceptibility to infections.

The disease is often fatal in childhood as a result of infection. More than 80% of patients developed an accelerated phase (accelerated reaction)—a nonmalignant lymphohistiocytic lymphoma-like infiltration of multiple organs. This stage may be advanced by viral infection, usually Epstein-Barr virus. It is related to the development of anemia, bleeding events, and devastating infections leading to death. Most common infections occur in the skin, respiratory tract, and lungs and are typically caused by *Staphylococcus aureus, Streptococcus pyogenes,* and *Pneumococcus* species. Chediak-Higashi syndrome also is associated with oculocutaneous albinism, a condition that produces atypically light pigmentation of the skin, hair, and eyes. Affected patients usually present with fair skin and light-colored hair, often with a metallic sheen.

The Chédiak-Higashi syndrome was first described by ***Béguez César*** (1943) in 3 siblings bearing the main clinical features of neutropenia and abnormal granules in leukocytes. ***Steinbrinck*** reported one case in 1948. ***Chédiak***, a Cuban hematologist, reported 4 cases in 13 Cuban siblings in 1952, and, in 1954, ***Higashi***, a Japanese

pediatrician, described 4 cases in 7 Japanese siblings characterized by misdistribution of myeloperoxidase in the neutrophilic granules of affected patients. Sato (1955) recognized the similarity between the Chediak and Higashi cases and first named the disease Chediak-Higashi syndrome.

Antonio María Béguez César (Mar 2, 1895–Feb 11, 1975) was a Cuban pediatrician. He was born in Santiago de Cuba to Don Antonio Béguez y Béguez and Doña Antonia César y de León. After his primary education at a private academy, in 1910, he entered the Institute of Secondary Education and obtained his bachelor's degree with outstanding grades in 1914. Then he learned medicine at the University of Havana, and in 1919, he received his graduate diploma with honors. After graduation, he received a offer to work as an internal doctor at the Hospital Santa Isabel de Cárdenas, in Matanzas. There he met Francisca López Comans, a nursing student, whom he married in 1921 and soon returned to Santiago de Cuba to care for his mother, who was seriously ill. In 1928, he was finally offered a medical position at the Saturnino Lora Hospital, but without a salary. In 1929, he managed to open the first Pediatrics Service in the former province of Oriente, and for more than 30 years, Béguez César remained in charge of the Alberto Parreño Children's Room, which he considered his second home because of the thousands of hours he dedicated to children's healthcare. In 1960, the Children's Room of the Provincial Hospital was moved to a modern care center, where Béguez César directed the Newborn and Premature Ward for 10 years. He was a founder of the Pediatrics Cuban Society.

William Steinbrinck was a German hematologist.

Alejandro Moisés Chédiak (Jan 6, 1903–Mar 2, 1993) was a Cuban physician and serologist. He was born in Santiago de Cuba.

Moisés Chediak Ahuayda was born in Cuba from Lebanese descent. Moisés studied at the Nuestera Señora de la Caridad school and graduated in 1920 as a bachelor at the Instituto de Segunda Enseñanza, now Instituto Preuniversitario Cuqui Bosch in Santiago de Cuba. He studied medicine at the University of Havana and obtained his degree in 1926. Moises Chediak was director of the Central Clinical Laboratory of the General Calixto Garcia Hospital from 1940 onward, the same year when he founded the first blood bank in Cuba. He was Associate Professor of Microscopy and Clinical Chemistry at the University of Havana. In 1944, the new facilities of the Institute of Hygiene, until then part of the Finlay Institute, were inaugurated in Havana, and Moisés Chediak was appointed its Director.

He participated in many congresses in the US, Europe, and Asia. Moisés Chediak was an outstanding member of the Cuban Societies of Clinical Pathology, Microbiology and Pediatrics, as well as various international organizations (e.g., the Cuban-French Society of Hematology, the American Association of Public Health, the International Societies of Hematology and Transfusions, the American Society of Clinical Chemists, the Italian and Swiss Societies of Hematology, and the National Association of Clinical Analysis of Spain).

The 1959 Communist Revolution in Cuba led to a significant exodus of doctors. Moisés Chediak Ahuayda emigrated to the US in 1961, where he continued his care, research, and teaching work. He died in Miami at the age of 90.

Otokata Higashi (1883–1981) was a Japanese pediatrician. He graduated from Tohoku University, Sendai, Japan, and later was Professor of Pediatrics at Akita University.

(**Publ**.: Béguez CA. Neutropenia cronica maligna familiar congranulaciones atipicas de los leucocitos. *Bol Soc Cubana Pediatr* 1943; 15(12):900–922.

Steinbrinck W. Uber eine neue granulationsanomalie der leukocyten. *Dtsch Arch Klin Med* 1948; 193:577–581.

Chediak M. Nouvelle anomalie leukocytaire de caractere constitutionnel et familiel. *Rev Hematol* 1952; 7:362–367.

Higashi O. Congenital gigantism of peroxidase granules. *Tohoku J Exp Med* 1954; 59:315–332.)

Chediak-Steinbrinck-Higashi syndrome see **Chediak-Higashi syndrome**

Churg-Strauss disease (**Churg-Strauss syndrome**, **Churg-Strauss vasculitis**, **Strauss-Churg-Zak syndrome**) is a rare type of autoimmune condition that causes inflammation of small- and medium-sized blood vessels (vasculitis) in persons with a history of airway allergic hypersensitivity. It usually manifests in 3 stages. The disease typically begins with allergic rhinitis, often with nasal polyposis and sinusitis. Symptoms are asthma-like respirational troubles. The second stage is characterized by hypereosinophilia. There is fever, and the main organs involved are skin, kidney, digestive tract, and lungs with eosinophilia and tissue damage. The third stage consists of vascular and extravascular granulomas at varying stages of evolution, vasculitis, which can eventually lead to cell death and can be life-threatening.

For their report in 1951, the results by ***Churg*** and ***Strauss*** at Mount Sinai Hospital in New York City were based on 13 cases, which had originally been diagnosed as polyarteritis nodosa. Churg and Strauss observed 3 features to differentiate their patients from other people with periarteritis nodosa and no asthma: tissue eosinophilia, necrotizing vasculitis, and extravascular granuloma. Therefore, they used this as evidence that these cases represented a different disease entity that they termed "allergic granulomatosis and angiitis." In 1954, Churg, together with a Columbia University pathologist Gabriel C. Godman, suggested that **Churg-Strauss syndrome**, **Wegener granulomatosis,** and microscopic polyangiitis were different but related types of vasculitis distinct from typical polyarteritis nodosa. In these diseases, small arteries, arterioles, capillaries, venules, and veins usually are affected and the association with glomerulonephritis is possible too. Absence of immunoglobulin depositions in tissues and the presence of circulating antineutrophil cytoplasmic antibodies (ANCA) in all 3 diseases greatly strengthened this conclusion.

Jacob Churg (Jul 16, 1910–Jul 27, 2005) was an US pathologist. He was born to a Jewish family in Dolhinow (then in Russia), a Belarusian city that later became a part of Poland, and in 1939, was ceded to Russia during the partition of Poland by

Russia and Germany. His grandfather on the father's side was a rather successful businessman who imported tea from China to Russia. On his mother's side, his great-grandfather was a rather well-known rabbi, who was famous for his knowledge of Jewish laws and interpretations of Jewish rules and traditions. Jacob's father, Wolf Ravich, was a physician, and his mother, Gita, was a dentist. Jacob recalled reading his father's medical books at the age of 8 and pestering him with many questions. He studied medicine at the University of Wilno (Poland), graduated in 1933, and in 2 years finished an internship at the Department of Internal Medicine at local hospitals. He then went to an assistant position at the Department of Pathology at the University and obtained his final medical doctorate in 1936. Still, because of the political turbulence and growing antisemitism in Europe, he moved to New York City, where Louis Chargin, his uncle, worked at the Skin Clinic in the Mount Sinai Hospital as a Chief Physician. Churg began to work in the bacteriological laboratory, then in the pathology laboratory. In 1943, he received US citizenship, but he had to postpone his research projects because of military duties during the last years of World War II. After the war, Churg continued his research and started his first collaboration with ***Lotte Strauss***.

Churg developed and validated new methodology of thin-sectioning and special staining of renal biopsy tissue specimens for electron microscopy examination. He and his collaborators published on almost every form of glomerular diseases, including studies on lupus nephritis, focal glomerulosclerosis, diabetes mellitus, hemolytic uremic syndrome, crescent-forming glomerulonephritis, amyloidosis, and glomerular fibrillose. Jakob Churg was appointed a Clinical Professor of Pathology in 1966. He also published classical works on asbestos-related diseases (e.g., mesothelioma and lung cancer). He published more than 300 scientific works, among them 10 textbooks on pathology.

Lotte Strauss (Apr 15, 1913–Jul 4, 1985) was born in Nuremberg, Germany. She started her medical training in Germany but was forced to finish them in Siena, Italy, in 1937. There she developed a great interest in laboratory medicine when she worked at the Bacteriological Institute in Siena. She immigrated to the US in 1938 and started to work at Beth Israel Hospital in New York as a research assistant in the bacteriology laboratory. After working with ***Sydney Farber***, a well-known pediatric pathologist at Children's Hospital in Boston, she decided to dedicate her research to the field of pathology. In 1941, Straus moved to Mount Sinai Hospital to work on pediatric pathology.

Strauss's research pioneered the field of perinatal pathology. Her particular focus was on intrauterine infections, ultrastructure of the placenta in various fetal diseases, and vascular diseases. Soon she was recognized as one of the most important founders of the field, and she helped establish the Society for Pediatric Pathology. In 1953, a pediatric pathology facility was created at Mount Sinai, and Strauss was selected to direct this service for more than 30 years until her death. In 1966, she was recognized as one of the founding faculty at the Mount Sinai School of Medicine at the rank of Professor. She also was appointed as Special Consultant in Perinatal Pathology to the National Institute of Health. The Lotte Strauss Prize was awarded to her by the Society of Pediatric Pathology.

Friedrich (***Frederick G.***) ***Zak*** (Feb 13, 1915–Feb 5, 2005) was a US physician. He was born and raised in Vienna, Austria. His father Emil Zak was Professor and Chair of the Department of Cardiology, University of Vienna. Friedrich was accepted in the Medical School in the fifth year of his studies in 1938. With the annexation (Anschluss) of Austria into Nazi Germany on March 13, 1938, he was forced to quit his studies for racist reasons without a chance to graduate. He requested to continue his studies in the context of the 2% Numerus Clausus (*limitations on the admission*) of Jewish students and was first allowed to continue for about 2 months, but finally had to leave the University of Vienna. In addition, his brother Dr. med. Georg Zak, a student at the philosophical school in his third year of chemical studies, was forced to leave the university. Their father, Prof. Dr. Emil Zak, lost his position at the University of Vienna in April 1938 and was forced to leave his position as Primarius of the Policlinic.

Friedrich and his brother Georg were both arrested and deported to the concentration camp Dachau after the so-called *Reichskristallnacht* ("Night of Broken Glass," November Pogroms) in 1939, when almost 300 synagogues were destroyed throughout Germany and Austria, more than 7000 Jewish businesses were damaged or destroyed, and about 30,000 Jewish men were arrested and incarcerated in concentration camps; hundreds of Jews were dead after the pogroms. Later in 1939, both brothers were released, and Friedrich Zak was allowed to emigrate to the US. By the end of November 1939, more than 120,000 Jews had left Austria for some 90 countries all over the world. George Zak escaped to England, worked there until 1951, and then emigrated to the US.

In the US, Friedrich Zak changed his name to "Frederick G. Zak," continued his medical studies, and graduated and became a physician at Mount Sinai Hospital in New York, later he became Professor of Pathology and Medicine at Mount Sinai Hospital and the Office of the Chief Medical Examiner, New York, and State University New York. He married Sylvia Zak and had 2 kids—Vivien and Ronald. Zak died at age 89 in New York.

(**Publ**.: Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol*, Philadelphia. 1951; 27:227–301.

Strauss L, Churg J, Zak FG. Cutaneous lesions of allergic granulomatosis: Histopathologic study. *J Investig Dermatol*, New York. 1951; 17:349–359.)

Churg-Strauss vasculitis see **Churg-Strauss disease**

Clara cells ("**Club cells**" since 2015) are nonciliated, secretory bronchiolar epithelial cells, which can function as stem cells for repairing the bronchioles and can divide into ciliated or nonciliated bronchiolar cells. The cells are located in the distal airway and have a hemispherical shape with microscopic hairlike strands called microvilli. Clara cells serve as a guard in the bronchial tissue against damage often caused by pollutants. The cells secrete a secretory protein and promote detoxification of the lungs.

Clara cell secretory protein 16KDa (CC16) (or Clara cell-specific 10 kD protein (CC10), Clara cell secretory protein (CCSP), Uteroglobin (UG, UGB), Uteroglobin-like antigen (UGL), Blastokinin) is the major secretory protein of the Clara cells. It is conveyed primarily in the respiratory tract and is a potent antiinflammatory agent that protects the airway from inflammation. It also is associated with Th2 modulation. The gene-encoding CC16 has been linked as potential susceptibility gene for asthma: The associations of the CC16 gene polymorphism with asymptomatic airway hyperresponsiveness, which is considered a risk factor for future asthma in adults, and the development of adult-onset asthma have been reported.

In 1937, anatomist ***Max Clara*** described a new secretory cell type in the human bronchial epithelium; this has been known as the "Clara cell" since at least 1955.

Max Clara (1899–1966) was an Austrian anatomist with an unusual biography (see (Winkelmann and Noack, 2010). He was born in 1899 in a small village in South Tyrol near Bozen, which was in Austria that time. He studied medicine in Innsbruck, Austria, and Leipzig, Germany. In 1923, he started to work at the Institute of Histology and Embryology in Innsbruck, but in 1924, he had to return home to take care of his father's general practice after his father death. He was able to continue his histology studies and even got an unpaid lecturing position at the University of Padua, Italy, in 1929. From 1935 on, Clara was the Chair of Anatomy at Leipzig University, and then, was the Chair of Anatomy in Munich from 1942 until the end of World War II.

It is possible that Clara's outstanding career was fervently supported by the Nazi institutions, such as the SA (Sturmabteilung, storm troopers) and Max de Crinis, who was a Nazi physician known to actively participate in SS (Schutzstaffel) actions; for instance, the Nazi "euthanasia" program to kill tens of thousands of people with mental and physical disabilities to "clean" the Aryan race of people considered genetically imperfect and financially problematic for society. Clara joined the National Socialist German Worker's Party (NSDAP) when he moved from Italy to Leipzig. One eminent general medical journal in Germany published Clara's call to welcome the "National Socialist revolution of 1933" and requesting scientists to "join the marching columns of our *Führer.*" He also enthusiastically contributed to university politics offering politically biased assessments for appointments and scholarship procedures.

At the same time, Clara's scientific publications did not have any political content that could contribute to a racist, xenophobic, or anti-Semitic "pseudoscience." In 1937, he discovered a new type of cell in the human terminal bronchiole. But he used specimens "stemming exclusively from executed individuals, who were preserved by vascular injection immediately after death." The Institute in Leipzig, where Clara worked, was given bodies on a regular basis from executions in Dresden, where more than 1300 prisoners from concentration camps were killed between 1933 and 1945. Clara was known to support this practice; being the Director of the Anatomical Institute in Leipzig, he officially requested the Saxon State Ministry of Education to extend laws that approved the use of the bodies of

executed prisoners. Archived materials also prove that Clara with his coworkers carried out studies with at least one prisoner punished by death to examine the consequences of oral vitamin C on the histochemical localization of ascorbic acid in cerebral cells.

In October 1945, together with many other members and officials of the Nazi Party, Clara was arrested by the US Army. When he was released in 1946, in spite of many attempts, he failed to find any permanent position at Munich University or other places in Germany. After 1945, his academic status in Germany was a persona non grata. In 1950, he finally obtained a Professor of Histology position at the University of Istanbul in Turkey, and worked there until 1961. In 1966, Max Clara died in Munich, Germany.

(**Publ**.: Clara M. Zur Histobiologie des Bronchalepithels [On the histobiology of the bronchial epithelium.]. *Z mikrosk anat Forsch* 1937; 41:321–347.)

Clarkson's disease (**Clarkson disease**, **Clarkson syndrome**), also known as idiopathic systemic capillary leak syndrome and spontaneous periodic edema, is a potentially fatal disorder characterized by stereotypic "attacks" of varying intensity of hypovolemic shock and generalized edema in association with hemoconcentration (i.e., elevated hematocrit concentration), hypoalb uminemia, typically occurring in the absence of albuminuria and the presence of serum M protein (monoclonal gammaglobulin or M-spike). An M protein can be detected by serum protein electrophoresis/immunofixation studies in almost 80% of patients and is of the IgG type. Nearly three-quarters of predominant light chains are of the kappa subtype. Unlike similar disorders, such as POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, and *s*kin changes), which is almost always associated with IgG-λ or IgA-λ, and **Schnitzler syndrome** (i.e., chronic urticarial rash, monoclonal gammopathy, fever, arthralgia, bone pain, and lymphadenopathy), which is associated with IgM monoclonal gammopathy, patients with Clarkson's disease predominantly have IgG-κ or IgA-κ monoclonal gammopathy.

The pathogenesis of **Clarkson's disease** remains unclear. Cytokines, leukotrienes, vascular endothelial growth factor (VEGF), and complement have been implicated. A substantial increase in the IL-2 receptor-positive peripheral blood M-cell count has been noted during episodes of hyperpermeability. Attempts to directly link M protein to endothelial damage, however, have been unsuccessful. Although the monoclonal immunoglobulin could act as an autoantibody to promote vascular endothelial hyperpermeability during acute episodes, limited prior studies have not identified a common target antigen or cell.

In 1960, ***Clarkson*** et al. described a case of a 32-year-old woman with an unremarkable family history who experienced "a strange cyclical illness in which she intermittently had a sudden massive movement of plasma from her vascular bed." The illness was characterized by recurrent episodes of edema, hypovolemic shock, hypoalbuminemia, hemoconcentration, and persistence of the serum M protein. Clarkson demonstrated that the albumin-binding dye T-1824 (Evans blue) was quickly cleared from the intravascular compartment in a patient suffering an acute

attack, suggesting a primary role for vascular endothelial hyperpermeability. Plasma from an acute attack induced a shock-like syndrome when injected into rats.

Less than 500 cases of Clarkson's disease have been reported since 1960, but the nonspecific presenting symptoms and signs and high mortality rate may have resulted in underrecognition of this disorder.

Bayard Clarkson worked at the Department of Medicine, New York Hospital - Cornell Medical Center in New York.

(**Publ**.: Clarkson B, Thompson D, Horwith M, Luckey EH. Cyclical edema and shock due to increased capillary permeability. *Am J Med* 1960; 29:193–216.)

Cogan's syndrome (**Cogan syndrome**) is a rare, rheumatic disease characterized by inflammation of the ears and eyes that can lead to vision trouble, hearing loss, and dizziness. The condition also may be associated with vasculitis in other areas of the body that can cause major organ damage and even death. It primarily affects young white adults, without a hereditary pattern. It is accepted that **Cogan's syndrome** is an autoimmune disease and autoantibodies can be revealed in the blood of some patients. Infection with the bacteria *Chlamydia pneumoniae* has been demonstrated in some patients prior to the development of Cogan's syndrome, leading to the hypothesis that the autoimmune disease may be initiated by the infection.

In 1945, the ophthalmologist ***David Cogan*** first described the "nonsyphilitic interstitial keratitis and vestibuloauditory symptoms" even though, in 1934, Morgan and Baumgartner had first described a nonsyphilitic interstitial keratitis associated with vestibuloauditory dysfunction (Mogan and Baumgartner, 1934). In 1963, the atypical form of Cogan syndrome, also known as "Logan syndrome" was first described (Bennett, 1963).

David Glendenning Cogan (Feb 14, 1908–Sept 9, 1993) was an US ophthalmologist. He was born in Fall River, MA, where his father was an Episcopal minister. He was introduced to ophthalmology by his mother, herself a practitioner and a pioneering ophthalmologist. Cogan studied at Dartmouth College (1925–1928) and then at Dartmouth Medical School (1928–1930). He continued his studies at Harvard Medical School and obtained his medical degree in 1932.

Cogan had a year of internship training at the University of Chicago Clinics and 2 years of residency training at the Massachusetts Eye and Ear Infirmary in Boston. In 1937, he received Harvard's Moseley Traveling Fellowship and continued his medical studies in Switzerland, Germany, and Holland. Later, Cogan was the acting director and the director of Harvard Medical School's Howe Laboratory of Ophthalmology (1940–1973) and the chair of Harvard Medical School's Ophthalmology Department (1962–1968).

Following his mandatory retirement in 1973, at age 65, Cogan moved to the National Institutes of Health, where he continued his research activities; from 1974 to 1985, he was the chief of neuroophthalmology at the NIH's National Eye Institute. Despite his age, the tempo of his work continued unabated, and he often put in 10-hour days and 6-day weeks. Despite his great workload, Cogan found time for his family and friends. His home in the city or in the countryside at Lake Michigan

were meeting places for ophthalmology scientists. His wife, Frances Capps Cogan, was also a medical doctor who did research on ophthalmology.

Cogan was a busy medical author, writing more than 500 articles and several books. His books, *Neurology of the Ocular Muscles* (1948) and *Neurology of the Visual System* (1966), were known as important aids for neuroophthalmology. As an ophthalmologist, he visited Germany after World War II to support the "heal the wounds" initiative and to redevelop special contacts between US and German ophthalmologists. Later, he was invited by the German Association of Ophthalmologists to deliver an honorary lecture, and he gave it in German. Cogan worked on the Atomic Bomb Casualty Commission, analyzing radiation-induced cataracts in survivors of Hiroshima. He did a lot for establishing contacts and collaborations between US and Japanese ophthalmologists. During his long career, Cogan received many awards. In 1988, the Cogan Award was established by the Association for Research in Vision and Ophthalmology. Cogan died in Wayne, MI.

(**Publ**.: Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. *Arch Ophthalmol* 1945; 33(2):144–149.)

Cohnheim's chemotactic theory or **Cohnheim's inflammation doctrine** is an early description of possible mechanisms of inflammation developed by ***Julius Cohnheim*** who stated that inflammatory cells originate in the circulation. He attributed this to an alteration of the vessel wall. From the historical perspective, the development of the concept of inflammation in the field of pathologic anatomy in the last century was dominated by the work of Cruveilhier, Rokitansky, and Virchow. Cohnheim opposed the opinion of his teacher and father of cellular pathology, ***Rudolf Virchow***, to make leukocytes the protagonists of inflammation, given their ability to develop ameboid movements directed by chemical signals. Cohnheim's analysis of leukocyte migration was based on a method of staining the lines of cell junctions with silver recognized by ***Friedrich Daniel von Recklinghausen***. One's pathobiochemical views of inflammation are ultimately based on the appreciation of changes in microcirculation and capillary permeability.

Julius Friedrich Cohnheim (July 20, 1839–Aug 15, 1884), a founder of experimental pathology, was born into a Jewish family in Demmin, a small town in the Prussian Province of Pomerania. After receiving his gymnasium education, Cohnheim moved to Berlin in 1856 to study medicine. Because his father was forced to flee the country and went to Australia, his early training was the responsibility of his mother who, in turn, depended on him for support; he had to interrupt his medical education. Later, he moved to Würzburg to study histology. After returning to Berlin and obtaining his medical degree, he prepared his dissertation under the mentorship of ***Rudolf Virchow***. Virchow, who admired Cohnheim knowledge and skills, offered him a chief assistant position in 1865. During the 1860s, Cohnheim's research centered on the mechanism of inflammation, which was being widely discussed at that time. After analysis of results from many animal experiments, he determined that acute inflammation was associated with migration of circulated leukocytes through capillary walls to the site of tissue injury and the

homing of blood cells causing formation of what was known as "pus." Yet, this concept challenged the interpretation of inflammation that had been proposed by his mentor Rudolf Virchow.

Cohnheim also engaged in a limited medical practice to support his mother and served as surgeon with the Prussian Army in the German-Danish War of 1864. In 1868, Cohnheim was called to Kiel as Professor of Pathology. He had become especially interested in the circulation as well as in venous obstruction and arterial embolism. Cohnheim moved to Breslau in 1872 where he helped create a pathological institute at the university.

Cohnheim moved to Leipzig in 1878 to accept the Chair of Pathology at the University. From the early 1870s on, he began to have recurrent attacks of gout. Cohnheim's rich scientific career was shortened by intractable gouty arthritis, and his final years were severely compromised by the affliction. On August 15, 1884, the closing day of the International Medical Congress, ***Rudolf Virchow*** announced the death of his most distinguished pupil, Julius Cohnheim, at age 45.

During his brief life, Cohnheim had a remarkable influence on experimental pathology and experimental medicine. In his scientific work, Cohnheim devoted his attention to several main topics: the study of inflammation, the pathology of circulation, the causes and development of tumors, the mechanisms of tumor metastasis, and the etiology of tuberculosis. The summary of his understanding of these fundamental problems of pathology has been described in his "Lectures on General Pathology." This monograph on pathology was the second most influential nineteenth-century text on the subject (after Rudolf Virchow's classic 1858 book on cellular pathology). Cohnheim was the first to use the now universal **method of freezing fresh pathological objects** for examination; he also was first to demonstrate nerve termination in "Cohnheim's areas." The worldwide reputation of Cohnheim was based specifically on his research into the causes of inflammation, where he experimentally confirmed the outward migration of leucocytes through the wall of blood vessels. Years before *tuberculosis bacillus* was discovered, he recognized the disease as a single entity. Cohnheim's work provides the basis for current notions of allergy, granuloma formation, and the pathologic changes associated with tuberculosis. Observations made by Cohnheim continue to form part of the contemporary body of knowledge—for example, the rejection of an acellular origin for inflammatory cells.

Cohnheim's work also significantly contributed to the understanding of neoplastic disease. He was the first to make a clear distinction between true neoplasm and lesions resembling it. He distinguished between epithelial and mesenchymal tumors. He also distinguished "tumors" of infectious origin from true neoplasms. Cohnheim's theory of the proliferation of developmental tissue rests contributed to the understanding of tumor etiology and pathogenesis. In contrast to the majority of his contemporaries, he correctly interpreted the process of metastasis. Long after his death, Cohnheim's influence resonates through his writings and the contributions of his students and colleagues, who established laboratories of experimental pathology modeled after those Cohnheim had developed in Germany.

(**Publ**.: Cohnheim J. Vorlesungen Über Allgemeine Pathologie, 2 volumes. Berlin: August Hirschwald, 1877, 1880.)

Coley's toxin (**Coley's toxins**, **Coley's vaccine**, **Coley vaccine**, **Coley's fluid**) is a vaccine made of heat-inactivated *Streptococcus pyogenes* and *Serratia marcescens*, although the original formula for Coley's toxins is no longer available. Supporters of this treatment suggest that the bacteria directly boosts the immune system to kill cancer cells. It is possible, however, that TNF-alpha, IL-12, and TLR ligand-stimulating innate immunity plays the major role. The treatment causes a high temperature, and it is possible that cancer cells are more sensitive to heat than normal cells. Heat-shock proteins (HSP) also may play a role in cell stimulation and antigen processing and presentation. Even though tumors really shrank in some of ***William Coley*'s** patients, no effects of treatment were observed in others. Furthermore, many clinicians failed to reproduce the effect in their patients. In clinical trials, tumor regression was seen in patients with certain types of cancer or patients lived longer than expected. But there was no proof of the mechanisms of any successful treatment—whether this was just by chance or because of other medications patients received.

Additionally, comprehensive comparative analysis of the trial results was impossible because of the variability of preparations of "the treatment formula" and the inconsistency of "toxin" administrations—from intratumoral to intravenous injections. Clinical trials could not conclude whether Coley's toxins could consistently cure cancer or provide higher efficacy when compared with other treatment modalities. Several forms of **Coley's toxins** were produced in the US by different drug companies until the early 1950s. Yet, other methods of cancer therapy became more popular and broaderly used. Some clinics in the US, Central America, Germany, and China still give it as a treatment. MBVax Bioscience, Coley Pharmaceutical Group, and Waisbren Clinic in Wisconsin reported they have used Coley's toxin to treat patients. But it is not clear whether these clinics are using the original Coley formula or a combination of Coley's toxins and other bacteria.

William Bradley Coley (Jan 12, 1862–April 16, 1936) was a US surgeon. William B. Coley was born in the Connecticut shoreline village of Saugatuck, just outside of Westport. His parents, Horace Bradley Coley and Clarina Wakeman Coley, had a family lineage from England that dated back to the seventeenth century and included religious leaders, schoolmasters, and farmers. Coley completed his undergraduate education and graduated from Yale in 1884. He then moved to Portland, Oregon, where he taught Greek and Latin at the Bishop Scott Government school. Two years later, he returned to New England to attend Harvard Medical School, receiving his medical degree in 1888. Then Coley studied surgery at New York Hospital and the Hospital for the Ruptured and Crippled, where he was named Surgeon in Chief in 1924, simultaneously holding the position of staff surgeon at New York Cancer Hospital (now Memorial Sloan-Kettering Cancer Center). His academic appointments included Clinical Professor of Surgery and Cancer Research at Cornell University Medical School.

Among Coley's earliest accomplishments was his development of a surgical technique to treat abdominal hernias in children. Although Coley's surgical skills were widely admired by patients and peers, it would be his cancer research from 1890 onward for which he would be both ridiculed and remembered. Elizabeth Dashiell, a 17-year-old presented to Coley's office with a hand injury and increasing pain. Analysis of a biopsy specimen showed that Bessie had a sarcoma. Chemotherapy and radiation therapy were not available that time and the only treatment offered to her was amputation. Following the amputation, however, he realized that the disease had already metastasized to Bessie's lungs and liver. Coley was so affected by her death that it motivated him for an exhaustive search of New York Hospital's archives to understand cancer development and progression. His determination helped him find the case of Fred Stein, a German immigrant.

In 1883, Fred Stein was admitted to New York Hospital with a tumor on his neck. Multiple attempts to remove the tumor failed; however, after one surgery, Stein developed an infection with *Streptococcus pyogenes*. Although penicillin had not been discovered yet, to everybody's surprise, Stein did not die; his tumor resolved, and he was subsequently discharged. Now, almost a decade later, with Coley going door to door looking for a man named Fred Stein, and after several weeks of searching, Coley found him alive and cancer-free. It was then that Coley hypothesized that Stein's Streptococcus infection had defeated the cancer.

In an era before informed consent and institutional review boards, Coley tested his theory on the most seriously ill patients. His first patient was Italian immigrant Zola with a cancer in the throat. Spending months trying to produce a systemic antitumor reaction with no result, Coley decided to use a more virulent bacteria strain. Luckily, the tumor began to soften and finally disappeared. Soon Zola had fully recovered.

William Coley was not the first clinician who tried to treat cancer by bacterial infection. The idea was announced by a German physician, Wilhelm Busch. Still, Coley was the first who used this method scientifically on many cancer patients. Following his death, Coley's daughter, Helen Coley Nauts, began to work on a biography of her father and found approximately 1000 files on patients who had been treated by him and his "Coley's Toxins." Helen devoted many years to data evaluation and determined that the success rate in certain types of tumors was very high—maybe similar or even higher than currently seen. Today, Coley is recognized as the "Father of Cancer Immunotherapy" for his contributions to the science.

(**Publ**.: Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases. *Am J Med Sci* 1893; 10:487–511.)

Coley's vaccine see **Coley's toxin**

Coombs reagent (**Coombs antiglobulin** or antihuman globulin) is used in both the **direct Coombs test** and the **indirect Coombs test**. Coombs reagent is an antihuman immunoglobulin. It is made by injecting human globulin fraction into animals, resulting in the production of polyclonal antibodies specific for human

immunoglobulins and human complement system factors. More specifically, Coombs reagents or monoclonal antibodies also being are used in specific tests.

Coombs test (**Coombs' test**, antiglobulin test) is a test for antibodies to recognize red blood cells in human blood. Common clinical uses of the Coombs test include the preparation of blood for transfusion in crossmatching, atypical antibodies in the blood plasma of pregnant women as part of antenatal care, and detection of antibodies for the diagnosis of immune-mediated hemolytic anemias.

There are two types of the Coombs test: direct and indirect. The **indirect Coombs test** is used in prenatal testing of pregnant women and in testing blood samples prior to a blood transfusion. An indirect Coombs' test determines whether there are antibodies to the Rh factor in the mother's blood. A normal (negative) result means that the mother has not developed antibodies against the fetus's blood. An abnormal (positive) result means that the mother has developed antibodies to the fetal red blood cells and is sensitized. It is also used to detect very low concentrations of antibodies present in a patient's plasma/serum prior to a blood transfusion. The **direct Coombs test** is used to detect whether antibodies or complement system factors have bound to erythrocytes surface antigens in vivo and is a common test for autoimmune hemolytic anemia.

Robert Royston Amos (***"Robin"***) ***Coombs*** (Jan 9, 1921–Jan 25, 2006) was a British immunologist. Robin Coombs was born Robert Royston Amos in Golders Green, the younger son of Charles Royston Amos and Edris Owen *née* Coombs. Reading *Microbe Hunters* by Paul de Kruif turned Robin ambitions to becoming a bacteriologist. He became friendly with a local veterinarian, who triggered his interest in a career in veterinary medicine. So far, he had studied veterinary medicine at the University of Edinburgh. He was a highly successful veterinary student and won all the available prizes. He qualified as a veterinarian in 1943 and was sent to the Ministry of Agriculture's Veterinary Research Laboratory at Weybridge to work on serological tests for horse diseases, which were considered as possible biological warfare agents used by the Japanese during the ongoing World War II. This first introduction to research aroused Robin's interest in the techniques for measuring antibodies in the complement system, and, indeed, in immunology in general. These interests he maintained throughout his life. Following his curiosity, Robin went to Cambridge and was admitted to Trinity Hall as a graduate PhD student in 1944. This was to be a permanent move because he never lived anywhere other than in Cambridge again.

Working with nonagglutinating or incomplete antibodies to Rhesus antigen, Robin discovered that second antiglobulin antibody can agglutinate Rhesus-positive cells if they are pretreated with serum samples comprising anti-Rhesus antibodies. This procedure is now known as the "indirect Coombs test." Antiglobulin sera also can agglutinate cells harvested from kids with hemolytic disease of the newborn and coated with maternal anti-Rhesus antibodies in utero. This is the "direct Coombs test." Robin Coombs published his novel results in 1945. This article brought him international recognition earlier than the defense of his PhD thesis entitled "The conglutination and sensitization reactions" in 1947.

In 1950, he went to a position of Assistant Director of Research in Animal Pathology, and in 1953, he was transferred to the Department of Pathology. Ten years later, he was promoted to Reader. At Cambridge at that time, such a promotion meant a personal recognition of substantial honor in research. In 1968, Robin Coombs became the Quick Chair of Biology and held this position until his retirement in 1988.

When pursuing various research projects, Robin liked to establish collaborators rather than attempting to learn all the expertise himself, and he enjoyed building a team of powerful colleagues. He attracted graduate students and postdoctoral fellows from all over the world, and his laboratory was always an extremely unusual combination of immunologists from various countries and with diverse scientific backgrounds.

(**Publ**.: Coombs RRA, Mourant AE, Race RR. Detection of weak and "incomplete" Rh agglutinins: A new test. *Lancet* 1945; 246 (6358):15–16.

Coombs RRA, Mourant AE, Race RR. A new test for the detection of weak and "incomplete" Rh agglutinins. *Brit J Exp Path* 1945; 26:255–266.)

Crohn's disease is an idiopathic chronic inflammatory disease of the intestines. It can affect any part of the digestive tract from the mouth to the anus. The inflammation causes uncomfortable and bothersome symptoms and could generate serious damage to the digestive tract. This involves intermittent, transmural inflammation through the whole bowel wall, as well as an inflammatory reaction with lymphoid aggregates and granulomas. **Crohn's disease** is sometimes called "regional enteritis" or ileitis. Together with ulcerative colitis, these conditions are referred to inflammatory bowel disease (IBD). The generally accepted hypothesis explaining Crohn's disease, in spite of its complex etiology, is that this immune-mediated condition is seen in genetically predisposed individuals and is prompted by environmental factors. Such agents change normal balance of the gut microbiota, disturb the mucosal barrier, and inspire unusual gut immune responses.

Several immunoregulatory abnormalities have been reported in patients with IBD, including the ratio of proinflammatory (TNF-α, IL-6, IL-1β) to immunoregulatory cytokines (IL-10, TGF-β, IL-35) and selective activation of T-helper (Th) lymphocyte subsets (Th1, Th2, Th9, Th17, and regulatory T cells). On the other hand, various immune intermediates, such as the IL-10 family members—IL-19, IL-20, IL-24, and Indoleamine 2,3-dioxygenase (IDO)—are elevated in the intestinal mucosa in patients with IBD. Interestingly, many genes linked to modifications in immune pathways were associated in **Crohn's disease**. For instance, they may be associated with imperfect killing of intracellular bacteria and development of innate immune responses (*CARD15/NOD2*, *LRRK2*, *IL23R*, *IRGM,* and *ATG16L1*), as well as malfunctional adaptive immunity—Th17 and IL-23 inflammatory pathway (*IL12B, IL23R*, *JAK2, STAT3,* and *TYK2*). Upregulation of expression of these genes in dendritic cells, CD4+ T, NKT, and NK cells suggests their role in the pathogenesis of Crohn's disease.

The disease was named after ***Burrill Bernard Crohn***, who with his colleagues at Mount Sinai Hospital in New York in 1932, reported a group of patients with

characteristic inflammation in the terminal ileum of the small intestine. This part of intestine is generally affected by Crohn's disease.

Burrill Bernard Crohn (Jun 13, 1884–Jul 29, 1983) was born in New York. Both his grandparents, as described by Burrill Crohn, "were 49'ers in the Gold Craze of California [who] came from the old country; one from Poland the other from Germany, religious, fully-bearded, Orthodox Jews." Forced out of the old country by the repression of the Poles and the Russians, they crossed the continent, presumably in a wagon train or else down by boat to the isthmus of Panama and across the peninsula to Sacramento, California; they returned to New York after the brief gold craze was over. Thus, his mother lived in New York. His father came over independently during the Civil War and tried out himself in Oil City, Pennsylvania; Central City, Colorado; and Rockdale, Texas. He then returned to New York, married and grew 11 children. The family was very Orthodox Jewish traditionalists with only Kosher food, no work on Saturdays, and a lot of time spent in the synagogue. Crohn described: "As an intern at Mount Sinai Hospital, I ate for the first time outside my home and was allowed to ride on a Saturday trolley when the occasion demanded. This was the first time I could break away from this ultra-pharisaical tradition of which I had been a part."

He entered City College at the age of 13, and by the age of 18, had a degree of Bachelor of Arts (BA). In 1907, he graduated from the College of Physicians and Surgeons. He did internships in pathology and internal medicine. He developed a special interest in digestive diseases, which led to a long career in research, teaching, and the clinical practice of gastroenterology. Crohn said that his father's constant complaints about "indigestion" led to his concentrated attention on intestinal diseases.

Crohn worked in the Mount Sinai Hospital for many years and was the first Chair of the Department of Gastroenterology (from 1920). He also had a successful private practice in gastroenterology in New York City and helped many patients with IBD. He consulted for a lot of VIP patients from the US and other countries, including President Dwight D. Eisenhower in 1956. He practiced medicine until he was 90 years old constantly traveling between the Upper East Side of Manhattan and a country home in New Milford, CT. In 1983, the Burrill B. Crohn Research Foundation was established at Mount Sinai by original funding from Rose Crohn and later his daughter Ruth Crohn Dickler.

Crohn also was known for his interest in medical history and his historical articles and obituaries. Once he stated that he would side with Chekhov who said that "medicine was his wife but history was his mistress." In one interview, Crohn described his visit abroad to attend the 50th anniversary of the Russian Revolution: "I just went there out of interest and I had a very interesting time. I was in Moscow on May Day with that great big parade and celebration. We spent 3 weeks in Moscow. When I came back, and I was asked to give a lecture on Russia, I prepared two illustrated lectures: one on Czarist Russia and one on post-revolutionary Russia."

(**Publ**.: Crohn BB, Ginsburg L, Oppenheimer GD. Regional ileitis; a pathological and clinical entity. *J Am Med Assoc* 1932; 99:1323–1329.)

Cronkhite-Canada syndrome (allergic granulomatous angiitis of Cronkhite-Canada, **Canada-Cronkhite disease**) is a rare non inherited condition characterized by multiple gastrointestinal polyposis, hair loss (alopecia), cutaneous hyperpigmentation, nail dystrophy and diarrhea. Diarrhea is the most common initial symptoms, with the dermatologic symptoms often occurring later. An imbalance of electrolytes may be seen due to chronic diarrhea. A biopsy of polyps usually reveals them to be hamartomas, i.e., mostly benign. However, the question of whether polyps in **Cronkhite-Canada syndrome** patients possess malignant possibility is controversial. Patients may also have concomitant autoimmune disorders, including scleroderma, rheumatoid arthritis, hypothyroidism, vitiligo, systemic lupus erythematous, etc. To date, >500 cases have been reported worldwide with most of the cases being reported in Japan. Despite being first described almost 70 years ago, Cronkhite-Canada syndrome has an unclear etiopathogenesis. While etiology is probably autoimmune, infectious trigger was also considered because of common infiltration with mononuclear cells and eosinophils. Given increased immunoglobulin G4 mononuclear cell staining in Cronkhite-Canada syndrome polyps, an autoimmune mechanism may be involved. Therefore, one test that can be positive with this syndrome is IgG4 plasma cells, but a negative result does not rule out the syndrome. The ANA test is also often positive. As immunosuppression with corticosteroids or long-term azathioprine therapy may eradicate or lessen manifestations of Cronkhite-Canada syndrome, involvement of the immune system in disease pathophysiology should be considered.The syndrome was initially identified in 1955 by Leonard Cronkhite Jr. and Wilma Canada. They reported two cases of 42- and a 75-year-old female patients with unusual fatal syndrome of abdominal pain, diarrhea, nausea and vomiting. Patients also displayed loss of hair and eyebrows, discoloration of the face, hands and neck, and malformation of the nails. Anaemia and gastrointestinal polyposis were also reported. Jarnum and Jensen introduced the term Cronkhite-Canada syndrome in 1966.

Leonard Wolsey Cronkhite Jr. (May 4, 1919 - July 20, 1996) was an American internist. He was born in Newton, Massachusetts. After pre-medicine program at Bowdoin College, he enrolled in the Maine National Guard, and nine months later, was given a commission as a second lieutenant. In 1941, he was mobilized and sent to Artillery School at Fort Monroe. In 1943, he graduated from Command and General Staff School at Fort Leavenworth as a Major. During World War II, Cronkhite served in the Caribbean and Pacific and received Legion of Merit with Oak Leaf Cluster, the Army Commendation Medal and Distinguished Service Medal. Later after getting his BS in Science from Bowdoin College, he got his medical education in Harvard Medical School receiving his M.D. degree in 1950. Then he was trained in internal medicine and published his eponymous paper in 1955 being a resident. He then received staff appointments at Harvard Medical School and Massachusetts General Hospital. In 1961, Cronkhite left his practice and returned to active duty in military intelligence being in charge of an airborne command serving for the Department of the Army in Georgia, Alaska and the Aleutian Islands and held the rank of major general. However, in 1962, he accepted

the position of general director of Children's Hospital in Boston. In 1973 he was awarded the Bowdoin Prize, given to a graduate of national distinction. He also received an honorary Doctorate in Humanities from Curry College. After leaving Children's Hospital in 1977, Cronkhite accepted the position of President of the Medical College of Wisconsin in Milwaukee. In 1985, he retired and moved to live in Brunswick, Maine. At his death he was chairman of the Maine Maritime Museum in Bath and a senior fellow of the Institute of Medicine of the National Academy of Sciences.

Wilma Jeanne Canada Diner (Jan 21, 1926 - Jan 5, 2017) was an American radiologist. She was born in West Virginia to William Edward, who ran the butcher store in the little coal mining town, and Thelma May Canada, and raised in Hardy, Kentucky. In 1946, she got her BS degree in Medical Technology, Honors in Bacteriology, from the University of Kentucky and became a registered medical technologist. In 1950, she graduated from Duke University School of Medicine. In 1954, she completed her residencies in Pathology and Radiology at Massachusetts General Hospital in Boston and) and married medical illustrator Jack Diner whom she met in Boston followed him to Little Rock, Arkansas. From 1956 she worked at Radiology Department at the University of Arkansas Medical Sciences, where she was a Professor of Radiology from 1971 and a director of the radiology residency program. In 1988, she received the Marie Curie award for outstanding contribution to the advancement of women in radiology by the American Association for Women Radiologists. After she retired from medical practice in 1997, she launched her second career as an educator. She was a President of the Board of Directors at the Congregation B'nai Israel and educator of Israeli students in English as a second language in Little Rock, Arkansas.

(**Publ**. Cronkhite LW, Jr, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. *N Engl J Med.* 1955; 252:1011-1015.)

Crow-Fukase syndrome (**Takatsuki-Crow-Fukase syndrome**, **Takatsuki disease**, POEMS or PEP syndrome, **Japanese multisystem syndrome**) is a rare paraneoplastic syndrome caused by a clone of aberrant plasma cells. This is a multisystemic disease secondary to a plasma cell dyscrasia. The name POEMS is an acronym for some of the disease's major signs and symptoms (**p**olyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**yeloma protein, and **s**kin changes), as is PEP (**p**olyneuropathy, **e**ndocrinopathy, and **p**lasma cell dyscrasia). The primary clinical feature of **Crow-Fukase syndrome** is a progressive polyneuropathy with a predominant motor disability. The disease is potentially fatal, and the patient's quality of life deteriorates because of a progressive neuropathy, peripheral edema, pleural effusion, and ascites. Furthermore, up to 25% of patients with Crow-Fukase syndrome also have **Castleman's disease**.

The causes of this condition remain unknown; however, chronic overproduction of proinflammatory cytokines (TNF-α, IL-1, and IL-6) and increased serum vascular endothelial growth factor (VEGF) appears to be a major contributor, as primary

contributors to vascular leak and polyneuropathy. Both IL-1 and IL-6 can stimulate VEGF production, which may be responsible for many clinical characteristics of Crow-Fukase syndrome, including organomegaly, edema, skin changes, neuropathy, and microvascular permeability with endoneurial edema. It also has been proposed that clonal B/plasma cells with genetic mutations of the V-region of the Igλ gene could produce excess cytokines (primarily VEGF) through an unknown mechanism, leading to the clinical manifestations of Crow-Fukase syndrome.

Scheinker's autopsy case in 1938 was the first report of what is now called POEMS or Crow-Fukase syndrome (Scheinker, 1938). ***Crow***, working in Bristol in 1956, first described the combination of osteosclerotic myeloma, polyneuropathy, and various unusual features (e.g., pigmentation and clubbing) in two patients. Two cases of solitary myeloma accompanied by polyneuropathy and endocrinological disorders were reported by ***Fukase*** et al. in 1968 and by Shimomori and Kusumoto in 1970 in Japan. The term Crow-Fukase syndrome was first used in 1984 in a study performed by Nakanishi et al. that involved 102 Japanese patients (Nakanishi et al., 1984). The acronym POEMS was coined by Bardwick et al. in 1980 (Bardwick et al., 1980).

R. S. Crow

M. Fukase

K. Takatsuki

(**Publ**.: Crow RS. Peripheral neuritis in myelomatosis. *Br Med J* 1956; 2(4996):802–824.

Fukase M, Kakimatsu T, Nishitani H, et al. Report of a case of solitary plasmacytoma in the abdomen presenting with polyneuropathy and endocrinological disorders [abstract]. *Clin Neurol* 1969; 9:657.

Takatsuki K, Uchiyama T, Sagawa K, Yodoi J. Plasma cell dyscrasia with polyneuropathy and endocrine disorder: Review of 32 cases. Int Congr. Hemat. (Kyoto). *Excerpta Medica* 1978; p. 454.

Takatsuki K, Sanada I. Plasma cell dyscrasia with polyneuropathy and endocrine disorder: clinical and laboratory features of 109 reported cases. *Jpn J Clin Oncol* 1983; 13:543–555.)

Letter D



Dalziel's syndrome (**Dalziel's disease**) is **Crohn's disease**. "I have pleasure in drawing your attention to this condition, which, I think, has not yet been fully described." With these words, a Glasgow surgeon, ***T Kennedy Dalzeil***, drew the attention of members of the British Medical Association to the intestinal disease that he called chronic interstitial enteritis. The address, accompanied by a demonstration of resected specimens, was given to the Annual Meeting of the BMA in Glasgow in July 1913. He described how in 1901 he had seen a professional colleague who had numerous attacks of colic associated with slight attacks of diarrhea, who had gone on to have an intestinal obstruction. Dalzeil's description of the condition that later became known as **Crohn's disease** was quite comprehensive. He proposed that the disease was caused by the same organisms as those responsible for chronic enteritis, **Johne's disease**, in animals described a few years earlier (1895). Dalziel's dilemma was that he could see acid-fast bacilli in the diseased animal tissues but not in the diseased human tissues.

Thomas Kennedy Dalziel (***Sir Kennedy Dalziel***) (Oct 25, 1861–Feb 10, 1924) was born at Merkland, Penpont, Dumfriesshire, Scotland, to a farm family. His early education was from a private school in Dumfries. In 1883, he graduated with a medical degree from Edinburgh University but continued his medical education in Berlin and Vienna, selecting experimental surgery and pathology as his specialty. He opened his private practice in Glasgow in 1885, joined the Western Infirmary as staff surgeon in 1889, and moved to the Royal Hospital for Sick Children in 1891. Dalziel also was very active in teaching, being the first lecturer on anatomy at the Western Medical School, then Professor of Medical Jurisprudence and Surgery in Anderson's College. During World War I, he served at the Advisory Council to the Director-General of the Royal Army Medical Corps as Scotland's representative. For his outstanding job, in 1917, he received the Honor of Knighthood from the King.

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Dalziel's remarkable teaching talents, gentleness, unique charisma, and ability to solve complex problems explains his successes in all public positions he achieved. He was regarded as the best surgeon in the West of Scotland. He was also a proliferative author and contributed a lot to the medical literature, especially in abdominal surgery techniques. He provided an excellent description and characterization of chronic interstitial enteritis as a new disease entity, which later became known as Crohn's disease. The commonly accepted belief is that Dalziel was the first to "draw attention to this condition."

(**Publ**.: Dalzeil TK. Chronic interstitial enteritis. *Br Med J* 1913; 11:1068–1070.
Dalziel TK. Practical points in abdominal surgery, being the "James Watson Lectures" delivered before the Royal Faculty of Physicians and Surgeons, 11, 14 March 1913. *Glasg Med J* 1914; 82(5):338–349.)

Davidsohn Differential test (**Paul-Bunnell-Davidsohn test**) is a modification of the **Paul-Bunnell test** that differentiates among three types of heterophile sheep agglutinins: those associated with infectious mononucleosis, serum sickness, and natural antibodies against **Forssman antigen**. The Paul-Bunnell test is based on the agglutination of sheep erythrocytes by the inactivated serum of patients with the disease. It is an example of the Monospot tests. Heterophil antibodies have the ability to agglutinate red blood cells of various animal species. The Paul-Bunnell test uses sheep erythrocytes; the Monospot test, horse red cells. Sheep red cells (RBC) have been widely used as an aid to the diagnosis of infectious mononucleosis. Still, sheep red cells are by no means the only animal cells that will react with these antibodies. It has been shown, for instance, that horse, goat, and ox red blood cells also are agglutinated by the same antibody.

The first description of heterophile antibodies was provided by ***Paul*** and ***Bunnell*** in 1932. Five years later, Davidsohn perfected the diagnostic specificity by the preabsorption of serum. Another 31 years elapsed before Henle and colleagues (1968) identified the etiologic agent of infectious mononucleosis as a virus of the Herpes group, which had been isolated 4 years previously by Epstein and Barr (1964) from **Burkitt lymphoma** cells.

Epstein-Barr virus (EBV) infection induces specific antibodies to it and various unrelated non-EBV heterophile antibodies. These heterophile antibodies react to antigens from animal RBC. In infectious mononucleosis, IgM heterophile antibodies usually are detectable for the first 3 months of infection. Characteristically, they are able to agglutinate sheep erythrocytes; it is absorbed by ox red blood cells but not guinea pig kidney cells.

See **Paul-Bunnell test** for explanation.

Israel Davidsohn (Apr 20, 1895–Dec 3, 1979) was a US pathologist. He was born in the Ukrainian city of Tarnopol (Ternopil), then the Austro-Hungarian Empire, to a Jewish family. His father suffered from severe back pain and young Davidsohn observed as therapy provided by a family doctor alleviated his father's pain. From that time on, he was fascinated with the concept of medical treatment and chose to be a physician. Yet, he was able to finish only a year of his medical

course at the University of Vienna in 1914 when World War I started in Europe. He came back home to Tarnopol, which was less than 20 km from the Russian border. He was only 19 years old and working in a local hospital when the Russians conquered that part of Austria. Returning to the University of Vienna after the war, he received his MD degree in 1921, and then went to Berlin for graduate studies in pathology.

Davidsohn came to the USA, Philadelphia in 1923. Soon he received his medical license in clinical and anatomic pathology and in 1926–1930 directed the Department of Pathology at Mount Sinai Hospital in Philadelphia. Then he moved to Chicago to Mount Sinai Hospita, working there as a pathologist (1930–1965) and as the Director of the Department of Experimental Pathology (1965–1979). Davidsohn served as the President of the American Society of Clinical Pathologists (1951–1952) and the American Board of Pathology (1963–1965). In 1960, the American Society of Clinical Pathologists and the College of American Pathologists nominated him "Pathologist of the Year." Specializing in hematopathology and being a pioneer in defining hematopathology and blood banking as parts of laboratory medicine, he participated in the founding of the American Association of Blood Banks and was its president in 1952–1953. He also served as an Editor-in-Chief (1943–1946) and an editor of the Board of Editors (1946–1975) of the *American Journal of Clinical Pathology*.

For his achievements in hematopathology, he obtained the Ward Burdick Award (1954), the John Elliott Award (1961), and the Philip Levine Award (1971). His textbooks, *A Curriculum for Medical Technologists* and *Clinical Diagnosis by Laboratory Methods,* were highly recognized in laboratory medicine. During his half-century teaching career, he was a professor and directed many courses in various medical schools, such as Rush Medical College (1934–1941, 1973–1979), University of Illinois (1941–1947), and Chicago Medical School (1947–1968). Thousands of medical technologists and laboratory technicians, medical students, and medical residents and fellows have benefited from his exceptional teaching and mentoring.

Davidsohn published 165 papers on hematology and immunopathology. Since the late 1930s, his name has been synonymous with the differential test for infectious mononucleosis. Davidsohn normally worked 6 days a week for long hours, but still had time for his family, friends, and colleagues. He was a polyglot, fluent in Ukrainian, Hebrew, Yiddish, and Polish—languages of his youth—and he afterward learned English, French, German, and Russian. Frequently, he greeted and welcomed his Japanese and Chinese colleagues and collaborators in their native languages. He enjoyed art and literature and loved to play chess with his grandson Mike. His huge collection of medical cartoons and jokes was very well known.

John Rodman Paul see **Paul-Bunnell test**

Walls Willard Bunnell see **Paul-Bunnell test**

(**Publ**.: Davidsohn I, Walker PH. The nature of the heterophile antibodies in infectious mononucleosis. *Am J Clin Pathol* 1935; 5:455–465.

Davidsohn I. Serologic diagnosis of infectious mononucleosis. *JAMA* 1937; 108:289–294.

Davidsohn I. Further studies on heterophile antibodies in serum sickness. *J Immunol* 1930; 18:31–49.)

Destombes-Rosai-Dorfman syndrome/disease see **Rosai-Dorfman disease**

Devic disease (**Devic's disease**, **Devic's syndrome**, Neuromyelitis optica) is a relapsing inflammatory demyelinating disease that most commonly affects optic nerves and the spinal cord, leading to sudden vision loss or weakness in one or both eyes, and loss of sensation and bladder function. Recent studies have indicated that presence of serum antibodies against aquaporin 4 (AQP4), a water channel protein, is a hallmark of Devic disease and could be essential for making the diagnosis. These antibodies target the AQP4 in the cell membranes of astrocytes. In one study, anti-KIR 4.1 antibodies occurred in approximately 50% of patients; this finding is of interest because the KIR 4.1 channel is expressed close to the aquaporin channel on astrocytic endfeet. The blood–brain barrier (BBB) is weakened in **Devic's disease**, but it is currently unknown how the autoantibodies cross the BBB. Some reports point to metalloproteinase-2 and IL-6 as culprits for the BBB failure.

Devic's disease is similar to multiple sclerosis, but unlike standard multiple sclerosis, it is not believed to be mediated by T cells, but rather by antibodies called NMO-IgG, or simply NMO antibodies, where NMO is neuromyelitis optica. The inflammatory lesions in Devic's disease have been classified as type II lesions (i.e., complement-mediated demyelination), but they differ from multiple sclerosis pattern II lesions in their prominent perivascular distribution. Therefore, the pattern of inflammation is often quite distinct from that seen in multiple sclerosis.

Eugène Devic (Oct 24, 1858–Jan 1, 1930) was a French neurologist. He was born in southern France in La Cavalerie, a little village in Aveyron. His father was a wine trader and planned that his only son would continue this business. But young Devic was interested in medicine and graduated from the medical college in Lyon. In 1882, he worked in a hospital as a resident and in 1886, obtained his MD degree. He passed the *agrégation* (highest teaching diploma) in 1892. In 1894, he got his first hospital position to work in a pathology laboratory but soon switched to clinical practice job at la Croix Rousse Hospital and then at the Hôtel-Dieu Hospital in Lyon.

Devic's clinical interests included various topics in neurology, pediatrics, and gastroenterology, but he was mostly attracted by doing studies on typhoid fever and cardiovascular diseases. He published numerous medical papers and many of them were prepared together with his students. In 1894, Devic and his student, Fernand Gault, described a rare nervous condition that affected the spinal cord and optic nerves that resembled multiple sclerosis. They described 16 patients with loss of vision in one or both eyes, who subsequently developed spastic weakness of the lower limbs. Today, this disorder is referred to as Devic's disease or neuromyelitis optica. Eugène Devic was the first in a family of brilliant neurologists, with his son

André Devic and his grandson Michel Devic, who also reported on neuromyelitis optica.

(**Publ**.: Devic E. Myélite subaiguë compliquée de névrite optique. *Bull Med* (in French) 1894; 8:1033.)

DiGeorge syndrome (**DiGeorge anomaly**, **Shprintzen syndrome**, **Takao syndrome**, **Sedlackova syndrome**, **Strong syndrome**) is a disorder caused by a defect in chromosome 22. DiGeorge Syndrome is one of the most common genetic disorders known, occurring in about once in every 4000 live births. It results in the poor development of several body systems and associated medical problems include heart defects, poor immune system function, a cleft palate, complications related to low levels of calcium in the blood, and delayed development with behavioral and emotional problems. **DiGeorge syndrome** includes a pattern of more than 200 different defects. Salient features can be summarized using the mnemonic CATCH-22 to describe DiGeorge syndrome, with the 22 to remind one the chromosomal abnormality as following: **C**ardiac abnormality (commonly interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot), **A**bnormal facies, **T**hymic aplasia, **C**left palate, and **H**ypocalcemia/**H**ypoparathyroidism. DiGeorge Syndrome is caused by a hemizygous deletion of part of the long arm (q) of chromosome 22, region 1, band 1, subband 2 (22q11.2). The exact mechanism that causes all the associated features of the syndrome is unknown. Of the 30–50 genes in the deleted region, a number have been identified as possibly playing a role in the development of some of the signs and symptoms.

Thymic hypoplasia or aplasia leading to defective T-cell function is one of the main features of DiGeorge anomaly. Depending on the T-cell-proliferative response to mitogens, the immunologic features can be classified as partial or complete. Patients with partial DiGeorge anomaly have a below-normal proliferative response to mitogens, and the immune parameters may improve with time. IL-7 can play a critical role in T-cell homeostasis in patients with partial DiGeorge anomaly. Nevertheless, in subjects with thymic hypoplasia, despite a compensatory increase of T-cell numbers, the TCR repertoire is reported to be decreased. Only a small fraction of patients present with marked impairment of T-cell function associated with a complete absence of thymus and T cells and severe systemic infections consistent with severe combined-immunodeficiency phenotype. These patients usually have very few detectable T cells in peripheral blood (1–2%). Although DiGeorge anomaly is commonly associated with T-cell immunodeficiency, B-cell defects also occur. About 6% of patients older than 3 have hypogammaglobinemia; selective antibody deficiency also may be present.

Impaired T-cell generation may predispose patients to autoimmune diseases including juvenile rheumatoid arthritis, idiopathic thrombocytopenic purpura, autoimmune uveitis, severe eczema, and autoimmune hemolytic anemia; however, no specific pattern of autoimmune disease appears to be associated with DiGeorge anomaly. In patients with partial DiGeorge anomaly, cytopenias and hypothyroidism may be the most common autoimmune conditions. Children with high or

normal naive CD4 T-cell counts early in childhood had a lower risk of autoimmune disease. Association with **Graves disease** and asthma, but not with allergic rhinitis, has been reported.

DiGeorge Syndrome takes its name from ***Angelo DiGeorge***, who described it in 1968. In the same year, ***William Strong***, a physician from Cleveland, reported an association of cardiac abnormalies (right-sided aortic arch), learning differences, and a characteristic facial appearance in 4 members of one family. Interestingly, in 1955, a pattern of velar hypoplasia, causing hypernasal speech and associated facial dysmorphism, was observed in 26 children of Czech origin by ***Eva Sedláčková*** (Sedláčkova syndrome). During the 1970s, ***Robert Shprintzen***, a speech pathologist, described a group of patients with similar clinical features including cleft lip and/or palate, conotruncal heart defects, absent or hypoplastic thymus, and some of these patients also had hypocalcemia. Shprintzen named this group of features velo-cardio-facial syndrome, but the syndrome also was referred to as Shprintzen syndrome.

In the early 1970s, ***Atsuyoshi Takao*** had recognized a characteristic facial appearance, which was then called "the Takao syndrome," or conotruncal anomaly face syndrome. Takao syndrome is diagnosed when the patient primarily has cardiac disease, with normal T-cell and parathyroid function. Atsuyoshi Takao asked Akiko Kinouchi to write a paper about the syndrome, and in 1976 she wrote one in Japanese. During the early 1990s, 22q11.2 deletion was identified as the common molecular etiology for all these syndromes.

Angelo M. DiGeorge (Apr 15, 1921–Oct 11, 2009) was an Italian-American physician and pediatric endocrinologist. He was the son of two Italian immigrants, Antonio and Emilia (Taraborelli). He was born in South Philadelphia. His story was that his primary school teacher transformed his Italian surname DiGiorgio into the US style—DiGeorge. He finished South Philadelphia High School for Boys in 1939 at the top of his class and received a White Williams Scholarship at the Temple University. In 1943, he graduated from the university with distinction in chemistry, obtained his medical degree with Honors from the Medical School at the same university in 1946, and completed his internship training at Temple University Hospital.

After World War II from 1947–1949 he was a Captain and Chief of the Medical Service for the US Army 124th Station Hospital in Linz, Austria. He then returned to Philadelphia, where he was introduced to his future wife, Natalie Picarello, a Registered Nurse at Temple Hospital. After a pediatric residency at St. Christopher's Hospital for Children and postdoctoral training in endocrinology at the Jefferson Medical College, DiGeorge was offered a position at the Department of Pediatrics, Temple University School of Medicine (1952). In 1967, he became Professor of Pediatrics and an Emeritus Professor in 1991. At the same time, DiGeorge worked as an attending physician at St. Christopher's and later as Chief of Endocrinology and Metabolism and Director of the Pediatric Clinical Research Center from 1965 to 1982.

DiGeorge published more than 230 medical articles, abstracts, and textbook chapters. He traveled all around the world presenting his data and teaching at

numerous meetings, symposia, and seminars. Interestingly, once in Rome for the first time, DiGeorge met Robert Shprintzen, another "father" of an unusual disorder, even though they had studied the same disease for many years and both lived in the US.

DiGeorge is remembered as a brilliant physician with unique diagnostic capabilities that were highly recognized by his patients and colleagues. He was a perfect teacher and lecturer, a fascinating storyteller, writer, and a passionate reader. He had many additional interests and hobbies such as stamp collecting, arts, politics, and gardening. He also was interested in sports, especially in the legendary Philadelphia team, and everything related to Phillies baseball. He also loved all things Italian. He died at age 88 kidney failure at his home in Philadelphia.

Robert J. Shprintzen (Jul 12, 1946–) is a US pathologist. He was born in Brooklyn, New York, and studied psychology at the University of Rochester and Speech-Language Pathology at the University of Rhode Island and Syracuse University, getting his PhD degree in 1973. He is often credited with discovering velo-cardio-facial syndrome (VCFS) in 1978 when he reported a detailed analysis of the clinical findings in 12 patients including a familial case passed from mother to daughter. In 1992, he founded the VCFS Institute devoted specifically to the syndrome and staffed by an inclusive interdisciplinary group of clinicians and scientists. He is the Director of Center for Diagnosis, Treatment, and Study of Velo-Cardio-Facial Syndrome, Professor of Otolaryngology and Pediatrics at the Upstate Medical University in Syracuse, NY.

Shprintzen has published more than 220 medical papers, chapters, monographs, and 7 textbooks. He was invited to present his data and teach in 25 countries in Europe, Asia, Africa, Australia, and North and South America. He won many awards and honors and was the recipient of many grants from various governmental and nongovernmental funds.

William Strong – a US physician.

Eva Sedlackova (***Sedláčková***) – a Czech phoniatrician.

Atsuyoshi Takao (Feb 22, 1925–Aug 8, 2006) was a Japanese pediatric cardiologist rightly known as "the father of pediatric cardiology in Japan." The Takaos originated from an ancestor who started to serve as local ruler in Kyushu Island a few centuries ago. *Takao*'s grandfather settled in Tokyo as a doctor at the end of the Edo era (the era of Tokugawa rule, 1603–1868, in Japan is known eponymously as the Edo period). His father established a private practice in the center of Tokyo; he had 9 children. After his death, the family had to return to Kyushu to join their relatives. Takao graduated from the high school and medical school in Nagasaki, Kyushu, in 1945. Interestingly, out of 9 children in the family,6 selected medical careers.

At the end of the World War II, Takao served at the Army Medical School. He was working in the Yamagata prefecture (Tohoku region) in the northern part of Japan when the atomic bomb exploded in Nagasaki ending the War in August 1945. For the next 5 years, Takao continued his medical studies at Nagasaki and Yamaguchi medical schools, focusing on general pediatrics. In 1950, he began to serve at the

Atomic Bomb Casualty Commission in Nagasaki, working as a medical assistant in the Division of Pediatrics. In 1952, Takao traveled to the US west coast by ship, and from Los Angeles to Chicago by train to visit the New York University for further training in general pediatrics. He spent 4 years at New York University. After finishing his residency, he went to Texas Children's Hospital and spent 3 years as a clinical fellow in pediatric cardiology.

In 1958, Takao returned to Japan as an Assistant Professor at the Department of Cardiac Surgery. He became Professor and Chief of Pediatric Cardiology in 1968. In 1990, Takao retired, but began to study molecular biology. Even though he did not carry out laboratory experiments by himself, he became a decent molecular biologist, which helped him to build the International Molecular Cellular Immunological Research Center. He served as its Director until 2006.

Takao was interested in thanatology. In the textbook of pediatric cardiology, *Clinical Developmental Cardiology*, he wrote a chapter on thanatology (i.e., the scientific study of death). He stressed the role of thanatology in pediatric cardiology and wrote: "The art of dying is the art of living," "We can live just because we die," and "Pediatric cardiology should become longitudinal cardiology if we look at patients with congenital heart disease from the point of view of thanatology."

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Burn J, Takao A, Wilson D, Cross I, Momma K, Wadey R, Scambler P, Goodship J. Conotruncal anomaly face syndrome is associated with a deletion within chromosome 22q11. *J Med Genet* 1993; 30(10):822–824.)

Di Guglielmo's syndrome see **Révol's syndrome**

Dohle leukocyte inclusions see **May-Hegglin anomaly**

Donath-Landsteiner antibodies are the antibodies of the IgG class directed against the P blood group antigen. They are associated with various infections and are responsible for paroxysmal cold hemoglobinuria, an autoimmune disease—also called **Donath-Landsteiner syndrome**. The antibody acts as a biphasic hemolysin binding specifically to the P antigen of red blood cells at low temperatures, leading to complement activation and red cell lysis at 37 °C.

Donath-Landsteiner test is a blood test to detect antibodies (anti-P antibody) related to a paroxysmal cold hemoglobinuria. The antibodies destroy erythrocytes when the body is exposed to cold temperatures. Paroxysmal cold hemoglobinuria (also known as **Donath-Landsteiner syndrome**) is an autoimmune or postviral disease in which there is a biphasic IgG antibody directed against the P blood group antigen. It is seen as episodes of hemoglobinemia and hemoglobinuria after exposure to cold. The test is based on the fact that the blood of patients with this disease contains isohemolysin and autohemolysin that unite with erythrocytes only at low temperatures (2–10 °C), hemolysis occurring only after warming with the complement to 37 °C.

Donath-Landsteiner syndrome (paroxysmal cold hemoglobinuria) is a rare autoimmune hemolytic anemia that can occur following an infection that can trigger the formation of antibodies that cross-react with the P antigen on erythrocytes. Infections include influenza, measles, mumps, adenovirus, chickenpox, cytomegalovirus, Epstein-Barr virus, syphilis, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*. Anti-P autoantibody binds to erythrocyte surface antigens in a susceptible individual as blood passes through chilly extremities in cold weather. When the blood returns to the warmer central circulation, the red blood cells are lysed with complement, causing intravascular hemolysis. The disease is characterized by the sudden presence of hemoglobin in the urine (hemoglobinuria), typically after exposure to cold temperatures.

Julius Donath (Nov 11, 1870–Sept 1, 1950) was an Austrian internist. He was born in Vienna to a Jewish family—the son of the businessman Leopold Ludwig Jacob Donath from Prostějov (Moravia) and his wife Ida Donath, née Rothwas. After graduating from the Franz-Joseph-Gymnasium in 1889, he studied medicine in the University of Vienna, graduating with an MD in 1895. He received his further education as an Aspirant at the Allgemeines Krankenhaus, and from 1898 to 1907, he was an assistant physician at the medical clinic, becoming Titular Professor in 1927. He worked on paroxysmal hemoglobinuria, diseases of the renal fascia, chondrodystrophic dwarfism, and malaria.

After the annexation of Austria by Germany in 1938, Donath lost his position and was thrown out of the university because of his Jewish origins and was admitted as a so-called patient handler for the exclusive treatment of Jewish patients. Later, he took over the management of the internal department at the Rothschild Hospital. He survived the time of the National Socialist dictatorship in Vienna, protected by his marriage to a non-Jewish woman, Anna Donath, née Kindler.

Together with ***Karl Landsteiner***, Donath described IgG antibodies (incomplete antibodies), which are directed against the P blood group antigen on the erythrocyte membrane, and which temporarily lead to “paroxysmal cold hemoglobinuria” when exposed to cold.

Karl Landsteiner (14 Jun 1868–26 Jun 1943), an Austrian-American immunologist and pathologist, was born in Vienna to a Jewish family. He was the only child of Dr. Leopold Landsteiner, a famous journalist and the founder of the Vienna daily

PRESSE, and Fanny Hess Landsteiner. Karl was 6 years old when his father suffered a massive heart attack and died. Karl was brought up by his mother to whom he was so devoted that a death mask of her hung on his wall until he died. In 1885, Landsteiner was admitted to Medical School at the University of Vienna. He took a year off from school at the age of 20 for his obligatory military service. When he was 21, Landsteiner and his mother converted from Judaism to Catholicism and Karl was christened ***Karl Otto Landsteiner***.

After medical school, Landsteiner spent time on chemical studies in Germany and Switzerland and published many journal articles with famous scientists. Later, at the newly established Institute of Hygiene at the University of Vienna, he worked on bacterial agglutination and prepared his first research articles that discussed agglutination and immune reactions. In 1897, he joined the Institute of Pathology in Vienna. After a few years of experimental work with his own blood and blood samples from his colleagues, he published his most important and innovative findings on interagglutination, which may follow mixing serum and blood cells of several humans (1900). He speculated that this is not a pathological reaction but a physiological phenomenon reflecting the unique nature of normal blood in humans. He then classified human blood into three groups—A, B, and C (later 0). The fourth blood group was described in 1902 and named AB. Identification of distinct blood groups opened opportunities for safe and practical blood transfusion.

In 1907, Reuben Ottenberg from Mt. Sinai Hospital in New York described the first effective blood transfusion. Further development of this important procedure was achieved in 1913 by Richard Lewisohn, a surgeon from the same institution, when he revealed that blood coagulation could be prevented by the addition of citrate salts. This brought the possibility of blood preservation for a few weeks and created a basis for developing the modern blood banks and modern techniques for blood transfusion. The first transfusion using Lewisohn's citrate method was performed by Howard Lilienthal. During World War I, transfusion of compatible blood was performed on a large scale and saved many lives. Operations on the heart, lungs, and circulatory system, previously impracticable because of the magnitude of the blood loss involved, became possible.

Landsteiner's work added an important test to forensic medicine. In 1902, Landsteiner with Max Richter presented a lecture at the Institute of Forensic Medicine, Vienna University, in which they described a new method of typing dried blood stains to help solve crimes when blood stains are left at the scene. In addition, in 1924, the theory about the inheritance of blood groups was established, and since then, denying paternity has never been the same.

During this period, Landsteiner also worked on characterizing and evaluating the physiological meaning of cold agglutinations in human blood serum. In 1904, he and Austrian internist, ***Julius Donath***, described a test for the diagnosis of paroxysmal cold hemoglobinuria. This test is now known as the **Donath-Landsteiner phenomenon** or **test**. During 1905–1906, Landsteiner, Ernest Finger, Otto Pötzl, and Rudolf Müller explained the previously unknown mechanism that occurs in the **Wassermann reaction**. In 1906, Landsteiner and Viktor Mucha developed the technique of dark-field microscopy to identify and study the microorganisms that cause

syphilis. Later, while directing laboratories of the Royal-Imperial Wilhelmina Hospital in Vienna, Landsteiner, with his assistant Erwin Popper, worked on poliomyelitis and postulated the existence of a so-called invisible virus. Today, the World Health Organization (WHO) still credits Landsteiner and Popper with having found the polio virus during their experiments.

During the World War I, Landsteiner served at a war hospital. He married Leopoldine Helene Wlasto, and they had a son, Ernst Karl. In 1922, Landsteiner moved to New York after accepting an offer from the Rockefeller Institute. In 1927, he discovered new blood groups: M, N, and P, refining the work he had begun 20 years earlier. Landsteiner officially retired in 1939, at the age of 71, but continued to work and in 1940, together with Alexander Wiener and Philip Levine, described a new human blood factor—the Rh factor, named for Rhesus monkeys, in which the factor was first discovered.

Before the introduction of the Euro, Landsteiner was the last to have his portrait on a 1000 shilling banknote, sharing such an honor with Erwin Schrödinger. He was an excellent pianist, and by nature, somewhat pessimistic; he preferred to live away from people. It was characteristic of him that he died with a pipette in hand. On June 24, 1943, Landsteiner had a heart attack in his laboratory and died 2 days later in the hospital of the Institute in which he had done such distinguished work. He accumulated a lot of awards and honors, and in 1930, he received the **Nobel Prize** in physiology or medicine "for his discovery of human blood groups." He was granted a Lasker Award in 1946 posthumously and is recognized as the father of transfusion medicine.

(**Publ**.: Landsteiner K, Popper E. Übertragung der poliomyelitis acuta auf affen. *Z Immun Exp Ther* 1909; 2:377–390.

Landsteiner K. Zur kenntnis der antifermentativen, lytischen und agglutinierenden wirkungen des blutserums und der lymphe. *Centralbl Bakteriol Parasitenkd Infektionskrankh* 1900; 27:357–362.

Donath J. Landsteiner K. Uber paroxysmale haemoglobinurie. *Munich Med Wochenschr* 1904; 51:1590–1593.)

Döhle-like bodies are 1–2 microns, light blue or blue-gray, oval structures usually found at the periphery of the neutrophils and consist of ribosomes and endoplasmic reticulum. They can be found in bacterial infections and in a benign inherited condition known as **May-Heggling anomaly**. They also may be found in poisoning, burns, infections, and following chemotherapy. They are named after a German pathologist, ***Karl Döhle***.

Karl Gottfried Paul Döhle (Jun 6, 1855–Dec 7, 1928) was a native of Mühlhausen and a student in Tübingen, Leipzig, Strassburg, and Kiel in Germany. He studied medicine in Kiel graduating in 1881 and receiving his doctorate degree in 1882. He started his career as an assistant to Arnold Ludwig Heller at the Kiel Pathological Institute in 1883 and stayed there for many years until his retirement in 1924. He finished his specialized training in pathology in 1889 and continued his career as Titular Professor (1896), Chair of the Department (1908), Professor Extraordinary

(1909), Ordinarius and Honorary Professor (a professor of the highest rank at a German university) (1915), and a Full Professor (1921).

Döhle was probably the first clinician who could differentiate syphilitic inflammation of the aorta from atherosclerotic lesions. Comparing various parasitic lesions, he recognized the inclusion bodies in leukocytes in patients with scarlet fever (i.e., a bacterial infection caused by group A *Streptococcus*). His original thoughts were that they represented spirochetes, and he hoped to be able to discriminate leukocyte inclusion bodies in scarlet fever and those seen in other infections. Nevertheless, this did not work.

Döhle was somehow unrecognized outside his institute in spite of the fact that he was a very knowledgeable and respectable histopathologist. That may be because he was an introvert who avoided medical conferences and did not publish a great deal. It was through Heller's efforts that Döhle's study of syphilitic aortitis was finally acknowledged. At the same time, he was a especially popular teacher and mentor of medical and postgraduate students and fellows. A sometimes used synonym of syphilitic aortitis is "Döhle-Heller aortitis," named after Döhle and Arnold Ludwig Gotthilf Heller.

(**Publ**.: Döhle KGP. Ein Fall von eigentümlicher Aortenerkrankung bei einem Syphilitischen. (Treatise on syphilitic aortitis). Kiel; 1885.

Döhle KGP. Leukocyteneinschlüsse bei scharlach. *Zentralbl Bakteriol Parasitenkd Infektionskrankh Hyg* 1912; 61:63–68.)

Dressler's syndrome (**Harley's syndrome**, **Dressler** (**D.**) **syndrome**) is a very rare autoimmune hemolytic disorder affecting less than 200,000 people in the US population. Hemoglobinuria is characterized by the sudden passage of dark brownish to black urine following exposure to cold; it is often associated with leg pain, abdominal cramps, malaise, chills, fever, vasomotor disorders, pallor, and blanching of the ears and lips. **Dressler's syndrome** of hemoglobinuria is named for ***Lucas Dressler***, who characterized it in 1854. Some authors have used **Donath-Landsteiner syndrome** as a substitute for this disease's name.

Lucas Anton Dressler (1815–1896) was a German physician.

George Harley (Feb 12, 1829–Oct 27, 1896) was a Scottish physician. The only son of George Barclay Harley and Margaret Macbeath, he was born at Harley House, Haddington, East Lothian and started his medical studies in Edinburgh at the age of 17. In 1850, while he was still a student at the maternity hospital, one of the expectant mothers died of a heart attack. Harley, without assistance or previous experience, successfully performed a Caesarean section and delivered a living child. After receiving his doctorate, he continued his studies in France, Germany, and Italy. In Padua, however, Harley was disappointed by the standards of the faculty and stayed only a few days prior to returning to England in 1855. When he was studying in Vienna during the height of the Crimean War, he attempted to join the army of Omar Pasha as a civil surgeon, but passport issues meant he was arrested instead.

Harley was a Curator of the Anatomical Museum at the University College. He also taught a lecture course in histology and practical physiology. Right after his paper confirming Heinrich Gustav Magnus's theory about formation of a complex between respired oxygen and blood components (hemoglobin) was published, he was nominated as a fellow of the Royal Society. He also was the first scientist who demonstrated that experimental animals poisoned by strychnine could be protected by injection of another toxin—curare.

In 1856, Harley opened a practice but had little success: in 12 months he saw only 2 patients. Still, at the meeting of the Pathological Society, he caught the attention of the Society's president, Sir Thomas Watson, who invited Harley as a consultant for patients with liver and kidney diseases. In 1859, Harley was appointed Professor of Medical Jurisprudence at the University College. In 1861, he received the triannual prize of the Royal College of Surgeons. At that point, his eyes were completely fatigued after many years of looking into a microscope; therefore, he had to spend 9 months in complete darkness. After recovery, he wrote a book describing his feelings and experiences in the dark.

In addition, Harley expressed unusual interest in the strange manifestations of hysteria. In 1863, he reported a case of a 33-year-old woman who made an extremely loud noise from her vagina by expelling gas. Using gas analysis, he revealed that this was just air that had been earlier sucked in by voluntary contractions of her abdominal muscles. In addition to his medical work, Harley wrote numerous short stories. He also was a formidable protagonist of cremation, and after peculiar neurological complications resulted in walking difficulties, he died suddenly. He was cremated, granting his own wish, and buried in Woking Cemetery in England. Harley had married Emma Jessie, who survived him with 3 children: Vaughan Harley, M.D.; Ethel Brilliana Tweedie, author; and Olga Harley.

(**Publ**.: Dressler LA. Ein fall von intermittirender albuminurie und chromaturie. *[Virchow's]. Arch Pathol Anat Physiol Klin Med* 1854; 6:264–266.

Harley G. On intermittent haematuria; with remarks upon its pathology and treatment. *Med Chir Trans London* 1865; 48:161–173.)

Dressler's syndrome (**Dressler syndrome**, postmyocardial infarction syndrome) is a type of autoimmune pericarditis—inflammation of the sac surrounding the heart (i.e., pericardium). Inflammation associated with Dressler's syndrome is believed to be an immune system response (autoimmune) following damage to heart tissue or the pericardium (e.g., a heart attack, surgery, or traumatic injury). Leukocytosis, an elevated sedimentation rate, eosinophilia, and anti-heart antibodies are envisaged. **Dressler syndrome** has an incidence rate of approximately 5% after cardiac events, with 50% of them being diagnosed in the second or third week after infarction.

William Dressler (Aug 9, 1890–Oct 10, 1969) was an Austrian-American-Jewish physician. He was born and educated in Vienna, Austria, and achieved MD qualification from the University of Vienna in 1915. Then he worked as a cardiologist in Vienna. In 1938, after occupation of Austria by Germany, Dressler immigrated to the US as a refugee. From that year until 1967, he was Chief of the Cardiology

Clinic and Head of Electrocardiographic Laboratory at Maimonides Medical Center in New York. He wrote 6 cardiology texts, 3 in German, and 3 in English. His *Clinical Cardiology* (1942) became the classic book of cardiological diagnostic tool. Dressler's syndrome is named after him for discovering the condition in 1956.

(**Publ**.: Dressler W. A post-myocardial infarction syndrome: preliminary report of a complication resembling idiopathic, recurrent, benign pericarditis. *JAMA* 1956; 160:1379–1383.

Dressler W. Clinical Cardiology. New York: Hoeber; 1942.

Dressler W. Existenz und Arbeit: Das Problem der Konkretion des Abstrakten Existenzbegriffes in der Philosophie J. P. Sartres. Munich: Dressler; 1969.

Dressler W. Clinical Aids in Cardiac Diagnosis. New York: Grune & Stratton; 1970.)

Dreyfus-Dausset-Widal syndrome see **Hayem-Widal syndrome**

Duncan's disease (**Duncan disease**, **Duncan syndrome**, **Purtilo syndrome**, X-linked lymphoproliferative disease) is a rare inherited immunodeficiency/lymphoproliferative disorder that is characterized by a predilection for hemophagocytic lymphohistiocytosis, fatal or near-fatal Epstein-Barr virus (EBV)-induced infectious mononucleosis in childhood, subsequent hypogammaglobulinemia, and a markedly increased risk of lymphoma or other lymphoproliferative diseases. In boys with X-linked lymphoproliferative disorder, there is an inability to mount an immune response to EBV, which often leads to death from bone marrow failure, irreversible hepatitis, and malignant lymphoma. Patients produce insufficient numbers of CD27 memory B cells. There are 3 main illnesses associated with Duncan's disease (i.e., glandular fever, lymphoma, and low immunoglobulin levels). Patients can suffer from one or more of these conditions.

A mutation associated with a T- and NK-cell lymphoproliferative disorder was identified on the long arm of the X chromosome at position 25 (Xq25). This mutation is responsible for a deletion in the *SH2D1A* gene, which encodes a src-homology 2 domain (SH2) on a SLAM-associated protein (SAP)—a signal transduction protein. SAP as an adaptor protein regulates activation of T and NK cells by binding to the cytoplasmic domain of the surface receptor; this signals the lymphocyte activation molecule (SLAM), which causes the modulation of IFN-γ. In Duncan's disease, a deletion in the *SH2D1A* gene inactivates the SH2 domain on the SAP protein, thus preventing its binding to the SLAM receptor. This results in abnormal IFN-γ modulation and unrestrained cell proliferation.

Consequently, deficiency of SAP results in sustained T-cell proliferation in response to EBV infection because of reduced ability to kill EBV-infected B cells. In the absence of SAP, interaction of CD48 on EBV-infected cells with 2B4—a receptor belonging to the immunoglobulin superfamily found on NK cells as well as a small subset of T cells—on NK cells inhibits their ability to kill the EBV-infected cells. In addition, in the absence of SAP, SLAM molecules interact with SHP-2, resulting in an inhibitory effect on T-cell function. Therefore, the defect in X-linked

lymphoproliferative syndrome converts normally activating signals into inhibitory signals.

The **Duncan disease** was named after the local community in which it was first discovered. Of 18 boys in the ***Duncan kindred*** (in Omaha, Nebraska), 6 died as a result of unusual lymphoproliferative conditions. They all showed a slight but progressive combined variable immunodeficiency seen as benign or malignant proliferation of lymphocytes, histiocytosis, and changes in immunoglobulins in the blood. Specifically, atypical lymphocytosis was associated with fever; lymphadenomegaly; and hepatosplenomegaly, pharyngitis, and gammaglobulin abnormalities, varying from agammaglobulinemia to polyclonal hypergammaglobulinemia. Postmortem examination revealed lymphocyte depletion in the thymus and T cell-dependent regions of the lymph nodes and spleens. Histological analysis revealed that disseminated infiltrates were comprised of histiocytes, lymphocytes, and plasma cells. The 2 half-brothers were diagnosed with lymphomas of the ileum and central nervous system. Almost 50% of boys, including the half-brothers, but not girls, were impacted, suggesting sex-linked recessive inheritance.

Duncan disease also is called **Purtilo's syndrome**, after ***David Purtilo***, a pathologist and immunologist, who discovered it in the early 1970s while at the American Army Center for Pathology in Washington. In 1975, he summarized and characterized clinical cases observed during 6 years there. His definitive published work stemmed from observations drawn over a 6-year period with a classic case of autopsy from 1969 at Children's Hospital of Boston. An 8-year-old boy, formerly healthy, suddenly died a month after the onset of infectious mononucleosis and development of fulminant hepatitis and bone marrow malfunction. His spleen, lymph nodes, bone marrow, and liver showed diffuse infiltration by histiocytes, lymphoblasts, and plasma cells. In addition, 2 of his brothers died at a young age from an acutely infectious mononucleosis and acute lymphoblastic leukemia. Furthermore, 3 maternally related nephews developed infectious mononucleosis associated agammaglobulinemia and cerebral lymphoma, and extranodal lymphoma not related to infectious mononucleosis. All these boys were related to a shared ancestor with the surname **Duncan**. This created a new entity termed Duncan's disease affecting males with X-chromosomal mutation who encountered EBV infection.

David Theodore Purtilo (Apr 13, 1939–Sept 28, 1992) was a US physician. He was born in Duluth, Minnesota, and received his bachelor's degree from the University of Minnesota. He received a master's degree from the University of North Dakota and, in 1967, his doctorate from Northwestern University. He was a major at the Armed Forces Institute of Pathology in Washington before joining the faculty of the University of Massachusetts Medical School in Worcester. He was named Professor of Pathology and Pediatrics in 1978. In 1981, Purtilo became the Chair of Pathology at the University of Nebraska Medical Center and quickly expanded the research capabilities of the department, bringing to it worldwide recognition. Research staff and clinical faculty were added in larger numbers than previously. In 1984, the Department of Microbiology joined with the Department of Pathology, being renamed Pathology and Microbiology.

Purtilo was noted for having discovered X-linked lymphoproliferative disease, or XLP. Males with XLP inherit a mutant gene in the X chromosome, leaving them incapable of withstanding the EBV, which is linked to infectious mononucleosis. He wrote nearly 300 scientific papers and 6 textbooks. In 1992, Purtilo, who lived in Omaha, was in Naples, FL, to deliver a talk during the American Association for Cancer Research meeting when he suffered a stroke and died at the age of 53.

(**Publ**.: Purtilo DT, Cassel CK, Yang JP, Harper R. X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). *Lancet* 1975; 1(7913):935–940.)

Letter E



Eales disease (**Eales's disease**) is an idiopathic occlusive vasculitis affecting the midperipheral retina. The disease is characterized by periphlebitis (i.e., retinal venous inflammation), vascular occlusion, and consequent retinal neovascularization with recurrent vitreous hemorrhage being the disease's hallmark. Eales's disease mostly affects young males with a male-to-female ratio of 20:1. The common concept proposes immunological, biochemical, and molecular mechanisms for the disease with hypothesized roles of oxidative stress, free radical-mediated tissue and cell damage, human leukocyte antigens, retinal autoimmunity, and *Mycobacterium tuberculosis*. Immunologic pathways include T-lymphocyte infiltration and homing because T cells are detected in recovered epiretinal and subretinal membranes. It is possible that local immunological reactions are triggered by the exposure of some known and unknown exogenous agents. For instance, possible hypersensitivity to tuberculoprotein that was developed after infection with *Mycobacterium tuberculosis* could be one of etiological mechanisms.

Eales's disease was first reported by ***Henry Eales*** in 1880 and 1882 when he described the clinical features of recurrent retinal hemorrhage in young adults. He treated 7 young men (ages 14–29 years) who had a common history of headache, epistaxis (nosebleeds), dyspepsia, and chronic constipation. Eales thought that the disease was not retinal vasculitis but was a vasomotor neurosis.

Henry Eales (1852–1913) was a British ophthalmologist. He was born at Newton Abbot, Devon, England, to the priest family of William Eales and Emily Weatherdon. He graduated in 1873 and completed his internship at the Birmingham and Midland Eye Hospital. He was a teacher and medical tutor at Queen's College until he got a position of an honorary surgeon at the Eye Hospitals in 1878. He worked there for 35 years. Eales established a large consulting practice and was very well known for his familiarity with the ophthalmoscope. He published many documents, and one of his famous papers was a review of the appearance of the retina in patients with renal disease. He died due to pulmonary embolus.

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M. R. Shurin et al., *Basic and Clinical Immunology by Names*,
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(**Publ**.: Eales H. Causes of retinal hemorrhage associated with epistaxis and constipation. *Birmingham Med Rev* 1880; 9:262.

Eales H. Primary retinal haemorrhage in young men. *Ophthalmol Rev* 1882; 1:41.)

Eaton-Lambert syndrome see **Lambert-Eaton syndrome**

Ehrlich's finger test is an in vivo test to indicate hemolysis associated with biphasic cold hemolysin (**Donath-Landsteiner antibodies**). Technically, the patient's venously clogged finger is first placed in ice-cold water for 10 min and then in 40 °C water. If the capillary blood from the tip of the finger demonstrates a hemolysis in the serum, this indicates a positive reaction. In addition, phagocytosis of erythrocyte often can be visible in blood smear preparations.

Do not confuse with Ehrlich's test that is used to examine urine for the presence of urobilinogen; based on the use of Ehrlich's diazo reagent, it is a sodium *p*-diazobenzenesulfonate solution.

Paul Ehrlich see **Heinz bodies**

Ehrmann-Sneddon syndrome see **Sneddon's syndrome**

Elejalde syndrome (**Griscelli/Elejalde syndrome**, also known as "**Griscelli syndrome type 1**") is a rare autosomal recessive syndrome consisting of moderate pigment dilution, profound primary neurologic defects, hair with a metallic silvery sheen, and an increased susceptibility to bacterial infection. It is associated with MYO5A, a protein involved in the intracellular transport of vesicles, organelles, and protein complexes along the actin filaments. See more in **Griscelli syndrome.**

Elejalde syndrome should not be confused with another Elejalde syndrome also known as **acrocephalopolydactylous dysplasia**. Elejalde syndrome was first described in 1977 in 3 consanguineous families in Columbia.

Benigno Rafael Elejalde (***Benigno R. Elejalde***, ***Rafael B. Elejalde***) (March 7, 1943?–) is a Clinical Geneticist who graduated from the University De Antioquia, School of Medicine, Medellin, Colombia, in 1967. He has worked at the Wisconsin Clinical Genetics Center, Department of Medical Genetics and the University of Wisconsin Center for Health Sciences & Medical School in Madison. He also is affiliated with Aurora Sinai Medical Center, Aurora St Luke's Medical Center, and Wheaton Franciscan Healthcare St. Francis Hospital in Milwaukee.

Claude Griscelli see **Griscelli syndrome**

(**Publ**.: Elejalde BR, Valencia A, Gilbert EF. Neuro-ectodermal melanolysosomal disease: an autosomal recessive pigment mutation in man [abstr]. *Am J Hum Genet* 1977; 29:39A.)

Epstein's syndrome see **Révol's syndrome**

Epstein-Goedel syndrome see **Révol's syndrome**

Erasmus syndrome is a rare connective tissue disease which is characterized by the progressive systemic sclerosis with or without silicosis after the inhalation of silica or silicates containing mineral dust. It occurs usually after 15 years of initial exposure. It is associated with the development of other diseases, including pulmonary tuberculosis, lung cancer and autoimmune diseases. Crystalline silica is not only responsible for the development of silicosis but also may be associated with other autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis-Caplan syndrome, systemic sclerosis and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis. The rare occurrence of systemic sclerosis developing after silica exposure is termed Erasmus syndrome. Although not much is understood about the mechanisms by which silica exposure leads to the development of systemic sclerosis, it has been suggested that silica might induce the activation of the innate immune system with lung inflammation, activation of the adaptive immunity and generation of autoantibodies. In fact, it was shown that exposure to silica may be associated with a more than 3-fold increase in the relative risk of systemic sclerosis, while the absolute risk in the general population is less than 0.5%. This syndrome was named after the physician who first described 17 cases of systemic sclerosis in gold miners in South Africa in 1957. However, in 1914, Bramwel first reported an association between scleroderma and occupations associated with silica exposure (Bramwell B. Diffuse scleroderma: Its frequency; its occurrence in stonemasons. *Edinburgh Med J.* 1914; 12:387–401.) In 1957, Erasmus described a high prevalence of progressive systemic sclerosis in gold miners exposed to dust containing a high percentage of free silica compared with a large male non-mining hospital population. Devulder et al. suggested that the eponym "Erasmus syndrome" should be used when describing the co-existence of silicosis and progressive systemic sclerosis (Devulder B, Plouvier B, Martin JC, Lenoir L. The association: Scleroderma-silicosis or Erasmus' syndrome. *Nouv Presse Med.* 1977; 6:2877-287.)

L.D. Erasmus (Leslie D. Erasmus ?) - South African physician.

(**Publ**.: Erasmus LD. Scleroderma in goldminers on the Witwatersrand with particular reference to pulmonary manifestations. *S Afr J Lab Clin Med*. 1957; 3:209-231.)

Erdheim-Chester disease (**Erdheim-Chester syndrome**, polyostotic sclerosing histiocytosis) is a rare disease most commonly characterized by multifocal osteosclerotic lesions of the long bones demonstrating sheets of foamy histiocytes on biopsy with or without histiocytic infiltration of extraskeletal tissues. Histologically, Erdheim-Chester disease differs from **Langerhans cell histiocytosis** because it does not stain positive for S-100 proteins or Group-1 CD1a glycoproteins, negative for **Birbeck granules** on electron microscopy, however, the section is CD68+. Thus, the disease is considered one of the histiocytic diseases and is often described as a rare multisystem non-Langerhans cell histiocytosis.

Although the cause of the disease is unknown, recent findings suggest a neoplastic or "cancer-like" disorder, with more than 50% of patients testing positive for an activating point mutation of the BRAF isoform of RAF (BRAF V600E). Chronic,

uncontrolled inflammation is also a significant component of the disease process. There has been an ongoing discussion as to whether **Erdheim-Chester disease** is a cancer or an autoimmune disorder. Some studies, however, demonstrated inducible production of TNF-α, spontaneous secretion of IL-6 and CXCL8/IL-8, known to attract monocytes and polymorphonuclear cells; increase in the serum levels of IL-12, IFN-α, but not IFN-y; decrease in serum IL-4 and cellular infiltration by Th-1 lymphocytes histiocytes expressing CXCL10/IP-10 and IL-1. Subsequent studies demonstrated this to be significant in untreated ECD patients compared with controls.

The first cases were reported as "lipid granulomatosis" by ***William Chester***. In 1930, while completing a fellowship with the Austrian pathologist ***Jakob Erdheim***, the US physician (future cardiologist) William Chester, published the clinical and pathologic findings of 2 patients who he believed had a distinctive lipidosis not previously described. The eponym Erdheim-Chester was coined later, despite the fact that Chester, who then worked in a pathological institute in Vienna, was the sole author. In 1972, Jaffe reviewed the findings of Chester's original patients and reported on a patient of his own. He postulated that these patients represented the same histiocytic disorder and coined the eponym **Erdheim-Chester disease**. Jaffe described the disease as a rare histiocytic disorder of adults characterized by an infiltrate of lipid-laden macrophages, multinucleated giant cells, inflammatory infiltrate of lymphocytes and histiocytes in the bone marrow, and a generalized sclerosis of the long bones sparing the epiphysis.

Jakob Erdheim (May 24, 1874–Apr 18, 1937) was a Jewish-Austrian pioneering neuroendocrinologist and cranial pathologist. He was born in Boryslaw, Galicia, a region of the former Austro-Hungarian Empire (now Ukraine), obtained his medical degree at the School of Medicine in Vienna in 1900, and the same year decided to join the Pathological-Anatomical Institute of the Vienna General Hospital. From 1901 to 1923, he worked as an assistant, professor, and chief at the Institute of Pathological Anatomy in Vienna. In 1923, Erdheim was appointed chief pathologist (chairman) of the pathologic–anatomical institute at the Vienna Municipal Hospital, Lainz, and he remained in this position until his death. Now this is The Jakob-Erdheim Institute of Pathology at Vienna.

Erdheim was well known as a skilled and prestigious pathologist in Vienna, in possession of an encyclopedic knowledge in his area of expertise. "Quite simply, he knew more about human disease than any other living man" was an evaluation of him given by Fuller Albright, a very well-known US physician and endocrinologist. Erdheim's brilliant teaching skills, knowledge, and enthusiasm attracted a lot of young researchers and students. Many of them thus began their research studies and scientific career in Vienna. One was ***William Chester***, the US clinician who later in 1931 defined a rare type of histiocytosis, which was then termed by H. Jaffe the "Erdheim-Chester disease."

Jakob Erdheim's life as a pathologist was somehow secluded and private. He was never married, had few close friends, and lived in a room at his hospital. He was hospitalized with typhoid fever and tuberculosis and recovered, but none of his students or colleagues knew about this. He died unexpectedly when he was alone in his room because of a former but unidentified cardiac failure in 1937.

He was never politically active, but with growing anti-Semitism, he experienced some problems during his academic career. He was quite wealthy because his family he had received oil-rich land in Galicia. Erdheim used part of his inheritance to establish a pathological institute in Tel Aviv. He was a Jew and knew about Nazi expansion from Germany to other countries. Therefore, just a few months prior to his death and a year before the Viennese Anschluss—annexation of Austria by Germany and incorporation of German anti-Jewish legislation into Vienna and Austrian territories when many people were killed by the Nazis—he was able to send his entire collection of unique pathological specimens hidden in a rug to the US. After his death, Ernst Freund, his friend and student, rescued most of the manuscripts, illustrations, and other materials saved by Erdheim to document his work and findings. Freund moved from Vienna to Florence and then to the US.

William Chester (1903–1974) was a US clinician.

(**Publ**.: Chester W. Über lipoidgranulomatose. *Virchows Arch Pathol Anat Physiol Klin Med* 1931; 279(2):561–602.)

Eustachian tonsil (tubal tonsil) is a mass of lymphoid tissue at the pharyngeal opening of the eustachian tube. The tubal tonsils are a collection of lymphoid nodules in the mucous membrane located at the roof of the nasopharynx near the opening of the middle ear tube. They are bilateral. See also **Gerlach tonsil** and **Waldeyer's ring**.

Bartolommeo E. Eustachio (***Eustachi***, ***Eustachius***) (c.1500–1510–Aug 27, 1574) was an Italian anatomist. He was born in San Severino, a little town situated in the center of Italy, to Mariano, a physician, and Francesca (Benvenuti) Eustachi. Bartolommeo had a good humanistic education and gained such an excellent knowledge of Greek, Hebrew, and Arabic that he was able to edit the Hippocratic glossary of *Erotian* (1566) and has made his own translations of *Avicenna* (Ibn Sīnā) from the Arabic. He appears to have studied medicine at the Archiginnasio della Sapienza in Rome. He was then invited to be a physician first to the Duke of Urbino, and then, in 1547, to the duke's brother, Cardinal Giulio della Rovere.

He was Professor of Anatomy at the School of Medicine in Rome. During 1562–1563, he conducted a few series of investigations of the kidney, ear, nerves, and teeth, and many of his studies were the first in the field. Eustachius also documented the adrenal glands (1563). He also is known for a series of extraordinary drawings of 47 anatomical features. Eustachius died in Fossombrone, Central Italy.

(**Publ**.: Eustachio B. The opuscula anatomica (Venice, 1564); reprinted in Leiden in 1707, and in Delft in 1726.

Eustachio B. The tabulae anatomicae (Rome, 1714); republished in Amsterdam in 1722.)

Evans's syndrome (**Evans syndrome**) is a rare autoimmune disease where autoantibodies (i.e., antiplatelet and hemolytic antibodies) destroy patient's red blood cells and platelets. Its overall pathology resembles a combination of autoimmune hemolytic anemia and immune thrombocytopenic purpura. Nevertheless, the exact pathophysiology is unknown. Autoantibodies targeted at various antigenic determinants on red blood cells and platelets are assumed to cause isolated episodes of hemolytic anemia and thrombocytopenia, respectively. **Evans syndrome** may occur by itself as a primary (idiopathic) disorder or in association with other autoimmune disorders or lymphoproliferative disorders as a secondary disorder. Secondary Evans syndrome can be associated with other disorders, including autoimmune lymphoproliferative syndrome, lupus, antiphospholipid syndrome, **Sjogren's syndrome**, common variable immunodeficiency, IgA deficiency, certain lymphomas, and chronic lymphocytic leukemia.

In a pediatric cohort, inborn error of immunity (IEI) and specifically primary immunoregulatory disorders (PIRD) play a significant role in the development of autoimmune cytopenias. Recent studies have revealed several pathogenic variants on *CTLA4*, *LRBA*, *STAT3*, and *KRAS* genes in children with Evans syndrome and have discovered an inherent genetic defect in 65% of cases. Similar results were reported where 45% of the cases were observed to have an underlying genetic defect on *FAS*, *TNFSF13B*, *CASP10*, *ADA2*, *LRBA*, *CTLA4*, *CARD11*, *STAT3*, *IKBGK*, and *LIG4* genes. The syndrome was first described in 1951 by ***Robert Evans*** and colleagues.

Robert S. Evans (May 29, 1912–Sept 25, 1974) was a US physician. He graduated from the Harvard University Medical School in 1934. From 1941 to 1951, he was Professor at the Stanford University School of Medicine. From 1951 on, he was Chief of Medicine at the Seattle Veterans Administration Hospital and the Department of Medicine at the University of Washington School of Medicine. He retired at 62 and was killed in a 3-car collision 2 months later. He was well known for research contributions in hematology.

(**Publ**.: Evans RS, Takahashi K, Duane RT, Payne R, Liu C. Primary thrombocytopenic purpura and acquired hemolytic anemia: evidence for a common etiology. *AMA Arch Intern Med* 1951; 87(1):48–65.)

Letter F



Farr method (**Farr assay**, **Farr immunoprecipitation assay**) quantifies the antidouble-stranded DNA (anti-dsDNA) antibodies—that is, antinuclear antibodies (ANA). It measures the capacity of radiolabeled antigen to bind with antibody. Between 60% and 80% of patients with systemic lupus erythematosus (SLE) have circulating antibodies to dsDNA at some time during their illness, and the Farr assay is considered to be the most specific method for detecting these ANA.

The best method for detecting anti-dsDNA remains controversial. The techniques most commonly used for this purpose are enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence using the hemoflagellate *Crithidia luciliae* (CLIF), and the Farr immunoprecipitation radioimmunoassay. The most common ELISA and CLIF identify autoantibodies with both high or low avidity. The **Farr assay** is quite specific and well documented and uses a step of ammonium sulfate precipitation of antigen–antibody complexes (formed if the sera contains antibodies to dsDNA) at high salt concentrations because this condition allows dissociation of dsDNA-anti-dsDNA complexes of low avidity. Therefore, Farr assay detects only antibodies with high avidity including both IgG and IgM antibody. High-avidity anti-dsDNA antibodies are more specific for SLE than those with low avidity and have high predictive value for the development of SLE. Thus, the Farr assay is used as a prognostic test for overall disease activity, as well as certain organ-specific involvement. For instance, marked increase in dsDNA autoantibody concentrations in serums confirms the diagnosis of SLE: Doubling the level of dsDNA autoantibody or levels higher than 30 IU/mL in less than 10 weeks are reliably predictive of aggravations of SLE.

Richard S. Farr (Oct 20, 1922–May 21, 1997) was a US physician and clinical scientist. He completed his MD degree at the University of Chicago in 1946 and interned at the Naval Medical Research College. Farr spent a big part of his career at the University of Chicago, where he served as Head of the Section of Clinical Immunology. He also devoted 7 years to the Scripps Clinic and Research Foundation,

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La Jolla, CA, first as Head of the Division of Allergy, Immunology, and Rheumatology and then as Chairman of the Department of Medicine. In 1969, Farr went to Denver as Head of Allergy and Immunology and later as Chairman of the Department of Medicine at National Jewish Health in Denver from 1969–1977.

Farr was a prominent scientist and physician. As a researcher, he was the first to realize that lymphocytes recirculate. Still, he is most known for the development of a precise assay for detecting an antibody reaction with an antigen, a method used later to measure levels of a given antigen or antibody in biological fluids. This method, which is known as the "Farr assay," was essential to the progress of quantitative immunology and set the basis for development of a radioimmunoassay—a technology that earned its inventors a Nobel Prize. As a physician, Dr. Farr was a skilled practitioner known for his kindness, integrity, and loyalty. He had a unique ability to understand the strengths and weaknesses of his patients and to use this understanding for the best treatments. Farr had a turn of phrase, which was suggestive of Will Rogers. He used this in his lectures explaining the states of mind of his patients categorized, for instance, as "Humpty Dumpty" or "Eeyore." He coined the term "twitchy lung" to refer to the lungs of asthmatic patients. He had a 48-h rule—a specific time-out to be used before responding to any particularly annoying situation.

Among Farr's many achievements were presidency of the Academy of Allergy and Clinical Immunology in 1969–1970, receipt of the Distinguished Service Award from the University of Chicago in 1975, and an Honorary Fellowship from the Canadian Society of Allergy and Immunology. Furthermore, in his honor, a lectureship at the American Academy of Allergy and Clinical Immunology is given each year.

(**Publ**.: Wold RT, Young FE, Tan EM, Farr RS. Deoxyribonucleic acid antibody: A method to detect its primary interaction with deoxyribonucleic acid. *Science* 1968; 161(3843):806–807.)

Felix's reaction see **Weil-Felix test**

Felty's syndrome (**Felty syndrome**) is an atypical form of rheumatoid arthritis (RA) with fever, splenomegaly, and leukopenia and, in some cases, anemia and thrombocytopenia. The syndrome is more often seen in females, Caucasians, and 50–70-year-old people. It also appears in people who suffer from prolonged rheumatoid arthritis. Many patients suffer from swollen, stiff, and painful joints of the arms, hands, and feet. They are also more vulnerable to certain infections because of neutropenia. Keratoconjuntivitis sicca because of secondary **Sjogren syndrome** also has been detected in some patients. The etiology of Felty syndrome is still unclear. Soluble serum HLA-DR4 was detected in some patients. Because immunosuppressive therapy for rheumatoid arthritis commonly recovers granulocytopenia and splenomegaly, it supports the view that Felty's syndrome is an immune-mediated disease. **Still disease** or syndrome, also is called **Still-Chauffard-Felty syndrome** in its juvenile form.

It is named for ***Augustus Roi Felty***, who described his patient in 1924. The eponym Felty's syndrome was established by Hanrahan and Miller when they described a case in the *Journal of the American Medical Association* in 1932.

Augustus Roi Felty (Aug 27, 1895–Feb 4, 1964) Augustus Roi "Bus" Felty was a US physician. He was born in Abilene, KS, where his father, John Wellington Felty, and his uncle were in general practice. He entered Yale College in 1912, intending to become an academic in classical languages, Greek, and Latin. After hearing Sir William Osler lecture, however, he changed plans. He graduated from Yale in 1916, and then commenced studying medicine at Johns Hopkins Medical School. During his residency in medicine at Johns Hopkins Hospital, Baltimore, from 1922 to 1924, he observed a patient with arthritis, splenomegaly, and leukopenia, and recognized that this was an unusual disease picture. Felty also published a few papers on infectious diseases and epidemiology, but took over his father's practice in Hartford, CT, where he remained until he retired in 1958.

(**Publ**.: Felty AR. Chronic arthritis in the adult, associated with splenomegaly and leucopenia. A report of 5 cases of an unusual clinical syndrome. *Bull Johns Hopkins Hosp* 1924; 35:16.)

Fiessinger-Leroy disease see **Reiter's syndrome**

Fiessinger-Leroy-Reiter disease see **Reiter's syndrome**

Fiessinger-Rendu syndrome see **Stevens-Johnson syndrome**

Fisher syndrome see **Miller-Fisher syndrome**

Flajani's disease see **Graves's disease**

Flajani-Basedow syndrome see **Graves's disease**

Forssman antigen is an antigenic constituent occurring in animals without regard to biological relationship—a heterophile antigen. This antigen is present in a variety of species but not in all. Species, therefore, can be categorized into Forssman-positive or -negative, depending on the antigen expression. The mouse and dog can be classified as Forssman-positive, while humans and other anthropoid apes are Forssman-negative because primates lack Forssman synthase activity and have naturally occurring **Forssman antibodies** in plasma.

The Forssman antigen can be detected in nonmammal species as well. For instance, it was found in turtles, chickens, and carps but not in pigeons, frogs, and geese. In spite of the fact that the **Forssman antigen** was originally documented on sheep red blood cells, its expression on erythrocytes is uncommon and is usually restricted to various tissues. Expression of Forssman antigens in distinct cells was relatively well documented in mice. For example, dendritic cells and macrophages localized around the microvessels express it, but no expression was detected on

endothelial cells, pericytes, fibroblasts, myocytes, and neural cells. Interestingly, in chickens, both erythrocytes and tissue cells express the Forssman antigen. Tissue-specific expression of the Forssman antigen also was observed in other Forssman-positive mammals.

The Forssman heterophilic glycolipid antigen has structural similarity to the histoblood group A antigen. In nonprimates, the Forssman antigen is synthesized by Fs synthase (i.e., globoside 3-α-*N*-acetyl-D-galactosaminyltransferase, EC2.4.1.88), an enzyme homologous to the ABO transferase. Some findings qualify Forssman antigen as a new histoblood group system with potential implications for both transfusion/transplantation medicine and pathogen susceptibility.

In 1911, ***John Forssman*** discovered that rabbits injected with a suspension of kidney tissue from guinea pig or horse, but not from cow or rat, produced antibodies that caused hemolysis of sheep erythrocytes in the presence of complement. The heterophilic antigen on sheep erythrocytes was later named as the Forssman antigen for its discoverer.

Magnus John Karl August Forssman (Nov 22, 1868–Mar 12, 1947) was a Swedish bacteriologist and pathologist. He was born in Kalmar, a city in the south-east of Sweden. He obtained his medical education at the University of Lund. Later, he was Professor of General Pathology, Bacteriology and Public Health Science at the same University and a director of the university hospital from 1927 to 1930. He is remembered for his description and characterization of the "Forssman antigen" and his name also is associated with the following terms: "Forssman antibody" (heterophile antibody) and "Forssman reaction" or "Forssman antigen–antibody reaction."

(**Publ**.: Forssman J. Die herstellung hochwertiger spezifischer schafhämonysine ohne verwendung von schafblut. Ein beitrag zur lehre von heterologer antikörpebildung. *Biochem Z* 1911; 37:78–115.)

Franklin's disease (**Franklin disease**), also known as a gamma-heavy chain disease, is a very rare B-cell/lymphoplasma cell proliferative disorder with less than150 cases reported in the literature. It is characterized by lymphadenopathy, fever, anemia, malaise, hepatosplenomegaly, and weakness. The fever is considered secondary to impaired cellular and humoral immunity, and thus recurrent infections are the common clinical presentation in Franklin disease. The most distinctive symptom is palatal edema, caused by nodal involvement of **Waldeyer's ring**. Exact etiology and all pathogenic pathways of **Franklin's disease** is still not well understood. Autoimmune symptoms, however, are displayed by almost 30% of affected patients. This includes, but is not limited to, symptoms of rheumatoid arthritis (the most common condition), systemic lupus erythematosus, vasculitis, Sjögren syndrome, and myasthenia gravis. Autoimmune cytopenias, like idiopathic thrombocytopenic purpura, also may be associated with gamma-heavy chain disease. Appearance of autoimmune diseases and symptoms is commonly seen many years prior to the diagnosis of gamma-heavy chain disease. The link between Franklin disease and autoimmune diseases may be explained by somatic hypermutation or preceding

immunosuppressive therapy. In fact, almost 90% of patients with Franklin disease have confirmed systemic or localized lymphoplasmacytic malignancies.

Franklin's disease belongs to the 3 known forms of the heavy-chain diseases (HCD). They are all B-lymphocyte/plasma cell proliferative disorders identified by the presence of physically unfinished, atypical heavy chains of immunoglobulins, which cannot bind light kappa (κ) or lambda (λ) chains. This is the outcome of genetic mutations—insertions or deletions, which often cause damage or loss of a fragment of the constant-1 (CH1) domain of the heavy-chain molecule; this is needed for interaction and binding with the light chain. The effects on the variable (V), diversity (D), and joining (J) regions are not constant.

The HCD are categorized based on the affected classes of immunoglobulin. α-HCD (IgA), γ-HCD (IgG) (Franklin's disease), and μ-HCD (IgM) have been identified, and incidences vary from rare to very rare. Still, clinical cases of ε-HCD (IgE) or δ-HCD (IgD) have not yet been described. α-HCD is normally identified as an extranodal marginal-zone lymphoma of the mucosa-associated lymphoid tissue (MALT) and can be classified as a type of MALT lymphoma. It is the only HCD variant that may transform into diffuse large B-cell lymphoma. μ-HCD are clinically similar to chronic lymphocytic leukemia or small-cell lymphoma. Clinical cases of γ-HCD are histomorphologically variable; some tumors look like extranodal MALT lymphoma or splenic marginal-zone lymphoma, whereas other cases resemble lymphoplasmacytoid lymphoma (LPL). ***Edward C. Franklin*** first described the disease in 1964.

Edward C. Franklin (Apr 14, 1928–Feb 20, 1982) was a US immunologist and clinician. He, the only child in a Jewish family of a prosperous attorney and his wife (then ***Freundlich***), was born in Berlin, Germany. The family did not flee Germany until late 1938, likely reflecting the ambivalence well-assimilated German Jews felt about leaving their homeland. After an enforced 15-month stay aboard a ship in Cuba, they were finally able to emigrate to New York City in 1940.

Franklin graduated from Townsend Harris High School at the age of 15, got a full scholarship at Harvard University, and graduated as a biochemistry major at the age of 18. He obtained his medical education from New York University in 1950. A year each of internship at New York's Beth Israel Hospital and residency in internal medicine at Montefiore Hospital were followed by 2 years of military duty and then completion of his residency at the Bronx Veterans Administration Hospital. Then, Franklin was recruited to Henry G. Kunkel's laboratory at the Rockefeller Institute for Medical Research. Kunkel's enthusiasm for newly initiated studies on antibodies and multiple myeloma persuaded Franklin to work in those areas. His early work in the laboratory involved the relationship between the high- and low-molecular weight antibodies and the nature of the autoantibody-like factors seen in patients with rheumatoid arthritis (rheumatoid factor, RF). Franklin isolated and characterized the RF as an antibody. His work led to new insights into the mechanism of rheumatoid arthritis.

Other famous investigations, after he became independent, dealt with the myeloma proteins, structural differences between human IgA1 and IgA2

immunoglobulins, description of the disulfide connections in various antibody types, and the unusual hinge region of IgG3. Franklin is highly recognized for his distinguished accomplishments in the characterization of mixed cryoglobulinemia, heavy-chain disease, and amyloid proteins; he published 250 papers. He considered the one who discovered the heavy-chain diseases, which was he main force of his clinical research; and he defined it in a brief autobiography he wrote for his election to the National Academy of Sciences in 1980.

Franklin was diagnosed with glioblastoma at the end of 1980, and his wife, Dorothea Zucker-Franklin, had to present his talk on heavy-chain diseases at The Harvey Society meeting on November 19, 1981, with Franklin in the audience. He died 3 months later. Dorothea Zucker-Franklin was Franklin's collaborator on several programs and is well known as a pioneer and proponent of the use of electron microscopy in hematological research.

Franklin was a calm and not public person without common excitement episodes known to his wife. In early years, the Zucker and Freundlich families lived in Berlin in nearby houses and met again after emigration from Germany right prior to the World War II, with the Zuckers' escaping through the Netherlands and Freundlichs' through Cuba. By remarkable luck, the parents met once again in 1952 while on vacation in Lake Placid. To their surprise, they realized that again they resided very close to each other in Forest Hills, New York. Edward and Dorothea had a blind date, which she recalled as "a bore." Still, the mutual interests developed into a happy marriage. Truly, they had to prepare2 separated offices in their house because being together with nonstop discussions did not give them a chance to complete their work. In 1957, the Franklins bought a nice farm in the Berkshires, the western parts of Massachusetts, and many friends were invited there for weekends. There was a large garden with apple trees, and almost 50 gallons of the cider was prepared every year, which created a beloved memory for visiting friends and colleagues.

Franklin was Professor of Medicine at the New York University School of Medicine and Director of the Irvington House Institute and was a member of the National Academy of Sciences. He also participated in many study sections and councils of the National Institutes of Health and advisory boards of several research foundations. He was on various editorial boards and was a member of diverse professional societies and served as a president of the Council of the American Society for Clinical Investigation in 1972–1973. The Edward C. Franklin Award, which is given for achievements in immunology, was established in his name. *The New York Times* called Franklin "an international authority on the human immune system."

(**Publ**.: Franklin EC, Lowenstein J, Bigelow B, Meltzer M. Heavy chain disease—a new disorder of serum gamma-globulins: Report of the first case. *Am J Med* 1964; 37:332–50.)

Frei's antigen is an antigen produced with pus from patients with lymphogranuloma inguinale. The Frei antigen is usually a sterile preparation of inactivated *chlamydiae* from domestic fowl. It is common to all chlamydial species and is not specific to lymphogranuloma venereum. During 1930s and 1940s, the Frei test

antigen prepared from human pus was not readily available because cases of lymphogranuloma venereum with fluctuant inguinal buboes were infrequent even in large venereal disease clinics. Thus, 3 other sources of antigen were recognized: (1) pus aspirated from the inguinal bubo of a patient with early lymphogranuloma venereum, (2) macerated material from diseased glands, and (3) emulsions of the brains of mice intracerebrally infected with virus. The mouse brain antigen was first described by Grace and colleagues (Grace et al., 1940). Other sources of antigen also have been explored, most deriving from various tissues of mice infected with *Chlamydia*. In addition, a heat-inactivated lymphogranuloma venereum specimen, grown in yolk sac of embryonated egg, is injected intradermally on the forearm and a control material is prepared from noninfected yolk sac on the other forearm—that is, a control.

The **Frei antigen** was used in the **Frei's test**. Previously, the it was the only method available to identify a chlamydial infection, but now it represents only an historical interest. The test was based on a positive-hypersensitivity reaction after an intradermal standardized-antigen injection of Frei's antigen, which indicated past or present chlamydial infection. Commercial manufacturing of Frei antigen was discontinued in 1974.

Wilhelm Siegmund Frei see **Frei's test**

Frei's test (**Frei test**, **Frei skin test**, **Frei-Hoffmann reaction**, **Frei-Hoffman reaction**) was developed in 1925 by ***Wilhelm Frei*** to identify lymphogranuloma inguinale (lymphogranuloma venereum caused by the invasive *Chlamydia trachomatis*). Antigen (**Frei's antigen**) made from sterile pus aspirated from previously unruptured abscesses, produced a reaction in patients with lymphogranuloma inguinale when injected intradermally. After 48–72 h, an inflammatory nodule more than 6 mm in diameter develops at the test site. A positive-delayed type reaction is not diagnostically specific for lymphogranuloma venereum and is used rarely. The test, thus, is no longer used but stands as a milestone to understanding of immunological reactions. Today, mostly it has been replaced by electromicroscopy, indirect fluorescence, or molecular tests (e.g., RT-PCR and others).

Wilhelm Siegmund Frei (Sept 5, 1885–Jan 27, 1943) was a German-Jewish dermatologist. He was born in Neustadt, Upper Silesia (presently Poland). His father, Emil Frei, was a director of a mining company and was from Neustadt also and his mother, Frederika Ring, came from Austria. Frei had 2 sisters—Josephina and Gerta (likely killed by Nazis). Frei got his education in Freiburg and Breslau and finished his doctorate thesis in Göttingen in 1913. He met his future wife Magda Frankfurter when they studied medicine in Freiburg, and they were married in 1912. He finalized his training and examinations in dermatology in 1923.

In 1926, Frei was appointed Extraordinary Professor at the Berlin-Spandau Municipal Hospital. In 1929, he became a head physician at the Department of Dermatology in the Berlin-Spandau Municipal Hospital. He also practiced at the University Medical Polyclinic and University Skin Clinic in Breslau, Robert Koch Institute in Berlin, and Institute of Hygiene in Göttingen. Frei devoted his efforts to

the study of allergic skin diseases, experimental syphilis, and lymphogranulomatosis inguinalis.

Because of the rise of the Nazis, Frei immigrated to the US with his family in 1937, where he worked as a resident physician in dermatology at the Montefiore Hospital, Bronx, New York, until he fell ill and died, leaving behind his wife and 3 children.

Freidrich Hoffmann

(**Publ**.: Frei WS. Eine neue hautreaktion bei "lymphogranuloma inguinale." *Klin Wochenschr*, Berlin. 1925; 4:2148–2149.)

Frei-Hoffmann reaction see **Frei's test**

Freund's adjuvant is one of the most commonly used adjuvants in research. It is used as a water-in-oil emulsion and prepared from nonmetabolizable oils (e.g., paraffin oil and mannide monooleate). If it also contains killed, dried mycobacteria (usually *Mycobacterium tuberculosis*), it is known as Complete Freund's Adjuvant. Without the bacteria, it is Incomplete Freund's Adjuvant. Basically, Freund's adjuvant is a solution for injecting antigen emulsified in mineral oil and used as an immunopotentiator to enhance the immune response to the immunogen.

Freund's adjuvants are irreplaceable components of induction protocols of many experimental animal models. Elements of the adjuvant are ingested by the professional antigen-presenting cells (e.g., dendritic cells and macrophages), causing activation of phagocytosis, expression of cytokines and chemokines by polymorphonuclear leukocytes, and consequent activation and proliferation of T-helper cells. The mycobacterial parts of **Complete Freund's Adjuvant** support Th1-cell differentiation and thus initiation of a robust delayed-type hypersensitivity (DTH) reaction. Without mycobacteria components, T cells differentiate toward Th2 phenotype-stimulating B cells for production of antibodies. The mycobacterial elements also are responsible for several week-long regulations of hematopoiesis pathways, resulting in a marked formation of $CD11b^+$ (Mac-1or Macrophage-1 antigen) immature myeloid cells. These cells, including $CD11b^+Gr\text{-}1^+$ cells, are known to be involved in various pathogenetic mechanisms of numerous diseases or tolerogenic pathways (i.e., regulatory myeloid cells). Consequently, in the models of experimental autoimmune diseases, Complete Freund's Adjuvant induced both stimulation of innate immune cells in the early induction phase and effector and regulator cells in the late phase.

Freund's adjuvant is forbidden for use in humans because of its toxicity. Existing regulatory guidelines also limit its use in animal studies because of associated painful responses and the possibility of tissue and organ injury. Complete Freund's Adjuvant should be administered subcutaneously or intraperitoneally in animals if approved because intradermal injections often result in skin damage, ulceration, and necrosis. Intramuscular administration of Complete Freund's Adjuvant can cause temporary or permanent muscle lesions, whereas intravenous injections can induce lipid embolism in the lung. It is named after ***Jules T. Freund***.

Jules (Julius) Freund (Jun 24, 1890–Apr 22, 1960) was a Hungarian-born US immunologist, most famous for the Freund's adjuvant. He was born to a Jewish family in Budapest and studied at the Royal Hungarian University. After receiving the MD degree at the age of 23, he served as a medical intern in the Austrian Army and was attached to the Department of Hygiene at the University as an assistant. Following the outbreak of war in 1914, he returned to the University in Budapest as the army's Commissioner for Hygiene. He then held the position of Assistant Professor in Preventive Medicine.

In 1922, Freund went to Hamburg to work at the Department of Hygiene at the Medical School. He received a fellowship to go to Harvard University's Antitoxin and Vaccine Laboratory in Boston. Then, he was offered a full-time position as a bacteriologist in Asheville, NC, at the Laboratory for Tuberculosis, and 2 years later he moved to the Henry Phipps Institute in Philadelphia. In 1932, 6 years later, he moved to the Department of Pathology at Cornell Medical College in New York. In 1938, Freund became an Assistant Director of the Department of Health in New York City and spent several years in Otisville, NY, supervising the production of biologicals at the farm maintained by the City's Department of Health. After formation of the Public Health Research Institute in New York City in 1943, Freund assumed the position of Chief of the Division of Applied Immunology. In 1956, he became a Chief of the Laboratory of Immunology at the National Institute of Allergy and Infectious Diseases in Bethesda, MD.

Freund also was involved in improvements in the annual programs of the American Association of Immunologists; for several years, he was Secretary-Treasurer, Councilor, and President of the American Association of Immunologists. He served on the editorial board of the *Journal of Immunology* and several other journals and was Chairman of the Board of the Federation of American Societies for Experimental Biology. Public recognition of his services to immunology came in the form of a special citation and a scroll presented in June 1959 by the Allergy Foundation of America. In October of the same year, he received the distinguished American Public Health Association–Albert Lasker Award for achievements in medical research.

(**Publ**.: Freund J, Casals J, Hosmer EP. Sensitization and antibody formation after injection of tubercle bacilli and paraffin oil. *Pros Soc Exper Biol Med* 1937; 37:509–513.

Opie EL, Freund J. An experimental study of protective inoculation with heat killed tubercle bacilli. *J Exper Med* 1937; 66:761–788.

Freund J, Opie EL. Sensitization and antibody formation with increased resistance to tuberculous infection induced by heat killed tubercle bacilli. *J Exper Med* 1938; 68:273–298.)

Fuchs' syndrome see **Stevens-Johnson syndrome**

Letter G

Gänsslen-Erb syndrome see **Minkowski-Chauffard disease**

Gaucher's disease (**Gaucher disease**) is a rare genetic disorder characterized by the deposition of glucocerebroside in cells of the macrophage–monocyte system seen as accumulation of the fatty materials in the spleen, liver, lungs, bone marrow, and brain. The disorder results from enzyme glucocerebrosidase deficiency. It is the most widespread of the inherited lysosomal storage diseases, and it is also the most common genetic disease affecting Ashkenazi-Jewish people (i.e., Eastern, Central, and Northern European ancestry).

There are three clinical subtypes of **Gaucher disease**. Type 1, the most common form, causes liver and spleen enlargement; bone pain and broken bones; and, sometimes, lung and kidney problems. It does not affect the brain and can occur at any age. The first category is called type 1 (or nonneuropathic). Symptoms may begin early in life or in adulthood. People in this group usually bruise easily because of few blood platelets and experience fatigue caused by anemia. Type 2, which causes severe brain damage, appears in infants; most who have it die by age 2. With type 3, there can be liver and spleen enlargement, and the brain is affected gradually. This type usually starts in childhood or adolescence. Diagnosis can be confirmed through measurement of glucocerebrosidase activity in the peripheral blood leukocytes.

The disease is named after ***Philippe Gaucher***, who originally described it in 1882; while still a student, he discovered the disease in a 32-year-old woman who had an enlarged spleen. This case was explained in his doctoral thesis. Gaucher accurately depicted progressive splenomegaly accompanied by weakness, weight loss, bleeding gums, and bloody nose. Morphological microscopic analysis of a spleen specimen revealed infiltration by irregularly shaped large cells (now known as **Gaucher cells**). Summarizing the clinical and laboratory data, Gaucher concluded that the woman presented with a rare form of spleen cancer. These findings were published in his doctoral thesis "De l'epithelioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie."

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No additional cases of Gaucher disease were reported for more than 10 years until several clinical instances documented similar patients' characteristics in 1895. As a result, a distinct disorder, initially reported as "splenomegaly of the Gaucher type," was proposed. In addition, it has been recognized that the disease can be seen in a few members of a family and that both adults and children may suffer from this disease. In 1965, Roscoe Brady and his colleagues determined the biochemical basis of Gaucher disease.

Philippe Charles Ernest Gaucher (Jul 26, 1854–Jan 25, 1918) was a French dermatologist born in the district of Nièvre. He received his medical doctorate in 1882 and during the subsequent years was an instructor at several hospitals in Paris. He taught classes on pathological anatomy, bacteriology, and histology, as well as dermatology. In 1902, he became Chair of Dermatology and Syphilography. Although Philippe Gaucher is well known for his discovery of Gaucher disease, his clinical studies and published papers focused on a variety of clinical diseases in several areas, including pathological anatomy, histology, dermatology, bacteriology, and sexually transmitted diseases. In Paris, he was known as an excellent and knowledgeable lecturer and established a medical journal on venereal disease. Gaucher was an active member of a number of French medical societies, including the Anatomical Society, Association for the Study of Cancer, the Society of Tropical Medicine, and the Academy of Medicine. In 1917, he was awarded the most prestigious honor in France—the Legion of Honour.

(**Publ**.: Gaucher PCE. De l'epithelioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie [Academic Thesis]. Paris; 1882.)

Gaucher cells are large, finely and uniformly vacuolated ones derived from the reticuloendothelial system and mainly are found in the spleen, lymph nodes, liver, and bone marrow of patients with Gaucher disease.

pseudo-Gaucher cells are plasma cells, microscopically resembling a Gaucher cell and, in some cases, are found in the bone marrow of multiple myeloma patients.

Gänsslen-Erb syndrome see **Minkowski-Chauffard disease**

Gee's disease see **Gee-Herter-Heubner disease**

Gee-Herter's disease (**Gee-Herter disease**) see **Gee-Herter-Heubner disease**

Gee-Herter-Heubner disease (**Gee's disease**, **Gee-Herter's disease**, **Gee-Herter disease**, **Heubner-Herter disease**, celiac/coeliac disease) is a chronic autoimmune inflammatory disorder that primarily affects the small intestine. Celiac disease affects ~1% of the population, making it one of the most common gastrointestinal disorders. Celiac disease is caused by a reaction to gluten found in wheat and in other grains (e.g., barley and rye). Gliadins and glutenins are the two main components of the gluten fraction of the wheat seed. There are three main types of gliadin

(i.e., α, γ, and ω) to which the body is intolerant in celiac disease. Gliadin proteins have the ability to provoke an autoimmune enteropathy caused by an abnormal immune response in genetically susceptible individuals. Specific amino acid sequences within the gliadin proteins are responsible for this activity.

The risk of developing celiac disease is increased by certain variants of the *HLA-DQA1* and *HLA-DQB1* genes. In it, the villi of a small intestine become shortened and eventually flattens out. Intestinal damage causes diarrhea and poor absorption of nutrients, which may lead to weight loss. Abdominal pain, swelling (distention), and food intolerances are common in celiac disease. Inflammation associated with the disease could lead to an increased risk of developing certain gastrointestinal cancers (e.g., cancers of the small intestine or esophagus). The antiendomysial antibody is a highly specific and sensitive test for celiac disease. These antibodies have been shown to recognize the noncollagenous extracellular matrix protein made by fibroblasts and can be detected on monkey esophageal tissue slides.

In 1997, it was discovered that the antigen against which endomysial antibodies were being formed was the enzyme tissue transglutaminase, which converted glutamine on tissue proteins to glutamic acid. Thus, the antitissue transglutaminase IgA (or IgG) autoantibody test is a common serological one for diagnosing celiac disease. An antideamidated gliadin peptide antibody test (IgA and IgG) is the latest generation serologic test to be used as the primary screening test. Interestingly, an estimated 2% of people with celiac disease also have selective IgA deficiency. The only available treatment for celiac disease is a strict gluten-free diet in which the affected person does not ingest any gluten.

Samuel Gee gave the first modern-day description of celiac disease in a lecture at the Hospital for Sick Children, London, in 1887. His interest in the history of medicine and the ability to read ancient Greek support the notion that Gee was familiar with the work of Aretaeus of Cappadocia (Ἀρεταῖος, AD 250), who first described "coeliac affection" or "coeliac diathesis." Gee's account is published in the St. Bartholomew's Hospital Reports of 1888, but it was not Aretaeus but Samuel Gee who for the first time observed that this celiac affection was "a kind of chronic indigestion which is met with in persons of all ages" and that it was "especially apt to affect children between 1 and 5 years old."

Gee also theorized on the importance of diet in its control. His contribution led to the eponym **Gee's disease**. ***Christian Herter***, a US physician, wrote a book in 1908 on children with celiac disease, which he called *Intestinal Infantilism*. He noted that children's growth was retarded and that fat was better tolerated than carbohydrates. The eponym **Gee-Herter disease** was sometimes used to acknowledge contribution of both physicians. The disease also is known as **Heubner-Herter disease** in Germany, acknowledging its description by a German pediatrician ***Johann* Heubner** in 1909. Links to wheat ingestion was presented by Dutch physician William Dicke, who observed an increase in and reduction of symptoms during wheat shortages in the course of World War II.

Samuel Jones Gee (Sept 13, 1839–Aug 3, 1911) was an English physician and pediatrician. He was born in London. His father, William Gee, was a businessman

but the family was not wealthy. Samuel got 2 years of formal primary education, supplemented by home schooling. After graduation from the University College School, London, he studied medicine at the University College Hospital, gaining an MB in 1861 and MD degree in 1865. Gee then worked at the University College Hospital and Hospital for Sick Children. He practiced as a private family surgeon, assistant physician, physician, and then consulting physician. He practiced at Great Ormond Street Hospital and St. Bartholomew's Hospital in addition to his private practice. In 1875, Gee married Sarah Cooper and they had 2 daughters. In 1911, while on vacation in Keswick, Cumbria, northwestern England, he died unexpectedly of an obstruction of a coronary artery.

Christian Archibald Herter (Sept 3, 1865–Dec 5, 1910) was a US physician and pathologist noted for his work on diseases of the gastrointestinal tract. He was born in Glenville, CT. His father, also Christian Herter, was a notable and wealthy artist and interior designer. Christian was educated privately and began studying for his medical degree at the early age of 15. By 18, he had received an MD from the College of Physicians and Surgeons at Columbia University, and then studied pathology at Johns Hopkins University and in Zurich. Herter married Susan Dows in 1885, and they had 3 daughters.

Initially, Herter mainly practiced neurology and wrote a manual for "students and practitioners" entitled, *The Diagnosis of Diseases of the Nervous System* in 1892. But soon he resigned his medical practice because of his growing interest in laboratory medicine and reconstructed the fourth floor of his house into a laboratory area. He received a position of Professor of Pathological Chemistry at the University and Bellevue Hospital Medical College in 1897 but moved back to his alma mater when he was offered a title of Professor of Pharmacology and Therapeutics in 1903. There his research focused mostly on gastrointestinal diseases. Herter was the first to notice and describe the retarded growth of children affected by celiac disease, which he called "intestinal infantilism." Later, his contribution was acknowledged by the eponym **Gee-Herter disease**.

Herter was a member of the original Board of Scientific Directors of the Rockefeller Institute for Medical Research because of his important efforts in its establishment. In 1905, he cofounded and edited, together with John Jacob Abel, the *Journal of Biological Chemistry*. He then financially supported the unprofitable journal until his death at age 45 of a neurological illness, presumably myasthenia gravis. After that, a trust was created in his memory to help continue the journal's publication.

Johann Otto Leonhardt Heubner (Jan 21, 1843–Oct 17, 1926) was a German pediatrician and was known as the father of German pediatrics. He was born in Mühltroff, a small town in the Vogtlandkreis region of Saxony. His younger years were greatly influenced by the destiny of his father, Justice Otto Leonhard Heubner, who was sentenced to death for his participation in the Uprising in Dresden in May 1849. The Dresden uprising was a part of actions known as the Revolutions of 1848, when the newly formed National Assembly called for a constitutional monarchy to rule a new, united German nation. Although Heubner father's punishment was

changed to a life imprisonment, and he was released in 1859, the family never reached their previous financial and social position.

Johann Heubner graduated from the Royal School in Grimma and completed his medical education at the University of Leipzig, receiving financial support from his relatives. He aspired to a career in surgery; however, no positions were available so he started studies in internal medicine. He finished his dissertation "Uber die Unvollstandige Reaktion im Choleraanfall [On Incomplete Reaction to Attacks of Cholera]," a work that led to his promotion in 1868 to the position of private lecturer (Privatdozent) in internal medicine. Five years later, Heubner was promoted to an internal medicine full professorship.

Early in his career, Heubner immersed himself in cerebrovascular studies. In 1872, he described the artery that bears his name; it was first called "Heubner's artery" in 1909 by H. F. Aitkens. Based on his early research involving anatomical studies of the circulation of the brain, he described syphilitic endarteritis, a disease that received his name (Heubner disease). Heubner was appointed director of the district outpatient clinic in Leipzig in 1876. Because of an unequal population of pediatric patients and a fact that infant mortality in German hospitals reached almost 70% at that time, he developed a serious interest in a pediatric healthcare system. Heubner's focus on child hygiene, baby nutrition, and social welfare was very important and highly acknowledged. He got the first German Full Professor position in Pediatrics and was Chairman of the German Society of Pediatrics in 1901–1905.

Heubner's scientific focus was on infectious disease, with a special concern on infectious diseases of the central nervous system (CNS). He was a pioneer in many fields and his achievements have been well documented. In 1896, he detected, for the first time, meningococci bacteria in the cerebrospinal fluid from a living patient; in 1898, he linked a pineal tumor with early puberty in a boy; in 1908, he first used electrocardiography in children; in 1909, he provided the first description of celiac disease, which is still recognized as **Heubner-Herter disease** in Germany. In collaboration with **Eduard Henoch**, Heubner was the first to apply an antitoxin, identified by **Emil Behring**, for the treatment of a diphtheria patients. Working with the physiologist Max Rubner, he conducted critical studies on energy metabolism in infants, which allowed assessing overall dietary quality and food behaviors and development of the nutrition quotient scoring system.

For his important achievements in pediatrics, Heubner received many awards and honors. In commemoration of his 70th birthday, the German Society of Pediatrics established the Otto Heubner prize for contributions to the field of pediatrics. In 1913, Heubner retired and became Professor Emeritus of Pediatrics at the University of Berlin. Fourteen years later at the age of 83 years, Heubner died in Loschwitz near Dresden.

(**Publ**.: Gee SJ. On the coeliac affection. *St. Bartholomew's Hosp Rep* 1888; 24:17–20.

Herter CA. On Infantilism from Chronic Intestinal Infection; Characterized by the Overgrowth and Persistence of Flora in the Nursing Period. New York: Macmillan & Co; 1908.

Heubner OJ. Uber schwere Verdauungsinsuffizienz beim Kinde jenseits des Sauglingsalters. *Jahrb Kinderheilkd Phys Erzieh* 1909; 70:667.)

Lou Gehrig's disease (amyotrophic lateral sclerosis, ALS) is a progressive neurodegenerative disease of the upper- and lower-motor neurons located in the midbrain, brainstem, and spinal cord. In ALS, the motor neurons in these areas become dysfunctional and slowly die leaving muscles without innervation and causing muscle atrophy, resulting eventually in muscle paralysis. ALS patients progress rather quickly, and only 5% of them survive beyond 5 years after diagnosis. The cause(s) of ALS remain unknown. One theory is that an important neurotransmitter, glutamate, is overexpressed, resulting in damage to motor neurons and eventually death. Although all causes of **Lou Gehrig's disease** remain unknown, accumulative evidence suggests a possible autoimmune mechanism of pathogenesis.

There is increasing evidence that inflammation accompanies the death of motor neurons in ALS. Evidence so far, however, does not completely support that ALS is an autoimmune disease. Chronic bacterial and viral infections of the CNS documented in ALS patients can play a role in induction of cell death in the brain. In fact, bacterial infections caused by the *Mycoplasma* species has been discovered in almost 85% of ALS patients and 100% of Gulf War veterans with ALS. Neurotrophic viruses (e.g., the Echo-7 enteroviruses), known to induce death of infected cells, also were identified in many patients with ALS. Furthermore, the spirochete *Borrelia burgdorferi*, the causative agent of **Lyme disease,** also may be implicated in ALS.

Some intracellular bacteria can induce death of nervous cells through an upregulated production of reactive oxygen species (ROS), including superoxide, peroxides, hydroxyl radical, and singlet oxygen. Exposure to high-ROS concentrations can lead to nonspecific damage to cellular macromolecules (e.g., lipids, proteins, and nucleic acids) causing apoptotic cells death. One of the major defects documented in ALS is the decreased expression or function of superoxide dismutase (SOD)—an enzyme that participates in decreasing the ROS level. Finally, although ALS is not normally accepted as an autoimmune disease, some reports have demonstrated the presence of autoantibodies to the membrane components of motor neurons in patients with ALS. These autoantibodies may damage nerve cells similar to multiple sclerosis.

ALS is often called **Lou Gehrig's disease** after the famed baseball player, whose struggle with it and his death in 1941, brought it to national attention.

Henry Louis "Lou" or ***"Buster" Gehrig*** (Jun 19, 1903–Jun 2, 1941) was a US baseball player who played 17 seasons in the Major League for the New York Yankees (1923–1939). A native of New York City and attendee of Columbia University, Gehrig signed with the Yankees in 1923. He was famous for his skills as a hitter and for his strength, the characteristics that got him his nickname, "The Iron Horse." Gehrig won the Triple Crown in 1934 for being All-Star champion 7 times and World Series champion 6 times. He was also named the American League's Most Valuable Player twice. Gehrig is remembered for major league achievements

and his records include the most career grand slams and the most consecutive games played. The Yankees were unbeatable for 56 years. Gehrig's streak ended in 1939 after he was diagnosed with ALS, which forced him to retire at age 36 and claimed his life 2 years later.

Gerlach tonsil (tubal tonsil) is a collection of lymphoid nodules near the pharyngeal opening of the auditory tube. It is located posterior to the opening of the Eustachian tube on the lateral wall of the nasopharynx. **Gerlach tonsil** is one of the 4 main tonsil groups comprising **Waldeyer's tonsillar ring**. The tonsils are lymphoepithelial organs acting as a guardian at the entrance of the upper aerodigestive tract. *See* also **Eustachian tonsil**.

Joseph von Gerlach (Apr 3, 1820–Dec 17, 1896) was a German anatomist. He was a native of Mainz. Joseph attended school in Aschaffenburg, where his father was employed as a law officer in the Bavarian civil service. After graduation in 1837, he studied medicine in nearby Würzburg, switching to Munich in 1838 and Berlin in 1839. He passed the state examination in 1844 at the University of Giessen. Then for 2 years he worked at medical schools in Paris, Dublin, and London to expand his clinical competencies. Finally, he returned to Mainz to start his general medical practice in 1846, married Therese Moritz in 1847, and had 2 children. Even with a very busy clinical practice, he was able to reserve time for additional research and educational duties. He lectured on the importance of microscopic anatomical examinations and established the "Anatomical Society" of Mainz. Later, he was offered a position at the University of Erlangen to lead teaching and clinical and research studies in anatomy, physiology, and pathoanatomy. Gerlach developed and improved many methods of histochemical staining being a pioneer in the field. He understood the importance of examining the fine structural elements and cells in various tissues and established a routine for histological staining in clinical practice. He was one of the very first clinicians who began to use photomicrography for clinical research.

Gerlach's technical, teaching, and clinical accomplishments were well recognized. In 1865, he was designated Prorector of the University of Erlangen, while by tradition the rector is the Bavarian King. He was granted the title of Royal Bavarian Privy Councilor. Gerlach was an active member of the Royal Bavarian Academy of Sciences and the German Academy of Natural Scientists. One of his highest awards was the Bavarian Crown Order, which was associated with personal nobility; he then was able to call himself ***Joseph Ritter von Gerlach***. Hi died in Munich.

(**Publ**.: Gerlach D. Die Anfänge der Histologischen Färbung und der Mikrophotographie. Josef von Gerlach als Wegbereiter. Ostwalds Klassiker der Exakten Wissenschaften, Band 283. Frankfurt: Harri Deutsch; 1998.

Gerlach J. Handbuch der Allgemeinen und Speciellen Gewebelehre des Menschlichen Körpers für Aerzte und Studirende. Mainz: E. Janitsch; 1848.

Gerlach J. Mikroskopische Studien aus dem Gebiete der Menschlichen Morphologie. Erlangen: Ferdinand Enke; 1858.)

Gerota's syndrome see **Ormond's disease**

Giemsa stain see **May-Grünwald stain**

Glanzmann's syndrome (**Glanzmann's thrombasthenia**, **Glanzmann-Nägeli syndrome**, platelet fibrinogen receptor deficiency, **Révol's syndrome**) is a rare congenital abnormality of blood platelets, characterized by easy bruising and excessive bleeding after trauma and epistaxis. It can be inherited in an autosomal recessive manner or acquired as an autoimmune disorder. This type of coagulopathy (i.e., bleeding disorder) is driven by the abnormal or low levels of fibrinogen receptors—glycoprotein IIb/IIIa (GpIIb/IIIa)—in the platelets. These defects cause increased bleeding time because of no fibrinogen bridging between platelets, important for coagulation, cannot be formed. Coagulopathy in **Glanzmann's thrombasthenia** can vary from minimal bruising in some patients to severe, recurrent, and potentially deadly hemorrhages in others.

It is named for ***Eduard Glanzmann*** (Apr 12, 1887–Feb 2, 1959), the Swiss pediatrician who originally described it. Glanzmann graduated from the Lyceum Lucernense in 1909 and studied medicine in Zürich, Berlin, and Bern. He graduated in 1912 and obtained his medical doctorate in Bern in 1914. He undertook postgraduate studies at the pediatric clinic in the Berlin Charité and settled in Bern as a specialist in children's disorders. He was the Chair of Pediatrics and Dean of the University of Bern for several years.

In 1920, when still in his early 30s, Glanzmann introduced the term "Anaphylaktoide Purpura"; therefore, this disease is sometimes called **Schönlein-Henoch-Glanzmann disease**. He recognized the allergic components to this clinical syndrome. In 1930, he characterized the features of the fever of the lymphatic glands in children, which is known today as infectious mononucleosis. In 1950, Glanzmann and ***Paul Riniker*** described two infants with "Essentieller Lymphocytophthise," the first cases of severe combined immune deficiency.

Oskar Naegeli (***Nägeli***) (Feb 25, 1885–Nov 19, 1959) was a Swiss dermatologist who was born in Ermatingen and died in Fribourg, Switzerland. His father, Otto Naegeli, was a physician, and his brother Otto Naegeli was a hematologist. Oskar studied medicine in Geneva, Zurich, Munich, and Heidelberg and graduated in Zurich in 1909 with a medical license. He received additional training and studied dermatology and venereology in Bern and obtained a position of Extraordinary (Associate or Adjunct) Professor and Director of the University Dermatology Clinic in 1917. He also practiced at the Institute of Pathology in Freiburg and the Medical Policlinic in Zurich. His clinical research focused on immunological reactions in dermatology and syphilology. He also is well known as a chess master. He represented Switzerland at the Chess Olympiads in 1927, 1928, 1931, and 1935, as well as at the unofficial Olympiad in 1936 in Munich.

(**Publ**.: Glanzmann WE. Hereditäre hämorrhägische thrombasthenie. Ein beitrag zur pathologie der blutplättchen. [Hereditary haemorrhagic thrombasthenia. A

contribution to the pathology of platelets.] (German). *Jahrb Kinderheilkd [Yearb Pediatr]* 1918; 88(1–42):113–141.)

Glanzmann's thrombasthenia see **Glanzmann's syndrome**

Glanzmann-Nägeli syndrome see **Glanzmann's syndrome**

Glanzmann-Riniker syndrome (**Glanzmann-Riniker alymphoplasia**) is a hereditary, severe immunodeficiency syndrome. Onset is usually from early infancy, 3–6 months. The major manifestations of this disease are failure to thrive, severe persistent and/or recurrent infections, and death, often within the first 2 years of life. In addition to susceptibility to bacterial, viral, and fungal infections, patients present with agammaglobulinemia (i.e., failure to form antibodies), absence of the thymus, and severe cytopenia. Watery diarrhea with *Salmonella* and *Escherichia coli* in the stools and lung abscesses because of *Pseudomonas aeruginosa* and *Pneumocystis carinii* pneumonia are commonly seen. Inheritance is a spectrum of X-linked and autosomal genetic defects causing an inability to mount regular cell-mediated and humoral immunity.

In many cases, mutations in the gene encoding of the common gamma chain (γ_c or CD132), also known as interleukin-2 receptor subunit gamma or IL-2RG, were detected. This is a cytokine receptor subunit that is shared by the receptor complexes for at least 6 different interleukin receptors: IL-2, IL-4, IL-7, IL-9, IL-15, and interleukin-21. The result is low or absent T and NK cells and nonfunctional B cells. In approximately 15–20% of patients, there is an association with a deficiency of the enzyme adenosine deaminase. The **Glanzmann-Riniker syndrome** often is called severe combined immunodeficiency (SCID) or "bubble boy" disease because its victims are extremely vulnerable to infectious diseases; some of them (e.g., David Vetter) have become famous for living in a sterile environment.

In 1950, ***Glanzmann*** and ***Riniker*** reported 2 children with "Essentieller Lymphocytophthise," the first clinical cases of severe combined immune deficiency. They died of an illness associated with diarrhea, candidiasis, lymphopenia, and a prominent reduction of lymphatic tissue. By the early 1960s, almost 30 cases had been recorded, and the number of names for the disorder nearly matched the quantity of cases described.

Eduard Glanzmann see **Glanzmann's syndrome**

Paul Riniker was a Swiss pathologist and a Professor of Pathology in Bern, Switzerland.

(**Publ**.: Glanzmann E, Riniker P. Essentielle lymphocytophtie. Ein neues Krankheitsbild aus der Säuglingspathologie. *Ann Paediatr. Int Rev Pediatr* 1950; 175:1–32.)

Glanzmann-Saland syndrome is an acute febrile polyneuritis associated with diphtheria infection. Clinically, it can be characterized by abnormal heart rhythm,

vomiting, respiration problems, and occasionally albuminuria and paralysis (Landry type). The term Glanzmann-Saland syndrome (misnomer) also was used as a synonym for the **Guillain-Barré syndrome** (acute ascending polyradiculoneuritis), but these are distinct entities.

Eduard Glanzmann see **Glanzmann's syndrome**

S. Saland was a Swiss physician.

(**Publ**.: Glanzmann E, Saland S. Seltene postdiphtherische Lähmungen. *Schweiz Med Wochenschr* 1935; 16:2–5.)

Gleich's syndrome (**Gleich syndrome**, episodic angioedema with eosinophilia) is known as episodic angioedema with hypereosinophilia and an elevation of immunoglobulin M (i.e., monoclonal or polyclonal) or cryoglobulinemia. The main clinical, laboratory, and immunological findings include systemic angioedema, urticaria, weight gain, and leukocytosis with eosinophils of ~75%. Circulating IgM, IgE, and T-helper lymphocyte may be elevated. On the contrary, complement proteins C4 and C3 were most often reduced. Skin histologic studies show eosinophil and neutrophil infiltration and degranulation in the dermis, and biopsies revealed deposits of the cationic eosinophilic protein.

The particular pathophysiology of the **Gleich syndrome** is unclear, but eosinophils and neutrophils play a critical role in the disease manifestation, which is associated with the activation of the immune system and the production of IL-5 and IL-6. Serum cytokines, which also may be involved in the pathogenesis of the disease, are seen to have cyclical magnitudes: particularly IL-3, IL-6, IL-1, and soluble IL-2 receptors. Although the exact pattern actually has not been defined, IL-6 reaches top levels only after the peak of eosinophilia. Cyclic elevations of IL-5 also have been associated with the periodicity of eosinophilia in patients with this syndrome. The presence of antibodies and migration of eosinophils are linked to increased serum viscosity, causing angioedema and weight gain. The presence of endothelial antibodies also has been demonstrated, suggesting the role of the antibodies in increasing capillary permeability or adherence of the eosinophils to the capillary wall.

This syndrome was described first by ***Gerald Gleich*** et al. in 1984. They reported on a novel disorder manifested as recurrent sporadic nonallergic angioedema with fever, weight gain, skin rash with red itchy bumps, and eosinophilia. Unlike the idiopathic hypereosinophilic syndrome, Gleich syndrome manifests as irregular cases of angioedema with elevated levels of IgM and eosinophilia but with no risk of cardiovascular disease and mortality.

Gerald Joseph Gleich (May 14, 1931–) is a US allergist and immunologist with a practice focused on the treatment of eosinophil-associated diseases. He was born in Escanaba, Michigan. He attended and graduated with honors from the University of Michigan Medical School in 1956; did his residency on Internal Medicine at Jackson Memorial Hospital; and was a faculty member at the Department of Immunology of the Mayo Clinic and Foundation, Rochester, MN, for 36 years. In his tenure there, he

was honored as a Distinguished Investigator, Professor of Immunology and Medicine, and he was Chairman of the Department of Immunology. Then, he was Professor of Medicine and Professor of Dermatology at the University of Utah School of Medicine.

(**Publ**.: Gleich GJ, Schroeter AL, Marcoux JP, Sachs MI, O'Connell EJ, Kohler PF. Episodic angioedema associated with eosinophilia. *N Engl J Med* 1984; 310(25):1621–1626.)

Gomm-Button disease see **Sweet's syndrome**

Good's syndrome (**Good syndrome**, thymoma with immunodeficiency) is a rare syndrome of combined T- and B-lymphocyte immunodeficiency in an adult population. Clinically, it manifests as an augmented susceptibility to encapsulated bacterial infections and opportunistic viral and fungal infections. Commonly, it is observed as recurrent sinopulmonary infection, which is secondary to encapsulated organisms. In Good's syndrome, opportunistic infections are caused by the abnormal development of cell-mediated immunity unlike infections associated with X-linked agammaglobulinemia (XLA) and common variable immune deficiency (CVID). In fact, cytomegalovirus (CMV) colitis and retinitis, mucocutaneous candida infections, *Pneumocystis carinii* pneumonia and varicella zoster, herpes simplex, and human herpesvirus infections are diagnosed commonly in Good's syndrome. Patients with thymomas also often develop opportunistic viral and fungal infections and present characteristic deficiencies of cell-mediated immune reactivity.

Good's syndrome frequently is associated with hematological disorders. Anemia is present in more than 50% of patients. Approximately 55% of patients have a low white blood cell count and 20% have thrombocytopenia. Neutropenia occurs in 18% of patients with Good's syndrome. Monoclonal gammopathies (i.e., benign and malignant) and T-cell tumors also have been described.

Low levels of serum immunoglobulins, B- and $CD4^+$ T lymphocytes, abnormal $CD4^+$:$CD8^+$ T-cell ratios, and decreased T-cell proliferation in response to nonspecific mitogen stimulation are the key immunological features of Good's syndrome. In fact, almost half of patients with Good's syndrome demonstrate lower T-cell proliferation after stimulation with phytohemagglutinin (PHA) and marked downregulation of cytokine expression in activated T lymphocytes. Decreases in serum IgG, IgA, and IgM are common in most patients, although normal IgA concentrations, and even increased IgM values, have been reported.

The etiology and pathogenesis of Good's syndrome are still not completely clear. Clinical research data suggest that the basic abnormalities of the bone marrow hematopoiesis (e.g., diminished maturation of erythroid and myeloid precursors) and pre-B cell differentiation are prevented. There are two hypothesis that have been proposed to explain the association of thymoma with antibody deficiency. The first, pathogenic mechanism, is the effect of the bone marrow stromal cell-derived cytokines and growth factors on the proliferation and differentiation of both thymic and B-cell precursors. The second is another pathway that may lead to direct or

indirect inhibition of erythropoiesis (pure red-cell aplasia) by T cells or autoantibodies described in the paraneoplastic phenomena in thymoma.

Even though generally accepted diagnostic criteria for this disease have not been established, the expert committee of the World Health Organization–International Union of Immunological Societies on primary immunodeficiencies considers it a distinct entity. The connection between thymoma development and immunodeficiency was first reported by ***Robert Good*** in 1954, when he revealed a case of thymoma with hypogammaglobulinemia in an adult patient.

Robert Alan Good (May 21, 1922–Jun 13, 2003) was a US pediatrician, microbiologist, and pathologist. He was born in Crosby, MN. He graduated in 1944 from the University of Minnesota, where he received both a PhD and later an MD in 1947. After finishing his pediatric residency at the same university, he did a fellowship at the Rockefeller Institute for Medical Research. He then returned to the University of Minnesota Medical School,l working there in 1950–1973 as Instructor and then Professor of Pediatrics and Microbiology. From 1973–1982, Good worked at Sloan-Kettering Institute for Cancer Research in New York as the chief scientist, president, and director, as well as Professor of Medicine, Pediatrics, and Pathology at Cornell University Medical College. From 1982–1985, he was Professor of Pediatrics, Immunology, and Microbiology at the University of Oklahoma, and in 1985–2003, he was Chairman of the Department of Pediatrics at the University of South Florida in Tampa. He died at his home in St. Petersburg, FL at the age of 81 from esophageal cancer. At his death, he was the Physician-in-Chief and Director of Research at All Children's Hospital in St. Petersburg, and a distinguished research professor at the University of South Florida.

Good is recognized internationally for his pioneering research on the thymus and tonsil function and for performing the first successful human bone marrow transplantation in 1968. In 1970, he received the Albert Lasker Medical Research Award. His name is associated with 2500 research papers, abstracts, book chapters and reviews and with editing more than 50 books. He trained and mentored more than 300 students and fellows and most of them are currently professors or department chairs all over the world.

(**Publ**.: Good RA. Agammaglobulinaemia—a provocative experiment of nature. *Bull Univ Minn* 1954; 26:1–19.

Good RA, Varco RL. A clinical and experimental study of agammaglobulinemia. *Lancet* 1955; 75(6):245–271.)

Goodpasture syndrome is a rare autoimmune disease that affects both the kidneys and the lungs. A diffuse pulmonary hemorrhage and acute or rapidly progressing glomerulonephritis are the disease's characteristics. Goodpasture disease is a term used to describe glomerulonephritis, with or without pulmonary hemorrhage, and the presence of the circulating antiglomerular basement membrane (anti-GBM) antibodies. Definitions of these terms have not been consistent, however.

GBM is part of the glomeruli and is composed of collagen and other proteins. The autoantibodies bind to their reactive epitopes in the basement membranes and

activate the complement cascade, resulting in tissue injury. Autoantibody targets a 28-kD monomeric subunit of the noncollagenous domain of the alpha3 chain of type-IV collagen (alpha3[IV]NC1). Only the glomerular and alveolar basement membranes are affected in **Goodpasture syndrome** in spite of the general belief of their universal anatomical structure. It is possible that autoantibody preferentially binds to the glomerular and alveolar basement membranes because of higher expression of alpha3 collagen units and the higher availability of antigenic epitopes. It also is possible that, structurally, the alpha3 collagen chains of glomerular basement membranes are different and are more accessible to autoantibodies. Although Goodpasture syndrome is a prototypic autoantibody-induced immune-mediated disease, T lymphocytes also play a crucial role in disease development. T cells regulate B-cell differentiation, activity, and antibody production and could have a pathogenic role in kidney and lung damage. Goodpasture disease is strongly associated with the DRB1*1501 and to a lesser extent the DRB1*1502 allele.

Ernest Goodpasture first characterized the syndrome in 1919 during the influenza pandemic. He described a patient who died from lung bleeding and kidney collapse. Because special methodologies to diagnose Goodpasture syndrome were not present at that time, it is impossible to prove whether the patient had actual Goodpasture syndrome or suffered from vasculitis. In 1955, Parkin et al. described three cases of lung hemorrhage and nephritis in the absence of arteritis (Parkin et al. 1955). In 1958, Stanton and Tang reported a series of young men with pulmonary hemorrhage and glomerulonephritis, similar to Goodpasture's original description (Stanton and Tange 1958). In 1950, Krakower and Greenspon had identified GBM as the antigen (Krakower and Greenspon 1951). In 1967, Lerner and colleagues confirmed that the antibodies taken from the diseased kidneys produced nephritis in experimental animals (Lerner et al. 1967). The discovery of anti-GBM antibodies led to the understanding of the pathogenesis of Goodpasture syndrome.

Ernest William Goodpasture (Oct 17, 1886–Sept 20, 1960) was a US pathologist and physician. He was born on a farm near Clarksville, Montgomery County, TN, the son of Albert Virgil and Jennie Wilson Dawson Goodpasture. He graduated from the Johns Hopkins School of Medicine, where he received a Rockefeller fellowship in pathology after graduation. Subsequently, he joined the faculty of Harvard Medical School, as an attending pathologist at the Peter Bent Brigham Hospital and an Assistant Professor of Pathology in Boston. During that time, Goodpasture took a 2-year leave of absence to serve during World War I as a medical officer in the US Navy.

After leaving Harvard in 1921, Goodpasture worked at the University of the Philippines College of Medicine in Manila, served as the director of William H. Singer Memorial Laboratories in Pittsburgh, and from 1924–1955 was Professor and Chairman of the Department of Pathology at the Vanderbilt University School of Medicine. After retirement, he was invited to serve as director of the Armed Forces Institute of Pathology in Washington, DC, for 4 years; then he resigned his position to return to Tennessee. His retirement was not to last long. He died

suddenly in September 1960 of a myocardial infarction while engaged in yard work at his home.

(**Publ***.:* Goodpasture EW. The significance of certain pulmonary lesions in relation to the etiology of influenza. *Am J Med Sci* 1919; 158(6):863–870.)

Gottron's papules (**Gottron papules**) are faint red or violet papules occurring over the knuckles and sometimes the interphalangeal joints in patients with dermatomyositis—a progressive condition characterized by symmetric proximal muscular weakness with elevated serum levels of muscle enzymes and a skin rash. Symmetrical erythematous to violaceous papules and plaques cover surfaces of metacarpal and interphalangeal joints. Other large joints (e.g., knees, elbows, and ankles) also may be involved. Affected muscles display chronic inflammatory cell infiltration and fiber degeneration.

Dermatomyositis, polymyositis, and myositis belong to the group of rare autoimmune connective tissue diseases associated with weakness and muscle inflammation. Diagnostic criteria include recognition of antinuclear antibodies (ANA): anti-Ro/SSA, anti-La/SSB, antiribonucleoprotein (RNP), and anti-**Sm** autoantibodies. In addition, detection of specific myositis-associated antibodies (e.g., anti-Jo-1 and other antisynthetase antibodies) should be considered. Autoantibodies targeting the PM/Scl, Ku, Mi2, and SRP antigens also can be added for diagnostic purposes. **Gottron's papules** may serve as diagnostic markers of dermatomyositis.

Heinrich Adolf Gottron (Mar 10, 1890–Jun 23, 1974) was a German physician who lived in Tübingen. He was born in Oppenheim on the Rhine; studied medicine at the universities in Freiburg, Berlin, Munich, Heidelberg, Leipzig, and Bonn; and received his doctorate in 1916. During World War I, he served as a military doctor and became a Colonel. In 1919, he went to the Charité in Berlin, habilitated in 1930, and moved to an Adjunct Professor position in 1933.

In 1935, Gottron became the Chair of Dermatology at the University of Breslau—the facility established under ***Albert Neisser*** and ***Joseph Jadassohn***, which was one of the leading skin clinics worldwide. His predecessor ***Max Jessner*** had been forced to resign because of his Jewish ancestry. Gottron joined NSDAP, more commonly known as the Nazi Party (details from *MEMIN Encyclopedia*), in 1937 and from 1939 onward served as head physician of Dermatology at the University Hospital. Simultaneously, Gottron was clearly recognized as having high ethical standards that were visible during the Nazi regime. He defended Jewish dermatologist Stephan Epstein against Nazi party assaults until he could emigrate to the US. After internment of Polish dermatologist Franz Walter in the concentration camp at Oranienburg, Gottron managed to arrange his release a few months later.

From 1946 until his retirement in 1961, Gottron was Professor of Dermatology at the Eberhard-Karls University of Tübingen, being a chief physician in the Dermatology Clinic. He was also a cofounder of the Society for Research in 1949 and was one of the major dermatologists after the war. He also was known as an

expert in history, especially military, and as a chain smoker, always having a cigarette in his lips. He died in Mainz.

Gottron published a wide range of articles on contact dermatitis, amyloid and leukemic infiltrates, and skin manifestations. He was the first to classify dermatological neoplasms as precancerous, cancerous, and pseudocancerous; 6 diseases bear his name in eponyms.

(**Publ**.: Gottron HA, Schönfeld W. Dermatology and Venereology. Including Occupational Diseases, Dermatological Cosmetics and Andrology. 5 vols in 10 subvols. Stuttgart: Thieme; 1958–1970.)

Gottron's sign is defined as the presence of erythematous to violaceous macules, patches, or papules on the extensor surfaces of joints in sites other than the hands, particularly the elbows, knees, or ankles. Characteristic of dermatomyositis, but not pathognomonic, it also can occur in other conditions, although much less frequently. Nevertheless, some authors have used the term **Gottron's papules** to refer to papules in these areas, reserving Gottron's sign for macular or patch-like lesions.

Heinrich Adolf Gottron see **Gottron's papules**

Gougerot's syndrome see **Sjögren's syndrome**

Gougerot-Houwer-Sjögren syndrome see **Sjögren's syndrome**

Gougerot-Sjögren syndrome see **Sjögren's syndrome**

Graves's disease (**Graves disease**, **Basedow's syndrome**, **Basedow's disease**, **Morbus-Basedow disease**, **Graves-Basedow disease**, toxic diffuse goiter, **Parry's disease**, **Begbie's disease**, **Flajani's disease**, **Flajani-Basedow syndrome**, **Marsh's disease**) is an autoimmune disease characterized by hyperthyroidism because of circulating autoantibodies. Thyroid-stimulating immunoglobulins (autoantibodies) bind to and activate thyrotropin receptors, causing the thyroid gland to grow and thyroid follicles to increase synthesis of the thyroid hormone. Graves's disease, along with **Hashimoto thyroiditis**, is classified as an autoimmune thyroid disorder.

In Graves's disease, B and T lymphocyte-mediated autoimmunity is directed at several thyroid antigens: thyroglobulin, thyroid peroxidase, sodium-iodide symporter, and the thyrotropin receptor. The thyrotropin receptor itself, however, is the primary autoantigen of **Graves's disease** and is responsible for the manifestation of hyperthyroidism. These thyroid-stimulating antibodies, commonly the immunoglobulin G1 subclass, bind to the thyrotropin receptor and activate cyclic AMP signaling, causing the release of thyroid hormone and thyroglobulin. This is associated with the upregulation of iodine uptake and growth of the thyroid gland. At the same time, although detected, autoantibodies to the thyroglobulin, sodium-iodide symporter, and thyroid peroxidase do not play a significant etiological role in hyperthyroidism. In clinical diagnostics, they serve as markers of the autoimmune process.

Intrathyroidal infiltration of thyroid tissue by lymphocytes correlates with the level of thyroid autoantibodies and is another histological marker of autoimmune thyroid disease.

Several genes associated with susceptibility to autoimmune thyroid diseases have been recognized. They include genes encoding CTLA-4, CD40, TSH receptor, thyroglobulin, and PTPN22 (protein tyrosine phosphatase nonreceptor type 22) proteins. Several susceptibility genes have been shown to be specific to Graves's disease or Hashimoto thyroiditis, whereas other genes may reflect susceptibility to both disorders. Recent studies also revealed solid associations of thyroid-stimulating hormone receptor and major histocompatibility complex class II (MHC II) variants with autoantibodies to thyroid-stimulating hormone receptors. In addition to the genetic predisposition, environmental factors and previous health conditions play an important role in the development of thyroid autoimmunity.

Graves's disease owes its name to ***Robert James Graves***, who described a case of goiter with exophthalmos in 1835. The term *Graves disease* was suggested by French physician Armand Trousseau in *Du Goître Exophthalmique, ou Maladie de Graves* in 1862. ***Karl Adolph von Basedow***, who practiced medicine in Merseburg in Germany, in 1840 independently reported many of the main features of what is now known as hyperthyroidism. Although Basedow's publication was 5 years later than Graves's, the disease is referred to as **Basedow's disease** or **Basedow's syndrome** in many non-English speaking countries.

Graves's disease also has been called exophthalmic goiter. Much less commonly, the disease was known as **Parry's disease**, **Begbie's disease**, **Flajani's disease**, **Flajani-Basedow syndrome,** and **Marsh's disease**. Early reports, not broadly issued, of cases of goiter with exophthalmos were published by the Italians, ***Giuseppe Flajani*** and Antonio Giuseppe Testa, in 1802 and 1810, respectively. ***James Begbie*** and ***Henry Marsh*** also described cases of the disease independently. Prior to all these publications, ***Caleb Hillier Parry*** noted the condition in 1786 when he treated Mrs. Grace B, a 37-year-old woman a few months after childbirth who had palpitations, tachycardia, goiter, and prominent eyes. His description usually is believed to be the first on thyroid-associated exophthalmos. Parry briefly reported the case in his *Elements of Pathology and Therapeutics* (1815). Yet, his findings were only published by his son in 1825, 3 years after his father's death, which was still 10 years ahead of Graves.

Furthermore, according to Jan-Gustaf Ljunggren, in an article in the Swedish journal *Läkartidningen* (1983; pp. 32–33), eponymic priority may be a result of a twelfth-century Persian physician, Sayyid Ismail al-Jurjani, who noted the association of goiter and exophthalmos in his *Thesaurus of the Shah of Khwarazm*; it was the major medical dictionary of its time. Probably the first association between goiter and exophthalmos can be found in legal documents. Around 200 AD, Roman jurist Dometius Ulpianus legislated that a slave with goiter and prominent eyes had no work capacity (https://litfl.com/diffuse-toxic-goitre/). The first medical association was recorded by Avicenna (980–1037) in his million-word masterpiece, *Al-Qanoon*, in which he gave detailed descriptions of exophthalmos, goiter, and symptoms of hyperthyroidism.

Robert James Graves (Mar 27, 1796–Mar 20, 1853) was an Irish surgeon who was born in Dublin. After a bright undergraduate career in the arts, he received a degree in medicine in 1818 and left for London to study surgery. He continued his medical education during his visits to various medical schools in Edinburgh, Vienna, Berlin, Copenhagen, Göttingen, Hamburg, and other places in France and Italy. Graves was a very talented polyglot. Once he spent 10 days in prison in Austria because of traveling without a passport, and the people in charge believed that he was a German spy because an Irishman could not speak their language so well. When he was in the Swiss Alps, Graves met Joseph Mallord William Turner, known as William Turner, a well-known English Romantic painter. They became friends and traveled together for several months.

In 1821, Graves went back to Dublin to start his private practice where he could use the novel clinical approaches he had learned in Europe. He also took a professor position at the Irish College of Physicians and the Institute of Medicine where he taught physiology. In 1843, he published *Clinical Lectures* which gave him European recognition. He was an excellent clinician, and his name is remembered for identification of *hyperthyroidism*. He observed 3 patients with tachycardia and 1 young women had enlarged and expanded thyroid (goiter); a fourth patient suffered from severe exophthalmos (i.e., proptosis or bulging or protruding eyeballs). Graves suggested that this new syndrome, which he accidentally discovered, had a cardiac nature. His observation was distributed as part of the London Medical Society's Clinical Lectures in 1835.

Graves served as the President of the Royal College of Physicians of Ireland in 1843 and 1844. From 1849 on, he was a Fellow of the Royal Society of London. He was also an honorary member of various medical and research societies in Hamburg, Tübingen, Berlin, Vienna, and Montreal. In addition to his linguistic and clinical diagnostic gifts, Graves was a talented painter. He was married 3 times, and 2 of his wives and 2 daughters predeceased him. He got sick in 1852 and died of abdominal cancer at 57.

Karl Adolph von Basedow (Mar 28, 1799–Apr 11, 1854) was a German physician most famous for reporting the symptoms of what is now known as exophthalmic goiter. He was born in Dessau, the capital of Anhalt, Germany, to a reputable family. His grandfather founded the famous "Philanthropinum" in Dessau in 1774; it was the first boarding school of its kind and was later expanded into Germany and Switzerland. Von Basedow's father and elder brother were presidents of the council of the principality of Anhalt. He graduated from Halle University, where he received a doctorate in the name of the King of Prussia at age 22. The subject of his thesis (written in Latin) was a new method for surgical amputations.

Von Basedow began his general medical practice in Merseburg in 1822 after being certified as general practitioner, surgeon, and obstetrician. In 1823, he married Louise Friederike Scheuffelhuth who was a daughter of the public notary. From their daughters, they had 11 grandchildren. Von Basedow soon became the town's chief medical officer, a position he held for the rest of his life. He loved music and enjoyed going to concerts and playing music with his daughters. Evening parties,

performances, and receptions at the von Basedow's were very popular in their social circle. He also enjoyed hunting and hiking.

Von Basedow frequently treated his patients for free. In 1831, he willingly assisted in treating patients during a cholera epidemic in Magdeburg. After the strange death of his youngest child, he often investigated the postmortem substances from many of his patients and did autopsies by himself. Von Basedow died in Merseburg after contracting spotted fever from a corpse he was dissecting.

Carl von Basedow had broad and diverse scientific interests which he documented in some 60 publications dealing with topics related to surgery, internal medicine, and gynecology. The most historically significant, however, was the detection and first description of the "Basedow's disease" in March 1840. The term was suggested by Georg Hirsch in his *Klinische Fragmente*.

Caleb Hillier Parry (Oct 21, 1755–Mar 9, 1822) was an English physician credited with the first description of **Parry-Romberg syndrome** published in 1815, as well as one of the earliest descriptions of exophthalmic goiter published in 1825. He was born in Cirencester, where his father, Joshua Parry, was a recalcitrant minister at the local chapel. Caleb was in Grammar School in Cirencester when he met Edward Jenner. In memory of their lifetime friendship, Jenner dedicated his "An Enquiry into the Causes and Effects of the Variolae Vaccinae" to Parry; it was published in 1798. In 1773–1778, Parry got his medical education in Edinburgh and London. In 1778, he married Sarah Rigby of Warrington whom he had met when a student at the Academy. After touring Europe for 9 months, they moved to Bath, Somerset, in 1779, where Parry stayed for the rest of his life.

Throughout his medical practice, Parry was known for his kindness, integrity, insight into the patients' problems, and his great charisma. His "playfulness of manner" and ability to tell comical stories opened many households in Bath to him. He loved the arts and was a talented singer who performed at special occasions in his house. In 1807, he founded Bath's Geological Society. Parry loved to travel and visit new places, and probably this interest inspired his youngest son, William Edward, to become one of the well-known Arctic explorers.

The very busy medical practice and lifestyle ultimately affected Parry's health. He had kidney stones and gout and had a major stroke in 1816; after that his right side was paralyzed and it damaged his speaking ability. For the next 6 years until his death, in spite of constant pain, he continued to be interested in research, classified his fruit trees and plants, and dictated memoirs to his daughter.

Even after his death, his reputation as a talented clinician and researcher continued to grow when his findings showed that he often was the first to identify several symptoms and syndromes. His son, Charles, collected all unpublished materials into 2 volumes and published them in 1825. There was an excellent description of 5 clinical cases of exophthalmic goiter. The first case dated back to 1786 and provided a characterization of a patient with enlarged jugular veins and other specific clinical signs of the disease. Some clinicians have stated that Graves did not add a lot to his description of the disease in 1835 and suggested calling it Parry's disease. Parry

died in Bath and was buried in Bath Abbey. The medical professionals of Bath commissioned a monument to his memory in the Abbey.

Giuseppe Flajani (1741–Aug 1, 1808) was an Italian surgeon and anatomist. He was born near Ascoli, where he received his initial education. He obtained his doctoral degree of philosophy and medicine in Rome and started his medical practice in the Santo Spirito Hospital. He was interested in anatomy and founded and directed an anatomical office in Sassia, a city near Rome. He was Chief of Operations in the Santo Spirito Hospital from 1772 onward, and he became a personal physician to Pope Pius VI in 1775. In 1802, Flajani published a paper about a case of a patient with exophthalmos and goiter. He had 2 sons who also were clinicians, and one of them continued his medical practice after his death.

James Begbie (Dec 18, 1798–Aug 26, 1869) was a British physician, was born in Edinburgh, and received his medical education at the University of Edinburgh in 1821. In 1822, he was a fellow of the Royal College of Surgeons. From 1847 on, he was a Fellow of the Royal College of Physician and the President of that College from 1854–1856. He was also the President of the Royal Medical-Surgical Society from 1850–1852. He was a physician to the Scottish Widow's Fund and Life Assurance Society for several decades and published several papers on vital statistics based on his practice. He also prepared articles dedicated to the use of arsenic in chronic rheumatism, potassium bromide in neurological disorders, and nitric-hydrochloric acid in hyperoxaluria. For the final 20 years of his career, Begbie worked as a consulting physician and died in 1869 in Edinburgh.

Sir Henry Marsh, 1st Baronet (1790–Dec 1, 1860), was an Irish physician and surgeon. He was born in Lougrhea, Galway County, Ireland, and was a son of the Reverend Robert Marsh and his wife Sophia Wolseleyand. Marsh wanted to be a farmer, then study religion, but eventually became interested in surgery. Unfortunately, his surgical career was ended by an injury and loss of his right forefinger during a section surgery. He obtained his doctorate at Dublin in 1818, then undertook scientific journeys to Paris for 2 years and later became an assistant physician in Stephen's Hospital in Dublin.

In 1822, with ***Robert James Graves*** and other physicians, he founded the Park Street Medical School. He taught pathology there until 1927, and then moved to the Royal College of Surgeons of Ireland to teach surgery. In 1832, he was offered a position as a medical doctor for Queen Victoria. In 1839, he was knighted as a baronet. In 1840, he became the President of the King's and Queen's College of Physicians in Ireland. He died suddenly at his residence in Dublin. A statue of Sir Henry, executed by Foley, is in the King's and Queen's College of Physicians.

(**Publ**.: Graves RJ. New observed affection of the thyroid gland in females. (Clinical lectures.) *Lond Med Surg J* (Renshaw) 1835; 7(part 2):516–517.

Von Basedow KA. Exophthalmus durch hypertrophie des zellgewebes in der augenhöhle. [Casper's] *Wochenschr Gesammte Heilkunde* 1840; 6:197–204, 220–228.

Von Basedow KA. Die glotzaugen. [Casper JL] *Wochenschr Gesammte Heilkunde*. Berlin: G. Reimer; 1848; pp. 769–777.

Flajani G. Sopra un tumor freddo nell'anterior parte del collo broncocele. (Osservazione LXVII). In: Collezione D'osservazioni e Reflessioni Dichirurgia. Vol. 3. Rome: Michele A. Ripa Presso Lino Contedini; 1802; pp. 270–273.

Testa AG. Delle Malattie del Cuore, Loro Cagioni, Specie, Segni e Cura. 2nd ed. Vol. 3. Bologna, 1810. Florence, 1823; Milano: Schiepatti, 1831; [German translation] Halle, 1813.

Parry CH. Enlargement of the thyroid gland in connection with enlargement or palpitations of the heart. In: Collections from the Unpublished Medical Writings of Late Dr. Parry. London: Underwoods; 1825; pp. 111–129.

Begbie J. Anaemia and its consequences; enlargement of the thyroid gland and eyeballs. Anaemia and goitre, are they related? *Mon J Med Sci* 1849; 9:496–508.

Marsh H. Dilatation of the cavities of the heart. Enlargement of the thyroid gland. *Dublin J Med Chem Sci* 1842; 20:471–474.)

Griscelli syndrome (**Griscelli-Prunieras syndrome**) is a rare autosomal recessive disorder characterized by albinism (i.e, hypopigmentation) with immunodeficiency. It is characterized by frequent pyogenic infection, enlargement of the liver and spleen, a low blood neutrophil level, and a low blood platelet level. Very often there also is impaired natural killer-cell activity, absent delayed-type hypersensitivity, and a poor cell proliferation response to antigenic challenge. This may be caused by the loss of 3 different genes, each of which has several additional effects, resulting in 3 types of syndromes. **Griscelli syndrome** is caused by mutations in 1 of 3 genes. Two of these genes are located at band 15q21: *RAB27A* and *MYO5A*. These 2 genetic defects result in both similar and distinct physical and pathologic findings. A third form of Griscelli syndrome, the expression of which is restricted to the characteristic hypopigmentation of Griscelli syndrome, results from mutation in the gene that encodes melanophilin—*MLPH*: (1) with primary and severe neurological disorder (GS1 also known as **Griscelli/Elejalde syndrome**); (2) with severe disturbed B- and T-cell immunity (GS2, as originally described by Griscelli); and (3) without extracutaneous abnormalities (GS3 or GS restricted to hypopigmentation/pigment dilution). Children with Griscelli syndrome caused by a defect in the *RAB27A* gene develop an uncontrolled T lymphocyte and macrophage-activation syndrome—known as hemophagocytic syndrome or hemophagocytic lymphohistiocytosis. Activated T cells and macrophages infiltrate various organs. Leukocyte infiltration in the brain probably leads to secondary neurologic impairment with convulsions and/or cerebellar manifestations. Children with a defect in the *MYO5A* gene develop neurologic problems but no immunologic problems.

Griscelli and ***Prunieras*** initially described Griscelli syndrome, or partial albinism with immunodeficiency, in 1978.

Claude Griscelli (Mar 2, 1936–) is a French physician. He was born in Rabat, Morocco, and came to France in 1956. He was an intern at the Paris hospitals in 1962 and in 1972 was appointed Professor of Pediatrics and Medical Genetics at the

Necker Enfants-Malades Hospital in Paris. He served as Advisor to the Minister for Higher Education and Research from1993 to 1994, then Advisor to the Minister of Health in 2004 and 2005. He served as General Manager of France's National Institute of Health and Medical Research (INSERM) from 1996 to 2001; he has led medical research in France and participated in the coordination of the European scientific program.

Michel Prunieras (Oct 11, 1925–) has been research director ("Directeur de Recherche") at the French National Institute of Health and Medical Research (INSERM) and the Head of the Laboratory on Human Skin Tumors, Fondation Adolphe de Rothschild in Paris. He also has been affiliated with the Laboratorie de Recherches sur les Tumeurs de la Peau Humaine, Fondation Adolphe de Rothschild in Paris.

(**Publ**.: Griscelli C, Prunieras M. Pigment dilution and immunodeficiency: a new syndrome. *Int J Dermatol* 1978; 17(10):788–791.

Griscelli C, Durandy A, Guy-Grand D, Daguillard F, Herzog C, Prunieras M. A syndrome associating partial albinism and immunodeficiency. *Am J Med* 1978; 65(4):691–702.)

Griscelli-Prunieras syndrome see **Griscelli syndrome**

Gruber-Widal reaction see **Widal test**

Guillain-Barré syndrome (acute febrile polyneuritis, **Guillain-Barré-Strohl syndrome**, **Landry's paralysis, Landry's syndrome**, **Landry-Guillain-Barré syndrome**, **Landry-Kussmaul syndrome**, **Kussmaul-Landry syndrome**) is a rare progressive form of ascending polyneuropathy. It is an acute immune-mediated polyradiculoneuropathy comprising a broad spectrum of clinical variants, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and the **Miller Fisher Syndrome** (MFS). All forms of Guillain-Barré syndrome are autoimmune diseases with a molecular mimicry and a cross-reactive immune response mechanism, where the immune system is reacting to microbial substances, but the resultant antibodies also react with epitopes occurring naturally in the body. The targets are thought to be gangliosides (i.e., GM1, GD1a, GT1a, and GQ1b) naturally present in large quantities in human peripheral nerve tissues. Autoimmune reaction results in myelin damage and a nerve-conduction block leading to muscle paralysis that may be accompanied by sensory or autonomic disturbances.

Various forms of **Guillain-Barré syndrome** are associated with several types of immune attack. The demyelinating variant features damage to the myelin sheath by T cells and macrophages, while the axonal variant is mediated by IgG antibodies and activated complement, recognizing the cell membrane covering the axon. In mild cases, nerve axon function remains intact, and recovery can be rapid if remyelination occurs. In severe cases, axonal damage occurs, and recovery depends on the regeneration of this important tissue. Guillain-Barré, unlike multiple sclerosis,

is a purely peripheral nerve disorder and in general does not cause nerve damage to the brain or spinal cord.

Two-thirds of people with Guillain-Barré syndrome have experienced an infection before the onset of the disease. Most common are episodes of gastroenteritis or a respiratory tract infection. Approximately 30% of cases are provoked by *Campylobacter jejuni*; another 10% are attributable to cytomegalovirus. Significantly, only a very few people with *Campylobacter* or cytomegalovirus infections develop Guillain-Barré syndrome. It is likely that the strain of *Campylobacter* may determine the risk because distinct forms of the bacteria have several lipopolysaccharides on their surfaces. Epstein-Barr virus, varicella zoster virus, the tropical viral infection dengue fever, and bacterium *Mycoplasma pneumoniae* also have been associated with episodes of Guillain-Barré syndrome. Some cases may be triggered by the influenza virus and possibly in rare cases by the influenza vaccine.

French physician ***Jean-Baptiste Octave Landry*** first described the disorder in 1859. The syndrome, however, is named after the French physicians ***Georges Charles Guillain*** and ***Jean Alexandre Barré***, who described it with ***André Strohl*** in 1916 in 2 soldiers who developed acute paralysis with areflexia but spontaneously recovered. In 1956, ***Charles Miller Fisher*** reported the variant of Guillain-Barré syndrome, now known as **Miller Fisher syndrome**.

Jean Baptiste Octave Landry de Thézillat (Oct 10, 1826–Oct 1865) was a French physician. He was born in Limoges, Haute-Vienne, where his uncle Dr. de Thézillat, a psychiatrist and neurologist, supported his interest in a medical education. Landry de Thézillat volunteered to help in a cholera epidemic in the French area of de l'Oise and reveived a medal from the grateful people of Oise. In 1859, he described 10 cases of the disorder that he termed "ascending paralysis," which is now commonly termed Guillain-Barré syndrome. In 1857, he married Claire Giustigniani. When his father died and left his family in difficult conditions, Landry de Thézillat had to look after other family members. He had to quit hospital research and practice and moved to a spa/water resort—Établissement hydrothérapeutique—for the treatment of patients with nervous diseases at Auteuil. In addition to his professional duties, Landry de Thézillat was a proficient dancer, notable outstanding musician. He was known as a skilled hunter, mountain climber, and horseman; he loved geology and collected crystals. In 1865, he came to the Paris suburbs to help people during a spread of cholera and died from the infection.

Georges Charles Guillain (Mar 3, 1876–Jun 29, 1961) was born to a middle-class family in Rouen, a city in northern France. His father Louis worked as an engineer and his mother Gabrielle was the daughter of a mill spinner owner in Normandy. Guillain studied medicine in Rouen for 2 years, then continued in Paris. He worked in several hospitals there after receiving his medical degree in 1902 and soon developed an interest in neurology. Guillain's first research project focused on the plexus brachialis. He became Chief of Neurology and was habilitated in 1910. After the war, he served at the Hospital Charité, and in 1920, with his friend ***Barré***, he published a substantial work on clinical experiences during the war. He received a neurology professorship at the famous Hospital de la Salpêtrière in Paris in 1923.

He held this position until his retirement in 1947. In 1909, Guillain married Juliette Chauffard and had 5 girls. Very little is known about Guillain's private life, as it seems that he devoted it to his professional work. Guillain received many honors and was a member of French, US, and Japanese academies of science. In 1949, he was appointed commander of the Legion of Honor. He died in Paris.

Jean Alexandre Barré (May 25, 1880–Apr 26, 1967) was a French neurologist who, in 1916, worked on the identification of the Guillain-Barré syndrome. He studied medicine in Nantes and got his internship in Paris. In 1912, he obtained his medical doctorate with a thesis on osteoarthropathy associated with tabes dorsalis. During World War I, he worked in a neurological unit of the Sixth Army, directed by ***Georges Guillain***, with whom he began a long-term collaboration. In 1919, he was appointed Professor of Neurology in Strasbourg. He was one of the founders of the journal *Revue D'oto-Neuro-Ophtalmologie*.

André Strohl (Mar 20, 1887–Mar 10, 1977) was a French physiologist who was a native of Poitiers, a city in west-central France. He graduated from the university when he was 17 and began his initial medical study at Sorbonne. In a few years, however, he switched to learning chemistry, mathematics, and physics for several years but decided to finish his medical education and graduated with his doctoral thesis in 1913. Interestingly, in 1914, he also received his second doctorate degree in physics. During World War I, serving as a radiologist in the Neurological Centre of the French Sixth Army, Strohl used various projection techniques to localize bullets and shell splinters. There he met ***Georges Guillain*** and ***Jean Alexandre Barré***. Soon the team of colleagues discovered unusually high levels of proteins in the spinal fluid samples from 2 soldiers with muscular weakness, pain, and paresthesias. Strohl was responsible for electrophysiological tests on treated paralyzed soldiers who later recovered. All clinical findings from 2 patients with infectious polyneuritis were summarized and published in 1916.

In 1927, Draganesco and Claudion introduced the term "Guillain-Barré syndrome," seemingly omitting Strohl's involvement in the discovery of a new disease. His name mysteriously did not appear in later publications of Guillain and Barré. It seems regrettable to ignore the name of André Strohl when the syndrome is cited. His name merits to be reintroduced to Guillain-Barré-Strohl syndrome. It has been speculated that Strohl's age was a reason of his omission: he was only 29 years old at the time of the publication, which may have been considered as a sign of immaturity by some authors. Furthermore, Strohl's name also may have added to his exclusion from future papers. After World War I, a well-known anti-German attitude was widely seen in France: Strohl's surname was of German origin and his inheritance from a primarily German province of France were not readily accepted.

From 1924 on, Strohl worked as Professor of Physiological Medicine in Algiers, Algeria. In 1926, he returned to the University of Paris to the same position. He was a member of the National Academy of Medicine. He authored more than 200 clinical and research publications, including several books and he clearly contributed significantly to medical knowledge and obtained genuine academic respect. Strohl retired in 1957.

Charles Miller Fisher see **Miller Fisher syndrome**

(**Publ**.: Guillain G, Barré J, Strohl A. Sur un syndrome de radiculo-nevrite avec hyperalbuminose du liquide cephalorachidien sans reaction cellulaire. Remarques sur les caracteres cliniques et graphiques des reflexes tendineux. *Bull Soc Med Hop* 1916; 28:1462–1470.

Guillain G, Barré JA, Strohl A. Le réflexe médico-plantaire: Étude de ses caracteres graphiques et de son temps perdu. *Bull Mem Soc Med Hop* 1916; 40:1459–1462.

Guillain G, Barré JA. Travaux neurologiques de guerre. Paris: Masson; 1920. [Book in French.]

Landry JB. Note sur la paralysie ascendante aiguë. *Gazette Hebd Méd Chir* 1859; 6:472–474, 486–488.)

Guillain-Barré-Strohl syndrome see **Guillain-Barré syndrome**

Guillain-Laroche-Léchelle reaction was probably the first test evaluating local (intrathecal) immunity in inflammatory diseases of the nervous system. ***Guillain***, ***Laroche***, and ***Lechelle*** fist reported on a new test for the diagnosis and prognosis of syphilitic disease of the central nervous system. The test that analyzed the cerebrospinal fluid was called the colloidal benzoin reaction. They reported that their test was significantly better than the gold chloride or the mastic tests in neurosyphilis diagnostics. The authors demonstrated several advantages of their new test. This included an easier observation of positive results because precipitation is more visible than color changes. Preparation of the benzoin suspension was a much simpler procedure than the preparation of a consistent colloidal gold solution. Nevertheless, authors also described the importance of using purified reagents, fresh distilled water, and clean glassware. Benzoin is the sap or gum resin harvested from the trunk of the Styrax family of trees. Its purity also was important and the amygdaloid benzoin from Sumatra was recommended. The authors also demonstrated that the results of the **Guillain-Laroche-Léchelle reaction** correlated with the results of the **Wassermann reaction**, but the test was simpler to perform and provided much faster results.

Georges Charles Guillain see **Guillain-Barré syndrome**

Guy Laroche (1884–1984) was a French gastroenterologist.

Léchelle P. (? – 1955?) was a French clinical scientist.

(**Publ**.: Guillain G, Laroche G, Lechelle P. La reaction du benzoin colloidal avec le liquide cephalo-rachidien dans l'encéphalitie lethargique. *Rev Neurol* 1921 (January): 80.

Guillain G, Laroche G, Lechelle P. Technique de la reaction du benjoin colloïdal. A short monograph of 34 pages. *Arch Intern Med Chicago* 1927; 40(2):252.)

Guillain-Thaon syndrome is a rare syndrome as a result of syphilis of the central nervous system.

Georges Charles Guillain see **Guillain-Barré syndrome**

Louis-Albert Thaon (1846–1886) was a French neurologist. Thaon's major contribution in medicine was toward the disambiguation of the tuberculosis symptomology (*Recherches sur l'anatomie pathologique de la tuberculose,* 1873).

Letter H



Hand-Schüller-Christian disease is associated with multifocal **Langerhans cell histiocytosis**. It is linked with a triad of exophthalmos (protruding eyeballs), lytic bone lesions, and diabetes insipidus. It is an inflammatory histiocytosis probably associated with disturbance of cholesterol metabolism. Also see **Abt-Letterer-Siwe disease** for a historical overview.

In 1893, ***Alfred Hand*** described the first clinical case of a 3-year-old patient seen with polyuria, thirst, and exophthalmos and assumed an association of these signs with tuberculosis. ***Artur Schüller*** in 1915 and ***Henry Asbury Christian*** in 1920 disclosed analogous cases, and their reports encouraged Hand to reassess the tuberculosis etiology of the disease. In 1929, Rowland provided the first histomorphological characterization of typical lesions in various tissues associated with the disease. In 1942, Green and Farber confirmed the presence of eosinophilic granuloma in the bone, suggesting that **Hand-Schuller-Christian disease** and **Letterer-Siwe syndrome** have identical pathological signs. Later, the clinical triad of calvarial (or bone) lesions, diabetes insipidus (imbalance of fluids causing polyuria and thirst), and exophthalmos was termed "Hand-Schuller-Christian disease" after the physicians who reported it for the first time.

Alfred Hand Jr (Feb 7, 1868–Sept 1, 1949) was a US pediatrician. He graduated from the University of Pennsylvania in 1892 and was an intern at the Children's Hospital and the German Hospital. He worked as a physician/pediatrician at the Children's Hospital of Philadelphia, the Children's Hospital of the Mary Drexel Home, the Methodist Hospital, and as a teacher at the University of Pennsylvania and its Graduate Medical School in Philadelphia. Alfred Hand married Ophelia Louiza Gregg and had 4 children. He passed away in Bridgewater, Susquehanna, PA.

Artur Schüller (***Arthur Schüller***) (Dec 28, 1874–Oct 31, 1957) was an Austrian-Jewish neurologist and radiologist. His father was an otolaryngologist and a friend of Georges Politzer, a French philosopher and Marxist theoretician of Hungarian-Jewish origin who was executed in Paris in 1942. Arthur was born in Brünn,

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Czechoslovakia (now Brno, Czech Republic), was outstanding in school, and studied medicine in Vienna. He graduated in 1899 with the highest honors, being awarded a prize by Emperor Franz Joseph at a special audience, which had only been given twice during the emperor's 60-year reign. He was habilitated in neurology and psychiatry in Vienna, and then joined an X-ray department. In 1906, he married Margarete Stiassni, and his son Franz Ferdinand was born in 1908, and a second son, Hans/Jan Heinrich, followed in 1909.

During World War I, Schüller worked as an army physician, and in 1915 reported on a patient with Hand-Schüller disease. After the war, he visited special advanced classes on X-ray diagnosis, focusing on head and neck diseases. Later, based on his work, he prepared a unique collection of images of skull lesions, which unfortunately disappeared when he had to move from Vienna. Schüller published more than 300 articles, monographs, and book chapters. He was a very talented violinist and performed with the Vienna Doctors' Orchestra.

After the annexation of Austria by Germany in 1938, Arthur and Margarete Schüller had to escape from Austria at the ages of 64 and 52, respectively. It is still not clear, however, how their sons were barred from leaving Vienna at the very last moment. The Schüllers stayed in England for short period and in 1939 settled in Australia. Schüller was welcomed by Australian colleagues and got a position at the radiology department of St. Vincent's Hospital in Melbourne. He became a very acknowledged X-ray consultant and evaluated X-ray images from around the country. He bought a house in a Melbourne suburb named, in a strange twist of irony, Heidelberg. In spite of his busy practice, it was tough for the Schüllers to live a new life without their family. On top of this, after the end of World War II, the Schüllers received confirmation that their sons had been killed. They were, like countless Jews, "exterminated in a Nazi concentration camp" in Auschwitz after spending a year in another concentration camp in Terezin, where their grandmother was killed. Both the wife and daughter of the Schüllers' son Hans/Jan also were exterminated in the Terezin and Auschwitz camps. Thus, the desperate hope of the Schüllers was destroyed by this most dreadful stroke of fate, which heavily overshadowed their remaining years. During the latter years, he was troubled by depression and developed Parkinson's disease.

Henry Asbury Christian (Feb 17, 1876–Aug 24, 1951) was a US internist. He was born in Lynchburg, VA, a descendant of Thomas Christian, who first settled in that state in 1657. He graduated from Randolph-Mason College in 1895, received his MD at Johns Hopkins in 1900, and then worked at Boston City Hospital. In 1908, he was appointed Jersey Professor of theory and practice and became the first physician-in-chief at Peter Bent Brigham Hospital, retiring in 1939. He was an outstanding teacher and clinician who wrote a number of texts and guided many young people into academic medicine. He died while on vacation in Whitefield, NH.

(**Publ.:** Hand A. Polyuria and tuberculosis. *Proc Pathol Soc Phil* 1893; 16:282–284; *Arch Pediatr*, New York 1893; 10:673–675.

Schüller A. Über eigenartige Schädeldefekte im Jugendalter («Landkartenschädel»). *Fortschritte auf dem Gebiete der Röntgenstrahlen* 1915–1916; 23:12–18.

Christian H. Defects in membranous bones, exophthalmos, and diabetes insipidus; an unusual syndrome of dyspituitarism. In: *Contributions to Medical and Biological Research, Dedicated to Sir William Osler*. New York: P. B. Hoeber, 1919; 1:390–401. *Med Clin of N Am* 1920; 3:849–871.)

Hanot-Chauffard syndrome see **Troisier-Hanot-Chauffard syndrome**

Harley's syndrome see **Dressler's syndrome**

Harrington-Hollingsworth experiment is the title of an experiment in hematology, where the academic staff of Barnes Hospital gave themselves transfusions of the plasma from a patient with immune thrombocytopenic purpura (**Werlhof's disease**) to observe the effect on platelet counts in normal subjects. The staff observed reduced platelet counts that recovered after a period of several days. This experiment established the autoimmune etiology of immune thrombocytopenic purpura.

Idiopathic thrombocytopenic purpura is the rare condition caused by antibodies destroying platelets and producing symptoms of a low platelet count and unusual hemorrhaging, including intracranial hemorrhage, mucosal and gingival hemorrhaging, abnormal menstruation, petichiae, purpura, and a general propensity to bruise easily. Although a description by Avicenna (Abu Ali ibn Sina) of purpura with characteristics of idiopathic thrombocytopenic purpura can be found in 1025's *The Canon of Medicine*, the pathogenesis and mechanisms of thrombocytopenia have been unclear for a long time. For instance, in 1915, Frank speculated that the disease was as a result of inhibition of megakaryocytes by spleen-derived factors, whereas Kaznelson suggested that the disease was the result of platelet damage in the spleen.

In 1950, ***Harrington*** and ***Hollingsworth***, hematology fellows at Barnes Hospital in St. Louis, tested their hypothesis that idiopathic thrombocytopenic purpura is caused by an unknown agent in blood that damages white blood cells. Harrington administered a 500-ml transfusion of blood to himself that had been harvested from a patient who matched his blood type and was treated in the hospital for idiopathic thrombocytopenic purpura. A few hours after blood administration, Harrington had a major seizure with a significant drop in platelet count. For almost 4 days, he demonstrated a low platelet count related to bruising and petichiae (i.e., small spots of bleeding under the skin). Improvement was seen on day 5 and became conspicuous over 4 days although complete recovery was not noted until 5 days later.

Analysis of Harrington's bone marrow sample did not reveal any effect on megakaryocytes, which allowed conclusions about the effect of patient's blood on platelets instead of bone marrow. Interestingly, this experiment was then conducted on other members of the Department of Hematology, and replicated results showed a reduction in platelet numbers within 3 hours of transfusion of plasma from patients with idiopathic thrombocytopenic purpura. The significance of the **Harrington-Hollingsworth experiment**, together with additional results published in 1951, was in the final understanding of the mechanism of the disease, which also resulted in

changing the name of the disease—from idiopathic thrombocytopenic purpura to immune thrombocytopenic purpura.

William J. Harrington (Sept 21, 1923–Sept 5, 1992) was born in Norwood, MA. He did his premedical studies at Boston College and graduated from Tufts University Medical School in 1947. After conducting his self-experiments, when Harrington was in training as a hematology fellow at Washington University Medical School in St. Louis, he conducted research projects at Washington University and attained a position of Director of the Division of Hematology in 1954. In 1964, he was invited by the University of Miami School of Medicine to establish the Center for Blood Diseases and to serve as the Chairman of the Department of Medicine. The Blood Center was later named for him. He was also a founder of the PhD–MD program at the University of Miami.

Harrington devoted his career to the study of blood diseases and autoimmune disorders. He also was dedicated to the improvement of medical education in Latin America, working on that project for almost 25 years. In appreciation of his efforts, he was awarded honorary appointments from medical schools in Brazil, Chile, the Dominican Republic, Panama, and Colombia. In addition, he actively participated in the disaster relief programs in undeveloped countries and was one of the first physicians who went to Managua in Nicaragua in 1972 after the earthquake during which nearly 10,000 people were killed.

He died when he was fixing a generator outside of his home because there was no electricity and water after Hurricane Andrew passed through southern Florida in 1992.

James W. Hollingsworth

(**Publ**.: Harrington WJ, Minnich V, Hollingsworth JW, Moore CV. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. *J Lab Clin Med* 1951; 38(1):1–10.)

Haserick's factor is thermolabile antinuclear (anti-DNA) antibodies (ANA) occurring in lupus erythematosus. The revealing of high titers of ANA is a general diagnostic benchmark for many connective tissue diseases, including systemic lupus erythematosus (SLE); detectin of ANA of SLE came from the 1948 case when neutrophilic polymorphonuclear leukocytes with engulfed Feulgen-staining nuclear material were detected in the bone marrow of a patient (Hargraves et al., 1948). These cells were termed LE cells (i.e, lupus erythematosus cells). It was well documented later that treatment of healthy bone marrow cells with serum harvested from a patient with SLE provoked formation of LE cells (Haserick and Bortz, 1983).

Many experimental and clinical studies revealed that serum from rabbits receiving cell-nuclei material could induce LE cells and that serum antibodies, specifically ANA, were responsible for the phenomenon (Miescher and Fauconnet, 1954). In 1957, four teams identified antibodies recognizing DNA in SLE patients' sera, which resulted in the development of the immunofluorescence method for detection and characterization of ANA documented by George Friou. In the following years,

indirect immunofluorescence using tissue sections or cultured cell lines was adopted for the detection of ANA, and indirect immunofluorescence using a human tumor cell line HEp-2 cells remains the gold standard for ANA screening to this day.

John R. Haserick (Sept 23, 1915–May 1, 2006) was a US physician. He graduated from the University of Minnesota Medical School in tne Twin Cities in 1941 and became the internal medicine resident there. From 1942 on, Haserick was on the medical service of US Army for 3.5 years, servicing in England, North Africa, and Italy. In Italy, he was transferred to the dermatology unit and developed his interest in skin diseases. After World War II, he finished residency in dermatology and joined the Department of Dermatology of the Cleveland Clinic in 1948. In 1960, he became the head of the section. His clinic and research focused on systemic lupus erythematosus and the blood factor in systemic lupus erythematosus.

Haserick is remembered for his achievements in the diagnosis and treatment of disseminated lupus erythematosus. He described and characterized the phenomenon of LE cells, which was the key diagnostic test for the disease for many years. Haserick did not get actual credit, however, for this, probably because his report was published several months after the report of Hargraves's Mayo Clinic team; it simultaneously described the same phenomenon. Nevertheless, Haserick seems to be the first who defined that the phenomenon resulted from a circulating "factor," which was identified later as the antinuclear antibodies. He published more than 75 articles in various medical journals. He was a Full Professor of Medicine (Dermatology) at Case Western Reserve University from 1967–1970. Haserick moved to Pinehurst, NC, in 1970 and established The Pinehurst Dermatology Clinic. He retired in 1987 and died in 2006.

(**Publ**.: Haserick JR, Bortz DW. Normal bone marrow inclusion phenomena induced by lupus erythematosus plasma. *J Invest Dermatol* 1949; 13:47.

Haserick JR, Lewis LA, Bortz DW. Blood factor in acute disseminated LE. 1. Determination of gamma globulin as specific plasma fraction. *Am J Med Sci* 1950; 219:660–663.)

Hashimoto's disease (**Hashimoto autoimmune thyroiditis**, lymphocytic thyroiditis) is a chronic inflammatory autoimmune disease characterized by lymphocyte infiltration of glands, mainly T lymphocytes, and the presence of antibodies against several thyroid tissue components. Physiologically, antibodies against thyroid peroxidase (TPO) (also TPOAb) and/or thyroglobulin cause gradual destruction of follicles in the thyroid gland. TPO is produced by the thyroid gland and used along with iodine to synthesize the thyroid hormones triiodothyronine (T3) and thyroxine (T4). According to the phase of the disease, it can present in a euthyroid and goiter state (type I); with goiter and glandular hypofunction (type IIA, classic Hashimoto); without goiter and hypothyroidism (type IIB, atrophic thyroiditis); or, finally, it can begin as transitory thyrotoxicosis (type IIC, postpartum thyroiditis). **Hashimoto's disease** is the most widespread among middle-aged women. Family history of thyroid abnormalities is common, and association with the *HLA-DR5* gene and *CTLA-4* gene polymorphisms have been established.

Hashimoto's disease was the first disease to be recognized as an autoimmune one. It was first described by the Japanese physician ***Hakaru Hashimoto*** in a paper published in Germany in 1912; he reported the symptoms of 4 patients with *struma lymphomatosa*, an intense infiltration of lymphocytes within the thyroid. In 1931, the paper was evaluated by Graham and McCullagh, who described the same disease, and the disease was recognized as an independent illness. Since then, the disease has been referred to as Hashimoto's thyroiditis in the US and Europe, but it was not until the 1950s when the name Hashimoto's disease was reintroduced in Japan.

Hakaru Hashimoto (May 5, 1881–Jan 9, 1934) was a Japanese surgeon. He was born in the village of Midau, Nishitsuge, in Mie Prefecture to a family of medical practitioners. He graduated from Kyushu University Medical School in 1907. After obtaining his MD., Hashimoto spent 3 years in Berlin, Göttingen, and London, returning to Japan after the outbreak of World War I. In 1916, he went back to his hometown, Igamachi, joined the family practice, and became a prosperous surgeon. He married at the age of 39 and had 3 sons and 1 daughter. He died of typhoid fever, which he was exposed to by a patient.

(**Publ**.: Hashimoto H. Zur kenntnis der lymphomatösen veränderung der schilddrüse (struma lymphomatosa) [Report on lymphomatous goiter]. *Archiv für Klinische Chirurgie* 1912; 97:219–248.)

Hashimoto's encephalopathy (**Hashimoto encephalopathy**) is a rare disease associated with abnormal brain function and possible immune dysfunction. Therefore, it is believed to be an immune-mediated or immune-mediated inflammatory disorder. Clinically, encephalopathy appears as impairment of attention, consciousness, cognition, orientation, and the sleep–wake cycle. Additional symptoms could include fatigue, nervousness, poor appetite, psychosis, seizure, and cerebral ischemia. Antithyroid autoantibodies are commonly present in affected individuals although many patients with **Hashimoto encephalopathy** have normal thyroid function in spite of detectable levels of antithyroid antibodies. It is unclear at which point these autoantibodies play a pathogenetic role in the development of encephalopathy, but their presence suggests some autoimmune abnormalities. In fact, the presence of antialpha enolase antibodies, recently discovered in patients with Hashimoto encephalopathy, supports this notion. Favorable clinical response to corticosteroids also suggests the immune-mediated nature of the disease. Nevertheless, the exact cause of the disease is unknown.

Hakaru Hashimoto see **Hashimoto's disease**

Hassall's corpuscles (**Hassall's bodies**, **Virchow-Hassall corpuscles**, **von Gierke's corpuscles**) are spherical or oval eosinophilic bodies, diameter 30–100 μm, present in the medulla of the thymus gland. Each consists of central area of degenerated cells surrounded by concentrically arranged flattened or polygonal cells. The number increases until puberty, then decreases. Studies indicate that Hassall's corpuscles differentiate from medullary thymic epithelial cells (mTEC) after they lose

expression of the transcription factor—autoimmune regulator (AIRE). AIRE is part of the mechanism that controls removal of self-reactive T cells to prevent autoimmune diseases. In addition, it has been suggested that Hassall's corpuscles represent the terminally differentiated stage of mTEC.

The function of Hassall's corpuscles is currently unclear. They have been projected to function in the removal of apoptotic thymocytes or the maturation of developing thymocytes. High levels of thymic stromal lymphopoietin (TSLP) were detected in the Hassall's corpuscles. This cytokine has been shown to control the maturation of dendritic cells, the most potent antigen-presenting cells, and increase the dendritic cell-mediated differentiation of naive thymocytes to FoxP3-expressing regulatory T cells. Other cytokines and chemokines identified in **Hassall's corpuscles** also may control differentiation and function of various cell subsets in the thymic medulla. Therefore, it is quite possible that the corpuscular system is involved in the process of expression and presentation of tissue- and cell-specific autoantigens for initiation of central immune tolerance.

In fact, tissue-specific autoantigens in Hassall's corpuscles have been implicated in the pathogenesis of autoimmune diseases (e.g., autoimmune thyroiditis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and **Goodpasture's syndrome**). Hassall's corpuscles are named for ***Arthur Hill Hassall***, who discovered them in 1846, which might have been first identified by ***Rudolf Virchow*** however (see Virchow R; 1860, p. 444).

Arthur Hill Hassall (Sept 13, 1817–Apr 10, 1894) was a British physician and chemist. He was born in Teddington near London. The son of Thomas Hassall, surgeon, and Ann Sherrock, Hassall was apprenticed to his uncle, Sir James Murray, a Dublin physician. He studied in Dublin, became a physician to the Royal Free Hospital in London, and in 1851 became a doctor of the London University. With a growing interest in microscopic visualization of small objects, Hassall developed a great interest in the miniature flora and fauna and published the pioneer work, *A Catalogue of Irish Zoophytes*, in 1841 while still a student in Dublin. After graduation, he opened a general practice in Notting Hill where he continued his microscopic analysis and in 1845 published his classic work, *A History of British Freshwater Algae*. In 1849, *The Microscopic Anatomy of the Human Body* appeared as the first microscopic anatomy textbook in English in which, in addition to other findings, he described the thymic corpuscles that bears his name.

In his later years, Hassall contracted pulmonary tuberculosis and in 1866, when the disease progressed, he moved to the Isle of Wight. There he founded a tuberculosis sanatorium, The Royal National Hospital, at Ventnor 2 years later. Still, from 1878 on, he stayed mostly in Italy and Switzerland because of his disease. He died at San Remo, Italy, at 77. Hassall published many papers and books on anatomy, physiology, botany, zoology, hygiene, and public health. His report on food fabrication and hygiene resulted in the Parliamentary Act against the falsification of food products.

Edgar Otto Conrad von Gierke (Feb 9, 1877–Oct 21, 1945) was a German pathologist. He was born in Breslau (Wroclaw), Silesia; studied in Heidelberg,

Breslau, and Berlin; and received his medical doctorate in Heidelberg in 1901. He subsequently worked as a pathologist at the universities in Heidelberg, Berlin, and Freiburg. He also worked at the Cancer Institute in London for a short time and then moved to the city hospital in Karlsruhe, Germany, as a pathologist. In 1910, he received the Professor of Bacteriology position at the Polytechnical University in Karlsruhe, now known as the Karlsruhe University of Applied Sciences, and worked at the university until his retirement in 1938. von Gierke, in spite of a serious illness, took up his position again when his successor was at military service during World War II.

von Gierke had a keen sense of humor, and in addition to his other talents, he was an outstanding sportsman. At the age of 47, he won a gold medal for athletics. In research, he specialized in glycogen synthesis, which led him to the discovery of glycogen synthesis type I in 1929. Edgar von Gierke published 68 articles and several books.

Rudolf Ludwig Karl Virchow (Oct 13, 1821–Sept 5, 1902) was a German doctor, anthropologist, biologist, historian, writer, editor, and politician. He is known as "the father of modern pathology"; the founder of social medicine and veterinary pathology; and, to his colleagues, the "Pope of medicine."

Rudolf was born in the town of Schivelbein in the German Kingdom of Prussia. Today, the town is in Poland and called Świdwin. He was the only son of Carl Christian Siegfried Virchow, a farmer and town treasurer, and Johanna Maria Hesse. From his earliest days at school, Rudolf was observed to be exceptionally gifted intellectually, and his parents paid for extra lessons to push him forward. He had a notable ability for learning languages. In addition to the required Greek and Latin, he learned Dutch, English, Italian, French, and Hebrew. First, he wanted to be a pastor, but had some doubts about the strength of his voice as an effective preacher. Following his interest in medicine, he received a scholarship to study at the Friedrich-Wilhelms University in Berlin.

Rudolf Virchow planned to be an army physician and studied medicine at the Army Medical School; however, in 1843, after finishing his studies, he changed his mind and moved to Charité—the largest hospital in Berlin. He worked as an unpaid prosector, getting support from his parents. Being able to use the physiology, anatomy, and embryology laboratories, Virchow wrote his first scientific papers. In 1845, he described leukocytosis and coined the term **leukemia**—he named the disease by combining the Greek words *leukos* (white) and *aima* (blood). In 1846, he offered other new terms—**thrombosis** and **embolism**. Interestingly, pushed by his concerns that publication of his results took too much time, and being supported by his friends, Virchow founded his own journal, *Archive for Pathological Anatomy and Physiology and Clinical Medicine*, now known as *The Virchow's Archives*, to expedite his publications.

In the year 1848 was a one of revolutions in Europe, and Virchow joined the movement, he struggled on the barricades in Berlin armed with a pistol he got from a friend's father. Later, when answering the question about using his pistol during the revolution, he stated, "No, because the soldiers shot at us from a great distance,

out of range for a pistol." He was a proponent of the social significance of medicine and believed that physicians must support people's well-being, working conditions, and freedom from autocracy. As an elected vice president of the Berlin Revolutionary Committee, Virchow called for freedom of the press, constitutional government, and a public healthcare system for all workers.

After the collapse of the revolutionary movement in Berlin, Virchow's position at the Charité Hospital was terminated, and he had to escape from persecution. Virchow accepted a pathology professorship at Würzburg in Bavaria. There he devoted his time and efforts to the study of cells in pathological specimens and finally recognized as the leading cellular pathologist. In 1858, Virchow was offered a position created for him of Professor and Chairman of Pathological Anatomy and Director of the new Institute of Pathology in Berlin. This institute still carries his name today.

Virchow contributed to medicine and pathology by publishing almost 2000 papers, monographs, and books, which significantly improved medical practice, medical concepts, and the public healthcare system in Germany and the whole world. His *Cellular Pathology* (1858) book with 20 lectures created a solid foundation for modern pathology and fundamental medical concepts. He provided the first characterization of carcinoma invasion, kidney amyloid degeneration, myelin structure, spina bifida, neurologia, teratomatous (dermoid) cyst of the ovary, congenital encephalitis, strawberry gallbladder, and the part of the brain known as the Virchow-Robin space. During 1859–1860, Virchow fully characterized the life cycle of *Trichinella spiralis* in pigs, explaining how worms infect humans. He educated the public that pork must be cooked thoroughly to prevent parasitic infection. He helped to organize meat inspections in slaughterhouses by veterinarians in Berlin as a necessary public health measure, which then spread throughout Prussia, Germany, and other countries. In his publications, he introduced the terms **chromatin**, **agenesis**, **heterotopia**, **parenchyma**, **osteoid**, **ochronosis**, **leukemia**, **thrombus,** and **embolus**. Virchow is best remembered for his revolutionary scientific pronouncement, *Omnis Cellula e Cellula* [All Cells Arise from Cells]. This was in opposition to a common thought that new cells are created from a fluid called blastemal, suggested by Theodor Schwann who established that all animal tissues are made of cells.

Over the last 35 years of his life, in addition to pathology, Virchow was influential in other fields of public life. In politics, he organized and led the German Progressive Party. For 13 years, he served as a member of the German Reichstag. Virchow cofounded the German Anthropology Association, where for many years he was president. He designed Berlin's water supply and sewage system, organized regular medical examinations of children in schools, and founded polyclinics and hospitals for patients who could not afford regular medical care. In 1901, Virchow's eightieth birthday was celebrated as a national holiday in Germany. A big parade in Berlin and plentiful greetings in various medical and research centers around the world demonstrated his international recognition. In 1902, Virchow fell from a streetcar in Berlin and broke his hip. Agony from unusual inactivity seriously destabilized his health, and he died several months later of cardiac insufficiency.

(**Publ**.: Hassall AH. *The Microscopic Anatomy of the Human Body, in Health and Disease.* 2 vols. London: Taylor, Walton and Maberly; 1846; 1849, p. 9.

Virchow R. *Cellular Pathology as Based upon Physiological and Pathological Histology*. London: Churchill, 1860.)

Hayem-Widal syndrome (**Widal syndrome**, **Abrami's syndrome**, **Lederer-Brill syndrome**, **Dreyfus-Dausset-Widal syndrome**) is an obsolete term for acquired hemolytic icterus, acquired hemolytic anemia associated with abnormal hemolysins and sometimes with hemoglobinuria. It is now recognized as having an autoimmune substrate and thus is not a disease sui generis.

Georges Hayem (Nov 25, 1841–Aug 27, 1933) was a French physician and hematologist. He was born in Paris, the son of Simon Hayem, a successful Jewish businessman, and Flore Abraham (she was also engaged in commerce). The family had a great medical tradition and preserved with pride the portrait of an ancestor of Hayem's, Isaie Ulman, medical practitioner of Metz, who had treated Louis XV for severe dysentery; and while doing so, he gained improved conditions for the Jews in Lorraine.

Hayem studied medicine in Paris and received the Gold Medal of the Academy of Medicine. He was later a Professor of Therapy and Medicine. He practiced medicine at the Hospital Tenon and Hospital St. Antoine. From 1893 until 1911, he held the Chair of Clinical Medicine. Georges Hayem is regarded as one of the creators of modern hematology. He invented a hemocytometer and hemoglobinometer, studied microscopically the characteristics of red blood cells and their relationship to hemoglobin, and described numerous clinical studies on blood diseases and hemorrhagic diathesis. He explained the normal and pathological morphology of the erythrocyte.

Hayem was well known for his fundamental studies on the formation of leukocytes and erythrocytes. He developed a solution of sodium chloride, sodium sulfate, and mercury bichloride to dilute blood samples for accurate counting of erythrocytes using a hemocytometer. He described the first correct counting of blood thrombocytes. In 1874, he provided a primary picture of chronic interstitial hepatitis. He was said to have saved 30% of his patients in the cholera epidemic by giving them an isotonic saline solution (Hayem serum) to combat the dehydration, Hayem introduced an intravenous solution of saline and was later nicknamed "Dr. Cholera." Hayem retired in 1911 but remained active for a long time. He died in Paris.

Georges-Fernand-Isidor Widal see **Widal test**

Pierre Abrami see **Samter's syndrome**

Max Lederer (Jul 21, 1885–Sept 13, 1952) was a US pathologist. He was born in Manhattan, New York City; graduated from Columbia University Vagelos College of Physicians and Surgeons in 1906. For 40 years, he was director of laboratories for the Brooklyn Jewish Hospital and served as consulting pathologist for several other New York institutions. He was a fellow in pathology of the Academy of Medicine and a member of the American Medical Association; he was honored by New York

City in 1935 with a distinguished service certificate for long civic activity. He died in Brooklyn at the age of 67.

Nathan Edwin Brill (Jan 13, 1860–Dec 13, 1925) was a US internist. He was born in New York. He obtained his medical doctorate at the New York University College in 1880 and did his internship at the Bellevue Hospital in 1879–1881. From 1882 on, he was a physician at the Mount Sinai Hospital and later a professor at the College of Physicians and Surgeons. Brill was a remarkable diagnostician and, for instance, discovered a new form of typhus in immigrants from Eastern Europe without body lice; it was termed recurrent typhus or Brill-Zinsser's disease. The disease was likely a recurrent form of a latent infection after initial lice/tick-born typhus.

Jean-Baptiste-Gabriel-Joachim Dausset (Oct 19, 1916–Jun 6, 2009) was a French immunologist. He was born in Toulouse, France, and was the youngest of 4 children of Henri and Elisabeth Dausset. When Jean Dausset was 11, his family moved to Paris. After earning his BS in mathematics, he was convinced by his father, who was a rheumatologist, to study medicine at the University of Paris. During World War II, Dausset joined the Free French Forces in North Africa and worked in an ambulance in Morocco and Tunisia doing many blood transfusions on wounded soldiers. In 1944, he returned to Paris and worked in the Regional Blood Transfusion Center at the Saint-Antoine Hospital.

In 1948, Dausset went to the US to work in the Children's Hospital in Boston, where he spent about 4 years. His first paper was published in 1950. In 1952, he returned to France and continued his research, focusing on hemolytic anemia and publishing on various forms of blood cell agglutination. In 1954, Dausset first observed an antileucocyte agglutinating substance and identified an isoantibody specific to leucocytes in 1958. He was the Head of Research at the Immunohematology Laboratory in the Broussais Hospital. In 1963, Jean Dausset became the Head of Immunology at Hospital Saint-Louis. There he discovered the HLA system with Felix Rapaport. Dausset was the assistant director of the Research Institute in Blood Diseases until 1968, then he was the director of the INSERM transplantation immunogenetics research unit.

For his contribution to hematology and immunology research, as well as his ultimate role in the discovery of crucial HLA antigens, Jean Dausset received the **Nobel Prize** in Physiology and Medicine in 1980, which he shared with Baruj Benacerraf and George Davis Snell. Dausset received numerous other prestigious prizes and awards. He died in Palma de Mallorca, Spain.

B. Dreyfus

(**Publ**.: Dreyfus B. Role probable d'un facteur hereditaire dans ledeterminisme de certaines anemies hemolytiques par auto-anticorps. *Nouv Rev Fr Hematol* 1964; 4:669–690.

Dausset J, Colombani J. The serology and the prognosis of 128 cases of autoimmune hemolytic anemia. *Blood* 1959; 14:1280–1301.

Lederer M. A form of acute hemolytic anemia probably of infectious origin. *Am J Med Sci* 1925; 170:500–510.

Widal F, Abrami P, Brule M. Auto-agglutinations des hematies dans l'ictere hemolytique acquis. *C R Seances Soc Biol Fil* 1908; 64:655–657.

Hayem G. *Du Sang et de ses Alterations Anatomiques*. Paris: G Masson; 1889.)

Heaf test is a diagnostic skin test. It was used commonly to determine whether children had been exposed to tuberculosis infection. The test, also known as the Sterneedle test, was named after ***F.R.G. Heaf***, who introduced and used a "Heaf gun" (trademarked "Sterneedle")—a spring-loaded device with 6 needles arranged in a circular fashion. In 2005, the **Heaf test** was discontinued because the manufacturer stopped its production owing to financial unsustainability. Until 2005, the test was widely used in the UK because of the general belief that the test was easier to read and had less variability between viewers with less training need to inject and interpret it. The Heaf test has been replaced with the **Mantoux test**.

Frederick Roland George Heaf (Jun 21, 1894–Feb 4, 1973), until 1916 ***Fritz Rudolf Georg Hief***, was a British physician who, on the advice of a colleague, changed his name to something a little more English. He was born in Desborough, Northamptonshire, England, of German ancestry, Julius Hief, a maker of scientific instruments, and Alice Beavon. Heaf studied geology as his undergraduate major but switched to medicine a year later and obtained his BA degree in Natural Sciences. He was a medical student at the University of Cambridge and St. Thomas's Hospital, but his studies were interrupted by World War I. He rejected for service in 1916 and worked in France on an ambulance unit in the Society of Friends. In 1918, Heaf returned to his medical studies at St. Thomas's Hospital in London and graduated the same year.

After holding various house appointments at St. Thomas's and the Brompton hospitals, he turned his attention exclusively to tuberculosis and followed a career in public health. He served as adviser on tuberculosis to the Ministry of Health, the Scottish Health Department, and the Colonial Office. In 1949, he became the David Davies Professor of Tuberculosis at the University of Wales, Welsh National School of Medicine. In 1961, he retired as Emeritus Professor.

Heaf married Madeleine Denison in 1920 and they had 2 sons, one of whom was a consulting physician, and a daughter who was also a doctor. After his wife's death in 1966, Heaf left Wales and moved to Freeland, near Oxford, where he was able to follow his early interest in geology and archeology and lived an active life entertaining his friends at his bungalow. He became a brilliant cook and organized 2 to 3 lunches or dinners per week, cooking and serving by himself.

(**Publ**.: Heaf FRG, McDougall JB. *Rehabilitating the Tuberculous*. London: Faber and Faber; 1945.)

Heinz bodies (**Heinz-Ehrlich bodies**) are insoluble inclusions of hemoglobin precipitated within the red cell. Their presence reflects a metabolic imbalance or abnormality in the primary structure of hemoglobin. Genetic mutations or oxidation often cause Heinz body formation. The formation of this particle is frequently triggered by injury, toxins, or drugs. In veterinary medicine, Heinz bodies are associated with

the consumption of acetaminophen (paracetamol) and onions and garlic by cats, dogs, and various primates. Thiosulfate (N-propyl disulphide) compounds in the flesh of onions have been identified as the cause because it can damage red blood cells and trigger anemia and typically is poisonous to pets. **Heinz bodies** usually are removed by macrophages in the liver (**Kupffer cells**) or in the spleen but may appear as "bite cells" (degmacyte)—abnormally shaped red blood cells with one or more semicircular portions removed from the cell margin. They are named after ***Robert Heinz***.

August Robert Theodor Heinz (May 11, 1865–Mar 6, 1924) was a German physician, pharmacologist, and pathologist. He did research in dermatology and metallic colloids, and, in 1890, described cellular inclusions in connection with cases of hemolytic anemia. He was a Privatdozent at the University of Erlangen. He died in Erlangen, Bavaria, Germany.

Paul Ehrlich (Mar 14, 1854–Aug 20, 1915) was a German physician and scientist who worked in the fields of hematology, immunology, and chemotherapy, and in 1908 received the **Nobel Prize** jointly with ***Élie Metchnikoff*** in Physiology or Medicine for contributions to immunology. He is noted for curing syphilis and for his research in autoimmunity, calling it "horror autotoxicus." He coined the term **chemotherapy** and popularized the concept of a "magic bullet."

Paul Ehrlich was born into an affluent Jewish family in Strehlen near Breslau, Germany (now in Poland). Paul was the second child of Rosa (Weigert) and Ismar Ehrlich. His father was a distiller of liqueurs, the royal lottery collector, and the leader of the local Jewish community. Interestingly, Rosa Weigert's nephew was the great bacteriologist Karl Weigert.

Paul studied medicine at the Universities of Strasbourg, Breslau, Freiburg, and Leipzig. He was appointed an Assistant to Professor at the Berlin Medical Clinic and continued his work on tissues staining. Ehrlich showed that all the dyes could be classified as being basic, acid, or neutral, and his work on the staining of granules in blood cells laid the foundations for future work on hematology and the staining of tissues. In 1882, Ehrlich published his method of staining the tubercle bacillus, and this method was the basis of the subsequent modifications still used today. This helped develop the Gram method of staining bacteria which continues to be used.

Ehrlich was a Titular Professor from 1882 and Privatdozent (teaching authorization) from 1887 at the Department of Medicine, University of Berlin. He was also a Senior House Physician to the Charité Hospital in Berlin. In 1890, ***Robert Koch***, Director of the new Institute for Infectious Diseases, offered Ehrlich an assistant position, which gave him the opportunity to continue his immunological experiments. In 1896, Ehrlich was appointed a director of the newly established Royal Institute of Serum Research and Examination (Königlichen Instituts für Serumforschung und Serumprüfung) in Steglitz, Berlin. His research on hemolysins allowed him to formulate his famous side-chain theory of immunity.

From 1897, Ehrlich was a Public Health Officer at Frankfurt-am-Main. In 1899, the Royal Institute of Experimental Therapy was moved to Frankfurt and extended into the Institute of Experimental Therapy (Institut für Experimentelle Therapie)

with Ehrlich being its Director. There he devoted himself to chemotherapy with the aim, as he put it, to find chemical substances with special affinities for pathogenic organisms, and would be, as Ehrlich expressed it, "magic bullets" to go straight to the organisms at which they were aimed. Working on syphilis, he described "Salvarsan"/"Neosalvarsan" that were accepted for the treatment of human syphilis. Ehrlich discovered that some chemical agents could alter cell functions and longevity and proved experimentally that these chemicals could cure diseased cells fighting infection. These findings opened new opportunities for the treatment of infectious diseases. In 1904, Ehrlich was awarded a honorary professorship position at the University of Göttingen.

Ehrlich was a honorary member of more than 80 foreign academies and institutions in many countries around the world, including Austria, Belgium, Brazil, Denmark, Egypt, Finland, France, Germany, Great Britain, Greece, Hungary, ltaly, Netherlands, Norway, Romania, Russia, Serbia, Sweden, Turkey, the US, and Venezuela. In Frankfurt, the street on which the Ehrlich Institute was situated was renamed Paul Ehrlichstrasse after him, but later, when the Jewish persecution began, this name was removed. After the World War II, however, when his birthplace, Strehlen, came under the jurisdiction of the Polish authorities, they renamed it Ehrlichstadt in honor of its great son.

Ehrlich married, in 1883, Hedwig Pinkus, who was then 19. They had 2 daughters, Stephanie (Mrs. Ernst Schwerin) and Marianne (Mrs. Edmund Landau). Ehrlich was a diligent worker during all his life. Early in life, he was diagnosed with tuberculosis, but he was a hard smoker and never had any concerns about the influence of smoking on his lungs. He always had a box of cigars in his hands and smoked all the time, enjoying 20–30 cigars per day. He died of a stroke in Hesse, Germany; he was 61 years old.

(**Publ**.: Heinz R. Morphologische Veränderungen des roten blutkörperchens durch gifte. *Virchows Arch Pathol Anat Physiol Klin Med* 1890; 122:112–116.

Heinz R. *Beiträge zur Pathologischen Anatomie und zur Allgemeinen Pathologie*. Stuttgart: Gustav Fischer Verlag, 1901; pp. 299–404.

Ehrlich P. *Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes*. Berlin: Hirschwald; 1891. Üeber schwere anämische zustände. Verhandlungen des Congresses für Innere Medizin; 1892; 33–52.)

Heinz-Ehrlich bodies see **Heinz bodies**

Henoch-Schönlein purpura (**Schönlein-Henoch purpura**, anaphylactoid purpura, purpura rheumatica, IgA vasculitis) is a rare immune-mediated inflammatory disease of the small blood vessels (capillaries) and is usually a self-limited disease. It is the most common form of childhood vasculitis and results in inflammatory changes in the small blood vessels. The etiology of Henoh-Schönlein purpura is not fully understood because both the autoimmune reactions and allergic reactions can be detected. It is likely that Henoch-Schönlein purpura is an immunoglobulin A (IgA) vasculitis and is an immune complex vasculitis. The disease is characterized

by unusual deposition of IgA in the small blood vessels of the skin, joints, kidneys, and digestive organs. IgA1 levels frequently are raised in the serum of patients, resulting from an increase in their production and a defect in their clearance, and probably unusual glycosylation of IgA1. Increased IgA synthesis may be related to antigen exposure within the mucosa-associated immune system. Bacteria, virus, or parasitic agents have been assumed to trigger the disease in genetically prone individuals, but contributing agents and factors await recognition. The role of genetic predisposition was supported by the documentation of susceptibility genes in the HLA system, including HLA-DRB1.

The disease was first described by an English physician, William Heberden, and the dermatologist Robert Willan in 1802 and 1808, respectively; however, the name *Heberden-Willan disease* has fallen into disuse. The disease is named after ***Eduard Heinrich Henoch*** and his teacher ***Johann Lukas Schönlein***, who described it in the 1860s. Schönlein associated the purpura and arthritis, and Henoch the purpura and gastrointestinal involvement. ***William Osler*** was the first to recognize the underlying allergic mechanism of **Henoch-Schönlein purpura**. Quite seldom purpura rheumatica is also called **Schönlein-Henoch-Glanzmann purpura** or **Schönlein-Henoch-Glanzmann disease**.

Eduard Heinrich Henoch (Jun 16, 1820–Aug 26, 1910) was born in Berlin to Jewish parents. His father Joseph was a tax inspector; his mother Sara was a member of the distinguished Romberg family. After obtaining the MD degree in Berlin in 1843, Henoch remained in the capital city, beginning his academic career as assistant in the neurological clinic of his famous uncle Moritz Heinrich Romberg, a Jewish physician who published his classic textbook in sections between 1840 and 1846; he also described what is now universally recognized as "Romberg's sign" in his original account of *tabes dorsalis*—a disease caused by syphilis damaging the back of the spinal cord.

Henoch worked at the pediatric clinic at the University of Berlin where he got a Privatdozent position in 1850, Assistant Professor in 1858, and the Professorship position at the University and Chair of the Pediatric Polyclinic in the Royal Charité Hospital in 1860. He then spent years running a private practice helping poor patients, but in 1872 he was back to the Charité as a Director of the Pediatric Clinic and to the University of Berlin as a senior lecturer in pediatrics. In recognition of his clinical and teaching efforts in developing pediatric medicine in Germany, Henoch received the honorable title "Geheimrat" (Privy Councilor, title of the highest advising officials). In 1893, he resigned and retired with the title "Medicinalrath." He lived in Meran, northern Italy, but moved to Dresden in 1898. Henoch married Helena Louisa Behrens, daughter of a Hamburg merchant in 1854, and they had a daughter.

In addition to his publications on abdominal diseases, Henoch is perhaps best known for his textbook, *Lectures on Children's Diseases*, first published in 1881. The fourth edition, in 1888, was translated and published in English the following year by the great Dr. John Thomson of Edinburgh.

Johann Lukas Schönlein (Nov 30, 1793–Jan 23, 1864) was born ***Johannes Schönlein***, and only later added the middle name of Lukas. He was the son of Thomas Schönlein, a wealthy rope maker. His mother Margarethe was probably more influential in his choice of a career in medicine and instead of learning his father's craft, he attended the Bamberg Gymnasium. Schönlein studied medicine and natural sciences at Landshut, Jena, Göttingen, and Würzburg. In 1817, when still only 23, Schönlein became a privatdozent and a university lecturer in Wttrzburg. From 1819, he was acting director of the medical department of the University Hospital in Wtirzburg, with the rank of a visiting professor; in that year he declined a call to Freiburg (Breisgau) and received an honorary doctorate from the University of Munich. From 1824, Schönlein was a chair of Internal Medicine and was also full director of the University Hospital. After teaching at Würzburg and Zurich, he was called to Berlin in 1839, where he taught therapy and pathology. He served as a physician to Frederick William IV.

Schönlein had an exceptional reputation as a teacher and clinician. He introduced the bedside teaching for doctors, and historic and classification studies in medicine. He was the first physician in Germany who consistently used auscultation, percussion, chemical analyses, and microscopical investigations of patients' specimens for diagnostic purposes. He was one of the first German professors who prepared his lectures in German not Latin. In 1839, he discovered the anthropophilic pathogenic favus fungus (honeycomb ringworm), which is named *Achorion* or *Trichophyton Schönleinii* after him. This was the first time that a vegetable pathogen had been recognized as the cause of an illness in humans, and Schönlein can be regarded as the founder of the discipline of dermatomycoses. This opened a new field—mycology—and allowed therapy to be aimed specifically at the cause of the disease. In 1839, Schönlein also presented the terms **hemophilia** and **tuberculosis**. The term "tuberculosis," derived from "tubercle," was first used in 1689 by English physician Richard Morton to define the typical lesions of consumption; prior to Schönlein's designation, tuberculosis had been called "consumption."

Interestingly, Schönlein wrote relatively little—his doctoral thesis and 2 papers of 1 and 3 pages, respectively. Schönlein's description of purpura rheumatica was written down by his students. His students and followers in Berlin include significant persons such as Albrecht von Graefe, ***Theodor Billroth*****,** and ***Rudolf Virchow***, who worked particularly closely with Schönlein. He had a very specific personality and when some physicians tried to justify his ignorance by pointing to his grey hair, he used to answer that donkeys are also grey. Virchow concisely described his teaching as "little system, many facts."

Schönlein had poor health and for many years suffered from goiter. After his wife's death in 1846 and a tragic death of his son Philipp during a botanical expedition in West Africa in 1856, he decided to retire. In 1859, together with his 2 daughters he moved to his native city of Bamberg. He devoted himself to research into the history of science and to history in general. After his retirement, Schönlein was offered the title and the form of address "Your Excellency," but he turned it down as he had done with an offer of "Nobility."

Eduard Glanzmann see **Glanzmann's syndrome**

(**Publ**.: Heberden W. *Commentarii di Morborium-Historia et Curatione*. London: Payne; 1802.

Schönlein JL. *Allgemeine Undspecielle Pathologie und Therapie*. Wurzburg: Etlinger; 1832.

Henoch EH. Über den zusammenhang von purpura und intestinalstörungen. In: *IV Verhandlungen Ärztlicher Gesellschaften*. Berlin: Klinische Wochenschrift; 1868; 5:517–519.

Henoch EH. *Über Eine Eigentümliche Form von Purpura*. Berlin: Klinische Wochenschrift; 1874; 11:641–643.)

Hermansky-Pudlak syndrome is a heterogeneous group of autosomal recessive disorders characterized by oculocutaneous albinism, a condition of abnormally light pigmentation of the skin, hair, and eyes. Additional clinical features can include diathesis owing to a thrombocyte storage pool deficiency, granulomatous colitis, pulmonary fibrosis, and immunodeficiency. Lungs, kidneys, intestine, and heart may be affected. Neutropenia and immune abnormalities are usually associated with Hermansky-Pudlak syndrome (HPS) type 2. Mutations in 1 of 9 genes—*HPS1, AP3B1* (*HPS2*), *HPS3*, *HPS4, HPS5, HPS6, DTNBP1* (*HPS7*), *BLOC1S3* (*HPS8*), and *BLOC1S6* (*PLDN*)—are known to cause **Hermansky-Pudlak syndrome** and may be associated with an abnormality of the formation or movement of lysosome-like vesicles. In fact, a product of AP3B1 codes for the beta-3A subunit of the adaptor complex-3 (AP-3) involved in vesicle formation and protein sorting.

The function of the other HPS gene products is unknown, but they interact with each other in biogenesis of lysosome-related organelle complexes (BLOCs); BLOC-3: HPS1 and HPS4; BLOC-2: HPS3, HPS5, and HPS6; BLOC-1: HPS7 and HPS8. Affected lysosome-related organelles include melanosomes in melanocytes, delta granules in platelets, lamellar bodies in pulmonary type II cells, and secretory granules in T cells. Defective lytic granule exocytosis in cytotoxic T lymphocytes, as well as defective conjugation of NK cells with target cells and impaired cytokine and chemokine secretion (e.g., TNF-α and IFN-γ from NK cells), may account for immunological manifestations in HPS2 patients. Similar to HPS2, impaired cytotoxicity of CTL and freshly isolated NK cells can be detected in HPS10 cells.

In 1959, ***Hermansky*** and ***Pudlak*** described 2 patients with oculocutaneous albinism who had bleeding diathesis. Both patients had pulmonary disease.

František Heřmanský (Feb 22, 1916–Dec 8, 1980) was a Czech internist. He was born in Prague but grew up in Slovakia where his father was the director of a grammar school. He studied in Bratislava, where he entered a medical school, but transferred to the Prague Medical Faculty. He did not graduate because of German occupation and World War II. During the war, he worked as a nurse at a hospital and trained himself in clinical and laboratory hematology. After his release, he completed his final exams and graduated in 1946. After graduation, he joined the Department of Internal Medicine in Prague-Motol and also held the position of head of the central hematology laboratory. In 1969, he was the head of the clinic, then he

was appointed a Rector and Full Professor of Internal Medicine, and in 1972, he was appointed the Head of the First Internal Clinic. František Heřmanský published more than 170 works in the field of hematology and internal medicine.

Pavel Pudlák (Oct 8, 1927–Dec 4, 1993) was a Czech internist. He was born in the small village of Papín in eastern Slovakia. He graduated from high school in Michalovce in 1946 and then studied medicine at Charles University in Prague, which he completed in 1952. After graduation, he joined the General University Hospital in Prague, where his collaboration with ***František Heřmanský*** grew into a long-term friendship. Heřmanský later recalled that he considered Pudlák to be "an extremely talented worker with both a sharp clinical insight and an extraordinary talent for research, didactic and organizational work."

During 1955–1971, Pudlák worked at the Institute of Hematology and Blood Transfusion but kept in close contact with the first Internal Clinic and Heřmanský. In 1959, they published the results of examinations of 2 patients with skin and eye albinism and symptoms of increased bleeding. They showed that in bone marrow, patients present macrophages with more pigments of a green-black color. This rare disorder was later named Heřmanský-Pudlák syndrome. During this period, Pudlák published more than 70 scientific papers. In 1971, The Minister of Health of the Czech Republic named him his deputy. A year later, Pudlák was appointed a Director of the State Sanatorium in Prague. In 1975, he was appointed a Professor of Pathology and Therapy of Internal Diseases. In addition to the State Prize for the Discovery of Heřmanský-Pudlák syndrome, he was awarded a number of other honors and recognitions. He also served as a chairman of the Czechoslovak Society of Hematology from 1982–1986.

In 1954, Pudlák married the doctor Božena Pudláková and they had 2 children. His friends described him as a sociable, energetic, optimistic, and open man with an excellent sense of humor and a great love of literature and art.

(**Publ**.: Heřmanský F, Pudlák P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: Report of two cases with histochemical studies. *Blood* 1959; 14(2):162–169.)

Herxheimer's reaction see **Jarisch-Herxheimer reaction**

Heubner-Herter disease see **Gee-Herter-Heubner disease**

Hines-Bannick syndrome (hypothermia-sweating syndrome) is related to an allergic reaction with profuse sweating followed by recurrent crises of hypothermia. In 1934, ***Hines*** and ***Bannick*** described a clinical entity of recurrent hypothermia associated with disabling sweating. Their patient, a man aged 22, had intermittent attacks of sweating, chills, and subnormal temperature. He had had these attacks for 10 years. They usually began each year in December or January and would continue for 4–6 weeks. At the onset of each attack, there had been a period of nausea and vomiting from 5–7 days following the usual cycles of sweats and chills. The patient was markedly exhausted and completely disabled.

Edwin George Bannick (Jan 30, 1896–Jan 22, 1988) was a US physician, associated with the Division of Medicine of the Mayo Clinic.

Edgar Alphonso Hines, Jr. (Nov 9, 1905–Sept 13, 1978) was a US physician associated with Mayo Clinic in Rochester, MN.

(**Publ**.: Hines Jr., EA, Bannick EG. Intermittent hypothermia with disabling hyperhidrosis: Report of a case with successful treatment. *Proc Staff Meet, Mayo Clin* 1934; 9:705.)

Hodgkin's lymphoma (**Hodgkin's disease**) is a type of lymphoma, a cancer of the lymphatic system and is one of 2 common types of cancers of the lymphatic system. The other type, non-Hodgkin's lymphoma, is far more common. Hodgkin's lymphoma is characterized by the presence of lymphatic cells called **Reed-Sternberg cells**, which are giant lymphocytes derived from B cells. Classical **Hodgkin lymphoma** can be subclassified into 4 pathologic subtypes based on Reed-Sternberg cell morphology and the composition of the reactive cell infiltrate seen in the lymph node biopsy specimen. Risk factors can include a weakened immune system, HIV or EBV infection, and a family history of the disease.

In 1832, ***Thomas Hodgkin*** published a paper "On some morbid appearances of the absorbent glands and spleen" in the *Journal of the Medical and Chirurgical Society* in London. He reported unusual postmortem results in 7 patients with enlarged lymph nodes and spleen. Samuel Wilks verified Hodgkin's results in 15 patients 33 years later and proposed the name for the disease—"**Hodgkin's disease**"—based on the uncertain status of the disease, infectious or neoplastic: "Cases of enlargement of the lymphatic glands and spleen (or Hodgkin's disease) with remarks."

Carl Sternberg and ***Dorothy Reed*** independently described the typical bi- and multinucleated cells in Hodgkin's disease in 1898 and 1902, although they did not understand the neoplastic nature of it. The neoplastic nature of the Hodgkin's cells and their common B-lymphocyte origin was proven later, changing the name of the disease from "Hodgkin's disease" to "Hodgkin's lymphoma."

Thomas Hodgkin (Aug 17, 1798–Apr 5, 1866) was a British physician. He was born into a Quaker family in Middlesex, England. In 1819, he entered medical school at St. Thomas's and Guy's Medical School (affiliated today with King's College in London). He also studied at the University of Edinburgh. In 1821, Hodgkin went to France, where he learned to work with the stethoscope—a recent invention of René Laennec. In 1823, he earned his MD at the University of Edinburgh Medical School with a thesis on the physiological mechanisms of absorption in animals. Two years later, Hodgkin was appointed lecturer in morbid anatomy and curator of the Pathology Museum at Guy's Hospital Medical School. Hodgkin had an interest in both physical anthropology and the cultural aspects, and his role as keeper of the Museum at Guy's was to collect specimens from people from around the world. In spite of his important role, in 1837 he could not get a clinical staff position, and he resigned from Guy's Hospital.

When in Paris, Hodgkin was introduced to Benjamin Thorpe, who was suffering from tuberculosis and was a banker for Rothschild's. Hodgkin agreed to work as his physician and was able to cure Thorpe. After this, Hodgkin was invited to treat Abraham Montefiore, who was seriously ill with tuberculosis and was married to a daughter of Mayer Amschel Rothschild. He joined the couple for travel in Italy. Although this job was short and not successful, Hodgkin established a lifelong friendship with Moses Montefiore—a successful financier, philanthropist, and Abraham's brother. Moses Montefiore, an orthodox Jew, was a fellow of the Royal Society and received a baronetcy from Queen Victoria in 1846 for his philanthropical efforts on behalf of Jews. From 1857, Hodgkin and Moses Montefiore made 5 trips on behalf of Jews, Christians, and Arabs to several countries.

Hodgkin was reputed to have a hot temper but was also greatly appreciated as a lecturer. He opposed slavery, advocated for reforms in medical education, and founded the British and Foreign Aborigines Protection Society. He explained the importance and supported development of sanitary measures and the protecting of child workers during the industrial revolution in England. Hodgkin often provided free medical care for the poor, especially Jews in London. His devoted his life to the disadvantaged and underprivileged people in North America, Australia, Africa, and the British West Indies.

In 1829, Hodgkin published 2 volumes of *The Morbid Anatomy of Serous and Mucous Membranes*, which became a classic pathology textbook. His *Lectures on Morbid Anatomy* were published in 1836 and 1840 becoming his main contribution to pathology teaching. Hodgkin was one of the earliest and greatest supporters of preventive medicine. He is remembered for the first description of acute appendicitis, biconcave shape (like a doughnut but without a hole at the center) of red blood cells, and the striated shape of muscle fibers. Although Hodgkin was a very talented and successful pathologist and clinician, he was a terrible businessman. Even when he had blank checks from very rich patients for his day-and-night caring work, he filled in the blank with only 10–15 pounds. His friends and colleagues hesitated to ask him for consultation because he always refused to charge them.

In 1850, Hodgkin married Sarah Frances Scaife, but they had no children. When Lady Montefiore died in 1862, Hodgkin assured her that he would always travel with her husband taking care of his health. He joined Moses Montefiore on a trip to Palestine in 1866 but contracted dysentery and died there. He was buried in Jaffa. His grave reads: "Here rests the body of Thomas Hodgkin MD of Bedford Square, London. A man distinguished alike for scientific attainments, medical skills and self-sacrificing philanthropy."

(**Publ**.: Hodgkin T. On some morbid appearances of the absorbent glands and spleen. *Med Chir Trans* 1832; 17:68–114.)

Howell-Jolly bodies are histopathological 1–2 μm granules of basophilic nuclear remnants (clusters of DNA) in circulating erythrocytes on a standard H&E-stained blood smear. During maturation in the bone marrow, late erythroblasts normally expel their nuclei, but in some cases a small portion of DNA remains. Howell-Jolly

bodies are seen with markedly decreased splenic function. Common causes include asplenia (post-splenectomy), trauma to the spleen, and autosplenectomy caused by sickle cell anemia. Other causes are radiation therapy involving the spleen (e.g., that used to treat Hodgkin lymphoma). **Howell-Jolly bodies** are also seen in severe hemolytic anemia, megaloblastic anemia, hereditary spherocytosis, and myelodysplastic syndrome. It is named after ***William Henry Howell*** and ***Justin Marie Jolly***.

William Henry Howell (Feb 20, 1860–Feb 6, 1945), a US physiologist, was born in Baltimore, MD, and graduated from the Baltimore City College high school in 1878 and Johns Hopkins University in 1881. Howell then lectured on physiology at Johns Hopkins, the University of Michigan, and Harvard University. In 1893, he was offered a position as the first Professor of Physiology in the new Johns Hopkins Medical School in Baltimore, where later he was a dean from 1899 to 1901. Howell's research focused on blood coagulation. He first isolated **thrombin** and determined its role in the clotting pathway. Together with his student, Jay McLean, Howell described a new anticoagulant, which he called **heparin** because of its high levels in the liver. Because of his research focus, Howell always had several assistants and volunteers in the laboratory who were members of families with hemophilia patients. In 1905, Howell published the *Textbook of Physiology for Medical Students and Physicians*, which was justifiably adopted by many US medical schools, and it had 14 editions during Howell's lifetime.

Justin Marie Jolly (Aug 6, 1870–Feb 1, 1953), a French hematologist and histologist, was born in Melun, Seine-et-Marne, and studied medicine at the Collège de France. He directed laboratory service at the medical clinic in the Hôtel-Dieu de Paris and the histological laboratory at the École des Hautes Etudes. He was a professor at the Collège de France from 1925 to 1940. He was known as the first hematologists in France who worked with live tissue to link morphology with physiology and pathology in vivo. He was famous for the generation of the earliest "microscopic movies" of mitosis in living cells in 1913. In 1923, he published an influential textbook on hematology called *Traité Technique d'Hématologie*, which became a classic book in France, and was used by innumerable students there.

(**Publ**.: Howell WH. The life-history of the formed elements of the blood, especially the red blood corpuscles. *J Morphol* 1890; 4(1):57–116.

Jolly J. Recherches sur la formation des globules rouges des mammifères (in French). Paris: Comptes Rendus de la Société de Biologie. 1908; 58:528–531.)

Hughes syndrome see **Soulier-Boffa syndrome**

Hughes-Stovin syndrome is a rare autoimmune disorder characterized by deep venous thrombosis (DVT) and pulmonary and/or bronchial aneurysms. The pathogenesis is not clear, but it is assumed to be a consequence of angiodysplasia and vasculitis similar to those in **Behcet disease**. Yet, unlike Behcet's, which causes symptoms throughout the body, Hughes-Stovin generally only inflames the arteries of the lungs and the body's veins. This results in weakness of the arteries, leading to

multiple aneurysms in the lungs, and frequent occurrences of DVT. Although ***Hughes*** and ***Stovin*** described a syndrome consisting of multiple pulmonary aneurysms and peripheral venous thrombosis in 1959 in a total of 4 male patients, less than 50 cases have been published in the literature, with most of the patients being young males aged 20–40 years. Most commonly, immunosuppressive therapy involving a combination regimen of glucocorticoids and cyclophosphamide has been employed as a first-line medical management.

Hughes-Stovin syndrome was named after2 British physicians, ***John Patterson Hughes*** and ***Peter George Ingle Stovin***.

John Patterson Hughes was a British physician.

Peter George Ingle Stovin was a British physician.

(**Publ**.: Hughes JP, Stovin PG. Segmental pulmonary artery aneurysms with peripheral venous thrombosis. *Br J Dis Chest* 1959; 53(1):19–27.)

Hughes syndrome see **Soulier-Boffa syndrome**

Hurst disease (Weston-Hurst syndrome, Weston Hurst syndrome, acute hemorrhagic leukoencephalitis) is a rare severe, sudden and fatal demyelinating disease of the central nervous system that is typically diffuse, multifocal and associated with petechial hemorrhage. It is characterized by a quickly progressive severe inflammatory process that leads to neurological deficiencies and respiratory depression. The disease is often preceded by an upper respiratory tract infection, Epstein-Barr virus or Mycoplasma infection.

The clinical presentation is inconsistent with fever, abnormal mental activity, headache, vomiting, nausea, seizures and coma. The hallmark characteristics of Hurst disease are rapid progression, dismal prognosis and high mortality rate with most patients dying within one week of disease onset. The total number of reported cases is less than 100.

The pathogenesis is thought to be an intense immune response to the possible antigen(s) present, which leads to central nervous system demyelination. Hurst disease is probably related to autoimmune cross reaction to the myelin antigens. Many clinicians consider it a fulminant variation of acute disseminated encephalomyelitis, forming a spectrum of disease. The disease may be associated with snake bite, ulcerative colitis, Crohn's disease, immune complex deposition, multiple sclerosis, autoimmune myopathy, mixed connective tissue disorders, systemic lupus erythematosus, complement hyperactivation and other underlying conditions. The disease was also reported in patients with severe COVID-19, where oligoclonal bands were identified on cerebrospinal fluid analysis suggesting intra-thecal immune response.

The first case was described by ***Hurst*** in August 1941 when two cases in a housewife aged 33 and a male munition worker aged 33 were reported. The principal clinical feature was a rather rapid abrogation of the higher cerebral functions in two previously healthy persons who suffered also with headache, vomiting and slight fever. At autopsy the brains presented identical edematous and hemorrhagic lesions

in the white matter. Other authors described very similar encephalitic cases with petechial hemorrhage and inflammation, as early as 1875.

Edward Weston Hurst (June 22, 1900 - Dec 16, 1980) was a UK pathologist. He was born in Birmingham in England to Edward William and Clarinda Hurst, educated at King Edward VI School and graduated from the University of Birmingham in 1922. From 1926, he worked at the National Hospital, London, and then as a clinical pathologist at the Miller General Hospital International Fund for Research on Poliomyelitis at the Lister Institute. He also got an additional training (1932-1934) at the Rockefeller Institute for Medical Research in the USA. From 1935, he became William Withering lecturer at the University of Birmingham.

In 1936, Hurst was invited by South Australian Government as foundation director of the Institute of Medical and Veterinary Science with an additional appointments as director of the Adelaide Hospital laboratories of pathology and bacteriology and professor of experimental medicine in the University of Adelaide. In 1943, he returned to England as a member of the research staff of Imperial Chemical Pharmaceuticals Limited, in Manchester, and later the Central Toxicological Laboratory of ICI. He retired in 1967 and moved to live in Malta.

Weston Hurst research focused on pathology, and he was known as an excellent teacher and educator. His hobbies were alpine walking and photography.

(**Publ**.: Hurst EW. Acute hemorrhagic leukoencephalitis: a previously undefined entity. *Medical Journal of Australia* 1941; 2(1):1-6.)

Hübener-Friedenreich-Thomsen phenomenon (red-cell T activation, polyagglutination, T-activation) is characterized an enzymatic modification of the membrane of red cells resulting in exposure of the T antigen or **Thomsen-Friedenreich antigen**. The T antigen is located on the surface membrane of red blood cells in the normally masked form by constructs composed of terminal N-acetyl neuraminic acid (NeuAc or sialic acid), d-galactose, N-acetyl-d-galactosamine (GalNac), and serine or threonine. An enzyme neuraminidase may cleave these terminal residues, unmasking the T antigens. Neuraminidase is expressed by various microorganisms, including *Clostridia* species, *Streptococcus pneumonia*, and influenza viruses.

Polyagglutination is a phenomenon of red blood cell agglutination in the presence of human serum because of the infection-induced or inherited disorder-induced unmasking of normally hidden antigens. In several forms of polyagglutination, cryptantigens–antigens on the surface of erythrocytes, which are not normally visible, are recognized by benign IgM antibodies present in most human serum. Those antibodies induce the diffuse agglutination or polyagglutination of activated red blood cells, regardless of the ABO type of the cells.

The common example of acquired polyagglutination is known as T activation or the **Hubener-Thomsen-Friedenreich phenomenon**. This type of polyagglutination is found in children with some bacterial infections. T activation is often associated with *Streptococcus pneumoniae*, *Clostridium perfringens*, or *Vibrio cholerae*. Furthermore, T activation was detected in children with influenza virus infections. Enzymes from the bacteria cleave sialic acid residues (N-acetylneuraminic acid or

"NeuNAc") from glycophorins A and B, exposing the underlying T antigen to full view. Most of these patients have no symptoms, but occasionally, someone with T activation may present with hemolysis, even without being transfused. More significantly, patients with T activation may suffer significant hemolysis when they are transfused with human plasma.

Tn polyagglutination is another example of polyagglutination, which is acquired and has no association with an infection. It is a result of a gene mutation on the X chromosome causing an abnormal synthesis of sialic acid residues on glycophorins A and B. Tn polyagglutination induces serious clinical problems associated with hemolytic anemia, thrombocytopenia, and leukopenia. Tn Polyagglutination, unlike the transient T activation, is permanent because it is triggered by a mutation. Another form of polyagglutination is Th polyagglutination, characterized by early and mild T activation because of just a small quantity of sialic acid cleaved from red blood cells. Th activation is not associated with an infection and is seen in children with hypoplastic anemias and some healthy pregnant women and newborns. Another form is Tk activation that occurs because of the activity of endo- and exo-β-galactosidases and is connected with *Serratia marcescens*, *Bacteroides fragilis*, and *Candida albicans* infections. Tx activation was reported in children with pneumococcal infection.

Hübener (1925) and ***Thomsen*** (1927, 1928) reported that red blood cells from old blood samples occasionally may be agglutinated by sera regardless of the ABO types. Thomsen called this phenomenon "panagglutinable" and speculated that it was secondary to red blood cells agglutinating with bacteria. His student ***Friedenreich*** (1930) discovered that this phenomenon was the result of blood contamination with specific enzyme-producing bacteria. That induced a new agglutinogen "T," which is expressed on the red blood cell surfaces and reacts with an agglutinin "T" produced in all adult sera, but not in newborns. The antigen uncovering or unmasking the process is now known as the **Hubener-Thomsen-Friedenreich phenomenon**.

G. Hübener

Oluf Thomsen see **Thomsen-Friedenreich antigen**

Viggo Friedenreich see **Thomsen-Friedenreich antigen**

(**Publ**.: Hübener G. Untersuchungen über Isoagglutination mit besonderer Berücksichtigung scheinbarer Abweichungen vom Gruppenschema. *Z. Immun Forsch Exp Ther* 1926; 45:223–226.

Thomsen OZ. Ein vermehrungsfahiges Agens als veranderer des isoagglutinatorischen verhaltens der roten Blutkorperchen, eine bisher unbekannta Quelle der Fehlbestimmungen. *Zeitschrift für Immunitäts Forschung* 1927; 52:85–90.

Thomsen O. *C.R Soc Biol*, Paris 1927; 96:556.

Thomsen O. *Z Immun Forsch* 1928; 57:301.

Friedenreich V. *The Thomsen Hemagglutination Phenonicnon. Production of a Specific Receptor Quality in Red Corpuscles by Bacterial Activity*. Copenhagen: Levin and Munksgaard; 1930.)

Letter I



Isaacs's syndrome (**Isaacs-Mertens syndrome**, **Isaacs-Zschoke-Mertens syndrome**, immune-mediated neuromyotonia) is an antibody-mediated disfunction of potassium channels. Clinically **Isaacs's syndrome** is seen as muscle cramps, myokymia (I,e., eye twitching), gradual relaxation after muscle contractions (I,e., pseudomyotonia), and hyperhidrosis (i.e., excessive sweating). The antigen was identified as a protein associated with voltage-gated potassium channels (VGKC), particularly dendrotoxin-sensitive fast potassium channels. Autoantibody-induced inhibition of voltage-gated outward K^+ current because of the direct blockage of VGKC or decreased channel density can induce hyperexcitability of the peripheral nerve, which is relieved by the administration of Na+ channel blockers and immunotherapy.

Autoantibodies to voltage-gated potassium-channel complexes also have been identified in **Morvan syndrome** (i.e., neuromyotonia, peripheral nerve hyperexcitability), several autonomic disorders, temporal epilepsy, and autoimmune limbic encephalitis. VGKC antibodies or VGKC-complex antibodies can target specific proteins that develop with VGKC, such as leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR-2). Usually, anti-LGI-1 antibodies are seen in limbic encephalitis, whereas anti-CASPR-2 antibodies have been detected in patients with Morvan syndrome.

Denny-Brown and Foley, in 1948, described electrophysiological features of "undulating myokymia" that account for the first report characterizing the clinical and electrophysiological motor features of generalized peripheral nerve hyperexcitability. The initial full description of the syndrome of "continuous muscle-fiber activity" was formulated in 1961 by ***Hyam Isaacs***, who established the peripheral nerve origin of the spontaneously occurring discharges. Later, ***Hans-Georg Mertens*** added other characteristics of the disease. Further synonyms for the diseases include hereditary continuous muscle fiber activity syndrome, neuromyotonia syndrome, and pseudomyotonia syndrome.

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Hyam Isaacs (May 9, 1927–May 11, 2003) was a South African neurophysiologist and physician, who worked at the Clinical Neuromuscular Research Unit, Department of Physiology, Witwatersrand University Medical School in Johannesburg. From 1945–1950, he was a student in medical school, although initially he planned to be an engineer. He was a Professor of Physiology and had his private practice. He was born, worked, retired, and lived in Johannesburg. Isaacs had a teaching position as a senior lecturer (1961–1990) at the Witwatersrand University and parallel work in private practice. From 1965 onwards he was Medical Director of the Muscular Research Foundation of South Africa in Johannesburg.

Isaacs was a recipient of the Sailor Malan award from the Saila Malan Foundation for Research into Parkinson's Disease in 1976 and 1977; the Smith & Nephew award in 1977; and a Honorary Professor award from the Department of Psychology, Witwatersrand University in 1998. He was a Fellow of the Royal College Physicians (Edinburgh) and a member of the World Muscle Society (a founding member).

Hans-Georg Mertens was a German neurologist. He held the Chair of Neurology at the University of Würzburg from 1968–1989. He also was affiliated with the Neurological University Hospital Hamburg-Eppendorf, Germany.

S. Zschocke was a German neurologist.

(**Publ**.: Isaacs H. A syndrome of continuous muscle-fibre activity. *J Neurol Neurosurg Psych* 1961; 24:319–325.

Mertens HG, Zschocke S. Neuromyotonie. *Klin Wochenschr* 1965; 43:917–925.)

Isaacs-Mertens syndrome see **Isaacs's syndrome**

Isaacs-Zschoke-Mertens syndrome see **Isaacs's syndrome**

Letter J



Jabs syndrome see **Blau syndrome**

Jabs-Blaus syndrome see **Blau syndrome**

Jadassohn-Bloch skin test is the very earliest test for allergic conditions; it was developed by ***Josef Jadassohn*** in 1895 and used for the first time as a diagnostic tool. At the V Congress of the German Dermatological Society in Graz in 1895, he reported about differences in response of the same individual to the same drug depending on the route of administration. The reaction was different for the systemic versus external application and for the various sites of external administration (e.g., mucous membranes, healthy skin, or ulcerated skin). Jadassohn compared reactions to the antiseptic iodoform and discovered that a dermatitis could be generated in susceptible patients only when iodoform was applied to intact skin. Importantly, Jadassohn's "functional skin test" was the first model of the patch test for detection of delayed-type hypersensitivity (DTH) reactions and the very first skin test for allergy diagnostics. Sulzberger brought the technique to the US in the 1930s.

More than 3000 chemicals are known to cause allergic contact dermatitis. Unquestionably, patch testing that many chemicals is not practical and only a small number of these known agents account for a large percentage of cases of allergic reactions. In 1995, the US Food and Drug Administration (FDA) officially approved the first ready-to-use patch test model system—the Thin-Layer Rapid Use Epicutaneous Test (TRUE Test). The initial TRUE Test used 23 allergens to be applied to the patients' skin as two panels with 12 allergens in each. In 2007, 5 additional allergens were added to the TRUE Test. At that time, the TRUE Test had been expanded to include 3 full panels of 35 different allergens. Many dermatologists and dermatology centers routinely use an expanded version of the patch test (e.g., the NACDG Screening Series) with 50–80 allergens.

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Joseph (Josef) Jadassohn (Sept 10, 1863–Mar 24, 1936) was a German-Jewish dermatologist. He was born in Liegnitz, Silesia (now Poland) into a Jewish family. He studied medicine in Göttingen, Heidelberg, Leipzig, and Breslau; the latter is where he got his medical degree in 1886. While at Breslau, Jadassohn was fascinated by ***Julius Cohnheim***, a pathologist who for the first time presented how leukocytes could migrate through vessel walls using intravital microscopy. In 1887, after military service, Jadassohn started his dermatology residency at the University of Breslau supervised by ***Albert Neisser***. He finished his residency in 1892 and continued his clinical focus on available public health regulations to control sexually transmitted diseases and prostitution. He also was interested in cutaneous lesions observed in tuberculosis and introduced a new classification of dermatologic diseases based on disease etiology rather than anatomic presentation.

In 1896, Jadassohn became a director of the skin clinic of the University of Berne in Switzerland. He married Margarete Kern who enormously supported his career as his coworker and secretary. They had a son, Werner, who later was a Chairman of the Department of Dermatology at the University of Geneva. Of note: Naegeli-Franceschetti-Jadassohn syndrome was not named after Josef Jadassohn but after his son Werner Jadassohn.

In 1917, Jadassohn returned to the University of Breslau to succeed his teacher, ***Albert Neisser***. Jadassohn received the title of "Geheimrat" (privy council). He was very well respected by his patients because, in addition to his exceptional knowledge of medicine, he always showed patience and empathy. Jadassohn was a short man with a large head, shaggy eyebrows and mustache, and large gray-blue eyes that showed his mood and emotions. He was a heavy pipe smoker and his trips throughout the clinic were well known by the loud sound he created by knocking the dottle from his pipe on an ashtray.

In 1930, Jadassohn resigned his chair position and was succeeded by his long-term assistant, ***Max Jessner***. In 1933, the Nazi regime in Germany forced Jadassohn and his Jewish colleagues to step down from their positions and medical duties. In 1934, Jadassohn immigrated to Zurich. In 1936, he was diagnosed with colon cancer and died from abdominal surgery-associated complications.

Jadassohn was a pioneer in the field of allergology and clinical immunology. He was a very solid proponent of bringing immunological tools into clinical analysis of dermatological diseases. He was considered the **father of the patch test**. He published the *Handbook of Skin and Venereal Diseases*, the most complete dermatology textbook of his time. Jadassohn was a member and cofounder of many clinical and research dermatologic societies. He served on the editorial board of many journals, including the key dermatologic journal at the time, *Archiv für Dermatologie und Syphilis.* He was the first to describe numerous clinical symptoms, conditions, and abnormalities, including nevus sebaceous, blue nevi, incontinentia pigmenti, pityriasis lichenoides chronica, congenita (Jadassohn-Lewandowsky syndrome), granulosis rubra nasi, pachyonychia, and the Borst-Jadassohn phenomenon. His name is also linked to Jadassohn-Dössekker disease and Tièche-Jadassohn naevus.

Bruno Bloch (Jan 19, 1878–Apr 10, 1933) was a Swiss dermatologist. He was born in Endingen, Canton Aargau, Switzerland, and attended the University of Basel, where he graduated in 1900 and obtained his doctorate in 1902. He also was trained at the medical and dermatological clinics in Basel, Berlin, Vienna, Paris, and Bern. In 1908, he secured a head of dermatology position at the University of Basel, was habilitated for dermatology and syphilology (1909), and became a Full Professor in 1913. In 1916, he moved to the University of Zurich to become a Chair of Dermatology and held this position until his death.

Bloch learned a lot from his teacher and friend, Jadassohn, and continued expanding his efforts in applying laboratory techniques to understand skin disorders. He contributed a lot to experimental and clinical allergology and significantly improved the knowledge of pigmentation disorders. He expanded patch testing by introducing, for the first time, a way to grade the intensity of the reaction to tests, as well as suggesting a standardized battery of tests. He also described the dopa reaction, which opened new avenues for the study of melanocytic neoplasms and pigmentary disorders.

(**Publ**.: Jadassohn J. Zur kenntnis der medicamentösen dermatosen. *Verh Dtsch Derm Ges* 1895; 5:103–129.

Bloch B. Das problem der pigmentbildung in der haut. *Arch Derm Syph* 1917; 124:129–208.)

Jarisch-Herxheimer reaction (**Herxheimer's reaction**) is an unusual temporary clinical reaction seen in patients infected with spirochetes who are receiving antibiotic treatment. This phenomenon may appear within 24 h after initiation of antibiotic therapy associated with different infections (e.g., syphilis, Lyme disease, leptospirosis, and relapsing fever—lice/tick-transmitted disease). Clinically it is characterized by fever, hyperventilation, chills, headache, rigors, nausea, tachycardia, hypotension, vomiting, flushing, myalgia, and aggravation of skin lesions. Despite some advances, the precise mechanism of **Jarisch-Herxheimer reaction** is still uncertain and may be multifactorial. The reaction is supposed to be caused by an acute inflammatory reaction when cytokines and lipoproteins from dying microorganisms enter patients' bloodstream. Jarisch-Herxheimer reaction causes an increase in inflammatory cytokines during the period of exacerbation, including IL-6, IL-8, and TNF-α, which results in the development of body aches, fevers, rashes, nausea, and vomiting. It is an acute, self-limiting condition, and it is important to identify the reaction and distinguish it from allergic reactions.

Adolf Jarisch and ***Karl Herxheimer*** are credited with the initial characterization of the Jarisch-Herxheimer reaction. It was first reported by Jarisch in the late 1800s when he observed an aggravation of skin reactions in a patient with syphilis after therapy with a mercurial mixture. In the early 1900s, a similar incident was presented by Herxheimer.

Adolf Jarisch (Feb 15, 1850–Mar 21, 1902) was an Austrian dermatologist. He was born in Vienna, studied medicine there, and got his first position in general

medicine practice in Vienna in 1868. In 1871, he published a work on the inorganic components of blood. He graduated with an MD in 1874, and that year began working at the world's first dermatological clinic in Vienna. In 1880, Jarisch finished his training in dermatology and became Dermatology Chair in the Wiener Allgemeine Poliklinik. In 1888, he went to a position as a Professor of Dermatology and Syphilology in Innsbruck. In 1892, he moved to Graz as a professor and was promoted to full professorship in 1901. Soon after that he died of typhoid fever.

Karl Herxheimer (Jun 26, 1861–Dec 6, 1942) was a German-Jewish dermatologist. He was born in Dotzheim, now Wiesbaden, Hessen, Germany, to Hermann Herz Herxheimer and Charlotte Jeanette Johannette Herxheimer. He studied medicine at the universities in Freiburg, Strasbourg, and Würzburg, receiving his doctorate in 1885 with a thesis on cerebral syphilis. Following graduation, he worked at the Institute of Pathology in Frankfurt am Main and at the University Skin Clinic in Breslau. In 1894, he became director of the municipal dermatology clinic in Frankfurt and, together with ***Paul Ehrlich***, he was instrumental in founding the University of Frankfurt. In 1914, he became a professor for skin and venereal diseases at the University of Frankfurt.

In 1933, Herxheimer, who was a Jew, had already resigned his positions because of his age when the Nazis came to full power. Despite of his friends' and colleagues' suggestions and requests, he persistently refused to leave Germany. He was arrested and detained in the autumn of 1941. One year later in August 1942, at the age of 81, he was transferred to the Theresienstadt, Czechoslovakia, concentration camp, where he died in a few months.

(**Publ**.: Jarisch A. Therapeutische versuche bei syphilis. *Wien Med Wochenschr* 1895; 45:721–742.

Herxheimer K, Krause D. Ueber eine bei syphilitischen vorkommende quecksilberreaktion. *Dtsch Med Wochenschr* 1902; 28(50):895–897.)

Jenner's cowpox vaccine is the world's first vaccination available as a preventive treatment for smallpox—a disease that had killed millions of people over the centuries. It represented the earliest scientific attempt to control an infectious disease by the deliberate use of vaccination. Jenner's work is regarded widely as the foundation of immunology even though he was neither the first to suggest that infection with cowpox-conferred specific immunity to smallpox nor the first to attempt cowpox inoculation for this purpose. Cowpox virus is one of the originally described members of the genus *Orthopoxvirus*. Historically, researchers have referred to the ailment known as cowpox and even have suggested that it could provide immunity against smallpox. Nevertheless, it was Jenner's publications in 1798 and 1799 that provided the **first scientific description of a vaccination** by detailing the efficacy of cowpox virus "scarification" in inducing protective immunity against challenges with variola virus.

Edward Jenner (May 17, 1749–Jan 26, 1823) was an English doctor. He was born in Berkeley, Gloucestershire, to the local vicar's family. At the age of 14, he

started helping a local surgeon, learning basic medicine from him, and then continued his medical education in London. In 1772, he returned to Berkeley as a doctor and worked there for the rest of his career.

In 1796, he conducted his legendary vaccination experiment on 8-year-old James Phipps to test his theory that milkmaids who contracted the mild disease of cowpox never developed smallpox. Jenner harvested pus from a cowpox pustule and administered it into a small cut on the boy's arm. The results demonstrated that inoculation with cowpox induced immunity to smallpox. His paper submitted to the Royal Society in 1797 was rejected. Jenner continued his experiments on other children, including his own 11-month-old son. Jenner's paper was published in 1798, and he invented the term **vaccine** from the Latin "vacca" for cow. One room in Jenner's house, which he called the "Temple of Vaccinia," was used to vaccinate the poor people for free. This Chantry House was converted to the Jenner Museum in 1985.

(**Publ**.: Jenner E. An Inquiry into the Causes and Effects of the Variolae Vaccinae: A Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of the Cow Pox. London: Printed for author by Sampson Low; 1798:116 p.

Jenner E. Further Observations on the Variola Vaccina, or Cowpox. London: Printed for author by Sampson Low; 1799:64 p.)

Jessner disease see **Jessner-Kanof disease**

Jessner-Kanof disease/syndrome (**Jessner disease**, benign lymphocytic infiltration) is a benign cutaneous disorder clinically characterized by recurrent asymptomatic erythematous papules and plaques sometimes grouped with an arciform disposition on the face, neck, and back. The clinical course varies with remissions and exacerbations. The lesions can persist indefinitely, and some may disappear spontaneously without sequelae.

This T-cell infiltrative disease has remained poorly understood, and several etiologies have been proposed. **Jessner disease** might be a variant of lupus erythematosus or a $CD8^+$ polyclonal-reactive pseudolymphoma. It may be a polymorphic light reaction, cutaneous lymphoid hyperplasia, or reticular erythematous mucinosis. Additional evidence links some cases of **Jessner-Kanof disease** to *Borrelia burgdorferi*. Yet, *Borrelia* infection may present with similar histology findings and can represent a pseudolymphomatous reaction (*Borrelia* -associated pseudolymphoma) and should be excluded, especially in countries with high rates of *Borrelia* infections. One occurrence of Jessner-Kanof disease, as a consequence of a **Koebner response** to patch testing, has been reported. Jessner-Kanof disease might be a variant within the spectrum of cutaneous T-cell pseudolymphoma. The lymphocytic infiltration was first described by ***Jessner*** and ***Kanof*** in 1953.

Max Jessner (Nov 2, 1887–Aug 27, 1978) was a German-American dermatologist. He was born to a Jewish family in Stolp, Pommerania, a region on the southern shore of the Baltic Sea in northern Europe, split between Germany and Poland. He studied in Munich and Königsberg, obtaining his doctorate in 1910. From 1912 on,

he was an assistant to ***Josef Jadassohn***, a very well-known dermatologist in Germany, first in Bern, then in Breslau as "Oberarzt" (Associate Professor). He published his thesis for habilitation in dermatology in 1922 about experimental sporotrichosis, and subsequently worked on a vaccine against leishmaniasis. He became a professor in 1926 and after Jadassohn resigned as chairman of dermatology at the University of Breslau, Jessner, having been his assistant and associate of many years, took over the chairmanship position.

In 1933, many of Jessner's colleagues and assistants at the department were fired according to the Law for the Restoration of Professional Civil Service that had been enacted on April 7, 1933, and allowed the government to legally withdraw Jews and political opponents from public service positions. The law excluded veterans and, therefore, did not apply to Max Jessner who had been a World War I frontline physician. Nonetheless, in the fall of 1934, in spite of the fact that Jessner had officially converted to the Lutheran faith, he was a Jew in the eyes of the Nazis and was fired, given that it was considered to be "imperative for the new development of the medical faculty in Breslau, which was almost entirely Jewified, that the last remnants of this Jewification vanish, even if those involved are war veterans."

Together with many other Jewish physicians from Breslau, Jessner was able to escape to the US. He immigrated to New York City via Switzerland and established a successful private practice, as well as serving on the staff of the Skin and Cancer Unit of the New York Postgraduate Medical School that later merged with New York University Department of Dermatology. Here he described lymphocytic infiltrate of the skin with Norman Kanof in 1953. He died in Switzerland.

Norman B. Kanof (May 31, 1920–Feb 14, 2009) was a US physician. He was born in New York City, graduated from the George Washington University in 1941, and received a doctoral degree in medical science from Columbia University in 1949. He was affiliated with the New York University School of Medicine from 1949 onwards, being a Clinical Professor of Dermatology.

(**Publ**.: Jessner M, Kanof NB. Lymphocytic infiltration of the skin. *Arch Dermatol* 1953; 68:447–449.)

Jo antigen belongs to a heterogenous group of extractable nuclear antigens (see **Sm antigen**). In 1980, Nishikai and Reichlin described the Jo-1 antibody system named after the patient ***John P***., the donor of the prototype serum. This patient suffered from polymyositis and interstitial pulmonary fibrosis.

Anti-Jo-1 antibodies are anti-histidyl tRNA synthetase antibodies commonly seen in patients with pulmonary manifestations of the antisynthetase syndrome—a chronic autoimmune disease associated with interstitial lung disease, dermatomyositis, and polymyositis. Anti-Jo-1 autoantibodies are the most common antisynthetase antibodies; they are found in ∼20% of the adult patients with polymyositis or dermatomyositis. Other antibodies that may be seen in association with antisynthetase syndrome are anti-PL7 (threonyl-tRNA synthetase), -PL12 (alanyl-tRNA synthetase), -EJ (glycyl-tRNA synthetase), -OJ (isoleucyl-tRNA synthetase), -KS (asparaginyl-tRNA synthetase), -Zo (phenylalanyl-tRNA synthetase), -Ha-YRS (tyrosyl-tRNA synthetase), and -SRP (signal-recognition particle).

(**Publ**.: Nishikai M, Reichlin M. Heterogeneity of precipitating antibodies in polymyositis and dermatomyositis. Characterization of the Jo-1 antibody system. *Arthritis Rheum* 1980; 23:881–888.)

Job syndrome (**Job's syndrome**, **Job-Buckley syndrome**, **Buckley syndrome**, Hyper IgE syndrome) is a very rare primary immunodeficiency disorder with approximately 250 reported cases. The clinical manifestations are rather homogeneous with recurrent subcutaneous infections and infections in the respiratory tract, mostly with juvenile onset. Arthritis, which is marked by constant erosion of bones at their joints, also is frequent in patients. Laboratory tests show minor eosinophilia, and elevated immunoglobulin E levels are always seen, partially specific to *Staphylococcus aureus*. Also varying decreases of polymorphonuclear leucocyte-chemotactic response can be seen. In general, there is a defective immune response involving T lymphocytes, neutrophils, and the cytokines they produce, especially interferon-γ (IFN-γ); increased levels of IFN-γ result in marked elevation of immunoglobulin E.

In correct terminology, **Job's syndrome** is the autosomal dominant form of hyperimmunoglobulinemia E syndrome. Symptoms of autosomal recessive hyper-IgE syndrome often become apparent at birth or early during infancy or childhood. The disorder is characterized by the triad of highly elevated levels of IgE in serum, recurring abscesses of the skin, and recurrent pneumonia. The clinical triad of autosomal recessive hyper-IgE syndrome is shared with the more frequent autosomal-dominant hyper-IgE syndrome, but other features (e.g., persistent cutaneous viral infections and neurological symptoms) are unique to the autosomal-recessive hyper-IgE syndrome form. In 2007, a heterozygous mutation in the gene encoding the transcription factor, STAT3, was found to underlie most cases of autosomal-dominant (Type I) hyper-IgE syndrome. In 2009, mutations and deletions in the DOCK8 gene were found to underlie the majority of cases of autosomal recessive (Type 2) hyper-IgE syndrome.

Hyperimmunoglobulinemia E syndrome was first described by Davis et al. in 1966 in 2 girls with red hair, chronic dermatitis, and recurrent staphylococcal abscesses and pneumonias. They named the disease after the biblical figure ***Job*** (The Book of Job), whose body was covered with boils by Satan: Job was "smote with sores from the sole of his foot unto his crown" (Job 2:7). In 1972, ***Buckley*** et al. described 2 boys with similar symptoms, as well as coarse facies, eosinophilia, and elevated serum IgE levels. These 2 syndromes are thought to be the same and are under the broad category of IgE syndrome.

Job is mentioned as an historical figure by the prophet Ezekial in the book of James. He was a rich farmer living in the land of Uz: "He had seven sons and three daughters, and he owned seven thousand sheep, three thousand camels, five hundred yoke of oxen and five hundred donkeys, and had a large number of servants." This must have bothered Satan because he came to God, who mentioned: "There is no one on earth like him [Job]; he is blameless and upright, a man who fears God and shuns evil." But Satan said to God: "Does Job fear God for nothing? … But now stretch out your hand and strike everything he has, and he will surely curse you to your face." God lets Satan to test Job. Soon Job lost all of his livestock, a desert

wind destroys his house, killing Job's sons and daughters. As Job remains with his faith in God, Satan punishes him with terrible sores all over his body. After all, God appears to Job in a storm and gives a spectacular account of his impressive works and effort. Job accepts God's right as Creator to do everything he wants. God gives Job twice as much wealth he had earlier, including 7 sons and 3 daughters. Job lived 140 more years to see his children into the fourth generation.

Rebecca Hatcher Buckley (1933–) is a US pediatrician. She was born in the tiny village of Hamlet in the Sandhill district of North Carolina to Dr. Martin and Nora Hatcher. She graduated from Duke University with an AB degree in 1954 and obtained her MD degree from the University of North Carolina-Chapel Hill School of Medicine in 1958. She married Dr. C. Edward Buckley when she was a medical student, and they have 4 children. Still at Duke, Buckley received her residency training in pediatrics and fellowships in allergy and immunology. She then joined the Department of Pediatrics, was a Chief of the Division of Allergy and Immunology from 1974–2003, and became a Distinguished Professor of Pediatrics and Professor in the Department of Immunology at Duke in 1979. Buckley has authored more than 350 publications. In 2022, she announced her retirement following 64 years of service at Duke University.

In 2003, Buckley was elected to the Institute of Medicine of the National Academy of Sciences. In 2006, she received the William G. Anlyan, MD, Lifetime Achievement Award from the Duke Medical Alumni Association. In 2007, she was appointed by the US Secretary of Health and Human Services to a 4-year term on the HRSA Advisory Committee on Heritable Disorders of Newborns and Children.

Buckley also was elected a member of the National Academy of Sciences (NAS) for her life-saving research in pediatric immunological diseases in 2011. The NAS affiliation is one of the main honors for a scientist or engineer in the US. Interestingly, Albert Einstein, Robert Oppenheimer, Thomas Edison, Orville Wright, and Alexander Graham Bell have been NAS' famous members.

(**Publ**.: Davis SD, Schaller J. Wedgwood RJ. Jobs Syndrome: recurrent cold staphylococcal abscesses. *Lancet* 1966; 1:1013–1015.

Buckley RH, Wray BR, Belmaker EZ. Extreme hypcrimrnunoglobulinemia E and undue susceptibility to infection. *Pediatrics* 1972; 49:59–70.)

Job-Buckley syndrome see **Job syndrome**

Johne's disease or Paratuberculosis is a contagious, chronic, progressive, granulomatous enteritis in ruminants including cattle, sheep, goats, and farmed deer caused by *Mycobacterium avium subspecies paratuberculosis*. This disease and bacterium have received wide interest some time ago because of data suggesting that human infection with this microorganism could causing several, and "possibly all," cases of **Crohn's disease**. Recent studies have shown that a high percentage of people with Crohn's disease are infected with *M. avium subsp. paratuberculosis*; whether the association of this bacterium and Crohn's disease is causal or coincidental is not known. Although some clinical similarities can be seen between **Johne's disease** in cud-chewing animals and inflammatory bowel disease (IBD) in humans,

epidemiologic studies in general provide dubious results as to the presence of infective agents or immune responses to these microorganisms in patients with IBD when compared with asymptomatic people.

The immunological hallmark of paratuberculosis is a change from Th1 to Th2 immunity. Immunological reactions started with Th1 response and high levels of IFN-γ and cell-mediated reactions. Infection quickly downregulates proinflammatory cell activity by stimulating immunosuppressive cytokines and diminished CD40 signaling—an important pathway for macrophage-mediated maintenance of Th1 immunity. Pathogenic mycobacteria initiate signaling via TLR2 on bovine mononuclear phagocytic cells activating MAPK-p38 pathways and causing upregulation of IL-10 production, decreases in IL-12 expression, and inhibition of macrophage antimicrobial responses and antigen presentations.

In 1894, a veterinarian examined the cow that failed to produce milk or gain weight in the Oldenburg region of Germany and suspected intestinal tuberculosis. The tuberculin skin test, however, was negative. After the cow's death, her organs were examined in the Veterinary Pathology Unit in Dresden, Germany, by ***H. A. Johne*** and L. Frothingham, a visiting clinician from the Pathology Department in Boston, MA. The histological data revealed that the intestinal wall was greatly infiltrated by leukocytes and epithelioid cells. Furthermore, the inflamed tissues were rich in bacteria, which morphologically resembled the bacteria associated with tuberculosis, but they were unable to cause disease when injected into guinea pigs. Johne and Frothingham concluded that the disease was not induced by *Mycobacterium bovis,* known to cause tuberculosis in cattle, but was caused by *Mycobacterium avium* that causes tuberculosis in birds. They also introduced the "pseudotuberculous enteritis" for the birds' disease. Consequently, the name "**Johne's disease**" also was used. The incidence of Johne's disease in the US was first reported by Leonard Pearson in 1908 (Pearson, 1908).

Heinrich Albert Johne (Dec 10, 1839–Dec 5, 1910) was a pathologist, bacteriologist, and veterinary surgeon in Dresden, Germany. He was known by his publications focusing on actinomycosis and trichinosis and introducing a histochemical method for staining bacterial capsules. He also was known in Germany as a very effective proponent of meat inspections.

Jones-Mote reaction (i.e., cutaneous basophil hypersensitivity) is a form of hypersensitivity reaction characterized by infiltration of the skin by basophil granulocytes that may occur, for instance, with allergic contact dermatitis.

Initially, Jones-Mote reactions, as delayed, erythematous, and mildly indurated cutaneous reactions, were originally described in humans sensitized by skin injection of heterologous proteins. Similar reactions in guinea pigs were shown to contain many basophils and have been called cutaneous basophil hypersensitivity. In contrast, guinea pigs immunized with mycobacterial adjuvants have classical tuberculin-type delayed hypersensitivity reactions, which contain few basophils. This led to a new classification of delayed responses, based largely on the presence or absence of basophils. The general understanding was that the 2 reactions are

different: the former was historically termed "Jones-Mote" hypersensitivity to differentiate it from the classic delayed hypersensitivity induced by complete **Freund's adjuvant**.

It is common, however, to consider **Jones-Mote reactivity** as a milder form of classic delayed hypersensitivity—a weak type IV-hypersensitivity reaction accompanied by basophil infiltration a few days after priming with a protein antigen in aqueous solution or incomplete Freund adjuvant. Importantly, Jones-Mote hypersensitivity exclusively refers to the delayed type hypersensitivity induced by injection of protein in adjuvant or protein conjugated to haptens. The response is mediated by the $CD4^+$ T cells. The skin hypersensitivity reactions or Jones-Mote responses to rabbit serum proteins were described by ***T. Duckett Jones*** and his medical student ***John Mote*** in 1934.

Thomas Duckett Jones (Feb 2, 1899–Nov 22, 1954) was a US physician. He was born in Petersburg, VA, into a colonial family greatly associated with medical service. His father and sister were physicians, his brother was a surgeon, and 2 other sisters were married to physicians. Jones graduated from the Virginia Military Institute in 1919. Then, in 1923, he received his MD degree from the University of Virginia, where he also was an intern and resident. In 1925, he worked at the Massachusetts General Hospital, and then spent a year as a National Research Council Fellow at University College Hospital in London. In 1928, he returned to Boston where he organized the clinics and the research department, which he directed for the next 20 years.

In 1947, because of his eminence in the field of rheumatic fever, he was asked to become the medical director of the newly established Helen Hay Whitney Foundation in New York City. Jones was a president of the American Rheumatism Association, a member of the Advisory Council of the National Heart Institute, a vice president of the American Heart Association, a president-elect of the National Health Council, a president of the Protein Foundation, a chairman of the Committee on Plasma Fractionation and Related Processes at the Laboratory of Physical Chemistry at Harvard University. T. Duckett Jones died at the Johns Hopkins Hospital of diffuse vasculitis and malignant hypertension.

John R. Mote was associated with the House of the Good Samaritan (Good Samaritan Hospital) in Boston.

(**Publ**.: Jones TD, Mote JR. The phases of foreign protein sensitization in human beings. *New Engl J Med* 1934; 210:120–123.

Mote JR, Jones TD. The development of foreign protein sensitization in human beings. *J Immunol* 1936; 30:149–167.)

Letter K

Kabuki syndrome (**Kabuki make-up syndrome**, **Niikawa-Kuroki Syndrome**) is a rare multisystemic disorder characterized by a distinct face, postnatal growth deficiency, mild-to-moderate intellectual disability, skeletal and visceral malformations, and dermatoglyphic abnormalities. The disease is caused by mutations of 2 genes that function as epigenetic modulators: KMT2D (histone-lysine N-methyltransferase 2D) and KDM6A (lysine-specific demethylase 6A). Various human disorders have been linked to the mutations of genes involved in the epigenetic regulation—alterations of DNA and histone proteins that modulate gene expression in the absence of DNA mutations. These disorders share developmental faults, disrupted growth, multiple congenital organ defects, and hematological and immunological abnormalities. In fact, many patients with **Kabuki syndrome** experience low levels of serum immunoglobulin, increased susceptibility to infections, and a high risk of autoimmune diseases, including hemolytic anemia, idiopathic thrombocytopenic purpura, autoimmune thyroiditis, and vitiligo. Defects of B-cell terminal differentiation also have been described in patients with Kabuki syndrome.

In 1968, ***Yoshikazu Kuroki*** observed a boy in Fukuoka who presented with unusual and unknown set of abnormalities. Within 12 years another 4 children with similar characteristics had been seen in Kanagawa. In parallel, in 1967, ***Norio Niikawa*** observed a girl with unique malfunctions and found 4 other patients from Hokkaido, a north island in Japan, with similar defects. Altogether these findings formed a new malformation syndrome described in 1981 and termed "Kabuki make-up" or "Kabuki" syndrome. This name was chosen because of the facial similarity to the makeup of actors in Japanese traditional theater—Kabuki.

Norio Niikawa (May 8, 1942–Apr 4, 2022) was a Japanese physician and medical geneticist. He completed his MD at the Hokkaido University School of Medicine in 1967. He then finished his pediatric residency at Hokkaido University Hospital. He worked in the embryology and cytogenetics laboratory in the Cantonal Hospital within the Department of Gynecology and Obstetrics at Geneva University from

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1972–1975. In 1984, he was offered a position of Professor and Chair of the Department of Human Genetics at Nagasaki University. After retirement, he was Professor Emeritus and Director of the Research Institute of Personalized Health Sciences, University of Hokkaido. His awards/honors included the Prize for Science and Technology (Research Category) in 2006 and an Academic Award from the Japan Society of Human Genetics in 2008.

Yoshikazu Kuroki (1937–) is a Japanese physician. He was born in Kagoshima and studied medicine at Kyuishu University in 1963. He trained in pediatrics at Kyushu University and in cytogenetics at Hokkaido University. From 1974 on, he has been affiliated with the Kanagawa Children's Medical Centre, Yokohama, becoming a Professor of Medical Genetics in 1976. Since 1982 he has been a Director of the Division of Medical Genetics, Kanagawa Children's Medical Centre, Yokohama, and from 1987 he has been a Professor of Pediatrics at the St. Marianna University School of Medicine.

(**Publ**.: Niikawa N, Matsuura N, Fukushima Y, Ohsawa T, Kajii T. Kabuki make-up syndrome: A syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. *J Pediatr* 1981; 99(4):565–569.

Kuroki Y, Suzuki Y, Chyo H, Hata A, Matsui I. A new malformation syndrome of long palpebralfissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and mental retardation. *J Pediatr* 1981; 99(4):570–573.)

Kahn's test is a test for syphilis based on the formation of a precipitate in a mixture of serum and antigen. An alcoholic extract of bovine heart tissue with added cholesterol serves as an antigen or the precipitation agent. **Kahn's test** was introduced as a modification of the **Wassermann test**, which required a 2-day incubation time. Although it can be done in several minutes, both false positive and negative results could be observed. Interestingly, Kahn determined that by changing the salt concentration, temperature, and serum dilutions, the test could reveal antigens of various infections, including malaria, tuberculosis, and leprosy. He thus named his test the universal serological reaction.

Reuben Leon Kahn (Jul 26, 1887–Jul 22, 1979) was a US immunologist. He is perhaps most widely known for the precipitation test for syphilis that bears his name. He was born in Swir, a little town near Kovno (now Kaunas), Lithuania (then Russian Empire), the fourth of 6 children of a Jewish family of Lazarus and Lottie (Wolpert) Kahn. His father was the cantor and reader of at a small congregation in his hometown. Reuben was brought to the US at the age of 12 in 1899. After arrival, the family lived briefly in Brooklyn, then in Troy, NY, where the elder Kahn had been invited to become the cantor of a synagogue.

In 1907, Reuben was accepted as a freshman medical student at Valparaiso University in Indiana, but soon switched to science. In 1909, he received the bachelor's degree from Valparaiso University. in 1913, the MS degree from Yale University, and a DSc from New York University in 1916. He served the following year as a research chemist in the Harriman Research Laboratory in New York City. In World War I, he was a First Lieutenant in the Sanitary Corps of the US Army

from 1917–1918 and Captain from 1918–1919. While in the US Army, Kahn discovered that a careful mixture of blood samples with beef heart extract and cholesterol solution from infected people caused a visible clouding of precipitates. Soon, the Kahn's test had been proven to be more practical for syphilis testing than the longer **Wassermann test** in spite of providing some false-positive results in recently vaccinated individuals or in patients with several other infections. After his service, he worked at the Michigan State University Department of Health from 1920–1928.

In 1928–1948, Kahn was an Assistant Professor of bacteriology at the University of Michigan, Ann Arbor; then from 1951–1957, a Professor of Serology; and from 1957 on, an Emeritus Professor. In 1951, he published *An Introduction to Universal Serologic Reaction in Health and Disease* in which he explained several aspects of his test and serological diagnostic procedures. Kahn also studied the effects of radiation on immune reactions and demonstrated that radiation could alter the strength and localization of antibody reactions with foreign proteins in animal models. These studies were supported by the Atomic Energy Commission (1957–1967). From 1968–1973, he was a Professor of Microbiology at Howard University in Washington, DC. Kahn remained an active researcher until the age of 85. With his wife Dina Hope Weinstein, he had 2 children—Lyra and David. He and his wife were active in the National Conference of Christians and Jews. Kahn's concern with racial equality had been demonstrated as early as 1928, when he hired the first black to work in the University Medical Center laboratories. He died in Miami, FL.

Kahn authored more than 170 scientific publications and attained many honors and recognitions. In addition to a honorary MD from the National University of Athens, he received the LL.D. (Doctor of Laws) from his alma mater Valparaiso University in 1943; the D.Sc. (Doctor of Science) from the Institutum Divi Thomae of Cincinnati in 1954; and a honorable PhD from the Far Eastern University of Manila, Philippines. He was the recipient of the 11th Annual Award of the American Association for the Advancement of Science in 1933, the gold medal of the Phi Lambda Kappa fraternity in 1937 for contributions to medical science, and in 1948 the bronze medal commemorating the 25th anniversary of the Kahn reaction. In 1965, at a dinner in his honor at the Statler-Hilton Hotel in Detroit, attended by more than 300 people, it was announced that a new Reuben L. Kahn Laboratory of Immunology would be established at the Hebrew University-Hadassah Medical School in Israel. The distinguished Dr. ***Albert B. Sabin***, developer of the oral polio vaccine, was the principal speaker on that occasion.

(**Publ**.: Kahn RL. A simple quantitative precipitation reaction for syphilis. *Arch Dermatol* 1922; 5:570–578, 734–743.

Kahn RL. Rapid precipitation phase of the Kahn test for syphilis, with new method for indicating results. *JAMA* 1923; 81:88–92.

Kahn RL. Serum Diagnosis of Syphilis by Precipitation: Governing Principles, Procedure and Clinical Application of the Kahn Precipitation Test. Baltimore: Williams & Wilkins; 1925.)

Kaposi's sarcoma is a tumor associated with infection with human herpesvirus 8 (HHV8), also known as Kaposi sarcoma-associated herpesvirus (KSHV). It became more widely known as one of the AIDS-defining illnesses during the 1980s. Before the AIDS epidemic, Kaposi's sarcoma was seen mainly in elderly Italian and Jewish men and, rarely, in elderly women. Among this group, the tumors developed slowly. This sarcoma usually appears as tumors on the skin or on mucosal surfaces (e.g., inside the mouth), but tumors also can develop in other parts of the body (e.g., in the lymph nodes, lungs, or digestive tract). **Kaposi's sarcoma** can be primarily categorized into 4 types: epidemic of AIDS-related, immunocompromised, classic, or sporadic, endemic (African). AIDS-related Kaposi's sarcoma, unlike other forms of the disease, tends to have an aggressive clinical course. It is the most common presentation of the sarcoma.

Moritz Kaposi first characterized the sarcoma in 1872, calling it "idiopathic multiple pigmented sarcoma of the skin." Kaposi's sarcoma was believed to be a fairly rare, slow-growing tumor, mostly found in middle-aged and elderly men. Everything changed in 1981, however, with the appearance of HIV-associated Kaposi's sarcoma.

Moritz Kaposi or ***Moriz Kohn Kaposi*** (in Hungarian: ***Kaposi Mór***) (Oct 23, 1837–Mar 6, 1902) was a Hungarian-Jewish physician and dermatologist. ***Moriz Kohn*** (***Cohen***) was born to a very poor Jewish family in Kaposvár, a city in the southwestern part of Hungary. Because of his many talents, he was able to study medicine in Vienna from 1856 and got his degree in 1861. Instantly, he was offered a position of an assistant to Ferdinand Ritter von Hebra, the very famous Austrian dermatologist and the founder of the New Vienna School of Dermatology, where Moriz Kohn worked until 1867. During this time, Kohn met and fell in love with Hebra's daughter Martha. They married and had 3 sons and 2 daughters. Even though Hebra was Catholic, Kohn changed his Jewish name to Kaposi—the place of his birth was Kaposvár. Because he changed his name several years after marriage, it is possible that this was to avoid being mistaken with 5 other physicians at the Vienna Hospital who had the same last name.

In 1875, Kaposi received a professorship position at the university. He was a director of the Skin Clinic in Vienna from 1880 onward. He published more than 150 papers and books. He was well known for active implementation and improvement of pathologic examination of skin lesions in the diagnosis of dermatologic disorders. Kaposi studied syphilis, its lesions on the skin and mucosa, etiology, and treatment. He established dermatitis herpetiformis as an entity and also lymphoderma perniciosa and lichen ruber moniliformis. He provided some of the early descriptions of skin lupus erythematosus and noted the systemic involvement in 1872, and in 1875 described the rash as "butterfly." Kaposi also described both rhinoscleroma and rhinophyma.

(**Publ**.: Kaposi M. Idiopathisches multiples pigmentsarkom der haut. *Arch Dermatol Syph* 1872; 4:265–273.

Kaposi M. Idiopathic multiple pigmented sarcoma of the skin. *CA Cancer J Clin* 1982; 32(6):342–347 [English translation of article describing Kaposi's sarcoma].)

Kaposi-Besnier-Libman-Sacks syndrome see **Libman-Sacks syndrome**

Kaposi-Irgang syndrome/disease, a historical name for lupus erythematosus profundus (LEP), cutaneous lupus erythematosus. It is a rare variant of chronic cutaneous lupus erythematosus characterized by inflammatory lesions in the lower dermis and subcutaneous tissue. LEP is seen in 2% of patients with systemic lupus erythematosus and clinically presented with no or mild signs of systemic manifestations. Skin lesions normally are detected in the arms, head, neck, buttocks, and thighs. In some clinical cases that show no dermal pathology, the disease may be because of ongoing vasculitis. LEP is usually a chronic disease with cycles of remission and aggravation. The pathophysiological pathways of LEP are not clear. It is quite possible that the panniculitis, or inflammation of the subcutaneous tissue, is an expansion of the inflammatory reactions of the overlying skin. Another possibility is that lupus panniculutis may be an aggravated result of local tissue damage or trauma (e.g., skin biopsy). Autoimmune etiology also has been suggested.

Kaposi first proposed the term "lupus panniculitis" in 1883. In 1940, ***Irgang*** introduced the term "lupus erythematous profundus" for a disease in which involvement of the breast is called lupus mastitis.

Samuel Irgang (Sept 5, 1895–Oct 1972) was a US dermatologist in New York.

Moriz Kohn Kaposi see **Kaposi's sarcoma**

(**Publ**.: Irgang S. Lupus erythematosus profundus: Report of an example with clinical resemblance to Darier-Roussy sarcoid. *Arch Dermatol Syph* 1940; 42:97–108.

Kaposi M. *Pathologic und Therapie der Hautkran Kheiten*, 2nd ed. Vienna: Urban Schwarzenberg; 1883: p. 642.)

Kaposi-Juliusberg syndrome (**Kaposi-Juliusberg dermatitis**, pustulosis acuta varioliformis, eczema herpeticum) is considered to be a dermatoallergological disease. This is a "classical" herpes complication of atopic dermatitis—a severe herpes simplex virus cutaneous infection, accompanied by general signs. It also can develop on other predisposing territories (e.g., acantholytic dermatitis, including pemphigus vulgaris, Hailey-Hailey's disease, and Darier's disease). Because most commonly it is caused by a disseminated HSV infection in patients with atopic dermatitis and, for this reason, is often referred to as eczema herpeticum. **Kaposi-Juliusberg syndrome** is frequently initiated by herpes simplex virus type 1 or 2 but also may be caused by coxsackievirus A16 or vaccinia virus. It appears as numerous umbilicated vesicles superimposed on healing atopic dermatitis and is often accompanied by fever and lymphadenopathy.

This complication of atopic eczema was first recorded by ***Moriz Kaposi*** in 1887, as a disease resembling chickenpox and occurring in children with allergic eczema. Kaposi originally suggested the title "eczema herpetiforme," but he suspected a fungus as the cause. The syndrome was initially identified with a virus diseases by

Fritz Juliusberg (1898), who, although confusing the issue himself, drew attention to the close resemblance of the individual lesions to vaccination pustules.

Moriz Kaposi see **Kaposi's sarcoma**

Fritz Juliusberg (Feb 16, 1872–Mar 25, 1939) was a German-Jewish dermatologist. He was born to a Jewish family in Breslau, where his father was a physician. He studied medicine at the University of Breslau, University of Würzburg, and University of Freiburg where he graduated in 1896 with the thesis "On Bacteriological Examination of Several New Disinfectant Agents." Juliusberg then started his dermatology training in Frankfurt am Main, Bern, and Breslau. He chaired the Department of Dermatology in the Municipal Hospital in Posen, Prussia (now Poznań in Poland), from 1910–1918, being the first and primary dermatologist in Posen.

After the revival of the independent Polish state following World War I in 1918, Juliusberg moved to Germany in 1919 and organized a private dermatology practice in Braunschweig, where he was also a Full Professor of Dermatology. As a Jew, he experienced all possible discriminations and humiliations after 1933, when the Nazis came to power in Germany. He lost his medical license in 1936, closed his medical practice in Braunschweig, and went to Berlin, where he committed suicide in his apartment in 1939.

Juliusberg was an excellent clinician with his main interests in the analysis of clinical cases and discussion of atypical or unusual findings. He published many papers, reviews, and books on various subjects in dermatology, including tuberculosis, amyloidosis, venereal disease, and streptococcal infections. For many years, he served as a Coeditor of *Archiv für Dermatologie und Syphilis*.

(**Publ**.: Kaposi M. Pathologie und therapie der hautkrankheiten. In: *Vorlesungen für Präktische Aerzte und Studirende*. Vienna: Urban & Schwarzenberg; 1887.

Juliusberg F. Ueber pustulosis acuta varioliformis. *Arch Dermatol Syph* 1898; 46:21–28.)

Katz syndrome a very rare syndrome characterized mainly by enlarged liver, diabetes, short stature, and a thickened skull. In its relation to clinical immunology, there was the development of diabetes and high levels of serum immunoglobulins (IgG) seen by serum protein tests—that is, serum protein electrophoresis or total serum protein electrophoresis and serum immunoelectrophoresis.

Nearly 30 cases have been reported. Autosomal recessive inheritance with consanguinity is a risk factor. The genetic defect has been mapped to 6q21-q22.

Kawasaki disease is an autoimmune disease in which the medium-sized blood vessels throughout the body become inflamed. The disorder also has been called "mucocutaneous lymph node syndrome" and "infantile periarteritis nodosa." The illness initially was thought to be benign and self-limited. Still, subsequent reports have indicated that nearly 2% of patients with Kawasaki disease later die from the

illness. This is an acute febrile vasculitis syndrome during early childhood that can lead to death from coronary artery aneurysm in a small number of patients.

Kawasaki disease is a generalized vasculitis affecting small- and medium-sized arteries. Vascular inflammation is very noticeable in the coronary vessels. Vasculitis, however, also can affect veins, capillaries, small arterioles, and larger arteries. At the beginning of Kawasaki disease, the endothelial cells may be edematous (i.e., swollen with fluid), but the internal elastic lamina is normal. Then, an influx of neutrophils occurs, which is quickly followed by a proliferation of cytotoxic $CD8^+$ T-lymphocytes and IgA-producing plasma cells. Eosinophils are preferentially accumulated in microvessels. The inflammatory cells secrete various cytokines (e.g., IL-1, IL-4, IL-6, TNF-α, VEGF, monocyte chemotactic, and activating factor) and matrix metalloproteinases (primarily MMP3 and MMP9) that target the endothelial cells and result in fragmentation of the internal elastic lamina and vascular damage. The internal- and external-elastic laminae can be fragmented also, which may cause formation of aneurysms.

After initial onset, over the next few weeks to months, inflammatory cells are replaced by fibroblasts and monocytes, and fibrous connective tissue is formed in the vessel wall, which eventually becomes narrowed or occluded as a result of stenosis or thrombus. Cardiovascular death may occur from a myocardial infarction secondary to thrombosis of a coronary aneurysm or from rupture of a large coronary aneurysm.

The etiology of **Kawasaki disease** remains unknown. Much epidemiologic and immunologic evidence indicates that the causative agent possibly is infectious. Suspected pathogens and infections may include parvovirus B19, meningococcal septicemia, bacterial toxin-mediated superantigens, measles, *Mycoplasma pneumoniae*, *Klebsiella pneumoniae*, bacteremia, adenovirus, cytomegalovirus, EBV, and tick-borne diseases. Autoimmune reactions and genetic predisposition, however, have been suggested as possible etiologic factors. Immune response in Kawasaki disease is oligoclonal rather than polyclonal, suggesting involvement of a conventional antigen. It is possible that an infective agent in Kawasaki disease may be a RNA virus; it causes an asymptomatic infection in most people but can induce Kawasaki disease in a population of genetically predisposed individuals.

A genetic predisposition to Kawasaki disease has long been suspected and patients are more likely to express HLA-Bw22J2, which is seen predominantly in the Japanese population. A functional polymorphism of the inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene on band 19q13.2, the Fcg RIIa polymorphism, and genetic variants in the chemokine receptor gene-cluster CCR3-CCR2-CCR5 also have been found to be associated significantly with an increased susceptibility to developing Kawasaki disease.

The disease was first reported by ***Tomisaku Kawasaki*** in a 4-year-old child with a rash and fever at the Red Cross Hospital in Tokyo in January 1961, and he later published a report on 50 similar cases. In 1974, the initial description of this disorder was published in the English-language literature. In 1976, Melish et al. reported Kawasaki disease in the US in a group of 12 children from Honolulu, HI, examined from 1971–1973 (Melish et al. 1976). Melish and Kawasaki had independently

developed the same diagnostic criteria for the disorder, which are still used to make the diagnosis of classic Kawasaki disease.

Tomisaku Kawasaki (Feb 7, 1925–Jun 5, 2020) was a Japanese pediatrician. Kawasaki, the youngest of 7 children in his family, was born in Tokyo. After graduating from Chiba University Medical School in 1948, as an intern he moved through various fields of medicine, became interested in pediatrics, and did his residency in Chiba immediately after World War II. Then he received an appointment in the pediatrics department at the Red Cross Hospital in Hiroo, Tokyo, and stayed there for 40 years.

In 2007, Kawasaki estimated that more than 200,000 cases of Kawasaki disease had been detected in Japan since 1970. Interestingly, knowing that the original name of the disease, "acute febrile mucocutaneous lymph node syndrome," is quite long, Kawasaki never used the eponymous name for the disease by himself. After he retired in 1990, however, he founded and led the Japan Kawasaki Disease Research Center as a director and honorary chairman until 2020.

(**Publ**.: Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugī Allergy* (in Japanese) 1967; 16(3):178–222.

Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974; 54(3):271–276.)

Kell antigen system (also known as **Kell-Cellano system**) is a group of antigens on the human red blood cell surface that are important determinants of blood type. The Kell antigens are peptides found within the **Kell protein**, a 93 kD transmembrane zinc-dependent endopeptidase responsible for cleaving endothelin-3. **Kell antigens** are important in transfusion medicine, autoimmune hemolytic anemia, and hemolytic disease of the newborn. Individuals lacking a specific Kell antigen may develop antibodies against them when transfused with blood containing that antigen. Subsequent blood transfusions may be associated with destruction of the new cells by these antibodies (i.e., hemolysis). People without Kell antigens (K_0) must be transfused with blood from donors who are also K_0 to prevent hemolysis. **McLeod phenotype** (or McLeod syndrome) is an X-linked anomaly of the Kell blood group system in which Kell antigens are inadequately detected by laboratory tests. The McLeod gene encodes the XK protein—a protein with structural characteristics of a membrane transport protein but with an unknown function.

Kell antigens were discovered in 1945–1946 when an antibody in Mrs. ***Kellacher*** was identified as reacting with her newborn infant, her older daughter, her husband, and about 9% of the white population. The antigen was named after her—**Kell**. Mrs. ***Cellano*** was likewise a pregnant woman with the first-described antibodies to K_2. The K_0 phenotype originally was described in 1957, and the McLeod phenotype was found in 1961 in Hugh McLeod—a Harvard dental student.

Interestingly, blood group incompatibility between Henry VIII and his wives could have led to the Tudor king's reproductive despairs. The numerous

miscarriages suffered by Henry's wives could be explained if the king's blood carried the **Kell antigen**. Henry was almost 18 when he married Catherine of Aragon who was 23. Their first daughter was born dead. A newborn son, their second child, lived only 52 days. The next 4 pregnancies ended in either stillborn or children with very short lives. The exact number of miscarriages is impossible to calculate. Their only surviving child was Mary, who ultimately would be crowned the fourth Monarch in the Tudor dynasty. A Kell-negative woman who has multiple pregnancies with a Kell-positive man can produce a healthy, Kell-positive child with a first pregnancy; but the antibodies she produces during that pregnancy will cross the placenta and attack a Kell-positive fetus in subsequent pregnancies. A Kell-positive father may be responsible for the inability of a woman to have a healthy baby after the first Kell-negative pregnancy.

(**Publ**.: Coombs RRA, Mourant AE, Race RR. A new test for the detection of weak and incomplete Rh agglutinins. *Br J Exp Pathol* 1945; 26:255.

Chown B, Lewis M, Kaita K. A new Kell blood-group phenotype. *Nature* 1957; 180(4588):711.

Allen FH Jr, Krabbe SM, Corcoran PA. A new phenotype (McLeod) in the Kell blood-group system. *Vox Sang* 1961; 6:555–560.)

Khavkin's lymph was a name given to vaccines against cholera and bubonic plague developed by ***Vladimir Khavkin*** in Paris and tested in India. It was an attenuated form of the bacterium. He was the first to make a vaccine for infection prophylaxis by killing virulent culture by heating it at 60 °C. During the 1898 cholera outbreak in the Russian Empire, the vaccine got its name, "limfa Havkina" or Havkin's lymph, and its use saved thousands of lives across the empire. For 40 years after the creation of "Khavkin's lymph" more than 35 million people were vaccinated around the world.

Vladimir Aaronovich Khavkin (***Havkin*** or ***Chavkin***) (***Waldemar Mordechai Wolff Haffkine***) (Mar 15, 1860–Oct 26, 1930) was a Ukrainian-Russian-Jewish bacteriologist, immunologist, and epidemiologist, remembered as the creator of the first antiplague and anticholera vaccines. He was born in Odessa, Russian Empire, and at birth received the name ***Markus-Wolf***. His father, Aaron Khavkin, was a teacher at the State Jewish School, and his mother, Rosalia Landsber, was a daughter of the Hebrew language teacher from the same school. Markus-Wolf graduated from the cheder, a Jewish school for boys, and then from the Russian men's gymnasium in Berdyansk, Ukraine. He continued his studies at the Department of Physics and Mathematics at the Imperial Novorossiysk University in Odessa. Young Khavkin was a part of the Jewish League for Self-Defense in Odessa and helped defend Jewish houses during pogroms. He defended his dissertation in 1884, but as a Jew, he was not able to carry out research studies in Russia unless he accepted Russian Orthodoxy; but he refused. Khavkin had to leave Russia, and on the recommendation of ***Ilya Mechnikov***, he took a position at the newly established Pasteur Institute in Paris in 1889.

Khavkin's work focused on infection immunology, and in 1892, he reported on the preparation of the first successful vaccine against cholera after proving its safety on himself. Although most of European countries refused to use the new vaccine, the British authorities allowed testing it in their colony—India. Khavkin went to a village near Calcutta where the cholera epidemic broke out. Vaccination there and later in Bombay proved the vaccine's efficacy. In 1897, Queen Victoria herself presented Khuffkin with the Order of the Knight of the Indian Empire. For his help and saving lives, he got his own laboratory at the Bombay Medical College—a room with a laboratory assistant. Experimental animals, rats, were caught by sailors on ships coming from Europe. Today, the Bombay Bacteriological Institute, the largest center to study infectious diseases in Southeast Asia, is named after Khuffkin.

In 1915, Havkin retired while suffering from malaria and left India for Europe. He finally settled in Lausanne, Switzerland, on the shore of Lake Geneva, where he died of heart disease in 1930. In 1929, he founded the Haffkine Foundation to promote Jewish education in Eastern Europe. His will stated that all the money he saved (around $300,000), and a giant library, should go to the Jewish society.

Kikuchi-Fujimoto disease (**Kikuchi disease**, **Kikuchi's disease**) also is known as histiocytic necrotizing lymphadenitis, Kikuchi necrotizing lymphadenitis, phagocytic necrotizing lymphadenitis, subacute necrotizing lymphadenitis, and necrotizing lymphadenitis. It is a benign (noncancerous) condition of the lymph nodes and usually is characterized by cervical (neck) lymphadenopathy associated with general flu-like symptoms. Other occasional symptoms may be headache, fatigue, nausea, and arthralgia. After 2–3 months, the disease can resolve spontaneously. The immunophenotype of **Kikuchi disease** is primarily composed of mature CD8-positive and CD4-positive T lymphocytes. It also is represented by an influx of large numbers of plasmacytoid dendritic cells to the lymph nodes' paracortex and the programmed death of these cells in situ, by apoptosis. B cells and NK cells rarely are detected. Ki-M1P-positive cells can be detected in Kikuchi disease but not in malignant lymphoma specimens.

Although etiology is not clear still, a microbial/viral or autoimmune cause has been suggested. Numerous infectious candidates have been associated with or implicated in the etiology of Kikuchi's disease: *Yersinia enterocolitica*, *Bartonella henselae*, *Brucellosis*, *Entamoeba histolytica*, *Toxoplasma gondii*, *Mycobacterium szulgai*, parainfluenza virus, Epstein-Barr virus, cytomegalovirus, herpes viruses, parvovirus, paramyxovirus, rubella, human T-lymphotropic virus type 1, hepatitis B virus, human immunodeficiency virus, and the dengue virus; all have been noted in Kikuchi-Fujimoto disease. Nevertheless, none of these have been found to be associated with this disease consistently.

Thus, **Kikuchi-Fujimoto disease** is an unusual hyperimmune response—for instance, an exuberant T cell-mediated immune response—to various infectious, physical, chemical, and neoplastic stimulations in genetically susceptible individuals. Many autoimmune conditions have been related to Kikuchi's disease and, in addition to systemic lupus erythematosus, include arthritis, systemic juvenile idiopathic arthritis, antiphospholipid syndrome, polymyositis, bilateral uveitis, and

cutaneous necrotizing vasculitis. A genetic predisposition to the autoimmune reactions has been linked to the human leukocyte antigen class II genes.

The disease initially was recorded by ***Masahiro Kikuchi*** in 1972 in the *Japanese Journal of the Haematological Society*. He described a patient with lymphadenitis, focal proliferation of reticulocytes, abundant histiocytes, and extensive nuclear debris. ***Y. Fujimoto*** reported a similar case in another Japanese journal at the same time. Kikuchi also presented his clinical findings to his colleagues in Western countries, which stimulated detection of the disease outside Japan (Pileri and colleagues, Germany, 1982; Turner et al., US, 1983; and Ali and Horton, UK, 1985).

Masahiro Kikuchi (1935–Apr 28, 2012) was a Japanese hematologist and pathologist. He was born to a modest family in Kitakyushu, Fukuoka Prefecture. He studied medicine and was trained in internal medicine at Kyushu University. Then, he received extended training in general histopathology and hematopathology at the Department of Pathology, School of Medicine, Kyushu University in Fukuoka. Later, he studied lymph node and bone marrow pathology at Kiel University in Germany. In 1973, he became a Professor of Pathology at the Medical School of Fukuoka University, where for almost 40 years he worked in the field of hematopathology.

Kikuchi was known as a very enthusiastic and hard-working pathologist. His expertise, outstanding knowledge, and warm personality attracted many hematopathologists from all over the world to visit his laboratory. For the last 4 years of his life, Kikuchi suffered from an anaplastic large-cell lymphoma, which he diagnosed by himself. Yet, this disease did not affect his clinical duties as a pathologist until his death.

Y. Fujimoto (Sept 24, 1935–Jun 10. 2019) was a Japanese physician.

(**Publ**.: Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes. *Acta Hematol Jpn* 1972; 35:379–380.

Fujimoto Y, Kojima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. A new clinicopathological entity. *Naika* 1972; 20:920–927.)

Kimmelstiel-Wilson syndrome (**Kimmelstiel-Wilson disease**), also known as intercapillary glomerulonephritis, is a kidney condition associated with long-standing diabetes, when the microvasculature in the glomerulus is affected. Damage to the glomerular basement membrane allows proteins in the blood to leak through, leading to accumulation in Bowman's space as distinct periodic-acid Schiff-positive nodules called Kimmelstiel-Wilson nodules. Features of the syndrome include the nephrotic syndrome with proteinuria, hypertension, and progressively impaired kidney function. When severe, **Kimmelstiel-Wilson syndrome** leads to kidney failure, end-stage renal disease, and the need for chronic kidney dialysis or a kidney transplant. The cause of diabetic nephropathy is not well understood, but it is thought that high blood sugar, advanced glycation end-product formation, and cytokines may be involved in the development of diabetic nephropathy.

The disorder is named after ***Paul Kimmelstein*** and ***Clifford Wilson***, who described changes in the kidney in 1936 that they called intercapillary glomerulosclerosis, consisting of homogeneous, hyalinized masses in the center of lobules. Seven of the 8 patients they reported on had diabetes mellitus; no history was available on the other patient. They mentioned in a footnote several other examples of the lesion, only one of which was not in a known diabetic patient.

Paul Herbert Kimmelstein (Mar 21, 1900–Oct 7, 1970) was a German-born pathologist living in the US. He was born in Hamburg, Germany, to a Jewish family of Hanseatic merchants. After finishing elementary and secondary schools in Hamburg, he studied medicine at the universities in Kiel, Munich, Hamburg, Bonn, and Tubingen. In 1923, he obtained his MD degree in Tubingen. Then he devoted his residency and internship years to learning bacteriology and serology at the University Hospital of Hamburg-Eppendorf, pathology at St. Georgs Hospital in Hamburg, and biochemistry at the University of Breslau. Kimmelstiel started his research career when he was a student and prepared his first research paper in 1922 (*Zbl. Bakt.* 89:113). In this work, he analyzed "peculiar bactericidal properties of the root bacillus" and discovered that "a bacteriolytic agent" was lethal for *staphylococci* and other microorganisms. This was the very first description of antibiotics 6–7 years earlier than Sir Alexander Fleming's discovery of penicillin. The clinical significance of Kimmelstiel's discoveries, however, was not recognized at that time. His clinical and research career in Germany was interrupted by the ascendancy of National Socialism in 1933, as were the careers of many other Jews. He, his wife Lotte, and their 2 small daughters were forced to move to the US.

Kimmelstiel was lucky to obtain an instructorship at Harvard University. It was here that he and ***Clifford Wilson*** initially described nodular intercapillary glomerulosclerosis. From 1935–1940, Kimmelstiel served as an Associate Professor of Pathology at the Medical College of Virginia. In 1936, he went a position of coroner for the City of Richmond. Soon he became a Laboratory Director at Charlotte Memorial Hospital in Charlotte, NC, and led the lab for 18 years. In 1940–1958, Kimmelstiel had to practice general pathology to make adequate money to support his family. He was the first to organize a school for cytology technicians, which played an important role in local public health; in 1958, when he left Charlotte, 30% of the total white female residents of the city were enrolled in consistent cytology screening programs.

Kimmelstiel moved to Milwaukee, WI, and worked as a Director of Laboratories in the Milwaukee County Hospital (1958–1964) and a Professor of Pathology at Marquette University (1958–1966), focusing his clinical research on renal pathology. He was also a Distinguished Professor of Pathology at the University of Oklahoma Medical Center in Oklahoma City. Kimmelstiel was the author and coauthor of more than 100 scientific papers covering many branches of clinical and morphologic pathology.

Clifford Wilson (Jan 27, 1906–Nov 10, 1997) was an English physician. He was born into a Baptist family and got an initial education in classics. He developed a great interest in chemistry while working in his spare time as a laboratory technician

at the Heath School in Halifax. He then won the Brackenbury Scholarship to Balliol College in Oxford and graduated ranked First in Natural Sciences in 1928. By 1934, he had finished his clinical and junior medical training in the London Hospital and obtained a Rockefeller Traveling Fellowship to move to Harvard. There he met and worked with ***Kimmelstiel*** to achieve eponymous fame.

In 1936, he married Kathleen Hebden and they had a son and a daughter. At the beginning of the World War II, Wilson worked as a clinician and teacher at Billericay Hospital, developing a program for clinical students to teach them the basics of collecting medical histories and examining patients. His clinical research focused on dietary therapies was interrupted by service in the Medical Research Section of the Royal Army Medical Corps dealing with infectious hepatitis until the end of the war in 1945.

Wilson became a Professor of Medicine at The London Hospital in 1946, and his research was on the relationship between the kidneys and blood pressure. He was President of the Renal Association (1962–1965), Director of the Medical Unit at The London Hospital (1946–1971), and Dean of the Department of Medicine (1968–1971). He was committed to academic medicine and during post-war time actively participated in the transformation of medical schools in London into appropriate university units. In spite of an intense resistance to these ideas, Wilson took the lead to achieve university status for medical schools, which was finally won by the late 1960s.

(**Publ**.: Kimmelstiel P, Wilson C. Intercapillary lesions in the glomeruli of the kidney. *Am J Pathol* 1936; 12:83–97.)

Kimura's disease (**Kimura disease**, eosinophilic granuloma) is a chronic, allergic inflammatory disease of unknown etiology. About 400 patients with Kimura disease have been described worldwide, having a painless mass or masses in the head and neck region, with occasional pruritus of the overlying skin. Renal disease, nephrotic syndrome in particular, is present in up to 20% of patients with **Kimura disease**. The disease is manifested by an abnormal proliferation of lymphoid follicles and vascular endothelium. Soft-tissue mass in the head and neck regions, elevated serum immunoglobulin E (IgE), and raised eosinophils are the 3 most prominent features of this disease. Although the pathophysiology of Kimura's disease remains unknown, it is considered to be associated with an immunological reaction because the disease has been accompanied by an immune disorder.

Comparison of the disease recognized in Asian medicine as Kimura's disease with that termed, in the Western clinics, as angiolymphoid hyperplasia with eosinophilia has a long history. These 2 disorders were originally speculated to characterize 2 ends of the same pathogenetic spectrum because of many similarities. The tissue lesions, mostly seen in the head and neck region and histologically, are considered as lymphoid infiltration with vascular proliferation and tissue eosinophilia. At the same time, some differences between the 2 abnormalities have been reported repeatedly, suggesting their distinct entities. It is generally accepted now that Kimura's disease and angiolymphoid hyperplasia with eosinophilia are 2 distinct

diseases. Kimura disease may be characterized as a primary inflammatory reaction with secondary vascular proliferation.

The pathophysiology of Kimura disease remains unknown, although an allergic reaction, trauma, and an autoimmune process all have been implicated as the possible cause. It is possible that a toxin or infection agents may initiate an autoimmune response or trigger an IgE-mediated type I hypersensitivity reaction. Detection of blood eosinophilia and the occurrence of eosinophils in the inflammatory infiltrate advocate for the hypersensitivity reaction. Other clinical data point to the predominance of Th2 cells. Other analyses of patients with Kimura disease revealed elevated levels of tumor necrosis factor-α (TNF-α), granulocyte macrophage-stimulating factor (GM-CSF), soluble IL-2 receptor (sIL-2R), IL-4, IL-5, IL-10, and IL-13. Other results propose a special role for IL-21 and IL-22 in the pathogenesis of Kimura disease.

The initial description of Kimura disease came from China in 1937, when Kimm and Szeto (Kim 1937) reported on 7 cases of a new disease they called "eosinophilic hyperplastic lymphogranuloma." The disease got its eponym name in 1948 after ***Kimura*** et al. described the vascular pathological module and defined it as an "unusual granulation combined with hyperplastic changes in lymphoid tissue." The disease subsequently became known as Kimura's disease, with the majority of reports describing cases from China and Japan.

T. Kimura – Japanese physician.

(**Publ**.: Kimura T, Yoshimura S, Ishikawa E. On the unusual granulation combined with hyperplastic changes of lymphatic tissues. *Trans Soc Pathol Jpn* 1948; 37:179–180.)

Klauder's syndrome see **Stevens-Johnson syndrome**

Kline test is a test for syphilis in which the formation of a microscopic precipitate in a mixture of the patient's serum and an antigen indicates a syphilitic condition. This slide-precipitation test was named after ***Benjamin Kline***, who developed the test in 1926 working at Case Western Reserve University (then Mt Sinai Medical Center), Cleveland, OH. Although the **Wassermann reaction** was the syphilis test most commonly used in many countries, elsewhere methods of serological examination of the flocculation and slide-precipitation type have gained equal prominence. Because the finger blood test offered by Kline took only a few minutes to do and required only a drop of blood, it was particularly useful in testing blood of infants and obese people with small veins and for checking the blood of professional donors immediately before transfusions.

Benjamin S. Kline (May 4,1886–Dec 17, 1968) was a US physician and pathologist.

(**Publ**.: Kline BS. Microscopic slide precipitation tests for the diagnosis and exclusion of syphilis. *J Lab Clin Med* 1930; 16:186.

Kline BS. Microscopic slide precipitation tests for the diagnosis and exclusion of syphilis. *Br J Vener Dis* 1931; 7:32.

Kline BS, Littman S. Clinical and serological comparison of microscopic slide precipitation tests for syphilis and Wassermann tests with the same antigen. *Am J Syph* 1931; 15:405.)

Koch's phenomenon is well known as a skin reaction that appears within a few days at the BCG vaccination site if the vaccination is given to a person infected with tuberculosis. The test represents the clinical application of a type IV (delayed-type) hypersensitivity reaction. In contemporary skin tests for tuberculosis, Koch's, or "old," tuberculin has been replaced by a tuberculin-purified protein derivative. Experimentally, it has been described as the response of a tuberculous animal to reinfection with tubercle bacilli observed by necrotic lesions that develop rapidly and heal quickly and are caused by hypersensitivity to products of the tubercle bacillus.

The **Koch phenomenon** is mostly a historical curiosity that has the potential for causing toxicity of therapeutic vaccines. In the preantibiotic period, it was accepted as a key part of the pathogenesis of tuberculosis (TB) responsible for the death of people. When ***Koch*** found tuberculin, he initially called it a specific cure for TB. In his therapeutic efforts, he worked with patients with skin TB as an appropriate visual model and administered huge doses of tuberculin subcutaneously and distantly from the presented lesions. In a few hours, TB lesions swell, redden, and develop necrotic areas. Koch also stated that tuberculin did not kill the tubercle bacilli but destroyed the tuberculous tissue. The inflammation was restricted to the unhealthy fragments. Still, even the smallest otherwise invisible TB lesions were made perceptible through the inflammation. In the experiments that followed, people proved particularly more sensitive to tuberculin than the guinea pig. Furthermore, patients with advanced pulmonary TB were more sensitive than patients with smaller tuberculous conditions. But soon it was concluded that tuberculin-based treatment could not cure TB. Administration of tuberculin resulted in perifocal reactions and recurrence of TB lesions in several organs. In the lung, for instance, these "tuberculin pneumonias" advanced quickly and caused death of numerous patients.

Heinrich Hermann Robert Koch (Dec 11, 1843–May 27, 1910) was a German physician and microbiologist. He was born in Clausthal, Germany, to Hermann Koch, a mining engineer, and Mathilde Julie Henriette (née Biewend). He showed extraordinary learning capabilities as a child and learned to read on his own using newspapers when he was only 5 years old. He completed his initial education in 1862, having outclassed others in science and math. At the age of 19, Koch entered the University of Göttingen to study natural science but later switched to medicine. After graduation in 1866, he briefly worked in the General Hospital of Hamburg and then started his own practice in Langenhagen near Hanover. During the Franco-Prussian War, he was in the German army as a volunteer surgeon. Later he was a regional doctor in Wollstein (now Wolsztyn, Poland) and his family settled there. His wife gave him a nice microscope for his birthday celebration. This gift pushed him to use the microscope for his research and organize a private laboratory. This was a start of his career in microbiology.

Koch was transferred to Breslau and later to Berlin as government advisor at the Imperial Health Office. After his discovery of tuberculosis bacterium, he was promoted to a senior executive position in 1882. He was then a Professor at Berlin University, Director of Hygienic Institute and Chair of the Department of Medicine, and Director of the Royal Prussian Institute for Infectious Diseases (now the Robert Koch Institute). The Prussian Ministry of Health, after the 1890 scandal with tuberculin, insisted that any of Koch's inventions would belong completely to the government and he would not be compensated. Koch lost the right to apply for patent protection. He traveled a lot, studying the tropical diseases of Africa and India. He also successfully made vital observations about several diseases that had been contracted previously by cattle in those regions. In 1910, Koch suffered a heart attack and never made a complete recovery. He died in Baden-Baden at the age of 66.

Koch first introduced the use of **oil immersion lens**, **condenser**, and **microphotography** in microscopic research. His developed bacterial culture methodology that used agar and glass dishes, which were later developed as the **Petri dish** by his assistant ***Julius Richard Petri***. Thus, this made Koch the first to be able to culture bacteria in a laboratory. He was famous for introducing a new medical concept known as Koch's postulates—4 comprehensive clinical principles to establish the association of pathogens with specific diseases. For his basic and clinical studies on tuberculosis, he received the **Nobel Prize** in Physiology or Medicine in 1905. The day he reported the finding of tuberculosis bacterium, March 24, has been observed annually by the World Health Organization as "World Tuberculosis Day" since 1982.

(**Publ**.: Koch R. A further communication on a remedy for tuberculosis. *Br Med J* 1890; 2:1193–1199.

Koch R. Weitere mittheilungen uber ein heilmittel gegen tuberculose. *Dtsch Med Wochenschr* 1890; 16:1029–1032.

Koch R. Uber neue tuberkulin praparate. *Disch Med Wochenschr* 1897; 23:209–213.

Koch R. Uber die agglutination der tuberkelbazillen und uber die verwerthung dieser agglutination. *Dtsch Med Wochenschr* 1901; 27:829–834.)

Kolmer test (**Kolmer reaction**) is a complement-fixation test for the diagnosis of syphilis. The test is a serology one for assessment of antigen-specific antibodies by mixing patient serum with antigen, complement, and marker red blood cells. This test is based on the process of complement cascade activation by the immune complexes formed in the presence of antibodies in tested serum specimens. When complement components bind to antibody–antigen complexes, they are no longer available for inducing hemolysis of indicator erythrocytes. In the lack of antigen-specific antibody in a testable serum sample, available complement causes lysis of added red blood cells.

The Kolmer test was developed by ***John A. Kolmer*** in 1922 as a standard quantitative method for the **Wassermann test**. Today, it is known as an obsolete, nonspecific cardiolipin-based serologic complement-fixation test for syphilis, which has been superseded by the Venereal Disease Research Laboratory (VDRL) test.

John Albert Kolmer (Apr 24, 1886–Dec 11, 1962) was a Philadelphia physician whose interests included infectious diseases and public health. He was born in Lonaconing, Allegheny County, MD, to Leonard Echkard Kolmer and Selma Louisa Kolmer (born Reichelt). He graduated from the Charlotte Hall Military Academy in 1904 and began his medical training at the Medical School of the University of Maryland. He earned his MD degree from the University of Pennsylvania in 1908 and the degree of Doctor of Public Health in 1914. He then worked as an intern in St. Vincent's and St. Agnes hospitals in Philadelphia, and next as a pathologist in the Philadelphia Hospital for Contagious Diseases (1910–1918). He was also a pathology teacher at the undergraduate school of the University of Pennsylvania School of Medicine and the Philadelphia Polyclinic and College Graduate School of Medicine.

From 1932 on, Kolmer oversaw the bacteriology and immunology programs at the Temple University School of Medicine. He improved the Wassermann test for syphilis, creating the Kolmer test. He also worked on evaluation of Salvarsan or compound 606, as the initial effective treatment for syphilis. Kolmer was a part of the early and tragic trial of a live polio vaccine in 1934, when because of a manufacturer mistake the vaccination caused deaths and paralysis in some people. After this, he ended his vaccination studies and focused on public health and prophylactic medicine. Kolmer also is remembered as a physician who was called in to treat President Calvin Coolidge's son, Calvin Jr., when the 16-year-old boy became ill in 1924 and died of systemic *Staphylococcus* infection.

Until his retirement in 1957, he also headed the Research Institute of Cutaneous Medicine, which he established with colleagues Jay Schamberg and George Raiziss. After retirement Kolmer continued his research as Emeritus Professor at Temple and Emeritus Director of the Institute of Public Health and Preventive Medicine. In December 1962, he suffered a fatal coronary thrombosis in his office. John A. Kolmer published several textbooks and at least 100 papers on various medical subjects. He was the fourth president of the American Association of Immunologists, serving from 1917–1918, and was a president of the American Society of Clinical Pathologists.

(**Publ**.: Kolmer JA. A superior antigen for complement fixation tests in syphilis. *Am J Syph* 1922; 6:74.)

Korovnikov's syndrome (**Korovnikov's disease**) is a distinct form of **Banti's disease**. Clinically, it is characterized by splenomegaly, thrombocytosis/subthrombocytosis, and gastrointestinal bleeding, but without esophageal varicose veins. It usually occurs between the ages of 20 and 40, commonly as acute hematemesis (i.e., vomiting of blood) and melena (i.e., blood in stools). Remission between these acute phases may be for a few years. Then, leukopenia, hypochromic anemia, and thrombocytosis may follow.

A. F. Korovnikov was a Russian physician.

(**Publ**.: Korovnikov AF. Splenopatia s subtrombocitozom i gastroenteroragiami. *Klin Med* 1936; 14(5):714–721.)

Kostmann syndrome (**Kostmann disease**, **Kostmann's agranulocytosis**, **Kostmann's syndrome**, congenital agranulocytosis, severe congenital neutropenia type 3) is a group of rare disorders that affect myelopoiesis, causing a congenital form of neutropenia, usually without other physical malformations. Children with this disease have no special problems with viral or fungal infections but suffer frequent infections from bacteria and have an increased risk of developing acute myelogenous leukemia. Affected patients often have increased plasma concentrations of granulocyte colony-stimulating factor (G-CSF), as well as circulating eosinophils and monocytes.

The disease was first clearly described by Kostmann in 1950. In his fundamental doctoral thesis in 1956, ***Rolf Kostmann*** analyzed 14 affected children from an inbred family in Norrbotten, a province in northernmost Sweden. He concluded that visible neutropenia was because of "a primary insufficiency of the bone marrow" and a "single recessive gene difference." Fifty years later, homozygous mutations in the gene encoding the mitochondrial protein HCLS1-associated X1 (*HAX1*) on chromosome 1q21 were identified in samples obtained from descendants of the original Swedish family discovered by Kostmann.

The syndrome was called **Kostmann syndrome** (Skokowa et al. 2007). HAX1 is critical to maintaining the inner mitochondrial membrane potential and protecting against apoptosis in myeloid cells; it is a major regulator of myeloid homeostasis and underlined the significance of genetic control of apoptosis in neutrophil development. HAX1 mutations affecting exclusively the full-length isoform A only resulted in neutropenia without neurologic symptoms. In contrast, mutations affecting both HAX1 isoforms A and B were associated with an additional neurologic phenotype. Up to 21% of affected individuals develop a clonal proliferative disease leading to myelodysplastic syndrome or overt acute leukemia, often preceded by mutations in the gene encoding the granulocyte colony-stimulating factor receptor (CSF-R).

Research has proved that congenital neutropenia is a genetically heterogeneous group of related diseases that demonstrate several modes of inheritance, including autosomal recessive, autosomal dominant, sporadic and X-linked forms. Several genetic causes of severe congenital neutropenia have been identified, but a common thread among the variants is excessive neutrophil apoptosis. Nonsyndromic variants of congenital neutropenia are caused by mutations in *ELA2*, *HAX1*, *GFI1*, or *WAS*. Syndromic variants of congenital neutropenia may be attributable to mutations in genes controlling glucose metabolism (*SLC37A4 or G6PC3*) or lysosomal function (*LYST*, *RAB27A*, *ROBLD3/p14*, *AP3B1*, or *VPS13B*).

Rolf Kostmann (Sept 18, 1909–Jun 8, 1982) was a Swedish pediatrician. He was born in Abo, Finland, and raised in a traditional middle-class Swedish family. He was educated in medicine at the Karolinska Institute in Stockholm, where he received his MD in 1937. Between 1937 and 1941, he completed his pediatric training at Norrtull's Children's Hospital. Between 1942 and 1952, he worked at the Army Hospital in Boden. In 1942, at the age of 33, he was the youngest ever head

of a Swedish pediatric department. At that time, he was medically responsible for 5000 refugee children from Finland during the very cold winter of 1942.

In March 1949, Kostmann worked on a 2-month-old girl who her mother brought from Dirivaara, a small village in northern Överkalix, after traveling 160 km on small mud roads. The child had a high fever, otitis media (i.e., inflammation of the middle ear), mastoiditis (i.e., an inflammed mastoid bone of the skull located behind the ear), and several various-sized boils (i.e., painful, pus-filled bumps under the skin). A blood count revealed agranulocytosis. Kostmann discovered that the girl was the ninth child, with 4 infants who died of a febrile condition and 3 also having boils. Several infants from the father's side also suffered from similar clinical problems. Kostmann concluded that the case represented a novel hereditary disease associated with abnormal granulocytopoiesis.

To verify this, he borrowed a car and drove to the church in Överkalix to see registration documents counting all residents in the area. The initial genealogical research took 2 days of register searching. In a month, Kostmann had many documents on families with 12–15 children, where 5 or 6 infants had died from unknown causes. The mortality rate in some groups was almost 4 times higher than in other parts of the same district. Kostmann continued his research and traveled a lot by foot through deep forests to get to isolated houses and villages to question parents who lost their children. In 1956, he already had 700 documented inherited analyses ready for presentation. He finalized his study in 1975 with 1700 people in his records covering 200 years of the area's history.

In 1952, Kostmann was offered a position of Clinical Director of the Department of Pediatrics at the Central Hospital in Norrköping in eastern Sweden. Chronic depression did not allow him to defend his doctoral thesis until 1956. He retired early, in 1972, and returned to his earlier research, publishing several papers. Rolf Kostmann was known as an outstanding speaker and writer when communicating with bureaucratic authorities. One of his hobbies was the art of linoleum printing. He was also a talented caricaturist who drew pictures of the children in his notes when their cases were unusual.

(**Publ**.: Kostmann R. Hereditär reticulos—en ny systemsjukdom. *Sven Laekartidn* 1950; 47:2861–2868.

Kostmann R. Infantile genetic agranulocytosis; agranulocytosis infantilis hereditaria. *Acta Paediatr Suppl* 1956; 45:1–78.

Kostmann R. Infantile genetic agranulocytosis: A review with presentation of ten new cases. *Acta Paediatr Scand* 1975; 64:362–368.)

Kounis syndrome is an episode of angina or even a heart attack triggered by an allergic reaction. It has been described as "the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults" (Kounis 2013). Inflammatory mediators, including histamine, proteases, prostaglandins, platelet-activating factors, and proinflammatory cytokines are released in blood during allergic episodes and acute

coronary syndromes can cause coronary artery spasm and/or atheromatous plaque erosion or rupture.

There are 2 types of the syndrome that have been identified. Type 1 is allergy-related angina (angina pectoris) because of coronary spasm. Type II is allergy-related myocardial infarction (heart attack) as a result of plaque rupture and thrombus formation. The type III reaction has been added recently as drug-eluting stent thrombosis (late stent thrombosis) secondary to hypersensitivity responses. Allergic reactions associated with bee or wasp stings, some drugs, or even general anesthetics or stents may be linked with **Kounis syndrome**. Because mast cells present in most organs, including the brain, the cerebral arteries, and the mesenteric arterial system, Kounis syndrome can affect not only the coronary arteries but also the mesenteric and cerebral arteries.

Nicholas Kounis, a Greek cardiologist, first reported that the syndrome could be induced by chemicals (e.g., histamine) released during an allergic response. These agents may cause the coronary spasm, thus limiting the blood flow and causing angina-like chest pain. ***Paul Ehrlich*** published his seminal description of mast cells in 1878. Anaphylaxis was characterized by Richet and Portier in 1901, and in 1913 ***Auer*** reported ECG changes during animal anaphylaxis. The earliest case of myocardial infarction during an allergic reaction in humans was reported in 1950 (Pfister and Plice, 1950). Kounis and Zavras reported a "syndrome of allergic angina" when chest pain and allergic reactions occur simultaneously or when angina pectoris may be induced by inflammatory mediators secreted during an allergic reaction.

Kovanen demonstrated that coronary mast-cell degranulation at the sites of erosion is significantly greater than the ones in adjacent zones (Kovanen et al., 1995). Braunwald reported that histamine and leukotrienes secreted during allergic responses may trigger vasospastic angina by affecting coronary smooth muscles (Braunwald, 1998). Kounis in 1991 summarized and analyzed all clinical data and, for the first time, confirmed the syndrome of "allergic angina."

The description of Kounis allergy-associated acute coronary syndrome has paved the way to discovering that the same proinflammatory molecules released during acute allergic episodes also are present in blood or urine of patients suffering from acute coronary events of nonallergic etiology. It seems likely that a common pathway between allergic and nonallergic coronary syndromes exists (Kounis, 2013). Therefore, a new possibility emerges for prevention of the coronary plaque to become unstable and to lead to the development of angina and myocardial infarction. This can be done by inhibition of mast-cell degranulation, which already has been achieved experimentally (Nemmar et al., 2004).

Nicholas George Kounis (Aug 15, 1940–) is a Greek physician. He was born in Patras to Greek parents after his father's return from the US where he emigrated in 1914, served in the US Army, was injured in France during the World War I, and obtained US citizenship. Nicholas graduated from the Athens University Medical School with an MD degree and served in the Greek Army, followed by additional service as a medical practitioner in rural Greek areas. In 1971, Kounis moved to the

UK for postgraduate medical training in general medicine and cardiology and worked there for 10 years.

In 1981, he returned to Greece as the Director of the Intensive Care Unit at Saint Andrews University Hospital, Department of Medicine, University of Patras Medical School. There he studied and treated 2 patients who had acute heart attack after an allergic reaction to shellfish. He tried to publish a paper on a new syndrome that he named "allergic angina syndrome" caused by inflammatory mediators released from mast cells and representing a manifestation of endothelial dysfunction. He did not get disappointed when several medical journals refused to publish his work. One of the reviewers had written: "Despite of the lack of information the author presents the concept of allergic angina." Kounis persisted and finally the syndrome of allergic angina was published in the *British Journal of Clinical Practice* in 1991. Ultimately, in 2003 and 2005 Greek and US scientists named allergic angina and allergic myocardial infarction the **Kounis syndrome**.

In 1991, Kounis, was appointed a Professor of Medicine in the Western Greece Highest Institute of Education and Technology and continued his clinical work, teaching students and doing research on allergic angina, allergic myocardial infarction, and anaphylactic shock; thus, he proved that the heart, and especially the coronary arteries, constitute primary targets of anaphylaxis. From 2007 on, Nicholas Kounis has been an Emeritus Professor of Medicine; research advisor to the cardiology department of University of Patras, Greece; Chief Editor of the medical journal *Achaiki Iatriki*; and is doing some private practice sessions. He lives in Patras, Achaia, Greece, with his wife, daughter, son, and a grandson.

(**Publ**.: Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991; 45:121–128.

Kounis NG, Zavras GM. Allergic angina and allergic myocardial infarction. *Circulation* 1996; 94:1789.)

Köbner's syndrome (**Kobner's phenomenon**, **Köbner phenomenon**, **Koebner phenomenon**) is the development of vitiligo at sites of a specifically traumatized skin, most often seen in patients with psoriasis, eczema, flat warts, and lichen planus. This is an isomorphic cutaneous reaction occurring in response to trauma and affecting previously uninvolved sites—also called *isomorphic response*. This phenomenon has been further reported in various systemic diseases including systemic lupus erythematosus, discoid lupus erythematosus, systemic sclerosis, dermatomyositis, and even in sarcoidosis. All these are noninfectious inflammatory diseases and most of them are autoimmune diseases. The provocation factors of the **Kobner's phenomenon** are nonspecific ones in which inflammatory reactions are common: trauma, needling, scratches, pressure, sun exposure, X-rays, cold, heat, drug administration, silica granulomas, tattooing, scars, and inflammatory dermatoses.

Heinrich Köbner presented his clinical observations in 1872 at the meeting of the Silesian Society for National Culture. He observed patients who developed psoriasis at sites of excoriations (i.e., scratch or abrasion of skin), horse bites, and

tattoos. He published his clinical results 4 years later. The method of inducing a reaction experimentally was known as the Köbner experiment.

Heinrich Köbner (Dec 2, 1838–Sept 3, 1904) was a German dermatologist. He was born in Breslau (now Wroclaw, Poland) to a Jewish family. He studied in Berlin from 1855–1859 and obtained his medical doctorate at Breslau in 1859. After hospital service in Vienna and Paris, he settled in Breslau where he initiated the first policlinic for syphilis and diseases of the skin in 1861. In 1872, he was appointed to the newly established Chair at the University of Breslau. In 1876, he established the University Policlinic for Diseases of the Skin and Syphilis, becoming its director. Yet, because of some health issues and the necessity to spend time at southern health resorts, he had to resign his positions and moved to Berlin. In 1884, he built a new policlinic in Berlin where he established special courses for physicians that attracted a large number of participants.

Köbner demonstrated many skin infections by inoculating his forearms and chest with materials harvested from patients' skin. At his lectures and special presentations, he exposed various parts of his body to convince his audience. His main interests were in understanding pathogenesis and therapy of tuberculosis, syphilis, and leprosy. He died in Berlin.

(**Publ**.: Köbner H. Zur Aetiologie der Psoriasis. *Vierteljahresschr Dermatol Syph* 1876; 8:559–561.

Köbner H. On the aetiology of psoriasis. *Vjschr Dermatol* 1877; 9:204–207.

Köbner H. Clinical, experimental and therapeutic communications on psoriasis. *Berl Klin Wochenschr* 1878; 15:631–632.)

Königstein-Urbach reaction (**Urbach-Königstein reaction**, **Urbach-Königstein method**) was a diagnostic procedure for demonstrating antibodies in allergy. Allergen administered percutaneously, cutaneously, or intracutaneously causes a local reaction, which will develop into a blister when a cantharidal dressing is placed on it. Cantharides was known as a poisonous, blistering preparation made from the powdered, dried bodies of beetles, *Cantharis vesicatoria*. The application of cantharides, or Spanish fly, was done in the form of a plaster or cantharidal collodion. The **Königstein-Urbach method** of passive transfer, in which blister fluid was used instead of blood serum and antigen was applied by contact or by injection, was devised to demonstrate cell-fixed antibodies.

During 1924–1925, ***Urbach*** and ***Königstein*** worked on a patient who developed allergic sensitivity to a pentavalent arsenic compound. The **Prausnitz-Küstner test** was nonreactive, but they were able to create a blister on a skin reaction site with cantharidin (a chemical derived from the excretions of several blister beetles). Extracted blister liquid provoked a reaction to arsenic compound if injected in a control subject. This technique became recognized as the **Königstein-Urbach reaction**. Urbach also reported that the reaction sometimes could be delayed, as with tuberculosis, and discussed immediate-versus-delayed hypersensitivity pathways, although he did not consider the role of lymphocytes in the whole procedure.

Hans Königstein (***Koenigstein***) (Sept 2, 1878–1960) was an Austrian physician. He was born in Vienna, the son of the ophthalmologist and university professor Leopold Königstein and Henriette Leontine Königstein (Héndlé). Hans studied in Vienna and Bern and received his doctorate in 1903. He worked at the Franz-Josef-Spital and focused on the pigment and chemistry of the skin, internal secretion of the skin, amyloids of the skin, and the nervous system in early stages of individuals' lives. In 1912, he became head of the dermatological ward of the Rothschild Hospital of the Jewish Community. Königstein was habilitated for skin and venereal disease at his alma mater in 1913, becoming Titular Professor in 1927. He was lecturer for dermatology and venereal diseases with the title of an Extraordinary Professor ("Privatdozent. tit.ao.Prof.") at the Medical School of the University of Vienna.

Königstein was persecuted in times of Nazism as a Jew, lost his position on April 22, 1938, and was forced to leave the university. His daughter, Henriette Königstein, and his son, Leopold Königstein, could not finish their studies and were also expelled from the University of Vienna. He managed to emigrate to Palestine (Israel). Königstein died in Tel Aviv, Israel at the age of 81.

Erich Urbach (Jul 29, 1893–Dec 17, 1946) was an Austrian-American allergologist and dermatologist. Born in Prague, Czechoslovakia, to a Jewish family and the son of a textile factory owner. He studied at the University of Vienna Medical School for 2 years and served in the Austro-Hungarian Army as a lieutenant and a member of the surgical group during World War I. He received an awarded for bravery.

Urbach worked in Vienna in various clinical departments, including the skin department at the Breslau Skin Clinic (with ***Josef Jadassohn***), and was an assistant at the skin department in Vienna. In 1929, he was habilitated for skin and venereal diseases at his alma mater, becoming Dozent. He subsequently was assistant physician at the skin clinic. In Vienna, he married Dr. Josepha Kronstein, who became a radiologist. The couple had 2 sons: Friedrich (later Frederick) and Hans (later John).

From 1936, Urbach worked at the Merchant's hospital in Vienna as a chief physician at the Department of Dermatology and Allergy. In 1938, with the Nazis occupation and massive persecution of Jewish physicians and scientists, he had to leave. Within 48 hours, Urbach left Austria, taking his most valuable scientific materials, and went to Switzerland, London, and then Philadelphia. He remained in Philadelphia and was able to bring his family in August 1938. He started as an associate of dermatology at the University of Pennsylvania, but soon became a chief of the Allergy Department of the Jewish Hospital in Philadelphia. He published a lot and his book, *Allergy,* prepared together with P. M. Gottlieb, was a very popular textbook for physicians and students. Many medical conditions have been named after Urbach.

In 1946, Urbach decided to obtain the US board-certification in dermatology to get an academic position at the University of Pennsylvania. After intensive preparations, in December 1946 he traveled to Chicago for the examinations at the American Board of Dermatology. Having a 3-day exam and an overcrowded train trip from Chicago to Philadelphia led to him having 2 myocardial infarctions; this proved to be too much for Urbach. He developed acute chest pain and was rushed from the

railway station to the hospital but developed complications and died from coronary thrombosis.

His son, Frederick Urbach, who left Vienna with him, was trained at the University of Pennsylvania in Philadelphia and became a prominent photobiologist and chaired dermatology at the Skin and Cancer Hospital of Temple University Medical School for 2 decades.

(**Publ**.: Königstein H, Urbach E. Ueber eine familiäre lokale Lipoidose der Haut und Schleimhäute. *Arch Dermatol Syph* 1924; 148:146.

Urbach E. Zur pathogenese der cutanen idiosynkrasien. *Arch Dermatol Syph* 1925; 148:146–157.

Urbach E. Zur passiven übertragung der überempfindlichkeit und zur desensibilisierung allergischer hauterkrankungen. *Arch Dermatol Syph* 1928; 154:550–554.)

Kotb disease is a rare variant of biliary atresia (absence or blockage of bile duct between the liver and the small intestine). Biliary atresia is a congenital obliterative cholangiopathy of unknown etiology. Many etiological and pathogenetic factors and mechanisms may be associated with biliary atresia and include vascular insult, immune-mediated pathways, genetic factors, structural malformation and viral infections such as reo-3 virus, rotavirus, Epstein-Barr virus and cytomegalovirus infection.

It was suggested that the **Kotb disease,** as a biliary atresia variant, may be due to congenital aflatoxicosis in GSTM1 null neonates. Aflatoxicosis is a poisoning that occurs following the consumption of foods that are contaminated with aflatoxins, while the GSTM1 gene encodes a glutathione S-transferase that functions in the detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins and products of oxidative stress, by conjugation with glutathione.

Neutrophil probably play a pivotal role in Kotb disease, and it is likely that the pathogenesis of Kotb disease involves immune-mediated tissue damage through neutrophil elastase and CD14+ activated monocytes/macrophages. The presence of CD4+, CD8+ lymphocytes, CD68+ macrophages, CD14+ macrophages, NK cells and neutrophils were detected in all portal tracts in affected infants and in almost 70% of cases immune inflammatory cells widely distributed in the parenchyma. A subset of infants may demonstrate T helper type 2 cytokine involvement, while the role for Th17 inflammatory pathway was also suggested. Resulted massive inflammation, induced by neutrophils, causes obliteration followed by fibrosis of extrahepatic biliary radicals, accelerated cirrhosis and portal hypertension.

Kotb and colleagues in 2005 described 32 infants with extrahepatic biliary atresia and progressive development of hepatic fibrosis and cirrhosis despite timely surgical intervention. They described CD4+ helper T lymphocyte, cytotoxic CD8+ T lymphocyte and CD68+ macrophage infiltration of portal tracts and lobules concluded that immune-mediated destruction of portal tracts is an integral part of pathogenesis of extrahepatic biliary atresia.

Magd Ahmed Kotb is a physician in Egypt. He is a Professor of Pediatrics and Pediatric Hepatology at the Department of Pediatrics, Cairo University, Cairo, Egypt. He is also a Coordinator of Undergraduate Pediatrics Evidence Based Medicine Teaching Program. He was also a Director of Center for Preventive and Social Medicine at Cairo University.

(**Publ**.: Kotb MA, El Henawy A, Talaat S, Aziz M, El Tagy GH, El Barbary MM, Mostafa W. Immune-mediated liver injury: prognostic value of CD4+, CD8+, and CD68+ in infants with extrahepatic biliary atresia. *J Pediatr Surg*. 2005; 40:1252-1257.

Kotb MA, Azeez M. Antineutrophil cytoplasmic antibodies and other autoantibodies in idiopathic neonatal hepatitis and extrahepatic biliary atresia. *Sci Med J*. 2000; 12:41-52.)

Kupffer cells (**Kupffer-Browicz cells**) are specialized macrophages located in the liver. Kupffer cells represent more than 80% of all tissue macrophages. They are located within the lumen of the liver sinusoids and are responsible for removing gut-derived bacteria, endotoxins, debris, aged and damaged erythrocytes, and the circulating malignant cells. **Kupffer cells** are an important part of innate immunity—first and rapid response to potentially dangerous agents and stimuli.

Kupffer cells can release cytokines, prostanoides, nitric oxide, and reactive oxygen species. These factors regulate Kupffer cells themselves, as well as neighboring hepatocytes, stellate cells, endothelial cells, and other immune cells that travel through the liver. Therefore, Kupffer cells are involved intimately in the liver's response to infection, toxins, ischemia, resections, and other stresses. During hepatocellular damage of the liver or in the state of chronic inflammation, Kupffer cells release enzymes and cytokines that may damage hepatocytes, but that also take an active part in the recovery of the extracellular matrix. In addition, Kupffer cells express the scavenger receptor CD163, which have been involved in clearance and endocytosis of hemoglobin–haptoglobin complexes thereby protecting tissues from free hemoglobin-mediated oxidant injury.

The cells were first observed by ***Karl Wilhelm von Kupffer*** in 1876. He called them "Sternzellen" (star or hepatic stellate cells). Focusing on the characterization of nerve fibers in the liver using tissue staining with gold chloride solution, Kupffer noticed black "stellate cells" with long cytoplasmic processes in hepatic lobules. He suggested that these cells should be from the family of connective tissue perivascular cells or pericytes. Yet, only further studies using various methods have proved that the original Kupffer stellate cells were neither the sinusoidal endothelial cells nor the perisinusoidal cells storing vitamin A (Ito cells). In 1898, after several years of research, ***Tadeusz Browicz*** identified them, correctly, as macrophages.

Carl (Karl) Wilhelm von Kupffer (Nov 14, 1829–Dec 16, 1902) was a German pathologist. (His first name sometimes appears as the Germanic "Karl," but Kupffer signed his name as "Carl.") He was the eldest son of Pastor Karl Hermann Kupffer at Lesten in Kurland, a Baltic duchy then part of Russia (now in Latvia). In 1854, he obtained his medical doctorate from the University of Dorpat (the German name for Tartu in what is now Estonia). In 1856–1857, he took a scientific journey to Vienna,

Berlin, and Göttingen to study physiology. He went to a position of an Associate Professor at the University after returning to Dorpat. In 1866, he became a chair of anatomy at the University of Kiel but moved to Königsberg and served as a Professor of Anatomy for several years. From 1880 on, Kupffer was the Chair of the Anatomy Department at the University of Munich and retired in 1901.

Kupffer's research focused on the development of the brain, spleen, pancreas, and kidneys. He was highly recognized for his major contributions to embryology and comparative neuroanatomy. The noble "von" was officially awarded to add his name for his research work.

Tadeusz Browicz (Sept 15, 1847–Mar 20, 1928) was a Polish pathologist. He was born in Lviv (was Russian L'vov, now Ukranian Lviv). He received his MD degree in 1873 after studying medicine in Kraków, Poland, and he obtained his habilitation in pathology also in Kraków in 1875. He was a Professor of Anatomical Pathology at the Jagiellonian University, Kraków, from 1880–1919, where he worked as its Rector from 1894–1895.

Browicz is known for a few important contributions to medical knowledge. He was the first to identify and describe, in 1874, the bacillus that induces typhoid fever, which later was named *Salmonella typhi*. He properly identified Kupffer cells in the liver as specialized macrophages in 1898. Browicz also worked on jaundice, liver cancer, and cardiac muscle disorders. He published a great deal and is remembered for the publication of a Polish Medical Dictionary in 1905.

(**Publ**.: von Kupffer C. Ueber sternzellen der leber. Briefliche mitteilung an Prof. Waldyer. *Arch Mikrosk Anat* 1876; 12:353–358.

Browicz T. *Ueber Intravasuläre Zellen in den Blutcapillaren der Leberacini. Separat aus dem Anzeiger* der *Akademie der Wissenschaften in Krakau*; 1899; pp. 6–8.)

Kupffer-Browicz cells see **Kupffer cells**

Kuttner tumor (**Küttner tumor**, **Küttner's tumor**, chronic sclerosing sialadenitis or cirrhosis of the salivary gland) is a fibroinflammatory disease of the salivary glands. Despite the term *tumor*, it is a nonneoplastic condition. It is classically described in relation to the submandibular gland but less commonly also can affect the other salivary glands and occasionally the lacrimal gland. Clinically, it produces a firm swelling of the glands and may be difficult to distinguish from neoplasia. It is characterized histologically by periductal fibrosis; dense lymphocytic infiltration with lymphoid follicle formation; loss of the acini; and, eventually, marked sclerosis of the salivary gland. The etiology of **Kuttner tumor** is still unknown. The effects of microliths (sialoliths), infectious agents, secretory dysfunctions, duct abnormalities, and immune processes have been considered. Chronic sclerosing sialadenitis belongs to the spectrum of IgG4-related diseases, which are chronic inflammatory conditions characterized by tissue infiltration with lymphocytes and IgG4-secreting plasma cells, various degrees of fibrosis (scarring), and a prompt response usually to oral steroids. Inflammation resulting in fibrosis, the deposition of connective

tissue, in affected anatomical sites can lead to organ dysfunction, or even organ failure if not treated.

It was initially described in 1896 by ***H. Küttner*** who depicted 4 patients with a unilateral, hard, tumor-like mass of the submandibular gland, which histologically showed features of chronic sclerosing sialadenitis.

Hermann Küttner (Oct 10, 1870–Oct 10, 1932) was a German physician and maxillofacial surgeon. He was born in Berlin, a son of the manor owner, Otto Küttner, on Eichwerder near Soldin in Neumark. After attending grammar schools in Waldenburg, Silesia, Berlin, and Hameln, he studied medicine at the Eberhard Karls University in Tübingen. Then, he moved to the Friedrich-Alexander University of Erlangen and the University of Kiel. In 1894, he was promoted to Dr. med. PhD. He received his medical training first in anatomy, then in surgery. In 1897, he completed his habilitation in surgery in Tübingen, and in 1900 he was appointed Associate Professor of Surgery. In 1904, he moved to the Philipps University of Marburg to become a Full Professor in 1906. Then he worked in Berlin and Friedrich Wilhelms University as Chair of Surgery.

Küttner's research focused on the lymphatic tracts of the diaphragm, vascular surgery, and transplantation of recently deceased tissues, as well as with surgical diseases in the area of the brain and facial skull. He developed many new surgical procedures and was considered a brilliant surgeon. In 1914, he organized the first international exchange in surgical training together with the Johns Hopkins University. As a surgeon and a delegate of the German Red Cross, he introduced X-ray diagnostics into war surgery in the Turkish-Greek War, Second Boer War, and Boxer Rebellion. In 1927, he was president of the German Society for Surgery. He is remembered for the Küttner tumor of the salivary gland. After a brief heart disease, he died at the age of 62.

(**Publ**.: Küttner H. Über entzündliche tumoren der submaxillarspeicheldrüse. *Beitr Klin Chir* 1896; 15:815–828.)

Letter L



La antigen is recognized by antibodies in patients with autoimmune disorders (e.g., systemic lupus erythematosus and Sjögren's syndrome). It is a 46/48 kDa phosphoprotein. La antigen belongs to a heterogenous group of extractable nuclear antigens (see **Sm antigen**). It is named after the patient who provided the prototype serum. La antigen also is known as SS-B. The SS-B/La antigen has RNA recognition motifs that bind to uridine-rich residues on the 3′ terminus of scRNAs and may act as a shuttle to carry RNA transcripts from the nucleus to the cytoplasm. The antibody to SS-B/**La antigen** is detected in 15–20% of systemic lupus erythematosus and in 45–60% of Sjögren syndrome patients.

Lambert-Eaton syndrome (**Lambert-Eaton myasthenic syndrome**, **Eaton-Lambert syndrome, Lambert-Eaton-Rooke syndrome**) is a rare autoimmune disorder owing to the formation of autoantibodies against presynaptic P/Q-type voltage-gated calcium channels, and likely other nerve-terminal proteins in the neuromuscular junction. Antiglial nuclear antibodies (or SOX1 antibodies) are common also. The quantal release of acetylcholine is impaired, causing a unique set of clinical characteristics, which include proximal muscle weakness, depressed tendon reflexes, posttetanic potentiation and autonomic changes. **Lambert-Eaton syndrome** may be developed together with other autoimmune diseases, including hypothyroidism and type 1 diabetes. It also may be considered a paraneoplastic syndrome because almost 60% of patients with Lambert-Eaton syndrome are diagnosed with common malignancy (e.g., small-cell lung cancer).

The first case of potential clinical findings of Lambert-Eaton syndrome was published by Anderson from St. Thomas' Hospital, London in 1953 (Anderson et al., 1953). ***Lambert***, ***Eaton*****,** and ***Rooke*** from the Mayo Clinic first provided a comprehensive description of clinical and electrophysiological characteristics of the disease in 1956. Later studies established an autoimmune nature of the disease and demonstrated the link with antibodies against P/Q-type voltage-gated calcium channels.

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Edward Howard Lambert (1915–Jun 27, 2003) was a US physician recognized as the "father of electromyography." He was born in Minneapolis to parents with Norwegian and French-Scottish roots. During his childhood years, he was interested in music and biology. When the family moved to Chicago, he received his BS, MS, and MD degrees from the University of Illinois, the latter in 1939. Then he did his internship at Michael Reese Hospital in Chicago and defended his PhD thesis in physiology.

Lambert for many years worked at the Mayo Clinic and the Mayo Medical School in Rochester, MN, as Professor of Physiology and Professor of Neurology. His research focused on neurophysiology and applicability of electromyography, and he developed the basic concepts of neuromuscular disorders. For instance, together with Vanda Lennon, his wife, he discovered and characterized the immunological basis of *myasthenia gravis* and Lambert-Eaton myasthenic syndrome.

He retired in 1985 but maintained his research for almost 9 years at the University of Minnesota. He worked on developing animal models to study synaptic pathophysiology. In 1996, he described the generation of a mutated muscle acetylcholine receptor—the first mouse model to study the slow-channel syndrome.

Lealdes (Lee) McKendree Eaton (Feb 3, 1905–Nov 18, 1958) was born in Owaneco, IL. In 1927, he received his BS degree from the University of Chicago and in 1932 his MD degree from Rush Medical College. He then did an internship at Cook County Hospital and a fellowship at the Mayo Clinic in Rochester, MN, in medicine and neurology. In 1936, he joined the Mayo Clinic where he received an MS degree in neurology in 1938 and a professorship in 1950. From 1954 on, he was a chairman of neurology.

Eaton's major research was in neuromuscular disease, especially myasthenia gravis and polymyositis. He promoted the term "polymyositis" for clinical cases with no dermatological abnormalities. He and Lambert presented the initial clinical report and electrophysiological description of the myasthenic syndrome linked to malignant tumors, known now as the Eaton-Lambert syndrome. Eaton published more than 50 papers on various topics in neurology and its association with psychiatry.

Edward Douglas Rooke (Oct 1, 1912–Jun 18, 2001) was a Canadian physician. He was born in Toronto, Ontario. He received his degree from Queens University in 1937 and trained in internal medicine and neurology at the Mayo Clinic. During the 5 years of World War II, he served as a military Chief Medical Officer in Western Canada. He married Avis Bjerke in 1946 and they raised 2 children. In 1949, he joined the Mayo Clinic as a neurologist, where he stayed until his retirement in 1977. He was the first to recognize and explain the differences between the muscle weakness disease, known as the myasthenic or Eaton-Lambert syndrome, and myasthenia gravis. He reported that in myasthenic syndrome the patient became stronger with action, while with myasthenia gravis the patient gets weaker with exertion. Rooke died in Rochester, MN.

(**Publ**.: Lambert EH, Eaton LM, Rooke ED. Defect of neuromuscular conduction associated with malignant neoplasms. *Am J Physiol* 1956; 187:612–613.)

Lambert-Eaton-Rooke syndrome see **Lambert-Eaton syndrome**

Landry's paralysis see **Guillain-Barré syndrome**

Landry's syndrome see **Guillain-Barré syndrome**

Landry-Guillain-Barré syndrome see **Guillain-Barré syndrome**

Landry-Kussmaul syndrome see **Guillain-Barré syndrome**

Lane-Hamilton syndrome is a rare disease, which coexists with celiac disease and idiopathic pulmonary hemosiderosis hemorrhage. Idiopathic pulmonary hemorrhage (IPH), also known as **Ceelen-Gellerstedt syndrome**, is characterized by the triad of iron deficiency anemia, pulmonary infiltrates, and hemoptysis with no other cause. The association between IPH and celiac disease (see **Gee-Herter-Heubner disease**) initially was described by Lane and Hamilton in 1971 and can be referred to as the **Lane-Hamilton syndrome**. It typically is seen in children under the age of 15 but can occasionally be seen in adults.

This association between the 2 diseases may be because both share a common pathogenic immune/autoinflammatory pathway. The clinical importance of this association is that a significant improvement can be obtained with a gluten-free diet not only in intestinal but also in pulmonary symptoms. Thus, treatment is based on a gluten-free diet and immunosuppressive agents. This syndrome was originally described by ***Lane*** and ***Hamilton*** in 1971.

D. J. Lane, an English physician, is known to be associated with the Nuffield Departments of Medicine and Anesthetics, Radcliffe Infirmary and the Churchill Hospital, Oxford, UK.

W. S. Hamilton, an English physician, is known to be associated with Churchill Hospital, Oxford.

(**Publ**.: Lane DJ, Hamilton WS. Idiopathic steatorrhoea and idiopathic pulmonary haemosiderosis. *Br Med J* 1971; 2(5753):89–90.)

Langerhans cells belong to the dendritic cell family of myeloid antigen-presenting cells. Langerhans' cells are normally found in the basal layer of the epidermis and also can be localized in the respiratory, digestive, and urogenital tract epithelia. They participate in antimicrobial immunity, skin immunosurveillance, contact hypersensitivity, carcinogenesis, and pathogenesis of chronic inflammatory diseases of the skin or mucosa. Langerhans' cells function as antigen-presenting ones and include attaining antigens in peripheral tissues; antigen processing; transportation of antigenic peptides to regional lymph nodes; and presentation of antigens to naive T cells, their activation, and thus initiation of adaptive immune responses. **Langerhans' cells**, on the other hand, also may induce development of immune tolerance. The Langerhans' cell is named after ***Paul Langerhans***.

Paul Langerhans see **Langerhans' cell histiocytosis**

Langerhans' cell histiocytosis belongs to the group of clinical syndromes termed histiocytosis, which are characterized by an anomalous proliferation of histiocytes (an out-of-date term for macrophages and dendritic cells). Clinical features of Langerhans' cell histiocytosis range from localized bone lesions to multisystem syndromes. Although the epidermal Langerhans' cell has been presumed to be the cell of origin, diverse cell subsets may possess phenotypic features similar to Langerhans' cells (e.g., **Birbeck granules** in the cytoplasm and expression of CD207). These cells may include dermal Langerin$^+$-dendritic cells, lymphoid tissue resident Langerin$^+$-dendritic cells, and monocytes that can acquire a Langerhans' cell phenotype under specific conditions of the local environment. It can be speculated that Langerhans' cell histiocytosis is not a specific disease of epidermal Langerhans' cells, but rather one of mononuclear phagocyte dysregulation.

The disease has been known by various names: **Hand-Schüller-Christian disease**, **Abt-Letterer-Siwe disease,** and histiocytosis X. However, the Histiocyte Society renamed it in 1985. Historically, in 1953, to unify these diseases, Lichtenstein presented the term Histiocytosis X to stress the histiocytic nature of the disorder. In 1973, ***Nezelof*** reported that Histiocytosis X is attributable to the propagation of Langerhans-like cells and suggested the term Langerhans' cell histiocytosis. Lieberman proposed the term Langerhans' cell granulomatosis to avoid confusion with histiocytosis X. Nevertheless, **Langerhans' cell histiocytosis** is the generally accepted and favorite terminology.

Paul Langerhans (Jul 25, 1847–Jul 20, 1888), a German pathologist and physician, was born in Berlin. His father was a physician and president of the Berlin City Council. His 2 younger stepbrothers were also medical doctors. One of them, Robert, worked with ***Rudolf Virchow*** and was a professor of pathology at a later time. From 1865–1866, Langerhans studied medicine at the University of Jena; then he continued his medical studies in Berlin, where he was particularly influenced by ***Rudolf Virchow*** and later became his close friend.

In 1868, while an undergraduate student and working on his first research project, Langerhans discovered and described a new group of epidermal cells in his paper entitled "On the nerves of the human skin." He used the Julius Cohnheim gold chloride-staining techniques in skin specimens and visualized the nonpigmentary dendritic-like cells in the epidermis. He speculated that these cells were intraepidermal sensory receptor cells that transferred extracutaneous signals within the nervous system. For a century, the real function of these cells, termed later as **Langerhans' cells**, was unknown to dermatologists, and only in 1973 did Inga Silberberg report that the epidermal Langerhans' cells belong to the immune system as cells with an antigen-presenting function (Silberberg, 1973). Currently, Langerhans' cells are recognized as a subset of epidermal immature dendritic cells.

While working with Friedrich Albin Hoffmann in Virchow's laboratory, Langerhans was involved in another authoritative contribution in the immunology of the macrophage system. They recorded the intravital redistribution of cinnabar (i.e., a toxic mercury sulfide mineral) after its intravenous administration in guinea pigs and rabbits. The researchers saw that cinnabar was engulfed by white, but not

red, blood cells and then detected in cells in the bone marrow, capillary system, and connective tissue in the liver. These original findings created a fundamental basis for ***Ludwig Aschoff***'s concept of the reticuloendothelial system.

Langerhans finalized his dissertation in 1869 when he discovered distinctive cell islands in the pancreas, which were named Langerhans' islands after him. In 1870, he joined the team of the geographer Johann Samuel Heinrich Kiepert to travel to Egypt, Syria, and Palestine to study lepra in addition to doing some anthropological and ethnographical research. During the Franco-Prussian War he worked as a physician in the German army in a military hospital. In 1871, he was offered the position of prosector in pathology at the University of Freiburg, a position arranged for him by Rudolf Virchow. He became Privatdozent in the same year and, later, Associate Professor.

In 1874, Paul Langerhans contracted tuberculosis, very likely because of his work in the dissecting room. Attempts at a cure in Switzerland, Italy, and Germany failed; and in 1875, he settled in Madeira. While there, he practiced medicine in the capital, Funchal, and studied the etiology of tuberculosis. He also maintained his original basic biology investigation of the fauna of Madeira and the Canary Islands, which resulted in an important contribution to invertebrate zoology in a series of publications. He died of a kidney infection and was buried in the cemetery of an English church.

(**Publ**.: Langerhans P. Uber die nerven der menschlichen haut. *Arch Pathol Anat* 1868; 44:325–337.)

Langhans giant cells see **Pirogov-Langhans cells**

Leiner's disease (**Leiner's syndrome**, **Leiner-Moussous disease**) is a rare condition resembling and probably identical with severe seborrheic dermatitis and is characterized by generalized exfoliative dermatitis and marked erythroderma. It also is known as "erythroderma desquamativum." The 4 cardinal features are: (1) generalized seborrheic dermatitis; (2) intractable, severe diarrhea; (3) recurrent local and systemic infections, usually of gram-negative etiology; and (4) marked wasting and dystrophy. Some cases suggest that this is a genetic disorder with an autosomal recessive pattern of inheritance. It is caused by the ineffective or decreased biosynthesis of the fifth complement component, C5; however, case reports have described it in relation to deficits in either C3 or C4. Thus, the C5 defect may not be the sole cause of **Leiner disease**, as has been suggested; diminished C3, C4, or C5 dysfunction or deficiency with hypogammaglobulinemia or any other lymphoid deficiency also is required for its expression.

The etiology of this disease is not completely understood because some infants may have severe cases and others may have immunodeficiency. C5 deficiency also may be acquired acutely postinfection. If C5 is adequately synthesized, its rapid depletion may result in a functional deficiency. C5 dysfunction leads to decreased serum phagocytosis (i.e., opsonic activity), eczema, seborrhea, erythroderma, diarrhea, recurrent gram-negative infections, muscle wasting, and failure to thrive.

Deficiency of serum C5 and its major cleavage product, C5b—a component of the membrane attack complex—increases susceptibility to Neisserial infections. **Leiner disease** may be present at birth but more commonly develops within the first few months of life. It begins as seborrhoic eczematoid lesions of the scalp and face or the gluteal region, eventually spreading to other areas. Keratitis and corneal ulcers can occur.

In 1908, ***Leiner*** studied 43 children with a triad of diarrhea, weight loss, and dermatitis. Later this clinical phenotype became known as Leiner syndrome.

Carl (Karl) Leiner (Jan 23, 1871–Apr 24, 1930) was an Austrian pediatrician. He was born in Flöhau, Bohemia, to Nathan Leiner and Ludowiga Leiner (born Hirsch). He obtained his education in Prague and Vienna, and after graduation in 1896, he worked in the Skin Clinic and the Institute of Pathology in Vienna. He finished his training in pediatrics in 1912. From 1920 onward he was a director of the Mautner-Markhof Kinderspital der Stadt Wien. From 1922 on, he was a Titular Professor.

Leiner's clinical research focused on pediatric infections. He was also the first to use an intracutaneous technique for smallpox vaccination and was the first to recognize its relationship to postvaccine encephalitis. He investigated poliomyelitis and other viruses and bacteria at the Weichselbaum Institute. He was an unusual combination of clinician, practitioner, consultant, laboratory worker, and scientific investigator. He died in Vienna.

André-Charles-Antoine (André) Moussous (Jun 6, 1857–1926) was a French pediatrician. He was born in Bordeaux and studied in Bordeaux and Paris; he received his doctorate in Bordeaux in 1885. He became a qualified teacher in clinical pediatrics in 1890 and in 1898 became a Full Professor at the Medical Hospital in Bordeaux.

(**Publ**.: Leiner C. Über erythrodermia desquamativa, eine eigenartige universelle dermatose der brustkinder. *Archiv Dermatol und Syph* 1908; 89:65–76, 163–189.

Leiner C. Erythrodermia desquamativa [universal dermatitis of children at the breast]. *Brit J Children's Dis* 1908; 5:244–251.)

Leiner-Moussous disease see **Leiner's disease**

Leschke's syndrome see **Troisier-Hanot-Chauffard syndrome**

Letterer-Siwe disease see **Abt-Letterer-Siwe disease**

Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy) is a chronic inflammatory demyelinating neuropathy—a neurological condition affecting primarily upper limbs (arms and hands). It is a rare disease with a total of 90 cases reported by 2009. It is closely related to **Guillain-Barré syndrome,** and it is considered the chronic counterpart of that acute disease. The syndrome is an acquired disorder; although the exact cause of the condition is not

known, it is considered an autoimmune disorder that destroys myelin. In some cases, **Lewis-Sumner syndrome** is a side effect of a therapy using antagonists of TNF-α (anti-TNF-α Abs)—for instance, arthritis and inflammatory bowel disease therapy.

In 1982, ***Lewis*** et al. described patients with a chronic asymmetrical sensorimotor neuropathy involving multifocal peripheral nerves mainly on the arms. The disease did not look like conditions reported in 1988 by Parry and Clarke, as a neuropathy associated with IgM autoantibodies targeting GM1 gangliosides, and is now known as a multifocal motor neuropathy. It is important to make a distinction between both syndromes because multifocal motor neuropathy is sensitive to intravenous globulin (IVIG), whereas chronic inflammatory demyelinating polyneuropathy in addition to IVIG is also sensitive to steroids and plasma exchanges. Thus, multifocal motor neuropathy differs from chronic inflammatory demyelinating polyneuropathy by pathogenetic mechanisms and Lewis-Sumner syndrome should be considered a different variation of chronic inflammatory demyelinating polyneuropathy.

Richard A. Lewis is a US neurologist. He graduated from Medical School at Virginia Commonwealth University Health System in 1974 and finished his residency and fellowship at the Hospital of the University of Pennsylvania in 1978. In 1980, he was offered a position at the University of Connecticut to organize the Neuromuscular Program with Electromyography Laboratory and establish an Adult Muscular Dystrophy Clinic focusing on **Lou Gehrig's disease**. He then worked at Norfolk's Eastern Virginia Medical School as a clinical assistant professor of neurology (1983–1993) and a director of a Muscular Dystrophy Association clinic (1990–1993). Then he was professor and associate chair of neurology at Wayne State University School of Medicine, directing the Hiller Amyotrophic Lateral Sclerosis Center. Later in Detroit, MI, he served as a director of the Inflammatory Neuropathy Center, codirector of the Muscular Dystrophy Association Clinic at Detroit Medical Center, and a vice chief of neurology and a director of clinical neurophysiology at Harper University Hospital in Detroit. In 2012, Lewis joined the Cedars-Sinai Medical Center, Los Angeles, CA, as a director of the Electromyography Laboratory at the Department of Neurology and a codirector of the Neuromuscular Clinic.

The research of Richard Lewis during his lifetime focused on neuromuscular disorders, **Lou Gehrig's disease**, inherited neuropathies, Charcot-Marie-Tooth Disease, inflammation neuropathies, and myasthenia gravis.

Austin J. Sumner *(*Aug 24, 1938–) is a US neurologist. He was born and educated in Hokitika, New Zealand. After initial training in neurophysiology, he obtained his MD degree from the University of Otago School of Medicine in 1963. He then was trained in the residency and internship programs at Wellington Hospital, Newtown, NZ, and became first a member of the Royal Australasian College of Physicians and then a fellow of the Royal Australian College of Physicians in 1973. He received the Nuffield Foundation Postdoctoral Traveling Fellowship in Medicine in 1967 and worked at the National Hospital for Neurology and Neurosurgery in

London, UK. Then he was an assistant professor of neurology at the University of California San Francisco and a professor of neurology at the University of Pennsylvania in Philadelphia, PA. Sumner was a Professor and Chair Emeritus of the Department of Neurology at Louisiana State University Health Sciences Center in New Orleans, LA, from 1988 onward and retired in 2013.

Sumner was active at the following: American Academy of Neurology Foundation, National Multiple Sclerosis Society, American Board of Electrodiagnostic Medicine, American Neurological Association, European Neurological Society and serves on the editorial board of several medical journals. His research interests focus on the diagnosis and treatment of peripheral neuropathies, neuromuscular diseases, multiple sclerosis, and clinical neurophysiology.

(**Publ**.: Lewis RA, Sumner AJ, Brown MJ, Asbury AK. Multifocal demyelinating neuropathy with persistent conduction block. *Neurol* 1982; 32:958–964.

Lewis RA, Sumner AJ, Shy ME. Electrophysiologic features of Inherited neuropathies: A reappraisal in the era of molecular diagnosis. *Muscle Nerv* 2000; 23:1472–1487.)

Libman-Sacks syndrome (**Libman's endocarditis**, **Libman-Sacks disease**, **Kaposi-Besnier-Libman-Sacks syndrome**, **Osler-Libman-Sacks syndrome**) is the final stage of systemic lupus erythematosus: an atypical, verrucous, nonbacterial, valvular, and mural endocarditis. A visceral manifestation of systemic lupus erythematosus disseminatus is characterized by the presence of systolic and diastolic apical murmurs and verrucous lesions composed of fibrin strands. Polymorphonuclear leukocytes, lymphocytes, and histiocytes infiltrate can be seen in the affected structures. The syndrome is seldom autonomous but is part of a more widespread systemic collagen/connective tissue disorder.

Emanuel Libman (Aug 22, 1872–Jun 28, 1946) was a US internist. He was born in New York to Fajbal Libman, a wealthy Jewish picture framer who came to the US from Poland in 1865. He graduated with his doctorate degree from the College of Physicians and Surgeons, Columbia University in 1894 and was on internship for 2 years at Mount Sinai Hospital. He then continued his medical education and learned from leaders in medicine in Europe, visiting Vienna, Berlin, Munich, Graz, and Prague.

Libman was very well known for his legendary, spectacular, and untraditional diagnostic approaches. Although he was credited officially for his diagnostic sixth-sense, he explained his unique talent as the ability to smell certain diseases and paying attention to the smallest details and facts. He introduced an unique method of putting pressure on patient's mastoid bone to determine their pain sensitivity. Libman treated many famous people, including Sara Bernhardt, Fanny Brice, Thomas Mann, and Albert Einstein. Einstein sent him a signed photo with his own writing: "To the noble-minded Dr. Libman with the secret-divining eyes." In 1944, prior to President Franklin D. Roosevelt's election for a fourth-term, Libman told to his friend: "It doesn't matter whether Roosevelt is re-elected or not. He'll die of a cerebral hemorrhage within six months." He was right and in answer to the question

about his prediction he said: "I only saw him in the newsreels. But, I've seen that special wasting look many times. He couldn't last six months."

Libman had private and lonely life commonly working for 20 hours a day. He was an extraordinary and innovative teacher who is remembered for introducing various interesting and useful initiatives into medical education throughout the world including the Hebrew University in Jerusalem. He worked at Columbia University and founded the Department of Cardiology at Mount Sinai Hospital in New York. In 1957, he donated a gift of $10,000 to the School of Medicine to initiate a lectureship in honor of ***Paul Ehrlich***. Libman's friend, the Nobel Prize laureate Alexis Carrel, used to say that "Libman is medicine itself."

Benjamin Sacks (Aug 14, 1896–May 2, 1971) was a US physician. He was born in Baltimore, Baltimore County, MD, to a Jewish family of Louis Sacks, who came from Riga, Latvia, and Fannie Gotthelf (Sacks), who immigrated from Russia. He obtained his MD degree in 1922 from Johns Hopkins School of Medicine in Maryland. He then worked at Mount Sinai Hospital, New York, with his mentor Emanuel Libman. It was in 1923–1924 when they identified a new type of endocarditis as atypical verrucous endocarditis, known now as Libman-Sacks disease or a sign of systemic lupus erythematosus. Although the disease had been described earlier by other dermatologists, Libman and Sacks reported the first comprehensive clinical features with and without skin lesions and other signs of the disease. Sacks also was interested in Hindu medicine and published on this topic.

During the 1950s, because of weakening health, he retired from practicing medicine and started to work as a special technical advisor in the film industry. Later, he also published as a historian, mainly on the history of the US Southwest. The results of his general study, "The Sacks Collection of the American West," is kept at the Arizona Historical Foundation in the Hayden Library at Arizona State University in Tempe. Sacks was a scientist to the very end—he died with boxes of historical documents at his bedside in his Baltimore house.

(**Publ**.: Libman E, Sacks B. A hitherto undescribed form of valvular and mural endocarditis. *Arch Intern Med* 1924; 33:701–737.)

William Osler see **Osler nodes**

Moritz Kaposi see **Kaposi's sarcoma**

***Ernest Besn*ier** see **Besnier-Boeck-Schaumann disease**

Liebow-Carrington syndrome see **Wegener's granulomatosis**

Loeys-Dietz syndrome is an autosomal-dominant genetic syndrome, which has many features similar to **Marfan syndrome**, and the vascular type of Ehlers-Danlos syndrome. Loeys-Dietz syndrome is a recently described connective tissue disorder that predisposes to the development of aortic aneurysms and other connective tissue defects. It primarily is characterized by aortic aneurysms, which are prone to rupture at a smaller size than other aneurysms, putting children with Loeys-Dietz at

greater risk for dying. **Loeys-Dietz syndrome** is known to be a result of mutations in the TGF-β-receptor I (TGFBR1) or II (TGFBR2) genes.

The disorder initially was observed and described by Belgian physician ***Bart L. Loeys*** from the Centre for Medical Genetics in Ghent, Belgium, and US pediatric geneticist ***Hal Dietz*** (***Harry C. Dietz***) at the Johns Hopkins University School of Medicine in 2005.

Bart L. Loeys (May 15, 1970–) was born in Ghent, Belgium and received his MD degree at Ghent University in Belgium. He subsequently trained as a pediatrician in Ghent and did his residency in clinical genetics at Johns Hopkins in Baltimore. As of 2022, he works at the Center for Medical Genetics of the University of Antwerp/Antwerp University Hospital in Belgium. His main interests are cardiogenetics and connective tissue disorders, especially those with aortic aneurysm as a component. His lab focuses on identifying the genetic basis of syndromic and non-syndromic forms of thoracic aortic aneurysm.

Hal C. Dietz (Apr 28, 1958–) is a Victor A McKusick Professor of Medicine and Genetics, Institute of Genetic Medicine, Howard Hughes Medical Institute, and a Director of the William S. Smilow Center for Marfan Syndrome Research, Johns Hopkins University School of Medicine, Baltimore, MD. He was born in New York and received his undergraduate degree at Duke University and his MD degree at SUNY Upstate Medical University. His subsequent training in pediatrics, pediatric cardiology and genetics occurred at Johns Hopkins. His lab uses genetics and mouse models to identify molecular determinants of vessel-wall homeostasis and to better understand the etiology of the heritable disorders of connective tissue.

(**Publ**.: Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005; 37(3):275–281.)

Lou Gehrig's disease see in G section

Louis-Bar syndrome (**Boder-Sedgwick syndrome**, ataxia telangiectasia) is a rare, neurodegenerative, autosomal recessive, inherited disease with a variety of immunological abnormalities. The disease is caused by a defect in the *ATM* gene. Ataxia-telangiectasia mutated (ATM) is a serine/threonine protein kinase recruited and activated by DNA double-strand breaks. It phosphorylates several key proteins that initiate activation of the DNA damage checkpoint, leading to cell cycle arrest, DNA repair, or apoptosis. The disease is characterized by extreme sensitivity to ionizing radiation or radiomimetic drugs because of a defect in DNA repair. In addition to numerous neurological and blood vessel problems, there are many immunological and immune-mediated abnormalities. The most common defects are decreased levels of one or several classes of immunoglobulins (i.e., IgG, IgA, IgM, or IgG

subclasses), absence of antibodies in response to vaccines or infections, and low numbers of lymphocytes—in particular, T cells in the blood. Patients experience frequent infections of the upper- (e.g., colds and sinus and ear), and lower- (e.g., bronchitis and pneumonia) respiratory tract. Patients with ataxia telangiectasia have a highly increased incidence (approximately 25% lifetime risk) of cancers, particularly lymphomas and leukemia; broken pieces of DNA in chromosomes involved in the V(D)J recombination in lymphocytes tend to recombine with other genes (translocation), making the cells prone to the development of cancer. Chronic lung disease can occur because of recurrent lung infections because of immunodeficiency. Individuals with this problem are at risk of developing bronchiectasis, a condition in which bronchial tubes are permanently damaged, resulting in recurrent lower-airway infections.

The first observation of ataxia-telangiectasia patients was recorded by the internist Ladislav Syllaba and the neurologist Kamil Henner, who published their paper in French in 1926. They described 3 young Czech siblings with advanced choreoathetosis and ocular telangiectasia (Syllaba and Henner, 1926). ***Denise Louis-Bar*** recorded a 9-year-old girl with progressive cerebellar ataxia, bilateral oculocutaneous telangiectasia, and mental retardation in 1941. ***Elena Boder*** and ***Robert P. Sedgwick*** described 8 cases from 5 unrelated families, including 6 familial cases in 1958. They suspected a genetic basis of the disease and highlighted the patients' susceptibility to sinopulmonary infections. They also announced the term ataxia telangiectasia. Yet, this clinical entity has received other designations that include **Louis-Bar syndrome**, suggested by Centerwall and Miller (Centerwall and Miller, 1958); and **Boder-Sedgwick syndrome**, suggested by Sagarra (1959), Jablonsky (1969), and François (1972). Some authors proposed a new definition for this entity: "ataxia with immune deficiency" or "ATM syndrome."

Denise Louis-Bar (Apr 3, 1914–Nov 2, 1999) was a Belgian neuropathologist. She was born as ***Denise Bar*** in Liège, Belgium, but spent the first decade of her life with her parents in Spain. After returning and schooling, she obtained her medical degree from the Free University of Brussels in 1939. She married F. Louis, a civil engineer, and started to use the hyphenated last name of Louis-Bar. In 1940, she joined the Bunge Institute of Neurology in Antwerp, Belgium. In 1943, she started to work as instructor in pharmacology at the University of Liège, and in 1945, she received a position of neuropsychiatrist at the Department of Internal Medicine. In 1957, Louis-Bar moved to Brussels with her husband, and she devoted her career to people with mental problems.

Elena Boder (Sept 22, 1908–Sept 15, 1995) was a Russian-American pediatrician and neurologist. She was born in Lida, Belarus, to the Jewish family of David Pablo Boder (born Aaron Mandel Mikhelson in Latvia) and Pesia (Paula) Evensky. Her father had to leave Russia at the height of the Bolshevik Revolution and fled with her, first to Siberia, then to Japan; in 1919, Elena and her father entered Salina Cruz, Mexico. Elena attended school in Mexico City, and while in Mexico, her father married a Polish immigrant, Dora Neveloff, and the 3 of them made their way to the United States finally in 1922. Elena teceived her BS and MD (in 1932) from

the University of Chicago and Rush Medical College. She interned at the University of Chicago Clinics and had residency training at Children's Memorial Hospital in Chicago. As the Pediatrician-in-Charge in the Schools of Physically Handicapped Children in the Los Angeles City Schools, she began to observe, in the late 1940s, children with the syndrome later designated Ataxia Telangiectasia, and she dedicated 25 years to the care and ultimate cure of children. She was a Clinical Professor of Pediatrics, University of California School of Medicine at Los Angeles; a Neuropediatrician-in-Charge, Pediatric Neurology Clinic, Cedars-Sinai Medical Center; and the member of consulting staff, Division of Neurology, Children's Hospital, Los Angeles. Besides her contributions to ataxia telangiectasia, she is remembered for her work on dyslexia.

She is the author of about 60 scientific papers and 16 chapters for pediatrics and pediatric neurology, and multidisciplinary medical textbooks. Respected by her colleagues and loved by her patients, few people knew about her marital problems, the life-long combative relationship with her stepmother, and the posttraumatic stress she had to deal with after the death of her mother and 2 half-sisters in the Holocaust. Elena's mother was executed in the Lida Ghetto in 1941, and her sisters, Ida and Toshia Gorenstein, died of typhoid fever a few days before liberation while on the way to the hospital. Elena's father, Dr. David Boder, was one of the first people to go into the Displaced Persons camps after World War II, collecting more than 120 hours of interviews with survivors. Following these recordings and his research and analysis, he wrote the book, *I Did Not Interview the Dead*, published in 1949 by the University of Illinois Press.

Elena Boder was diagnosed with ovarian cancer but continued to work and publish during her chemotherapy treatments. Five years later, she was diagnosed with breast cancer and died in her home in Beverly Hills.

Robert P. Sedgwick was a US pediatric neurologist. He graduated in 1943 from the University of Southern California, Keck School of Medicine. He was associated with the Department of Neurology, University of Southern California School of Medicine, Los Angeles Children's Hospital, and the Cedars of Lebanon Hospital.

(**Publ**.: Louis-Bar D. Sur un syndrome progressif cormprenant des télangiectasies capillaires cutanées et conjonctivales symétriques, à disposition naevoïde et des troubles cérébelleux. *Confinia Neurol* 1941; 4:32–42.

Boder E. Ataxia-telangiectasia: an overview. *Kroc Found Ser* 1985; 19:1–63.

Boder E, Sedgwick RP. Ataxia-telangiectasia; a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. *Pediatrics* 1958; 21(4):526–554.)

Lutzner cells see **Sézary cells**

Letter M

Macaulay's disease (lymphomatoid papulosis, **Macaulay's lymphomatoid papulosis**) is a nonaggressive chronic lymphoproliferative disease of the skin, characterized by recurrent crops of papules. The lesions are usually small at the beginning and then become larger; they can bleed or ulcerate prior to becoming scaly and crusty. These recurrent papulonodular lesions are described cytomorphologically by highly atypical large lymphoid cells, which nearly always express CD30. Papules appear anywhere but commonly develop on the trunk, arms, and legs, although can be seen on the hands, face, and genitalia. The papules heal spontaneously over 1–2 months.

Pathogenesis is unknown but some evidence points to hereditary of the disease. Although lymphomatoid papulosis usually is not classified as a cancer, it has characteristics of lymphoma (CD30 (Ki-1) positive lymphoproliferative disorder), and people with lymphomatoid papulosis have a life-long increased risk of developing lymphoma. Often, lymphomatoid papulosis is considered a form of indolent cutaneous T-cell lymphoma because CD30 signaling has been reported to affect growth and survival of lymphoid cells. Other hypotheses implicate reactive phenomena inducing CD30+ overexpression.

The term lymphomatoid papulosis originally was used by ***Macaulay*** in 1968 to describe "a self-healing rhythmical paradoxical eruption, histologically malignant but clinically benign." In the spring of 1964, he saw a 38-year-old woman (Mrs. F.) who presented with a strange history of recurrent papules and nodules, which could spontaneously regress, but then appeared again. Although other dermatologists also observed patients with similar conditions, Macaulay recognized the unique character of the disease.

Warren L. Macaulay (Sept 29, 1915–Jan 11, 2006) was a US dermatologist. He was born in West New York, New Jersey, graduated from the University of Minnesota, and obtained his MD degree in 1943 from the medical school at the same university. He received his internship training at San Bernardino County

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Hospital in Long Beach, CA, and then joined the US Navy to serve as a medical officer aboard the *USS Radford*. He received the Purple Heart and 11 Battle Stars.

After the war, Macaulay was trained in dermatology at the University of Minnesota. In 1949, he moved to Fargo, ND, with his family and practiced at the Fargo Clinic (now MeritCare Medical Center) for 39 years, retiring in 1985 at the age of 70. He was a Clinical Professor and Chief of the Division of Dermatology, Department of Internal Medicine, University of North Dakota School of Medicine and head of the Department of Dermatology at the Fargo Clinic for 31 years.

(**Publ**.: Macaulay WL. Lymphomatoid papulosis: A continuing, self-healing eruption, clinically benign--histologically malignant. *Arch Dermatol* 1968; 97:23–30.

Macaulay WL. Lymphomatoid papulosis. *Int J Dermatol* 1978; 17:204–212.

Macaulay WL. Lymphomatoid papulosis: thirteen years later. *Am J Dermatopathol* 1981; 3:165–167.)

Mackle-Wells syndrome (urticaria-deafness-amyloidosis syndrome) is a rare autosomal-dominant disease that causes sensorineural deafness, recurrent hives, and amyloidosis. It is a type of periodic fever syndrome. The syndrome is caused by a mutation in the *CIAS1* gene or *NLRP3* gene (nucleotide-binding domain, leucine-rich family [NLR] pyrin domain containing 3) located on the long arm of chromosome 1 and encoding for cryopyrin (NALP3).

NALP3 is expressed predominantly in macrophages and belongs to the NOD-like receptor (NLR) subfamily of functions as a pathogen-recognition receptor (PRR) that recognizes pathogen-associated molecular patterns (PAMPs). NALP3 together with the adaptor ASC protein PYCARD forms a caspase-1 activating complex known as the NALP3 inflammasome. Thus, as a component of the inflammasome, cryopyrin detects products of damaged cells (e.g., extracellular ATP and crystalline uric acid). Caspase-1 within the activated NALP3 inflammasome complex activates the inflammatory cytokine, IL-1β. Mutations in the NLRP3 gene are associated with inflammation and several specific autoimmune diseases.

Muckle-Wells syndrome is closely related to 2 other syndromes: familial cold urticaria and neonatal onset multisystem inflammatory disease. In fact, all 3 are related to mutations in the same gene and subsumed under the term cryopyrin-associated periodic syndromes (CAPS)—a spectrum of dominantly inherited autoinflammatory diseases. Familial cold autoinflammatory syndrome is more common in the US, and Muckle-Wells syndrome is more common in Europe.

The syndrome was first described in 1962 by ***Thomas Muckle*** and ***Michael Wells***. This disease was the basis of an episode on the television show *House* in which the patient was suffering from a difficult-to-diagnose mystery illness that turned out to be Muckle-Wells syndrome.

Thomas James Muckle (1938–Nov 2014) was a physician at Newcastle Medical School in his native England before moving to Canada. Muckle moved to Hamilton with his young family, including 3 girls (Simone, Kristina, and Fiona) in 1970 to

work at McMaster University and went on to become head of laboratory medicine at Chedoke Hospital.

Muckle purchased 32 acres of land in Beamsville in 1980 with dreams of making great wine. He launched what grew to become Thirty Bench Winery 2–3 decades ago with McMaster Professor Yorgos Papageorgiou and local wine shop owner Frank Zeritsch. The trio planted some vines and started experimenting with small batches of wines, preferring quality over quantity, a tradition that continues at the winery today.

Muckle, a former pathologist, physician, professor, musician, and wine lover, was also a man of many interests and many names and nicknames. He was Tom to most of his colleagues and friends in Canada, T.J. to some friends, Jim to his sister Eileen in England, and finally "fuzzy" to his 4 grandchildren because of his beard. One of his prized students was James Orbinski, who went on to become a founding member and president of Doctors Without Borders and accepted the 1999 Nobel Peace Prize on behalf of that organization. Orbinski mentioned Muckle in his book, *An Imperfect Offering*. Muckle died after complications from late-stage Parkinson's.

Michael Vernon Wells (April 22, 1929–May 24, 2007) was an English physician. He was born in Hassocks, Sussex, to Arthur Gilbert Wells, who worked in memorial masonry, and Dorothy Wells née Vernon, the daughter of a farmer. After primary education at Lewes County Grammar School for Boys, he went into the Royal Navy for his National Service. He started his medical education in 1949 at Charing Cross Hospital Medical School and graduated in 1955 with the Gordon Holmes prize in medicine. He married Doreen McCurdy Sponder the same year, and they had 3 daughters, Claire, Lizzie, and Rosie. Wells worked as a house physician at Putney Hospital and then a casualty medical officer at Charing Cross Hospital. In 1956, he was a senior house physician at Oldham Royal Infirmary, and later at St Margaret's Hospital in Epping. He was also a medical registrar at Derbyshire Royal Infirmary (1958–1960) and a research registrar at West London Hospital.

During the 1960s, Wells was a senior registrar at Nottingham General Hospital and at Sheffield Royal Infirmary and a consultant physician in Nottingham. He also was an internist in British Columbia, Canada, and a consultant physician in Saudi Arabia. In 1962, with Thomas James Muckle, he described Muckle-Wells syndrome. Wells had a few hobbies and loved walking, fishing, horseback riding, and gardening.

(**Publ**.: Muckle TJ, Wells M. Urticaria, deafness, and amyloidosis: a new heredofamilial syndrome. *Q J Med* 1962; 31:235–248.)

Mancini immunodiffusion (**Mancini method**, **Mancini technique**) is an immunodiffusion technique used in immunology to determine the quantity or concentration of an antigen in a sample. Immunodiffusion is a serological procedure in which antigen and antibody solutions are permitted to diffuse toward each other through a gel matrix; interaction is manifested by a precipitin line for each system. The **Mancini method** also is called a single radial-diffusion assay. ***Mancini*** determined that the precipitin ring diameter, in a radial immunodiffusion method, stopped

increasing at the point where diffusible antigen had been reduced and antigen–antibody complexing had attained equivalence. Thus, at this equivalence point, there is a linear relationship between the concentration of an antigen and the corresponding ring diameter. The antigen is quantitated by measuring the diameter of the precipitin circle, formed by insoluble precipitin complexes, and comparing it with the diameters of precipitin circles formed by known quantities or concentrations of the antigen. Single radial immunodiffusion according to Mancini was used for quantification of the immunoglobulins IgG, IgA, and IgM in human serum.

Giuliana Mancini, an Italian physician and biochemist, is known for introduction a popular immunological method. She obtained her degree in medicine and surgery and a postgraduate diploma in hematology from the University of Rome. She joined the Research Department of Internal Pathology, Cliniques Universitaires St. Pierre, Louvain, Belgium, in 1962. She then worked at the Department of Genetics, Biology and Chemical Medicine, University of Torino, Italy.

(**Publ**.: Mancini G, Vaerman JP, Carbonara AO, Heremans JF. A single radial diffusion method for the immunological quantitation of proteins. In: Peeters, H. (ed.). Protides of the Biological Fluids: Proceedings of the 11th Colloquium. Amsterdam: Elsevier. 1964; pp. 370–373.

Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* (Oxford: Pergamon Press) 1965; 2(3):235–254.)

Mantoux test (**Mendel-Mantoux test**, **Mantoux screening test**, tuberculin sensitivity test, **Pirquet test**, or PPD test for "purified protein derivative") is a diagnostic screening test for tuberculosis (TB). It is one of the main tuberculin skin tests used around the world. Mantoux test replaced the **Heaf test** that was used in the UK until 2005. Tuberculin is a glycerol extract of the tubercle bacillus. In 1932, US biochemist Florence Seibert purified tuberculin by ammonium sulfate precipitation, obtaining a purified protein derivative—PPD. PPD, thus, is a precipitate of nonspecies-specific molecules obtained from filtrates of sterilized, concentrated cultures.

The skin reaction to tuberculin was first reported by ***Robert Koch*** in 1890 after he isolated *M. tuberculosis* in 1882. At a medical congress in Berlin, he presented results of development of an ingredient that can prevent the growth of the bacterium. He called this "Tuberculin" and kept its formulation secret. Koch also observed that tuberculin administered into the skin induced a reaction spot within 48 hours in people who had had tuberculosis before. Actually, it was a glycerin-broth culture he used to grow *M. tuberculosis*, which he then evaporated to a tenth of its volume at 100 °C prior to filtering.

Immediately, journalists around the world broadcast that Koch had a cure for tuberculosis. Tuberculin, however, really did not treat tuberculosis, but could make patients with the advanced disease sick. When ***Rudolf Virchow*** reported negative results about tuberculin in January 1891, Koch felt compelled to disclose its simple preparation. In addition to terrible disappointment over tuberculin, the public learned in the same year that the 50-year-old Koch was divorcing to marry his

teenage mistress, an actress named Hedwig Freiberg. Speculation swirled that tuberculin had been a trick to finance the doctor's adventures. In any event, Koch won the 1905 Nobel Prize for Physiology or Medicine.

In 1906, Viennese pediatrician ***Clemens von Pirquet*** observed that people who received injections of horse serum usually had faster and more severe reactions to second injections. He coined the term "allergy." In 1907, von Pirquet discovered that a subcutaneous injection of a very small amount of tuberculin could be used as a test for tuberculosis.

The TB test was first developed and described by the German physician ***Felix Mendel*** in 1908 when began inoculating tuberculin intradermally, which produced a more reliable reaction and became the preferred method. The test is named after ***Charles Mantoux***, a French physician who built on the work of Koch and von Pirquet to create his test. Mantoux reported on the test of the intradermal injection of tuberculin in 1910. Although Felix Mendel published the same technique in 1909, the clinical community most often used the name of Mantoux for the intradermal technique of tuberculin administration.

In 1939, ***M. A. Linnikova*** in the USSR created a modified version of PPD. In 1954, the Soviet Union started mass production of PPD-L, named after Linnikova (Ленникова).

Denis Charles (***Charles***) ***Mantoux*** (May 14, 1877–May 3, 1947) was born in Paris and attended the University of Paris and graduated in medicine in 1904. Because he contracted tuberculosis while a student, Mantoux moved to Cannes and began to work in a tuberculosis sanatorium. Because it had quite long vacations for employees, he could continue to work in Paris. In 1908, Mantoux presented his explanation of intradermal reactions to the French Academy of Sciences and published his paper on the subject in 1910. He reported that the intradermal test was more sensitive than the subcutaneous test of Pirquet. Therefore, the Mantoux test soon totally replaced the Pirquet test in all countries, except Norway. Because the **Mantoux test** was developed initially by Felix Mendel, it is often mentioned as the Mendel-Mantoux test.

Mantoux worked on various aspects of tuberculosis. For instance, he established a test for screening cattle, pigs, and horses for it; this had a big influence on public health. Mantoux also carried out radiological studies of tuberculosis and published on pleural effusion and the fever of tuberculosis. He was one of the pioneering doctors to use artificial pneumothorax and learn its effects on the lung. Interestingly, all of Mantoux's clinical research work was done outside of major universities and institutions. He died in Le Cannet, Alpes-Marites, France.

Felix Frederick Mendel (Mar 2, 1862–Dec 19, 1925) was born to Benjamin Mendel and Johanna Mendel in Essen, North Rhine-Westphalia, Germany. He received his education in Bonn, Freiburg, Berlin, and Marburg. After obtaining his doctorate degree in Leipzig in 1884, he started his general practice in Essen. He is remembered for the very first description of the tuberculin skin reaction, which was mistakenly called Mantoux reaction in spite of its initial development by Felix Mendel. Mendel died in 1925 during his travels.

Clemens Peter Freiherr von Pirquet (May 12, 1874–Feb 28, 1929) was an Austrian pediatrician and clinical researcher known for his studies in the fields of bacteriology and immunology. (Note: *Freiherr* is a title, translated as *Baron*, not a first or middle name.) He was born in Vienna and studied theology at the University of Innsbruck and philosophy at the University of Leuven. He graduated from the University of Graz with his medical degree in 1900. He then worked at the Children's Clinic in Vienna. In 1906, he observed that patients who were injected with horse serum, or smallpox vaccine, had faster and more intense reactions to a second injection. Together with ***Bela Schick***, he coined the word **allergy** (from the Greek *allos* meaning "other" and *ergon* meaning "reaction") to define this hypersensitivie reaction. These results led Pirquet to understand that tuberculin, which ***Robert Koch*** isolated from the bacteria that causes tuberculosis in 1890, may induce a similar kind of reaction. This understanding allowed him to propose an "allergy test for tuberculosis." In 1909, he declined a position at the Pasteur Institute in Paris and accepted a professor position at Johns Hopkins University. In 1910, he returned to Europe taking positions in Breslau (now Wrocław) and then Vienna. Although Pirquet was nominated 5 times for the Nobel Prize for the tuberculin test, he never won it. In 1929, von Pirquet and his wife committed suicide together using potassium cyanide.

(**Publ**.: von Pirquet C. Die Allergieprobe zur Diagnose der Tuberkulose im Kindesalter. *Wien Med Wochenschr* 1907; 57:1370–1374.

von Pirquet C. Tuberkulindiagnose durch cutane Impfung. *Berl Klin Wochenschr* 1907; 44:644–645.

Mendel F. Therapeutische monatshefte, Berlin 1903; 16:177.

Mendel F. Die von Pirquet'sche hautreaktion und die intravenöse tuberkulinbehandlung. *Med Klin*, München 1908; 4:402–404.

Mendel F. Über intrakutane tuberkulinanwendung zu diagnostischen zwecken (intrakutanreaktion). *Beitr Klin Tuberk* 1909; 13:139–144.

Mantoux C. L'intradermo-reaction de la tuberculine et son interpretation clinique. *La Presse Med* 1910; 2:10–15.)

Marburg disease (**Marburg multiple sclerosis**, **Marburg's variant of multiple sclerosis**) also known as acute, fulminant, or malignant multiple sclerosis, is characterized by extensive and fulminant acute demyelination, often resulting in death within a year after the onset of clinical signs. It is considered one of the multiple sclerosis borderline diseases, which is a collection of diseases classified by some as multiple sclerosis variants and by others as different diseases. Other diseases in this group are neuromyelitis optica, Balo concentric sclerosis (see **Balo disease**), and Schilder's disease. The crucial course is one form of malignant multiple sclerosis, with patients reaching a significant level of disability in less than 5 years from their first symptoms, often in a matter of months. It is usually lethal, but it has been found to be responsive to Alemtuzumab—a monoclonal antibody that binds to CD52, a protein present on the surface of mature lymphocytes in autologous stem cell transplantation.

Although etiology is unclear, an antibody-mediated process appears to be responsible for most cases of Marburg disease. It does not seem to follow infection or vaccination. It was first described in 1906 by ***Otto Marburg***.

Otto Marburg (May 25, 1874–Jun 13, 1948) was an Austrian neurologist. He was born to a Jewish family in Römerstadt in then Austrian Moravia, today Rýmarov in the Czech Republic. His father was a successful factory owner and benefactor, and his mother devoted her time to the children giving Otto and his 7 brothers and sisters an excellent education. (She died from dysentery in the Theresienstadt concentration camp in 1942, where she was taken at the age of 92 together with Sigmund Freud's sister Esther Adolphine and another 16,000 victims.) Marburg entered high school in Olmütz (now Olomouc in the Czech Republic), where his interest was the natural sciences. He studied medicine at the University of Vienna and graduated with his MD degree in 1899.

Marburg was appointed lecturer (Privatdozent) of neurology in 1905, Associate Professor (Extraordinarius) in 1912, and Professor (Ordinarius) and Director of the Neurological Institute in 1919 at the University of Vienna. He held this position for 19 years. The Institute was very well known and attracted students and fellows from many countries, including Denmark, Belgium, Russia, the US, Italy, and Greece. In 1911, Marburg was the first to describe the clinical course and pathogenesis of acute multiple sclerosis, focusing on the role of inflammatory reactions in the disease. His *Microscopic Topographic Atlas of the Central Nervous System of Man* (1904) served as a bible for several generations of neurologists.

Following the 1938 Anschluss (the annexation of Austria into Nazi Germany in March), Marburg was forced to immigrate to the US as a Jewish refugee. His US sponsor was Bernard Sachs, after whom Tay-Sachs disease is named. He joined Columbia University's College of Physicians and Surgeons in New York City as clinical professor of neurology. In November 1940, the Supreme Court Justice engaged the New York State Board of Regents and the Commissioner of Education to approve Marburg's Austrian medical license to practice medicine without taking an examination. The Board had already refused to do this 2 times.

In March 1941, the Trial Court and Appellate Division of the Third Department in Albany, calling those acts "arbitrary and unreasonable," ruled 4 to 1 in favor of Dr. Marburg, and ordered the Commissioner to apply discretionary power in approving the foreign license of an applicant who was in a position of "conceded eminence." But, in July 1941, the Court of Appeals maintained the state's 5 to 2 ruling in rejecting Marburg's application to be allowable to practice medicine in the US. Nevertheless, with the help of friends and colleagues, Marburg was eventually granted a *honoris causa* license.

Marburg's broad anatomical, physiological, histopathological, and clinical knowledge and his role in endorsing the fields of neuropathology and neurology in the US was clearly recognized and appreciated. He published more than 200 papers and 10 books and edited another 10 books on various parts of neuroanatomy, neuropathology, neurology, and neurosurgery.

On a personal level, Marburg is remembered as a very kind and highly educated person, a typical representative of old Austria. He and his wife Malvine were extremely interested in art and regularly hosted many artists and scientists at their home in Vienna. Students of Otto Marburg refer to their bright teacher as a paternal friend and an unlimited source of well-ordered bibliographic information. Marburg died at Mount Sinai Hospital, after 10 years of living in the US.

(**Publ**.: Marburg O. *Die Sogenannte Akute Multiple Sklerose* (Encephalomyelitis periaxialis scleroticans). Leipzig: F Deuticke; 1906.

Marburg O. Bemerkungen über die körnerschichte im bolfactorius des meerschweinchens. *Arb Neurol Inst Wiener Univ* 1902; 8:233–238.

Marburg O. Ein neues längsfasersystem der medulla oblongata. *Wien Klin Wochenschr* 1906; 19:1572.)

Marfan syndrome (**Marfan's syndrome**) is a genetic disorder of the connective tissue. More than 30 different signs and symptoms are variably associated with Marfan syndrome. It is carried by the gene *FBN1*, which encodes the connective protein fibrillin-1. Marfan syndrome is a dominant genetic trait, meaning that people who inherit only a single copy of the Marfan *FBN1* gene from either parent will develop Marfan syndrome and be able to transmit it to their children. In addition to be a connective protein that forms the structural support for tissues outside the cell, the normal fibrillin-1 protein binds to TGF-β, which plays an important role in **Marfan syndrome**. Fibrillin-1 directly binds a latent form of TGF-β, keeping it sequestered and unable to exert its biological activity. In this syndrome, reduced levels of fibrillin-1 allow TGF-β levels to rise because of inadequate sequestration. Elevated TGF-β causes inflammation and releases proteases that degrade the elastin fibers and other components of the extracellular matrix. The critical role of TGF-β signaling was confirmed with the description of the similar **Loeys-Dietz syndrome** involving the *TGFβR2* gene on chromosome 3 encoding a receptor for TGF-β. Therefore, Marfan syndrome has been confused frequently with Loeys-Dietz syndrome because of their substantial clinical overlap.

Marfan syndrome is named after ***Antoine Bernard-Jean Marfan***, a French pediatrician who first described the condition in 1896, when he presented the case of a 5-year-old girl, Gabrielle P., to the Société Médicale des Hôpitaux de Paris. Marfan worried about Gabrielle's excessively long limbs, hands and feet, and asthenic figure; her fingers and toes were remarkably long and slim, creating a spider-like impression. Marfan used the term "pattes d'araignée," spider's legs, and named the condition dolicostenomely (Greek: *stenos*, meaning narrow, slender; *melos*, meaning limb). Gabrielle's prominent skeletal system anomalies increased until her death in early adolescence.

Antoine Bernard-Jean Marfan (Jun 23, 1858–Feb 10, 1942) was a French pediatrician. He was born in Castelnaudary to Antoine Prosper Marfan and his wife Adelaide Thuries. His father was a provincial medical practitioner and discouraged his son from the medical profession. Still, Marfan entered the Toulouse Medical School, moved to Paris 2 years later in 1879, became an extern in 1880, and started

an internship in 1882. After taking time out to do his military service, he graduated with a silver medal in 1886 and received his doctorate in 1887. His doctoral thesis, "*Troubles and gastric lesions in pulmonary tuberculosis*," also supported his interest in pulmonary tuberculosis. This publication created the basis for the concept known as the **Marfan law**, which recognized the scarcity of pulmonary tuberculosis subsequent to the curing of local tuberculosis lesions as a result of the development of immunity.

Marfan was one of the very first clinicians who realized the significance of skin reactions, and after ***von Pirquet*** reported his technique for tuberculosis skin testing, he instantly used this test in his clinical research; it became classic. Antoine Marfan worked at the Department of Medicine, University of Paris, in the Hospital des Enfants Malades, and at the Hospital for Sick Children. In 1914, he was offered a position as First Professor of Infantile Hygiene at the newly organized pediatric clinic at the University of Paris. Morfan worked in the Hospital des Enfants Malades in the Rue des Sèvres until his retirement in 1928.

Marfan was especially interested in art and literature. He loved music concerts and visiting Italy where he particularly enjoyed Venetian paintings. After retirement, he prepared and published a biography of his friend, Emile Broca.

(**Publ**.: Marfan A. Un cas de déformation congénitale des quartre membres, plus prononcée aux extrémitiés, caractérisée par l'allongement des os avec uncertain degré d'amincissement [A case of congenital deformation of the four limbs, more pronounced at the extremities, characterized by elongation of the bones with some degree of thinning]. *Bull Mem Soc Med Hôp Paris* 1896; 13(3rd series):220–226.)

Marsh's disease see **Graves' disease**

MataHari T cells ("**Matahari**" **T cells**) or CTLL clones are CD8 T cells from MataHari TCR transgeneic mice. They express TCR specific for the immunodominant male antigen (H-Y)-derived peptide WMHHNMDLI (from the *Uty* gene), usually called H-Yp^b, multifaceted with the MHC class I molecule, H-2D^b. The exact name of exotic dancer and courtesan, ***Mata Hari***, was selected for these male antigen-specific T cells because it has become synonymous with spying, espionage, intrigue, and sensuality.

Mata Hari (Aug 7, 1876–Oct 15, 1917) was born ***Margaretha Geertruida Zelle*** in Leeuwarden, Netherlands. She was the second child of Adam Zelle and his wife Antje van der Meulen and was the only girl in a family of 4 boys. The legend says that at an early age, Mata Hari decided that sexuality was her ticket in life. She was married at 19, delivered 2 kids and divorced 9 years later. Then, she moved to Paris and became the mistress of a French diplomat who helped her hatch the idea of supporting herself as a dancer. She billed herself as a Hindu artist, draped in veils, which she artfully dropped from her body. Completing her dramatic transformation from military wife to the courtesan, she coined her stage name, "Mata Hari," which is the term for the sun; literally speaking, it means "eye of dawn."

In a few years, she supplemented her income by seducing government and military men; sex became strictly a financial practicality for her. In 1916, Mata Hari fell in love with a 21-year-old Russian captain, Vladimir de Masloff, but soon he was sent to the Front and injured. Determined to earn money to support him, Mata Hari accepted an assignment to spy for France. Not long after, however, Mata Hari was accused of being a German spy and soon executed for espionage by firing squad in Paris.

(**Publ**.: Valujskikh A, Lantz O, Celli S, Matzinger P, Heeger PS. Cross-primed CD8(+) T cells mediate graft rejection via a distinct effector pathway. *Nat Immunol* 2002; 3:844–851.)

Matuhasi-Ogata phenomenon is a nonspecific binding of antibody. When a specific antigen–antibody complex is formed, another antibody is present at the same time, or is introduced to the complex subsequently; it can attach to and be excluded from the complex, although the antigen to which it is directed is not present. For instance, several observers have reported that red cells coated with a specific blood-group antibody can take up a second blood-group antibody nonspecifically. Thus, nonspecific binding of IgG to red blood cells because of the presence of other antibodies binding the red blood cell surface is an effect known as the **Matuhasi-Ogata phenomenon**.

Matuhasi (1959) suggested that antibodies of one specificity may adhere to antigen–antibody complexes of a different specificity and further evidence was published by ***Ogata*** and ***Matuhasi*** (1962, 1964). Later, this effect, now known as the Matuhasi-Ogata phenomenon, had been reported with sera containing warm- and cold-acting autoantibodies and alloantibodies of many specificities; these included immune and naturally occurring anti-A or anti-B, with the precipitate formed between syphilitic antibody and VDRL antigen. The phenomenon has been seen with whole serum and with its IgM and IgG fractions and has been considered responsible for, among other things, loss of desired antibody during the absorption of serum to prepare blood-typing reagents.

Tyoku Matuhasi (Mar 3, 1922–) was born in Kawaguchi, Saitama, Japan. He received his MD degree from the University of Tokyo in 1946 and DMS degree in 1955. He was associated with the Department of Allergology, Institute of Medical Science, University of Tokyo.

Tomio Ogata (1901–) was born in Osaka, Japan, and graduated from Tokyo University in 1926, where he specialized in serology. He was a professor at Tokyo University.

(**Publ**.: Matuhasi T. Plasma protein and antibody fractions observed from the serological point of view. *Proc 15th Gen Assem Jpn Med Congr*, Tokyo, 1959; 4:80.

Ogata T, Matuhasi T. Problems of specific and cross reactivity of blood group antibodies. *Proc 8th Congr Int Soc Blood Transfus*, Tokyo, 1960; p. 208.

Ogata T, Matuhasi T. Further observations on the problem of specific and cross reactivity of blood group antibodies. *Proc 9th Congr Int Soc Blood Transfus*, Mexico, 1964; p. 528.)

May-Hegglin anomaly, or "**Dohle leukocyte inclusions** with giant platelets and macrothrombocytopenia with unique leukocyte inclusions," is a rare genetic disease of the blood thrombocytes in which their size increases abnormally. The pathogenesis of the disorder was discovered to be mutations in the gene-encoding nonmuscle myosin heavy chain IIA (*MYH9*). Abnormal cytoplasmic inclusion bodies are aggregates of the altered protein and have been detected only in granulocytes. It still is unclear why inclusion bodies are not seen in platelets, monocytes, and lymphocytes, as well as how giant thrombocytes are formed. The inclusions are caused by accumulation of free ribosomes. Remarkably, the *MYH9* gene also is responsible for a few related syndromes associated with macrothrombocytopenia and leukocytes inclusion—for instance, Sebastian, Fechtner, and Epstein syndromes. The May-Hegglin anomaly is named after German physician ***Richard May***, who first described it in 1909, and Swiss physician ***Robert Hegglin***, who subsequently characterized it in 1945.

May published a paper entitled "Leukocyteneinschlüsse" (leukocyte inclusion) in which he described a 24-year-old female with bilateral edema of her legs; mild anemia; and no fever, splenomegaly, or lymphadenopathy. May detected many leukocytes in the blood smear—neutrophils, eosinophils, and basophils with 2–4 pale-blue inclusion bodies—visualized with various staining methods. Both an increased number of platelets and of giant platelets were detected. No family studies were performed because the patient left the town and was not available. Thus, this was the first description of this disorder done by May, who correctly identified both characteristic leukocyte inclusions and giant platelets.

In 1945, Robert Hegglin who worked at the University Hospital of Zurich depicted the **Döhle-like**, or **Amato bodies**, and giant thrombocytes in a father and his 2 sons. Platelets were larger than red cells and neutrophils had 1–2 cytoplasmic basophilic granules that were seen similar to the **May-Grunwald stain**. Bone marrow megakaryocytes had not increased but were characterized by immature cytoplasm. All affected patients displayed thrombocytopenia and bleeding predispositions. In his paper, Hegglin stated 3 new points about the disorder that were missing in May's paper. First, he highlighted the abnormalities in 2 lineages of blood cells: leukocytes and platelets. Second, he revealed thrombocytopenia. Third, he acknowledged the hereditary nature of the disorder, and hypothesized that the disorder may be transferred dominantly by a single gene mutation. He also believed that the disease is because of cytoplasmic maturation arrest in 2 lineages. Interestingly, Hegglin did not cite May's 1909 paper in his publication.

Richard May (Jan 7, 1863–1936) was a German physician. He was born in Munich into a respected family with an artistic background. His grandfather was a collector of pictures and sculptures and was a Counselor in the Kingdom of Bavaria. His father was a notable financial officer in the Privy Council. May graduated with his MD degree in 1886 and joined the University Hospital of Munich in 1893, where he was a professor of internal medicine until his retirement. He made many notable contributions to hematology, including inventions for new staining methods (**May-Grunwald stain** with ***Ludwig Grünwald***, an otolaryngologist who worked in May's

laboratory) and May's pipette—a micropipette used for diluting blood in counting blood cells. He served as director of the University Hospital and being an accomplished physician was appointed as a medical adviser to the royal family in 1926. He died in 1936 as a result of angina.

Robert Marquard Hegglin (May 5, 1907–Nov 22, 1969) was a Swiss physician. His father was a physician, and Hegglin studied medicine at the universities in Geneva, Munich, Berlin, Paris, and Zurich and was qualified in medicine in 1932. In his early career, he worked as an assistant to a famous hematologist, Otto Naegeli, the brother of ***Oskar Naegeli***, at the University Hospital of Zurich. Hegglin was an all-around player in medicine, making contributions to everything from cardiology and hematology to pulmonary disease. During the World War II, Hegglin was a representative of the Swiss Red Cross in Riga, Daugavpils, and Pskov; he reported in his diary about the mass killing of Jews, stating that this is a question "to be touched and discussed."

From 1947 on, Hegglin worked in Zurich as a specialist in internal medicine and cardiology. His name also is associated with Hegglin's syndrome, a type of cardiac failure. In 1952, he published his famous *Differential Diagnosis of Diseases*, a textbook that was widely used by medical professionals and has had many editions. He was a director of the University Hospital of Zurich and served at this position until his death.

(**Publ**.: May R. Leukocyteneinschlüsse. *Dtsch Arch Klin Med* 1909; 96:1–6.

May R, Grunwald L. Über blutfärbungen. *Zbl Inn Med* 1902; 23:265–270.

May R. Uber eine pipette zur blutkörperchenzählung mit automatischer einstellung. *Münch Med Wochenschr* 1903; 6:253–255.

Hegglin R. Gleichzeitige konstitutionelle veränderungen an neutrophilen und thrombocyten. *Helv Med Acta* 1945; 12:439–440.)

May-Grünwald/Giemsa stain is a staining for the peripheral blood film/smear and bone marrow. This stain has been used to color neutrophil granules and granulocyte inclusion bodies. May-Grünwald-Giemsa may be useful in the diagnosis of Malassezia folliculitis, a fungal mediated disorder. **May-Grünwald stain** is a German equivalent of the Jenner stain, used for blood staining and in cytology; often used in combination with **Giemsa stain**; and valuable in demonstrating parasitic flagellates.

Ludwig Grünwald (Feb 10, 1863–Aug 11, 1927) was a German otolaryngologist. He was born in Vienna to a Jewish family of Samuel Grünwald, a Jew who came from Arad in Hungary, and Bertha Biel. Ludwig grew up in Vienna but studied medicine in Munich. After getting his Doctor of Medicine degree, he opened a private practice in internal medicine specializing on otolaryngology. Grünwald also focused his clinical research on hematology. He worked in ***Richard May***'s laboratory in Munich when they prepared the initial famous staining procedure, now known as May-Grünwald stain. Furthermore, he was perhaps the first clinician who characterized the Haller cells in the nasal mucosa, originally found by Albrecht von

Haller in 1765. One of Grünwald's most famous patients was the then Nuncio of Bavaria, Monseigneur Eugenio Pacelli, who became Pope Pius XII. Ludwig Grünwald married Baroness Wilhelmine, Johanna Barbara von Rad from Augsburg. They had 3 children: 2 sons and a daughter.

Richard May see **May-Hegglin anomaly**

Gustav Giemsa (***Berthold Gustav Carl Giemsa***) (Nov 20, 1867–Jun 10, 1948) was a German pharmacist, chemist, and bacteriologist who is remembered for creating a dye solution commonly known as "Giemsa stain." He was also an inventor of apparatuses to disinfect whole ships. He was born in Kędzierzyn-Koźle, Poland. Giemsa learned mineralogy and pharmacy at the University of Leipzig and bacteriology and chemistry at the University of Berlin. He served as a pharmacist in Dares-Salaam, German East Africa in 1895–1898. He worked at the Institut für Tropenmedizin in Hamburg, where in 1900 he became the head of the Department of Chemistry.

When Giemsa was asked to improve the **Romanowsky stain**, he investigated the nature of the new dye and succeeded in identifying it as azure B (i.e., trimethylthionine). In 1904, Giemsa published about the development of a special staining procedure for visualizing flagellates, blood cells, and bacteria. He also improved the well-known Romanowsky stain (Eosin Y and methylene Blue) by stabilizing this dye solution by adding glycerol. This improvement allowed for reproducible staining of cells for microscopic evaluation. In his publication, he noted that the solution was available commercially under the label "Giemsa's solution for Romanowsky's stain." This method is still used in laboratories.

Giemsa also is known for his work in tropical hygiene and pharmacology—that is, new agents and derivate of quinine, bismuth, and arsenic for malaria treatment. In 1933, he joined the National Socialist German Workers' Party (NSDAP), commonly referred to in English as the Nazi Party. On November 11, 1933, he participated in a special ceremony, "Mit Adolf Hitler für des deutschen Volkes Ehre, Freiheit und Recht!" where, together with other German university professors and teachers, Giemsa signed a thankful letter to Adolf Hitler (see Klee, 2005). Nothing is known as to whether he participated in any other Nazi-regime movements or work.

(**Publ**.: (For a brief history of the evolution of the modern blood stain, see Woronzoff-Dashkoff, 1993.)

Giemsa G. Färbemethoden für malariaparasiten. *Zentralbl Bakteriol* 1902; 31:429–430.

Giemsa G. Eine vereinfachung und vervollkommnung meiner methylenblau-Eosin-färbemethode zur erzielung der Romanowsky-mocht'schen chromatinfärbung. *Centralbl Bakteriol I Abteilung* 1904; 32:307–313.

Giemsa G. Bemerkungen zur färbung der spirochate pallida (schaudinn). *Dtsch Med Wochenschr* 1905; 31:1026–1027.)

McClure-Aldrich test (**Aldrich-McClure test**) is an intradermal salt solution test. ***McClure*** and ***Aldrich*** published results of their study of intradermal injections of saline into normal and edematous skin in 1923. They intradermally administered 0.2 ml of saline (in the classic version 0.8% NaCl solution) and determined by palpation the dynamic and time of disappearance of the skin elevation. They reported that the fading time of the wheal was shorter in edematous skin than in the normal, and that it reversely correlated with the degree of edema at the place of injection. Their further analysis revealed that the vanishing time was constantly rapid in cases of exfoliative dermatitis, dermatitis hypostatica, urticaria, and subacute disseminate lupus erythematosus. Analyzing patients with eczematous lesions, they determined that the disappearance time was quick if the test was made at a distance near to a clinical lesion (within 5 cm), although the area with saline injected looked normal. The bullous dermatoses also gave a fast disappearance time. This test is not used in dermatology in modern times.

William B. McClure was associated with the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital in Chicago.

Charles Anderson Aldrich (Mar 4, 1888–Oct 5, 1949) was a professor of pediatrics at the Mayo Clinic and father of ***Robert Anderson Aldrich***, known for the **Wiskott-Aldrich syndrome**. He was born at Plymouth, MA, and received his BS from Northwestern and MD degree from the Northwestern Medical School in 1915. He also was trained in the Evanston Hospital and Children's Hospital in New York. Aldrich opened his private practice in Winnetka, IL, in 1917 and retired in 1941. Nevertheless, he accepted the offer of a chief of staff of the Children's Memorial Hospital in Chicago, working there until 1944. After this he was a director of the Rochester Child Health Project of the Pediatric Department of the Mayo Clinic.

Aldrich was Chairman of the Section on Pediatrics of the American Medical Association in 1930 and participated in several medical societies. He served as the President of the American Pediatric Society and the President of the American Board of Pediatrics. He published numerous research papers and several famous books. In 1929, he made public his first book, *Cultivating the Child's Appetite*. In 1938, he wrote *Babies Are Human Beings*, which has survived many editions. In 1941, he published *Feeding Our Old-Fashioned Children*. For his studies on child behavior, he received the *"Medal"* of *Parent's Magazine*, and in 1948 the Lasker Award. In 1916, he married Mary McCague, who was associated with him in writing his last 2 books. He died at his home in Rochester, MN, after an extended illness.

(**Publ**.: McClure WB, Aldrich CA. Time required for disappearance of intradermally injected salt solution. Preliminary report of observations with special reference to cases of edema. *JAMA* 1923; 81:293–294.

Aldrich CA, McClure WB. The intradermal salt solution test. *JAMA* 1924; 82:1425–1428.)

McCrae-Auer rods see **Auer rods**

Melkersson-Rosenthal syndrome (**Melkersson-Rossolimo-Rosenthal syndrome**) is a rare granulomatous disorder of unknown etiology characterized by a triad of recurring facial paralysis, swelling of the face and lips, and the development of folds and furrows in the tongue. The cause of Melkersson-Rosenthal syndrome is unknown, but there may be a genetic predisposition. Infectious, benign lymphogranulomatosis, allergic and genetic causes, and abnormal reactivity of the cranial neurovascular system have all been proposed as important factors in the development of the disease. For instance, possible susceptibility to herpes simplex virus-1 (HSV-1) infections has been suggested when autosomal recessive single-gene mutations, leading to intracellular UNC-93B protein deficiency, were established. Such a deficiency impairs cellular interferon antiviral responses to HSV-1 but does not compromise immunity to other pathogens. In addition, clinical and immunological examinations of adults and children with **Melkersson-Rossolimo-Rosenthal syndrome** have revealed immune deficiency—that is, a decrease in the number of T and B cells, low immunoglobulin concentrations, and the presence of the "neuroallergic" syndrome confirming the increased levels of cerebral antibodies. Cases of Melkersson-Rosenthal syndrome associated with allergic and coeliac diseases also have been reported.

Melkersson-Rosenthal syndrome is occasionally a manifestation of **Crohn disease** or orofacial granulomatosis. The latter term is used when there is no evidence of Crohn disease, but some patients progress to manifest it. Other etiologies include sarcoidosis and granulomatosis with polyangiitis. Cheilitis granulomatosa (or granulomatous cheilitis) is a chronic swelling of the lip because of granulomatous inflammation. Miescher cheilitis is the term used when granulomatous changes are confined to the lip. Miescher cheilitis is generally regarded as a monosymptomatic form of the **Melkersson-Rosenthal syndrome**, although the possibility remains that these may be 2 separate diseases. Thus, the terminology can be confusing.

Early descriptions of this condition were made by Russian neuropathologist ***Grigory Rossolimo*** in 1901 and Paul Hübschmann in 1894. The condition is named for ***Ernst Melkersson*** and ***Curt Rosenthal*** who described it in 1928 and 1931, respectively. The common triad of clinical findings became known as Melkersson-Rosenthal syndrome in 1949.

Ernst Gustaf Melkersson (Jan 22, 1898–Dec 2, 1932) was a Swedish physician. He was born in Örebro, studied at Uppsala University, and worked at the Sahlgrenska University Hospital in Gothenburg. He died as a result of angina complicated by sepsis at the age of 34.

Curt Rosenthal (Aug 7, 1892–Apr 4, 1937) was born in Breslau, Germany (now Wroclaw, Poland), to a Jewish family, studied at the University of Wroclaw, and received his doctorate degree in 1920. As a medical student, he volunteered for the army and served as a paramedic on the fronts of the World War I. He then worked at the psychiatry and meurology clinic at the University of Breslau, publishing many papers in the fields of genetics, dermatology, and neurology. In 1933, he was

recommended for the position of professor but was not granted approval by the Ministry of Culture because of his Jewish heritage. He was forced to resign from the position of senior consultant in Wroclaw and moved to Switzerland where he worked at the Department of Neurology, University of Bern. He died tragically in a car accident in Paris.

Grigory (***Grigorii***) ***Ivanovich Rossolimo*** (Dec 5, 1860–Sept 29, 1928) was a Russian neurologist. He was born in Odessa of Greek origin; his grandfather survived a shipwreck and was found near Odessa, Russia, where he settled down and stayed the rest of his life. In 1884, Grigory graduated from the University of Moscow, then worked at the hospital of neurological diseases, and finally obtained his medical doctorate in 1887. In 1890, he received a Chair of the Department of Neurology position. In 1911, together with many other academic faculties at the University of Moscow, he resigned in protest against unreceptive transformations developed by the Tsar's minister of education. Later, with his own funds he opened Russia's first clinic of pediatric nervous disease, but in 1917 he transferred his clinic to the University of Moscow and accepted the position of Chair of Neuropathology. He also founded a department for child psychoneurology and "defectology." From 1918 on, he worked in different People's Commissariats, the Revolutionary Military Council, and was the main Military Sanitary Physician of the Red Army.

Rossolimo is remembered for his work in experimental psychology. He wrote more than 100 papers on the subject and invented many medical instruments and apparatus, including the dynamometer, clonograph, and brain topographer. He was a member of the Roman Medical School Academy of Sciences, the Paris Society of Psychiatrists, the Philadelphia Society of Neuropathologists, and a member of the Presidium of the International Bureau of Psychotechnics. Rossolimo had a versatile and broadly formed personality. He spoke 8 languages, understood and appreciated music, drew well, knew literature, and loved the theater. He died in Moscow.

(**Publ**.: Rossolimo GJ. Recidivirende facialislähmung bei migräne. *Neurol Zentralbl* 1901; 20:744–749.

Melkersson E. Ett fall av recidiverande facialispares i samband med ett angioneurotiskt ödem. *Hygiea* (Stockholm) 1928; 90:737–741.

Rosenthal C. Klinisch-erbbiologischer beitrag zur konstitutionspathologie. Gemeinsames auftreten von Facialislähmung, angioneurotischem gesichtsödem und lingua plicata in arthritismus-familien. *Z Gesamte Neurol Psychiatr* 1931; 131:475–501.)

Melkersson-Rossolimo-Rosenthal syndrome see **Melkersson-Rosenthal syndrome**

Meltzer's triad consists of palpable purpura, arthralgia (i.e., joint pain), and weakness. This classic triad of symptoms suggests the diagnosis of cryoglobulinemia of polyclonal cryoglobulins. These usually are seen in people who have type II and type III cryoglobulinemia, associated with some viral infections and connective tissue diseases. **Meltzer's triad** is the most common presentation in those with

HCV-related mixed cryoglobulinemia. It has seen in up to 30% of patients with cryoglobulins. In 1956, Meltzer and Franklin described arthralgia, purpura, and weakness as the 3 core symptoms of essential cryoglobulinemia.

Martin Meltzer, H'Levi (May 19, 1930–Jun 19, 2019) was a US physician. He was born in Lakewood, NJ, graduated from Princeton University in 1951, and received his MD from Johns Hopkins University School of Medicine in 1955. He was a Lieutenant in the US Navy from 1957–1959. As a rheumatologist, he spent his career teaching and in clinical practice at the Departments of Pathology and Medicine and the Rheumatic Diseases Study Group, New York University School of Medicine. He died in New York City.

(**Publ**.: Meltzer M, Franklin EC. Cryoglobulinemia—A study of twenty-nine patients. I. IgG and IgM cryoglobulins and factors affecting cryoprecipitability. *Am J Med* 1966; 40(6):828–836.

Meltzer M, Franklin EC, Elias K, McCluskey RT, Cooper N. Cryoglobulinemia—a clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. *Am J Med* 1966; 40(6):837–856.

Meltzer M, Franklin EC. Cryoglobulins, rheumatoid factors and connective tissue disorders. *Arthritis Rheum* 1967; 10(5):489–492.)

Mentzer index was established for differential diagnosis of iron-deficiency anemia and beta-thalassemia—that is, anemia because of mutations in the *HBB* gene and low production of hemoglobin. The index is calculated based on the results of a complete blood count. If the proportion of the mean corpuscular volume (MCV, in femtoliters) divided by the red blood cell count (RBC, in millions/microliter) is < 13, β-thalassemia is likely. If the result is > 13, then iron-deficiency anemia is most likely. With an iron deficiency, the bone marrow cannot produce as many RBCs, and they are small (microcytic), so the RBC count will be low along with the MCV. As a result, Mentzer's index is not as low, > 13 comparatively, in thalassemia, which is a disorder of globin synthesis. RBC production is preserved, but the cells are smaller and more fragile. Therefore, the Mentzer's index is < 13. The **Mentzer index** was described in 1973 by ***William Mentzer***.

William C. Mentzer (1936 (?)–) is a US hematologist with the Division of Hematology/Oncology, Department of Pediatrics, University of California San Francisco. He received his medical degree from Stanford University School of Medicine and his residency training from the Children's Hospital in Boston and St. Mary Medical Center in Long Beach, CA.

(**Publ**.: Mentzer WC Jr. Differentiation of iron deficiency from thalassaemia trait. *Lancet* 1973; 1(7808):882.)

Metchnikoff's cellular (**phagocytic**) **theory of immunity**. This is basically the first recognition that the phagocyte is the initial line of defense against pathogens in most animals, including humans, and that phagocytic cells are leukocytes. This theory was introduced by ***Mechnikov*** (***Metchnikoff***) when he observed in the larvae

of starfishes, mobile cells that might, he thought, serve as part of the defense against these organisms. He called the cells **phagocytes** (from Greek words meaning "devouring cells") and named the process **phagocytosis**. To test this idea, Mechnikov introduced into a starfish small thorns from a tangerine tree and found that the thorns became surrounded by the moving cells. Knowing that leukocytes can escape from the blood vessels during inflammation in animals, Mechnikov speculated that leukocytes might take up and digest bacteria that gets into the body. He discussed his hypothesis with Carl Friedrich Wilhelm Claus, Professor of Zoology at the University of Vienna, who suggested to him the term "phagocytes" for cells that can surround and kill pathogens.

Thus, Mechnikov had built a concept of cellular phagocytosis as a part of the self-defense system in both vertebrates and invertebrates, and its association with inflammation. He did not discover the process of phagocytosis; it was Haeckel from the University of Jena in Germany who observed in 1862 how white blood cells can uptake dye particles. But Mechnikov was the first to postulate that the process of phagocytosis is a part of a natural immune system.

Mechnikov's theory of phagocytosis was in conflict with the humoral theory of immunity generally accepted at the time. The humoral theory argued that only blood and blood components are the main protectors against invading bacteria. Although the humoral theory held sway for the following decades, scientists began to reexamine the role cells play in fighting infections. It required 25 years of intense effort to achieve recognition of the phagocytosis theory—the first experimentally based theory in immunology. This struggle culminated in 1908 with the awarding of the **Nobel Prize** to Metchnikoff and Ehrlich for their theories of immunity, "cellular" and "humoral," respectively. "That was an official recognition of the existence and importance of immunology, but modern immunology began at the moment of Metchnikoff's discovery, which is why 1982 may be considered the 100th-year anniversary of immunology" (Heifets, 1982).

Élie Metchnikoff (***Ilya Ilyich Mechnikov***) (May 16, 1845–Jul 16, 1916) was a famous Russian scientist. Mechnikov adopted the French form of his name, Élie Metchnikoff, for the last 25 years of his life. Ilya Mechnikov was born in the village called Ivanovka (Panasovka) not far from city of Kharkov (now Kharkiv, Ukraine) in the Russian Empire. He was the youngest of 5 children of an officer of the Imperial Guard and Ukraine landowner Ilya Ivanovich Mechnikov and his wife Emilia Nevakhovich; she was the daughter of the famous Jewish writer, Leib ben Noach (Leo) Nevakhovich, who had converted to the Lutheran faith (Russian Orthodox according to other sources) in response to Russia's persecution of Jews. Mechnikov went to school at Kharkov and expressed passionate interest in natural history (e.g., botany and geology). He gave lectures on these subjects to his siblings and other children when he was 6 years old. Later, being convinced by his mother to study biology instead of medicine, he joined Kharkiv University to study natural sciences and finished the 4-year course in 2 years. In 1864, he moved to Germany to study marine fauna on Heligoland, a small North Sea island. He then worked at the University of Giessen, where he made his first discovery of intracellular

digestion in flatworms. Then, Mechnikov moved to Naples, Italy, where he experimented on marine invertebrate embryos with zoologist Aleksandr Kovalevsky. Together, they left Naples in the fall of 1865 because of a cholera outbreak and traveled to St. Petersburg to finish their doctoral studies in 1867.

Mechnikov became a Professor of Zoology in Odessa, still quite young. He was 23 when he married Ludmila Feodorovitch. Unfortunately, after her tragic early death from tuberculosis, Mechnikov tried to kill himself by morphine overdose. He later married Olga Belokopytova, a 16-year-old student living in the apartment above him who expressed a great interest in the natural sciences. In 1880, Olga contracted typhoid fever, and he attempted suicide again. Because he wanted to save his wife, however, he inoculated himself with relapsing fever—a bacterial infection transmitted by lice or ticks—to determine whether it could be transmissible by blood. Mechnikov survived but was seriously ill and recovered after a long time.

In 1882, Mechnikov resigned from Odessa University because of political chaos after the assassination of Tsar Alexander II and moved to Messina, Italy, where he organized his private laboratory. He described the phenomenon of phagocytosis while working in his laboratory. In 1886, he returned to Odessa as a director of an institute with the goal of developing Louis Pasteur's vaccine against rabies. Without medical license, however, he experienced a lot of administrative problems and stopped his work in 1888, moving to his own research. He came to Paris for Pasteur's advice and received a position at the Pasteur Institute. Metchnikoff stayed at the institute for the rest of his scientific career and attracted many distinguished scientists from Russia and other countries, including ***Alexandre Bezredko***, ***Waldemar Haffkine*** (***Vladimir Khavkin***), *and* ***Jules Bordet***. Emile Roux, who subsequently became director of the institute, was a close friend and collaborator. In 1908, Mechnikov was awarded, together with ***Paul Ehrlich***, the **Nobel Prize** for Physiology or Medicine.

"Metchnikoff could be considered an outsider throughout his life, due to his Jewish-Russian origins, his nonmedical training and also in his championing of phagocytosis rather than antisera as a primary agent of immunity" (Gordon, 2016). Mechnikov also developed a concept of healthy aging, stating that aging is triggered by toxic bacteria in the gut and that lactic acid might extend life; based on his theory, he consumed sour milk every day. He wrote *The Prolongation of Life: Optimistic Studies*, advocating the life-lengthening properties of lactic acid bacteria. He credited the longevity of Bulgarian peasants to their yogurt intake.

Mechnikov died in 1916 in Paris from heart failure at the age 71. According to his will, his body was to be used for medical research and afterward cremated and placed in the Pasteur Institute library.

(**Publ**.: Mecznikow E. Nachträgliche bemerkungen über den stiel der Vorticellinen. (Further observations on the stem of the Vorticellinen). *Arch Anat Physiol Wiss Med* [Arch Anat Physiol Sci Med]. 1863; (1864):291–302.

Metschnikoff É. *Studien über die Entwicklung der Echinodermen und Nemertinen* [Studies on the Development of Echinoderms and Nemertea]. St. Petersberg: The Imperial Academy of Sciences; 1869.

Metschnikoff É. Über die phagocytäre rolle der tuberkelriesenzellen [About the phagocytic role of the large tubercle cells]. *Virchows Arch* 1888; 113:63–94.

Metschnikoff É. Lecture on phagocytosis and immunity. *Br Med J* 1891; 1:213–217.)

Mi antigen belongs to a heterogenous group of extractable nuclear antigens (see **Sm antigen**). Two precipitating antibodies against the Mi nuclear antigen were identified first in 1976 by Reichlin and Mattioli using the complement-fixation inhibition test. The initials of the donor of the reference serum were ***MI***, and thus the antibodies and the corresponding antigens were termed Mi-1 and Mi-2 (Reichlin and Mattioli, 1976).

Mikulicz's disease (**Mikulicz syndrome**) is a benign lymphocytic infiltration and enlargement of the lacrimal and salivary glands. It often has been referred to as benign lymphoepithelial lesion but is now regarded as a manifestation of IgG4-related disease. Unusual lymphocytic infiltration can appear in lymphatic and rheumatic diseases, tuberculosis, and syphilis. Prior to the era of cytogenetic and immunohistochemical analysis, the disease was treated as a variation of **Sjögren syndrome**, indicating the common manifestation of the salivary and lacrimal gland infiltration by lymphocytes. Modern cellular and molecular diagnostic tests have proved that Mikulicz disease is a different entity from Sjögren syndrome. For instance, there are no anti-SS-A and anti-SS-B antibodies in **Mikulicz's disease**, and there are classic symptoms (e.g., dry eye and dry mouth). As in other IgG4-related diseases, serum IgG4 levels may be elevated, as well as the total IgG and IgE concentrations. In addition, the key morphological features can include dense lymphoplasmatic infiltrate with IgG4-positive plasma cells.

Jan Mikulicz-Radecki (German: ***Johann Freiherr von Mikulicz-Radecki***) (May 16, 1850–Jun 4, 1905) was a Polish-Austrian surgeon. He was born in Czerniowce in the Austrian Empire (present-day Chernivtsi in Ukraine). His father Andreas Mikulicz was of Polish *szlachta* (nobility) origin and his mother Emilia Freiin von Damnitz was of German descent. Jan, in addition to his native Polish, spoke German, Russian, and English. Later when asked about his nationality, he usually answered "surgeon." He graduated from the University of Vienna. Then he directed surgery at the Jagiellonian University in Kraków, the University of Königsberg in Germany (now Kaliningrad, Russia), and from 1890 onward at the University of Breslau (now Wrocław, Poland). He is known as an inventor of new operating techniques and tools, and as one of the pioneers of antiseptics and aseptic techniques. In 1881, he developed improved models of the esophagoscope and gastroscope. He was the first to suture a perforated gastric ulcer (1885), surgically restore part of the esophagus (1886), remove a malignant part of the colon (1903), and describe what is now known as **Mikulicz's disease**. As an ardent advocate of antiseptics, he did much to popularize Joseph Lister's antiseptic methods. He created **a surgical mask** and was the first to use **medical gloves** during surgery.

In Poland, he is regarded as one of the founders of the Kraków School of Surgery. Mikulicz-Radecki was a talented amateur pianist and a friend of Johannes Brahms. At the end of 1904, he developed a large inoperable stomach tumor with metastases to the liver cavity. Just a few weeks before his death, he reviewed the scientific works of his assistants. At the same time, Mikulicz also wrote to Professor Eiselberg in Vienna, "I am dying without regrets, and I am satisfied with my life. I worked to the best of my abilities, and I found happiness and recognition in the world." Jan Mikulicz-Radecki died at the age of 55 at his home in Breslau.

(**Publ**.: Mikulicz J. Über das rhinosclerom (Hebra). *Arch Klin Chir* 1877; 20 485–534.

Mikulicz J. Beitrag zur genese der dermoide am kopfe. *Wien Med Wochenschr* 1876; 26:953–956.

Mikulicz J. Kasuistiche beiträge zur exstirpation solider geschwülste des uterus und der ligamentalatadurch die laparotomie. *Wien Med Wochenschr* 1879; 29:513–515, 544–545, 599–602.

Mikulicz J. Die antiseptische wundbehandlung und ihre technik, *Mitt Ver Ärzte Nieder-Österreich* 1879; 5:58–62, 77–82, 92–95, 122–124, 146–153, 161–163, 183–187.)

von Mikulicz-Gougerot-Sjögren syndrome see **Sjögren's syndrome**

Miller Fisher syndrome (**Fisher syndrome**) is an extremely rare autoimmune disorder of the nervous system that is often triggered by infections and is considered to be a variant of **Guillain-Barré syndrome**. It is characterized by peripheral neuropathy that manifests in the form of descending paralysis. Although the etiology behind this disorder is not clear yet, it has been associated with certain viral and bacterial infections and molecular mimicry, involving the mimicry of gangliosides present in the nerve tissue that trigger an autoimmune response. Certain infectious agents, like *Campylobacter jejuni*, express their membrane lipopolysaccharide molecules that mimic the structure of gangliosides, which are complex glycosphingolipids located on the surface of cells present in the nervous tissue. The **Miller Fisher syndrome** is named after the pioneering neurologist, ***Charles Miller Fisher***, who first described it in 1956 as a limited variant of the ascending paralysis, Guillain-Barré syndrome.

Charles Miller Fisher or ***C. Miller Fisher*** (Dec 5, 1913–Apr 14, 2012) was a Canadian neurologist. He was born in Waterloo, Ontario, Canada, into a family of 9 children. In 1938, he graduated from the University of Toronto Medical School. During World War II, starting in 1940, he volunteered for the Canadian Navy and soon was transferred to the British Royal Navy as a naval medical officer. In 1941, an armed merchant cruiser the *Voltaire*, on which he served as the ship doctor, was attacked and crippled by a German vessel in the South Atlantic. The survivors had to jump into the water and were rescued by the enemy 6 or more hours later. Fisher spent the next 3.5 years as a physician in a German prisoner of war camp, where he learned German to be able to read available German medical literature. He was

repatriated in September 1944 as one of the supervisory doctors participating in an exchange of wounded prisoners of war.

When he resumed his medical career in Canada, he had a rotation and residency at the Montreal Neurological Institute. Then he did a neuropathology fellowship at Boston City Hospital. At age 36, Fisher returned to Montreal to become the neuropathologist at the Montreal General Hospital. In 1954, Fisher was invited to return to Boston, where he spent the next half century at Masschusetts General Hospital and Harvard University, and created and led the first formal stroke service. Fisher's teaching, care, and contributions were panneurological. He was a devoted teacher, supervisor, and mentor. Every day he spent at least 5 hours with his stroke fellows using a "Socratic" method of teaching. The fellows first checked the stroke patients, then met with Fisher at dinner, then from 6 pm to 11 pm or later they saw the patients together. Fisher repeatedly asked each fellow about his observations and opinions. Many of his stroke service trainees became well-known leaders in the field in various clinics in many countries.

Even as he approached the age of 96, Fisher still published journal articles. He died in Albany, New York. In the weeks before his death, the 30-year-old Greater Boston Stroke Society was renamed the C. Miller Fisher Society. The most known awards were his induction into the Canadian Medical Hall of Fame, the annual C. Miller Fisher Award for excellence in stroke care/research by the New England Branch of the American Heart and Stroke Association, the C. Miller Fisher Chair of Neurology, and the Annual Stroke Lecture.

(**Publ**.: Fisher M. An unusual variant of acute idiopathic polyneuritis: Syndrome of ophthalmoplegia, ataxia and areflexia. *N Engl J Med* 1956; 255:57–65.)

Milton urticaria see **Quincke's oedema**

Milton-Quincke syndrome see **Quincke's oedema**

Minkowski-Chauffard disease/syndrome (**Minkowski-Chauffard-Gänsslen syndrome**, **Gänsslen-Erb syndrome**, hereditary spherocytosis) is an autosomal-dominant congenital hemolytic anemia with spherocytosis, splenomegaly, and jaundice. Hereditary spherocytosis is caused by several mutations in the genes that encode the red blood cell membrane proteins, including spectrin, ankyrin, band 3 protein, and protein 4.2. These mutations result in a deficiency of membrane surface area and formation of spherocytes with reduced deformability. Spherocytes normally are destroyed in the spleen as abnormally shaped red cells. In the spleen, the passage from the **cords of Billroth** (**Billroth's cords**) into the sinusoids may be understood as a bottleneck, where red blood cells have to be elastic to pass through. In hereditary spherocytosis, erythrocytes fail to move across and are removed by phagocytosis, causing extravascular hemolysis.

Oskar Minkowski (Jan 13, 1858–Jul 18, 1931) is most famous for his research on diabetes. He was born in Aleksotas, Russian Empire (now Kaunas, Lithuania), of Jewish origin. Minkowski was the son of Rachel (née Taubmann) and Lewin Boruch

Minkowski, a first-guild merchant who subsidized construction of the Choral Synagogue in Kovno. In 1872, antisemitic procedures implemented by the Russian tzarist government forced the Minkowski family to emigrate to Königsberg in Prussia. Oskar's older brother, Max, took care of the family business and became wealthy as a middleman trading in grain. Oskar's younger brother, Hermann, became a well-known professor of mathematics who was Albert Einstein's teacher at the Zürich Polytechnic (1896–1900), although Einstein was not interested in mathematics at the time and skipped most of his lectures.

Oskar Minkowski completed his medical studies at the University of Königsberg and moved to Strasbourg where he later was the Chair of Internal Medicine. In 1904, he moved to the Augusta Hospital in Cologne and was the Chair of Internal Medicine in Greifswald. From 1909–1926 he was the Chair of Internal Medicine in Breslau (now Wroclaw). In Breslau, Minkowski became one of the leading German internists and was consulted by famous individuals, including Vladimir Ilyich Lenin (Ulyanov)—a Russian communist revolutionary, politician, and founder of the USSR.

Oskar was legendary for his manual skill and performed the world's **first successful hepatectomy** in a goose in 1888. One day in 1889, he met with Joseph Freiherr von Mering—a German physician who was the first person to discover (in conjunction with Oskar Minkowski) that one of the pancreatic functions is the production of insulin and helped to discover barbiturates—to discuss the role of Lipanin. That is a commercial preparation of pancreatic enzymes, and pancreatic enzymes break down fatty acids in the gut. Although, according to Claude Bernard, pancreatectomy would be impossible, Minkowski tried the surgery that same afternoon. That famous experiment showed **pancreatic diabetes** following pancreatectomy in dogs.

Importantly, Minkowski connected the polyuria resulting from the operation with diabetes, which allowed him to **test the urine for glucose**. Together with Josef von Mering, they were able to point out that the pancreas contains regulators to control blood sugar; they also provided a model for the study of diabetes. When later he was accused of taking overwhelming credit due to the Aryan von Mehring, however, Minkowski did not defend himself publicly but wrote a letter in 1926 telling about the discovery and placed it in the archives in Breslau in case "at some future time a student of the history of diabetes may be interested in the true facts." Two university professors, dismissed following the Nazi takeover in 1933, saved the letter from the archives prior to leaving.

Minkowski died in Fürstenberg, Mecklenburg. He and his famous brother Hermann were buried in the cemetery in Heerstrasse, Berlin. This place is protected by the city of Berlin as a historical monument. In recognition of the Minkowski's discovery, the European Association for the Study of Diabetes annually awards the Minkowski Prize for excellent research work of a young diabetes research investigator.

Minkowski married Marie Johanna Siegel in 1894. In 1938, their daughter, Laure Minkowski, with her husband and 2 sons, were forced by the Nazi government to leave Germany. They stayed in Buenos Aires, where Laure tried very hard to bring

her mother there. At the end of 1940, Marie Siegel was able to leave Germany; she died in Buenos Aires in 1983.

Minkowski's son, Rudolph, obtained his PhD in physics but had to emigrate from his Nazi-ruled homeland in 1935 to get a position at the Mount Wilson Observatory in Los Angeles, CA. There he became well known as a radio-astrophysicist and had a galaxy named after him—Minkowski's object, which is located around 300 million light years from Earth. It was first identified as "interesting" in 1958 by Rudolph Minkowski.

Anatole Marie Émile Chauffard see **Still disease**

Wilhelm Heinrich Erb (Nov 30, 1840–Oct 21, 1921) was a German neurologist. He was born in Winnweiler, Bavarian Palatinate, Germany, the son of the forester Friedrich Erb and Sophie née Hoffmeister. It was within this family upbringing that Erb developed the diligent personality for which he came to be known. He started his medical education at 17, first in Heidelberg, then in Erlangen and Munich. In 1880, Erb was a chair of special pathology at the University of Leipzig and served as the director of the outpatient neurology clinic. But in 1883, he returned to Heidelberg where he stayed for most of his life. He was a Professor of Internal Medicine at the University of Heidelberg and a head of a new neurological hospital. In 1876, Erb married Anna Gaß, and they had 4 sons. He retired in 1907. Later, 2 sons died, and a third was killed at the Front on the first day of World War I; Erb became very depressed. One day on the way home from listening to Beethoven's *Eroica* he got a cold and, a few days later, died from bronchopneumonia.

Erb's research initially focused on toxicology, histology, and therapeutics, but later he was interested mostly in neurology. He was well known for identifying, classifying, characterizing, and treating various muscular dystrophies, many of which still bear his name: Erb's palsy, Erb–Charcot paralysis, Erb's point, Erb's dystrophy, Erb's phenomenon, Erb's reflex. Erb also pioneered and advocated the use of electricity in the diagnosis and treatment of nervous disorders and determined the effect of electrical current on the human body. He promoted electrodiagnostics in neurology and confirmed increased motor nerve irritability in tetanus.

Erb is remembered as a very cultured gentleman, who was always perfectly dressed and kept his professorial beard trimmed to the last hair. He was punctual to the second and always prepared. The title Seine Excellent was conferred on him by the local ruling prince, the Grand Duke of Baden. He was an honorary member of many scientific societies. Erb remained Honorary President of the Society of German Neurologists until his death. His 70th birthday was a special town occasion of celebration in Heidelberg. His statue of bronze was unveiled in the park near the Akademisches Krankenhaus (Academic Hospital), and a street was named after him.

Max Gänsslen (Mar 24, 1895–Mar 30, 1969) was a German internist. He was born in Weinsberg, Germany, and studied medicine starting in 1912 at universities in Munich, Leipzig, and Tübingen, getting his doctorate in 1920. He then worked at the Medical University Hospital in Tübingen. He developed a liver extract for the treatment of pernicious anemia, which made him world famous at the time. In 1935, Gänsslen became the head of the Medical Polyclinic of the University of Frankfurt.

In 1937, he joined the NSDAP—the German Nazi Party. After World War II in 1945, he was temporarily suspended and ran a private practice in Frankfurt. In 1950, he was appointed director of the newly founded second Medical University Hospital and headed it until his retirement in 1960.

(**Publ**.: von Mering J, Minkowski O. Diabetes mellitus nach pankreasextirpation. *Centralbl Klin Med* 1889; 10(23):393–394.

von Mering J, Minkowski O. Diabetes mellitus nach Pankreasextirpation. *Arch Exp Pathol Pharmakol* 1890; 26:371–378.

Minkowski O. Über eine hereditäre, unter dem bilde eines chronischen icterus mit urobilinurie, splenomegalie und nierensiderosis verlaufende affection. *Verh Kongresses Inn Med* 1900; 18:316–321.

Chauffard MA. Pathogénie de l'ictère congénital de l'adulte. *Sem Med* 1907; 27:25–29.

Chauffard MA. Les ictères hémolytiques. *Sem Med* 1908; 28:45, 49.

Chauffard MA. Pathogénie de l'ictere hémolytique congénital. *Ann Med Interne* 1914; 1914:1–17.

Gänsslen M. Über hämolytischen Ikterus. Nach 25 eigenen beobachtungen und 10 milzexstirpationen. *Dtsch Arch Klin Med* 1922; 140:210–226.)

Minkowski-Chauffard-Gänsslen syndrome see **Minkowski-Chauffard disease**

Moloney test (**Moloney Reaction test**) is used for determining delayed hypersensitivity to diphtheria toxoid by injection of 0.1 ml of 1:10 dilution of diphtheria toxoid intradermally on the flexor surface of the forearm; the appearance in 12–24 h of an area of redness with induration of more than 12 mm in diameter is a positive reaction. It is an obsolete skin test for immunity to diphtheria. The diphtheria toxoid-reaction test was introduced in 1927 by ***P. J. Moloney*** and C. J. Fraser, in association with the **Schick test** (since replaced by the control by diluted toxoid) for the purpose of detecting those individuals who would be likely to give undesirable reactions on the injection of toxoids for diphtheria prophylaxis. The test soon was used as a routine measure in Toronto, Canada. O'Brien and Parish (1932) described the results of testing 906 individuals and decided that the **Moloney test** was equally effective in picking out persons who were likely to react unfavorably to the much stronger toxoids, which they had used because it indicated the Canadian workers who would react to the weaker toxoids. They associated Moloney's name with the test (O'Brien and Parish, 1932).

Peter Joseph Moloney (Jun 29, 1891–Aug 12, 1989) was a Canadian immunologist. He was born in Penetanguishene, Ontario, Canada, to Thomas Henry Moloney, an Irish immigrant, and Elizabeth Byrnes. In 1893, the family moved to Powassan, Ontario, where Peter's father went to manage a hotel and where Peter spent most of his future life. After studies at elementary school, Peter entered a "Continuation School" because there was no high school at the district. Then, at 16, he registered at St. Michael's College in Toronto. He continued his education at the University of Toronto receiving his BA in 1912 and MA in 1915. He then studied at the University

of California at Berkeley where he met and married a university student, Angelina Chapman, and they had 5 children. Moloney received his PhD degree in chemistry in 1924 from the University of Toronto. In Toronto, he was a professor in the School of Hygiene and staff member and an Assistant Director of the Connaught Medical Research Laboratories. After retirement, Moloney continued to work as a consultant and active researcher at Connaught Laboratories Limited.

Moloney's long career in Toronto was associated with his work on diphtheria and diabetes. With C. B. Weld, he succeeded in producing the first diphtheria toxoid in North America and in developing a reliable reaction test, known as "the Moloney test." That was not the only research outcome Moloney had in his name. The "Moloney Electrode" was another one of his accomplishments—a hydrogen electrode that could detect the acidity of bacterial cultures before the invention of the pH meter. With D. M. Findlay, he contributed to developing methodologies of using benzoic acid for the concentration and purification of insulin. During the 1940s–1950s, Moloney played a very important role in standardizing and improving the preparation and production of penicillin and heparin. In the 1960s, he worked on developing sulphated insulin for diabetes' patients who were resistant to regular insulin.

Moloney published more than 80 research papers and authored numerous patents, including those for the preparation of insulin and heparin, and his last patent application was filed at the age of 90. Moloney was a member of the following: American Chemical Society, Canadian Society of Immunologists, British Biochemical Society, Royal Society of Canada, Canadian Physiological Society, and Canadian Federation of Biological Societies. For his clinical work on a gas gangrene antiserum during World War II, he was awarded the Order of the British Empire. In 1964, he received the Banting Medal; in 1967, the Gairdner Award; and in 1971, the first Charles H. Best Medal. Moreover, in 1977, the Connaught Laboratories Limited named "The Moloney Building" in his honor.

(**Publ**.: Moloney PJ, Fraser CJ. Immunization with diphtheria toxoid (ANATOXINE RAMON). *Am J Pub Health* 1927; 17(10):1027–1030.

Moloney PJ, Fraser CJ. The preparation and testing of Diphtheria toxoid (ANATOXINE RAMON). *Ann Inst Pasteur* 1928; 42:1420–1423.)

Mooren's ulcer (**Mooren's ulceration**, **Mooren ulcer**) is a rare disease that studies suggest is an autoimmune disorder or autoinflammatory disease. It is a painful, persistent, and chronic ulcerative keratitis (i.e., inflammation of the cornea). It starts peripherally and continues circumferentially and centrally. It is idiopathic, arising in the entire lack of any diagnosable systemic diseases that may be responsible for the cornea's gradual damage. Etiologically, it has been associated with various entities, including helminthiasis, hepatitis C, herpes simplex and zoster, syphilis, and tuberculosis. It has been speculated that the antigen–antibody reaction to helminth toxins deposited in the peripheral cornea provoke the inflammation and ulceration. Molecular mimicry also may be implicated, with the cross-reacting epitopes of hepatitis C virus stimulating an autoimmune reaction to corneal antigens. Furthermore, accumulation of immune complex deposits in limbal and peripheral

corneal tissues may initiate the inflammatory response and release of proteolytic enzymes causing tissue destruction. Additionally, autoinflammatory reactions were reported to be related to chemical burns; physical trauma; and surgical procedures associated with foreign bodies, cataract extraction, and penetrating keratoplasty.

The accurate pathophysiological mechanism of **Mooren's ulcer** remains unknown, but an autoimmune process, with both cell-mediated and humoral components, has been suggested. Cellular and humoral immune responses to bovine corneal antigen in a patient with Mooren's ulcer have been reported. Cornea-associated antigen (Co-Ag) is a member of the Ca^{2+}-binding protein of the S-100 family of proteins, which might have some sequence similarity with microbial proteins as possible substrate for molecular mimicry.

Neutrophils, mast cells, eosinophils, and plasma cells commonly are detected in the inflamed areas. Elevated homing of activated neutrophils in affected conjunctiva may well be the source of proteases and collagenases that degrade the corneal stroma. Cell-mediated autoimmune processes also can be demonstrated ex vitro as a positive macrophage migration-inhibition response to corneal antigens presented to lymphocytes using cells harvested from patients with Mooren's ulcer. Subsequently, abnormally regulated T-helper cells may induce production of autoantibodies, causing the deposition of immune complexes, activation of complement, infiltration by immune cells, and release of proteolytic enzyme. Complement activation induces chemoattraction of neutrophils, their activation and degranulation and secretion of collagenases, causing corneal destruction and further exposure and modification of corneal antigens. Circulated IgG antibodies to human corneal and conjunctival epithelium, elevated IgA levels, and circulated immune complexes also have been reported in patients with Mooren's ulcer.

Bowman initially reported Mooren's ulcer in 1849, and McKenzie did in 1854, as "chronic serpiginous ulcer of the cornea or *ulcus roden*." ***Albert Mooren***, however, was the first clinician who comprehensively described several cases in 1867 and evidentally defined this corneal condition as a clinical entity.During the 1960s, there was a renewed interest in this condition with many reports coming from developing countries.

Albert Clemens Maria Hubert Mooren (Jul 26, 1828–Dec 31, 1899) was a German ophthalmologist. He was born in Oedt in the western part of North Rhine-Westphalia and studied medicine at the universities of Bonn and Berlin. In 1841, Mooren married Ahaus Carolina Maria Theodora Oldenkott, and they had 10 children. In 1855, he received his license to practice medicine and surgery and opened his private practice in his hometown of Oedt. He soon made a name for himself by skillfully conducting eye operations and attracted patients not only from Germany but also from Holland, Belgium, and France. In 1862, he moved to Düsseldorf to lead the newly founded municipal eye clinic. In 1895, he was awarded with the title of professor. He also served as a manager at the Ophthalmology Institute of Liège and Limbourg. From 1883 on, he focused on his private practice in Düsseldorf working there until his death. He was credited with conducting more than 25,000 operations, helping people from various countries. Among his awards and honors

were the Royal Belgian Knight's Cross of the Order of Leopold II, Honorary Chairman of the Association of Doctors in Düsseldorf, and honorary citizenship of the city of Düsseldorf.

His name is associated with "Mooren's ulcer," which he described in several cases in 1867. In 1882, he was the first to describe *retinitis punctata albescens*. In the last days of 1899, Mooren suffered a stroke and died.

(**Publ**.: Mooren A. *Ulcus Rodens. Ophthalmiatrische Beobachtungen.* Berlin: A. Hirschwald; 1867; pp. 107–110.)

Morbus Behçet see **Behçet's syndrome**

Mortensen's disease (**Mortensen syndrome**) see **Révol's syndrome**

Morvan's syndrome (**Morvan's fibrillary chorea**) is a rare autoimmune disease associated with the formation of voltage-gated potassium channel complex antibodies (VGKC-Complex Abs), most commonly directed against contactin-associated protein-2 (CASPR-2). Some of the patients had a thymoma, but many did not have a tumor, and there was often a good clinical response to immunotherapies. **Morvan's syndrome** is clinically distinct from other VGKC-complex antibody-associated conditions, and usually is associated with high-titer CASPR2 antibodies, often accompanied by lower-titer leucine-rich glioma inactivated 1 (LGI1) antibody and netrin 1 receptor antibodies. CASPR2 and LGI1 antibodies bind to multiple brain regions, which helps to explain the multifocal clinical features of this disease.

The disease is named after the French physician ***Augustin Marie Morvan***. "La chorée fibrillaire" was coined first by Morvan in 1890 when describing patients with multiple, irregular contractions of the long muscles, cramping, weakness, pruritus, hyperhidrosis, insomnia, and delirium. A few cases of Morvan syndrome were reported over the following 100 years, mainly in the French literature.

Augustin Marie Morvan (Feb 7, 1819–Mar 20, 1897) was a French physician, politician, and writer. He was born in Lannilis in northwestern France to farmers Jean-Marie and Louise Marie Prudence née Floch, as the eldest of 8 children. He attended primary and secondary school in Lesneven, and began his medical studies at the Naval Health School—a training school for active military doctors—in Brest, a port city in Brittany, France. In 1839, he started to serve as a marine surgeon but had to resign in a few months because he was unable to tolerate seasickness. Instead, he continued his medical education in Paris and graduated with a doctoral thesis entitled "Varicose aneurism." After internship training, Morvan returned to Lannilis and opened a private practice. He was also very active in politics, quickly establishing a reputation and became Mayor, then a regional administrator and was elected Deputy in 1871. He was known for providing free medical care during his term as Deputy. He also developed the Morvan-Roussel law, the first regulation for the protection of children in problematic living conditions and very young mothers. Morvan worked very hard as a doctor until his last days. He was known throughout the

Brittany region: "An aotrou Morvan" or Monsieur Morvan—pronounced with fervor and respect by numerous patients.

(**Publ**.: Morvan A. De la choreé fibrillaire. *Gaz Hebd Med Chir* 1890; 27:73–200.)

Mosse syndrome (**Mosse's syndrome**, **Mosse's polycythaemia**) is the simultaneous presence of polycythaemia vera (see **Vaques' disease/**Vaques-Osler syndrome) and cirrhosis of the liver. A rare combination, which is often not diagnosed until necropsy. In addition, it may be associated with polyglobulinemias and polycythemias. Basically, this is a chronic myeloproliferative disorder characterized by the excessive production of mainly red blood cells by the bone marrow.

In 1914, ***Mosse*** described a male patient who suffered from polycythemia vera, complicated by cirrhosis of the liver. Ascites, edema, and jaundice were present, and a postmortem showed splenomegaly, atrophic cirrhosis, and thrombophlebitis of the portal circulation.

Max Mosse (May 21, 1873–Nov 16, 1936) was a German physician. He was born in Berlin to a Jewish family of Theodor and Anna Mosse. He received his education at the universities in Freiburg, Zurich, and Berlin and obtained his Doctor of Medicine degree from Freiburg in 1897. He worked as an internist in Berlin. In 1908, he received a title of Titular Professor. Mosse's clinical studies focused on physiological and pathological chemistry, hematology, histology, and social medicine.

(**Publ**.: Mosse M. Uber policythamie mit urobilinikterus und milztumor. *Dtsch Med Wochenschr* 1907; 33:21–75.

Mosse M. Polyglobulie and leberkrankung. *Z Klin Med* 1913; 79:431.)

Mott cells are plasma ones measuring 12–20 μm in diameter, which have spherical inclusions packed in their cytoplasm. The cells are defective in immunoglobulin secretion with resulting accumulation of immunoglobulins in dilated cisternae of rough endoplasmic reticulum, leading to formation 1–3 μm-diameter acidophilic globules (**Russell bodies**) filled with immunoglobulins and neurofibrillary material.

The term "Mott cell" is named after ***F. W. Mott***. He was a surgeon and first described these cells in the brains of monkeys with trypanosomiasis when studying sleeping sickness. His results were published by the Royal Society in 1901. He called it a morular cell (from the Latin *morus*, mulberry) and correctly identified them as plasma cells associated with chronic inflammation. Yet, Mott was not the first researcher who saw this phenomenon. The initial report from 1890 belongs to ***William Russell*** (see **Russell bodies**), who saw unusual formations but neither recognized the origin of the cell nor the clinical importance of the inclusions. Furthermore, Mott pointed out that priority is because of Dr. Cuthbert Christy who gave an account of these cells in a memoir at the Liverpool School of Tropical Medicine in 1904. So does the eponym distort history?

Mott cells are characterized by the expression of B220, CD5, CD43, and CD11b, and their formation has been linked to a genetic locus-microsatellite marker

(D4Mit70 and D4Mit48), in which they can be linked to several pathological conditions (e.g.,**Burkitt's lymphoma**, large B-cell lymphoma, reactive plasmacytosis, hematolymphoid malignancies, lymphoplasmablastic lymphoma, and multiple myeloma). Mott cells can also be detected in several syndromic conditions: **Wiskott-Aldrich syndrome** and von Recklinghausen's neurofibromatosis. Consequently, the cells are a pathologic status of plasma cells having intracellular inclusions of immunoglobulins (Russell bodies) and are common in lymphoid tissues of animal and human hosts suffering from autoimmune and malignant diseases.

Frederick Walker Mott (Oct 23, 1853–Jun 8, 1926) was an English neuropathologist. He was born in Brighton, Sussex, the only son of Henry Mott and his wife Caroline. He began his medical education at the Royal Sussex County Hospital but then moved to University College in London, where he graduated with an MD in 1886. In 1885, he married Georgina Alexandra Soley, and they had 4 daughters. In 1886, he became a member of the Royal College of Physicians and was elected to a fellowship in 1892.

Mott had a distinguished career at numerous universities and hospitals, including Liverpool University, Charing Cross Hospital, and University College. Mott was a simple, natural, and friendly man. He was remembered as an "indefatigable worker" and "extremely hospitable" in his obituary in the *British Medical Journal*. Mott was also a talented singer and dedicated to music and choral works. His accomplishment in music was recognized by his election as president of the Society of English Singers in 1923.

(**Publ**.: Christy C. The cemebro-spinal fluidl its sleepimug sickness (trypusnosonsiussis). *Liverpool Sch Trop Med Mem* 1904; III:57.

Mott FW. Observations on the brains of men and animals infected with various forms of trypanosomes. Preliminary note. *Proc R Soc Lond* 1905; 76:235–242.

Russell W. An address on a characteristic organism of cancer. *Br Med J* 1890; 2:1358–1360.)

Mucha-Habermann disease (**Mucha-Habermann syndrome**) is synonymous with *pityriasis lichenoides et varioliformis acuta* (PLEVA), a form of parapsoriasis that can be considered as the disease of the immune system. The etiology of this disease is unknown. Several clinical cases were linked to various infectious agents (e.g., Epstein-Barr virus, parvovirus B19, human immunodeficiency virus, cytomegalovirus, and *Toxoplasma gondii*). Immunohistologic analysis of the central epidermis of pityriasis lichenoides lesions revealed a decrease in $CD1a^+$ antigen-presenting dendritic (**Langerhans' cells**). Keratinocytes and endothelial cells are $HLA\text{-}DR^+$, which might suggest activation by T-cell cytokines. $CD8^+$ T cells predominate in PLEVA, and many of these rhem express memory proteins ($CD45^{RO}$) and cytolytic proteins (TIA-1 and granzyme B).

Complete understanding of the pathogenesis of parapsoriasis is limited. Pathology consists of superficial T-cell infiltrate with a common dominant clonality, which, however, does not necessarily connect to malignancy. Most patients with these and related diseases display a benign clinical course, and sometimes the

disease fully resolves. One feature of this group of scaly dermatoses is that they appear to be cutaneous T-cell lymphoproliferative disorders.

Pityriasis lichenoides was described first in 1894 by ***Neisser*** (Neisser, 1894) and ***Jadassohn*** (Jadassohn, 1894). In 1899, Juliusberg described the chronic form and named it *pityriasis lichenoides chronica* (Juliusberg, 1899). ***Mucha*** explained it as the acute form in 1916 and distinguished it from the chronic form. ***Habermann*** named the acute variant PLEVA in 1925.

Viktor Mucha (Apr 17, 1877–Jun 6, 1933) was an Austrian dermatologist. He was born in Königgrätz (now Hradec Králové, Czech Republic), a son of the director of a general hospital. Mucha studied medicine at the universities of Vienna and Strasbourg, receiving his doctorate in 1904. In 1912, he obtained his habilitation for dermatology and syphilology at the university, becoming an Associate Professor in 1921. He was a scientist at the Chemical Institute at Finger's Clinic. From 1905, more than 5 months before the detection of *Treponema pallidum*, Mucha started to work with ***Karl Landsteiner*** and other members of the Viennese School of Medicine on syphilis. Landsteiner and Mucha introduced the **dark-field microscopy** for the detection of *T. pallidum*. They noticed that serum from patients with syphilis reduced the motility of *T. pallidum* and established that the essential principle involves the *T. pallidum* immobilization test (TPI or Nelson-Mayer test). Finally, the team proved that it was not the antibodies specific to *T. pallidum* that participate in the **Wassermann reaction**, but "autotoxic" substances, which they called "reagines." Later in the 1980s, it was shown that these reagines are autoantibodies reactive with cardiolipin-like molecules and directed against parts of the inner envelope of the mitochondria.

During World War I, Victor Mucha directed the Department of Dermatology in the Austrian military hospital in Lwów, Poland (now Lviv in Ukraine).

Rudolf Habermann (1884–1941) was a German dermatologist working in Hamburg. His name can be found in the list of signatories—professors and lecturers from German universities and colleges who professed allegiance to Adolf Hitler and the National Socialist state. It was presented on November 11, 1933, "to celebrate the National Socialist revolution" at a ceremony in the Albert Hall in Leipzig (Moll et al., 2015). The title was "Mit Adolf Hitler für des deutschen Volkes Ehre, Freiheit und Recht!"]With Adolf Hitler for the German people honor, freedom and justice!] (seealsohttp://www.geni.com/projects/Confession-of-German-Professors-to-Adolf-Hitler/28571).

(**Publ**.: Mucha V. Uber einen der Parakeratosis variegate (unna) bzw, pityriasis lichenoides chronica nahestehenden eigentumlichen fall. *Arch Dermatol Syph* 1916; 123:586.

Habermann R. Uber die akut verlaufende, nekrotisierende unterart der pityriasis lichenoides (Pityriasis lichenoides et varioliformis acuta). *Dermatol Z* 1925; 45:42.)

Letter N



Naegeli-de Quervain-Stalder method is a method for demonstrating cell-combined allergic antibodies. The researchers by means of a Thiersch graft (a skin graft of thin strips or sheets of epithelium) succeeded in transplanting the hypersensitiveness in a fixed eruption as a result of antipyrine to a previously unaffected area of the skin of the same patient.

Oskar Naegeli (***Nägeli***) see **Glanzmann's syndrome**

Fritz de Quervain (***Fric de Kerven***) (May 4, 1868–Jan 24, 1940) was a Swiss surgeon. He was born in Sion (German name Sitten) in the Valais Canton, Switzerland. He graduated from the University of Bern with the Doctor of Medicine degree in 1892 and worked at the Institute of Physiology, Institute of Pathology, and surgical clinic at the University Hospital of Bern.

In 1894, de Quervain started to work as a surgeon in La Chaux-des-Fonds—a Swiss city in the canton of Neuchâtel. In 1897, he became a director of the hospital surgical unit. He habilitated for surgery in 1902 in Bern and received the title of a Titular Professor in 1907. In 1910, he was offered a position of Chair of Surgery at the University of Basel. From 1918 on, he was Director of the University Hospital of Bern and Professor of Surgery at the University of Bern. In 1919–1920, he was president of the Schweizerische Gesellschaft für Chirurgie (Swiss Surgical Society); in 1923–1924, Dean of the faculty; and in 1935–1936, Rector of the university. He retired in 1938.

De Quervain published almost 300 papers and many of them described his interest in thyroid disease, focusing from technical methodologies of thyroidectomy to the epidemiology of thyroid disease. He introduced **iodized table salt** in the treatment of thyroid disease. His textbook, *Special Surgical Diagnosis*, was one of the principal surgical textbooks at his time. De Quervain died of acute pancreatitis.

W. Stalder

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(**Publ**.: Naegeli O, de Quervain F, Stalder W. Nachweis der cellulären sitzes der allergie beim fixen antipyrin-exanthem (Autotransplantationen, versuch in vitro). *Klin Wochenschr*, 1930; 9:924–928.)

Nakajo syndrome see **Nakajo-Nishimura syndrome**

Nakajo-Nishimura syndrome (**Nakajo syndrome**) is a rare, genetic autoinflammatory disease caused by abnormal functioning of the multicatalytic system proteasome-immunoproteasome. It is characterized by the appearance of recurrent fever in the first months of life, along with characteristic skin lesions, lipodystrophy, and manifestations of multisystem inflammation. It was shown in 2011 that the disease is caused by a homozygous mutation in the *PSMB8* gene, which encodes the β35i subunit of immunoproteasome, and this may impair the normal assembly of immunoproteasomes. Analysis of patients' cells and tissues revealed that accumulation of ubiquitinated and oxidated proteins because of insufficiency of proteasome activities induced hyperactivation of p38 MAPK and overproduction of IL-6. Additional diseases with detected *PSMB8* mutations also have been reported in Europe and the US. Diseases from this group may have homozygous and compound heterozygous mutations in the genes encoding other subunits of the proteasome-immunoproteasome complexes; mutations in the proteasome-maturation protein (*POMP*) gene also have been reported.

Clinical features of **Nakajo-Nishimura syndrome** overlay with those of 2 other disorders that also are characterized by skin abnormalities and lipodystrophy: (1) joint contractures, microcytic anemia, muscular atrophy, and panniculitis-induced lipodystrophy (JMP) syndrome; and (2) chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. Although these 3 syndromes are considered distinct disorders, they are linked to mutations in the same *PSMB8* gene and could be just different forms of a single condition. As the diminished immunoproteasome activity is the hallmark of these syndromes, they are believed to form a new category of autoinflammatory diseases—a group of proteasome disability syndromes, described in various countries.

Overall, proteasome–immunoproteasome dysfunction causes a continuous state of inflammation with exacerbations. This results in constituent overexpression of type 1 interferons, and upregulated accumulation of waste proteins within the cells as a result of insufficient proteasome–immunoproteasome activity. Increase in waste proteins triggers cellular stress and further stimulation of type 1 interferons, supporting this circle of inflammation. Usual triggers, including cold temperature, physical or psychological stressors, or minor infections, augment type 1 interferon expression, and thus aggravate serious inflammatory reactions that can be seen in several organs.

Nakajo-Nishimura syndrome was reported initially as "secondary hypertrophic osteoperiostosis with pernio" in 1939 by ***Nakajo***. He reported a brother–sister case of a cognate family who displayed pernio (i.e., chilblains) and clubbed (i.e., swollen and spongy) fingers, periosteal thickening, and suspected cardiac insufficiency. In

1950, ***Nishimura*** described 3 cases of 2 cognate families with very similar symptoms and suggested inheritance of the disease.

A. Nakajo

N. Nishimura

(**Publ**.: Nakajo A. Secondary hypertrophic osteoperiostosis with pernio. *Jpn J Dermatol Urol* 1939; 45:77–86.

Nishimura N, Deki T, Kato S. Hypertrophic pulmonary osteo-arthropathy with pernio-like eruptions in the two families (Report of the three cases). *Jpn J Dermatol Venereol* 1950; 60:136–141.)

Neumann's syndrome see **Stevens-Johnson syndrome**

Netherton syndrome (**Comel-Netherton syndrome**, **Netherton-Comel syndrome**) is a rare inherited (as an autosomal recessive trait) disorder that affects the skin, hair, and immune system. It usually is evident at birth or during the first weeks of life as erythroderma (i.e., inflamed, red, and scaly skin), "Bamboo hair" (i.e., deformed short, brittle, and lusterless hair), and predisposition to allergic manifestations. Many patients develop a food allergy, hay fever, asthma, and atopic eczema; may suffer attacks of angioedema (severe allergic skin reaction) and urticaria (itchy weals, hives). Many patients have high levels of IgE in the serum and hypereosinophilia. Netherton syndrome may increase the risk of skin cancer developing. Symptoms tend to adjust with age. Phases of little or no disease may be followed by occasional aggravations.

Netherton syndrome is caused by mutations in the *SPINK5* gene on chromosome 5q32, which encodes an inhibitor of serine proteases, called lymphoepithelial kazal type-related inhibitor (LEKTI). The protein is expressed in the **Hassal corpuscles** of the thymus, mucous epithelia, and cultured epidermal keratinocytes. Nonfunctional LEKTI results in a loss of inhibition of several serine proteinases, including subtilisin A, plasmin, cathepsin G, trypsin, and elastase. LEKTI may play a role in antiinflammatory and antimicrobial protection of mucous epithelium because it may target the mast-cell tryptase, associated with immediate hypersensitivity reaction and activation of keratinocytes. Th1/Th2 imbalance and the involvement of Th17/IL23 pathways also have been suggested.

In 1958, ***Netherton*** described the bamboo-like deformity in the fragile hairs of a girl with erythematous scaly dermatitis, which he saw in November 1949. ***Comel***, the Italian dermatologist, however, reported on a 23-year-old woman with unusual scaly patches on her skin, which he had termed "Ichthyosis Linearis Circumflexa" 9 years earlier in 1949.

Earl Weldon Netherton (Apr 7, 1893–1967) was a US dermatologist. He was born in Gallatin, Missouri. He graduated from the University of Missouri and obtained his MD degree from Washington University in St. Louis in 1917. He then did his residency in dermatology at Barnard Skin and Cancer Hospital in St. Louis and moved to the Cleveland Clinic after his service in the U.S. Army. In the

Cleveland Clinic, he established and ran the Department of Dermatology. Netherton published many clinical papers covering various topics from Nodular Papillomatous Bromoderma to vaccine therapy.

M. Comèl (1902–1995) was an Italian dermatologist and angiologist associated with the Institute of Dermatologic Clinic, Department of Angiology, University of Pisa in Pisa, Italy.

(**Publ**.: Comèl M. Ichthyosis linearis circumflexa. *Dermatol* 1949; 98(3):133–136.
Netherton EW. A unique case of trichorrhexis nodosa: "Bamboo hairs." *AMA Arch Dermatol* 1958; 78(4):483–487.)

Nezelof's syndrome is an autosomal recessive congenital immunodeficiency condition as a result of underdevelopment of the thymus, also known as thymic dysplasia with normal immunoglobulins. The disease is characterized by absent T-cell function, deficient B-cell function, objectively normal immunoglobulin levels, and little or no specific antibody production. Underdevelopment of the thymus is the major finding among patients. Nezelof syndrome is the congenital hypoplasia of the thymus with retention of normal parathyroid function. It should be contrasted to DiGeorge syndrome in which there is an absence of the parathyroids.

Patients with **Nezelof's syndrome** gradually have developed, recurrent, and finally fatal infections. Clinical signs in infants and children include persistent pneumonia, chronic fungal infections, upper respiratory tract infections, otitis media, diarrhea, and hepatosplenomegaly. Infection may cause sepsis, which is the usual cause of death. The lymph nodes and tonsils may be enlarged, or they may be totally absent.

Diagnostic findings include decrease in the number of lymphocytes in the blood, defective B-cell and T-cell immunity in spite of a normal number of circulating B cells, medium-high increase in T cells, abnormal levels of one or more classes of immunoglobulins, low antibody response to specific antigen immunization, nonreactive **Schick test** after DPT immunization, no thymus shadow on a chest X-ray, and thymus-dependent regions with an abnormal lymphoid structure.

During the 1960s, ***Nezelof*** worked on describing a clinical condition of immune deficiency in childhood, where the existence of a "split" in the human lymphoid system toward T and B cells was recognized. An immune-deficient child was described as afflicted by a thymic hypoplasia, but with a normal level of immunoglobulins ("Lymphocytophtisie avec normogammagloblinemie"). In the pediatric literature, this condition became known as Nezelof's syndrome.

Christian Nezelof (Jan 19, 1922–May 18, 2015) was a French physician. He was born in Barrou, a small town in the Loire Valley in France. He studied medicine in Paris during and after World War II. In 1948, he finished his specialization in pediatrics at the Hospital des Enfants Malades. In 1956, he received additional training at the Department of Pathology at the Sick Children Hospital in London, and after returning to France, he completed training in pediatric pathology. During 1960–1968, Nezelof served as a full-time pathologist at Necker-Enfants Malades, where he

became Chairman of the Department of Pathology in 1968. At the same time, from 1970 for 15 years, he was head of the INSERM Research Unit and created the Groups of Pediatric Pathology located at the hospital.

Nezelof prepared almost 400 publications focusing on various aspects of pediatric pathology, studying histiocytosis, cytomegalovirus infections, cystic fibrosis, immunodeficiency, and even the history of medicine. He was a member of the French National Academy of Medicine, the Histiocyte Society, the French Division of the International Academy of Pathology, and the International Pediatric Pathology Association. He was a president of the European Society of Pathology. The Histiocyte Society sponsors an annual prize in honor of Christian Nezelof, founding member and first president of the society. Nezelof died peacefully in Paris at the age of 93.

(**Publ**.: Nezelof C, Jammet ML, Lortholary P, Labrune B, Lamy M. Hereditary thymic hypoplasia: Its place and responsibility in a case of lymphocytic, normoplasmocytic and normoglobulinemic aplasia in an infant. *Arch Fr Pédiatr* 1964; 21:897–920.)

Niemann disease see **Niemann-Pick disease**

Niemann-Pick cells see **Pick cells**

Niemann-Pick disease (**Niemann disease**) is a group of inherited autosomal recessive metabolic disorders known as lipid-storage diseases when harmful quantities of lipids accumulate in the spleen, liver, lungs, bone marrow, and the brain. The disease has at least 5 related types. Type A, the most severe form, occurs in early infancy and is characterized by an enlarged liver and spleen, swollen lymph nodes, and profound brain damage by 6 months of age. Type B involves an enlarged liver and spleen, which usually occurs in the preteen years. In types A and B, insufficient activity of sphingomyelinase causes the buildup of toxic amounts of sphingomyelin accumulated in lysosomes. Types C and D may appear early in life or develop in the teen or adult years. Affected individuals have only moderate enlargement of the spleen and liver, but brain damage can be extensive, causing progressive loss of vision and hearing and difficulty walking and swallowing. Types C and D are characterized by a defect that disrupts the transport of cholesterol between brain cells. Types C and D are caused by a lack of the NPC1 or NPC2 proteins used to transport lipids. Type E is adult nonneuropathic and not well characterized, and Type F also is called sea-blue histiocyte disease. The characteristic cells in this disease, **Pick's cells**, are similar in appearance to **Gaucher's cells**, although the cytoplasm of the cell is foamy.

Albert Niemann published the initial description of what is now known as Niemann-Pick disease, type A, in 1914. Niemann's description was of an 18-month-old girl with general damages to the central nervous system; she died at the age of 2 after emerging hepatosplenomegaly and lymphadenopathy. Niemann observed that the histological findings were similar to those of **Gaucher's disease**, although the

rapidly progressive course of the disease was quite unusual. ***Ludwig Pick*** in a series of papers during the 1930s reported the pathology of a disease with "lipid cell splenomegaly." In 1961, the classification of Niemann-Pick disease into types A, B, and C was introduced. There is also a type D, called the "Nova Scotian type" (or Crocker-Farber syndrome). Because genetic analysis revealed that type D is caused by the same gene as type C, the type D classification is no longer in use.

Albert Niemann (Feb 23, 1880–Mar 22, 1921) was a German physician born and lived in Berlin, Germany. His father Albert Niemann was a well-known tenor, who performed at the Berlin State Opera and appeared as Tristan at the Metropolitan Opera House in New York. His mother, Hedwig Niemann-Raabe, was also a renowned actress. Albert entered the medical world after attending the universities in Strasbourg, Freiburg, and Berlin, receiving his medical doctorate from Strasbourg in 1903. He later trained in pediatrics as an assistant at the *Säuglingsheim* (Infant Home) in Berlin, where he was a director from 1918 onward.

Albert Niemann frequently is confused with the chemist Albert Niemann (1834–1861) from the University of Göttingen who in 1859 isolated the plant-derived alkaloid cocaine.

Ludwig Pick (Aug 31, 1868–Feb 3, 1944) was a German pathologist. He was born in Landsberg, Germany, as the oldest of 7 children to a Jewish family, the son of Hermann Pick, who managed a distillery, and his wife Beatrice. As a child he was inspired by his maternal grandfather, a well-known mathematician. Ludwig had a talent for music, natural science, and mathematics. He led the school orchestra and played the cello (violoncello). Pick studied at the universities in Heidelberg, Leipzig, Berlin, and Königsberg and received his doctorate degree in 1893 from the University of Leipzig. He then worked on the development of the pathology institute in Leopold Landau's private clinic for women, where he worked until 1906. He then became a director of the Department of Anatomy and Pathology at the city hospital in Friedrichshain-Berlin. He received the title of Titular Professor in 1909, and Honorary Professor in 1921.

Pick was a very short and overweight man and a known workaholic who started work at 6 in the morning and finished at 8 in the evening. He was a known bachelor who characterized love as "a psychosis which may always be given a good prognosis."

Pick introduced a lot of innovations into histological techniques and used them for improved examinations of postmortem materials. He contributed a great dwal to academic pathology, especially in the areas of genitourinary diseases and melanotic pigmentation. In 1912, he coined the term "pheochromocytoma" to describe the chromaffin color change in tumor cells associated with adrenal medullary tumors. In 1926, he established histologically as Niemann-Pick—a separate entity from **Gaucher's disease**—and attracted attention to Niemann's original characterization of the disease.

Pick served with distinction in the German army during World War I. Despite this background, when Nazis arrived on the political scene, he was forced from his home and imprisoned in a Jewish hospital in 1942; he had been suffering with ill

health for some time because he was frequently bedridden as a result of operations in both his eyes. Pick was then sent to the Theresienstadt concentration camp because of his Jewish heritage, where he died at the age of 76.

(**Publ**.: Niemann A. Ein unbekanntes krankheitsbild. *Jahrb Kinderheilkd* 1914; 79:1–10.

Pick L. Der morbus gaucher und die ihm ähnlichen krankheiten (die lipoidzellige splenohepatomegalie typus niemann und die diabetische lipoidzellenhypoplasie der milz). *Ergeb Inn Med Kinderheilkd* 1926; 29:519–627.)

Niikawa-Kuroki Syndrome see **Kabuki syndrome**

Letter O

Omenn syndrome is an autosomal recessive form of severe combined immunodeficiency associated with high mortality. Characteristic symptoms, which may not appear simultaneously, are chronic inflammation of the skin that is seen as a red rash (i.e., early onset erythroderma), eosinophilia, failure to thrive, diarrhea, low immunoglobulin levels (i.e., except immunoglobulin E, which is elevated), low T cell levels, no B cells, lymphadenopathy and hepatosplenomegaly. Most cases known to date have hypomorphic mutations in the *RAG1* and *RAG2* genes (11p13). Additional known cases have mutations in the *RMRP*, *ADA*, *IL2RG*, *IL7RA*, *DCLRE1C*, *CHD7*, and *LIG4* genes (i.e., 9p21-p12, 20q13.11, Xq13, 5p13, 10p, 8q12.2, and 13q22-q34). Prognosis is poor and the disease is fatal if patients are not treated. Skin inflammation progressively deteriorates causing severe lesions and facilitating life-threatening and overwhelming viral, bacterial, and fungal infections in patients who are already immunocompromised. Appropriate treatment increases the survival rate to as high as 80%. **Omenn syndrome** originally was reported as "familial reticuloendotheliosis with eosinophilia" by ***Omenn*** in 1965.

Gilbert Stanley Omenn (Aug 30, 1941–) is a US internist and geneticist. He was born in Chester, Pennsylvania, to a Jewish family as a son of Leonard and Leah (Miller) Omenn. He studied at Princeton University getting his bachelor's degree in 1961, MD degree from Harvard University in Boston in 1965, and PhD degree in genetics from the University of Washington in 1972. Omenn worked in various institutions, including Massachusetts General Hospital in Boston; Harvard University; NIH, Bethesda, MD; University of Washington, Seattle; and Howard Hughes Medical Institute. He was a Professor of Medicine and Environmental Health, Chairman of the Department of Environmental Health, Dean of the University Washington School of Public Health and Community Medicine, Chief Executive Officer of the Health System of the University of Michigan Health Systems, Director of the Center of Biomedical Proteomics, Director of the Center of Computational Medicine and Bioinformatics, Professor of Molecular Medicine

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& Genetics, Professor of Human Genetics, and Professor of Public Healthin the School of Public Health at the University of Michigan in Ann Arbor.

(**Publ**.: Omenn G. Familial reticuloendotheliosis with eosinophilia. *N Engl J Med* 1965; 273:427–432.)

Oppenheim-Urbach disease (**Oppenheim-Urbach syndrome**, **Urbach's syndrome**) is a rare skin disease usually observed in diabetic patients (80–90%) and prevalent in females. It also has called necrobiosis lipoidica, skin delipidation, and necrobiosis lipoidica diabeticorum. This is a chronic granulomatous disease. The most common cause of **Oppenheim-Urbach disease** is diabetes mellitus (75%). The lesions are multiple red or yellowish papules 1–3 mm in diameter, which develop into round or oval scleroderma-like plaques with a cellophane-like surface. Ulceration of the lesion is frequent and seen on the most commonly affects lower limbs, as well as the trunk, palms, soles, and forearms. Granuloma is formed because of the defective neutrophil migration. Histologically, the collagen fibers are pale and absent in zones of necrobiosis, suggesting the replacement of collagen fibers by neutral fat. Liver and spleen may be enlarged in both forms. An immunologically mediated vascular disease has been suggested as the primary cause of the altered collagen. Deposits of fibrin, IgM, and complement-component C3 at the dermoepidermal junction of blood vessels has been shown in immunofluorescence studies.

The condition initially was described in 1929 by ***Oppehhein***, who called it dermatitis atrophicans lipoidica diabetica; in 1932, however, the disease was renamed by ***Urbach***—necrobiosis lipoidica diabeticorum.

Moriz (***Moritz***, ***Maurice***) ***Oppenheim*** (Jan 1, 1876–Oct 27, 1949) was an Austrian-American dermatologist. He was born in Vienna to the Jewish family of Carl Oppenheim and Regine Steiner Oppenheim. He received his medical training at the School of Medicine of the University of Vienna and graduated in 1899. He joined the University of Vienna dermatology clinic in 1902, working under ***Isidor Neumann***. In 1906, working with Rudolf Müller, he developed a complement fixation test for the gonococcus. Oppenheim was habilitated in 1906, became Titular Professor in 1915, and Extraordinary Professor of Dermatology in 1926. From 1918 on, he was the head of the skin department at the Hospital of the City of Vienna. He published several well-known textbooks on venereal disease and skin disorders. Oppenheim characterized necrobiosis lipoidica diabeticorum in 1932.

Oppenheim and his colleague ***Erich Urbach*** were Jews, and both had to escape Nazi Austria before the war. In 1938, he was compelled to leave Vienna and, after short stays in Paris, London, and New York, settled in Chicago, where he was appointed Chairman of the Department of Dermatology and Syphilology of the Chicago Medical School.

He was an honorary member of the following: Minnesota Dermatologic Society, London Dermatologic Society, Austrian Dermatologic Society, Spanish Academy of Dermatology, and Syphilology, College of Physicians of Vienna, French Dermatological Society, Argentina Association of Dermatology, Dermatologic Society of Berlin, Hungarian Dermatologic Society, as well as other professional

organizations. Oppenheim received numerous medals and citations for scientific discoveries. He published more than 300 articles and 7 books. He was an excellent debater and fought hard for his opinions, and, although his aggressiveness was often misunderstood by his opponents, he never meant offense. He died of coronary disease while asleep.

Erich Urbach see **Königstein-Urbach reaction**

(**Publ**.: Oppenheirn M. Eigentumlich disseminierte degeneration des bindegewebes der haut bie einem Diabetiker *Z Hautkr* 1929–1930; 32:179.

Urbach E. Beitrage zu einer physiologischin und pathologischen chemri der hant: Eine neue diabetische stoffwechsel dermatose, nekrobosis lipoidica diabeticorum. *Arch Dermatol Syph* 1932; 166:273–285.)

Ormond's disease (**Ormond disease**, **Gerota's syndrome**, **Albarran-Ormond syndrome**, retroperitoneal fibrosis) is a condition that has been described previously as chronic periaortitis. It is an uncommon fibrotic reaction in the retroperitoneum that typically presents with ureteral obstruction. The disease is part of a spectrum of entities that have a common pathogenetic process consisting of an inflammatory response to advanced atherosclerosis of the abdominal aorta, combined with autoimmune mechanisms. Currently, **Ormond disease** is considered part of a recently defined group of diseases known as IgG4-related ones.

IgG4-related diseases are chronic inflammatory disorders characterized by various organ- or tissue-infiltration leukocytes and IgG4-secreting plasma cells, several levels of fibrosis (scarring), and a rapid response to oral steroids. Without treatment, inflammation-associated fibrosis and deposition of connective tissue can cause organ dysfunction, or even organ failure.

Early casuistic descriptions were provided by ***Albarran*** in 1905, Oberling in 1925, Bachrach in 1928, Putschar in 1934, and Diekow in 1942. ***John Ormond*** rediscovered it in 1948 when he recognized the clinical and pathological entity of idiopathic retroperitoneal fibrosis working on 2 patients with diffuse fibrosis of the retroperitoneal tissues. Seventeen years later, he suggested that this is a systemic disease from the same group that includes lupus, scleroderma, and periarteritis. In his 1965 review, Ormond mentioned that at the time of reporting his 2 cases, he could not find similar cases in the literature. He stated that later, however, he saw papers citing 3 cases described by Albarran in the early 1900s; when he read those reports Ormond agreed that they probably represent the early cases of idiopathic retroperitoneal fibrosis.

Joaquin Maria Albarran y Dominguez (Aug 22, 1860–Jan 17, 1912) was a Cuban urologist. He was born in Sagua-Grande in Cuba. He studied in Havana and Barcelona, received his degree in 1877, then went to Paris to continue his education and stayed in France. During a cholera epidemic in Spain, he joined a scientific mission to Barcelona to prevent spread of infection and to treat people. During his internship in 1884, together with Halle, he discovered the *Bacillus pyogenes*, later named *Bacterium coli*. In 1888 and 1889, he was awarded the medal for surgery, a

faculty prize, and his doctorate degree. He became a chief of the Clinic for Diseases of the Urological Tract in 1890, Professor in 1892, and in 1906 became a Director of the Clinic of Urology at the Hospital Necker.

Albarran was the first in France to perform perineal prostatectomy and made catheterization of the ureter common, which he simplified. He was able to improve cystoscopy by introducing the so-called Alberran's lever—a maneuver for refining movement of the cystoscope during cauterization. He died in Paris.

Dimitrie D. Gerota (Jul 17, 1867–Mar 5, 1939) was a Romanian anatomist and surgeon. He was born in Craiova, the son of a priest (deacon), Dimitrie Constantin Gerota and of Maria Gerota. He obtained his doctorate in Bucharest in 1892 and was trained in topographical anatomy, finishing examination in 1900. From 1913 on, he was a Professor of Surgical Anatomy and Experimental Surgery and also a Professor at the Art Academy in Bucharest. He was the first radiologist in his country in 1898, where he was appointed head of the radiology laboratory of Coltea Hospital, which had just been established. Gerota was the first Romanian doctor severely affected by X-rays as a result of occupational exposure, suffering a radiodermatitis of the hands and was diagnosed subsequently with an epithelioma that required a hand amputation.

Gerota was a member of the Romanian Academy. He was a well-known surgeon with an outstanding reputation. He established the Bucharest Emergency-Care Hospital, now named the "Prof. Dr. Dimitrie Gerota Military Hospital." In 1935, he officially criticized King Carol II, whose controversial reign eventually gave rise to a monarchical dictatorship. Gerota was immediately arrested and guided to Malmaison Prison in Bucharest. Nonetheless, within 4 days he was liberated after widespread protests of medical students. In 1936, he was arrested a second time and sent to Jilava Prison. After sentencing he died in Bucharest.

John Kelso Ormond (Mar 25, 1886–Feb 25, 1978) was a US urologist. He was born in in Armstrong County, Pennsylvania. He was one of 6 children born to Alexander Thomas Ormond, Professor of Mental and Moral Philosophy at the State University in Minnesota and later at Princeton, and Mary Huston (born Simons). John Ormond married Charlotte. They had 3 children and lived in Flint, MI. He was in charge of the Department of Urology at a Detroit hospital for many years. From 1952–1955, he worked in a urology department in a medical centre in India. He later engaged in private practice. He died in Ann Arbor, MI.

(**Publ**.: Albarran J. Retention renale par periure'te'rite´. Liberation externe de l'uretere. *Assoc Fr Urol* 1905; 9:511.

Ormond JK. Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process. *J Urol* 1948; 59(6):1072–1079.

Gerota D. Zur Technik der Lymphgefassinjection. Ein neue Injections-masse für Lymphgefässe. Polychrome Injection. *Anat Anz Berlin XII* 1896; 8:216–224.)

Osler's disease see **Vaquez' disease**

Osler-Libman-Sacks syndrome see **Libman-Sacks syndrome**

Osler's nodes are raised tender nodules on the pulps of fingertips or toes, an autoimmune vasculitis that is suggestive of subacute bacterial endocarditis. They are associated with a number of conditions, including infective endocarditis, and are caused by immune-complex deposition. The resulting inflammatory response leads to swelling, redness, and pain that characterize these lesions. They are named after ***Sir William Osler*** who described them in the early twentieth century.

William Osler see **Osler's triad**

Osler's triad is the association of pneumonia, endocarditis, and meningitis.

William Osler (***Sir William Osler, Baronet***) (Jul 12, 1849–Dec 29, 1919) was a Canadian physician, born in Bond Head, Tecumseth, Canada. His father, the Reverend Featherstone Osler, came to Canada as an Anglican missionary with his wife Ellen. William was the youngest of the 9 children. He, like his father, planned his career in religion, but found a book of Sir Thomas Browne's, *Religio Medici* (1643), and developed an interest in natural history. He studied arts at Trinity College in Toronto, but in 1868 switched to the Toronto Medical School. He then studied at McGill University in Montreal and obtained his medical degree in 1872. Then, for 2 years, he visited medical centers in London, Vienna, Berlin, and Leipzig. After returning, Osler opened his general practice in Dundas, Ontario, but soon was invited as a lecturer at the McGill University Medical Institute in Montreal. He taught physiology, pathology, and medicine, becoming a professor in 1875. He was also a pathologist and physician at the Montreal General Hospital.

In 1884, Osler became a chair of clinical medicine at the University of Pennsylvania in Philadelphia. In 1888, he moved to the new Johns Hopkins University Medical School in Baltimore as the first Professor of Medicine. For his first several years, there were no students at Johns Hopkins, and Osler worked on his book *The Principles and Practice of Medicine*, which he published in 1892. It became a popular medical textbook and helped Osler establish himself as the most outstanding medical educator of his time. In 1897, the book was read in its entirety by Frederick T. Gates, the philanthropist and businessman, after reading a book inspired John D. Rockefeller; it was intended to be used to focus Rockefeller's foundation on medical research and to establish the Rockefeller Institute of Medical Research in New York.

In 1904, while visiting England, Osler was invited to take the Regius Chair of Medicine at the University of Oxford, which was a Crown appointment for which only Crown citizens were eligible. Osler qualified because he had kept his Canadian nationality. Osler mainly was responsible for establishing the Association of Physicians of Great Britain and Ireland, and the *Quarterly Journal of Medicine*. In many ways Osler was able to combine the best of German and English medicine, and thus supported the eventual shift of the center of progress in medical science to the US. William Osler died following bronchopneumonia and empyema in Oxford and was buried in a chapel at Christ Church, Oxford.

(**Publ**.: Osler W. Chronic infectious endocarditis. *Quart J Med* (Oxford) 1909; 2(2):219–230.)

Osler-Vaquez disease see **Vaquez' disease**

Ouchterlony double immunodiffusion (**Ouchterlony method**, agar gel immunodiffusion, passive double immunodiffusion) is an immunological technique used in the detection, identification, and quantification of antibodies and antigens (e.g., immunoglobulins and extractable nuclear antigens). The technique involves preparing small holes in the agarose layer that is hardened in a glass plate or dish. The wells are loaded with solutions of antibody or antigen. During dish incubation, antigen and antibody diffuse through the agarose toward each other from the loaded holes and create the so-called precipitin line when they bind and form immune complexes.

There are 2 types of immunodiffusion reactions commonly used to assess the presence or relative concentrations or purity of antibodies or antigens and to compare antigen or antibody preparations. They are radial immunodiffusion or the **Mancini method** and double immunodiffusion or the **Ouchterlony method**. The Ouchterlony technique is one of the simplest developed and widely used to check sera for the presence of antibodies for a specific antigen and to establish antibody titer. The procedure is called "double" because antigen and antibody are allowed to migrate toward each other in an agar gel. A line of precipitation is highly specific because it is formed where the 2 reactants meet. The method is still in use today for research purposes and for medical laboratory diagnosis for protein detection—comparing antigens or antisera and assessing the presence of autoantibodies in patient serum. The technique is named for ***Örjan Ouchterlony*** who developed the test in 1948.

Örjan Thomas Gunnarsson Ouchterlony (Jan 14, 1914–Sept 25, 2004) was a Swedish bacteriologist and immunologist. He was born in Johannes, Stockholm. He completed his medical studies in 1942 at the Karolinska Institute, married Marianne Schröder in the same year, and had 6 sons. He then worked at the Statens Bakteriologiska Laboratory. He was a Professor of Bacteriology at the University of Gothenburg from 1952–1980 and was elected a member of the Royal Swedish Academy of Sciences in 1968. He died in Kungälv, Sweden.

(**Publ**.: Ouchterlony O. In vitro method for testing the toxin-producing capacity of diphtheria bacteria. *Acta Pathol Microbio Scand* 1948; 25(1–2):186–191.

Ouchterlony Ö. Antigen-antibody reactions in gels. *Acta Pathol Microbiol Scand* 1949; 26(4):507–515.

Ouchterlony O. Antigen-antibody reactions in gels. IV. Types of reactions in coordinated systems of diffusion. *Acta Pathol Microbiol Scand* 1953; 32:230–240.)

Letter P



Pappenheimer bodies are abnormal granules in red blood cells. They are basophilic inclusions that are usually seen at the periphery of the cell. They contain iron in ferritin aggregates and can be visualized with Prussian blue staining. They also stain with **Romanowsky stains** as a result of coprecipitation of clumps of ribosomes with the iron-containing organelles. These differ from **Howell-Jolly bodies** in that they are usually not round, tend to be clustered, and are smaller. Pappenheimer bodies can be seen in sideroblastic anemia and hemolytic anemia. They are cleared by the spleen explaining why splenectomy is connected with a rise in **Pappenheimer bodies**. Cells containing these bodies cannot be easily distinguished from late reticulocytes, but Prussian blue stain, which is not picked up by reticulocytes, is helpful in differentiating the two.

In 1945, ***Pappenheimer*** et al. described 3 patients whose red blood cells, after splenectomy, showed inclusions when stained with Giemsa or Wright stain. Siderotic granules in erythrocytes, however, have been described prior to Pappenheimer's paper. Gruneberg identified Prussian blue-positive inclusions in erythrocytes of human fetuses and splenectomies patients (Gruneberg, 1941). He introduced the term "siderocyte" for these red cells with Prussian blue-staining granules. Otto and Rezek described these unusual inclusions in a splenectomies patient and decided that they were *Bartonella* organisms (Otto and Rezek, 1943), but Pappenheimer et al. reviewed material from their patient and found that the granules are stained for iron. None of these early reports, except Pappenheimer et al., observed the granules on Wright- or Giemsa-stained blood smears. McFadzean and Davis, still complaining that they had "no desire to add yet another eponym to medical literature," stated that the inclusions should be termed "Pappenheimer bodies" (McFadzean and Davis, 1947).

Alwin Max Pappenheimer (Dec 4, 1877–1955) was born in New York City to Max and Henriette Pappenheimer of Jewish heritage ("Who's Who in American Jewry, 1938"). Alwin graduated from Harvard in 1898 and passed his doctor's

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examination at Columbia University College of Physicians and Surgeons in 1902. After spending a 2-year internship at Bellevue Hospital, he received a position of an assistant in pathology there. In 1910, he moved to the Department of Pathology at Columbia and stayed there until his retirement in 1945. He was in the army during World War I. Even after retirement, he continued his research projects, working as a volunteer at Harvard and Boston Children's Hospital until his death. He published more than 150 papers on various subjects: from studies on the thymus gland structure to studies on trench fever (*Bartonella quintana* infection that is spread by the body louse). He was an excellent teacher and an experienced microscopist. His paper on "Pappenheimer bodies," published in the year of his retirement when he was 66 years old, was his only report on red blood cells.

Pappenheimer married Beatrice Leo in New York, NY, in 1907 and had a daughter and 2 sons. All 3 children pursued careers in science and all became professors at Harvard University. The eldest child of Alwin Max, "Pap" Pappenheimer Jr., received his PhD in organic chemistry and worked on diphtheria toxin. He isolated, crystallized, and characterized it in the late 1930s and after World War II studied the immunological responses of adults to immunization with diphtheria toxoid, which resulted in a series of seminal contributions covering fundamental aspects of antigen–antibody reactions and mechanisms of delayed-type hypersensitivity. He was the 38th president of the American Association of Immunologists, serving from 1954–1955.

(**Publ**.: Pappenheimer AM, Thompson WP, Parker D, Smith KE. Unidentified inclusions within the erythrocytes in certain gases of febrile anemia. *Exp Biol Med* 1944; 56(2):145–148.

Pappenheimer AM, Thompson WP, Parker DD, Smith KE. Anaemia associated with unidentified erythrocytic inclusions, after splenectomy. *Q J Med* 1945; 14:75–100.)

Parry's disease see **Graves's disease**

Parry-Romberg syndrome (**Romberg syndrome**, progressive facial hemiatrophy) is a rare, acquired disorder characterized by gradually progressive atrophy of the skin and soft tissues of half of the face (i.e., hemifacial atrophy) and, in rare cases, both sides of the face. The severity is highly variable from patient to patient. Additional symptoms may include neurological abnormalities or abnormalities of the eyes or teeth. Parry-Romberg syndrome usually is misleading during the first decade of life.

The exact cause of **Parry-Romberg syndrome** is unknown. Detection of circulating serum antinuclear antibodies (ANA) in patients with Romberg syndrome, however, supports the concept that this syndrome may be a variant of localized scleroderma—an autoimmune disease. One theory is that inflammation in the nerves innervating skin and fat causes an autoimmune reaction.

The disease was described initially by ***Caleb Parry*** in 1825 in a series of his medical notes published by his son Charles Henry Parry after Caleb Parry death.

The disease was described again by ***Moritz Romberg*** and ***Eduard Heinrich Henoch*** in 1846. German neurologist Albert Eulenburg was the first to introduce the descriptive title "progressive hemifacial atrophy" in 1871 (Eulenburg, 1871).

Caleb Hillier Parry (Oct 21, 1755–Mar 9, 1822) was an English physician. He was born at Cirencester, a town west of London, and studied medicine in Edinburgh and London and after graduation with an MD in 1778 he was admitted licentiate of the Royal College of Physicians of London. He married Sarah Rigby the same year and they had 4 sons and 5 daughters. In 1779, he became a physician at Bath General Hospital, Somerset, where he remained for the rest of his life. In 1800, Parry was elected a Fellow of the Royal Society. In 1816, he suffered a stroke, which paralyzed the right side of his body and impaired his speech. After that, he could only read, dictate memoirs, and monitored his farm and garden. He worked on improvement of local agriculture at his farm near Bath. He also was devoted in introducing the merino sheep breed into the UK.

Parry habitually noted down case histories. Using these notes, he published *Elements of Pathology* in 1815 before he became disabled. Parry was buried in Bath Abbey, where there is a monument to his memory that was commissioned by the medical authorities of Bath.

Moritz Heinrich Romberg (Nov 11, 1795–Jun 16, 1873) was a Jewish physician from Berlin who published his classic textbook in sections between 1840 and 1846; they were translated into English in 1853. His nephew was ***Eduard Heinrich Henoch***, who was known for describing **Henoch-Schönlein purpura**.

Moritz Romberg was born in Meiningen, Saxony, and graduated with an MD from the University of Berlin in 1817. In 1820, he was named physician to the poor. Ten years later, he was admitted to the university as "Privatdozent" working on pathology, therapy, and clinical neurology. During the cholera epidemics, he also worked unselfishly in charge of the hospitals in Berlin. In 1840, he was given responsibility for the university dispensary. In 1845, he was elected Professor and Chair of Special Pathology and Therapy and attained a directorship of the Royal Policlinic. He resigned his medical officer position for the poor. In 1851, he was given the status of "Geheime Medizinalrath" (Medical Counsel). He retired in 1867 and died from chronic heart disease in Berlin at the age of 78.

Romberg was the first physician who paid special attention to neurological changes associated with disease manifestations. He taught at the "propaedeutic (or educational) clinic," announcing practical demonstrations and stressing the necessity of a comprehensive physical examination for a correct diagnosis. In his medical courses and classes, Romberg demonstrated with patients from his private and indigent practice. He was a very popular, well-recognized, and highly appreciated teacher known for building professional relationships with his students.

Romberg's main clinical contributions include: a characteristic description of achondroplasia (i.e., disproportionate dwarfism) in his graduation thesis "Congenital rickets" in 1817, progressive facial hemiatrophy, and a distinct picture of the pupillary presentation found in patients with tertiary syphilis. The pupil in tertiary syphilis was rediscovered in the mid-1860s by Douglas Argyll Robertson, a Scottish

ophthalmologist and surgeon. Romberg defined what is now generally recognized as "Romberg's sign" in his original account of *tabes dorsalis* (i.e., a late consequence of neurosyphilis by damage to the back of the spinal cord).

Romberg was one of the really groundbreaking neurologists in Europe who introduced the importance of clinical observation and created neurology as a discipline. He revolutionized European neurology, publishing his *Lehrbuch der Nervenkrankheiten des Menschen*—the first systematic textbook in neurology. He is credited with having been "the first clinical neurologist." In fact, in 1863, Fyodor Dostoevsky, one of the most influential Russian writers, consulted him for his epilepsy.

(**Publ**.: Parry CH, ed. *Collections from the Unpublished Medical Writings of the Late Caleb Hillier Parry*, M.D., F.R.S. 1. London: Underwoods; 1825; pp. 478–480.

Romberg MH, Henoch EH. Krankheiten des Nervensystems (IV: Trophoneurosen). Klinische Ergebnisse (in German). Berlin: Albert Förstner; 1846; pp. 75–81.)

Parsonage-Turner syndrome (brachial neuritis, neurologic amyotrophy) is a rare neurological autoimmune disease characterized by typically quite sudden and rapid progress of severe shoulder and arm pain followed by muscular atrophy in the affected areas. In addition to the motor consequences, there may be sensory losses.

The etiology is unclear, although localized infectious or immunological process is suspected. Believed triggers include viral and bacterial infections, parasitic infections, surgery, vaccinations, injury, childbirth, vigorous exercise, and different health conditions. Although traditionally not considered an autoimmune disease, immunological or inflammatory pathways are generally believed to contribute to the manifestation of **Parsonage-Turner syndrome**. Interestingly, HIV and Lyme disease may cause similar symptoms as Parsonage-Turner syndrome. Immune mediated mechanisms may explain the incidence of attacks but do not clarify why some individuals are predisposed to neuralgic amyotrophy. Evidence suggests that the syndrome is a disorder with mixed pathophysiological mechanisms when autoimmune, genetic and environmental factors all seem to play an interconnected role.

The syndrome is named after British neurologists ***Maurice Parsonage*** and ***John Turner*** who described 136 cases in a 1948. Although the first record of this syndrome date from 1887, described by Dreschfeld, it was 'classically' depicted in 1943 by Spillane. However, the clinical characteristics of this syndrome were only fully presented in 1948 by Parsonage and Turner. They named it "scapular belt syndrome".

Maurice John Parsonage (Apr 19, 1915-Dec 5, 2008) was a British neurologist. He was born in Nantwich, Cheshire, England, to John Hodson Parsonage, a dental surgeon, and Florence Sophie Parsonage née Martin. He earned a BSc degree from Victoria University Manchester in 1936 and studied medicine in Manchester. He then worked as a house physician at Manchester Royal Infirmary and an assistant medical officer at Booth Hall Hospital for Children in Manchester. During WWII he served in the Royal Army Medical Corps in the UK, India and Southeast Asia as a specialist in neurology and general medicine and was demobilized with the rank of lieutenant colonel.

After the war Parsonage continued his training in neurology in the department for nervous diseases at Guy's Hospital, where he published his paper on neuralgic amyotrophy, now known as Parsonage-Turner syndrome. From 1948 he worked in the department of applied electrophysiology at the National Hospital, Queen Square. From 1951 he was a consultant neurologist in Leeds. Then he directed the neuropsychiatric unit at Bootham Park Hospital in York, where he established a center for epilepsy for the north of England. He was also a founder trustee of the British Epilepsy Research Foundation. He was also a member of the Royal College Surgeons, Electroencephalographic Society Great Britain, Association British Neurologists, International League Against Epilepsy and British Epilepsy Association.

Parsonage's research and clinical interests focused on epilepsy: classification, neurophysiology, neuropharmacology and psychological aspects of the disease. In addition to his clinical and research interests, Parsonage enjoyed reading historical biographies, photography, music and play cricket, badminton and tennis.

John William Aldren Turner (Feb 13, 1911 - Oct 12, 1980) was a British neurologist. He was born in London where his father was a neurologist in King's College Hospital and the National Hospital. He got his education at Clifton and New College where he focused on anatomy and pathology and graduated in 1935. Then he was a physician at the National Hospital and Hurstwood Park Hospital. In 1942, he joined the Royal Army Medical Corps becoming command neurologist to the Northern Command at York and Western Command at Chester, then adviser in neurology to Southern Command, India, with the rank of lieutenant colonel. After WWII, Turner joined the staff of St Bartholomew's Hospital.

Turner's academic activities were abandoned by a serious illness, partial gastrectomy and numerous complications. He developed neurologic amyotrophy, a disease he named and studied. Although he made a satisfactory recovery, he was unable to continue his busy clinical and research activities. One of his hobbies was a study of the behavior of racehorses.

(**Publ**.: Parsonage MJ, Turner JW. Neuralgic amyotrophy; the shoulder-girdle syndrome. *Lancet* 1948; 1(6513):973-978.Spillane JD. Localised neuritis of the shoulder girdle. *Lancet*, London, 1943; 2:532-535.)

Paul-Bunnell antigen. This is a heterophile antibody that agglutinates or hemolyzes erythrocytes of some animals (e.g., sheep, ox, horse, and goat) that arise in patients with infectious mononucleosis. After the names of its discoverers, it is referred to as the Paul-Bunnell antigen. The antigen is present in humans only in trace amounts but may increase in certain neoplastic and inflammatory diseases. The Paul-Bunnell antigen was isolated from bovine erythrocytes and has been characterized as a sialoglycoprotein. See **Paul-Bunnell test** for an explanation.

Paul-Bunnell test (**Paul-Bunnel reaction**) is a method of testing for the presence of heterophile antibodies (see **Forssman antigen**) in the blood for the diagnosis of infectious mononucleosis, based on the agglutination of sheep erythrocytes by

the inactivated serum of patients with the disease. Serological testing for mononucleosis is based on the original results of studies by ***Paul*** and ***Bunnell*** on heterophile antibodies. Heterophile antibodies are antibodies that cross-react with similar antigens found in unrelated animals or microorganisms. These antigens (heterophile antigens, **Paul-Bunnell antigens**) are so similar that they cross-react with antibodies from several species. Paul and Bunnell described that patients with infectious mononucleosis produce heterophile antibodies that could agglutinate red blood cells from sheep and horses. ***Davidsohn*** improved the original **Paul-Bunnell test** by including an additional step. He introduced removal by absorption of cross-reacting **Forssman antibodies** and serum sickness antibodies allowing an improved interaction of the infectious mononucleosis heterophile antibody with sheep erythrocytes. The adaptation of the test, the **Davidsohn differential test**, became the gold-standard reference method for laboratory diagnosis of infectious mononucleosis.

Heterophile or **Paul-Bunnell antibodies** of infectious mononucleosis were discovered in 1932 and, ever since, serodiagnosis of it has been based primarily on detection of these antibodies in patients' sera. Thus, in the Paul-Bunnell test, sheep red blood cells agglutinate in the presence of heterophile antibodies. With the Monospot test, horse red blood cells agglutinate on exposure to heterophile antibodies. The Monospot uses this in conjunction with the principle of the Davidsohn differential test.

The significant historical aspect of the Paul-Bunnell assay is that the presence of a heterophile antibody served as the most reliable laboratory marker of this disease for 4 decades, until the Epstein-Barr virus was shown to be the etiologic agent of infectious mononucleosis. Paul and Bunnell recognized that their test might have some diagnostic value, but they reasoned that the test would be of a more theoretical than of a practical value. In this they were mistaken, because, over the years, the test has taken on a huge practical value in confirming the diagnosis of infectious mononucleosis and excluding other possible diagnoses (e.g., lymphatic leukemia).

John Rodman Paul (Apr 18, 1893–May 6, 1971) was a US physician. He was born in Chestnut Hill, Philadelphia, PA, the son of Henry N. Paul and the former Margaret C. Butler. He received his MD degree from Johns Hopkins Medical School in 1919. He then worked as an assistant pathologist at Johns Hopkins (1919–1920) and did his internship at the Pennsylvania Hospital in Philadelphia (1920–1922). In 1922, he married Miss Mary Leita Harlan. Paul was a member of the Yale School of Medicine faculty from 1928 until his retirement in 1961. He was a Professor Emeritus of Epidemiology and Preventive Medicine. Paul was awarded an honorary MA degree by Yale in 1940 and an honorary DSc degree by the University of Chicago in 1956. After his retirement, he continued as a lecturer on the history and science of medicine.

Paul was a leading researcher in the field of poliomyelitis and other microbial diseases. Working on familial rheumatic fever, he identified a streptococcus infection as the origin of the disease. In 1930, he published a large and comprehensive analysis of the epidemiology of rheumatic fever. In 1932, together with Bunnell, he

developed a laboratory test for infectious mononucleosis, which was based on their original finding of serum heterophile antibodies in people with this infection.

In 1956, he was in a group of 5 US clinical scientists who visited the Soviet Union to learn about the Russian healthcare system, vaccination programs, medical facilities, and biomedical research and teaching. Paul published a very interesting paper, "American Medical Mission to the Soviet Union," in *The Scientific Monthly* (Sept 1957; 85(3):150–156) describing their visit, its organization, and its results.

Paul was a member of many professional societies and received many awards and honors, including the Howard T. Rickets award, the United States Medal of Freedom, the Charles V. Chapin Award, and the Kober Medal of the American Association of American Physicians.

Walls Willard Bunnell (Jan 3, 1902–Apr 8, 1965) was a US physician. He was born to Willard Maine Bunnell and Margaret Irene Walls in Scranton, Lackawanna County, PA. He graduated from Yale in 1929. He practiced medicine in Farmington, CT for 30 years. He died in Hartford, CT.

(**Publ**.: Paul JR, Bunnell WW. The presence of heterophil antibodies in infectious mononucleosis. *Am J Med Sci* 1932; 183:91–104.

Bunnell WW. A diagnostic test for infectious mononucleosis. *Am J Med Sci* 1933; 186:346–353.)

Paul-Bunnell-Davidsohn test see **Davidsohn Differential test**

Pautrier's microabscess see **Sezary cells**

Pelger-Huët anomaly is an autosomal-dominant disorder characterized by abnormal nuclear shape and chromatin organization in blood granulocytes but is most evident in polymorphonuclear neutrophils. There are 3 forms of the Pelger-Huët anomaly: a benign hereditary disorder—an acquired anomaly and a drug-induced anomaly. This inherited anomaly of granulocytes is characterized by the presence of round, oval, peanut-shaped, or symmetric bilobed nuclei and abnormally clumped chromatin. Despite these structural abnormalities, however, function of granulocyte remains unchanged as detected in various functional tests (e.g., neutrophilic chemotaxis, phagocytosis, and cellular cytolytic activity). Therefore, patients with genetic Pelger-Huët anomaly do not demonstrate any predispositions to bacterial infections. The **Pelger-Huët anomaly** is caused by a decreased amount of the lamin B receptor (LBR). Abnormalities in the sequence of the *LBR* gene on chromosome 1q41–43 result in a lack of LBR protein that is essential for chromatin-binding to the nuclear membrane. LBR protein deficiency results in abnormal bilobular or monolobular nuclear forms and hypercondensed chromatin aggregation in affected neutrophils. Analysis of the cellular distribution of Pelger-Huet anomaly has shown that chromatin-hypercondensation also may be detected in lymphocytes, plasma cells, erythroblasts, monocytes, basophils, and eosinophils. Interestingly, 30% of megakaryocytes also were binucleated in patients with Pelger-Huet anomaly.

Karel Pelger described abnormal "short and compact" neutrophils in 1928 in 2 patients with disseminated tuberculosis. He suggested that the anomaly correlated with a bad prognosis because both patients died. But Pelger's assumptions were disproved by ***G. J. Huët*** in 1932; he identified the "Pelger anomaly" in a 7-year-old girl with tuberculosis who soon recovered. Her follow-up showed that hypolobulated neutrophils continued to be present. The "Pelger anomaly" was revealed in several of the girl's relatives, including her aunt who was one of the patients initially reported on by Pelger. Huët decided that the abnormal morphology of polymorphonuclear leukocytes, named the Pelger-Huët anomaly later, was an innocuous autosomal-dominant inherited trait rather than a developed pathology associated with tuberculosis infection.

Karel Pelger (Apr 14, 1885–1931) was a Dutch physician and tuberculosis specialist with a practice in Amsterdam. He was born at Nijeveen near Meppel, Netherlands; graduated from the University of Groningen; and started his general practice in Amsterdam. He was later trained in hematology in Berlin and was affiliated with the Department of Medicine at the University of Amsterdam. In 1914, he married Emma Pelger-Morel, and they had a son. His family life was happy and they preferred livin in the country at his farm in Havelte, Overijssel. His textbook on clinical hematology was not finished because of his sudden death on his farm at the age of 47.

Gauthier Jean Huët (Nov 23, 1879–Dec 13, 1970) was a Dutch pediatrician. He was born in Amersfoort, Netherlands, graduated in medicine from the University of Leiden, and received his doctorate degree in 1907 after studying sepsis. For almost 50 years he had a position of superintendent at Hoog-Blaricum Sanatorium for Children. Although Huët did not have any academic appointments, he published many papers and was elected president of the Dutch Pediatric Association. He died in Bussum, Holland, at the age of 91.

(**Publ**.: Pelger K. Demonstratie van een paar zeldzaam voorkomende typen van bloedlichaampjes en bespreking der patiënten. *Ned Tijdschr Geneeskd* 1928; 72:1178.

Huët GJ. Familiaire anomalie der leucocyten. *Ned Tijdschr Geneeskd* 1931; 75:5956–5959.

Huët GJ. Uber eine bisher unbekannte familiare anomalie der leukocyten. *Klin Wochenschr* 1932; 2:1264–1266).

Petri dish (**Petrie dish**, **Petri plate**, cell-culture dish) is a shallow flat-bottomed transparent cylindrical glass or plastic lidded dish that is used to culture cells. Petri dishes often are used to make agar plates for microbiology studies—for example, to grow fungi, bacteria, and other microorganisms. When used, the dish is partially filled with warm liquid containing agar and a mixture of specific ingredients or antibiotics. Once the agar cools and solidifies, the dish is ready to be inoculated with a microbe-laden sample. Petri dishes are also commonly used for eukaryotic cell culture in liquid media in various immunological and oncological studies to grow immune cells and tumor cell lines and to study their interactions.

The "classic" diameter is 90 mm. The diameter of **Petri dishes,** however, usually varies from 30 to 140 mm, and now even 100 mm square Petri dishes are available in both compartmentalized and noncompartmentalized formats. Special Petri dishes also may vary in color.

They are named after ***Julius Petri***, who invented them when he was a military physician working in bacteriologist ***Robert Koch***'s lab at Berlin University in Germany during the 1880s. One method in the Koch laboratory was associated with bacterial cultures on agar plates. The original methodology of microorganism growth was to decant the agar into a glass dish and cover it with a bell jar. This procedure, however, required cover removal prior to microscopic evaluation of the agar, which resulted in culture contamination and uncontrolled conditions. Prior to this technique, all cultures of microorganisms were grown in inclined glass tubes. Petri acknowledged the advantage of growing cultures in open dishes rather than tubes, and in 1887, he tested the deceptively simple idea of putting a little larger glass dish on top of the one where bacteria are growing, which acts as a transparent lid. Plus, that was important because not only could he keep contaminants from getting in but also he could slide it under the microscope. This method proved to be far simpler and more reliable than the bell jar. Petri wrote a 300-word paper describing the plating technique in 1887—"Eine kleine modification des Koch's chen plattenverfahrens." Thus, the "**Petri dish**" was born and is still in common use 135 years later.

During the mid-1960s, Petri dishes began to be manufactured from clear polystyrene because of the development of plastic-molding technology. Plastic dishes were bigger than glass the Petri dish, and they were inexpensive because crude oil and its by-products were inexpensive commodities at that time. In 1973, however, the Organization of Petroleum Exporting Countries (OPEC) took advantage of geopolitical and economic controlling of the market, triggering the price of petroleum-based products, including plastic Petri dishes, to increase rapidly. Therefore, Petri dish manufacturers decreased the large size and weight of the dishes to reduce their cost; thus, the 25-g "old" Petri dishes vanished. In the mid-1980s, the marked improvement of the injection-molding process for plastic preparation allowed reducing the weight of the Petri dishes to 15–17 g, making this an industry standard for many years.

Currently, Petri dishes of several standard sizes are made of disposable polystyrene and feature small "lugs" on the lid for a restricted air exchange. The plates are sterilized by gamma radiation or ethylene oxide gas.

Julius Richard Petri (May 31, 1852–Dec 20, 1921) was a German microbiologist. He was born in the German city of Barmen. Following his elementary and high school education, he embarked on training as a physician. Petri first studied medicine at the Kaiser Wilhelm Academy for Military Physicians in 1871–1875 and received his medical degree in 1876. He continued his studies at the Charité Hospital in Berlin and had active duty as a military physician until 1882, continuing then as a reservist. From 1877 to 1879, he was assigned to the Imperial Health Office (*Kaiserliches Gesundheitsamt*) in Berlin, where he became an assistant to ***Robert***

Koch. While in Koch's laboratory, Petri also developed a technique for cloning of bacterial strains on slants of agar formed in test tubes, followed by subculturing of the growth on the Petri dish. This technique is used to this day.

Petri's involvement in bacteriology continued after leaving Koch's laboratory. From 1882 until 1885, he ran the Göbersdorf Sanatorium for tuberculosis patients. In 1886, he assumed the direction of the Museum of Hygiene in Berlin, and in 1889 he returned to the Kaiserliches Gesundheitsamt as a director. In addition to his inventions and innovations, Petri published nearly 150 papers on hygiene and bacteriology. In his subsequent days, he was a rather vain, overweight man, who dressed in the uniform of a chief army doctor whenever the opportunity presented itself. The sash around his protruding abdomen reminded one observer of the equator around the globe. In 1921, Petri died in Zeitz, Germany, but his namesake invention lives on in labs around the world.

Peyer's patches (**Peyer glands**) are aggregated lymphoid nodules or lymphoid follicles, and an important part of gut-associated lymphoid tissue. They can be seen in humans in the lowest portion of the small intestine and have been described in the distal jejunum, ileum, and duodenum. The fetal human small intestine contains in average of 60 Peyer's patches before week 30 of gestation and their number steadily increases, reaching a maximum of 240 at puberty. Peyer's patches are egg-shaped lymphatic nodules structured as the lymph nodes but without a connective tissue capsule around them. Together with the tonsils and lymphatic tissue of the appendix, they represent a type of nonencapsulated lymphatic tissue known as lymphatic nodules.

Histologically, **Peyer's patches** consist of 3 major domains: the follicular, the interfollicular areas, and the follicle-associated epithelium. In mice, Peyer's patches are comprised of an average of 60% B cells, 25% T cells, 10% dendritic cells, and about 5% macrophages or polymorphonuclear neutrophils. Within the $CD3^+$ T-cell population, there are 45% of $CD4^+$, 35% of $CD8^+$, and 20% of $CD4^-/CD8^-$ T cells. Among $CD4^+$ T-helper cells, 85% of them are represented by memory T cells, 10% are naïve, and 5% are regulatory T cells.

The function of Peyer's patches was unknown until 1922, when Kenzaburo Kumagai reported an uptake of *Mycobacterium tuberculosis* inside the epithelial dome of Peyer's patches. Later results have revealed that they form a key component of the immune system that controls intestinal populations of bacteria and blocks the pathogenic microorganism growth in the intestines. Microbial antigens in the gut are endocytosed by microfold or M cells lining the surface of each Peyer's patch and are delivered to the lymphoid tissue. There they are picked up by antigen-presenting cells to induce the development of immune responses.

Peyer's patches are named after ***Johann Conrad Peyer*** who provided their detailed description in 1677. Interestingly, Peyer was a medical student when he made his original discovery. References to these follicular structures sometimes have appeared in the medical literature as places of ulceration or disease. This was until the early twentieth century, when the key role of the lymphatic system, as a fragment of the immune system, was understood and highlighted.

Johann Conrad Peyer (Dec 26, 1653–Feb 29, 1712) was a Swiss anatomist who was a native of Schaffhausen, Switzerland. Born into a patrician family, Peyer studied medicine in Paris and received his medical degree in 1681 at Basel. Later, he returned to Schaffhausen to practice medicine. In the late seventeenth century, Peyer was one of a group of physicians who made important contributions to the methodology of medical research. They sought to explain the symptoms of a disease in terms of the lesion, which was considered the site of the disease. In 1677, Peyer published "Exercitatio anatomico-medica de glandulis intestinorum earumque usu et affectionibus" in which he described the lymphatic nodules and masses located in the walls of the ileum that now bear his name (or sometimes that of Johannes Nicolaus Pechlin who had described them in 1672 in a work on the anatomy of the intestinal tract). Peyer was also the author of an influential work on veterinary medicine titled *Merycologia Sive de Ruminantibus et Ruminatione Commentariae*.

(**Publ**.: Peyer J. Exercitatio anatomico-medica de glandulis intestinorum earumque usu and affectionibus. Cui subjungitur Anatome ventriculi gallinacei; 1677.)

Pick's cells are histiocytes (~20–90 μm diameter) present in the spleen and bone marrow in **Niemann-Pick disease**. A Pick cell is a rounded or polygonal mononuclear one with indistinctly or palely staining, foam-like cytoplasm that contains numerous droplets of a phosphatide—sphingomyelin. Such cells are widely distributed in the spleen and other tissues, especially those rich in reticuloendothelial components. It is similar in appearance to "**Gaucher's cell**" containing phagocytosed material; however, the cytoplasm of the cell appears foamy.

Ludwig Pick see **Niemann-Pick disease**

Pirogov-Langhans' cells (**Langhans' giant cells**) are multinucleated giant cells (fused macrophages) found in granulomatous conditions (e.g., tuberculosis, syphilis, sarcoidosis, and deep fungal infections). They resemble foreign-body giant cells, but Langhans' giant cells contain less chromatin, and their nuclei are arranged peripherally in a horseshoe-shaped pattern. It has been shown that when activated CD4+ T cells and monocytes are in close contact, activation of CD40L/CD40 signaling and IFN-γ secretion by the T cells causes upregulation and secretion of fusion-related molecule DC-STAMP (dendritic cell-specific transmembrane protein) by the monocytes, which results in monocyte fusion. **Langhans' cells** occur frequently in delayed hypersensitivity and are often found in transbronchial lung biopsies or lymph node biopsies of patients suffering from sarcoidosis. These giant cells are named after ***Theodor Langhans*** and ***Nikolay Pirogov***.

Theodor Langhans (Sept 28, 1839–Oct 22, 1915) was a German pathologist. He was born in Usingon (Duchy of Nassau), Germany, as the son of Heinrich Langhans, a judge, and Wilhelmine Stein. He did his gymnasium training in Wiesbaden and then studied medicine in Heidelberg, Göttingen, Berlin, and Wörzburg, where he qualified in 1864 with a thesis on the structure of tendons. He then went to Marburg

for anatomical research and in 1868 described the giant cells in tubercle to which his name has been given. In 1872, he was appointed a professor of pathology in Giessen, then in Bern, where he worked on the histology of the breast and placenta, distribution of glycogen in normal and diseased organs, and described the cellular layer of the chorionic epithelium to which his name has been given. His later years were devoted mainly to studies on the morbid anatomy of goiter and cretinism. He retired from his chair 2 years before death in Bern, Switzerland.

Nikolay (***Nikolai***) ***Ivanovich Pirogov*** (***Pirogoff***, ***Pirogow***) (Nov 13, 1810–Nov 23, 1881) was a Russian scientist, surgeon, educator, and public figure. He was born in Moscow, the 13th child of a middle-class merchant family. Grandpa John Mokiyovych, who had already reached 100, with a smile took the baby in his arms and said, "Lord, have mercy! God bless! …." From an early age, Nikolay showed evidence of exceptional talent. He learned to read in several languages as a young child and received all his education at home. He entered Moscow University at the age of 14 and completed the medical curriculum at 17. In 1828, he entered the Postgraduate International Institute of the Baltic-German University of Dorpat (now Tartu, Estonia). He completed his studies at Dorpat and received his doctorate in 1832 after defending his thesis, and then he went to the Charité University Hospital in Berlin and the University of Göttingen to broaden his knowledge of anatomy and surgery. From 1835 on, Pirogov was a professor of Theoretical, Operational and Clinical Surgery at Dorpat University. He urged and helped students to start and conduct their research projects and mentored 12 scientific theses by students in Dorpat during the period 1836–1841. He continued to actively mentor his students' research studies after moving to Saint Petersburg, where he supervised another 10 dissertations.

One time while visiting the meat market in Saint Petersburg, Pirogov saw a butcher slicing frozen pig corpses and noticed the perfect display of positions of the internal organs. He took advantage of the cold Russian winters, froze cadavers "to the density of the thickest wood" and sliced them into thin platters. This methodology permitted him to prepare a very detailed topographical anatomy of the human body, and it took him 8 years to publish his new anatomical atlas.

In 1847, Russian Tsar Nikolas I sent Pirogov to the Caucasian War (an invasion of the Caucasus by the Russian Empire) to prove the usefulness of the recently uncovered ether-based anesthesia during surgery, which was effectively advocated by Pirogov in Russia. He anesthetized 100 wounded soldiers on the open battlefield; this was the first time ether anesthesia was used in a combat zone. As Pirogov tried to educate other wounded soldiers on the analgesic effect of ether, all surgeries were visible for them. This visual "propaganda" was very successful, and many soldiers began to accept operations fearlessly. Pirogov and his team dealt with more than 2000 firearm injuries, which gave him a chance to analyze the correlation between the velocity of various types of bullets and the appearances of the entry and exit wounds. Therefore, Pirogov can be considered a founder of the scientific methodology used by forensic ballistic pathologists.

During the Crimean War (war between the Russians and the British, French, and Ottoman Turks), Pirogov was appointed by decree of the Tsar as the overall head of the army medical services, something completely new in Russian history. Working with Grand Duchess Elena Pavlovna on her plan to establish a women's aid organization for the sick and wounded on the battlefield, Pirogov initiated the deployment of women to be trained as nurses and surgical assistants. After the war, all nurses who participated continued their nursing work in military hospitals in their home cities. These women created the groundwork for what turned into the Russian Red Cross. Although all medical students and doctors in Russia went into military service during the war, there was a profound shortage of necessary medical staff. The Russian authority had to engage doctors from allied countries, asembling Germans and Americans. About 30 US doctors volunteered to work for the Russian Army that time.

Observations made during the Crimean War deeply affected Pirogov's view on life, turning him toward humanitarian goals and education. Ruled by his liberal beliefs, stubborn personality, intolerance to intrigues and corruption, and the disagreements with the officials, he resigned from the Medical-Surgical Academy in 1856. He committed his life to improving the general and medical education in Russia. He retired to his estate in Vishnya (now Vinnitsa) in Ukraine. In spite of this, Pirogov treated patients locally, and he visited the battlefields and field hospitals during the Franco-Prussian War in 1870 as a representative of the Russian Red Cross. Again, during the Russo-Turkish War he was a field surgeon in 1877.

From 1847 onward, Pirogov was a corresponding member of the Russian Academy of Sciences. In 1881, he was awarded the Honorary Citizen of Moscow. Four years after his death the Pirogov Society was established in Russia with the goal of further improvements in medical education, training, and treatment. In addition to the foot amputation techniques (Pirogov amputation) he developed, several anatomical structures are named after him (e.g., the Pirogov angle, the Pirogov aponeurosis, and the Pirogov triangle).

Pirogov's body was preserved using embalming techniques he himself developed and rests in a church in Vinnitsa, Ukraine, in a specifically designed mausoleum on Pirogov's former estate; it is now a museum dedicated to his life and works. In contrast to the cadaver of Vladimir Lenin in Mausoleum in Moscow, which requires comprehensive weekly maintenance in an underground laboratory, the body of Pirogov rests intact and unchangeable. It resides at room temperature in a glass coffin, while Lenin's body is kept at a steady low temperature.

(**Publ**.: Langhans Th. Über die entzündlichen veränderungen der glomeruli und die akute nephritis. *Virchows Arch Pathol Anat Physiol Klin Med* 1865; 99:183–250.

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Pirogov NI. *Is Ligation of the Abdominal Aorta with an Aneurysm of the Groin a Readily Feasible and Safe Intervention?* [in Latin, German, and Russian]. Dorpat, Livonia: J. C. Schünmann; 1832.

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Pirogov NI. *A Full Course of Applied Anatomy of the Human Body. With Drawings of Pirogov* [in Russian]. Saint Petersburg: Olkhina; 1844.

Pirogov NI. *Broad Guidelines for General War Surgery, According to Reminiscences from the Wars in the Crimea and the Caucasus and from the Hospital Practice* [in German and Russian]. Leipzig: Verlag von F.C.W. Vogel; 1864.)

Pitcairne's disease (**Dalziel disease**, **Chron's disease**) is an orofacial granulomatosis. Maxwell Stuart family (Traquair House) in Edinburgh used the help of Archibald Pitcairne as a family physician. In one particular letter, dated 1703, there is a discussion of Lady Anne, the eldest of the 17 children of Lord Traquair. She was suffering both from a "little of a bloody flux" and an "old swelling on her lip." For both of these symptoms, Pitcairne prescribed cavew (cafew or catechu), the resin extracted from the acacia or uncaria tree that was widely used as an astringent to "stop all sorts of fluxes of the bowels, whether of blood or humours." In addition, it was used as a topical agent to treat oral lesions, ulcers, or a particular condition of a relaxed uvula or sore throat found in delicate females. In the description of the illness of Lady Anne, it is interesting to note the combination of bowel lesions and lip swelling. In 1996, MacFadyen and Ferguson wrote: "If there is need at all for an eponym to describe this condition of chronic granulomatous changes in the mouth and the lower alimentary tract, it would perhaps be more appropriate to suggest that the disorder be credited to ***Archibald Pitcairne***, who more than 200 years before Crohn and his colleagues or even ***Dalziel***, recorded the protean manifestation of this disorder" (MacFadyen and Ferguson, 1996).

Archibald Pitcairne (Dec 25, 1652–Oct 20, 1713) can be regarded as a physician and poet, and the forgotten father of mathematical medicine; he developed the theory of iatromathematics (i.e., medicine and mathematics). He was born in Edinburgh to Alexander Pitcairne, a merchant and magistrate, and his wife Sydserf. He did not follow in his father's footsteps but studied the law in Edinburgh and Paris, graduating with an MA from Edinburgh University in 1671. Although he developed his interest in medicine in France, he returned to study mathematics to take advantage of his unique mathematical talents and capacities. In 1675, he returned to Paris to learn medicine and received his MD degree from the Rheims (Reims) 5 years later. Pitcairne then returned to Edinburgh and opened his private medical practice. He was one of the very first members of the Royal College of Physicians of Edinburgh. He initially recognized the importance of Harvey's work on the nature of the circulation and, although unaware of the existence of capillaries, predicted their presence using a mathematical model.

Pitcairne had an outstanding medical reputation and was one of the most eminent physicians of his time. Based on his interest in mathematics and mechanical theories, he promoted medical science in all instances. His numerous publications were very popular because of their legendary style and power of clearly explanation.

His medical practice was very successful but most of his vast income was spent on charities. In spite of the successful career, he died poor. His library, known as one of the best private book collections at that time, after his death was bought by the Emperor of Russia Peter the Great (Peter I).

Ponfick's shadow see **Traube's corpuscles**

Prausnitz-Küstner antibody (atopic regain, reaginic antibody) is one of the IgE class of antibodies that was first described by passive transfer to the skin. Homocytotropic antibody of the IgE class has an affinity for tissues (notably mast cells) of the same or a closely related species and that, on combining with a specific antigen, triggers the release of anaphylactic mediators from the cells to which it is attached. Reaginic antibodies are found in the serum and skin of allergically hypersensitive individuals and in smaller amounts in the serum of normally sensitive people. Reagins are heat-sensitive, do not cross the placenta, and have a much longer lifespan than other classes of antibodies. Reaginic antibodies can be transferred passively to a second person; thus, blood transfusions from allergic donors occasionally have produced temporary identical allergies in the nonallergic recipient for a short time.

It was not until 1967 that the "reaginic" antibody—the transferable factor responsible for the sensitization phenomenon described by ***Prausnitz*** and ***Küstner*** in 1921—was eventually identified by Kimishige Ishizaka and Teruko Ishizaka (husband and wife) as IgE antibodies in 1967 (Ishizaka et al., 1967).

Carl Prausnitz see **Prausnitz-Küstner reaction**

Heinz Küstner see **Prausnitz-Küstner reaction**

Prausnitz-Küstner reaction (**Prausnitz-Küstner test**) is an immediate hypersensitivity response in a nonatopic individual to the injection of antigen who had received an intradermal injection of antitoxin from an atopic subject 12 hours earlier. Originally, this was the standard method for demonstrating a **reaginic antibody**, but it lost its practicability because of the risk of transmitting hepatitis or HIV infection, so in vitro assays to measure serum immunoglobulin E were developed. Thus, the **Prausnitz-Küstner test** is an immunologic test formerly used to demonstrate whether a patient has an allergic reaction to a specific antigen. The test has been replaced by the safer skin prick test that does not require serum transfer.

By 1920, both reactions to drugs and eczema (mainly atopic dermatitis) were believed to be initiated by antigen–antibody reactions. ***Carl Prausnitz*** in Breslau in Lower Silesia, Germany (now Wrocław, Poland), had injected himself in his abdominal skin with serum from his colleague ***Heinz Küstner***, who was known to have an allergy to fish. The next day Prausnitz argued that the injection sites with fish extract

could provoke a reaction. This became recognized as the **Prausnitz-Küstner reaction** and the standard technique for implying sensitization by passive transfer. Until the simple but ingenious experiment was reported by Prausnitz and Küstner in 1921, neither an exact pathophysiologic mechanism nor the mediator responsible for evoking the hypersensitive immediate wheal-and-flare response had been explained. This finding put an end to the belief that an anaphylactic or allergic reaction was triggered by poisons. Indeed, it proved the existence of the hypersensitivity factor that could be transferred to another person. It is now known that this factor is Immunoglobulin E or IgE, which can sensitize mast cells and basophils to respond to an allergic stimulus (e.g., allergen).

A **reversed Prausnitz-Küstner test** involves injecting antibodies into the skin of a person who already has the antigen. A wheal and flare in the skin also demonstrates a positive reverse test.

Otto Carl Willy Prausnitz (***Carl Prausnitz-Giles***) (Oct 11, 1876–Apr 21, 1963) was a German bacteriologist and hygienist, the "Father of Clinical Allergy." Prausnitz was born in Hamburg, Germany, to Otto Prausnitz, a German physician, and an English mother whose maiden name was Giles. She was a daughter of George Giles, a civil engineer who was working on the construction of the Hamburg-Berlin Railway. Thus, Carl Prausnitz learned English from early childhood. He studied at the universities of Leipzig, Kiel, and Breslau and earned his MD degree from the University of Breslau in 1903. He initially worked on differentiating *Vibrio cholerae* from other *Vibrio* species and studied hay fever and the allergenic nature of pollen. Prausnitz moved to London in 1905 and became an instructor at the Royal Institute of Public Health. It had been his intention to pursue a career in bacteriology in England. Until 1910, he taught students seeking a diploma in public health and published on the action of disinfectants. Prausnitz was not satisfied with various opportunities in England, however, and returned to Breslau to take the post of assistant at the State Institute of Hygiene.

In 1915, with the outbreak of World War I, Prausnitz served in the 14th German Army Corps as a hygiene inspector and advisor. Even during military service, Prausnitz's language skills led to a crossing of paths with infectious disease pioneers. Seeking critically needed tetanus antiserum, Prausnitz traveled to tap the known supply at the Institute Pasteur in Lille after the city's fall to the German army. Only Prausnitz's translation of laboratory protocols, pointing to use of an expended pigeon in experiments that led to the development of **BCG vaccine** and not for carrying covert messages, saved ***Leon Calmette*** and ***Camille Guerin*** from the fate of (mistakenly) being accused of spying (Frankland, 2004).

Prausnitz worked in the State Institute of Hygiene for many years. He also was invited to serve on various committees of the Health Organization of the League of Nations. His fluency in English, French, Italian, and some knowledge of Russian served him particularly well in Geneva.

Unfortunately, the Health Organization and the League itself were powerless to stem the rising tide of National Socialism in Germany. Because Prausnitz's father was a Jew, his position in Breslau became extremely difficult, and in 1933 he

resigned his post and went to England. He was invited to work in the Bacteriology Department of Manchester University and worked on cotton-spinners' asthma. In 1939, he became a British citizen and changed his name by deed poll to Prausnitz-Giles. He retired in 1961.

Prausnitz was a man of tremendous dynamism and enthusiasm. He was a hard worker who inspired his assistants by his own work ethic. In his enthusiasm as a researcher, he was often his own laboratory animal, as in his observations on hypersensitivity, the **Weil-Felix reaction**, the changes in the bactericidal power of the blood after specific and nonspecific stimulation, tolerance to carbon dioxide, and cotton spinners' asthma. Prausnitz was an honorary member of the British Society of Allergy and a corresponding member of the Collegium Internationale Allergologicum. In 1960, he accepted the award of an Honorary MD degree from the University of Hamburg.

Heinz (Heinrich) Küstner (***Joachim Heinrich ("Heinz") Küstner***) (Jan 16, 1897–Jan 1, 1963) was a German gynecologist. He was born in Breslau, Germany. His father, Otto Ernst Küstner, was Professor of Gynecology, Director of the Woman Hospital in Breslau, and a Rector of the University of Breslau for several years. After obtaining his initial medical education in Breslau in 1914, Heinz Küstner performed military service during World War I as a field physician and was awarded the Iron Cross Second Class. He received his doctorate degree in 1920 and was rehabilitated in 1924. During 1919–1923, he worked at the Hygiene Institute at the University of Breslau, Germany, where Otto Prausnitz was the head of the institute.

Küstner was an assistant of Prausnitz and worked on developing the Prausnitz-Küstner test. He then worked in several hospitals and clinics for women in Germany. After that he received a position as a Professor of Obstetrics and Gynecology and Chief Physician at a hospital in Leipzig, where he settled in 1936. His clinical research focused on gynecology, pregnancy, and puerperal fever (i.e., a uterine infection following childbirth). In 1930, he published an important study of job-related injuries to the reproductive system experienced by working women.

In 1933, Küstner joined the National Socialist German Workers' Party (NSDAP)—the Nazi Party. From 1939–1945, during World War II, he did army service as the chief physician of a military hospital train. After the war, he worked as a gynecologist in Dommnitzsch near Leipzig. In 1949, he directed the district hospital in Weißenfels. He died after an accidental inoculation while carrying out his own experiments with antibody production of infectious agents harvested after gynecologic operations.

(**Publ**.: Lubert A, Prausnitz C. Zur serumbehandlung des heufiebers. *Berl Klin Wschr* 1904; 41:273–277, 304–307.

Prausnitz C, Küstner H. Studien über die überempfindlichkeit. *Zentralbl Bakteriol Orig* 1921; 86:160–169.)

Purtilo syndrome see **Duncan's disease**

Letter Q

Quincke's oedema (angioedema, **Quincke disease**, **Quincke syndrome**, **Bannister disease**, **Bannister syndrome**, **Milton urticaria**, **Milton-Quincke syndrome**) is a syndrome presenting with the sudden onset of painless swelling of the face, tongue, feet, genitalia, and trunk, which persists from a few hours to 2 or 3 days. Involvement of the upper airways can result in severe life-threatening symptoms, including the risk of asphyxiation unless appropriate interventions are taken.

Angioedema (i.e., areas of swelling in cutaneous and mucosal tissues) may be hereditary or acquired. Hereditary angioedema (HAE) is an autosomal-dominant disease mediated by the generation of a vascular permeability-enhancing factor, usually bradykinin, which is controlled by C1 inhibitor (C1-INH)—a protease inhibitor from the serpin superfamily. It is the only known plasma inhibitor of C1r and C1s, the activated proteases of the first component of complement. HAE patients often have C1-inhibitor deficiency: the gene for C1-INH (*SERPING1*) mapping to 11q12-q13.1. Deficiency C1-INH allows activation of plasma kallikrein leading to the generation of the vasoactive peptide bradykinin; C4 and C2 cleavage is not inhibited, causing autoactivation of the complement system. Nearly 2% of HAE patients may have autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, glomerulonephritis, Sjögren syndrome, and pernicious anemia.

Acquired angioedema (AAE) Type I is connected with the generation of complement-activating factors, immune complexes or idiotype/antiidiotype antibodies that obliterate C1-INH activity. These are primarily various forms of lymphoproliferative disorders (e.g., monoclonal gammopathies and non-Hodgkin lymphoma). The reduction in C1-INH activity triggers activation of the classical complement pathway and utilization of C1q and subsequently C2 and C4, in parallel with the production of the vasoactive peptides and angioedema. Type II AAE is an autoimmune process characterized by an autoantibody against C1-INH, which inhibits its regulatory capacity.

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An altered expression of cytokines also has been reported in association with uncommon forms of angioedema. Best known cases are episodic angioedema with eosinophilia (**Gleich syndrome**), nonepisodic angioedema with eosinophilia, idiopathic capillary leak syndrome (i.e., **Clarkson syndrome**), NERDS (i.e., **n**odules, **e**osinophilia, **r**heumatism, **d**ermatitis, and **s**welling), and angioedema linked to the administration of Proleukin (aldesleukin)—human recombinant IL-2 and IFN-α.

The first picture of angioedema was presented by Marcello Donati in 1586. ***John Laws Milton*** reported it in 1876 and called it "giant urticaria." In 1894, ***Henry Martyn Bannister*** further described the condition. Angioedema, more commonly known as Quincke edema, was given its popular name in honor of the German physician ***Heinrich Quincke***, who described this condition in 1882.

Heinrich Irenaeus Quincke (Aug 26, 1842–May 19, 1922) was a German internist and surgeon. He was born in Frankfurt, Germany, and was the youngest of 4 sons of a titled physician, Hermann Quincke. His mother's predecessors were of the Huguenot faith and had fled to Germany following the Revocation of the Edict of Nantes in 1685. Heinrich studied medicine at Heidelberg, Würzburg, and Berlin and obtained his doctorate and qualification for internal medicine in Berlin in 1863 and 1970, respectively. After qualifying, in keeping with tradition, he visited hospitals in Switzerland, Paris, and London. These trips formed Quincke's belief that the light and airy conditions of these "ideal" hospitals and their valuable gardens offered the patients a much-needed sense of well-being. This became a lifelong preference for him. In 1873, Quincke was appointed to the Chair of Internal Medicine at the University of Bern, and 5 years later he moved to the Chair at the University of Kiel, where he remained until his retirement in 1908. He died in Frankfurt am Main.

Quincke's most notable contribution was to introduce the lumbar puncture ("Quincke's puncture"). He had taken cerebrospinal fluid by a self-constructed trocar (Quincke needle). This achievement was described as the "egg of Columbus" and as the "birth of one of the greatest discoveries of modern medicine." Heinrich Quincke was nominated for the Nobel Prize about 20 times between 1909 and 1922 being on the so-called shortlist of the Nobel Committee. In the nominations, other merits of Quincke had been mentioned, including his theories on iron metabolism, hemoglobin, experiments in dermatology, surgical treatment of lung diseases, nerve diseases (especially meningitis serosa, now known as idiopathic intracranial hypertension), and hydrocephalus. Therefore, he was considered to be a particularly promising candidate but failed being selected shortly before the finish each time.

Henry Martyn Bannister (Jul 25, 1844–May 1, 1920) was born in Cazenovia, New York, the son of Dr. Henry Bannister, a professor in the Garrett Biblical Institute. Bannister received his education at Northwestern University. After graduation in 1863, he worked in the Northwestern University Museum and was taken on a Western Union Telegraph Expedition to Alaska (1865–1867) as a meteorologist. After returning to Washington, Bannister delivered an expedition report to the Smithsonian Institution. This information was used later in the US Senate authorization for the purhase of Alaska from Russia.

Bannister also worked for the Illinois Geological Survey. He obtained his medical education from the National Medical College (now George Washington University) in Washington, DC, receiving his doctorate degree in 1871. For many years he practiced medicine in Chicago. His main publications were in the field of mental illness and nervous disorders. He died in Evanston, IL.

John Laws Milton (Nov 30, 1820–Aug 3, 1898) was born in Bishopwearmouth, UK, to Thomas Milton and Sarah Smith. He studied medicine in Edinburgh, London, Paris, and Vienna. He joined the Royal College of Surgeons of England in 1843. In 1850, he settled in London and became a surgeon and skin disease lecturer in 1863. With his single-minded effort to establish dermatology as a medical subspeciality, he established the St. John's Hospital for Diseases of the Skin in 1863. It existed in the vicinity of Leicester Square until 1990, then it was transferred to the St. John's Institute of Dermatology within the St. Thomas' Hospital.

Milton was interested in many different areas and published on some unusual fields such as spermatorrhea, pathology and treatment of skin diseases and gonorrhea, death in the pipe, the stream of life in the world, the laws of life for skin diseases, and utilization of tartar emetic (i.e., poisonous potassium antimonyltartrate) in tissue inflammation. He became a corresponding member of the New York Dermatological Society, a fellow of the Medical Society of London and a member of the Harveian Society.

(**Publ**.: Quincke HI. Über akutes umschriebenes Hautödem. *Monatsh Prakt Derm* 1882; 1:129–131.

Milton JL. On giant urticaria. *Edinburgh Med J* 1876; 22:513–526.

Bannister HM. Acute angioneurotic oedema. *J Nerv Mental Dis* 1894; 19:627–631.)

Letter R



Raji cells were the first continuous human cell line of hematopoietic origin that was derived 50 years ago from a Nigerian patient with **Burkitt's lymphoma**. Cell lines of Burkitt's lymphoma's origin were soon thereafter found to harbor the Epstein-Barr virus, leading to the discovery and isolation of this virus. Subsequent studies revealed specific chromosome translocations, involving the heavy- or light-chain immunoglobulin gene loci on chromosome 14 or 2, and the c-*myc* oncogene locus on chromosome 8, in biopsies and cell lines of Burkitt's lymphoma origin.

Raji cells as lymphoblast-like ones possess numerous receptors for certain complement components and thus are suitable for use in detection of immune complexes. Cells also express certain complement receptors as well as Fc receptors for immunoglobulin G. Therefore, there is the Raji Cell Assay for Detection of Immune Complexes, which was popular in clinical immunopathology laboratories 2 decades ago.

In 1963, at the University of Ibadan, Nigeria, **R.J.**V. Pulvertaft established the first continuous human hematopoietic cell lines—namely, a series of cell lines derived from an 11-year-old Nigerian male patient with Burkitt's lymphoma in suspension type cell cultures: lines JIJOYE, KUDI, OGUN, and RAJI. Suspension cultures, which were new at the time, contain cells that are free-floating, singly or in clusters, in the nutrient medium.

Robert James Valentine Pulvertaft (Feb 14, 1897–Mar 30, 1990) was an English pathologist. He was born in Cork, Ireland, to the English preacher T. J. Pulvertaft and his Irish wife. He received his education at Westminster School and then left England to serve in World War I, being an infantryman in Palestine, a fighter pilot in Egypt, and a bomber pilot in France. After the war, he continued his education focusing on physiology at Trinity College, Cambridge, and learning medicine at St. Thomas's Hospital in London. After graduation he worked in the laboratory at St. Joseph's, was the laboratory director at Westminster Hospital (1931), and obtained his final medical degree from Cambridge (1933). Around 1920, Pulvertaft married Isobel Costello, and they had 3 children.

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During World War II, Pulvertaft, as a lieutenant colonel, served in the Royal Army Medical Corps. He was a pathologist in the 64th General Hospital in Alexandria and then in the 15th General Scottish Hospital in Cairo, Egypt. In 1942, working on the battlefield, he led early studies on the effect of recently discovered penicillin on war wounds. Because of very limited supply of penicillin from Britain, he had to develop methods to produce a crude form of the drug locally. Penicillin was so valuable, and flushed so fast out of a patient's body, that researchers often recovered it from urine and purified it for reinjection. Pulvertaft's ingenuity in making a "home brewed" penicillin saved numerous lives.

In December 1943, Pulvertaft was escorted at gunpoint by 2 US officers to a large white villa in Carthage near Bizerta, Tunisia. There he met British Prime Minister Winston Churchill who had developed a severe pneumonia on his way back from the Tehran Conference; there he had met Russian leader Joseph Stalin and the US President Franklin D. Roosevelt to discuss the Western Allies' commitment to open a Ssecond Front against Nazi Germany through the invasion of northern Europe. Lord Moran, Churchill's personal doctor needed help, and he knew that there was no better pathologist in North Africa and southern Europe than Robert Pulvertaft. This visit undoubtedly saved Churchill's life. Pulvertaft established a makeshift laboratory for blood monitoring and found diagnostic tools and the necessary medicine. He was also responsible for suggesting 2 renowned clinicians—pharmacologist Gladwin Buttle and a top heart specialist Evan Bedford, both of whom would help. After 2 weeks at the villa, Pulvertaft returned to Cairo—his job extremely well done. He wrote a detailed account of Churchill's illness in his memoirs.

Later in 1943, Pulvertaft was transferred to Jerusalem. In 1944, he was named an Officer of the Order of the British Empire. After the war, he returned to Westminster Hospital and established new laboratory departments. He became the first professor of clinical pathology in London. He also was a president of the Association of Clinical Pathologists (1953) and an honorary fellow of the Royal Society of Medicine (1962). Working at Westminster, Pulvertaft used cinemicrography to study lymphocyte motility and proliferations, especially in the presence of tumor cells in tissue culture, He described the phenomenon of emperipolesis as an uncommon biological process in which a cell penetrates another living cell; he also led research studies on melanoma.

Pulvertaft left Westminster in 1962 and moved to Africa. He taught at the Makerere University College, Kampala in Uganda and was a visiting Professor at the Department of Pathology, University of Ibadan in Nigeria. There, together with his delightful Irish wife, Isabel, who became his laboratory assistant because of a shortage of suitable technicians, he conducted studies on Burkitt's lymphoma and developed several unique cell lines. At the age of 70 he returned to England, living in Dorset and later in Cambridge. He died in Macclesfield, England.

(**Publ**.: Pulvertaft RJV. Cytology of Burkitt's tumour (African lymphoma). *Lancet* 1964; 283(7327):238–240.)

Raynaud's syndrome (**Raynaud's disease**, **Raynaud's phenomenon**) is an excessively reduced blood flow in response to cold or emotional stress, causing discoloration of the fingers, toes, and occasionally other areas. **Primary Raynaud's phenomenon** (**Raynaud's disease**), where the cause is unknown, is associated with hyperactivation of the sympathetic nervous system causing extreme vasoconstriction of the peripheral blood vessels, leading to tissue hypoxia. **Secondary Raynaud's phenomenon** (**Raynaud's syndrome**) is caused by a known primary disease, most commonly connective tissue disorders (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis, **Sjögren's syndrome**, dermatomyositis, polymyositis, mixed connective tissue disease, and other inflammatory autoimmune disorders).

The syndrome is named after French physician ***Maurice Raynaud***, who while he was a medical student described the condition as part of his thesis for his medical doctorate in 1862. Raynaud saw the phenomenon in 25 patients and observed a loss of sensation, pain, and localized gangrene. He spent the next 30 years investigating his findings, and today the phenomenon is recognized as "a manifestation of a wide spectrum of clinical disorders."

Auguste Gabriel Maurice Raynaud (Aug 10, 1834–Jun 29, 1881) was the son of a university professor in Paris. After graduating from a classical grammar school, he was extended an invitation to join the *École Normale Supérieure*, one of Paris's elite schools. Raynaud refused because he would have had to swear an oath to the Emperor. He studied medicine at the University of Paris, obtaining his doctorate degree in 1862. He achieved eponymous celebrity with his doctoral dissertation in which he described medical conditions now known as Raynaud's disease. Concurrently to his doctoral thesis, Raynaud suggested his PhD thesis with 2 notable publications on the history of medicine: the 48-page article "Asclepiades of Bithynia, doctor and philosopher" ("De Asclepiade Bithyno medico ac philosopho") and the book *Medicine in Molière's Time* (*Les Médecins au Temps de Molière*). Thus, by 1863 when he qualified for a professional appointment, he possessed the equivalent of 2 earned doctorates as well as silver and gold medals awarded during his internship. For political reasons he was neither promoted to full professor, and he never received a chair position in the History of Medicine. His sincerity and devotion to the Catholic Church was suggested as one reason for the failure of the university to give adequate recognition to his talents at the bedside and with the pen.

Although Raynaud always wanted to hold the chair of Medical History at the University of Paris, he never received a senior position at any of the Paris hospitals but became *Médecine des Hôpitaux* (received hospital privileges) in 1865. He worked in various Paris clinics, occupied himself with many problems, and was considered to be a good academic teacher. In 1866, he became an agrégé—"an academic rank conferred by a French university on one who has passed a rigidly competitive examination and who is therefore entitled to appointment to the highest teaching post in a lycée or in one of the faculties of a university"—with the works *Sur les Hyperhémies non Phlegmasiques* and *De la Revulsion*. In 1866, he also received a gold medal for his work during the cholera epidemic. He was an officer of the Legion of Honor in 1871. Raynaud was elected to the National Academy of

Medicine in 1879. In 1897, he became a member of the Section Pathologie Médicale of the Académie de Médecine. Despite all these recognitions and honors, he was neither appointed a professor nor receive a chair position.

In 1881, Raynaud had registered to present a lecture at the International Medical Congress in London on the topic "Skepticism in Medicine—Then and Now." He died shortly before the meeting and his lecture was presented by a colleague in his honor.

(**Publ**.: Raynaud M. *De l'Asphyxie Locale et de la Gangrène Symétrique des Extrémités*. [*Local Asphyxia and Symmetrical Gangrene of the Extremities*]. Paris: Didier; 1862.)

Recklinghausen-Appelbaum syndrome see **Troisier-Hanot-Chauffard syndrome**

Recklinghausen's canals (**von Recklinghausen's canals**, **canals of Recklinghausen**) are the smallest lymph channels in connective tissue also known as lymphatic canaliculi.

Friedrich Daniel von Recklinghausen see **Troisier-Hanot-Chauffard syndrome**

Reed-Sternberg cells (**Sternberg-Reed cells**) are large multinucleated cells or cells with bilobed nucleus and prominent eosinophilic inclusion-like nucleoli seen in patients with **Hodgkin's lymphoma**. They usually are derived from B lymphocytes, typically CD15 and CD30 positive, CD20 and CD45 negative, and are considered crippled germinal center B cells that do not undergo hypermutation and do not express an antibody.

Identification of the Reed-Sternberg cells is used in the diagnosis of Hodgkin's lymphoma—the absence of these cells has a high negative predictive value. **Reed-Sternberg cells** also can be found in reactive lymphadenopathy (e.g., infectious mononucleosis and carbamazepine-associated lymphadenopathy) and very rarely in other types of non-Hodgkin's lymphomas. They are named after ***Dorothy Reed Mendenhall*** and ***Carl Sternberg***, who provided the first definitive microscopic descriptions of Hodgkin's disease.

Dorothy Reed Mendenhall (Sept 22, 1874–Jul 31, 1964) was born in Columbus, OH. Dorothy Mabel Reed graduated from Smith College in 1895, attended MIT, and became one of the first women to graduate from the Johns Hopkins School of Medicine. When still a pathology fellow, she discovered the cells that are a primary characteristic of Hodgkin's lymphoma and disproved the common belief that the disease was a form of tuberculosis. After that, she took an internship in pediatrics at the Babies Hospital in New York. Later she married Charles Mendenhall who was the chairman of the physics department at the University of Wisconsin–Madison. In 1915, Mendenhall established the first infant welfare clinic in Madison, WS. During the World War I era she was a medical officer at the US Children's Bureau. Dorothy Reed Mendenhall died of heart disease at the age of 89.

Carl (***Karl***) ***von Sternberg*** (Nov 20, 1872–Aug 15, 1935) was an Austrian pathologist. He was born in Vienna, a son of David Sternberg and Jeanette Rebecca Sternberg (Strisower). He attended the University of Vienna, and after training in general medicine, he worked as an assistant at the Institute for Pathology and habilitated for pathological anatomy in 1903. In 1908, he moved to Brünn and achieved the rank of professor. From 1914 and during the World War I, he served as a physician, spending time together with the combat troops. He was one of the most respected doctors of his military rank in Austria earning an outstanding reputation for advocating for the soldiers' rights and well-being.

After the war, he returned to Brünn. In 1920, he moved to Vienna and received a position of the head of the Pathology Department at the General Hospital of the Viennese Medical School. But he never achieved his wish of becoming the head of an academic unit. His clinical research focused on bowel infections, typhoid fever, tuberculosis, and leukemia. He died unexpectedly of a coronary occlusion.

(**Publ**.: Reed D. On the pathological changes in Hodgkin's disease, with special reference to its relation to tuberculosis. *Johns Hopkins Hosp Rep* 1902; 10:133–196.

Sternberg C. Uber eine eigenartige unter dem bilde der pseudoleukamie verlaufende tuberculose des lymphatischen apparates. *Ztschr Heilk* 1898; 19:21–90.)

Reiter's syndrome (**Reiter's disease**, **Reiter's arthritis, Fiessinger-Leroy disease**, **Fiessinger-Leroy-Reiter disease**, **Waelsch's disease**, **Stoll-Brodie-Fiessinger-Leroy syndrome**) is a reactive arthritis, formerly called **Reiter's syndrome**—a poorly defined disorder that has been described in the medical literature under many different names. Reactive arthritis is classified as an autoimmune condition and is a general term for a form of joint inflammation that develops as a "reaction" to an infection in another area of the body. Two other common symptoms of reactive arthritis are inflammation of the urinary tract and conjunctivitis. These 3 characteristic symptoms can occur separately, all at once, or not at all. Reactive arthritis usually develops following certain bacterial infections, including *Chlamydia*, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter*.

Reiter's syndrome is a rare multisystem autoimmune spondyloarthropathic disease commonly associated with the *HLA-B27* gene on chromosome 6. It includes a triad of nongonococcal urethritis, conjunctivitis, and predominantly lower-limb asymmetrical oligoarthritis in several joints. The associated group of diseases includes reactive arthritis, psoriatic arthritis, ankylosing spondylitis, undifferentiated spondyloarthritis, and spondyloarthritis connected with inflammatory bowel disease.

The disease was named after ***Hans Reiter***, who during World War I, was a German military physician on the Western Front. In 1916, he reported on, a Lieutenant of the Prussian Army, with arthritis, urethritis, and uveitis. Reiter initially concluded that the disease was caused by a spirochete, which he found in the patient's blood, and named it "spirochetosis arthritis." The syndrome became known as Reiter's syndrome but was renamed to reactive arthritis when Reiter's affiliation with the Nazi regime was proven. Also in 1916, within weeks after Reiter's account, the triad was reported by ***Feissinger*** and ***Leroy***. Several decades earlier, however,

English surgeon Sir ***Benjamin Collins Brodie*** in his legendary book, *Pathological and Surgical Observations on Diseases of the Joints*, referred to this syndrome in 5 patients with the classical triad of urethritis, arthritis, and conjunctivitis.

Nevertheless, the combination of at least 2 of the clinical signs had been known since the fifteenth century. Allison guessed that Christopher Columbus was the first European patient in North America who developed reactive arthritis (Allison, 1980). During his voyages between Puerto Rico and Santa Domingo in September of 1494, Columbus became "lame" and suffered from fever, confusion, and severe arthritis of the lower limbs. This was probably associated with a *Shigella flexneri* infection that was common in the tropics during that time; Columbus got it after arriving in the New World. Finally, another indication is that ***M. Stoll*** described arthritis following dysentery in 1776.

The term "reactive arthritis" is used synonymously with the term "Reiter's syndrome." Yet, in 1977, some doctors initiated a campaign to replace the term "Reiter's syndrome" with "reactive arthritis" because of proven facts about Reiter's involvement in the Nazi atrocities during World War II. Still, it seems that not all types of reactive arthritis can be regarded as Reiter's syndrome because it is more carefully described by the triad of arthritis, conjunctivitis, and urethritis. (For an interesting historical overview, see Iglesias-Gammara et al., 2005.)

Hans Conrad Julius Reiter (Feb 26, 1881–Nov 25, 1969) was a German physician convicted of war crimes for his medical experiments at the concentration camp at Buchenwald. He was born in Reudnitz near Leipzig in the German Empire, the son of a businessman; he studied medicine in Leipzig and Breslau (now Wrocław) and received a doctorate from Tübingen on the subject of tuberculosis. Then he studied hygiene in Berlin, the Pasteur Institute in Paris, and St. Mary's Hospital in London. During the World War I, Reiter was a military physician in the first Hungarian Army and served on the Western Front and in the Balkans.

After the war, Reiter was a chair in the Department of Hygiene at the University of Rostock. He was a political man and a spoken proponent of the eugenics movements. Reiter joined the Nazi Party on August 31, 1931. His career received an additional boost after he joined other professors to swear an oath of allegiance to Adolf Hitler in 1932. In 1933, he became a director of a department at the Kaiser Wilhelm Institute of Experimental Therapy. In 1936, his next career step was a position as Director of the Health Department of Mecklenberg-Schwerin and an honorary professorship in Berlin. Reiter was the Director of the Ministry of Hygiene, which had the support of the National Socialist Workers Party (NSDAP). He was called on by Hitler to take temporary charge of the Reich Health Ministry (Reichgesundheisant) on July 26, 1939. He was also a strong supporter of Hitler's antismoking campaign.

Reiter wrote 140 research papers and several books. As a member of the SS (the Nazi Party's Schutzstaffel organization) during the World War II, Reiter designed typhus inoculation experiments that killed more than 250 prisoners at concentration camps like Buchenwald. He created orders, supervised medical atrocities, and gave the stamp of approval for them. The results of his work on a vaccine against typhoid were published in one of his papers, "Vaccination therapy and vaccine diagnosis."

He was an enthusiastic devotee and participant in enforced racial sterilization and euthanasia. When he was a president of the Reich Health Office in 1937, Reiter declared a central task of the Nazi health leadership—to stop the further spread of inferior genes.

After the Nazis were defeated, Reiter was arrested by Russians in Soviet Union-occupied Germany and tried at Nuremberg. He was found guilty for his participation in the deaths of hundreds of prisoners at Buchenwald. But he was not convicted of any crime because of the difficulty of obtaining proof—the 2 top-ranking Nazi doctors, with whom Reiter had planned involuntary "medical experiments" at Buchenwald, committed suicide in 1945. He was included in a book about the top 5000 Nazis. He was imprisoned at a US prisoner-of-war camp for 2 years. After his release, Reiter continued his work in medicine and research in rheumatology in Kassel. He died at 88 at his country estate in Kassel-Wilhelmshöhe, Germany.

Noël Armand Fiessinger (Dec 24, 1881–Jan 15, 1946) was a French anatomist. He was born in Thaon-les-Vosges to Charles Albert Fiessinger, who was a physician, and Marie Joséphine Jacques. He studied in Lyon and Paris and received his doctorate degree in 1908. He became chief of clinical service at the Hospital Beaujon, in 1931 he was appointed as chair of experimental pathology, and in 1939 as the renowned Chair of Clinical Medicine at the Hôtel-Dieu. In 1912, he married Frédérique Mathilde Finck and had 3 children. During World War I, Fiessinger studied the pathobiology of war wounds, often right after severe artillery fire. After the war, he focused mostly on physiology. He developed the original principles of functional investigation of an organ and successfully applied them to his analysis of liver physiology and the histogenesis of cirrhosis.

Fiessinger first demonstrated the presence of enzymes in white blood cells. He discovered that, depending on their type, these cells express either protease or lipase. He speculated that cellular protease may be responsible for the dissolution of internal blood clots, even though lipase may deteriorate the lipidic membrane of the *Koch bacilli*, thus allowing their destruction by the protease-expressing white blood cells.

Edgar Leroy (***LeRoy***) (Apr 17, 1883–Apr 12, 1965) was a French physician. He studied in Roubaix, a city in northern France, receiving two BS degrees in modern literature and in science. He also studied medicine in Lille. He served during the Word War I and was put in charge of the Bertin hospital in Montdidier, where he worked with his friend and colleague Noël Fiessinger. After the war, in 1919, he moved to Saint Rémy de Provence to become a psychiatrist of Saint Paul de Mausole. He was mobilized again in1939 with the mission to organize the field hospitals of the Italian front. In 1945, he was elected a city council, but continued his medical practice and his research. He received many decorations: Gold Medal of the Epidemics, Knight of Orange Nassau, Croix de Guerre, Knight of the Legion of Honor.

He married Claire Vacher, and they had 8 children. He was the first to publish medical documents on Vincent Van Gogh and worked on Nostradamus.

Ludwig Waelsch see **Waelsch's disease**

Maximilien Stoll (Oct 12, 1742 – May 25, 1787) was an Austrian physician. He was a native of Erzingen, Baden-Württemberg. a country surgeon. Stoll first studied theology in Ingolstadt and then worked as a teacher. In 1767, he moved to Strasbourg to study medicine, which he continued in Vienna. In 1772, he received his doctorate and accepted the position of a physicist in a Hungarian county. In 1776, he returned to Vienna as the principal at the Trinity Hospital and continue his general practice and student teaching.

Stroll was a professor at the University of Vienna. He is credited with providing the first description of gall bladder cancer in 1777. Hel is remembered for his epidemiological and systematic approach to medicine. He suggested the importance of knowing the clinical details of a patient history, and introduced a practice of keeping daily records of patients.

Sir ***Benjamin Collins Brodie*** (Jun 9, 1783–Oct 21, 1862) was an English surgeon and physiologist who pioneered research on bone and joint disease. He was also a philosopher, writer, and statesman. He was born in Winterslow, Wiltshire, the third son of Reverend Peter Brodie, the rector of the parish of Winterslow, and Sarah Collins, the daughter of a banker from Salisbury. He received his medical education in London. In 1808, he was appointed assistant surgeon at St George's Hospital, on the staff of which he served for more than 30 years. His most important and widely acknowledged work was the book *Pathological and Surgical Observations on the Diseases of the Joints* in which he discussed the beginnings of disease in the various tissues that form a joint and described the symptom of pain as evidence of an organic disease. He received many honors during his career and attended to the health of the Royal Family, starting with George IV. He was also sergeant-surgeon to William IV and Queen Victoria and was made a Baronet in 1834. Brodie was once called to attend an operation for removal of a skin tumor performed on the king.

In 1816, Brodie married Anne Sellon, a daughter of a famous lawyer, and they had several children, among which only 3 survived. His oldest son was the well-known Oxford chemist Sir Benjamin Collins Brodie, Second Baronet, noted for the discovery of graphitic acid. Sir Benjamin Collins Brodie, the surgeon, died of a shoulder tumor in Broome Park, Betchwork, Surrey, at the age of 79.

(**Publ**.: Reiter H. Über eine bisher unerkannte spirochäteninfektion (Spirochaetosis arthritica). *Dtsch Med Wochenschr* 1916; 42:1535–1536.

Stoll M. (1776). Citation from Huette. De l'arthrite dysenterique. *Arch Gen Med* 1869; 14:29–30.

Brodie BC. *Pathological and Surgical Observations on Diseases of the Joints*. London: Longman. 1818; p. 54.

Fiessinger N, Leroy E. Contribution a l'etude d'une epidemie de dysenterie dans la Somme. *Bull Soc Med Hop* 1916; 40:2030–2069.)

Révol's syndrome (**Revol's disease**, **Di Guglielmo's disease II**, **Di Guglielmo's syndrome**, **Epstein's syndrome**, **Epstein-Goedel syndrome**, **Mortensen's disease/syndrome**) is an outdated, no longer used, term for hemorrhagic or essential thrombocythemia. Essential thrombocythemia is a hematological condition

characterized by thrombocythemia. Increased production of megakaryocytes and splenomegaly are typical for this myeloproliferative neoplasms. Importantly, an increased number of platelets in this disorder may be associated with prolonged bleeding time, often seen after minor trauma and at surgery. This is the result of the von Willebrand factor sequestration by the augmented number of platelets, leaving insufficient von Willebrand factor levels for platelet adhesion. Symptoms also may include bleeding in several parts of the body and clotting incidents (e.g., strokes, pain in the limbs, and troubled breathing). Mutations in the JAK2 kinase and calreticulin are present in the majority of cases. See also **Glanzmann's syndrome**.

Louis Aimé Stéphane Révol (Aug 1, 1905–Apr 3, 1981) was a French hematologist. He was born in Lyon and spent his life there. He received his pharmacy degree in 1928 and Doctor of Natural Sciences degree in 1931. He was a chair of the Department of Pharmacology, head of the laboratory of histochemistry, and Associated Dean at the School of Medicine and Pharmacy. He was a founder and director of the Lyons Transfusion Centre.

Revol published 180 papers focusing on his research on pharmaceutical chemistry, psychiatric therapy, alcoholism, and psychotropic drugs. He was a member of the following: Linnean Society of Lyon, Society of Pharmacy of Lyon, Society of Biological Chemistry of France, Botanical Society of France, Society of Biology, Society of Therapeutics, International Collegium of Neuro-psychopharmacology; he was also a member of the Committee "Functions and Diseases of the Brain."

In 1962, he was elected the National Correspondent of the Academy of Medicine for the Division of Pharmacy. He was also an officer of public instruction at the rank of Knight of the Legion of Honor.

Ole Mortensen was a Danish physician.

Emil Epstein (Aug 19, 1875–Feb 25, 1951) was an Austrian experimental pathologist and biochemist. He was born in Vienna. His father was a doctor; he was a Jew who had to join the Protestant church. Emil studied medicine at the University of Vienna and received his medical license in 1900. He then worked at the Institute for Pathological Anatomy. During World War I, he served as a pathologist in the Franz Joseph Hospital and the Rudolf Hospital. He was able to complete his medical examinations for general pathology with a special emphasis on serology in 1926 at the University of Vienna. He was Privatdozent (private lecturer) for General and Experimental Pathology at the Medical School of the University of Vienna. Epstein and Goedel worked in the Kaiserin Elisabeth-Spital in Vienna where they described their syndrome. Their patient developed extreme thrombocytosis, slight erythrocytosis, and recurrent mucocutaneous bleeding with the absence of prominent panmyelosis.

Epstein was persecuted during the time of Nazism because of racist antisemitic reasons—he was considered a "1st degree half-breed." He lost his position at the university in 1938 when Austria was annexed by Nazi Germany. After the war, he returned to the university and received a position of professor. He was in charge of his clinical chemistry laboratory.

Epstein was a known expert in the fields of syphilis serology and chemistry of lipoid metabolic diseases. He published 80 papers on clinical serology, immunology, bacteriology, and pathology. He was a member of the Association of German Pathologists, the Biological Society in Vienna, the Society of Physicians in Vienna, the Microbiological Society in Vienna, the Society of German Natural Scientists and Physicians, and the German Colloid Society. He died in Vienna, Austria.

Alfred Goedel was an Austrian pathologist who worked with Emil Epstein.

Giovanni Di Guglielmo (Sept 22, 1886–Feb 19, 1961) was born in Brazil to his Italian parents and returned to Italy when he was 6. After he finished his medical education, he went to Sao Paulo, Brazil, for private practice but returned to Naples 6 months later. During World War I, he served as medical lieutenant and started his clinical studies of hematological malignancies, focusing on erythroleukemia.

Di Guglielmo was appointed Professor of Medical Pathology at Pavia in 1928 and later Professor of Medicine at Catania. He held similar tenure in Naples and in Rome. He also founded and directed a few clinical research institutions, including the Center for the Study of the Brucellosis in Catania, and 2 medical journals—*Progresso Medico* and *Haematologica*. He was the author of more than 230 scientific publications and received international recognition for the discovery of acute erythroid leukemia, also known as "Di Guglielmo syndrome" or "Di Guglielmo's disease."

(**Publ**.: Di Guglielmo G. Megacariociti e piastrine negli organi emopoietici e nel sangue circolante. *Atti R Acad Chir Napoli* 1919; 83:19.

Epstein E, Goedel A. Hämorrhagische thrombocythämie bei vasculärer schrumpfmilz. *Virchows Arch Pathol Anat Physiol Klin Med* 1934; 292(2):233–248.

Mortensen O. Thrombocythemia hemorrhagica. *Acta Med Scand* 1948; 129:547–559.

Révol L. La myélose hyperthrombocytaire (thrombocytémie hémorrhagique). *Sang* 1950; 21:409–423.)

Richet's phenomenon (**Theobald Smith's phenomenon**) is an allergic hypersensitivity reaction of the body to a foreign protein or a drug. Sometimes this may be a fatal reaction in a sensitized individual after a second injection of an antigen.

Theobald Smith described the phenomenon observed in guinea pigs that had survived use for diphtheria antitoxin standardization, the animals having been rendered highly susceptible to subsequent inoculation of horse serum. He used guinea pigs that he injected with a small dose of blood serum containing diphtheria antitoxin. His experimenting with guinea pigs was conducted with the intention of determining a standardized or proper dose. He observed that a small dose of diphtheria antitoxin caused the guinea pigs to become highly susceptible to a somewhat larger dose of the same diphtheria antitoxin when injected several weeks later, perhaps causing the guinea pigs to die.

Charles Robert Richet (Aug 26, 1850–Dec 4, 1935) was a French physiologist. He was born in Paris. The son of surgeon Louis Dominique Alfred Richet, he

entered a medical school, but anatomy and surgery bored him, pushing him to write poetry and drama as a diversion. During his internship in a hospital, he was fascinated with parapsychology after witnessing hypnosis. He did his own studies and introduced the term **metaphysic** for parapsychological research. Richet received his MD in 1869 but abandoned surgery to devote himself to physiology. In his doctoral thesis, he described that sensory nerves that, deprived of the blood source, die progressively from the periphery toward the center. Exposing healthy volunteers to electrical stimuli, he discovered that stimuli too weak to be detected, if widely separated, could be felt if they were closer together.

From 1887 to 1927 on, Richet was a professor at the University of Paris, Sorbonne. In 1901, Prince Albert the First of Monaco asks Paul Portier and Charles Richet to study the toxicity of small jellyfish fishing filaments during one of his oceanography trips. Analyzing the effects of a hypnotoxin extracted from fluid filling the capsules of various jellyfish, they detected lethal accidents in animals that were not related to the dosage of the toxin. Dogs that responded all received an initial injection, but some dogs had no reaction to a second injection. Richet designated the term **anaphylaxis** for this phenomenon: *Phylaxis* is "protection" in Greek and the prefix *ana* means "away from protection." Anaphylaxis thus means the "state of an organism, in which it is rendered hypersensitive, instead of being protected." Importantly, Portier and Richet, who were not familiar with each other before the trip, working together for a few months, discovered that an immune response could be either pathogenic or healing. This critical finding opened new avenues in the growing field of clinical immunology. Interestingly, the first recorded death of anaphylaxis is believed to have been documented in hieroglyphics in 2641 BC, when a wasp from the *Hymenoptera* order (i.e., wasps, bees, ants, sawflies) stung Pharaoh Menes.

Paul Portier eventually returned to the Department of Sciences, but Charles Richer continued characterization of anaphylaxis phenomenon in his laboratory at the Department of Medicine. Fascinatingly enough, experiments leading to the clarification of the phenomenon of anaphylaxis possibly began when Richet and Jules Héricourt revealed a new type of staphylococcus bacterium in an epithelial tumor in a dog in 1888. Adopting the approach that had become classical after Pasteur's analysis of fowl cholera, they grew a pure bacterium culture. Rabbits who received injections of the culture extract died, while dogs responded with only a large swelling at the site of the injection. After years of intensive studies, Richet defined the phenomenon and coined the term anaphylaxis in 1902.

In 1907, he started building a general concept of anaphylaxis based on his own and some published results. Richet's theory helped explain hay fever, asthma, and other allergic reactions to foreign substances and elucidate many previously unsolved cases of intoxication and sudden death. He was awarded the **Nobel Prize** in Physiology or Medicine in 1913 "in recognition of his work on anaphylaxis."

Richet was a man of many interests, and his works included books about history, sociology, philosophy, psychology, as well as theatre plays and poetry. He was a pioneer in aviation. He also presided over the French Eugenics Society from 1920 to 1926. Richet was an active proponent of eugenics. He advocated sterilization and

marriage prohibition for those with mental disabilities. Being limited in understanding, Richet compared black people to apes and intellectually to imbeciles. Richet embraced "racist and eugenist" ideas in his book *La Sélection Humaine* (1919).

Richet devoted many years to the study of paranormal and spiritualist phenomena, coining the term "ectoplasm." He thought that the special ability of "spirit mediums" could be explained mechanistically as the external projection of a material substance or ectoplasm (which is not related to spirit) from the body of the practitioner. He rejected the spirit hypothesis of metaphysical practices as not adhering to the principles of science. He used to state that he "has the misfortune to believe more in science than theology." Richet died in Paris. In the Catholic notice, he was compared with Leonardo da Vinci. He also was named "the greatest physiologist that France has had since Pasteur."

Theobald Smith (***Schmitt***) (Jul 31, 1859–Dec 10, 1934) was a US pathologist and the premier US microbiologist of his day. He was born in Albany, NY, the son of German immigrants. His parents, Philip Schmitt, a journeyman tailor, and Theresia Kexel, a housekeeper, came from the Rhineland in Germany. They were married in 1854 and escaped political unrest by way of an 8-week voyage to the New World, settling in Albany, NY. The compilers of the city directory were unwilling to differentiate the various European cognates of "Smith" and reduced Schmitt to the common anglicized spelling. That is how Theobald Smith got his name.

Smith graduated from Cornell University in 1881 and received his MD degree at Albany Medical College in 1883. He then returned to Cornell for his graduate education. His first position was at the newly established Bureau of Animal Industry in Washington, DC. There Smith found a new species of bacteria (*Salmonella enterica*), but Daniel E. Salmon, Smith's boss and director of the bureau, claimed credit for the discovery, and the genus *Salmonella* was named after him. In 1886, Smith and Salmon reported the first evidence that killed bacteria can be used for inducing immunity in experimental animals. These results provided the basis for the generation of prophylactic immunization for human bacterial diseases (e.g., typhoid and cholera).

Smith was well known for his work on Texas cattle fever with the discovery of the protozoan agent and its transmission by ticks. This was the first finding showing that an arthropod, an insect, was connected with the transmission of an infectious disease. This was a collaborative effort of Smith with his colleagues, veterinarians Fred L. Kilbourne and Cooper Curtice. Smith also founded the Department of Bacteriology at Columbian University (now George Washington University), the first bacteriology department at a medical school in the US. There he taught from 1886 to 1895 and began his life-long research on tuberculosis.

In 1895, Smith moved to Cambridge, MA, to accept a dual appointment as professor of comparative pathology at Harvard University and director of the Massachusetts State Antitoxin and Vaccine Laboratory. Smith undertook many practical and theoretical studies on the production of tetanus and diphtheria antitoxins. He demonstrated the induction of immunity by killed microorganisms and proved that a mixture of diphtheria toxin and antitoxin conferred immunity. Under

Smith's control, production of diphtheria antitoxin increased from 1700 to 33,000 doses within 4 years. Patient deaths decreased from 25% to 11% during the first year. Smith estimated that during the first 7 years of antitoxin production in the state laboratory, 10,000 human lives had been saved by its administration.

One of Smith's essential contributions to immunology was indicating that animals develop hypersensitivity to bacteria after repetitive injections. What is now called anaphylaxis previously was accepted as the "Theobald Smith phenomenon." In 1915, Smith joined the Rockefeller Institute for Medical Research in Princeton, NJ, as Director of the Department of Animal Pathology, where he worked until his retirement in 1929. One of Smith's important scientific accomplishments at Princeton was the presentation of clear measures to separate the types of tubercle bacilli that can infect humans and bovines. Although ***Robert Koch*** declared that bovine bacilli could not attack the human body, Smith acknowledged that the bovine microorganism can infect humans, but it was not the normal cause of human infection.

Smith was known as a patient, persistent researcher whose experiments were accurately planned. He authored 305 scientific publications, addresses, and government reports, usually as the sole author. He was awarded 12 honorary degrees and 11 medals from well-known universities. One of them was the Copley Gold Medal of the Royal Society—one of the world's highest scientific awards at that time.

(**Publ**.: Charles C, Héricourt J. Sur un microbe pyogène et septique et sur la vaccination contre ses effets. *C R Acad Sci* 1888; 107:690–692.

Richet CR. *Our Sixth Sense*. [First published in French]. London: Rider, 1928.

Smith T. On the variability of pathogenic organisms, as illustrated by the bacterium of swine plague. *Am Mon Microsc J* 1886; 7:201–203.

Smith T. Parasitic bacteria and their relation to saprophytes. *Am Nat* 1887; 21:1–9.

Smith T. Modification, temporary and permanent, of the physiological characters of bacteria in mixed cultures. *Trans Assoc Am Phys* 1894; 9:85–106.)

Richter syndrome (**Richter's syndrome**, **Richter's transformation**, **Richter transformation**) is recognized as the development of a secondary and aggressive lymphoma during the clinical course of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). It occurs in approximately 2–10% of all CLL/SLL patients during the course of their disease. Even though the exact causes of Richter's syndrome remain unclear, certain factors are thought to elevate the risk of acquiring **Richter's syndrome** in patients with CLL/SLL. In fact, patients with advanced stage disease at first CLL diagnosis; and patients with 11q and 17p chromosome deletions, unmutated *Immunoglobulin Variable Heavy Chain* (*IgVH*) gene, shortened telomere length, Notch Receptor 1 (*NOTCH-1*) mutations, elevated expression of ZAP-70, beta-2-microglobulin, and CD38 protein are at a higher risk of developing Richter's syndrome.

The usual presentation is sudden clinical deterioration, asymmetric adenomegaly, hepatosplenomegaly, fever, weight loss, night sweats (B symptoms), increased lactate dehydrogenase (LDH), and monoclonal gammopathy. The specificity of these clinical signs for Richter's transformation is only 50–60%. In the remaining

cases, the histopathologic assessment can show either progressive CLL, aggressive CLL, or even solid cancer. Most histological transformations are to a diffuse large B-cell lymphoma and Hodgkin's lymphoma. Histopathological examination is a prerequisite for diagnosis.

The treatment for Richter's syndrome depends on the exact subtype of lymphoma in question, as revealed by the diagnostic excisional or core biopsy. The current standard first-line treatment is the immunochemotherapy using a combination of chemo drugs and a targeted anti-CD 20 monoclonal antibody. Although novel agents currently are being investigated, chemoimmunotherapy nevertheless remains the standard treatment.

A New York pathologist, ***Maurice N. Richter***, first described the syndrome in 1928. He wrote about a 46-year-old shipping clerk who was admitted to the hospital and had a progressively downward course leading to death. In the autopsy analysis, he determined that there had been one previously existing malignancy but that from it, a new malignancy seemed to have sprung up that was more rapidly growing and encroached on and destroyed the tissue that had been the old CLL. He theorized that the CLL had existed for much longer than anyone knew about in this patient, also writing about the 2 cancers, or lesions, stating: "It is possible that the development of one of the lesions was dependent on the existence of the other." The term "Richter's syndrome" was coined in 1964 by Lortholary et al. to describe the development of malignant reticulopathy in 14 patients with CLL (Lortholary et al., 1964).

Maurice N. Richter (Aug 26, 1897–Oct 15, 1988) was a US pathologist. He was born in Chicago. He graduated from the College of Physicians and Surgeons in 1921. Richter was Chairman of the Pathology Department at New York University Medical Center from 1949 to 1951 and was a professor of pathology until he retired in 1962. After retirement, he continued working as a senior consultant in pathology at the Good Samaritan Hospital in Phoenix. He died of bladder cancer at Friendship Village, a retirement center in Tempe, AZ. He was 91 years old.

(**Publ**.: Richter MN. Generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia. *Am J Pathol* 1928; 4(4):285–292.)

Riedel thyroiditis (**Riedel's struma**) is a chronic form of thyroiditis and often a multisystem disorder affecting pancreas, kidney, liver, salivary and orbital tissues, and retroperitoneum. The hallmarks of Riedel's struma are fibrosis and tissue infiltration by IgG4-producing plasma cells, suggesting that **Riedel's thyroiditis** is an IgG4-related disease.

These diseases, also known as IgG4-related systemic diseases, hyper-IgG4 diseases, IgG4-related autoimmune diseases, are a group of fibroinflammatory diseases or chronic inflammatory conditions with tumor-like lesions of unknown etiology and characteristic histopathological features. Affected tissues are characterized by infiltration with lymphocytes and IgG4-secreting plasma cells (i.e., lymphoplasmacytic inflammation) and various degrees of fibrosis. The deposition of connective tissue can cause organ dysfunction and even organ failure if not treated. Corticosteroids are the mainstay of therapy. The disease is named after ***Bernhard***

Riedel who first recognized the disease in 1883 and published its description in 1896.

Bernhard Moritz Carl Ludwig Riedel (Sept 18, 1846–Sept 12, 1916) was a German surgeon. He was born in Teschentin (Techentin) in the Grand Duchy of Mecklenburg to a priest's family. From 1866 onward, he studied medicine at Jena and Rostock and had to obtain an emergency degree to join the Franco-Prussian War (1870–1871). He was a corpsman with a rank of corporal in military service working at the Front and in military hospitals; he stayed in the medical corps until the end of the war. After that, Riedel returned to Rostock to finalize his medical examinations in 1872, being the best in his class. He then worked as a prosector in Rostock hospital. In 1875, he moved to Göttingen and was habilitated for surgery in 1877. In 1881, he was appointed chief physician of the surgical department at the Municipal Hospital in Aachen. In 1888, he became director of the surgical clinic at the University of Jena.

Riedel was well known as an innovator in the surgical treatment of appendicitis and cholecystitis who always supported "the earliest early operation." He was the first surgeon who showed that the abscess after appendicitis can be removed with an incision without any risk to the patient if it has not spread too widely. His name has been lent to Riedel thyroiditis and Riedel's lobe (i.e., a tongue-shaped abscess of the liver).

Riedel retired in 1910. Because of atherosclerosis and associated painful leg conditions it was amputated at the knee. Nevertheless, he continued his full activities when World War I started in 1914 but died of lung cancer within 2 years.

(**Publ**.: Riedel BMCL. Die chronische, zur bildung eisenharter tumoren führende entzündung der schilddrüse. *Verh Dtsch Ges Chir* 1896; 25:101–105.)

Ro antigen belongs to a heterogenous group of extractable nuclear antigens (see **Sm antigen**). In 1969, Clark et al. described complement fixation reactions between the serum of a systemic lupus erythematosus patient and saline homogenates of various human tissues. They also isolated the corresponding antigen and designated "Ro antigen" after the prototype patient's serum (Clark et al., 1969). Today, Ro antigen also is known as SS-A.

Romanowsky stain is a prototypical staining technique that was the forerunner of several distinct but similar methods, including Giemsa, Jenner, Wright, Field, and Leishman stains, which are used to differentiate cells in pathologic specimens, especially blood and bone marrow slides. Leukocytes contain no pigment and are colorless in unstained preparations; their designation is based on their staining reaction with a Romanowsky stain. Morphologic analysis of leukemic cells in smears stained with **Romanowsky stains** typically was used to distinguish acute lymphocytic leukemia (ALL) from acute myeloid leukemia (AML) and define 3 subtypes of ALL and 8 subtypes of AML. It was named after the Russian physicians ***Dimitri Romanowsky*** and Ernst Malachowski who both developed a staining method based on water-soluble eosin (i.e., anionic), methylene blue (i.e., cationic), and absolute methanol. Methanol was used because aqueous dye solutions were unstable. This staining technique made microscopic identification easier.

Dmitri Leonidovich Romanowsky (Oct 19, 1861–Feb 19, 1921) was a Russian physician. His mother was Anastasia Samsonova and his father was unknown. Based on the rules for an illegitimate child, he received his last name after a village Romanovo (Toropetchkii yezd, Pskov province, Russia), where he was born.

In 1880, he entered the St. Petersburg University to study physics and mathematics but 2 years later, he switched to the course in the Military Medical Academy. He graduated with honors in 1886, was appointed a junior resident of the Ivangorod Military Hospital, and then was transferred as an associate doctor to the Revel local infirmary where he worked in the therapeutics department. In 1889, he was attached to the Petersburg Nikolaevsky Military Hospital and worked there first in the clinical department, and in 1890 he became the head of the eye department of the hospital. The rumor is that once he refused to consult Russian Tsar's brother afterhours and was deported from Russia within 24 hours. He moved to Paris where he had a private clinic. In St. Petersburg in 1891, Dimitri Romanowsky observed that it was possible to differentially stain nuclei and cytoplasm of the plasmodia in infected erythrocytes (i.e., chromatin red and cytoplasm blue) with a mixture of eosin Y and methylene blue. Thus, in his 1891 monograph on the parasitology and treatment of malaria, he introduced the original eosin-methylene blue stain for blood smears and malaria parasites.

In 1912, Romanowsky was invited back to Sankt Petersburg to work at the Imperator Clinical Institute. After the Russian Revolution in 1917, however, he moved to his house in Kislovodsk in the south of Russia, where he died of angina pectoris (i.e., coronary artery disease) several years later.

(**Publ**.: Романовскій ДЛ. Къ вопросу о строеніи чужеядныхъ маляріи. *Врачъ* 1890; 52:1171–1173.

Романовскій ДЛ. Къ вопросу о паразитологіи и терапіи болотной лихорадки. Диссертація на степень доктора медицины. Спб. 1891 г.:118 с.

Romanowsky D. Zur frage der parasitologie und therapie der malaria. *St Petersburg Med Wochenschr* 1891; 16:297–302, 307–315.)

Rosai-Dorfman disease (**Destombes-Rosai-Dorfman syndrome/disease**) is a rare disorder of unknown etiology characterized by abundant histiocytes in the lymph nodes; it is a rare non-Langerhans' cell histiocytosis. It also is known as sinus histiocytosis with massive lymphadenopathy. Lymphadenopathy of the neck is the most common place of histiocyte accumulation, although accumulation outside of lymph nodes may occur in the skin, upper respiratory tract, and the sinuses. Affected tissues also demonstrate marked plasmacytosis. The disease often is characterized by a prolonged clinical course with exacerbation and remission phases. The etiology is not well understood, although molecular studies using polymorphic regions of the human androgen receptor locus have indicated its polyclonal nature. In addition, a variety of infectious agents, including herpes group viruses, *Brucella*, and *Klebsiella*, have been speculated to be involved. Etiologic hypotheses include immune dysregulation. Autoimmune phenomena are reported in 10–15% of cases. Commonly recorded immune abnormalities include autoantibodies against red blood cells, neutrophils, and platelets, as well as glomerulonephritis.

This condition has been named after ***Ronald F. Dorfman*** and ***Juan Rosai*** who in 1969 and 1972 described a total of 34 cases of patients with painless, bilateral, massive cervical lymphadenopathy, fever, and distinctive abnormalities in laboratory tests—that is, normochromic anemia, leukocytosis with neutrophilia, increased erythrocyte sedimentation rate, and often hypergammaglobulinemia. In their second paper published in 1974, they referred to 4 cases, that had been reported in French in 1965 by ***Pierre-Paul Louis Lucien Destombes***, a French pathologist, under a French term. Destombes described his findings of a biopsy on a 24-year-old man with lymphadenopathy and sinus histiocytosis, which he performed in 1959. Moreover, Juan Rosai had corresponded with Destombes and had exchanged slides with him; they agreed that they were dealing with the same disease.

Juan Rosai (***Giovanni Rosai***) (Aug 20, 1940–Jul 7, 2020) was an Italian-born US physician known for his clinical research in surgical pathology. He was born in Poppi near Florence, Italy. When he was 8 years old, his parents immigrated to Buenos Aires, Argentina, and at the age of 15, Rosai enrolled in the School of Medicine at the University of Buenos Aires. He did residency training in anatomic pathology at the same university, and then completed his residency and fellowship in anatomic pathology at Washington University School of Medicine, St. Louis, MO, in the US. He stayed at Washington University until 1974, when he received a position of Professor and Director of Anatomic Pathology at the University of Minnesota in Minneapolis. In 1985–1991, he worked at Yale University School of Medicine, and in 1991–1999 at Memorial Sloan-Kettering Cancer Center in New York City with similar positions. Then Rosai moved back to Italy as Chairman of the Department of Anatomic Pathology at the National Cancer Institute in Milan. He also developed the International Center for Oncologic Pathology Consultations, where he continues his consultation and educational activities, focusing on oncological surgical pathology. During his career, Rosai published 52 books, book chapters, and monographs, and a staggering total of more than 390 peer-reviewed papers, but perhaps the most famous publication by Juan Rosai is his textbook, *Rosai and Ackerman's Surgical Pathology*. Rosai developed Parkinson's disease in his late 60s. Although it was controlled for many years, the complications of the disease ultimately took his life. He died at 79 in Milan, Italy.

Ronald F. Dorfman (Mar 14, 1923–Jun 15, 2012) was born in Johannesburg, South Africa. He entered medical school at the University of the Witwatersrand in Johannesburg but his education was interrupted from 1944 to 1946 by military service in the No. 2 South African Field Surgical Unit serving with the Allied Forces in Egypt and Italy. He received his medical degree in 1948 followed by postgraduate training at the Johannesburg General Hospital, the Postgraduate Medical School of London, and the Royal Victoria Hospital in Edinburgh. After returning to South Africa to complete pathology training at the South African Institute for Medical Research, he served as a pathologist and lecturer at the University of Witwatersrand.

In 1955, he married Zelma, delighting both sets of parents who were best friends and fixtures in the Johannesburg Jewish community. In 1963, he and his family immigrated to the US, with a faculty appointment at Washington University in St.

Louis, MO. It was there that Ron Dorfman and ***Juan Rosai***, a surgical pathology fellow, shared identical examples of a rare, benign lymph node disorder that came to be known as **Rosai-Dorfman disease**.

In 1968, Dorfman was appointed to establish and codirect the Surgical Pathology Service in the Department of Pathology at the Stanford University School of Medicine. Dorfman held this post for nearly 35 years until his retirement in 1993. After retiring at the age of 70, he continued to be active in the Department of Surgical Pathology. Together with Harvey Klein, he developed a visiting fellowship for promising young Israeli pathologists with a special interest in hematopathology. In 1982, Dorfman and Costan Berard from the National Institute of Health founded the Society for Hematopathology to promote investigation and exchange of ideas among hematopathologists worldwide. Dorfman served as its second president from 1984 to 1986. In honor of his achievements and his contributions to Stanford, his field, and his patients, the Department of Pathology established the Ronald F. Dorfman Professorship in Hematopathology in 2002.

Dorfman took great joy in golfing (playing with the same group of colleagues for more than 30 years); attending Stanford sporting and cultural events, opera, photography; and traveling. He was devoted to his family—his wife, daughters, and beloved grandsons.

Pierre-Paul Louis Lucien Destombes (Aug 10, 1912–2002) was a French pathologist affiliated with Pasteur Institute in Paris.

(**Publ**.: Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. *Arch Pathol* 1969; 87:63–70.

Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: A pseudolymphomatous benign disorder: Analysis of 34 cases. *Cancer* 1972; 30:1174–1188.

Destombes P. Adenites avec surcharge lipidique, de l'enfant ou de l'adulte jeune, observées aux Antilles et au Mali (quatre observations). *Bull Soc Pathol Exot Filiales* 1965; 58:1169–1175.)

Russell bodies are eosinophilic, large, homogenous immunoglobulin-containing inclusions usually found in a plasma cell undergoing excessive synthesis of immunoglobulin. Also called "cancer body" because Russell described them as peculiar intracellular structures that he thought were fungi representing the etiological agent of cancer. Since then, the nature of those cells has been investigated both in lymphatic tissues and in tumors, and the results have revealed that the inclusions were immunoglobulins stored in the endoplasmic reticulum of plasma cells. Such plasma cells are called **Mott cells**. It now generally is accepted that Russell bodies are dilated endoplasmic reticulum cisternae-containing condensed immunoglobulins. Interestingly, D. King and D. Eisenberg revied information about "Russell's fuchsin body" in the *American Journal of Dermatopathology* in 1981 and confirmed that Russell bodies are immunoglobulins. They also stated that Russell was not the first to discover them because Cornil and Alvarez described them in rhinoscleroma in 1885 in a French journal. They added: "Hence, when the term Russell body is used

today, one should be aware that the eponym is as inaccurate as was Russell's perception of their significance."

In regard to their biogenesis, the synthesis of altered immunoglobulins that are not secreted and not degraded is appropriate to make **Russell body** formation in cells of different species and histotypes. Russell bodies were discovered in plasma cells, and their appearance rate in this cell type undoubtedly correlates with the process of somatic hypermutation of immunoglobulin genes. Nevertheless, dilated endoplasmic reticulum cisterns comprised of condensed abnormal proteins were seen in various types of secretory cells, signifying that concentration of transport-incompetent proteins in the endoplasmic reticulum may be the usual reason for the appearance of Russell bodies. Several cases of intraluminal protein accumulation have been described in association with distinct diseases. Known examples are thyrocytes in patients with congenital goiter and hepatocytes in patients with mutated α1-antitrypsin alleles.

William Russell (Apr 22, 1852–Aug 11, 1940), a Scottish pathologist and physician, was born in Douglas on the Isle of Man where his father was a fisheries officer. Russell studied medicine in Edinburgh and graduated in 1876. He worked as a family physician and pathologist at the General Hospital in Wolverhampton, but later settled in Edinburgh working as a clinical teacher and pathologist at Royal Infirmary, where in 1913 he was the first to be appointed to Moncrieff-Arnott Chair of Clinical Medicine. He held this position until his retirement in 1919. Russell's early research included investigations of the cancer cell and circulation disorders. He was the first editor of the *Scottish Medical and Surgical Journal*.

Russell was well known as a strong advocate for medical education for women, teaching at both the Edinburgh School of Medicine for Women and the Edinburgh College of Medicine for Women. He was one of the most highly regarded clinical teachers. He was a tall, good-looking, bearded gentleman whose dogmatism combined with his medical knowledge made him fittingly remembered by his students. At the age of 42, he married Beatrice Ritchie, aged 21 then, who had been one of his pupils in the extramural school. Of their 6 children, 4 became doctors. Their infant son Ivan died of tuberculosis; their third daughter immigrated to Russia.

(**Publ**.: Russell W. An address on a characteristic organism of cancer. *BMJ* 1890; 2:1358–1360.)

Russell viper venom test is one from the Lupus anticoagulant-testing series of assays used to detect lupus anticoagulant in the blood. The venom of Russell's viper (chain viper) *Daboia russelli*, found in Asia, acts in vitro as an intrinsic thromboplastin—factors that convert prothrombin to thrombin during the early stages of blood coagulation. Russell's viper was named in honor of ***Patrick Russell*** who first described many of India's snakes.

This test is based on the capacity of the venom harvested from the Russell's viper to initiate thrombosis. The venom comprises several agents, such as proteases (or Russellysin) RVV-V and RVV-X, which directly activate factor V and factor X that turn prothrombin into thrombin in the presence of phospholipid and calcium. In the

Russell viper venom test, low rate-limiting concentrations of both Russell's viper venom and phospholipid are used to give a standard clotting time, making the test sensitive to the presence of lupus anticoagulants because their presence results in a prolonged clotting time. A mixing study with the patient's plasma is then performed, and a prolonged clotting time suggests the presence of a lupus anticoagulant. An abnormal result for the initial Russell viper venom test should be followed by a confirmatory test.

The **Russell viper venom test** is a part of a diagnostic workup of a suspected antiphospholipid antibody. Additional assays include the serological testing for anticardiolipin antibodies and anti-β2 glycoprotein-I antibodies. The typical criteria for the diagnosis of the antiphospholipid syndrome require at least one positive test and at least one clinical manifestation of antiphospholipid syndrome (e.g., vascular thrombosis or fetal mortality/morbidity). Test results must be interpreted in their clinical context if a diagnosis of antiphospholipid syndrome is being considered.

Patrick Russell (Feb 6, 1726–Jul 2, 1805) was a Scottish surgeon and naturalist who worked in India. He was born in Edinburgh, the fifth son of John Russell, a lawyer of Edinburgh and his third wife Mary. Patrick studied medicine at the University of Edinburgh, graduated in 1750, and joined his half-brother Alexander Russell in Aleppo, Syria, who was a physician to the Levant Company's Factory; Alexander was involved in quarantine and disease control and was a keen naturalist with a knowledge of local languages and a close friend of the Pasha. Aleppo (Arabic name, Halab) was a major Ottoman city, dating back to the fourteenth century, in north-western Syria. In 1753, Alexander resigned and Patrick took the position and worked there for 18 years. He was highly respected by the Pasha of Aleppo who honored him with a turban.

Being a very careful observer of local traditions, Russell noticed the Arabian practice of inoculating children against smallpox using "variolus matter"—the fluid present in a vesicle or pustule of variola (smallpox)—that was a prevaccine prophylactic approach to preventing dangerous infections. Furthermore, during outbreaks of bubonic plague in Aleppo, he investigated individual conditions of infected people and was able to identify procedures to avoid infection—for example, breathing through a handkerchief soaked in vinegar.

In 1771, Russell left Aleppo and moved to London. In 1781, a younger brother, Claud, became a chief administrator of the East India Company. He was in poor health and the family insisted that Patrick follow him to take care of his conditions. Living in India, he studied the natural history of the region; soon the Governor of Madras personally offered the post of "Botanist and Naturalist" to Patrick. He studied the snakes of India and is considered the "Father of Indian Ophiology."

In 1791, Patrick, his brother Claud, and the family came back to England. Some of his unique collections were left in the museum at Madras, but many snake skins were brought home and are now in the collection of the Natural History Museum in London. Being back, Russell worked on a book on snakes. He was never married and provided specific instructions for his funeral: "It is my request to be interred in the nearest burial ground, in the most private manner that custom will permit, but not be deposited within the walls of any place dedicated to public worship."

Letter S

Sabin vaccine (**polio vaccine**; see also **Salk vaccine**) Although ***Jonas Salk*** introduced the first polio vaccines in 1953, another scientist in the US, ***Albert Sabin***, thought that Salk's vaccine—killed-virus vaccine—was not effective enough. His idea was to mimic the "real-life infection" by using a weakened form of the live virus. Sabin tested more than 9000 monkeys and 100 chimpanzees to harvest a very uncommon form of poliovirus that would replicate in the intestal tract but not in the central nervous system. Therefore, in 1957, he prepared an oral vaccine and was ready for the first human clinical trials. **Sabin vaccine** was tested in other countries, including the Soviet Union and Eastern Europe. In 1958, a live-virus vaccine for polio was tested in the US with the attempt to create questions about Sabin's "communist vaccine." But the vaccine worked, was licensed in 1962, and immediately became the vaccine of choice because it was less expensive and more practical in use than Salk's injectable vaccine.

Albert Bruce Sabin (Aug 26, 1906–Mar 3, 1993) was born ***Abraham Saperstein*** in 1906 in Bialystok, Russia (restored to Poland after 1918), to Ashkenazi Jewish parents, Jacob and Tillie Krugman Saperstein. At the age of 15, he immigrated with his family to the US to avoid persecution directed against Jews (*pogroms*). He received a naturalized citizenship in 1930, changed his name to Sabin, and assumed the middle name Bruce. After Sabin graduated from high school, his uncle decided to finance his college education, if Albert focused on dentistry. After 2 years of learning stomatology at New York University, Sabin changed to medicine, developing a true interest in virology. He lost his financial assistance, but various jobs and scholarships allowed him to continue his medical education. After receiving his BS in 1928, he entered the New York University College of Medicine. He obtained his MD in 1931, finished his internship, and moved to the Lister Institute of Preventive Medicine in London to learn how to carry out research projects. One year later, he received a fellowship at the Rockefeller Institute for Medical Research (now

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Rockefeller University) and returned to the US. Sabin's interest in poliovirus was developed while there.

During World War II, Sabin served as a lieutenant colonel in the US Army Medical Corps working on the development of a vaccine against Japanese encephalitis. After the war, he accepted a position of a professor of pediatrics research at the University of Cincinnati College of Medicine to continue his polio studies. Although Salk started his work on a killed-virus vaccine, Sabin conducted his project using an attenuated live-virus vaccine. He isolated many virus strains and characterized them in animals and tissue cultures and then tested these species on humans. His subjects included himself and his family, research colleagues, and adult volunteers from the nearby Chillicothe Penitentiary in Ohio.

Because of the fact that Salk's vaccine was proving to be successful, Sabin could not obtain any real support in the US for a large-scale controlled field trial similar to the trial of Salk's vaccine. In 1957, Sabin then turned to his colleagues abroad, including those in the USSR and Czechoslovakia. He knew Mikhail P. Chumakov, a director of the Poliomyelitis Research Institute in Moscow, from his visit to the US in 1956. Sabin provided enough vaccine to immunize many thousands of children in Eastern European countries and also supplied seed lots that were used by Russians to immediately prepare about 10 million doses. By the fall of 1959, millions of children in the Soviet Union had been vaccinated with Sabin vaccine. Between 1955 and 1961, the oral vaccine was tested on at least 100 million people in the USSR, Eastern European countries, Mexico, Singapore, and the Netherlands. During the 1960s, the USSR became the major producer of the Sabin vaccine. It was sold throughout the world and promoted as "the communist vaccine."

After the Russian clinical trial triumphed in 1960, the US Public Health Service authorized the vaccine in 1961 for manufacture in the US, and the World Health Organization (WHO) initiated use of the live-virus vaccine generated in the USSR. Sabin worked together with Pfizer to make that vaccine. His oral live-attenuated polio vaccine used as drops or on a sugar cube quickly replaced Salk's killed-virus injectable vaccine in many countries around the world. In 1994, the WHO proclaimed that the polio virus had been eradicated from the Western Hemisphere because of constant mass immunization operations with the Sabin vaccine in Central and South America. In 1999, however, a federal administration suggested that the US go back to Salk's vaccine because it cannot inadvertently cause polio. Based on a decade of further confirmation, this recommendation was reconfirmed in 2009.

Sabin continued his work and held a series of influential positions at organizations, such as the Weizmann Institute of Science in Israel (in 1969–1972); he lived and worked in Israel as the president of the Weizmann Institute of Science in Rehovot, then the US National Cancer Institute and the National Institutes of Health. Sabin also prepared vaccines against other viral diseases (e.g., encephalitis and dengue). He studied probable associations between viruses and some forms of cancer. In 1980, he visited Brazil to help with a new outbreak of polio. In 1983, Sabin developed calcification of the cervical spine with associated paralysis and intense

pain and retired in 1986. He had successful back surgery at Johns Hopkins Hospital in 1992 when he was 86. He died in Washington, DC, from heart failure.

(**Publ**.: Sabin AB, Ramos-Alvarez M, Alvarez-Amezquita J, Pelon W, Michaels RH, Spigland I, Koch MA, Barnes JM, Rhim JS. Live, orally given poliovirus vaccine. Effects of rapid mass immunization on population under conditions of massive enteric infection with other viruses. *JAMA* 1960; 173:1521–1526.

Sabin AB, Michaels RH, S Spigland I, Pelon W, Rhim JS, Wehr RE. Community-wide use of oral poliovirus vaccine. Effectiveness of the Cincinnati program. *Am J Dis Child* 1961; 101:546–567.

Sabin AB. Oral poliovirus vaccine. Recent results and recommendations for optimum use. *R Soc Health J* 1962; 82:51–59.

Sabin AB. Oral poliovirus vaccine: History of its development and use and current challenge to eliminate poliomyelitis from the world. *J Infect Dis* 1985; 151:420–436.

Sabin AB. Role of my cooperation with Soviet scientists in the elimination of polio: Possible lessons for relations between the USA and the USSR. *Perspect Biol Med* 1987; 31(1):57–64.)

Sabin-Feldman dye test (**Sabin-Feldman dye exclusion test**) is a serologic test for toxoplasmosis diagnosis. The test is based on the fact that *Toxoplasma gondii* organisms do not stain with alkaline methylene blue if they have been exposed to serum anti-*T. gondii* antibodies. The patient's serum sample is treated with *Toxoplasma* trophozoites (tachyzoites) and complements as activator. After incubation, methylene blue is added. In the presence of anti-Toxo antibodies, activated by complement, the parasite membrane is lysed, and *Toxoplasma* trophozoites are not stained, suggesting a positive result. In the absence of anti-Toxo antibodies, the trophozoite membrane is intact and stained blue under a microscope, suggesting a negative result.

The test was proven to be specific and sensitive in humans but unreliable in other species. The main disadvantage of the **Sabin-Feldman dye test** is the necessity of using live parasites and healthy human serum as an accessory factor. Because live virulent *T. gondii* are used for the test, it is hazardous and requires a great technical expertise and special conditions in reference laboratories. Furthermore, because tachyzoites are isolated from cell cultures they can induce false-negative results; tachyzoite generation from mice is preferred for the test. *Tachyzoites* are the actively proliferating *trophozoites*—a form of *Toxoplasma gondii* cell cycle.

The Sabin-Feldman dye test, initially developed by ***Sabin*** and ***Feldman*** in 1948, has been considered as a gold standard for the detection of anti-*T. gondii* antibodies in humans. Shortly after the publication of an article about this, Sabin's lab discontinued its work on toxoplasmosis to focus on researching other diseases (mainly polio). Feldman, however, continued to research the disease at his new lab at Syracuse University. For many years afterward, Sabin would receive specimens that physicians wanted him to test for toxoplasmosis, and he would send the materials on to Feldman in Syracuse and later the State University of New York.

Albert Bruce Sabin see **Sabin vaccine**

Harry Alfred Feldman (May 30, 1914–Jan 6, 1985) was a US epidemiologist. He was born in Newark, New Jersey, to Joseph Feldman, a contractor, and his wife Sarah. He graduated from Weequahic High School in 1931, received his bachelor's degree in zoology in 1935, and obtained his MD degree in 1939 from George Washington University. He did his internship and residency at Gallinger Municipal Hospital in Washington, DC. In 1942, he received a position as a research fellow at Harvard Medical School and an assistant resident physician at the Boston City Hospital's Thorndike Memorial Laboratory. He served in World War II and retired as a lieutenant colonel.

In 1948, Feldman and Sabin developed a test for toxoplasmosis, called the Sabin-Feldman dye test. Feldman's later research isolated and identified the intricacies in the chemical reaction of the dye test, which led to a better understanding of the disease.

Feldman started working in 1948 as an associate professor of medicine at the Syracuse University College of Medicine. In 1949, he was a director of research at the Wieting-Johnson Hospital for Rheumatic Diseases and an associate professor, full professor, and chair of the Department of Preventive Medicine. During his tenure, he concentrated on both research and teaching. In the early 1960s, he focused on the development of a safe killed-virus vaccine for measles. For many years, Feldman worked as an adviser to the US Armed Forces Epidemiology Board, mainly on respiratory viruses. He also advised the US Food and Drug Administration on vaccines for meningococcus and was a consultant to the US Surgeon General, the Department of Defense, the Department of Health, Education and Welfare, and the World Health Organization. Feldman also served as the president of the Infectious Disease Society of America and the American Epidemiological Society.

Between 1938 and 1983, he published 216 research papers, both in scientific journals and as book chapters. Feldman had a daughter, 3 sons, and 7 grandchildren. He died of complications caused by diabetes at the New England Medical Center in Boston.

(**Publ**.: Sabin AB, Feldman HA. Dyes as microchemical indicators of a new immunity phenomenon affecting a protozoon parasite (*Toxoplasma*). *Science* 1948; 108:660–663.)

Salk vaccine is a **polio vaccine** (see also **Sabin vaccine**). Poliomyelitis has been around since ancient times. This virus attacks the nerve cells and sometimes the central nervous system, triggering muscle wasting and paralysis and even death. Several cycles of epidemics have been seen since 1900, each appearing to get rougher and more devastating. The disease stricks primarily children, although adults, including Franklin Roosevelt, also can get it. In 1952, an epidemic year for poliomyelitis, 58,000 new cases were reported in the US with more than 3000 deaths. In 1953, ***Jonas Salk***, who worked at the University of Pittsburgh, PA,

announced on a national radio show that he had prepared and tested a vaccine against poliomyelitis.

Salk's procedure was intended to kill several strains of the virus and then inject the benign viruses into a healthy person to induce production of antibodies to resist future exposure to poliomyelitis. Salk performed his clinical trials on recovered polio patients and on himself and his family. He announced his findings on the CBS national radio network on the evening of March 25, 1953, and 2 days later in his paper published in the *Journal of the American Medical Association*. In 1954, new clinical trials testing the **Salk vaccine** were initiated on approximately 2 million US schoolchildren. Results reporting that the vaccine is effective and safe were announced in April 1955, supporting the initiation of a nationwide inoculation campaign. New poliomyelitis cases decreased to under 6000 in 1957, the first year when the vaccine was broadly available. In 1962, another poliomyelitis vaccine—an oral **Sabin vaccine** developed by ***Albert Sabin***—became accessible, greatly accelerating dissemination of the polio vaccine.

Jonas Edward Salk (Oct 28, 1914–Jun 23, 1995) was a US medical researcher and virologist. He was born in New York City, his family's eldest son. His mother was a Russian-Jewish immigrant, and his father was from the family of Jewish immigrants. He graduated from high school at the age of 15 and started to study law at the City College of New York. But his interests turned to medicine, and he graduated with a degree in science in 1933. Being a medical student at New York University, Salk started his research on viruses working on the development of flu vaccines. He received his MD degree in 1939, completed his internship at Mt. Sinai Hospital, and finished his National Research Council fellowship at the University of Michigan. In 1947, he started his research laboratory at the University of Pittsburgh and received a grant to study the polio virus and a possible vaccine in 1948. He was able to create an early version of his polio vaccine 2 years later. Salk established methodology for growing diverse strains of polio viruses on cultures of monkey kidney cells, which were then killed with formaldehyde. After purification, the vaccine protected monkeys from paralytic poliomyelitis. On July 2, 1952, Salk tested a vaccine on children who had recovered from poliomyelitis and demonstrated upregulation of specific antibodies. Next, he tested his vaccine on volunteers who had never had polio and included himself, his wife, and his children. They all generated antiviral antibodies, and none got infected.

In 1953, Salk published his results, which initiated a nationwide testing of the vaccine starting the mass injection of children in schools in April 1954. The results revealed an incredible 60–70% disease prevention. But, unexpectedly, vaccination induced about 200 cases of the disease, of those 11 people died. Vaccination was frozen until it had been proved that the disease-causing vaccine came from one drug company's inadequately prepared batch. Vaccination was resumed with much higher production and purification standards and with more than 4 million inoculations given by August 1955. The effect was spectacular: 28,985 cases of polio in 1955, 14,647 in 1956, and 5894 in 1957. Salk's vaccine was adopted by 90 other countries by 1959.

In spite of the fact that Salk was the first to produce a polio vaccine, he was not awarded the Nobel Prize and did not get a membership invitation from the National Academy of Sciences. Jonas Salk was nominated several times, but many of his peers felt that he did not deserve it since he did not truly "invent" anything new—he had simply put existing methodologies together in an innovative way. Also, Salk was Jewish, and antisemitism at that time, despite the horrors of World War II, could not be understated. The same applies to the oral Sabin version of the polio vaccine.

In 1962, Salk established the Salk Institute for Biological Studies in La Jolla, CA. He continued his research projects focusing on multiple sclerosis, cancer, and acquired immunodeficiency syndrome (AIDS). He spent many years on developing a killed-virus vaccine to prevent the development of AIDS in people infected with human immunodeficiency virus (HIV). He died in La Jolla because of heart failure. His life's philosophy is memorialized at the institute with his now famous quote: "Hope lies in dreams, in imagination and in the courage of those who dare to make dreams into reality."

(**Publ**.: Salk JE. Vaccination against paralytic poliomyelitis: Performance and prospects. *Am J Pub Health* 1955; 45:575.

Salk JE. Considerations in the preparation and use of poliomyelitis virus vaccine. *JAMA* 1955; 158:1239–1248.

Salk JE. Poliomyelitis vaccine in the fall of 1955. *Am J Public Health Nations Health* 1956; 46(1):1–14.)

Samter's syndrome (**Widal-Abrami-Lermoyez triad**, **Widal-Lermoyez syndrome**, **Widal's syndrome**) is a chronic condition in asthmatic and allergic diseases. It is characterized by the triad of bronchial asthma; vasomotor rhinitis, with or without nasal polyps; and intolerance to aspirin or aspirin-like medications. It is commonly called aspirin-exacerbated respiratory disease. Associated signs include eosinophilia of bronchial and nasal secretions and circulating blood, urticaria, and angioedema.

The first description of a hypersensitivity reaction triggered by aspirin was done by Hirschberg in 1902. He described a patient with acute angioedema and urticaria, occurring immediately after aspirin intake. Gilbert recognized for the first time an asthmatic reaction to ASA in 1911. The aspirin triad syndrome was first described by ***M. F. Widal***, ***Pierre Abrami***, and ***J. Lermoyez*** in 1922. Even though ***Samter*** did not "discover" the aspirin triad syndrome, he was the most prolific medical scientist in this area and described much of the biological basis for the disorder.

Georges-Fernand-Isidor Widal see **Widal test**

Pierre-Léon Abrami (Jul 1, 1879–Feb 28, 1943) was a French physician. He was born in Constantinople (now Istanbul), Turkey, and studied at the University of Paris, where he received his medical doctorate in 1910. He was appointed a hospital doctor in 1913 and became a collaborator of ***Georges-Fernand-Isidor Widal***. In 1936, he was a professor of medicine in Paris. He had a twin brother, Leon Abrami, who was a French politician. He died in Paris.

Jacques Lermoyez (?–1923) was a French physician. He was the son of the otolaryngologist Marcel Lermoyez, who is credited with establishing otolaryngology as a specialized medical field in France.

Max Samter (Mar 3, 1908–Feb 9, 1999) was a US physician and immunologist. He was born in Berlin, Germany, to a Jewish family of Paul Samter and Clara (Claire) Rawicz. He attended the universities of Freiburg and Innsbruck and completed an internship and received his MD from the University of Berlin in 1933. After Hitler came to power in Germany and excluded Jewish physicians from the university medical centers, big hospitals, and training, Samter spent the next 4 years in general practice in Karow, a small Berlin suburb.

During the 1930s, Samter wrote several short political novels, circulated them clandestinely, to satirize the Nazis. In an interview in 1983, he mentioned that he was a motorcycle enthusiast and became "almost friends" with storm troopers (*Sturmabteilung*, SA, the Nazi Party's original paramilitary wing) at the local repair shop. The fastest available BMW motorcycle, which he used on house calls as a doctor, brought him into "amiable" contact with Nazi storm troopers who congregated in a local group for "bike talk." Putting motorcycle camaraderie in front of officially stated antisemitism, storm troopers would warn him of approaching periodic Gestapo (abbreviation for *Geheime Staatspolizei*, Secret State Police) raids and a chance for Samter to temporarily hide in Bavaria.

In 1937, using a formal invitation for medical school appointment organized by supporters at Johns Hopkins University, Samter received permission to leave Germany for the US. For the next 6 years, he worked as a volunteer research assistant with no salary. First, he was assigned to hematology research at Johns Hopkins. Next, he studied lymphocytes at the University of Pennsylvania in the Department of Anatomy. Then he was self-supported at the Department of Pharmacology doing after-hours translations for *Biological Abstracts* using his fluency in French and German. Finally, he joined the US Army.

During World War II, Samter served in the 13th Field Hospital attached to division of the First Army during the invasion after D-Day (the start of the Allied offensive to free Europe from Nazi occupation) and later at the Battle of the Bulge. With the Army's need for officers knowledgeable in German, he served in an administrative capacity as a governor of a small region as the US Army started to take over German territory after the Battle of the Bulge. Unfortunately, he developed progressive percussion deafness from combat-related explosions, and after his rehabilitation he looked for a laboratory-based career. Samter went to the University of Illinois in Chicago in 1946 as a research associate in the biochemistry department. His deafness did not progress as quickly as had been feared, so he was able to resume treating patients as well. There he began his important research on allergies and clinical immunology and received a position of professor of medicine in 1969. During his career, Samter served as chief of staff at the University of Illinois Hospital, and associate dean for clinical affairs of the Abraham Lincoln School of Medicine.

After his official retirement, Grant Hospital in Chicago invited Samter to establish and direct an institute on education, research, and service in 1975. Later, the hospital, renamed the institute the Max Samter Institute of Allergy and Clinical Immunology as a tribute. He continued to treat patients until 1992.

Samter wrote the book *Immunological Diseases* during the 1950s and saw it through 4 editions. His wife Virginia Svarz Ackerman was a medical illustrator and helped him with preparation of it. The fifth edition was called *Samter's Immunologic Diseases* (Lippincott Williams & Wilkins, 1995). Samter died of cerebrovascular disease at his home in Evanston, IL, at the age of 90.

(**Publ**.: Widal MF, Abrami P, Lermoyez J. Anaphylaxie et idiosyncrasie. *La Presse Médicale* 1922; 30:189–192.

Samter M, Beers Jr. RF. Concerning the nature of intolerance to aspirin. *J Allergy* 1967; 40:281–293.)

Schaumann syndrome see **Besnier-Boeck-Schaumann disease**

Schimke syndrome (**Schimke immuno-osseous dysplasia**) is a very rare autosomal-recessive multisystem disorder characterized by spondyloepiphyseal dysplasia, progressive renal dysfunction, hypothyroidism and T cell immunodeficiency. Brief ischemic attacks, cerebral infarction and migraine-like headache are also frequent neurologic manifestations. Lymphopenia and low IgG accompanied by septicemia are also common. Hypertension and hyperlipidemia due to renal disease together with immune dysfunction could predispose patients to atherosclerosis. Two features of Schimke immuno-osseous dysplasia causing much morbidity and mortality are bone marrow failure and T cell deficiency with the subsequent opportunistic infections. Cerebrovascular disease is also an important cause of morbidity and mortality.

The disease is associated with pathogenic variants in the SMARCAL1 gene (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin, subfamily a-like 1), which encodes a DNA stress response enzyme with annealing helicase activity. It is not yet established whether mutations in the SMARCAL1 gene interfere with chromatin remodeling and the expression of other genes. However, many people with Schimke immuno-osseous dysplasia do not have recognized mutations in the SMARCAL1 gene. In these cases, the cause of the disease is unknown.

The disorder was first described in 1971 by *Schimke* and colleagues in a six-year-old girl with short stature, facial dysmorphism, discolored skin patches, skeletal abnormalities, progressive renal disease, lymphopenia and signs of defective cellular immunity.

Robert Neil Schimke (Jan 14, 1935 - April 28, 2016) was and American physician, Clinical Geneticist and Endocrinologist. He was born in Leavenworth, Kansas to Elmer and Nellie (Stucker) Schimke. He got his BS and MD degree from the University of Kansas in 1957 and 1962. He also studied organic chemistry in Bonn, Germany, and mammalian genetics at the Jackson Memorial Laboratory in Bar Harbor, Maine. He was a fellow at the Department of Human Genetics at Johns

Hopkins Hospital in Baltimore. In 1972-1976, Schimke was a Vice Chairman and Chief of Medicine at the Kansas City Veterans Administration Hospital. In 1977 - 2000, he served as the Director of the Division of Metabolism, Endocrinology and Genetics at the University of Kansas Medical Center.

Schimke published more than 180 medical papers and book chapters on birth defects and developmental delay, endocrinology, kidney and heart diseases, cancer and connective tissue conditions. His academic and teaching achievements were recognized via many teaching awards and distinguished alumni recognition.

(**Publ**.: Schimke RN, Horton WA, King CR. Chondroitin-6-sulfaturia, defective cellular immunity, and nephrotic syndrome. *Lancet* 1971; 2:1088-1089.

Schimke RN, Horton WA, King CR, Martin NL. Chondroitin-6-sulfate mucopolysaccharidosis in conjunction with lymphopenia, defective cellular immunity and the nephrotic syndrome. *Birth Defects* 1974; 12:258-266.)

Schönlein-Henoch purpura see **Henoch-Schönlein purpura**

Schick test (**Schick method**) is used to determine whether a person is susceptible to diphtheria. Susceptibility to *Corynebacterium diphtheriae* toxin can be tested by intracutaneous injection of diluted diphtheria toxin equal to 1/50 of the minimum lethal dose. Lack of immunity to diphtheria is indicated by redness and edema appearing at the injection site in 24–36 hours and lasting 4–5 days. This test largely has been replaced by hemagglutination inhibition tests.

At the end of eighteenth century, diphtheria used to be a major cause of child death in Europe and the US and promoted clinical research and efforts look into disease diagnostics and effective treatments. One of the early successes was the diphtheria test, which was developed by ***Béla Schick***. The **Schick test**, as it was called, was based on the toxin–antitoxin research of German bacteriologist Emil von Behring who in 1901 received the first Nobel Prize in Physiology or Medicine for his discovery of a diphtheria antitoxin. Schick's test was a big part of the overall success of the diphtheria vaccination, which radically lowered the incidence of diphtheria globally. There were 150,000–200,000 cases of diphtheria in the US annually until the 1920s, but the number of cases declined to less than 10 cases per year by the 1970s. A massive 5-year campaign, coordinated by Béla Schick, practically eliminated the dreaded disease that had taken countless young lives. As a part of this lifesaving operation, 85 million literature booklets were distributed by the Metropolitan Life Insurance Company with a request to parents to "Save your child from diphtheria." These illustrated brochures promoting the Schick test were created by a talented young artist, Gerta Ries, who had emigrated from Germany in 1921. Curiously enough, this same Gerta Ries (later Wiener) was awarded a commission by Jewish-American Hall of Fame more than 75 years later to create a sculpture to honor Doctor Béla Schick.

Béla Schick (Jul 16, 1877–Dec 6, 1967) was a Hungarian-born Austrian-American pediatrician. He was born in Bolgar, Hungary, to a Jewish family of Jacob Schick and Johanna Pichler Schick. Because Bela's father was a grain merchant, the family had to move to Graz, Austria. He received his medical degree from Karl

Franz University at Graz in 1900. Bela cited the Talmud—"*The world is kept alive by the breath of children*"—to convince his father to permit him to continue his medical education focusing on pediatrics instead of joining the family grain merchant business.

In 1902, Schick joined the Medicine Faculty of the University of Vienna where he remained until 1923. First, he was an assistant at the Children's Clinic in Vienna and later an associate professor of pediatrics at Vienna University. Schick was appointed to work with ***Clemens von Pirquet***, who was an assistant at the Children's Clinic. A lifelong bond sprang up immediately between these 2 geniuses. Studying problems of immunity, they coined the term "allergy" as a clinical entity. His development of a test for susceptibility to diphtheria ("Schick test"), however, made him world famous. Armed with the test, public health professionals were able to quickly and painlessly detect whether a child was or was not immune to diphtheria.

Schick immigrated to the US, where he became a citizen in 1929. From 1923 on, he was a chair of the Department of Pediatric at Mount Sinai Hospital in New York. Starting in 1936, he was a clinical professor at Columbia University. Schick also led the Department of Pediatrics in Beth-El Hospital in Brooklyn, NY (1950–1962). His research focused on scarlet fever, tuberculosis, and nutrition for infants.

He married Catherine Fries in 1925. Although they did not have children, Schick authored a popular and systematic guide for growing children, *Child Care Today*, in which he advocated against physical punishment. This was decades before such guidance was commonly accepted. He founded the American Academy of Pediatrics. Strangely enough, he always avoided publicity and spent most of his time with children in hospitals and in his medical practice. A residential building is named after him on the Stony Brook University campus. Schick died in New York.

(**Publ**.: Schick B. Die diphtherictoxin-hautreaktion del menschen als vorprobe der prophylaktischen diphtherie-heilseruminjection. *Münchener Med Wochenschrift* 1913; 60:2608–2610.)

Schmidt's syndrome (autoimmune polyendocrine syndrome type II, polyglandular autoimmune syndrome type II) is a rare autoimmune disorder affecting several glands simultaneously and causing decreased production of several essential hormones. It is the most common immunoendocrinopathy syndrome. It is seen as the mandatory incidence of autoimmune **Addison's disease** in combination with thyroid autoimmune diseases and type 1 diabetes mellitus (i.e., insulin-dependent diabetes mellitus). In addition, primary hypogonadism, myasthenia gravis, and celiac disease usually are detected in Schmidt's syndrome. Interestingly, Addison's disease, linked with **Hashimoto thyroiditis**, is the most frequent clinical association, whereas the least common clinical combination is Addison's disease, **Graves's disease,** and type 1 diabetes mellitus. The whole triglandular syndrome occasionally is referred to as **Carpenter syndrome**.

Two distinct autoimmune polyglandular syndromes have been characterized, originally referred to as type I (**Whitaker syndrome**) and type II (**Schmidt's syndrome** or Schmidt's complex). Whitaker syndrome has no known HLA association,

in contrast with Schmidt's syndrome, which is associated with HLA-DR3 and/or HLA-DR4 haplotypes, and the pattern of inheritance is autosomal dominant with variable expressivity. The 2 syndromes have a distinct etiology: Whitaker syndrome is clearly a monogenic disease, whereas it is likely that more than a single gene change is involved in Schmidt's syndrome. Differential diagnosis is based on the clinical signs specific to each disease. Schmidt's syndrome is manifested by a grouping of hypothyroidism with primary adrenocortical failure (**Addison's disease**), which also may be accompanyed by insulin-dependent diabetes mellitus, myasthenia gravis, and pernicious anemia (i.e., antiparietal cell antibody-mediated vitamin B12-deficiency anemia).

The pathogenesis of polyglandular autoimmune syndrome type II is poorly understood, but the following pathways might be involved. The individual with some degree of genetic susceptibility is exposed to the autoimmune trigger, which could be an environmental or intrinsic factor. The trigger mimics the molecular structure of a self-antigen or induces a breakdown in immunologic tolerance. This results in active production of organ-specific autoantibodies, autoimmune activity in the respective organ and progressive glandular destruction. Overt clinical disease subsequently develops when extensive organ damage has occurred.

The serum autoantibody test includes a panel of autoantibodies to 21-hydroxylase, 17-hydroxylase, thyroid peroxidase (TPO), glutamic acid decarboxylase-65 and islet cells, tissue transglutaminase antibodies, parietal cell, and anti-intrinsic factor antibodies.

The etiology of Schmidt's syndrome is also poorly understood. Some association has been reported between diabetes or hypothyroidism and congenital rubella infection. Animal studies have demonstrated that cytomegalovirus-infected mice may develop Schmidt's syndrome with lymphocytic infiltration of the thyroid, liver, myocardium, adrenals, pancreatic islets, and salivary glands. Yet, no infectious agents or noticeable immunodeficiency states have been associated with human Schmidt's syndrome. Immune stimulation by certain dietary proteins may be a possible etiologic factor. Additional possibilities include genetic susceptibility and idiopathic immunopathologic dysfunction. Some data has suggested that President John F. Kennedy suffered from Schmidt's syndrome.

In 1926, ***Schmidt*** described 2 patients with nontuberculous Addison's disease and chronic lymphocytic thyroiditis under the title "A biglandular illness adrenal and thyroid-in Addison's disease." Although neither of these patients had clinical signs of hypothyroidism, the coexistence of thyroid and adrenal insufficiency became known as Schmidt's syndrome.

Hermann Adolf Alexander Schmidt (May 15, 1831–Apr 10 (22), 1894) was a Russian-German-Estonian physiologist. He was born on the island of Mohn, the Governorate of Livonia in the Russian Empire, which is now known by its Estonian name, Muhu, in Estonia. He was a son of Gottlob Alexander von Schmidt and Eugenie Auguste von Poppen. He entered the University of Dorpat in Estonia in 1850 to study history but switched to medicine. He graduated with medical degree from Dorpat in 1858 and worked in Berlin, Vienna, and Leipzig. In 1869, he returned

to Dorpat as a professor of physiology and stayed there for the rest of his life. He was a University Rector from 1885–1889.

Schmidt is well known for his studies of blood coagulation and the discovery that the conversion of fibrinogen to fibrin was the result of an enzymatic reaction. He termed that theoretical factor "thrombin," and its precursor "**prothrombin**." Schmidt is recognized for offering a basis for understanding the anticoagulation system and accelerating the development of the blood transfusion. Schmidt died in Dorpat (Tartu), Estonia.

(**Publ**.: Schmidt MB. Eine biglandulare erkrankung (nebennieren und Schilddruse) bei morbus Addisonii. *Verhandl Dtsch Pathol Ges* 1926; 21:212.)

Schnitzler syndrome (**Schnitzler's syndrome**) is a rare autoinflammatory disorder characterized by a chronic urticaria and monoclonal IgM gammopathy. Symptoms associated with Schnitzler syndrome can include repeated bouts of fever, arthritis, arthralgia, bone pain, and lymphadenopathy. In classical Schnitzler syndrome, the monoclonal component was overwhelmingly IgM, and the light chain was kappa in 90% of cases. In a few cases, however, there was a single IgG-monoclonal component with a light-chain kappa in most instances. Approximately 10–15% of patients eventually develop a lymphoproliferative disorder (e.g., lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, or IgM myeloma). Therefore, it could be considered monoclonal gammopathy with clinical significance. Approximately 200 cases of Schnitzler syndrome have been reported in the literature. The original clinical case was from France, where the highest number of cases has been reported. The majority of known cases were described in Western Europe.

The precise pathogenesis of **Schnitzler's syndrome** is unknown. It is possible that the accumulation and deposition of the monoclonal IgM protein causes the formation of slow-resolving immune complexes and, thus, activation of the complement cascade causing cutaneous manifestations of Schnitzler syndrome. Monoclonal IgM (less likely IgG) deposits are found along the basement membrane of the skin or within the capillaries in 30% of cases. Using immunoelectron microscopy studies and immunoblotting, IgM-kappa antiskin autoantibodies have been identified at the dermal−epidermal junction. The presence of antiskin autoantibodies having the same isotype as the circulating monoclonal component suggests deposition of the monoclonal component in the skin.

Another proposed mechanism involves the uncontrolled activation of IL-1α. One study revealed polyclonal IgG autoantibodies targeting IL-1α cytokine in serum samples harvested from patients with Schnitzler syndrome. These autoantibodies prevented degradation of circulating IL-1α, altered its tissue distribution, and increased its proinflammatory effects. Consequently, this upregulation of IL-1α activity may account for the signs of urticaria and fever. Schnitzler syndrome is probably an acquired autoinflammatory characterized by recurrent episodes of inflammation because of an abnormality of the innate immune system. Because Schnitzler's syndrome has been associated with the development of lymphoproliferative disorders, it is a premalignant condition.

The disease is named after ***Schnitzler*** who first described this syndrome in 1972 and then published about it as an autonomous entity in 1974. Her description included monoclonal IgM gammopathy, chronic urticaria, inflammation, recurrent fever, bone pain, and arthralgia with occasional lymphadenopathy and/or hepatosplenomegaly.

Liliane Schnitzler (May 20, 1938–) is a French dermatologist, who was associated with Service de Dermatologie, Hospital Saint-Louis in Paris. She was the first woman to be made a professor of dermatology in France and head of the department at the age of 31 in 1970.

(**Publ**.: Schnitzler L. Lésions urticariennes chroniques permanentes (érythème pétaloïde?) Cas cliniques No 46 B. *J Dermatol Angers* 1972; Abstract 46.

Schnitzler L, Schubert B, Boasson M. Urticaire chronique, lons osseuses, macroglobuline IgM: Maladie de Waldenstrom. *Bull Soc Franc Derm Syph* 1974; 81:363.)

Schönlein-Henoch purpura see **Henoch-Schönlein purpura**

Schönlein-Henoch-Glanzmann disease see **Henoch-Schönlein purpura**

Schridde's granules see **Altmann-Schridde granules**

Sedlackova syndrome see **DiGeorge syndrome**

Senear-Usher syndrome (pemphigus erythematosus) is a dermatosis that combines the characteristics of lupus erythematosus and pemphigus foliaceus. Analysis of skin biopsies of patients with Senear-Usher syndrome shows acantholysis (i.e., loss of cohesion between keratinocytes) and deposition of immunoglobulins in desmosomes. Skin samples were positive in the lupus band test—a direct immunofluorescence staining of IgG and complement elements at the dermoepidermal junction. Both antiepithelial antibodies specific for desmogleins 1 and 3—that is, a family of desmosomal cadherins—and antinuclear antibodies (ANA) specific for **Ro**, **La**, **Sm,** and double-stranded DNA (dsDNA) antigens have been detected in patients with pemphigus erythematosus. Remarkably, cross-reactivity studies proved that autoantibodies in pemphigus erythematosus recognize various antigens and antigenic determinants and are produced by several clones of plasma cells, suggesting that **Senear-Usher syndrome** behaves as a multiple autoimmune disease.

The first patient known to have this disease was described by Ormsby and Mitchell, while ***Senear*** and ***Usher*** reported a group of 11 patients with blisters and sores on the skin or mucous membranes and acantholysis on skin specimens and all had clinical signs of lupus erythematosus. Later, pemphigus erythematosus was suggested to be a clinical variation of pemphigus foliaceus. The disease currently is considered to be a benign form of pemphigus foliaceus, which comprises signs and serological markers of lupus erythematosus.

Frances Eugene Senear (Nov 5, 1889–Feb 11, 1958) was born in Salamanca, New York, where he attended the elementary and high schools and enrolled at the University of Michigan in a combined literary and medical course. He received his bachelor of science and his medical degree in 1914. Then he was an intern and instructor in dermatology and syphilology at the University of Michigan Hospital, worked in Chicago, and was an instructor and professor at the University of Illinois College of Medicine. He held this position for 32 years until 1958, when he became a Professor Emeritus. Senear was secretary of the Section of Dermatology of the American Medical Association, president of the Chicago Dermatological Society, president of the American Board of Dermatology and Syphilology, and president of the American Academy of Dermatology and Syphilology.

He lived in a very large home in Winnetka, IL, and had a most delightful hobby that ultimately made him a connoisseur of English china and Georgian silver. His entire home was filled with treasures, and he seemed to know the value of each piece in his collection. He was married in 1917 to Anne E. Seitz who preceded him in death. He was survived by one son and 4 grandchildren.

Barney David Usher (Jul 1, 1899–Jul 14, 1978). the first Canadian dermatologist to have his name eponymically attached to a disease, was born in Montreal. He obtained his medical education and his MD degree from McGill University in 1922. He did his internship in Cleveland, OH, and began to focus on dermatologist. He received additional medical training at the University of Illinois in Chicago, where he met ***Francis Senear***. In 1926, in collaboration with Senear, Usher published their clinical report describing pemphigus erythematosus, generally known as Senear-Usher syndrome.

In 1926, Usher returned to Montreal, started his private practice, and received a faculty position at McGill University, where he trained students and fellows for more than 50 years. Teaching was his great love. He was one of the first clinicians in Canada who combined clinical research with clinical practice, and he was elected a member of the Canadian Dermatological Association, being its president on 2 terms. During his second presidency, he started the research aid award that was later to bear his name. Usher's research included studies on sweating, pathogenesis of eczematous diseases, and the occurrence of emotional disruptions in diverse dermatoses.

Although he enjoyed a moderate private practice, making money was of minor importance. He took pride in the fact that he saw patients only for an average of 2–3 visits. He enjoyed spending time with the patients and could never understand how anyone could get any fun out of in running what he called "a mill"—that is, in seeing 60–70 patients each day. Usher retired in 1964 and after that devoted himself to teaching residents and was active to the very end. He was planning his usual Friday morning teaching session when he suffered his final heart attack and died. He was survived by his wife Ruth, 2 children, and 4 grandchildren.

(**Publ.:** Senear FE, Usher B. Unusual type of pemphigus combining features of lupus erythematosus. *Arch Dermatol & Syphilol* 1926; 13:761–781.)

Sézary cells (**Lutzner's cells**, **Sézary-Lutzner cells**) are large (8–20 μm) T cells with irregularly shaped (i.e., prominently folded, convoluted, and often cerebriform) nuclei and pale, blue-to-gray cytoplasm, which may contain small vacuoles filled with mucopolysaccharide. Clusters of these cells in the epidermis are called **Pautrier's microabscess**. Sezary cells are associated with several diseases (e.g., **Sézary syndrome**, eczema, psoriasis, mycosis fungoides, HIV infection, and other viral illnesses). The tumor cells of **Sézary syndrome** in peripheral blood smear present cerebroid nuclei. The larger ones are called **Sézary cells**, and the smaller ones are called **Lutzner cells**. Lutzner cells are larger than normal lymphocytes and contain extensive folding in their membranes. They also contain a big nucleus with a minimum cytoplasm. Lutzner cells are more predominant in mycosis fungoides but can be seen in Sézary syndrome. Sézary cells are larger than Lutzner cells and have an overabundance of cellular folds in the membrane. Sézary cells can be found in both mycosis fungoides and Sézary syndrome.

Marvin A. Lutzner see **Sézary syndrome**

Sézary syndrome is a type of cutaneous lymphoma and sometimes is considered a late stage of mycosis fungoides with lymphadenopathy. Sézary syndrome and mycosis fungoides are T-cell lymphomas that have a primary manifestation in the skin. Usually, the **Sezary cell** is the malignant pleomorphic T cell seen in mycosis fungoides and has a convoluted nucleus. Cells were described first by ***Albert Sézary***.

Albert Sézary (Dec 26, 1880–Dec 1956) was a French physician/dermatologist. He was born in Algiers and studied in Paris. After an outstanding scholastic career, he became an intern in hospitals in Algeria in 1901. In 1903, he moved to Paris and worked first in neurology and then in dermatology and venereal disease. Sézary received his medical doctorate in 1909 and worked at the medical clinic in Hôtel-Dieu at the Laennec-Hospital. In 1921, Sézary announced a combination therapy with arsenic and bismuth that cured syphilis after reinfection in many of his patients. He became a professor of dermatology in 1927. In 1937, he was elected president of the French Society of Dermatology, and he was elected to the National Medical Academy in 1945. Sézary's publications covered topics such as disorders of the adrenal glands, tuberculin therapy, and antituberculous serotherapy. He was the author of a number of works on syphilis and its treatment and a dermatology textbook.

Marvin A. Lutzner (Nov 1930–) is a US dermatologist, who was affiliated with the Dermatology Branch, National Cancer Institute, NIH, Bethesda, MD.

Lucien-Marie Pautrier (Aug 2, 1876–Jul 9, 1959) was a French dermatologist. He commenced his medical studies in Marseille, where he was born, but transferred to Paris where he became a dermatologist at the Hospital Saint-Louis. During World War I, he was a medical officer to a field artillery regiment. He was awarded the Croix de Guerre (War Cross) for bravery under fire. He became a Chevalier (Knight) de la Légion d'Honneur (Legion of Honor), the highest French distinction for military accomplishments, in 1916. He finally became a Grand Officer. At the end of the

war, he founded a center for investigation of skin and venereal disease in Bourges in Central France. Pautrier received a position of a professor of dermatology in Strasbourg, where he was able to quickly build a domestic and international reputation and attracted students, residents, and fellows from many countries. He retired in 1947 and occupied himself with his great love of art and music. He founded a society of the Friends of Music in Strasbourg and created the Center for Research in Experimental Surgery at the university.

The history of the eponym is fully described by Cathrin Constanze Schmidt-Skrabs (2000). In 1937, Pautrier served as a president of Réunion Dermatologique de Strasbourg—a special meeting dealing with granulomatous skin manifestations in Strasburg, France. He presented an impressive histologic picture with 4 little nests of lymphocytes. In 1946, at the 66th Annual Conference of the American Dermatological Association, Louis Winer—a dermatologist from Los Angeles—during his lecture on mycosis fungoides used the term "intraepidermal microabscesses of Pautrier," giving credit to his outstanding histopathologic work. The eponymic term ultimately was established when Walter Lever, in 1949, identified 6 diagnostic differences seen in the plaque stage of mycosis fungoides (see **Alibert-Bazin syndrome**), with "Pautrier microabscesses" being one of them.

(**Publ**.: Sézary A. Pathogénie et sémiologie des mélanodernies du type addisonien. *La Presse Méd* 1921; 281–283.

Sézary A, Bouvrain Y. Erythrodérmie avec présence de cellules monstrueuses dans le derme et le sang circulant. *Bull Soc Franç Derm Syph* 1938; 45:254–260.

Lutzner MA, Jordan HW. The ultrastructure of an abnormal cell in Sézary syndrome. *Blood* 1968; 31(6):719–726.)

Pautrier LM. Erythrodermie quasi-généralisée, mais respectant des îlots de peau saine, avec petit tumeurs à formule histologique de mycosis fungoide et s'accompagnant de lésions sanguines du type leucémie lymphoide. *Bull Soc Franç Derm Syph* 1937; 44:1307–1320.)

Sézary-Lutzner cells see **Sézary cells**

Sharp syndrome (**mixed connective tissue disease, MCTD, mixed collagenosis**) is a systemic autoimmune inflammatory disease characterized by clinical and serological overlap of systemic lupus erythematosus (SLE), systemic sclerosis and polymyositis. Many patients with this uncommon disorder may also have Sjogren's syndrome. Hence, MCTD is sometimes called an "overlap disease". The term "Sharp syndrome" is predominantly used in the English-speaking countries.

The clinical pictures of MCTD commonly develop over several years, and the entire clinical signs are seldom seen at the initial stage of the disease. The most common manifestations of Sharp syndrome at onset are polyarthritis, Raynaud's phenomenon and swollen fingers or hands. However, a broad spectrum of joint disorders may also occur.

Although there are no highly specific diagnostic findings for MCTD, all patients with MCTD have a positive antinuclear antibody (ANA) results with a speckled staining pattern and high titer of U1-RNP autoantibodies. U1-nRNP antibodies,

known initially as anti-Mo antibodies and also known as anti-ribonucleoprotein antibodies, are a subclass of anti-RNP antibodies. U1-RNP is a component of the spliceosome complex that regulates splicing of pre-messenger RNA to mature RNA. Anti-U1-RNP are the "sine qua non" criterion for the MCTD, though they were reported in other connective tissue diseases (CTD), including SLE. About 30-100% of MCTD patients also have a positive Rheumatoid factor but usually do not have anti-Sm, Scl-70, dsDNA, anti-centromere or anti-Jo antibodies. Very few patients with MCTD might have positive SSA and SSB antibodies.

In 1972, *Sharp* and colleagues reported on 25 patients who demonstrated mixed features of scleroderma, polymyositis, dermatomyositis and systemic lupus erythematosus. The uniqueness of these patients were in the fact that their blood samples had speckled pattern of fluorescent antinuclear antibodies (ANA) associated with a high titer of antibodies to extractable nuclear antigen (ENA), now known as U1-RNP autoantibody. Clinical data revealed a high incidence of **Raynaud phenomenon**, arthralgias, arthritis, myositis and swollen hands. In 1973, Sharp et al reported additional 92 cases, and, by 1975, a total of 200 cases had been described from the combined experience of several medical centers. Sharp and his colleagues termed this group of disease "mixed connective tissue disease", which is commonly used today.

Gordon C. Sharp is an American internist. He described MCTD during his residency at the Department of Medicine, Stanford University School of Medicine in 1972. He then work as clinician and researcher at the Division of Immunology and Rheumatology, Department of Medicine, University of Missouri School of Medicine in Columbia, Missouri.

(**Publ**.: Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease-an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med*. 1972; 52(2):148-159.

Sharp GC, May C, Irvin WS, et al: Clinical and laboratory characteristics of patients with antibodies to the ribonucleoprotein (RNP) component of extractable nuclear antigen (ENA). Arthritis Rheum. 1973; 16:569. Sharp GC. Mixed connective tissue disease. *Bull Rheum Dis*. 1975; 25:828-831.)

Shoenfeld syndrome (**Shoenfeld's syndrome**, autoimmune syndrome induced by adjuvants, ASIA) groups various autoimmune conditions triggered by external stimuli. This syndrome is characterized by the appearance of myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, and the possible emergence of a demyelinating autoimmune disease caused by systemic exposure after vaccines and adjuvants.

During the 1990s, the term "functional somatic syndromes" was used commonly to describe several related syndromes. They included multiple chemical sensitivity, adverse effects of silicone breast implants, Gulf War syndrome (GWS), repetition stress injury, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and "sick building syndrome" (i.e., a set of clinical signs described by building occupants that have no clear cause). Then, ***Shoenfeld*** and Agmon-Levin proposed that 4

conditions—siliconosis, macrophagic myofasciitis, GWS, and postvaccination phenomena that have common clinical and pathogenic similarities—should be embraced under a common syndrome. This is the "autoimmune (autoinflammatory) syndrome induced by adjuvants," now known as **Shoenfeld's syndrome**.

ASIA also may include the side effects of silicone-filled breast implants, or "silicone implant incompatibility syndrome." Essentially, Shoenfeld's syndrome covers several different conditions that do not really belong to classic autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, or scleroderma, but can be encouraged by chronic stimulation of the immune system by materials or agents that may work as adjuvants. This chronic immune stimulation results in the appearance of those new symptoms, which include arthritis, myalgia, fatigue, and neurological manifestations.

The vestige of ASIA as a new syndrome was established after thought-provoking studies on Gulf War syndrome had been reported by soldiers who had not been deployed to the Gulf area but suffered from severe fatigue, myalgias, cognitive impairment, and arthralgias. This raised the hypothesis that it was some vaccines administered to the soldiers that induced the syndrome. Another condition—the "sick building syndrome"—seems to lead to similar clinical symptoms as GWS and manifests in people living in a specific room or building. Once they move to another location, however, individuals completely recover. It is believed that, in the original place, there is some substance that causes a reaction or behavior like the adjuvant.

The prevalence of Shoenfeld's syndrome is greater in subjects that carry the gene *HLA-DRB1*, the same HLA that has been found to be present in those who had developed an autoimmune disease following vaccine administration. The syndrome can be induced by the cascade of cytokines released in response to chronic stimulation, including IFN-γ, IFN-α, IL-1, IL-6, TNF-α, and others. This chronic stimulation also may alter the integrity of the blood–brain barrier, and aluminum particles from a vaccine can cross the barrier through macrophages and deposit them in the brain. In addition, chronic stimulation also could induce production of various autoantibodies.

Yehuda Shoenfeld (Feb 14, 1948–) is an autoimmune disease physician and researcher working in Tel Aviv, Israel. He was born in Slovakia; received his MD degree from Hadassah Medical School, Hebrew University in Jerusalem in 1972; and completed his postgraduate studies in internal medicine at the Postgraduate Medical School, Tel Aviv University in 1978. After residency at Beilinson Medical Center, Petach Tikva, Israel, he finished 3 clinical fellowship courses in hematology/oncology at the Department of Hematology, City of Hope, CA; Tufts New England Medical Center in Boston, MA; and Cornell Medical Center, New York Hospital. Since then he has worked at Beilinson Medical Center; Soroka Medical Center, Beer Sheva; Ben-Gurion University of the Negev, Beer Sheva; and Tel Aviv University.

His clinical and basic research focuses on autoimmune and rheumatic diseases. Shoenfeld has published more than 1700 papers in journals as follows: the *New England Journal of Medicine*, *Nature*, *Lancet*, *PNAS*, the *Journal of Clinical*

Investigation, the *Journal of Immunology*, *Blood*, *FASEB*, the *Journal of Experimental Medicine*, *Circulation*, *Cancer*, and so on. He has written more than 350 book chapters and edited 25 books, including *The Mosaic of Autoimmunity*, *Infections and Autoimmunity*, *Autoantibodies*, and *Diagnostic Criteria of Autoimmune Diseases*.

Shoenfeld is the founding director of the Zabludowicz Center for Autoimmune Diseases at the Sheba Medical Center and chair for research of Autoimmune Diseases at Tel Aviv University in Israel. He has received multiple awards, including a Life Contribution Prize in Internal Medicine in Israel, a gold medal from the Slovak Society of Physicians, and the Nelson's Prize for Humanity and Science. He is a honorary member of the Hungarian Association of Rheumatology and the Slovenian National Academy of Sciences.

Shoenfeld is on the editorial board of 43 journals in the fields of rheumatology and autoimmunity and is the founder and editor of the *Israel Medical Association Journal*, *Autoimmunity Reviews*, and *Harefuah* (the journal of the Israel Medical Association) and coeditor of *The Journal of Autoimmunity*. He has organized more than 20 international conferences and meetings to discuss the modern problems of autoimmunity.

(**Publ.:** Shoenfeld Y, Agmon-Levin N. "ASIA": Autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36(1):4–8.)

Shprintzen syndrome see **DiGeorge syndrome**

Shwachman-Bodian-Diamond syndrome see **Shwachman-Diamond syndrome**

Shwachman-Diamond syndrome (**Shwachman-Bodian-Diamond syndrome**, **Shwachman-Diamond-Oski syndrome**) is a rare congenital disorder that affects many parts of the body, particularly the bone marrow, pancreas, and skeletal system. Among hematologic abnormalities, intermittent or persistent neutropenia is the most common finding, although anemia and thrombocytopenia also can occur. Low neutrophil counts increase the risk of severe recurrent infections that may be life-threatening. Bone marrow typically is hypocellular, with maturation arrest in the myeloid lineages that give rise to neutrophils, macrophages, platelets, and red blood cells. Patients also may develop progressive marrow failure or transform to acute myelogenous leukemia. In 2003, mutations in the *SBDS* gene (**Shwachman-Bodian-Diamond syndrome**) were found to be associated with the disease. The *SBDS* gene is expressed in all tissues and encodes a protein of 250 amino acid residues. The function of this protein is not known with some data suggesting that it may be involved in an aspect of cellular RNA metabolism or ribosome assembly or function.

The disease was described initially in the early 1960s by ***Nezelof*** and Watchi, primarily as a syndrome encompassing pancreatic exocrine insufficiency and neutropenia. Later, as a coherent clinical entity, it was described in May of 1964 by ***Bodian***, Sheldon, and Lightwood. It subsequently was described by ***Shwachman***, ***Diamond***, Oski, and Khaw in November of the same year, reporting on a group of 5 children participating in a cystic fibrosis clinic at Harvard Medical School.

Harry Shwachman (Mar 19, 1910–Sept 9, 1986), a US physician, was born in Boston to a Jewish family running a kosher market there. He graduated from the Massachusetts Institute of Technology in 1932 and received his medical degree from the Johns Hopkins Medical School in 1936. Following a year of internship at Johns Hopkins Hospital, he went to Children's Hospital as a resident in pediatrics in 1937. During World War II, he served as a captain and later a major in the US Army Medical Corps. After the war, he became chief of the Chronic Nutrition Clinic at Children's Hospital and began a long association with Harvard Medical School, first as an instructor and then an associate and later assistant professor in pediatrics.

Shwachman directed the Children's Hospital's clinical laboratories in Boston from 1946–1971, where he founded and developed the Chronic Nutrition Clinic, one of the largest in the country. He authored more than 260 publications, trained generations of researchers, and was a dedicated clinician, legendary for his devotion to his patients and their families. He received the Borden Award from the American Academy of Pediatrics in recognition of his significant contributions to pediatric nutrition, including reports on cystic fibrosis and other nutrition-related subjects. He also received the academy's E. Mead Johnson Award and in 1965 was presented the Award of the National Cystic Fibrosis Research Foundation.

In addition, Shwachman was an accomplished violinist and founding member of the Newton Symphony Orchestra. He retired in 1976 from medical praticee but continued as an adviser and consultant at the Children's Hospital Cystic Fibrosis Center. He lived in Needham, MA, and died in Boston after a stroke. He had a wife, a son, and 2 daughters.

Martin Bodian (1910–Sept 25, 1963) was a pathologist and director of Department of Morbid Anatomy at the Great Ormond Street Hospital for Sick Children in London. Born in Vienna of Jewish descent, Martin Bodian qualified in medicine in 1934. He began his pediatric studies at the University Children Hospital in Vienna. In 1938, however, he, as well as all other Jews, was forced to leave Austria and went to England with his family and settled in London. He moved to Edinburgh and from there to the pathology department of the Postgraduate Medical School, London. After obtaining the diploma in clinical pathology, he was appointed temporary pathologist at the Hospital for Sick Children in 1943. In 1946, he was appointed to the permanent staff as a morbid anatomist. Martin Bodian was an excellent teacher of postgraduate students and was also in demand for the special courses held at the Institute of Child Health. In 1953, he received a British Empire Fellowship for the Campaign Against Cancer, which thereafter was renewed for him annually. He was a member of many professional societies, including the Pathological Society of Great Britain and Ireland, the Association of Clinical Pathologists, and the British Pediatric Association.

Martin Bodian was a man wih wide cultural knowledge. He was particularly interested in music and loved to attend concerts whenever he could. For many years, he lived with his mother and sister in a small apartment and devoted himself to them. His friends saw him as an inveterate bachelor. Nonetheless, in 1955 he married an English girl who was one of his secretaries. The marriage was very happy

and gave him the stable home environment he needed. Bodian became depressed when his wife was diagnosed with cancer. His many friends were shocked when he had a massive brain hemorrhage that proved fatal within 48 hours.

Louis Klein Diamond see **Blackfan-Diamond syndrome**

(**Publ**.: Nezelof C, Watchi M. L'hypoplasie congenitale lipomateuse du pancreas exocrine chez l'enfant (Deux observations et revue de la literature). *Arch Franc Pediat* 1961; 18:1135–1172.

Bodian M, Sheldon W, Lightwood R. Congenital hypoplasia of the exocrine pancreas. *Acta Paediatr* 1964; 53:282–293.

Bodian M. Fibrocystic disease of the pancreas. *Arch Dis Child* 1946; 21(107): 179 [Abstract].

Shwachman H, Diamond LK, Oski FA, Khaw KT. The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 1964; 65: 645–663.)

Shwachman-Diamond-Oski syndrome see **Shwachman-Diamond syndrome**

Sjögren's syndrome (**Sjögren disease, Gougerot-Houwer-Sjögren syndrome**, **Gougerot-Sjögren syndrome**, **Gougerot's syndrome**, **von Mikulicz-Gougerot-Sjögren syndrome,** sicca syndrome) is a chronic autoimmune disease—an inflammatory exocrinopathy—affecting mainly postmenopausal women (80–90%) or younger women after artificial menopause. Sjögren's syndrome is the second most common autoimmune rheumatic disorder, following rheumatoid arthritis. The autoimmune reaction in the salivary and lacrimal glands leads to the development of xerostomia (i.e., dry mouth) and keratoconjunctivitis sicca (i.e., dry eyes), which takes place in association with lymphocytic infiltration of the glands. The inflammatory process eventually damages or destroys the glands. The hallmark symptom of **Sjögren's syndrome** is a generalized dryness, typically including xerostomia and keratoconjunctivitis sicca. Sjögren's syndrome may cause skin, nose, and vaginal dryness and may affect other organs, including the kidneys, blood vessels, lungs, liver, biliary system, pancreas, peripheral nervous system, and the brain. As in the case of many autoimmune disorders, even though the cause of Sjögren's syndrome is unclear, a combination of genetic, environmental, and hormonal factors plays a crucial role in the disease's development.

Detection of serum autoantibodies is important for disease diagnosis and includes assessment of antinuclear antibody (ANA) and rheumatoid factors, because Sjögren's syndrome often arises secondary to rheumatoid arthritis. Characteristic Sjögren's syndrome ANA patterns are SSA/Ro and SSB/La autoantibodies, of which SSB/La is more specific. Although SSA/Ro often is present in Sjögren's syndrome, the antibody is known to be linked with a variety of autoimmune systemic connective tissue diseases.

It is named for ***Henrik Samuel Conrad Sjögren***, a Swedish ophthalmologist. ***Johann von Mikulicz-Radecki***, however, usually is credited for giving the first description of the clinical representation of Sjögren's syndrome. In 1892, he reported on a 42-year-old man with enlarged parotid and lacrimal glands associated with a round-cell accumulation in the tissue and acinar atrophy (i.e., distraction of

the acinar epithelial cells), but his diagnostic criteria had led to misdiagnosis as **Mikulicz's syndrome**. In 1925, ***Henri Gougerot*** described 3 clinical cases of salivary gland atrophy, which was associated with dryness of eyes, mouth, and vagina. ***Houwer*** in 1927 and Wissmann in 1932 explained the association of keratoconjunctivitis sicca and arthritis in a few patients. ***Sjögren*** described this syndrome in his doctoral thesis, "Zur Kenntnis der keratoconjunctivitis sicca," in 1933. He introduced the term "keratoconjunctivitis sicca" for the symptom of dry eyes. Yet, the thesis was not of a sufficiently high standard to be awarded the title of "docent"; thus, Sjögren was denied the opportunity for a career in academic ophthalmology. In 1943, however, the paper was translated into English, a fact that contributed to establishing the eponym. In France, the term **Gougerot's syndrome** has been used for decades.

Jan Mikulicz-Radecki see **Mikulicz syndrome**

Henri Gougerot (Jul 2, 1881–Jan 15, 1955) was a French dermatologist. He was born in Saint-Ouen-sur-Seine and earned his doctorate from the University of Paris. He chaired the '"Clinique des Maladies Cutanées et Syphilitiques" of the Department of Medicine, University of Paris, from 1928–1951 and became the well-known representative of French dermatology. Gougerot published more than 250 articles; he was known especially for his outstanding studies on infectious superficial dermatitis; hypodermitis; foreign-body granulomas; the capillaritis associated with the trisyndrome, which is named after him; the cutaneous allergies; and numerous studies on mycology, tropical pathology, and syphilography. For his achievements during World War I, he was awarded the French Croix de Guerre.

Adriaan Willem Mulock Houwer (May 2, 1884–Mar 7, 1983) was a Dutch ophthalmological surgeon.

Henrik Samuel Conrad Sjögren (Jul 23, 1899–Sept 17, 1986) was a Swedish ophthalmologist. He was born in Köping on Mälaren, Scheele, and was the son of the merchant Anders Conrad Johansson and Marta Emelie Sjögren. He studied medicine at the Karolinska Institute, graduated in 1922, and qualified as a physician in 1927. The next year he married Maria Hellgren, his student friend and the daughter of one of the most renowned ophthalmologists in Stockholm. Sjögren's interest in ophthalmology can be dated back to 1925 when he started to work at Seraphim Hospital in Stockholm and saw a 49-year-old woman with "his" syndrome. In 1936, he started to work as an ophthalmologist in Hospital Jönköping. In 1957, Sjögren received an appointment of associate professor (docent) at the University of Göteborg where he was awarded the title of honorary professor in 1961. Henrik Sjögren died in a nursing house in Lund, where he had been living since his retirement in 1967. He particularly loved to use the library there.

(**Publ**.: Sjögren H. On knowledge of keratoconjunctivitis sicca. Keratitis filiformis due to lacrimal gland hypofunction. *Acts Opthslmol* 1933; Suppl 2:1–151).
Sm antigen belongs to a heterogeneous group of more than 150 diverse extractable cytoplasmic and nuclear antigens characterized on a Hep2 cell line used to screen

for antinuclear antibodies (ANA). The detection of autoantibodies targeting these antigens is a well-established tool in the diagnosis of autoimmune connective tissue disorders. Antibodies targeting extractable nuclear antigens (ENA) or ANA were reported first in 1959, when Holman et al. noticed a precipitin reaction of serum specimens from SLE patients with ENA harvested from calf thymus (Holman et al., 1959). The ANA test is carried out by indirect fluorescent techniques using Hep2 cells. The nomenclature of an autoantibody-recognizing ENA has been historically determined—that is, the nuclear location of the antigen (RNP, ribonucleoprotein), the name of the patient offering the prototype serum (e.g., **Ro**, **La**, **Sm**, **Jo**, **Mi**), or the disease associated with the serum sample (**Sjögren's syndrome** [SS-A and SS-B], scleroderma [Scl-70], or polymyositis [PM]).

In 1966, Tan and Kunkel described an indirect immunofluorescence test as a new autoantibody assessing system and noticed a definite speckled-fluorescence staining in cell nuclei in several patients with SLE. The prototype serum for their report was harvested from a female patient who had suffered from SLE since early adolescence. Her name was ***Stephanie Smith***, and she was diagnosed with SLE at the age of 15 at the Rockefeller University Hospital. She presented with rash, arthritis, pleuritis, elevated sedimentation rate, and gammaglobulinemia without renal dysfunction. Stephanie succumbed to complications of her disease and in spite of treatment 7 years later. The autoantibody, therefore, was termed "anti-Sm antibody" (Tan and Kunkel, 2006). Sm was the first nonhistone antigen against which patients with SLE produce autoantibodies. Subsequently, many nonhistone antigens have been recognized, including Ro, La, and Ku.

It has been established that the Sm and RNP antigens are particles comprised of small nuclear (sn)RNAs, also known as snRNPs. Autoantibodies to snRNPs, including **anti-Sm** and anti-U1RNP, were one of the first autoantibodies described as nonhistone proteins. Common anti-snRNP autoantibodies are grouped into anti-U1RNP, which recognize U1snRNPs and anti-Sm, that recognize U1, U2, U4-6, and U5 snRNPs. Sera with anti-U1RNP or anti-Sm antibodies display a coarse nuclear speckled pattern in ANA assay, but sera with antibodies to other proteins of snRNP show nuclear dots staining, known as **Cajal body** and cytoplasmic staining in an ANA test.

The autoantibodies binding to Sm and RNP macromolecules were instrumental in expounding the structure of the snRNPs and in decoding their imperative function in splicing precursor mRNA. Autoantibodies to the Sm core particle are unique to SLE, whereas antibodies targeting RNP-antigenic determinants may be detected in scleroderma, polymyositis, and other systemic autoimmune diseases, as well as SLE. High levels of anti-snRNP antibodies, without anti-Sm, can be found in mixed connective tissue disease.

Smith's disease (**Carl Smith's disease**, acute infectious lymphocytosis) was described as a benign clinical condition usually seen in children and sometimes in young adults. It frequently is designated prominent lymphocytosis—an abnormal increase in the number of circulating white blood cells. The leukocyte count may range from 20,000–120,000 per mm^3, whereas the total leukocyte count in normal blood ranges from 5000–10,000 white cells per mm^3. Differing clinical signs include

moderate fever, morbilliform (i.e., measles-like, maculopapular) eruption (i.e., rashes), pharyngeal exanthema (i.e., acute infection of the pharyngeal mucosa), respiratory infection, gastrointestinal disorders, diarrhea, abdominal distension (i.e., swelling of the abdomen), and even meningoencephalitis. Other features can include cervical or generalized adenopathy and moderate splenomegaly. Smith's disease may be induced by infectious mononucleosis, whopping cough, German measles, and other diseases.

In 1944, ***Carl Smith*** first described the disease of infectious lymphocytosis—a principal feature of which is an increase in the lymphocytes. Clinical conditions of the disease have been described in many editions of ***Carl H. Smith****'s, Blood Diseases of Infancy and Childhood*, book. Interestingly, the same illness with most of its peculiarities was described by S. Rosenbaum (Tel Aviv) in his paper "Febris lymphocytotica" in 1938 in *Ann Pediatr* 152(Nov):117.

Carl Henry Smith see **Canale-Smith syndrome**

(**Publ**.: Smith CH. Acute infectious lymphocytosis: A specific infection. *J Amer Med Assoc* 1944; 125:342.)

Sneddon's syndrome (**Ehrmann-Sneddon syndrome**) is a rare form of slowly progressive arteriopathy impacting small- and medium-sized blood vessels. The disorder is primarily characterized by the involvement of a skin (i.e., livedo reticularis) and neurological abnormalities. The histopathology of skin and brain is notable for a noninflammatory thrombotic vasculopathy. Typical clinical signs include numerous episodes of transient reduction of blood flow to the brain (i.e., cerebral ischemia) causing ministrokes or stroke and patchy bluish-purple net-like patterns of discoloration of the skin adjacent to normal-looking skin. Decreased blood flow to the brain may cause headache, dizziness, memory loss, personality changes, and other neurological abnormalities. The skin signs may precede the neurologic symptoms by months or years.

The syndrome was described initially by ***Ehrmann*** in 1907; he considered it to be a symptom of syphilis, and it was recognized as a separate entity by ***Sneddon*** in 1965. It has not beem clear for a long time whether Sneddon syndrome is a distinct disease, component of a variety of disorders, or a subtype of antiphospholipid syndrome. There is a suggestion that **Sneddon syndrome** should be divided into primary and secondary diseases. Primary or idiopathic Sneddon syndrome may represent cases with no known cause, whereas secondary Sneddon syndrome should indicate cases that occur secondary to another disease or a thrombophilic (i.e., prothrombotic or hypercoagulable) state. Sneddon syndrome also may be differentiated by the presence (aPL-positive) or absence (aPL-negative) of antiphospholipid antibodies.

The exact cause of Sneddon syndrome often is said to be unknown. Most cases are sporadic, but some familial ones with autosomal-dominant inheritance have been described. Potential immunological, environmental, genetic, and other agents or conditions still are under consideration as possible triggers of the disease. Many affected patients have high levels of blood antiphospholipid antibodies. Sometimes,

Sneddon syndrome can be related to other autoimmune diseases (e.g., SLE, **Behcet's disease,** or mixed connective-tissue disease).

Salomon Ehrmann (Dec 19, 1854–Oct 24, 1926) was a Jewish-Austrian dermatologist and histologist. He was born in the village of Ostrovec, now part of the Czech Republic, to Marcus Ehrmann and Franziska Fanny Ehrmann. He first studied art history in Prague but then turned to medicine and began studying it in Vienna in 1874; he completed a doctorate in 1880.

Ehrmann's first research focused on the field of physiology. He then took up dermatology as a specialty and became an assistant to ***Kaposi*** and to ***Neumann*** at the University of Vienna. From 1908 on, he was placed in charge of a hospital department of dermatology and syphilology as a university professor and clinical director. Some of his main works were *Studies on Pigmentation, Physiology and Histology of the Skin*, *Origin of Neoplasms*, *Differential Diagnosis and Treatment of Skin Diseases*, and *Atlas of Skin Diseases* (masterfully illustrated by their author). In dermatology, he introduced many new drugs, medicaments, and methods. He developed the radiologic treatment of skin disease. For instance, he was one of the earliest advocates for using UV lamps: Psoriasis and other superficial scaling dermatoses were treated that way with encouraging results. He was the first to discover *Spirochaeta pallida* in the nerve sheath of syphilitic individuals.

Ehrmann was a member of the Austrian Society for Combating Venereal Diseases, vice president of the Vienna Dermatological Society, board member of the German Dermatological Society, and honorary member of several foreign dermatological societies. He was also a talented painter and head of the Vienna Jewish Community. He was a member of the honorary committee of the "Support Association of Jewish Students from Galicia in Vienna" and president of B'nai B'rith (בני ברית)—an Association for the Rescue of Abandoned Jewish Children of Galicia and Bukovina.

Ian Bruce Sneddon (Mar 6, 1915–Oct 10, 1987) was a Scottish dermatologist. He was born in Sheffield in England and was the only son of Kathleen Hield and Scottish general practitioner William Sneddon. He studied at the University of Sheffield, and in 1937 he graduated from medical studies. In 1938, Sneddon became a clinical assistant in the skin department of the university.

During the World War II, he served in the Royal Naval Volunteer Reserve as a physician and dermatologist. For 2 years, he served in the Pacific region and in Australia in Sydney Harbour, where he fell in love with sailing. All through the war, Sneddon saw numerous cases of neuropathy in prisoners of war expelled from Hong Kong. He noted the presence of ophthalmological and neurological abnormalities, which included weakening of visual acuity because of central and paracentral scotomata (i.e., a partial loss of vision or blind spot), fractional optic atrophy, macular degeneration, and failure of hearing; in addition, there nay be swelling of the ankles, paresthesia (i.e., abnormal sensation) of the limbs, and walking difficulty. After examining almost 200 sick prisoners who were transported to the Royal Naval Hospital in Sydney in 1945, in collaboration with Cyril Astley Clarke, he published an article and prepared a film on nutritional neuropathy in prisoners of war. They

linked these conditions with a toxic and low vitamin diet, primarily coupled with vitamin B complex deficiency.

After demobilization in 1946, Sneddon, who had reached the rank of Surgeon Lieutenant Commander, went back to Sheffield and received an appointment in the dermatology department at the Royal Infirmary as a supernumerary registrar in special residency training program. He married Joan Simon, a psychiatrist, and they had 3 daughters and 2 sons. Sneddon and Joan had common clinical interests in the psychiatric aspects of skin disease and worked together in that field. In 1950, Sneddon was appointed Clinical Dean and remained in that position for the next 18 years.

Sneddon was the author of more than 100 articles, including ones about the psychological and psychiatric aspects of skin disease. He suggested a 3-level classification of the skin conditions in which psychogenic factors play a role in causation and separated psychodermatosis from psychosomatic disease. Sneddon's and Wilkinson's description of subcorneal pustular dermatosis (Sneddon-Wilkinson disease) brought him eponymous fame and gave him a special interest in blistering eruptions, about which he wrote numerous papers and book chapters. Sneddon was president of the British Association of Dermatologists, the section of dermatology of the Royal Society of Medicine, the North of England Dermatological Society, and the Sheffield Medico-Chirurgical Society.

A coronary thrombosis caused Sneddon to resign the office of clinical dean and hampered his interest in gardening. He was in love with fly-fishing and painting. Yet, sailing continued to be his main interest; he sailed to France and back several times until he died. In his last year, he proudly passed the very special examination for Yachtmaster's Certificate.

(**Publ.:** Ehrmann S. Ein neues Gefäßsymptom bei Lues. *Wien Med Wochenschr* 1907; 57:777–782.

Sneddon IB. Cerebrovascular lesions and livedo reticularis. *Br J Dermatol* 1965; 77:180–185.)

Soulier-Boffa syndrome (**Soulier-Boffa's syndrome**, **Hughes syndrome**) is the antiphospholipid syndrome with fetal loss. It is used to describe repeated spontaneous abortions in women with circulatory antithromboplastin, anticoagulant, and thrombosis. Antiphospholipid antibody syndrome (APS) is an autoimmune disease characterized by a combination of vascular thrombosis and/or pregnancy-related complications and the long-term presence of antibodies directed against phospholipids (i.e., circulating anticoagulant and/or anticardiolipin antibodies and/or anti-β2 glycoprotein 1 antibodies). The disease can occur alone (primary APS) or combined with another disease (secondary APS)—generally SLE.

The history of the discovery of the antiphospholipid antibodies (aPL) and the eventual realization that their presence was intensely associated with the clinical constellation of thrombosis (both venous and arterial), recurrent fetal losses, and thrombocytopenia, which goes back to the early 1960s. The work and publications of Bowie et al. (Bowie et al., 1963) and Alarcon-Segovia and Osmundson (Alarcon

Segovia and Osmundson, 1965) laid the foundation of future research by specialists from various fields in many countries, who eventually recognized and documented the existence of the APS during the 1980s. In the early 1980s, solid-phase assays were devised for the detection of aPL, and the use of cardiolipin as antigen was prompted by the observation relating the presence of the lupus anticoagulant phenomenon to the frequent accompanying finding of false-positive venereal disease tests in these patients. The original radioimmunoassay for anticardiolipin antibodies (aCL) devised by Harris et al. (1983) was superseded by enzyme-linked immunosorbent assays (ELISA). ***Soulier*** and ***Boffa***, in 1980, and Carreras et al. (1981), stressed for the first time the triple association of recurrent fetal losses, thrombosis, and lupus anticoagulant. A new clinical entity was proposed, "Anticardiolipin Syndrome," in 1985 by ***Graham Hughes***.

Soulier and ***Boffa*** described a syndrome, known now as antiphospholipid syndrome, first in 1980. They noticed a strange extension of prothrombin time, called the lupus anticoagulant, in patients with a history of a vascular occlusion caused by a blood clot (thrombosis) and recurrent miscarriages in the third trimester of pregnancy. After the development of the anticardiolipin assay during the 1980s, a significant correlation between the presence of antiphospholipid antibodies and obstetrical complications in patients with SLE was reported repeatedly. Therefore, detection of aPL in women with a positive obstetric pathology mirrored a group of patients originally labeled as "obstetric lupus." This definition was discarded later because obstetric antiphospholipid syndrome was considered a distinct entity, which is not necessarily confronted in patients with systemic autoimmune diseases like SLE.

In 1994, at an international meeting in Leuven, Belgium, the name **Hughes syndrome** was suggested (at a time when there was a move against eponyms!).

Jean-Pierre Soulier (Sept 14, 1915–Jan 18, 2003) was a French physician and hematologist. He studied medicine at the University of Paris and graduated in 1937. He then did his additional medical training and in 1945 worked as a research fellow at Harvard University for a year. Later, he was a director of the laboratory at the National Blood Transfusion Service in Paris; in 1954, he became a director of the whole service. In 1961, he received a position of professor of hematology at the University of Paris, working at the Necker Hospital for Sick Children.

Soulier clinical research focused on blood coagulation. In 1947, he introduced a new anticoagulant phenylindanedione and successfully prepared a therapeutic fraction of human blood to treat factor IX and prothrombin complex deficiencies. In 1948, together with Jean Bernard, he described a young male patient with a serious bleeding defect—that is, prolonged bleeding time, low platelet number, and presence of very large platelets (i.e., macrothrombocytopenia). They called the disease "Dystrophie thrombocytaire-hémorragipare congénitale" (hemorrhagiparous thrombocytic dystrophy). Later, many similar clinical cases, often associated with consanguinity (i.e., relation by blood) and transmitted as an autosomal recessive trait, have been published. The disease is normally referred now as Bernard-Soulier syndrome.

Soulier was president of the International Congress of Thrombosis and Haemostasis, and from 1978–1980, he was president of the International Society for Blood Transfusion.

Marie-Claire Boffa (?) is a French immunologist associated with the following: Service d'Hématologie; Hospital Jean-Verdier; Hôpitaux de Paris, Laboratoire d'Hématologie; Unité d'Hémostase et Thrombose, AP-Hôpitaux de Paris in Bondy, France; the Department of Internal Medicine, Hospital de la Pitié in Paris, France; and Laboratoire d'Hemostase, Centre National de Transfusion Sanguine in Paris Cedex, France.

Graham Robert Vivian Hughes (Nov 26, 1940–) is an English rheumatologist. Hughes was born in Liverpool, England. His father, Robert Hughes, was a civil servant; his mother Emily was a homemaker. He studied at the Cardiff High School for Boys and qualified for the Licentiate of the Royal College of Physicians (LRCP); membership in the Royal Colleges of Physicians (MRCP); a postgraduate medical degrees from the Welsh School of Medicine in 1961; a Bachelor of Medicine, Bachelor of Surgery (MBBS); and an undergraduate dual degree from the London Hospital Medical College in 1967. Then he was a registrar in the Department of Rheumatology and a lecturer of medicine at London Hospital. After that, he spent 2 years (1969–1970) in the Columbia Presbyterian Hospital and the Hospital for Special Surgery in New York working on a team that developed the anti-DNA assays for the diagnosis and managemrnt of SLE.

In 1971, Hughes became a head of rheumatology at the Hammersmith Hospital in London and established Britain's first specialized SLE clinic. In 1978, together with one of his SLE patients, Cheryl Marcus, he founded the UK National Patients' Association, now called Lupus UK, becoming its life president. In 1985, he moved to the Rayne Institute in St. Thomas's Hospital to set up the Lupus Arthritis Research Unit. In collaboration with his colleagues in obstetrics, he established the Lupus Pregnancy Clinic in 1986—the first such clinic in the world.

In 1989, Hughes was nominated to the American Lupus "Hall of Fame"—the first non-American clinician to be honored. In 1993, he was awarded the International League of Associations for Rheumatology (ILAR) Rheumatology Research Prize—for the first time to a UK honoree—for his work on the clotting mechanisms associated with antiphospholipid antibodies. Hughes is an editor of the journal *LUPUS*, and he is on the editorial board of 23 professional medical journals.

Hughes has published more than 1000 research documents in peer-reviewed journals, books, book chapters, and case reports dealing with all aspects of rheumatology but, in particular, with the pathogenesis, diagnosis, and treatment of lupus and related conditions. Hughes is known to have a pleasant personality. He is an excellent speaker and a popular teacher. Happily married, he lives in Kent with wife Monica and children Sarah and Richard. His extracurricular interests include golf and music (classical and jazz).

(**Publ.:** Hughes GRV. Thrombosis, abortion, cerebral disease and lupus anticoagulant. *Brit Med J* 1983; 287:1088–1089.

Soulier JP, Gueguen J. Action de la phenylindane-dione sur le taux de la prothrombine; etude experimentale sur le lapin. *Rev d'Hemat* 1948; 3:180.

Soulier JP, Boffa MC. Avortments à repetition, thromboses et anticoagulant circulant antithromboplastin. *Nouv Presse Med* 1980; 9**:**859–864.)

Spiegler-Fendt lymphoid hyperplasia (**Spiegler-Fendt sarcoid**, **pseudolymphoma of Spiegler-Fendt**; and cutaneous lymphoid hyperplasia, reactive lymphoid hyperplasia, and lymphocytoma cutis) are all terms that describe a group of benign cutaneous disorders characterized by collections of lymphocytes, macrophages, and dendritic cells in the skin, where there is a dense proliferation of lymphocytes reminiscent of lymphoma, but the infiltrate is not malignant. Of late, the term "pseudolymphoma" began to be used widely for lesions that would have been referred to as one of the other terms in the past.

Pseudolymphoma may involve the facial skin in distinctive clinicopathologic forms (e.g., lupus erythematosus, polymorphous light eruption, **lymphocytic infiltration of Jessner**, angiolymphoid hyperplasia with eosinophilia, and Spiegler-Fendt sarcoid). Although distinctive, all forms commonly have varying degrees of dermal-lymphocytic infiltration and clinical chronicity. Clinically, lesions present as papules and/or nodules that can be shiny. They are not scaly and can be skin-colored, erythematous, brownish, or violaceous. Itching can occur.

In most cases, there is no identifiable cause, but common triggers include ear piercings, tattoos, phenytoin, vaccinations, infections from the herpes simplex virus and zoster, insect bites, and infection by the bacterium *Borrelia burgdorferi* (**Lyme disease**). Therefore, pseudolymphoma is not a clinical diagnosis but instead a histological description.

Spiegler described this condition in 1894. Fendt described it in 1900. Apparently, they believed that, although clinically the entity resembled that of a sarcoma, it behaved like a benign lesion. Therefore, they called it sarcoid. No relationship to sarcoidosis has been suggested ever. The term "sarcoid" was first employed by ***Kaposi*** to name a group of skin tumors that were, at that time, little understood.

Eduard Spiegler (Aug 14, 1860–Jul 20, 1908) was an Austrian dermatologist and chemist. He was born in Vienna, Austria, to Bernhard Spiegler, a Jewish textile industrialist, and Katharina Spiegler (Böhm) and first studied chemistry at Strasburg, Vienna, Zurich, and Graz, where he received his PhD degree in chemistry in 1885. He also studied medicine from 1981 in Vienna and Graz and obtained his medical degree in 1888. He worked in the Vienna General Hospital at the Chemical Institute and at the Hygiene Institute. He was an assistant at ***Moriz Kaposi***'s clinic from 1892 onward. He passed his habilitation exams for dermatology in 1897 and moved to the Kaiser Franz Josef Hospital. From 1900 on, he headed the Department of Dermatology at the General Polyclinic Vienna and led it until his death, being an associate professor starting in1903. Spiegler married Olga Lemberger from Poland, and they had 2 children.

He worked on sarcoid tumors, endotheliomas of the skin, pernicious dermatoses, and skin pigments in hairs. He also studied albumin and globulin in serum in

individuals affected by syphilis. Using his own money, he established a laboratory for experimental chemistry with 8 working stations—the Spiegler-Stiftung. The Spiegler reagent, the Spiegler tumor, Spiegler-Fendt pseudolymphoma, Ancell-Spiegler syndrome, and the Brooke-Spiegler syndrome were named after him. He died at age of 47 from leukemia in Vienna.

Heinrich Fendt (1872–?) was an Austrian dermatologist.

(**Publ**.: Spiegler E. Über die sogenannte sarkomatosis cutis. *Archiv für Dermatol Syph* 1894, 27:163–174.

Fendt H. Beiträge zur kenntnis der sogenannten sarcoiden geschwülste der haut. *Archiv für Dermatol Syph* 1900, 53:212–242.)

St. Peregrine tumor refers to a spontaneous tumor regression—that is, the process when a malignant tumor partially, substantially, or completely vanishes without any known treatment or because of the treatment is considered insufficient to exert a marked impact on neoplastic disease. A frequent theme in many cases of spontaneous tumor regression is the common cooccurrence of infection. A significant number of published cases of spontaneous regression of both solid tumors and hematological cancers appear to have occurred concomitant with infection, including influenza, hepatitis, diphtheria, smallpox, gonorrhea, malaria, measles, tuberculosis, and syphilis. Although occurring in an era prior to discovery of microorganisms, comments on cause and effect were mentioned in the very early published works. The first evidence of the treatment of cancer using microorganisms can be seen in the Iberian papyrus of 1550 BC; the Egyptian pharaoh Imhotep (2600 BC) used a poultice for the treatment of a tumor with the goal to facilitate the development of infection in the location of the lesions and to achieve tumor regression.

Peregrine Laziosi (1260–May 1, 1345) was a priest. He was born in Forli, Italy, a town that was governed by the Pope as part of the Papal States and was under the church penalty of interdict for antipapal political activity. Peregrine grew up in a family that was actively involved in the opposition. St. Philip Benizi, the Prior General of the Servants of Mary, was sent to Forli to preach the appeasement of the city and the elimination of the sentence. Young Peregrine was so extreme in his political enthusiasm that he interrupted St. Philip during the speach and even tried to hit St. Philip. The moment of striking St. Philip appeared to drastically change Peregrine. He began to switch his strengths into good works, and finally he joined the Servants of Mary. He then became a pastor or a chorus brother and undertook being an apostolate among the people of Forli. He mainly committed himself to the sick, the poor, and the marginal people of society.

The legend says that one day Peregrine had a tumor of the tibia. The tumor mass eventually grew extremely large and even came through the skin becoming viciously infected. The wound became so obvious, odorous, and painful that a local surgeon scheduled surgery to amputate the leg. Suddenly, Peregrine was confronted with the ugliness and suffering of his own life. The night before the operation, he prayed, and this guided him into a deep trance-like sleep when he envisioned the crucified Christ

leaving the cross and tapping his sick leg. When Peregrine woke up from the meditation trance, he noticed the wound had healed, the tumor had vanished, and the leg was saved. The tumor reportedly never returned. Peregrine lived many more years, and after death he was canonized. St. Peregrine has been called the patron saint for those who suffer from cancer.

St Vitus Dance see **Sydenham Chorea**

Sternberg-Reed cells see **Reed-Sternberg cells**

Stevens-Baader-Fiessinger-Johnson syndrome see **Stevens-Johnson syndrome**

Stevens-Johnson syndrome (**Baader's syndrome**, **Fiessinger-Rendu syndrome**, **Baader-Fiessinger-Stevens-Johnson syndrome**, **Fuchs' syndrome**, **Klauder's syndrome**, **Neumann's syndrome**, **Stevens-Baader-Fiessinger-Johnson syndrome**) is a rare, serious disorder of the skin and mucous membranes. The syndrome is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. It is usually a reaction to a medication or an infection and can be considered as an example of a type IV hypersensitivity reaction. More than 100 known drugs can cause Stevens-Johnson syndrome. Viral and bacterial diseases that have been reported to cause Stevens-Johnson syndrome include the following: herpes simplex virus, AIDS, Coxsackie viral infections, influenza, hepatitis, mumps, group A beta-hemolytic streptococci, diphtheria, brucellosis, lymphogranuloma venereum, mycobacteria, *Mycoplasma pneumoniae*, rickettsial infections, tularemia, and typhoid. As many as half of the cases, however, are idiopathic—that is, have no known cause.

Several genetic changes have been found to increase the risk of **Stevens-Johnson syndrome** in response to triggering factors like medications. Most of these changes occur in genes that are involved in the normal function of the immune system. The genetic variations most powerfully associated with Stevens-Johnson syndrome occur in the *HLA-B* gene. Certain variations in this gene (i.e., HLA-B*1502, HLA-B*5801, and HLA-B*44) occur much more often in people with Stevens-Johnson syndrome than in people without the condition. HLA-A29, HLA-B12, and HLA-DR7 frequently are associated with sulfonamide-induced Stevens-Johnson syndrome, whereas HLA-A2 and HLA-B12 often are encountered in Stevens-Johnson syndrome induced by nonsteroidal antiinflammatory drugs.

Stevens-Johnson syndrome often begins with a fever and flu-like symptoms. Within a few days, the skin begins to blister and peel, forming very painful erosions that resemble a severe hot water burn. The skin erosions usually start on the face and chest before spreading to other parts of the body. In most-affected individuals, the condition also damages the mucous membranes, including the lining of the mouth and the airways, which can cause trouble with swallowing and breathing. Stevens-Johnson syndrome (e.g., erythema multiforme) is characterized by confluent epidermal necrosis with minimal associated inflammation. Certain population groups

appear to be more susceptible to developing Stevens-Johnson syndrome. Slow acetylators are individuals whose liver cannot completely detoxify reactive drug metabolites and include, for example, patients who are immunocompromised (especially those infected with HIV) and patients with brain tumors undergoing radiotherapy with concomitant antiepileptics. Drugs and drug metabolites either may have direct toxic effects or act as haptens interacting with host proteins in various tissues, rendering them antigenic.

Antigen uptake by the local tissue dendritic cells; their activation and release of diverse cytokines; and presentation of antigen to T cells induce T-cell activation, proliferation, and recruitment to the skin. The activated $CD8^+$ cytotoxic T cells can induce epidermal cell apoptosis through the release of granzyme B and perforin or Fas/FasL interaction or through induction of ferroptosis. The cell death of skin keratinocytes results in separation of the epidermis from the dermis. Cell death causes release of various intracellular proteins, surrounding cell activation, chemokine release, and attraction of more immune cells. Together, this can prolong the inflammatory and tissue-damaging reactions that can lead to wide-ranging epidermal necrolysis.

Stevens-Johnson syndrome is named for ***Albert Stevens*** and ***Frank Johnson***, US pediatricians, who first described the disease in 1922. They characterized the cases of 7- and 8-year-old boys with "an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis." These clinical cases initially were misdiagnosed by primary care physicians as hemorrhagic measles. Nevertheless, the original description of "erythema exudativum multiforme" is attributed to von Hebra (von Hebra, 1866). He considered it a systemic and not a local disorder, identifying no causality. ***Fuchs***, in 1876, first described the ocular complications of this disorder. ***Rendu*** in 1916 and ***Fiessinger*** and Rendu in 1917 characterized a mucocutaneous eruption with no clear reason that was later called *Fiessinger-Rendu syndrome* or "pluriorificial erosive ectodermosis." Retrospectively, it looks quite similar to the cases reported by Stevens and Johnson in 1922. In Germany, *Fuchs syndrome* is used to explain a variant of erythema multiforme, which primarily involves mucosal surfaces. Because the skin could be totally uninvolved, it is an underrecognized diagnostic entity, which is difficult to confirm.

Albert Mason Stevens (Jul 22, 1884–Aug 6, 1945) was a US pediatrician and surgeon. He was born in India in 1884 to a Christian missionary. In 1894, he moved to the USA. He received his BS from Yale University in 1905, then studied at Balliol College Oxford University, and received his MD degree from College of Physicians and Surgeons, Columbia University in 1915. During World War I he served as an assistant surgeon in France, was captured by the Germans and repatriated to the US after the war. He resided the rest of his life in the US working as a surgeon. In 1934, he retired to Hawaii to grow tropical fruit and teach in the Hawaiian school system.

Frank Chambliss Johnson (1894–Jan 1, 1934) was a US pediatrician. He graduated from Rutgers College in 1916 and received his MD degree from Columbia University Physicians and Surgeons in 1920. He started his own pediatrics practice in New Brunswick, NJ. He worked also at Bellevue Hospital, where he met Albert

Stevens. He died in a quarry fall in New Jersey while studying geological formations and plant life.

Ernst Baader was a German internist working in Hannover.

Noël Armand Fiessinger see **Fiessinger-Leroy disease**

Joseph Victor Klauder (Oct 12, 1888–Apr 2, 1962) was a US physician and dermatologist. He was associated with the Department of Dermatology and Syphilology, University of Pennsylvania, Philadelphia, PA. He was a past president of the American Dermatological Association and Professor Emeritus of Clinical Dermatology at the University of Pennsylvania Graduate School of Medicine.

Isidor Neumann, Edler von Heilwart (Mar 2, 1832–Aug 31, 1906) was an Austrian dermatologist. He was born in Misslitz, Mähren (now Miroslav, Moravia, Czech Republic), to the Jewish family of Markus Mayer Neumann and Marie Neumann (born Schmiedl). He received his medical education in Vienna, obtaining his doctorate in 1858. He settled in Vienna, first as a dozent and then as a professor of skin diseases. Neumann was the director of the Vienna Clinic for Dermatology and Syphilis. In his 1886 publication, he described a type of pemphigus vulgaris, which would later become known as *pemphigus vegetans* of Neumann. He also was the first to publish a detailed study of prematurely aged skin caused by overexposure to various weather conditions. Yet, it was not until several years later that Paul Gerson Unna gave it a name: "sailors' skin." During the Austrian government's occupation of Bosnia-Herzegovina, Neumann was sent to the country to manage the public health problem of syphilis and leprosy. He was married to Phillipine "Filippine" Neumann (born Forchheimer) and Babette Neumann von Heilwart (born Singer). He died in Vöslau near Vienna.

Ernst Fuchs (Jun 14, 1851–Nov 21, 1930) was an Austrian ophthalmologist. He was born in Vienna. His ancestors had lived for generations as poor farmers in Böhmerwald, a rural area not far from Bavaria, but his father, Adalbert Fuchs, was a professor of agriculture at the technical college in Vienna. Although his father wanted him to become an engineer, Ernst's interests were much more directed toward astronomy and physics. He finally decided to study medicine. Ernst, when studying in Vienna, already held a position of an assistant at the Physiological Institute in Innsbruck. Having obtained his doctorate in 1874, he studied surgery and ophthalmology in Vienna. From 1880–1885 on, Fuchs was professor of ophthalmology in Lüttich and then a chair of ophthalmology at Vienna, holding this position until 1915. He published his textbook of ophthalmology, *Lehrbuch der Augenheilkunde*, in 1889, which was based on his lectures and was intended to help his students listen to his lectures rather than confuse themselves by taking notes. The book was translated into all European languages, Japanese, and Chinese. It was considered the bible of ophthalmology for approximately 50 years.

Fuchs was an innovator in surgery and presented early ophthalmoscopic investigations after eye operations. The Shah of Persia, Nasser al-Din, sent his favorite wife, who had a cataract, and several other women with cataracts, to Fuchs's clinic. He diagnosed the Shah's wife with glaucoma and could not help her. At the same

time, he removed the cataracts from the women who escorted her. The Shah could not understand how Fuchs was able to restore the vision of servants but could not help his favorite wife.

Prior to the World War I, Fuchs was a rich man. After the war, however, because of the inflation that ensued, his financial situation changed dramatically. He was helped greatly by his friends and admirers, who enabled him to undertake a lecture tour to the US; subsequently, he visited Spain, Egypt, and Asia Minor. Fuchs was a great traveler and also enjoyed walking on his vacations in out-of-the-way places. In addition to the field of medicine, Fuchs had a keen interest in botany, literature, geography, and art history. As a member of the Wiener Geographische Gesellschaft, the geographical society of Vienna, he regularly presented talks to a wide audience on his many travels around the globe. Following a trip to Scandinavia in 1875, Fuchs brought back a pair of "snowshoes," as they were called at the time; thus, introducing skiing to Vienna.

Ernst Fuchs was an honorary member in 39 scientific societies, was president of Honor of the Ophthalmological Society of Madrid, and held numerous honorary doctorates. He maintained his investigatory interest to the very end, when he died with angina pectoris in Vienna.

Henri Jules Louis Marie Rendu (Jul 24, 1844–Apr 16, 1902) was a French physician. He was born to an ancient family line of important French bourgeoisie in Paris. His mother was the daughter of a famous painter, and his father, Victor Rendu, was an inspector of agriculture. Rendu received his bachelor's degree when he was 16 and started to study medicine in the School of Medicine in Paris in 1865. He graduated first in his class, becoming extern in 1867 and intern at the Saint-Antoine Hospital in 1868.

During the Franco-Prussian War (1870–1871), Rendu served as surgeon to the Army. He did not allow evacuating his patients after surgery but took care of them by himself. After the war, he started a private practice and obtained a junior position in the Saint-Louis Hospital in Paris working in dermatology. In 1877, Rendu married Marie Labric, whose father was a physician at the Children's Hospital. In 1878, he received his professorship position. In 1885, he became a head of the Department of Medicine at the Hospital Necker, where he worked to the end of his professional career.

Rendu published more than 100 medical articles and had a large private practice. He had a brilliant, inquiring mind and a prodigious memory. He was known for his strict sense of duty and extensive medical knowledge. His very diverse interests were in botany, mathematics, and geology. He spent his spare time traveling in France looking for new and unusual items for his unique botanical collection. His grandfather had started it, and he was able to extend it into one of the finest collections of plants in France.

(**Publ**.: Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia: Report of two cases in children. *Am J Dis of Children* 1922; 24(6): 526–533.

Rendu R. Sur un syndrome caractérisé par une l'inflammation simultanée de toutes les muqueuses externes (conjonctivale, nasale, linguale, buccopharyngée,

anale et balano-prépuciale) coexistant avec une éruption varicelliforme puis purpurique des quatre membres. *J Prat* 1916; 30:351–352.

Fiessinger N, Rendu R. Sur un syndrome caractérisé par l'inflammation simultanée de toutes les muqueuses externes coexistant avec une éruption vésiculeuse des quatre membres, nondouloureuse et nonrécidivante. *Paris Méd* 1917; 25:54–58.

Neumann I. Ueber Pemphigus vegetans (frambosioides). *Vierteljahrsschrift Dermatol Syphilis* 1886, 13:157–178.

Baader E. Dermatostomatitis. *Arch.f. Dermat. U. Syph*. 1925; 149:261-268.

Hebra F. *Diseases of the Skin,* vol.1. Translated and edited by C. H. Fagge. London, New Sydenham Society, 1866.

Fuchs E. Herpes iris conjunctivae beobachtet. *Klin Monatsbl Augenh* 1876; 14:333.)

Stevens-Baader-Fiessinger-Johnson syndrome see **Stevens-Johnson syndrome**

Still's disease (**Still syndrome**, **Still-Chauffard-Felty syndrome,** Systemic juvenile idiopathic arthritis) is a juvenile form of **Felty's syndrome**. This is a rare type of inflammatory arthritis that features a sore throat, salmon-colored rash, high fever that spikes once or twice a day, enlargement of the liver and spleen, swollen lymph nodes, and leukocytosis. Joint pain can develop a few weeks after the initial symptoms. The cause of adult Still's disease is unknown, but some data agree, speculating that it might be triggered by some type of infection.

Still's disease does not show any association with *HLA* genes or with autoantibodies and is characterized by an uncontrolled activation of phagocytes with hypersecretion of IL-1 and IL-6. Based on clinical and laboratory structures, as well as on new achievements on the pathogenesis, it seems evident that the disease is an autoinflammatory disease related to abnormality in the innate immune system. Phagocytes, including monocytes, macrophages, and neutrophils, are the principal activated cells during the early course of Still's disease. It has been shown that these cells secrete very high levels of proinflammatory cytokines (i.e., IL-1, IL-6, and IL-18), as well as proinflammatory proteins (i.e., S100A8, S100A9, and S100A12).

Anatole Marie Émile Chauffard (Aug 22, 1855–Nov 1, 1932) was a French physician. Both his father and grandfather were physicians in France. Chauffard received doctor of medicine degree in 1882 and in 1907 was appointed a professor of internal medicine. He worked at the Cochin Hospital and Hospital Saint-Antoine, where he acquired a clinical chair in 1911. Chauffard was an exceptional clinician and teacher. His major investigative work was in liver disease to which he contributed to descriptive pathology.

Augustus Roi Felty see **Felty's syndrome**

Sir George Frederick Still (Feb 27, 1868–Jun 28, 1941) was an English pediatrician, the father of British pediatrics**.** He was born in Highbury, London, as the only surviving son of 12 children. His father was a surveyor for H. M. Customs (His or Her Majesty's Customs), the National Customs Service in England. At Caius College, Still received a classical education and was fluent in Greek, Latin, Hebrew,

and Arabic. His choice of profession, however, was medicine, and his knowledge of the natural sciences was outstanding. He learned medicine at Cambridge and later worked as a physician at London Guy's Hospital, Shadwell's Children's Hospital, Waterloo Hospital for Women and Children, Great Ormond Street Children's Hospital, and Children's Hospital in Cambridge. It was during this period in Cambridge that he compiled about 20 cases of children with an unusual form of progressing arthritis. He described his results in his paper, "On a form of chronic joint disease in children," published in 1897. In 1896, this topic was the subject of his MD thesis at Cambridge: "A special form of joint disease met with in children." It was the first characterization of juvenile rheumatoid arthritis or Still's disease. Thus, he shares with ***Maurice Raynaud*** and Howard Tooth the distinction of having an eponym syndrome/disease named after their MD theses (Raynaud's disease/Raynaud's phenomenon and Tooth muscular atrophy/Tooth syndrome).

In 1899, Still became a physician at King's College Hospital in London, focusing on pediatric diseases; it was the first hospital with a medical school that created a special segment for children. In 1906, he was appointed the first professor of pediatrics at that hospital and the first chair of pediatrics in England. He was the principal founder and first president of the British Pediatric Association. Still was undoubtedly one of the most popular pediatricians in London, and nearly every sick child of wealthy parents had visited him on one occasion or another. There were a lot of different toys in his waiting room to entertain children who were in line to see him. He was awarded countless honors and awards, and, on his retirement, he was knighted for having been the personal physician to Princesses Elizabeth and Margaret.

From his early days on, Still did not have any interest in sports or a social life, dedicating himself only to medicine, and he stayed a bachelor, living only for his work. He was very close to his widowed mother; he took her to church every Sunday and lived with her until her death. After retirement in 1937, Still moved to Salisbury, Wiltshire, at the confluence of the rivers Avon, Nadder, and Bourne. He taught English language and literature at the Salisbury Cathedral school and satisfied his passion for fly-fishing. He also wrote poetry and published a book of poems, *Childhood and Other Poems*. He is remembered as a shy and quiet man with a genuine love of children.

(**Publ**.: Chauffard A, Ramon F. Des adénopathies dans le rhumatisme chronique infectieux. *Rev Méd* 1896; 16:345.

Still GF. "A special form of joint disease met within children." Doctoral dissertation, Cambridge, 1896.

Still GF. On a form of joint disease in children. *Med Chir Trans* 1897; 80:47–59.)

Still-Chauffard-Felty syndrome see **Still's disease**

Stoll-Brodie-Fiessinger-Leroy syndrome see **Reiter's syndrome**

Strong syndrome see **DiGeorge syndrome**

Su antigen was identified as the microRNA (miRNA)-binding protein, Argonaute 2 (Ago2), in 2006. Ago2 is a key component of the RNA-induced silencing complex localized in cytoplasmic cores called glycine-tryptophan (GW) bodies. Autoantibodies were defined originally by the double immunodiffusion assay during the early 1980s. Anti-Su/Ago2 does not appear to have disease specificity because it is found in 10–20% of patients with various rheumatic diseases, including SLE, scleroderma, polymyositis/dermatomyositis, and Sjögren's syndrome, as well as apparently healthy individuals at lower frequency. The clinical significance and the mechanism of production of anti-Su/Ago2 remains to be clarified. The abbreviation "Su" was introduced based on the patient's name in whom the antibody was found.

(**Publ**.: Treadwell EL, Alspaugh MA, Sharp GC. Characterization of a new antigen–antibody system (Su) in patients with systemic lupus erythematosus. *Arthr Rheum* 1984; 27:1263–1271.

Treadwell EL, Muller UR, Volkman A. Extraction and differentiation of the Su autoantigen from calf thymus nuclei. *J Immunol Meth* 1991; 142:157–167.)

Susac's syndrome (**Susac syndrome**, retinocochleocerebral vasculopathy) is a microangiopathy involving the arterioles of the brain, retina, and cochlea and is characterized by encephalopathy, branch retinal artery occlusions, and hearing loss. Yet, these 3 main features are not always present at onset, and all do not necessarily develop in every case.

Susac's syndrome is an autoimmune endotheliopathy; however, why the microvasculature in the brain, retina, and inner ear is primarily affected is unclear. The skin also may be involved. Demyelination is not a representative sign of **Susac's syndrome**. Analysis of muscle biopsies could reveal nonspecific features of inflammation such as dense hyaline material (i.e., glassy and pink substances after hematoxylin and eosin staining) surrounding endomysial capillaries. This suggests a likely systemic module of this disease in spite of the prevalence of central nervous system involvement. It is possible that antibodies targeting endothelial cells are the pathogenic mechanism that causes the microscopic strokes in the brain, retina, and inner ear. The differential diagnosis of Susac's syndrome includes multiple sclerosis and vasculitides (e.g., SLE and **Behçet's disease**).

Susac's syndrome was named after ***John Susac***, who first described it in 1979. In 1975, Susac saw 2 patients with this syndrome within a matter of 3 weeks while serving in the US Army at Walter Reed Army Hospital. He reported the cases at the 1977 annual meeting of the American Academy of Neurology and subsequently described the findings as "microangiopathy of the brain and retina." Two women, aged 26 and 40 years old, presented with "personality changes and paranoid psychosis" associated with multiple-branch retinal artery occlusions, which suggested the development of an unusual microangiopathy that affected the brain and retina. Since then, approximately 60–70 cases have been reported in the medical literature. Hoyt proposed the eponym "Susac's syndrome" in 1986.

John O. Susac (1940–Feb 23, 2012) was a US physician. He was born in Powhatan Point, a small coal mining town in southeastern Ohio. He graduated from medical school at Ohio State University in 1964; married his high school sweetheart, Lois; and then entered the US Army and interned at Letterman Army Medical Center in San Francisco. To avoid being sent to Vietnam after his internship, he filled a vacant position in the Physiatry (Physical Medicine and Rehabilitation) Department at Letterman. During his third year of residency, he was on a required rotation in the neurology service. He liked it and switched his residency to neurology, divided between his services at Letterman and the University of California, San Francisco. After completing his residency in 1970, he became chief of the neurology service at the William Beaumont General Hospital in El Paso, TX. Thereafter, while still on active duty in the Army, he arranged a 2-year neuro-ophthalmology fellowship at the Bascom Palmer Eye Institute of the University of Miami in Florida; at that time it was the world's leading center in this subspecialty.

After finishing his fellowship in 1973, Susac was already the first author of 9 published articles. He then became assistant chief of neurology at Walter Reed Army Medical Center and associate professor of neurology with the Uniformed Services University of Health Sciences in Washington, DC. During his career in the Army, he rose to the rank of Colonel. In 1978, John decided to forgo an academic university career and joined a private practice at Neurology and Neurosurgery Associates in Winter Haven, FL. It was from this office that he conducted all his future scholarly works.

Susac had an insatiable intellectual curiosity, extraordinary clinical judgment, a wonderful sense of humor, and enormous compassion for patients. He was an animal lover, history buff, jazz enthusiast, and literary and language aficionado. He died at the office of the medical group where he worked for many years of lung cancer complications, even though he never smoked.

(**Publ**.: Susac J, Hardman J, Selhorst J. Microangiopathy of the brain and retina. *Neurol* 1979; 29(3):313–316.)

Sweet's syndrome (**Sweet syndrome**, **Sweet disease**, acute febrile neutrophilic dermatosis, **Gomm-Button disease**) is a skin disease characterized by the sudden onset of a fever; an elevated white blood cell count; and tender, red, well-demarcated papules and plaques that show dense infiltrates by neutrophil granulocytes on histologic examination. Although the skin is the primary organ affected, other systems, most notably the lungs and kidneys, also can be involved.

Sweet's syndrome is a reactive process (i.e., a hypersensitivity reaction) that occurs in response to systemic factors (e.g., hematologic disease, infection, inflammation, vaccination, or drug exposure). In 50% of cases, an underlying condition is seen and can include streptococcal infection, nonlymphocytic leukemia, and other hematologic malignancie; solid tumors; inflammatory bowel disease; and pregnancy. Almost 20% of cases are connected with cancer, mainly hematological malignancy, particularly acute myelogenous leukemia (AML).

The disease is mediated by neutrophil, as can be concluded from its histopathologic appearance, associated neutrophilia, and sensitivity to medications that target

neutrophil activity. The link between the development of **Sweet's syndrome** and exogenous granulocyte colony-stimulating factors (G-CSF) also supports the role of neutrophils and related endogenous cytokines in the disease. G-CSF concentrations in the blood in patients with active Sweet's syndrome are elevated markedly. Potential involvement of a tumor necrosis factor (TNF) and an imbalance of type 1 helper T cells also have been suggested.

The syndrome was described by ***Robert Sweet*** in 1964. It may range from classic Sweet disease, which may be seen in young women after a minor respiratory illness, to a more aggressive neutrophilic course that may be related to various inflammatory conditions or malignancy. Sweet defined a disease in 8 woman patients between the ages of 32 and 55 during the 15-year period (1949–1964) who had similar clinical findings—fever, leukocytosis, and erythematous plaques with neutrophil infiltration. Later, extracutaneous locations also were included in the disease's diagnosis. Sweet suggested calingl the disease **Gomm-Button disease** in honor of the first 2 patients suffering with the syndrome, whom he saw at his own practice. Nevertheless, the eponymic "Sweet's syndrome" has turned out to be more popular to describe the disease.

Robert Douglas Sweet (Dec 26, 1917–Sept 28, 2001) was an English dermatologist. He was born in Weybridge, a town in Surrey, England, but went to school in Wanganui, New Zealand. He studied medicine in Cambridge and St. Thomas's Hospital having been qualified in 1942. He then served at the Royal Army Medical Corps at the end of World War II (1944–1946). Later, Sweet worked as a medical registrar and senior registrar at the skin department at St. Thomas's Hospital. Then, he was appointed to the role of consultant dermatologist in a group of hospitals located in Plymouth, UK, where he worked from 1950 until his retirement in 1982. He also participated in the administration of the Plymouth hospitals, serving on the hospital medical executive board for several years and being the chairman of the hospital medical staff committee. Sweet loved teaching and was assigned for a year as consultant in charge of the Department of Dermatology at the University of the West Indies in Jamaica.

Sweet had an engaging personality and a keen sense of humor. He loved horseback riding, and he was a member and afterward chairman of the Spooners and West Dartmoor hunt. In his later years, he developed an interest in moorland farming and conservation. At his funeral, the service ended with a fine and rousing call on a hunting horn—a fitting end.

(**Publ**.: Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol* 1964; 76: 349–356.)

Sydenham chorea (**Sydenham's chorea**, rheumatic chorea, **St Vitus dance**) is an antineuronal antibody-mediated neuropsychiatric movement disorder caused by a poststreptococcal, autoimmune condition affecting control of movement, mood, behavior, and potentially the heart. Chorea is an involuntarily brief, random, and irregular movement of the limbs and face. Sydenham's chorea is a result of an autoimmune reaction that may be initiated by infection with group A β-hemolytic

streptococci. The results are the triggering of a signaling cascade or cell destruction in the corpus striatum (i.e., the striate nucleus) in the subcortical basal ganglia of the forebrain. Thus, molecular mimicry to streptococcal antigens, causing an autoantibody production against the basal ganglia, is the main pathogenic mechanism of the chorea condition. It has been shown that these antibodies cross-react with antigens in the bacterium membrane of group A streptococci and antigens in the neurons of the caudate and subthalamic nuclei, specifically intracellular tubulin and extracellular lysoganglioside. Serum antidopamine 2 receptor antibody can be seen in almost 30% of patients in a cohort of Sydenham's chorea. Antineuronal antibodies also have been detected in the cerebrospinal fluid in patients with acute rheumatic chorea. The main symptoms of Sydenham's chorea are believed to arise from an imbalance among the dopaminergic system, intrastriatal cholinergic system, and inhibitory gamma-aminobutyric acid (GABA) system.

Sydenham chorea is named after the British physician ***Thomas Sydenham***. Although the disease was first reported by German physician Gregor Horst in 1625, the eponym name was given subsequently to Sydenham, who provided a very detailed description of the clinical conditions in 1686. The term "chorea" is derived from the Greek word for dancing and was applied initially to epidemics of dancing mania in the Middle Ages, when a large number of people danced together for days. Sydenham used this term in his *Schedula Monitoria* to describe rheumatic chorea in 1686. Many similar dances have been described, but the most renowned was *chorea Sancti Viti* (**St. Vitus dance**). The alternative eponym, "Saint Vitus dance," relies on Saint Vitus, a Christian holy person who was offended by Roman emperors and died as a believer in 303 AD. Saint Vitus was believed to be the supporter of the dancers. The eponym was given in deference to the agitated dancing that historically happened in front of his statue during the feast of Saint Vitus in the Germanic and Latvian cultural traditions.

Thomas Sydenham (Sept 10, 1624–Dec 29, 1689) was an English physician. He was born at Wynford Eagle in Dorset, the son of William Sydenham, a wealthy Dorset Squire, and Mary, the daughter of Sir John Geoffrey. At the age of 18, Sydenham started his studies in Oxford, which were interrupted, because Sydenham had to serve as an officer in the Parliamentarian Army during the Civil War. He completed his Oxford course in 1648, graduating with a bachelor of medicine, and then he was elected a fellow of All Souls College. It was not until nearly 30 years later (1676) that he graduated with an MD degree from Cambridge, where his eldest son was by then an undergraduate. In 1663, he passed the examinations of the College of Physicians for their license to practice in Westminster. At that time, he married Mary Gee and remained in Westminster for the rest of his life. Sydenham never became a fellow of the Royal College of Physicians; he never held public office in a hospital and was never appointed to a university chair.

In his practice, Sydenham focused on bedside examination and patient histories, which gave him the opportunity to differentiate various diseases and recommend the best treatment. He acknowledged that atypical disorders had their own natural histories, which helped him to classify diseases and establish their origin. For instance, he reported the link between fleas and typhus fever. Sydenham introduced **opium**

into medical use, was the **first to use iron** in treating iron-deficiency anemia, and helped promote quinine for malaria therapy. His attempt to recommend fresh air and cooling drinks for fever treatment was an improvement on the sweating approaches used previously. In addition, he documented the recurrence of epidemics, their geographic location, and environmental variants and relations. Thus, Sydenham is known as one of the founders of epidemiology.

Almost nothing is known of Sydenham's personal story in London. In his last years, Sydenham was considerably disabled by gout and renal stones. He died at his house in Pall Mall at age 65. He is buried in St. James's Churchyard, Piccadilly, where a mural slab was put up by the College of Physicians in 1810.

Letter T



Takao syndrome (see **DiGeorge syndrome**)

Takatsuki disease (see **Crow-Fukase syndrome**)

Takatsuki-Crow-Fukase syndrome (see **Crow-Fukase syndrome**)

Takayasu arteritis is a rare, systemic, inflammatory large-vessel vasculitis and has been defined as "granulomatous inflammation of the aorta and its major branches." Takayasu arteritis, also known as "aortic arch syndrome," "nonspecific aortoarteritis," and "pulseless disease," often appeared as isolated, atypical, and appalling disease. It can affect any or all of the main organ systems. The disease has been seen all around the world, although some predominance is seen in Asian countries. Pathophysiologic consequences include hypertension, congestive heart failure, hypotensive ischemic retinopathy, vertebrobasilar ischemia, microaneurysms, carotid stenosis, hypertensive encephalopathy, and inflammatory bowel disease. Infrequently, **Takayasu arteritis** may accompany rheumatoid arthritis, polymyositis, glomerulonephritis, systemic lupus, polymyalgia rheumatica, **Still disease**, and ankylosing spondylitis.

The etiology of Takayasu arteritis is not fully understood. The main pathogenetic pathway is the inflammation associated with etiologic factors such as infection with spirochetes, *Mycobacterium tuberculosis* and streptococcal organisms, and/or systemic antibodies linked to a few autoimmune reactions. Patients with Takayasu arteritis commonly have higher levels of IgG, IgM, or IgA recognizing the *M. tuberculosis* when compared with patients without this disease. The cellular infiltrate in Takayasu arteritis contains about 15% each of $CD4^+$ and $CD8^+$ T cells.

One pathogenetic mechanism may be associated with the induction of the heat shock protein 65 expression in the aortic tissue, which, in turn, induces expression of MHC class I-related chain A (MICA). MICA acts as a stress-induced ligand for the activating C-type lectin-like receptor, NKG2D (natural killer group 2, member

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D). NK cells and gamma-delta T cells (γδ T cells) expressing NKG2D receptors, the activating receptors, can recognize MICA on vascular smooth muscle cells, infiltrate tissue, and cause acute inflammation by various pathways—for instance, release of the proinflammatory cytokines. These inflammatory reactions may induce additional MHC antigen expression on vascular cells, recruiting more mononuclear cells. Some data suggest the role of antiendothelial, anticardiolipin, and antiaorta antibodies.

Involvement of TLR also has been suggested. Th1 lymphocytes, through IFN-γ, activate macrophages and VEGF release. This ultimately results in smooth muscle migration and intimal proliferation. Th17 cells induced by the IL-23 microenvironment also contribute to vascular lesions through activation of infiltrating neutrophils. One study demonstrated an association between several cases of Takayasu arteritis and CD36 deficiency. CD36 is a multifunctional membrane glycoprotein from the class B scavenger-receptor family. It is expressed on monocytes, platelets, and endothelial cells and contributes to myocardial fatty acid transport.

Genetic factors also can play a role in the pathogenesis. Human leukocyte antigen Bw52 (HLA-Bw52), which is in linkage disequilibrium with human leukocyte antigen DR4 (HLA-DR4), has been observed with increased frequency. Patients with the Bw52 genotype had a higher rate of aortic regurgitation. Takayasu arteritis may be associated with HLA-B22 in the US.

The first case of the disease was reported in 1908 by ***Mikito Takayasu*** at the Annual Meeting of the Japan Ophthalmology Society. He characterized a weird "wreathlike" appearance of the blood vessels in the retina—a thin layer of tissue at the back of the eyeball on the inside. Interestingly, 2 other Japanese physicians at the same meeting, Onishi and Kagoshima, presented similar eye pathology in patients without wrist pulses. Takayasu published his case in the same year in the *Journal of the Juzen Medical Society* at Kanazawa University. He illustrated the arteries with his own hand-sketched image.

Mikito Takayasu (Jul 19, 1860–Nov 20, 1938) was a Japanese ophthalmologist. He was born in Saga prefecture in Kyushu Island in Japan as the fourth son of a priest. He finished Tokyo foreign language school and then graduated from Tokyo Imperial University in 1887. He worked initially in Kanazawa prefecture as a lecturer. Then for 2 years he learned and did clinical studies in Germany at Berlin City Hospital, Berlin Charité University Hospital, and Leipzig University.

Takayasu returned to Kanazawa and obtained his PhD degree in 1903. He then became a professor and principal of the medical school. In 1923, the medical school was reorganized as the Medical University, and he was appointed the university's dean.

In 1924, Takayasu retired and opened his own private practice near the university hospital. His clinic was very popular in spite of expensive fees because of his medical reputation, knowledge, skills, and experience. It was a general belief that water from the small river running by his office helped treat eye diseases.

Takayasu had 3 sons and 5 daughters. In 1933, he had a stroke and moved to Beppu on the island of Kyushu, famous for its hot springs, for recovery. He died of

rectal cancer in Beppu when he was 78. His funeral was at the Kanazawa University, and his grave is in the Hoenji Temple near the university. In 2002, Takayasu's statue was placed at the Kanazawa University.

(**Publ**.: Takayasu M. A case with peculiar changes of the central retinal vessels. *Acta Soc Ophthalmol Japn* 1908; 12:554–555.)

Theobald Smith's phenomenon is synonymous to anaphylaxis. It is an allergic or hypersensitivity reaction to a foreign material or drug. The eponymic term was coined by ***Paul Ehrlich***.

Smith demonstrated that animals may develop hypersensitivity to bacteria after repetitive injections. Specifically, this is a phenomenon seen in guinea pigs that had survived after being used for diphtheria antitoxin standardization—the animals having been rendered highly susceptible to subsequent inoculation of horse serum. Thus, in the course of his work on standardizing the antitoxin at the Massachusetts State Antitoxin Laboratory, he was the first to observe the phenomenon of serum anaphylaxis. In 1904, Smith mentioned this to ***Paul Ehrlich***, who assigned one of his research workers, Richard Otto, to study the problem. Ehrlich referred to the "Theobald Smith phenomenon" in his papers. What is now understood as anaphylactic response was previously accepted as the "Theobald Smith phenomenon." See also **Richet's phenomenon**.

Theobald Smith (see **Richet's phenomenon**)

Thomsen-Friedenreich antigen (**T-antigen**, **TF-antigen**, **Thomsen-Friedenreich receptor**)—Galβ1-3GalNAcα1—is a disaccharide and a cryptic antigen in membranes of erythrocytes, platelets, and glomerular capillary endothelial cells covered by N-acetylneuraminic acid moieties and exposed by *S. pneumoniae*-derived neuraminidase for removal of sialic acid. It usually is released into circulation in many different cancers and, thus, represents a tumor-associated molecule, which is assumed to be one of the few chemically well-defined antigens with a proven association with malignancy. The oligosaccharide chain of the T-antigen is called the **Thomsen-Friedenreich disaccharide**. The disaccharide Galβ1-3GalNAcα1-Ser/Thr is the core 1 structure of O-linked mucin-type glycans. In normal epithelium, the Galβ1-3GalNAcα1-Ser/Thr structure is concealed by sialic acids and sulfates or by addition of other sugar chains to form branched and complex O-glycans. With cancer and precancerous conditions, unsubstituted Galβ1-3GalNAc occurs in many human cancers including colon, breast, bladder, prostate, liver, ovary, and gastric cancer. Thus, in its simplest nonsialylated, nonextended form, the Thomsen-Friedenreich antigen acts as an oncofetal antigen, and its presence/expression is increased in malignant and premalignant epithelia.

The oncofetal Thomsen-Friedenreich carbohydrate antigen can be considered a pancarcinoma antigen because it is highly expressed by about 90% of all human carcinomas. It is possible that upregulated expression of the Thomsen-Friedenreich antigen in cancerous cells may support tumor progression by increasing the cell interactions with endogenous carbohydrate-binding proteins from the

galactoside-binding galectin family—for instance, lectins. Interestingly, carbohydrate tumor antigens are far more abundant than protein tumor antigens, rendering them suitable targets especially for antibodies. For example, highly expressed protein tumor markers, Her-2/neu, express about 10^6 copies per cell, whereas the Thomsen-Friedenreich antigen expresses about 10^7 copies per cell. Some data show that certain carbohydrate structures are not only targets for humoral but also for cellular immune responses.

All people display naturally occurring antibodies recognizing the Thomsen-Friedenreich antigen that are probably provoked by their own microbiota, which contain many types of microorganisms expressing the Thomsen-Friedenreich antigen.

The Thomsen-Friedenreich antigen was discovered as a laboratory curiosity 90 years ago when it was detected by the lectin peanut agglutinin on the surface of murine lymphocytes after treatment of cells with neuraminidase. In 1927, ***Oluf Thomsen*** reported that human blood corpuscles of any type (group) may be influenced by a propagative agent and within 12 hours to several days undergo such a change that they are agglutinated by all human sera, including their own serum.

Historically, Thomsen detected the antigen in a blood sample contaminated by bacteria. The bacterial neuraminidase induced the release of the sialic acid that covered the glycan chain, which opened a hidden structure on red blood cells. The transformation process is generally known as the **Hübener-Thomsen-Friedenreich phenomenon**. Anti-T antibodies, which normally circulate in human blood, caused the consequent hemagglutination. Thomsen's study was carried out in collaboration with ***Friedenreich*** and was published in 1930. The antigen was called the Thomsen-Friedenreich antigen and was known as the TF- or T-antigen. In 1960, 30 years later, the chemical structure of the T-antigen (Galβ1-3GalNAcα1-O-Ser/Thr) was determined by Klenk and Uhlenbruck.

Oluf Thomsen (Aug 21**,** 1878–May 19, 1940) was a Danish physician. He finished his medical studies in 1902 and earned a doctorate degree in 1905 with a classic thesis on pathoanatomical alterations in the placenta at syphilis. From 1909–1920, he worked for the State Serum Institute of Copenhagen. In 1918, he prepared his first paper on chronic, hereditary familiar icterus. In 1920, he received a professor position at the Institute of General Pathology at the University of Copenhagen; his studies focused on blood grouping, tissue typing, endocrinology, and genetic predisposition of diseases. In 1927, he published a paper about synpolydactyly, malfunctional bone fusions, and duplications in hands and feet. He reported an expanded family with 42 affected in 7 generations. In the same year, Thomsen was assigned the task of directing a grant to educate a younger physician. In 1935, he proposed to the Board of Education establishing an institute and a chair position at the University of Copenhagen. As a result, a new university Institute for Human Genetics was opened in 1938.

Viggo Friedenreich (1897–?) was a Danish physician.

(**Publ**.: Thomsen O. *Zeitschr f Immunitätsf* Bd. 1927; 52(H):1–2.

Friedenreich V. Investigations into the Thomsen hemagglutination phenomena. *Acta Patho Microbiol Scand* 1928; 5(1):59–101.

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Friedenreich V. Bactérie provoquant la panagglutinabilité des hématies humaines: Phénoméne de Thomsen. Paris, 1927.

Friedenreich V. *The Thomsen Hemagglutination Phenomenon*. Copenhagen: Levin & Munksgaard, 1930.)

Tolosa-Hunt syndrome (painful ophthalmoplegia, recurrent ophthalmoplegia, ophthalmoplegia syndrome) is a rare neuroimmunological disorder. It is characterized by a constant pain behind the eye, reduced eye movements, and signs of cranial nerve paralysis. The Tolosa-Hunt syndrome is caused by a sterile nonspecific inflammatory process within the cavernous sinus (i.e., an area at the base of the brain) of unknown etiology. No associations with any infectious agent have been reported. Its histopathology has been described as lymphocyte and plasma-cell infiltration, giant-cell granulomas, and proliferation of fibroblasts. Although the autoimmune etiology of Tolosa-Hunt syndrome has not been established, association of the syndrome with other autoimmune inflammatory diseases (e.g, systemic lupus erythematosus, sarcoidosis, and Wegener's granulomatosis) has been reported. Symptoms can resolve spontaneously after about 8 weeks without any therapy. Treatment may include the use of glucocorticoids or other immunosuppressive therapies.

Since its discovery in 1954, many cases of **Tolosa-Hunt syndrome** have been identified. It was first described in 1954 by ***Tolosa***, who discussed the case of a 47-year-old man admitted to the Neurological Institute in Barcelona, Spain, in 1949. The patient suffered from chronic severe left-sided orbital pain for 3 years and total ophthalmoplegia. The patient died 3 days after negative exploratory craniotomy. On autopsy, Tolosa found granulomatous inflammation and wrapping of granulation tissue around the intracavernous portion of the carotid artery. He described the process as "non-specific, chronic inflammation of the septa and wall of the cavernous sinus with the proliferation of fibroblasts an infiltration with lymphocytes and plasma cells." In 1961, ***Hunt*** et al. reported 6 cases of unilateral painful ophthalmoplegia that rapidly resolved with steroids. Hunt agreed with the Tolosa's observation and added that "such inflammatory changes, in a tight connective tissue, may exert pressure upon the penetrating nerves." In 1966, Joseph Smith and David Taxdal reviewed the available literature and suggested the eponym for the triad of unilateral orbital pain, palsies or weakness of cranial nerves, and a remarkable response to systemic corticosteroid treatment.

Eduardo Tolosa (Oct 24, 1900–Dec 4, 1981) was a Spanish neurosurgeon. He was born in Barcelona, Spain. He received his medical degree when he was 21 and his doctorate when he was 30. He then traveled around Europe to enhance his skills and knowledge in the field of neurology and neurosurgery. Later he was the director of neurology and neurosurgery at several hospitals and educational institutions in

Barcelona. Tolosa was a pioneer of stereotactic surgery, treatment of Parkinson's disease, and understanding brain tumor pathology. He was the best at in getting brain biopsies in Spain during his time.

He published more than 200 papers on several subjects, including tumor pathology and intracranial hematoma treatment. He was a founding member and elected president for the Portuguese Spanish Society of Neurosurgery, the Catalan Association of Neurology and Psychiatry, the Spanish Society of Neurology, and the Spanish Society of Neurosurgery.

Tolosa married the sister of famous Spanish neuropsychiatrist Ramon Sarró. They had a son, Eduardo, who became a prominent neurologist and now is a professor and chair of the Neurology Division at the Department of Medicine at the University of Barcelona, director of the Parkinson Disease and Movement Disorder Research Unit at the University of Barcelona Hospital, and founding director of the University of Barcelona Brain Bank.

Tolosa had Parkinson's disease, and after struggling with it for 17 years, he died in Barcelona, Spain.

William Edward Hunt (Nov 26, 1921–Jan 26, 1999) was a US neurologist and neurosurgeon. He was born in Columbus, Ohio, to William Willard Hunt and Marian Almina Lerch. He received his MD degree from the Ohio State University in 1945. After his internship training at the Philadelphia General Hospital, he served for 2 years in the US Army. He then continued his training in general surgery at White Cross Hospital in Columbus and in neurosurgery at Barnes Hospital of Washington University in St. Louis. From 1953 on, Hunt worked at the Ohio State University where he stayed for almost 25, being appointed professor in 1964, director of the Division of Neurological Surgery, and then director of the Spinal Cord Injury Research Center in 1973.

Hunt was known internationally for his outstanding work in cerebral vasculature and spinal cord injury. He was the first person to receive the Lifetime Achievement Award of the Neurological Society of America. He retired in 1991 and died in Columbus as a result of recurrent rupture of his thoracic aorta.

(**Publ**.: Tolosa E. Periarteritic lesions of the carotid siphon with the clinical features of a carotid infraclinoidal aneurysm. *J Neurol Neurosurg Psychiat* 1954; 17(4):300–302

Hunt WE, Meagher JN, Lefever HE, Zeman W. Painful ophthalmoplegia. Its relation to indolent inflammation of the cavernous sinus. *Neurology* 1961; 11:56–62.)

Traube's corpuscles (**Traube corpuscle**, **Ponfick's shadow**, achromocyte) are hypochromic, crescent-shaped erythrocytes, which have lost their hemoglobin. In a blood smear, a large, pale, curved cell forms from fragile red cells.

Emil Ponfick (Nov 3, 1844–Nov 3, 1913) was a German pathologist. He was born in Frankfurt am Main to Simon Moritz Ponfick and Charlotte Marie Emilie Stein. He studied medicine in Tübingen, Freiburg, and Heidelberg, where he obtained his doctorate at the latter in 1867. After pathological–anatomical studies at

Würzburg, he moved to the pathological institute in Berlin in 1868 as assistant to ***Rudolf Virchow***. He became the first assistant in 1873. He studied the pathophysiology of the liver, spleen, blood, and bone marrow. In 1874, Ponfick issued warnings about the dangers of animal-to-human blood transfusions. The reason was the death of a patient who had received blood from a sheep. In 1875, he accompanied the Grand Duke of Mecklenburg during his trip to Egypt, Nubia, Sinai, Cyprus, and Constantinople. In 1876, Ponfick moved to Göttingen as a Foundation Chair of Pathology and maintained his investigations on myelogenous leukemia and hemoglobulinemia.

In 1878, he moved to Breslau (Wroclaw), where he became director of the Institute of Pathology. He discovered the identity of aspergillosis in animals and humans and described actinomycosis. He also established that the ray fungus in man and in cattle are identical. He made important contributions to myxedema and severe hypothyroidism. He published his first textbook in 1882 and then prepared a large topographical atlas of medical and surgical diagnoses. His last work was "Bright Disease," which he studied because one of his sons died of chronic renal conditions. He was able to finalize his book just before he died in Breslau.

Ludwig (Louis) Traube (Jan 12, 1818–April 11, 1876) was a German internist. He was born in Ratibor, Silesia, to a Jewish wine merchant family, Wilhelm Traube and Eveline Traube. His younger brother Moritz Traube, a future wine merchant, also was known for his scientific works. From 1835 on, Ludwig studied medicine in Breslau (Wroclaw) and expressed a deep interest in physiology and physiological mechanisms. He received his doctorate in Berlin in 1840 with the thesis "Specimina nonnulla physiologica et pathologica," a work about pulmonary emphysema. He then continued to study pathology and started teaching young physicians. Traube was one of the first Jewish physicians to be habilitated as Docent at the University of Berlin. Based on the rules—Directorate of the Administration for the Poor (Armen-Direction von Berlin)—Traube was not provided by the material necessary for his classes. In 1844, he was prohibited from doing experiments and investigating human corpses, and thus he had to work with animal cadavers.

In 1849, he became ***Johann Lukas Schönlein***'s assistant at the Charité Clinic and was the first civilian colleague of Schönlein who was employed at there. In 1853, Traube took over leadership of a department in the Charité and was appointed extraordinary professor in 1857. Traube fought a continuous battle against the political factions of the state, mainly because he was a Jew. Only the friendship and support of colleagues enabled him to endure the repeated personal attacks that were leveled against him.

After Schönlein's retirement, Traube was one of the most famous and beloved clinicians. His practice at the Charité was very popular, and he was well known for his kind and honest handling of patients. In 1862, he was offered a professor position at an institute of military medicine. He received the title Privy Medical Counsellor, Geheimer Medicinalrath, in 1866.

Traube was an excellent scientist and one of the most popular teachers of his time. He was one of the leading practitioners of Europe with a reputation as a

pioneer of experimental pathology. He published a great deal on the diseases of the lungs, heart, and kidneys. Other interests were in digitalis, fever, and thermometry in medicine. Traube published his paper titled, "The causes and origin of those changes which the lung parenchyma suffers after section of the vagi." The work impressed ***Rudolf Virchow***, and a lifelong friendship between Traube and Virchow ensued. Together with Friedrich Wilhelm Felix von Bärensprung, in 1849 Traube introduced **measurement of temperature** as a routine clinical examination method. In 1852, he presented the very first graphic demonstration of a fever course with concurrent recordings of pulse and respiratory rate.

In his later years, he was often sick and frequently had to interrupt his work. He died in Berlin in 1876, and in 1878 a monument was erected to the memory of Traube in the second court of the Charité.

(**Publ**.: Traube L. *Gesammelte Beiträge zur Pathologie und Physiologie*, 2 vols. Berlin: Hirschwald, 1871–1878.

Traube L. Die Ursachen und die Beschaffenheit derjeningen Veränderungen, welche das Lungenparenchym nach Durchschneidung der Nn. vagi erleidet. Berlin: Albert Förstner, 1845.

Ponfick E. Die Actinomykose des Menschen, eine neue Infectionskrankheit. Monograph, Berlin, 1882.

Ponfick E. *Topographischer Atlas der Medizinisch-Chirurgischen Diagmostik*. Jena: G. Fischer, 1901.)

Troisier's syndrome (see **Troisier-Hanot-Chauffard syndrome**)

Troisier-Hanot-Chauffard syndrome (**Hanot-Chauffard syndrome**, **Troisier's syndrome**, **Leschke's syndrome**, **Recklinghausen-Appelbaum syndrome**, hypertrophic cirrhosis with skin pigmentation and diabetes mellitus). Sometimes called primary hemochromatosis, bronze diabetes, pigmentary cirrhosis, or iron overload disease. Diabetes mellitus associated with hypertrophic cirrhosis of the liver and dark brownish skin pigmentation is caused by deposits of excess melanin or iron pigment, or both, in tissues. Interestingly, the hemochromatosis gene (*HFE*) has been involved in the etiology of type 2 diabetes mellitus.

The condition was first described by ***Troisier*** in 1871 and in 1882 by ***Hanot*** and ***Chauffard***, although it is possible that this disease was initially described in 1865 by Armand Trousseau. In 1889, ***Recklinghausen*** coined the term *hemochromatosis* and was the first to provide the link between hemochromatosis and iron accumulation in body tissue. ***Leschke*** described congenital pigmentary dystrophy, known as Leschke's syndrome, which is an early manifestation of hemochromatosis.

Charles-Emile Troisier (Apr 6, 1844–Dec 11, 1919) was a French pathologist. He was born in Sévigny-Waleppe in Ardennes in northern France to Antoine Édouard Troisier, a health officer, and Marie-Louise Adeline Marache. After completing his medical studies in Paris in 1874, he became a professor of medicine at the University of Paris. He was a member of the Académie Nationale de Médecine (National Medical Academy). Troisier had a close relationship with Princess Marie

Bonaparte. His son, Jean Troisier, also became a doctor and led a research laboratory at the Pasteur Institute.

Anatole Marie Émile Chauffard (see **Still disease**)

Victor Charles Hanot (Jul 6, 1844–Oct 28, 1896) was a French physician. He earned his doctorate in 1875 and worked at the Hospital Saint-Antoine in Paris. Hanot specialized in hepatology and published on cirrhosis and hemochromatosis. He was the first to give a comprehensive description of primary biliary cirrhosis, which is sometimes referred to as Hanot's disease. His best-known written work is a book on hypertrophic cirrhosis.

Erich Friedrich Wilhelm Leschke (Oct 23, 1887–Jun 10, 1933) was a German internist. He was born in Bergneustadt, Rheinprovinz, as the son of Alwine Anna Sondermann and school director Johann Friedrich Ernst Leschke. Erich Leschke had above average talent: At the age of 10, he took a Latin textbook from his father's closet and read the Latin material of the first school year within 6 weeks. He attended the University of Bonn and received his doctorate in 1911 and extraordinary professor in 1919. During World War I, Leschke was an advisory internist of the III Army Corps and made a name for himself there by organizing the fight against epidemics. Later, he worked at the physiological institute and at the Friedrich-Wilhelm-Stift in Bonn, Eppendorfer Krankenhaus in Hamburg, and the II Medical Clinic at the Berlin Charité.

He had been invited several times to lecture in North and South America, England, and Russia. He was the inventor of the pneumothorax apparatus. Leschke syndrome (i.e., dystrophia pigmentosa) was named after him. By 1931, he had published about 170 papers, books, and brochures on his own investigations in the fields of the sympathetic nervous system, as well as heart, lung, metabolic diseases and psychology. He was a recipient of the Iron Cross II Class and the Red Cross Medal II Class. He died in Berlin-Charlottenburg. Leschke was diagnosed with appendicitis, but the diagnosis was wrong. He had a liver disease, probably hepatitis, which he probably had contracted through his medical work.

Friedrich Daniel von Recklinghausen (Dec 2, 1833–Aug 26, 1910) was a German pathologist who was born in Gütersloh, Westphalia. He studied medicine at the universities in Bonn, Würzburg, and Berlin; studied pathological anatomy under ***Rudolf Virchow***, the father of modern pathology; and obtained his doctorate with Virchow as his advisor. He was later a professor at the University of Würzburg and, for more than 3 decades, a professor at the University of Strasburg. He became Rector of the University in 1877 and remained there until his death. He was the father of physiologist Heinrich von Recklinghausen, remembered primarily for his study of blood pressure and contributions to devices to measure blood pressure—an oscillo-tonometer used to measure systolic and diastolic blood pressure. Recklinghausen died in Strasburg.

In 1882, Recklinghausen published a review analyzing clinical literature and characterizing the neurofibromatosis type 1 tumors (NF-1) as neurofibromas with an intense conflating of nerve cells and fibrous tissue. NF-1 sometimes can be

referred to as **von Recklinghausen syndrome**. He also developed a method of staining the cell junctions with silver-based dye. This procedure created the basis for ***Julius Friedrich Cohnheim***'s research on leukocyte migration and inflammation (see **Cohnheim's chemotactic theory**). In 1862, Recklinghausen prepared an outstanding characterization of the smallest lymph channels in connective tissue (**canals of Recklinghausen**) and stones seen in the pancreas during diabetes (1864). In 1889, he introduced the term *hemochromatosis* to a metabolic disorder associated with deposition of excess iron in the tissues, mostly the liver.

Leo Appelbaum was a German physician.

(**Publ**.: Troisier CE. Diabète sucré. *Bull Soc Anatom Paris* 1871, 16:231.

Hanot VC, Chauffard AME. Cirrhose hypertrophique pigmentaire dans le diabète sucré. *Rev Méd* 1882; 2:385–403.

Von Recklinghausen FD. Über Hämochromatose. *Berliner klinische Wochenschrift* 1889; 26:925; Tageblatt der Versammlungen deutscher Naturforscher und Aerzte, Heidelberg, 1889; 62:324.

Appelbaum L. Über Hämochromatose. *Medical Thesis*. Würzburg 1900.)

Troisier's node (**Troisier's sign**, **Virchow-Troisier node**), known as Virchow's node in the US and in most continental countries and as the node of Troisier in France, is a palpable enlargement of left supraclavicular lymph nodes (Troisier's node or ganglion), because of deposits of cancer cells that have metastasized from an obscurely located primary cancer, usually carcinoma of stomach or lung. See more in **Virchow's lymph node**.

Charles Emile Troisier (see **Troisier-Hanot-Chauffard syndrome**)

Rudolf Ludwig Karl Virchow (see **Hassall's corpuscles**)

Troisier's sign (see **Virchow's lymph node**)

Troisier's syndrome (see **Troisier-Hanot-Chauffard syndrome**)

Letter U



Upshaw-Schulman syndrome is the recessively inherited form of thrombotic thrombocytopenic purpura (TTP), a rare and complex blood coagulation disease. The clinical signs usually are mild during childhood, often with isolated thrombocytopenia. But their symptoms become more evident when patients have infections or get pregnant. Thrombotic thrombocytopenic purpura, first described by Moschcowitz (1924), is a life-threatening disorder characterized by thrombocytopenia, hemolytic anemia, neurological symptoms, renal dysfunction, and fever resulting from the formation of platelet thrombi within the microvasculature. Congenital TTP is associated with an inherited deficiency of ADAMTS13—a von Willebrand factor-cleaving protease. A disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS13), also known as von Willebrand factor-cleaving protease (VWFCP), is a zinc-containing metalloprotease enzyme that cleaves to von Willebrand factor (vWf)—a large protein involved in blood clotting.

Deficient ADAMTS13 activity in TTP patients may be attributable to 2 different mechanisms. In 70–80% of all TTP cases, there are circulating anti-ADAMTS13 autoantibodies that neutralize enzymatic activity and accelerate protease removal from the circulation. These conditions are known as acquired TTP. The second mechanism is the mutations in the *ADAMTS13 gene.* This is congenital TTP, also termed **Upshaw-Schulman syndrome**—a rare autosomal recessive disorder caused by homozygous or double-heterozygous mutations in *ADAMTS13 gene.* ***Schulman*** reported a clinical case of TTP in 1960. ***Upshaw***, in 1978, described relapsing TTP in a patient whom he had followed for 11 years. He also noticed some similarities with the Schulman case and hypothesized that both cases had a similar reason—a missing plasma factor. One year later, the disease was named **Upshaw-Schulman syndrome** by Rennard and Abe (1979). In 1996, the von Willebrand factor-cleaving protease was discovered and in the following year found to be the major issue in TTP's pathology. Later, the von Willebrand factor-cleaving protease was identified as ADAMTS13, the gene was mapped to chromosome 9q34, and the first Upshaw-Schulman syndrome-causing mutations were identified.

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Irving Schulman (Feb 17, 1922–Jun 11, 2009) was a US pediatrician and one of the founding fathers of pediatric hematology/oncology. He was born in New York City and earned his BA degree in 1942 and an MD degree in 1945, both from New York University. He then did his internship at Queens Hospital and, in 1949, completed his residency training in pediatrics at Bellevue Hospital in New York. There he met a young lab technician, Naomi Zion, who became his wife in 1950. After that he became a faculty member at Cornell University Medical Center and Northwestern University Medical School. During these years, he conducted pioneering studies on idiopathic thrombocytopenia purpura and was one of the first to describe hemophilia arising from a deficiency of blood clotting-factor IX in children. He was also among the first physicians to consider steroid treatment for childhood acute leukemia. In 1961, he became professor and head of pediatrics at the University of Illinois, and in 1972 he was recruited to Stanford as the chief of pediatrics. Soon Schulman realized that the Children's Hospital at Stanford, which was prepared as a recovering facility for tuberculosis, could not meet modern healthcare needs. Together with Lucile Packard, he designed a new hospital using input from community groups in the Bay Area.

In 1960, Schulman received the E. Mead Johnson Award, a top honor for outstanding achievement in clinical research in pediatrics.

Jefferson D Upshaw Jr. (Jul 19, 1929–Jan 6, 2008) was a US hematologist, born in Louise, MS, the son of Jefferson Davis Upshaw and Gladys Christine Ferguson. He received his medical degree from Johns Hopkins School of Medicine in 1954. He worked at the University of Tennessee College of Medicine and then at the Division of Hematology, Baptist Memorial Hospital, Memphis, TN.

(**Publ**.: Schulman I, Pierce M, Lukens A, Currimbhoy Z. Studies on thrombopoiesis, I: a factor in normal human plasma required for platelet production; chronic thrombocytopenia due to its deficiency. *Blood* 1960; 16:943–957.

Upshaw Jr JD. Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. *N Engl J Med* 1978; 298:1350–1352.)

Urbach's syndrome (see **Oppenheim-Urbach disease**)

Urbach-Königstein method (see **Königstein-Urbach reaction**)

Urbach-Königstein reaction (see **Königstein-Urbach reaction**)

Letter V



Vaquez's disease (**Osler's disease**, **Osler-Vaquez/Vaquez-Osler disease**, polycythemia vera) is a relatively rare chronic disease of the blood in which the red cells increase in number. The spleen becomes enlarged, and the face is a deep red rather than truly cyanotic. Occasionally reported in childhood, it occurs mostly in middle-aged males in which increased erythrocyte count (reaching sometimes 10,000,000 per μL), blood volume, erythroblastic activity, and blood viscosity are associated with cyanosis and splenomegaly. Etiology is unknown, but mutations of the *JAK2* gene are detected in 95% of cases. This gene plays a particularly important role in the production of blood cells from stem cells in the bone marrow. Because of this genetic mutation, the bone marrow begins to produce excess red blood cells—thus, its name "polycythemia"—and with a longer life span. The excessive concentration of red blood cells in relation to the total volume of blood causes a thickening of it, which flows more slowly, no longer provideing enough oxygen to the organs and increasing the risk of blood clot formation. Polycythemia vera belongs to the group of myeloproliferative syndromes. When associated with liver cirrhosis, this disorder is known as the **Mosse syndrome**. It is more frequently observed in people of Jewish origin.

Louis Henri Vaquez (Aug 27, 1860–Apr 15, 1936), a French internist, was born in Paris into a family of silk merchants—he was the son of François Ernest and Léontine Marie Fessard. He studied medicine in Paris, graduating with an MD in 1890. He became professor of clinical medicine in 1918 and was elected a member of the Academy of Medicine. During his long association with Saint-Antoine hospital, and into his retiring years while on the staff of la Pitié, he studied many clinical subjects. These included sphygmomanometry, the peripheral pulse, nephritis, hypertension and partial adrenalectomy in advanced cases, pheochromocytoma, phlebitis, paroxysmal hemoglobinuria, eclampsia, eosinophilia, erythromelalgia, pleurisy, anemia and other aspects of hematology, and chloride metabolism in cardiac failure. He described polycythemia vera in 1892. ***William Osler*** published his

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classic description of the disorder in 1903 and at first thought it was a new clinical entity but learned of Vaquez's report and acknowledged his priority. Vaquez was active both as an author and a journalist and was a prolific writer. He edited the *Archives of the Maladies of the Heart* (Paris) from 1908 to his death and prepared several monographs.

Apart from describing the disease that bears his name, he introduced to France the use of the electrocardiogram and the recording of the jugular pulse and used all kinds of new resources for both diagnosis and treatment. He received several awards and decorations, including the Legion of Honour in 1927.

William Osler **(see Osler's triad)**

(**Publ**.: Vaquez LH. The special form of cyanosis accompanying persistent hyperglobulinemia (Fr). *C R Soc Biol* 1892; 44:384–388.

Vaquez LH. Maladies of the Heart (Fr). Paris: J.-B. Bailliére; 1921.

Osler W. Chronic cyanosis with polycythaemia and enlarged spleen: a new clinical entity. *Am J Med Sci* 1903; 126:187–201.)

Vaquez-Osler disease (see **Vaquez' disease)**

Vici syndrome is a rare multisystem hereditary disease characterized by agenesis (i.e., developmental failure) of the corpus callosum, hypopigmentation, hypotonia (low muscle tone), developmental delay, cataract, cardiomyopathy, and immunological dysfunctions. The foremost clinical sign is seen in all patients with recurrent infections, mainly affecting the respiratory tract. This represents an important risk factor for morbidity and mortality. The immunological phenotype of patients is exceptionally flexible, varying from a combined immunodeficiency to almost normal immunity. Immunological studies detected lymphopenia associated with various combinations of specific T-cell subset defects, leukopenia and neutropenia, hypogammaglobulinemia, and the lack of skin responses to several recall antigens. Multiple data confirm the presence of a heterogeneous immunological phenotype in Vici syndrome. Therefore, each Vici patient can present a different pattern and degree of immunodeficiency, as it has been reported in other complex syndromes with immunodeficiency (e.g., DiGeorge syndrome and ataxia telangiectasia).

Vici syndrome is now linked with recessive mutations in the *EPG5* gene, which encodes ectopic P granules protein 5 homolog (EPG5). EPG5 also is involved in the TLR9 signaling through trafficking of its ligand, CpG, from early endosomes to late endosomes and lysosomes. Defective termination of TLR signaling, upstream to NF-kB nuclear translocation, is a probable underlying cause of increased cytokine secretion. TLR9 takes part in IgM memory B-cell differentiation and also in recognition of incoming cargo in the autophagic pathway, explaining the link between immune dysregulation and autophagy defects in Vici syndrome. EPG5 deficiency results in abnormal memory B-cell differentiation and thus hypogammaglobulinemia and susceptibility to bacterial infections.

Vici syndrome was described initially in 1988 in 2 brothers with agenesis of the corpus callosum, bilateral cataracts, cleft lip and palate, hypopigmentation of the skin and hair, combined immunodeficiency, and severe psychomotor retardation.

Thereafter, a dozen of similar cases have been reported, contributing to describing clinical and laboratory features of Vici syndrome.

Carlo Dionisi-Vici (Nov 15, 1956–) is an Italian pediatrician. He received his medical degree from the University "La Sapienza" in Rome, Italy, and postdoctoral training in Bern University, Switzerland, and Hospital Necker-Enfants Malades in Paris. From 2009, he has been a head of the Division of Metabolism, Department of Pediatric Medicine, Children's Hospital Bambino Gesu in Rome. He is also a professor of Inborn Errors of Metabolism affiliated with the School of Pediatrics; University "Tor Vergata," School of Medical Genetics; Catholic University "Sacro Cuore"; and School of Pediatrics, University "La Sapienza." His research focuses on identifying new diseases, disease biomarkers, disease genes, novel therapeutic approaches, and the development of guidelines in the field of inborn errors of metabolism.

(**Publ**.: Vici CD, Sabetta G, Gambarara M, et al. Agenesis of the corpus callosum, combined immunodeficiency, bilateral cataract, and hypopigmentation in two brothers. *Am J Med Genet* 1988; 29(1):1–8.)

Virchow's cell is a macrophage in Hansen's disease (also known as **leprosy**). Sometimes, it can be used to show a cavity in osseous tissue containing bone cells.

Rudolf Ludwig Karl Virchow (see **Hassall's corpuscles**)

Virchow's lymph node (**Virchow's node,** signal node or sentinel node, **Troisier's sign**) is in the area above the left clavicle or collarbone. The node takes its blood supply from lymph vessels in the abdominal cavity. The finding of an enlarged lymph node has long been regarded as strongly indicative of the presence of cancer in the abdomen, specifically gastric cancer that has spread throughout the lymph vessels. The left supraclavicular lymph node is known as one of the first places where the gastric malignancies metastasize. Therefore, this node is the standard Virchow's lymph node because it is located on the neck's left side. This body location is specific because the lymphatic drainage of the body from the thoracic duct joins the venous circulation through the left subclavian vein. The metastasis may occlude the thoracic duct, and this causes regurgitation into the neighboring nodes (e.g., Virchow's node).

This lymph node was named after ***Rudolf Virchow*** who in 1848 first identified it and its connection with gastric cancer. In 1889, ***Charles Emile Troisier***, a French pathologist, discovered that other abdominal cancers also can spread to the node.

Rudolf Ludwig Karl Virchow (see **Hassall's corpuscles**)

Charles-Emile Troisier (see **Troisier-Hanot-Chauffard syndrome**)

(**Publ**.: Virchow R. Zur Diagnose der krebse in unterleibe. *Med Reform* 1848; 45:248.

Troisier CE. L'adénopathie sus-claviculaire dans les cancers de l'abdomen. *Arch Gen Med* 1889; 1:129–138, 297–309.)

Virchow-Hassall corpuscles (see **Hassall's corpuscles**)

Virchow's node (see **Troisier's node**)

Vogt-Koyanagi-Harada disease is a multisystem autoimmune inflammatory disease. It presents with signs and symptoms of a loss of immune tolerance to melanocytes, leading to a nonnecrotizing granulomatous inflammation in the meninges, eyes, ears, skin, and hair. In the eye, these are detected as subretinal pigment epithelial aggregates called Dalen-Fuchs nodules, consisting of epithelioid histiocytes, which are also common for other granulomatous processes. Analysis of enucleated specimens shows B cells and T cells in choroid and loss of choroidal melanocytes. Clinically, the disease presents in 4 different phases—prodromal, uveitic, convalescent, and recurrent. Extraocular manifestations include headache, hearing loss, meningismus (i.e., meningeal irritation), poliosis (i.e., clusters of white hair), and vitiligo (i.e., patches of white skin).

The precise etiology of **Vogt-Koyanagi-Harada disease** is not recognized, but existing concepts suggest that patients develop T cell-mediated immunity against melanocytes after recovery from provoking viral environmental factors (e.g., Epstein-Barr virus and cytomegalovirus). Tyrosinase peptide is a known target of T cells. Contemporary genetic studies have established association of the disease with HLA-DRB4, HLA-DRB1-04*05, and HLA-DRB-04*01. Downregulation of microRNA in the production of IL-12 and IL-17, and changes in noncoding RNA, also may play a role in **Vogt-Koyanagi-Harada disease.**

The combination of poliosis and ocular inflammation was noted by the best-known Arab ophthalmologist of medieval Islam Ali ibn Isa al-Kahhal, identified in medieval Europe as Jesu Occulist. ***Vogt*** initially described bilateral iridocyclitis and eyebrow depigmentation in 1906, and ***Koyanagi*** described 16 similar cases in 1929. Interestingly, Koyanagi published his first report in the *Nippon Ganka Gakkai Zasshi* in 1914, but it was his later article of 1929 that linked his name with the disease. Both Vogt and Koyanagi reported the combination of primarily anterior uveitis with extraocular manifestations, including vitiligo, poliosis, alopecia, and hearing loss. In 1926, ***Harada*** described similar extraocular manifestations with exudative retinal detachments and pleocytosis in the cerebrospinal fluid.

Alfred Vogt (Oct 31, 1879–Dec 10, 1943) was a Swiss ophthalmologist. He was born in Menziken, State of Argovie, the German-speaking region of Northern Switzerland, to the family of a primary school teacher. He went to college in Aarau, where he developed interest in the natural sciences. In 1889, he received his bachelor's degree, 4 years after Albert Einstein, who attended the same very liberal college. Vogt studied medicine in Zurich and Basel and graduated in 1904. He was trained in ophthalmology and opened his private practice in 1906. It was at this time that he married Marie Bossardt. From 1909, he was the head physician of the Department of Ophthalmology in the cantonal hospital in Aarau. In 1917, he was invited as the professor extraordinary to direct the University of Basel's Eye Clinic. In 1923, he became the professor ordinarius and director of the Eye Clinic at the University of Zurich.

He had a genuine gift of observation and an enormous working capacity. He started his work in clinic at 6 am and commonly worked until 9 pm, expecting the same schedule from others. In memory of his son, Alfred Vogt Junior, who died in an avalanche accident in 1929, Vogt established the Alfred Vogt Foundation to encourage ophthalmology at the Eye Clinic of the University Hospital Zurich in 1938. He remained as the chair of the Department of Ophthalmology in Zurich until August 1943. He died in Zurich shortly after his retirement.

Vogt was a pioneer of specular microscopy and examination of the corneal endothelium and well known for the introduction of new techniques for retinoscopy and the surgical management of retinal detachment. Vogt was renowned for his amazing knowledge of literature and for his constant battles for priority over others. Vogt's merits, extraordinary memory for facts, and exceptional surgical skills were often overshadowed by his aggressive nature.

Yoshizo Koyanagi (Dec 10, 1880–1954) was a Japanese ophthalmologist. He was born in the Tokyo area. He graduated from Kyoto Imperial University in 1908 and studied ophthalmology at the same university. He was an ophthalmologist at the Red Cross Hospital in Osaka in 1912 and, in 1913, professor extraordinary in Kyoto. In 1917–1918, he studied in Europe. In 1915, he became the first professor of ophthalmology at the newly founded Tohoku Imperial University in Sendai, where he worked until his retirement in 1942. Koyanagi was well known as ophthalmic pathologist for his work on retinal pathology. Among his many publications was an essential textbook of ophthalmology. Koyanagi was buried in Sendai in spite of his wish to have his ashes spread in the Bay of Matsushima off Sendai.

Einosuke Harada (Feb 25, 1892–Dec 20, 1946) was a Japanese ophthalmologist. He was born in Goryo, Amakusa District, Kumamoto Prefecture, and graduated from Tokyo University in 1917 and after that worked as army surgeon. In 1923–1925, he continued to study ophthalmology and then conducted his clinical research at the Department of Pharmacology of Tokyo University finishing his dissertation thesis entitled "Experimental studies on changes of the aqueous humor by various drugs" and receiving the degree of Doctor of Medical Sciences (DMSc) in 1929. Harada practiced in Nagasaki in the hospital of his father-in-law, who was also an ophthalmologist. In 1943, he went to the World War II battlefront in the Philippines but soon terminated his work because of illness. On August 9, 1945, his hospital was destroyed by the atomic bomb. Harada had planned to build a new hospital but fell ill and died of pneumonia at the age of 54.

(**Publ**.: Vogt A. Frühzeitiges Ergrauen der Cilien und Bemerkungen über den sogenannten plötzlichen Eintritt dieser Veränderung. *Klin Monatsbl Augenheilkd* 1906; 44:208–242.

Koyanagi Y. Dysakusis, Alopecia und poliosis bei schwerer uveitis nicht traumatischen Ursprungs. *Klin Monatsbl Augenheilkd* 1929; 82:194–211.

Harada E. Beitrag zur klinischen Kenntnis von nicht eitriger Choroiditis (choroiditis diffuse acuta). *Acta Soc Ophthalmol Jpn* 1926; 30:356–378.)

Letter W



Waelsch's disease (see **Reiter's syndrome** Nongonococcal urethritis or Waelsch urethritis) is a part of now a familiar triad—namely, the conjunctiva of infants, the cervix of mothers, and the urethral scrapings from male partners.

Ludwig Waelsch (Nov 20, 1867–Apr 5, 1924) was a German-Czech physician. He was a son of Benedict Waelsch (Weltsch) and Karoline Waelsch born in Prague. After getting his education, he worked as an assistant at the Prague dermatological clinic. He was habilitated for skin and venereal diseases in 1898 and became a titular professor in 1907 and professor extraordinary in 1916. Waelsch was the first to describe the so-called nongonococcal urethritis and noted that "it was difficult to cure." He died in Prague.

(**Publ**.: Waelsch L. Uber nicht-gonorrhoische urethritis. *Arch Derm Syph Wien* 1904; 70:103–124.)

Waldenström's macroglobulinemia (lymphoplasmacytic lymphoma) is a chronic rare cancer occurring in B lymphocytes before they differentiate into plasma cells. Waldenström's macroglobulinemia is considered a type of non-Hodgkin's lymphoma. Clinically, it is seen as hepatomegaly, splenomegaly, and lymphadenopathy associated with a normochromic, normocytic anemia. All patients with **Waldenström's macroglobulinemia** have the monoclonal IgM protein detected in serum by protein electrophoresis and confirmed by immunoelectrophoresis. Sporadically high levels of the IgM monoclonal protein create a hyperviscosity syndrome displayed by oronasal bleeding and detected as type I cryoglobulinemia.

Waldenström's macroglobulinemia, as a form of plasma cell dyscrasia, is designated by an unrestrained clonal proliferation of B lymphocytes. The common mutations are a somatic one in MYD88 seen in almost 90% of patients and a somatic mutation in CXCR4 revealed in almost 30% patients.

In 1944, *Jan Waldenström* reported on 2 patients who presented with hepatosplenomegaly, anemia, oronasal bleeding, and a strange protein in the serum

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specimen. He observed that while normal serum globulin sedimented with a coefficient of 7S, serum globulin in his patients displayed a sedimentation coefficient of 19S. His original report had all the noticeable features of the low-grade lymphoplasmacytic disorder that now carries his name. He provided a description of a "hyperviscosity syndrome" in which symptoms are caused by abnormal lymphocytes that prevent normal bone marrow function, causing anemia and hepatosplenomegaly, and that secrete large immunoglobulins, causing bleeding complications.

In 1961, ***Jan Waldenström*** was the first to explain the key **concept of monoclonal**-versus-polyclonal gammopathy in the Harvey lecture series. Significantly, he first distinguished monoclonal proteins seen on serum protein electrophoresis as a narrow band of gamma globulins associated with multiple myeloma or macroglobulinemia from hypergammaglobulinemia. The latter is characterized by a broad area in the gamma region on serum protein electrophoresis as a polyclonal increase in antibodies associated with an inflammatory or reactive process.

Jan Gösta Waldenström (Apr 17, 1906–Dec 1, 1996) was a Swedish physician. He was born in Stockholm to a family with a solid history in medicine. His father, Johann Henning, was a professor of orthopedic surgery, and his grandfather, Johan Anton Waldenström, was a professor of internal medicine in Uppsala—a city in Sweden situated north of Stockholm. Waldenström received his medical degree from the University of Uppsala. He then studied organic chemistry at the Technical University of Munich in Germany. In 1941, he was a professor of theoretical medicine at the University of Uppsala. In 1944, he was a professor of practical medicine at the University of Lund. Then, he became a professor and chair of the Department of Medicine at Malmö General Hospital, where he worked until his retirement in 1972.

Waldenström was considered one of the finest clinicians of his time and conducted important clinical research on various blood diseases, including porphyria, pulmonary hemosiderosis, benign hypergammaglobulinemic purpura, **Bruton's hypogammaglobulinemia**, and carcinoid syndrome. His most significant contribution to medicine was his concept of monoclonal-versus-polyclonal gammopathies. He received many honors and award and received honorary degrees from the Universities of Oxford, Freiburg, London, Oslo, Paris, Mainz, Dublin, and Innsbruck. He was an honorary member of the Royal Society of Medicine in London, the National Academy of Science in the US, and the French Academy of Sciences.

(**Publ**.: Waldenström J. Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia—a new syndrome? *Acta Med Scand* 1944; 216:117.

Waldenström J. Studies on conditions associated with disturbed gamma globulin formation (gammopathies). *Harvey Lect* 1961; 56:211–231.)

Waldeyer's ring (Waldeyer's tonsillar ring) is comprised of 4 (i.e., pharyngeal, tubal, palatine, and lingual) tonsillar shapes and small collections of the pharynx lymphatic tissue also known as nasal-associated lymphoid tissue (NALT). These lymphoid tissues, situated at the gateway of the respiratory and alimentary tract,

belong to the mucosa-associated lymphoid tissue (MALT). Because tonsils, where B cells are generated in the germinal centers, are the initial site of contact with inhaled and ingested pathogens, they are the primary line of defense against exogenous infections. *Heinrich Wilhelm Gottfried von Waldeyer-Hartz* was the first clinician who identified the incomplete ring of lymphoid tissue seen in the **nasopharynx** and oropharynx regions in 1884.

Heinrich Wilhelm Gottfried Waldeyer (Oct 6, 1836–Jan 23, 1921), known as ***Wilhelm von Waldeyer-Hartz*** after 1916, was a German anatomist. He was born in Hehlen an der Weser and attended the Gymnasium Theodorianum in Paderborn. In 1856, he took up a place at the Universität Göttingen, with the intention of studying mathematics and natural sciences, but he changed to learning medicine in 1857. In 1861, he obtained his doctorate with a doctoral thesis, "De claviculae articulis e functione," which was written in Latin. Then he worked in Königsberg as assistant for physiology and histology and moved to Breslau to the Physiological Institute in 1864, where he was appointed to the role of nontenured professor and received a full professorships in 1867.

Waldeyer held various distinguished academic positions including as a full professor in Breslau, Strasbourg, and Berlin. He remained in Berlin for 33.5 years as full professor of anatomy and director of the Anatomical Institute. During his long tenure in Berlin, he was Dean and Rector Magnificus several times. In 1912, he was named to the (Prussian) House of Lords. In 1916, when given a peerage by the German Emperor Wilhelm II, he decided to add his mother's family name "Hartz" to his own, making him "Wilhelm von Waldeyer-Hartz" for his remaining years and for posterity.

Waldeyer published 269 papers throughout his career. He is known for coining the term "neuron" to describe the basic structural unit of the nervous system and for adopting the term "chromosome" in 1888. He was also the first to describe and name **plasma cells** in 1875. Now, Waldeyer's name mainly is attached to the term pharyngeal lymphatic ring. In 1884, in a talk at the Society of Internal Medicine in Berlin, Waldeyer suggested that there is a true ring of lymphatic tissue around the nasal and oral openings of the pharynx and that the tonsils are merely concentrations of such tissue. This has been proven to be an accurate anatomical description and a useful clinical concept.

Waldeyer retired from his chair position in 1917 at the age of 80 and died in Berlin after a cerebral apoplexy in 1921. Years before his death, Waldeyer decided to will his skull, brain, and hands to the Institute of Anatomy to be stored and examined there. He had discussed this with several colleagues and left detailed instructions. In 1923, Hans Virchow published an extensive report about Waldeyer's hands.

(**Publ**.: Waldeyer W. Hernia retroperitonealis, nebst bemerkungenzur anatomie des peritoneums. *Arch Pathol Anat Physiol Klin Med* 1874; 60:66–92.

Waldeyer W. Ueber den lymphatischen apparat des pharynx. *Dtsch Med Wochenschr* 1884; 10:313.

Waldeyer W. Hottentottenschürze. Verhandlungen der Berliner Gesellschaft fu¨r Anthropologie, Ethnologie und Urgeschi Chte. Berlin: Verlag von A. Asher & Co.; 1885; pp. 568–571.

Waldeyer W. Das Studium der medicin und die frauen. *Verh Deutsch Ges Naturforsch Arzte* 1988; 61:31–44.)

Warthin-Finkeldey cell is a type of giant multinucleate cell found in hyperplastic lymph nodes early in the course of measles, also in HIV-infected individuals, and more rarely in a number of neoplastic (e.g., lymphoma) and nonneoplastic lymph node disorders. Morphologically similar multinucleated giant cells also have been described in systemic lupus erythematosus, **Hashimoto's thyroiditis**, and **Kimura's disease**. Their origin is uncertain, but previously they have been shown to stain with markers similar to those of follicular dendritic cells, including CD21. Under the light microscope, these cells consist of a large, grape-like cluster of nuclei.

Multinucleated giant cells associated with measles were described by Ciaccio in 1910 (Ciaccio 1910), although Warthin and Finkeldey are cited most frequently for their early descriptive studies of these cells in 1931. Fifty years later, Kjeldsberg and Kim popularized the term polykaryocyte (sometimes called "mulberry cells") for cells "resembling Warthin-Finkeldey giant cells" in benign and reactive lymphoid disorders.

In 1931, **Warthin** and **Finkeldey** independently identified a specific type of multinucleated giant cell occurring in tonsils and adenoid lymphoid tissues during the prodromal stage of measles infection. They reported these cells as syncytial multinucleated giant cells, which contain several nuclei visualized as a grape-like cluster in the middle of affected cells. Although these cells initially were detected only in lymphoid tissues during measles infection, the cells, called Warthin-Finkeldey ones, later also were described in the lymph nodes and extranodal tissues of benign and neoplastic lymphoid disorders.

Wilhelm Finkeldey was a twentieth-century German pathologist.

Aldred Scott Warthin (Oct 21, 1866–May 23, 1931) was a US pathologist. He was sometimes considered "the father of cancer genetics" because his main research laid the foundation for understanding the heritability of certain cancers. He was born in Greensburg, Indiana, to Edward Mason Warthin and Eliza Margaret (Weist) Warthin.

Youth Warthin often accompanied his physician uncle collecting specimens. He also took piano lessons to please his invalid mother and entered the Cincinnati Conservatory of Music, where he was awarded a teacher's diploma in 1887. He studied at the University of Michigan Medical School. He supported himself by teaching music and serving as a church organist; he earned his MA degree in 1890, MD in 1891, and PhD in 1893. Warthin then joined the faculty at the University of Michigan, where he remained for the rest of his career. In 1895, he took charge of the pathology laboratory, and he was appointed the laboratory director and professor of pathology in 1903. He also served as a chair of the Pathology Department.

From 1893–1900 on, Warthin spent his summers in European pathology laboratories in Vienna, Dresden, and Freiburg.

In 1895, a young dressmaker of Warthin's friend told him about her family with a long history of cancer-associated deaths. Fascinated, he investigated her family's history, which he called "family G," by searching death and medical records accumulated for decades. His paper published in 1913 in the *Archives of Internal Medicine* was one of the very first to demonstrate that cancer was heritable in family G and is one of the extended and detailed cancer genealogies in the world. Later, it was determined that family G is prone to hereditary nonpolyposis colorectal cancer or Lynch syndrome. By 1913, Warthin had analyzed and described the ancestries of 29 cancer-susceptible families and recognized cases of identical twins who developed identical cancers in mirror-image sites. He was convinced that predisposition to cancer and potential protective immunity could be inherited.

Warthin is well known for his pioneering research on the heritability of cancer. Yet, he also worked on the problems of tuberculosis and constitutional aspects of hyperthyroidism. Some thought his most important work was his study of diseases of the reticuloendothelial system. Following World War I, he conducted interesting studies on mustard gas poisoning and pathological mechanisms of intoxication. He also focused on the social hygiene problems fundamental to the spread of venereal diseases. He and his research associate developed the Warthin-Starry stain still used to demonstrate the presence of syphilis spirochetes.

In 1900, Warthin married another physician, Katherine Angell, and they had 4 children. One of his hobbies was collecting artistic portrayals of death. He even published a scholarly monograph on the subject—*The Physician of the Dance of Death*. This book and two others, *Old Age: The Major Involution* (1929) and *The Creed of a Biologist* (1930), presented Warthin's ideas on immortality and human nature. Interestingly, at the Race Betterment Conference in Battle Creek in 1928, Warthin discussed his viewpoint that religion and the concept of forgiveness of sin weaken the human race by the persistent spread of social diseases. He also opposed marrying for passionate love and urged those who were married to check their ancestral backgrounds to avoid transferring hereditary diseases to future generations. Warthin thought that the only means to physical progress and a long life came by means of eugenics.

He died suddenly of asthma in Ann Arbor in 1931. He is buried in South Park Cemetery in Greensburg, IN.

(**Publ.:** Warthin AS. Occurrence of numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles. *Arch Pathol* 1931; 11:864–874.

Finkeldey W. Ueber riesenzellbefunde in den gaumenmandeln, zugleich ein beitrag zur histopathologic der mandelveranderungen im maserninkubationsstadium. *Virchows Arch Pathol Anat* 1931; 281:323–329.)

Wassermann test (**Wassermann reaction, Wassermann-Neisser-Bruck reaction**, *Bordet-Wassermann reaction*) is an antibody test (i.e., complement-fixation test) for syphilis; it is named after the bacteriologist ***August Paul von Wassermann***

who—together with ***Albert Neisser*** and ***Carl Bruck***—developed the initial serologic test for the diagnosis of syphilis in 1906. This was just a year after the causative organism, *Spirochaeta pallida*, had been identified by Fritz Schaudinn and Erich Hoffmann. Neisser suggested the method for testing for syphilis and provided the liver of a syphilitic fetus and sera from syphilitic patients; Wassermann assigned Bruck, then one of his trainees, to develop the test. The "Wassermann test" allowed for early detection of the disease and, in spite of nonspecific signs, helped prevent disease transmission. Wassermann credited the successful development of his famous test to the previous findings of ***Jules Jean Baptiste Vincent Bordet*** and Octave Gengou, who first discovered the complement-fixation reaction, and to a concept introduced by ***Paul Ehrlich*** in his interpretation of antibody generation. The study was done at the Berlin Institute of Infectious Diseases and at the Breslau (Wroclaw) Department of Dermatology.

The **Wassermann reaction** was used widely in syphilis diagnosis. The antigen was discovered empirically. Originally, the so-called antigens were partialy purified extracts of human or monkey tissue infected with *Treponema pallidum*. Later, the active substance, known as *cardiolipin*, was found in normal nonsyphilitic tissues, including the heart. ***Karl Landsteiner*** identified the antigen involved in the Wassermann reaction as a lipoid substance, which finally was recognized as diphosphatidylglycerol. Wassermann antibodies, generated in the course of syphilis disease, target cardiolipin in the presence of lecithin and cholesterol. The antigen–antibody reaction produces immune complexes that cause complement fixation through the classic pathway. Thus, this may be used to detect the level of antibodies in the serum. In the final step, visual marker cells (e.g. erythrocytes), together with a subagglutinating amount of antibodies (e.g., antierythrocyte), are added to the test tube. If there is still any complement left, these marker cells will be lysed and seen; if complement has been completely consumed by immune complexes, there is no lysis of the red cells.

The Wassermann test was used in many countries for a long time, and it remains a main means of syphilis detection and prevention in some areas. It has been replaced, however by more modern alternatives in all developed countries. Although the Wassermann reaction in general is no longer in use, it must be stressed that it was one of the very first serological, or serodiagnostic, tests used in medical practices.

The history of this great assay has been described thoroughly by a Polish serologist, Ludwik Fleck, in his book on the philosophy of scientific research published in 1935 in Basel. Fleck mentioned that Wassermann has attempted to claim sole responsibility for developing the test. Other scientists of that time, however, emphatically have endorsed the efforts of ***Neisser*** and ***Bruck***. The French, on the other hand, use the term *Bordet-Wassermann reaction* to honor the inventor of the complement-fixation test.

August Paul von Wassermann (Feb 21, 1866–Mar 16, 1925) was born in Bamberg with Jewish origins, the second son of Angelo Wassermann, a Bavarian court banker, and Dora Bauer. He studied medicine at the universities in Erlangen,

Vienna, and Munich, receiving the MD degree at Strasburg in 1888. In 1895, he married Alice von Taussig of Vienna; they had 2 sons.

In 1891, he entered the newly established Institute for Infectious Diseases, directed by Koch. In 1898, he became Titular Professor, and in 1901, he became Privatdozent (assistant or associate professor) of internal medicine at the Friedrich Wilhelm University in Berlin. He was promoted to the Professor Extraordinary in 1902 and honorary professor in 1911. In 1906, he was invited to be a director of the Division of Experimental Therapy and Serum Research at the Institute for Infectious Diseases. In 1913, the Kaiser Wilhelm Institute for Experimental Therapy in Berlin-Dahlem was created especially for him, and he held the director position until his death.

Working with ***Robert Koch***, Wassermann suggested that human and animal blood can be differentiated by means of specific antibodies for erythrocytes and proposed a method for the evaluation of precipitating serums. Following Paul Ehrlich's advice, Wassermann began to study the binding of toxin and antitoxin in the blood. After 1900, Wassermann focused on problems relating to complement, and based on the complementing fixation reaction, he initially developed a complement-fixation test for the diagnosis of tuberculosis. Later, Wassermann and ***Albert Neisser*** prepared an assay for detection of an antibody generated by a patient infected with protozoan *Spirochaeta pallida* (now known as *Treponema pallidum*)—the causative agent of syphilis. Wassermann explained the test as follows: "Inactive serum of infected monkeys is mixed with complement agents of the guinea pig. When specific hemolytic serum is added together with normal erythrocytes, hemolysis is prevented."

With the beginning of World War I, all Wassermann's technical supplies and the laboratory staff were moved to the Eastern Front in Russia. During the latter stage of the war, Wassermann served as a chief executive of the section for hygiene and bacteriology in the Prussian War Ministry and thus could not continue his research. In 1921, his research institute changed its name to Kaiser Wilhelm Institute for Experimental Therapy and Biochemistry. Although Wasserman worked very hard on tumor physiology and therapy and on the complement-binding reaction in tuberculosis, he was not as successful as he was during his early research on syphilis. Wassermann developed Bright's disease in 1924, and he continued to work as the institute's director until his death. After that, Wassermann's institute was closed and reopened later only as a department for immunochemistry within the Kaiser Wilhelm Institute for Biochemistry.

With Rudolf Kraus, Wassermann was cofounder of the Free Association for Microbiology. He also was a president of the Academy for Knowledge of Judaism. His many awards included orders, honors, and decorations from many institutes, organizations, and societies in Prussia, Belgium, Spain, Japan, Romania, and Turkey. In 1921, Wassermann was the first recipient of the Hans Aronson Foundation Prize. Nevertheless, he was never appointed to a chair position at the prestigious Berlin faculty and was never awarded the Nobel Prize in spite of being nominated.

Albert Ludwig Sigesmund Neisser (Jan 22, 1855–Jul 30, 1916) was a German dermatologist and venereologist who discovered the causative agent of gonorrhea, a strain of bacteria that was named in his honor—*Neisseria gonorrhoeae*. He was born in Schweidnitz in Silesia (now Świdnica in Poland) and was the son of a very well-known Jewish physician, Moritz Neisser. After elementary school in Münsterberg, Neisser studied in the St. Maria Magdalena School in Breslau (now Wrocław in Poland). In that school, ***Paul Ehrlich*** was a classmate, beginning a lifelong relationship. Neisser studied medicine in Breslau and Erlangen and wanted to be an internist. Nonetheless, he was not accepted by the department of internal medicine and entered the residency program in dermatology–venereology because at least the departments of pathology and dermatology lacked the prevailing anti-semitism. In 1877, he was appointed the first assistant of a newly founded Department of Dermatology in Breslau, and in 1882 at age 29, he became its head—a position he retained for the last 34 years of his life. After that he was promoted to the director of the hospital. In the following year, he married Toni Neisser, née Kauffmann.During his residency in 1879, the 24-year-old Neisser made both of his principal discoveries. His primary achievement was the discovery of *Neisseria gonorrhoeae*, the etiologic factor of gonorrhea. Neisser was also the codiscoverer of the causative agent of leprosy.

In 1905–1906, Neisser traveled to Java to study the possible transmission of syphilis from apes to humans. ***Carl Bruck*** accompanied him as his assistant. Neisser later cooperated with ***August Paul von Wassermann***, working on the famous diagnostic tool for the detection of *Treponema pallidum* infections. He also participated in the testing of the first chemotherapeutic agent for syphilis, Salvarsan, which had been discovered in 1910 by his earlier school fellow ***Paul Ehrlich***.

As a scientific groundbreaker, Neisser also was active in public health. He endorsed preventive and educational measures and advocated for improved sanitary conditions of prostitutes to fight the spread of venereal diseases. He one of the founders of the German Dermatological Society in 1888 and of the German Society for the Fight Against Venereal Diseases in 1902. In addition to his busy and active clinical and research work, he was a successful fundraiser, especially in the Jewish business community. These efforts resulted in a new building to accommodate the Dermatology–Venereology Department in 1892. Neisser was nominated for the Nobel Prize 22 times. He died of septicemia at the age of 61 in Breslau.

Carl Bruck (Feb 28, 1879–Jun 12, 1944) was a German-Jewish dermatologist and venereologist. He was born in Glatz in Lower Silesia in Germany (now Kłodzko, Poland) and grew up in Dresden. He received his medical education in Munich and Berlin. He worked with ***Robert Koch*** at the Institute of Infectious Diseases in Berlin and then with ***Neisser*** at the Department of Dermatology in Breslau (now Wroclaw). From 1914 on, he was the professor and chair of the Department of Dermatology of the City Hospital in Hamburg-Altona. His main accomplishments were made in the field of syphilology, including the initial development of the Wassermann-Neisser-Bruck reaction. He also was involved in research on tuberculosis.

Because of the national-socialist laws in Nazi Germany, he was forced to drop his position in 1935. To escape antisemitic persecution and the upcoming deportation by the Nazis in concentration camps, he and his wife killed themselves in Hamburg.

Jules Jean Baptiste Vincent Bordet (Jun 13, 1870–Apr 6, 1961) was a Belgian immunologist and microbiologist. The bacterial genus *Bordetella* is named after him. He was born in Soignies, Belgium. He obtained his medical education from the Brussels University in Belgium. In 1894–1901, he worked with ***Elie Metchnikoff*** at the Pasteur Institute in Paris. Then, in 1901, he established the Pasteur Institute in Brussels and was its director for many years. His greatest achievements were associated with complement-induced hemolysis (1899) and the complement-fixation test (1901). He published a well-known series of papers on immunology, including his debate with ***Paul Ehrlich*** about the nature of the function of antibodies and complement. From 1902–1920 on, he was nominated for the Nobel Prize 16 times, and, in 1919, he finally was awarded a **Nobel Prize** in Physiology or Medicine "for his studies in regard to immunity."

Bordet also was interested in several nonmedical subjects. He published an astronomy handbook and a few political books about the conduct of public affairs. Bordet retired in 1940, and his son succeeded him as director at the Pasteur Institute of Brabant and as professor of bacteriology.

(**Publ.**: Bordet JJBV, Gangou O. Sur l'existence de substances sensibilisatrices dans la plupart des sérums antimicrobiens. *Ann Inst Pasteur* 1901; 15:289–302.

Bordet J, and Gengou O. Le microbe de la coqueluche. *Ann Inst Pasteur* 1906; 20:731–741.

Wassermann A, Neisser A, Bruck C. Eine serodiagnostische reaktion bei syphilis. *Dtsch Med Wochenschr* 1906; 32:745–746.

Wassermann A, Ehrlich P. Über die gewinnung der diphterie-antotoxine aus blutserum und milch immunisierter thiere. *Z Hyg Infektionskr* 1894; 18:239–250.

Wassermann A, PIaut F. Ueber das vorhandensein syphilitischer antistofTe in der cerebrospinalfliissigkeit von Paralytikern. *Dtsch Med Wochenschr* 1906; 32:1769–1772.

Wassermann A. Eine serodiagnostische reaktion bei syphilis. *Dtsch Med Wochenschr* 1906; 32:745–746.)

Wassermann-Neisser-Bruck reaction see **Wassermann test**

Wegener's granulomatosis (**Wegener-Klinger syndrome**, **Wegener-Churg-Klinger syndrome**, granulomatosis with polyangiitis) is a rare multisystem autoimmune disease of unknown etiology. Its hallmark features include necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels. It is a part of a larger group of vasculitis syndromes (e.g., systemic vasculitides or necrotizing vasculopathies) featuring an autoimmune attack by circulating antibodies (i.e., antineutrophil cytoplasmic antibodies, ANCA) against small- and medium-sized blood vessels. Other diseases in the group are

Churg-Strauss syndrome and microscopic polyangiitis. A limited form has been known as **Carrington-Liebow syndrome**. A lymphoid variant has been termed **Liebow-Carrington syndrome**.

When referred to as Wegener's granulomatosis, it is named after ***Friedrich Wegener***, who described the disease in 1936. As a response to Wegener's association with the German Nazi Party, professional bodies and journals have replaced his name with a descriptive designation. However, the older name still is seen often. The condition was first described by Scottish otolaryngologist Peter McBride in 1897. The pathological–anatomical depiction was described by ***Heinz Karl Ernst Klinger*** in 1931. A detailed description was published by Friedrich Wegener in 1936 and 1939.

Friedrich Wegener (Apr 7, 1907–Jul 9, 1990) was a German pathologist. He was born in Varel, a district of Friesland in Lower Saxony, Germany. Wegener lived and worked in Berlin, Breslau, and Lübeck. He was in Breslau when he first reported the clinical condition that honors his name. After World War II, Friedrich Wegener was suspected of being a war criminal. He was interned by the Allies but was later cleared of the charges and "denazified." Still, some data have proved that Wegener was a dedicated Nazi. In 1932, 8 months before the Hitler regime obtained power, he joined the SA (Sturmabteilung), the largest and most feared paramilitary branch of the Nazi Party (NSDAP). He became a member of the Party on May 1, 1933. According to documents found by Alexander Woywodt et al. in the Bundesarchiv (Woywodt et al., 2006), Wegener became SA Sanitäts-Obersturmbannführer in 1938.

As a high-ranking military pathologist in Lodz, he spent time in a medical office 3 blocks from the Łódź Ghetto, a Jewish ghetto in Łódź, Poland. It is assumed that he was a part of experiments on concentration camp inmates. The first locked Jewish ghetto of the Third Reich had been opened in Lodz. Less than 1000 of the 250,000 prisoners held there survived the genocide. Some data from Wouwodt and colleagues indicate that Wegener, in his job as pathologist, may have collaborated in these events. No proof has been found, however, although records show that other members of the Lodz health office did such research and that he autopsied a prisoner using oxygen injected into his bloodstream for an embolism study. Wegener died in 1990 in Lübeck, Germany.

Heinz Karl Ernst Klinger (1907–?) was a German pathologist, who when a student of Friedrich Wegener at the University of Berlin in 1931, reported 2 patients who died having prolonged sepsis with inflammation of blood.

Jacob Churg **see Churg-Strauss disease**

(**Publ**.: McBride P. Photographs of a case of rapid destruction of the nose and face. *J Laryngol Rhinol Otol* 1897; 12:64–66.

Klinger H. Grenzformen der periarteriitis nodosa. *Frankfurter Zeitschrift Pathol* 1931; 42:455–480.

Wegener F. Über generalisierte, septische Gefässerkrankungen. *Verh Dtsch Ges Pathol* 1936; 29:202–210.

Wegener F. Über eine eigenartige rhinogene Granulomatose mit besonderer beteiligung des arteriensystems und der nieren. *Beiträge Pathol Anat Allge Pathol* 1939; 102:36–38.)

Wegener-Churg-Klinger syndrome see **Wegener's granulomatosis**

Wegener-Klinger syndrome see **Wegener's granulomatosis**

Weil-Felix test (**Weil-Felix reaction**, **Felix's reaction**) is an agglutination test for the diagnosis of rickettsia infections. The test determines antirickettsia antibodies based on cross-reactivity between antibodies induced by acute rickettsia infections with antigens of OX (i.e., OX 19, OX 2, and OXK) strains of *Proteus* species. Thus, the **Weil-Felix test** can reveal antibodies to several *Proteus* species that express antigens with cross-reacting epitopes to antigens expressed by the genus *Rickettsia* with the exception of *R. akari*. Whole cells of *Proteus vulgaris* OX-2 react effectively with serum samples harvested from individuals infected with *spotted fever group rickettsiae (SFG)* with the exception of those with *Rocky Mountain spotted fever (RMSF).* Whole cells of *P. vulgaris* OX-19 react with serum samples from people infected with the typhus group of rickettsia, as well as with *RMSF rickettsiae*.

A phenomenon of the detectable antigen-based cross-reactivity between *Rickettsia* spp. and certain serotypes of nonmotile *Proteus* spp. initially was reported by ***Edmund Weil*** and ***Arthur Felix*** in 1916. The serum specimens obtained from patients diagnosed with epidemic typhus were found to agglutinate in the presence of microorganisms, now known as *Proteus vulgaris*. Additional studies have reveled that it was in fact the somatic (O) antigen that cross-reacted with antirickettsial antibodies and, also, that various *Proteus O* antigens could cross-react with various species of *Rickettsia*.

In general, the Weil-Felix test demonstrated an overall sensitivity as low as 33% and a specificity of 46%. Therefore, it was replaced by other tests using various serological techniques, including indirect immunofluorescence antibody assay, which is the gold standard. Nevertheless, if clinical resources are very limited, it is still in use as a valuable tool in the diagnosis and documentation of public health concerns (e.g., outbreaks of epidemic typhus).

Edmund Weil (Apr 16, 1879–Jun 15, 1922) was an Austrian (Bohemian) bacteriologist. He was born in Neustadt near Haid, Westböhmen, and attended the German University of Prague. He obtained his doctorate in 1903 and then worked as an assistant to a pathological anatomist. In 1905, he continued his career at the Hygienic Institute, where he chaired the Department of Serology starting in 1918. He passed his habilitation exams for hygiene in 1909 and received a professor position in 1914.

In 1911, in collaboration with the neuropsychologist ***Viktor Kafka***, who was an assistant in the psychiatric clinic of the German University in Prague, Weil reported an unknown bacteriological reaction, now known as the Weil-Kafka reaction. In 1916, Weil and Felix described the Weil-Felix test for the diagnosis of rickettsial

infections. Weil died in Prague in 1922 from an infection of spotted fever he had contracted in a laboratory in Poland.

Arthur Felix (Apr 3, 1887–Jan 17, 1956) was a Polish-Jewish microbiologist and serologist. He was born in Andrychow, a small town 2 miles from Bielitz, which was then in Silesia (now in Poland), and 25 miles from Cracow, which was then in Galicia. He spoke German, Polish, and Yiddish. His parents were Orthodox Jews, and for some years from the age of 13 onward, he used to take part in reading the Scriptures in the synagogue. His father, Theodor Felix, was a manufacturer with an interest in printing textiles, and Felix studied chemistry when he went to the University at Vienna. In the thesis he wrote for his DSc degree, he described the discovery of several new indigoid dyes and published his first paper. While a student, he became very interested in mycology, and, despite his father's wish for him to work in his factory, Felix returned back to Vienna to study microbiology. Felix became interested in Zionism during his student days in Vienna and later developed into an authority on Palestine.

At the beginning of World War I in 1914, Felix was given a commission in the Austrian Army and was attached to a field hospital laboratory where he first met ***Edmund Weil***, who was in charge of the Fifth Austrian Mobile Epidemiological Laboratory. In 1914, they were sent to Silesia, where cholera broke out as an epidemic and then Weil and Felix were posted to Wadowice in Galicia. It was here in September 1915 that they developed the Weil-Felix test for diagnosis of typhus and other rickettsial diseases. In 1918, the German and Austrian armies occupied Ukraine, and Weil and Felix were transferred to Kherson near Odessa. Rapid alterations in the political and the military conditions there caused their transfer to Prague, where they continued to work together after the war.

Later, Felix, who had solid Zionist principles, decided to move to work in Palestine. In 1921, he received a position of director of the Bacteriological Laboratory of the Hadassah Medical Organization in Tel Aviv. In 1922, he started to work as chief bacteriologist of the Jerusalem Laboratory. Weil was going to join Felix in Palestine but suddenly died from typhus in 1922. Felix remained in Palestine for 6 years, also holding the important position of chairman of the Health Council in the Palestine Zionist Executive. In 1923, Felix married Leah Gluckman from Tel Aviv. In 1927, he moved to the Lister Institute of Preventive Medicine in London.

From 1939, when World War II was declared, until his retirement in 1954, he was director of the Emergency Public Health Laboratory Service, which became the central Enteric Reference Laboratory. In 1945, he resigned from the Lister Institute to work at Public Health Service; however, in 1954 he returned to the Lister Institute. In 1943 he was elected a fellow of the Royal Society. In 1956, Felix completed his long-term experiments to retire from the laboratory bench finally. He died suddenly, alone, while on his way back to fetch a reprint from the Lister Institute one Saturday evening.

(**Publ**.: Felix A, Weil E. Zur serologischen diadnose des fleckfiebers. *Wien Klin Wochenschr* 1916; 29(22).

Felix A, Weil E. Serologische fleckfieberdiagnose. *Feidärzl Blätter der k.u.k.2. Armee* 1916; 5.

Felix A, Weil E. Die kurve der dleckfieberagglutination und ihre praktische verwertung. *Feidärzl. Blätter der k.u.k.2. Armee* 1916; 11.

Felix A. Technique and interpretation of the Well-Felix least in typhus fever. *Trans R Soc Trop Med Hyg* 1944; 37:321.)

Weil-Kafka Hemolysin reaction was developed as a hemolysin reaction in the spinal fluid for detection of infectious diseases including purulent (being pus) and cerebrospinal meningitis. It was based on the mixture of the sheep blood solution with the cerebrospinal fluid (1:10 w/w). The hemolysins, usually in human blood, do not get into the spinal fluid under normal conditions.

Edmund Weil see **Weil-Felix test**

Viktor Kafka (Oct 12, 1881–May 5, 1955) was an Austrian-Jewish neuropsychologist and bacteriologist. He was born in Karlsbad (now Czech Rep) and studied at the University in Prague and the University of Vienna. He received his medical doctorate degree in 1906. From 1907–1911, he worked as an assistant at the psychiatric clinic at the German Medical Department at the University of Prague.

In 1911, Kafka and the bacteriologist ***Edmund Weil*** reported on a formerly unknown bacteriological reaction. He then moved to work in the State Hospital Friedrichsberg in Hamburg. In 1917, he became head of the Serological Department in the Bacteriological-Serological Institute. In 1919, he passed his habilitation exams for psychiatry in Hamburg, and in 1920 he became a head of the Serological Department of the University Psychiatric Clinicm as well as a professor starting in 1924. In 1925, Kafka developed the Kafka paraffin colloidal test on spinal fluid with specificity for syphilitic fluids. In 1927, he became the physician-in-chief at the Serological Department.

In Nazi-powered Germany, because of his Jewish descent, Kafka was removed from all his positions and duties. In 1939, he moved to Norway so he could survive, and, in 1942, he had to move to Sweden, where he stayed until his death in Stockholm. Kafka was buried in Hamburg.

(**Publ**.: Weil E, Kafka V. Über die durchgängigkeit der meningen, besonders bei der progressiven paralyse. *Wien klin Wschr* 1911; 24:10.

Weil E, Kafka V. Weitere untersuchungen über den hämolysingehalt der cerebrospinalflüssigkeit bei akuter meningitis. *Med Klin* 1911; 1911:1314.

Kafka V. Über technik und bedeutung der cytologischen untersuchung des liquor cerebrospinalis. *Mschr Psychiatr* 1910; 27:414.

Kafka V. Über cytolyse im liquor cerebrospinalis. *Z Neur* 1911; 5:252.

Kafka V. Untersuchungen zur frage der entstehung, zirkulation und funktion der cerebrospinalflüssigkeit. *I Teü Z Neur* 1912; 8:192.)

Wells syndrome (**Wells' syndrome**, eosinophilic cellulitis) is characterized by clinical features of cellulitis and a histopathologic picture of eosinophilic infiltrate of the dermis along with the presence of "flame figures." With immunofluorescent

stains, eosinophil major basic protein is identified in the granules of the flame figures. Although the eosinophilic infiltrate commonly is restricted to the epidermis and the dermis, it can be found in the subcutaneous tissue and the underlying muscle. A dermal infiltrate of histiocytes, eosinophils, and eosinophilic granules is detected between collagen bundles. This infiltrate also includes an increased proportion of $CD3^+$ and $CD4^+$ T cells. These lymphocytes express high levels of IL-5, suggesting that stimulated T cells participate in the pathogenesis of blood and tissue eosinophilia. The eosinophils degranulate in the dermis inducing edema and tissue inflammation.

The characteristic clinical appearance of the eosinophilic cellulitis is pruritic, recurrent, cellulite-like plaque. However, various clinical presentations have been reported and may include urticarial (i.e., itchy, red, or whitish raised patches), papulonodular (i.e., small hard bumps), and vesicobullous (i.e., vesicles and bullae—blisters—at the dermal–epidermal junction) lesions. The lesions generally diminish, and the course usually is benign.

The etiology of Wells syndrome is not known. It often may be linked to various pathologies such as arthropod (insect, spider) bites, colon cancer, myeloproliferative disease, reaction to a thiomersal (**an organomercury compound**)-containing vaccination, dermographism (**swelling or redness of the stroked skin**), **Churg-Strauss syndrome**, hypereosinophilic syndromes, onchocerciasis (parasitic worm disease), herpes simplex infection, immunobullous diseases (autoimmune blistering disorders), and drug reactions. At least some cases of Wells syndrome could represent hypersensitivity to an arthropod bite or sting. An impressive response of peripheral lymphocytes to mosquito salivary gland extracts has been documented in some patients with Wells syndrome.

In 1971, ***George Wells*** first described this syndrome as a recurrent granulomatous dermatitis with eosinophilia. The colorful term "flame figures" that he used for the characteristic clusters of eosinophils and histiocytes, which surround pink collagenous debris, has become the hallmark of this rare but distinctive process. Wells and Smith renamed it eosinophilic cellulitis in 1979.

George Crichton Wells (Jul 13, 1914–Jan 16, 1999) was a UK dermatologist. He was the son of Sir Richard Wells, 1st Baronet, and Mary Dorothy Maltby from a big Bedford beverage distilling family. The middle of 7 children, he was educated at Bedford School before obtaining a scholarship to Cambridge. At university, he excelled at rugby, swimming, diving, and rowing. He went on to St. Thomas's for his clinical work and qualified in 1939. After a course of service at the Royal Army Medical Corps as a major, he found himself with difficult general duties. He actively served in war theaters in Tunisia, Greece, Sicily, and France during World War II. Nonetheless, this significantly improved his medical skills because he treated diverse types of injuries.

Following demobilization from army service, Wells returned to St. Thomas's; because his record ensured special recognition, he was appointed registrar to medical unit. It was a prestigious job that he did not enjoy, although it gave him insight into and experience with academic medicine. Wells was attracted to dermatology

and biochemistry and moved to Chicago for 2 years for study. The chair of dermatology, Stephen Rothman, a Jewish emigrant from Budapest, had developed a world-renowned department at the Chicago University Medical School. Rothman knew W. N. Goldsmith, the chair of dermatology at University College Hospital in London; both had studied in Breslau (Wroclaw), ***Jadassohn***'s academic citadel, and when Wells returned, hw was appointed as senior registrar. Nevertheless, soon Wells (married in 1951) decided to return to Chicago with his new wife. Back as an assistant professor, he studied connective tissue biochemistry. In 1954, he returned home to England and set up his laboratory at the Institute of Dermatology at London University, worked at St John's Hospital for Diseases of the Skin, and consulted at St. Thomas's.

Wells wife was Margaret (Maggie) Bruce, a talented artist; unfortunately, they did not have children. They became enthusiastic gardeners, were enthusiastic travelers, and both continued as skilled skiers. Wells was very musical and liked his Spanish guitar. Maggie very much enjoyed her sketching, painting, and woodblock work. They shared a private sense of humor, each seeming to catalyze the other in a quiet, somewhat secretive way. George Wells died within 6 weeks of his wife; without her, any point in surviving had disappeared for him.

(Publ.: Wells GC. Recurrent granulomatous dermatitis with eosinophilia. *Trans St John's Hosp Dermatol Soc* 1971; 57(1):46–56.

Wells GC, Smith NP. Eosinophilic cellulitis. *Br J Dermatol* 1979; 100(1):101–109.)

Werlhof's disease (**Werlhof's purpura**, **Werlhof's syndrome**, **Werlhof-Wichmann syndrome**) is now known as idiopathic thrombocytopenic purpura (ITP), primary immune thrombocytopenia, primary immune thrombocytopenic purpura, or autoimmune thrombocytopenic purpura. ITP is an autoimmune disease with antibodies detectable against several platelet surface antigens. Most often, these antibodies act against platelet-membrane glycoproteins, IIb-IIIa or Ib-IX, and are of the IgG type. The coating of platelets with IgG renders them susceptible to opsonization and phagocytosis by splenic macrophages, as well by **Kupffer cells** in the liver. The IgG autoantibodies also are thought to damage megakaryocytes—the precursor cells to platelets.

A clinical syndrome of bleeding and purpura consistent with a diagnosis of immune thrombocytopenia was described by Werlhof long before platelets were identified as the cellular component of blood playing an essential role in primary hemostasis. After initial reports in 1556 by Portuguese physician Amato Lusitano and Lazarus de la Rivière, physician to the King of France, in 1658, it was German physician and poet ***Paul Gottlieb Werlhof***, who wrote the most complete report of the purpura of ITP in 1735. Platelets were unknown at the time. The name "**Werlhof's disease**" was used widely before the current descriptive name became more popular.

Paul Gottlieb Werlhof (Mar 24, 1699–Aug 16, 1767) was a German physician. He was born in Helmstedt, Germany, as the son of Johann Werlhof, a professor of

law at the university, and Maria Dorothea Werlhof. He was a remarkable youth interested in natural sciences and language and, at the age of 17, began the study of medicine at the university. After completing his studies, he settled in Peine near Hildesheim; then Werlhof moved to Hanover in 1825. He was an outstanding physician, and his practice attracted many patients, including those from the higher social circles. It became one of the best-known clinical practices in Europe being consulted by people as distant as Moscow and Rome. His clinical skill and fluency in English, French, and Swedish led to his counsel the royal families of England, Denmark, Braunschweig, Cologne, and Bonn. In 1740, he was appointed royal life physician—Königlicher Leibarzt. He rejected an appointment as a professor of medicine in his native town and stayed in Hanover until his death. He had been severely afflicted with gouty arthritis since his early 30s.

Werlhof was an erudite physician, insightful observer, and writer in his own style. He was well known among many German eighteenth-century poets. His poems and hymns were in German, but his clinical writings were in Latin.

Johann Ernst Wichmann (May 10, 1740–Jun 12, 1802) was a German physician born in Hanover. He studied at Göttingen, received his medical doctorate in 1762, and worked in his native town. He traveled to France and England, staying in London for a long time. He returned to Hanover in 1764, spending much of his efforts their translating various English medical works and was the first to introduce basic principles of English medicine in Germany. The term **pemphigus** is the Latinized form of the Greek πέμφιξ (pemphix), meaning bubble or blister, and was first used by Wichmann at the end of the eighteenth century to describe bullous diseases.

Wichmann won the friendship of ***Werlhof***, became physician to "everybody," and, after the death of Werlhof, became the second personal royal life physician (Leibarzt) while also preserving a very busy practice. His premature death at the age of 62 was probably triggered by grief over his wife's death.

(**Publ**.: Werlhof PG. Disquisitio Medica et Philologica de Variolis et Anthracibus. Hannoverae: Nicolai Foersteri; 1735.

Werlhof PG. Medical Works (L). Vol. 3. Hanover: Helwingiorum; 1775–1776.

Wichmann JE. Ideen zur Diagnostik: Beobacht-enden Aerzten Mitgetbeilet. Hanover: Helmingschen Hofbuchhandlung; 1802.)

Werlhof-Wichmann syndrome see **Werlhof's disease**

Whitaker syndrome (**Whitaker's syndrome**, autoimmune polyendocrine syndrome type 1 [APS-1], autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED], polyglandular autoimmune syndrome [PGA]) is a subtype of autoimmune polyendocrine syndrome, in which multiple endocrine glands dysfunction as a result of autoimmunity. It is a genetic disorder inherited in autosomal recessive fashion because of a defect in the *AIRE* (autoimmune regulator) gene. The three main components of APS-I are: (1) chronic mucocutaneous candidiasis (i.e., chronic infections of mucosal surfaces, skin, and nails with *Candida*), (2)

hypoparathyroidism, and (3) autoimmune adrenal insufficiency. The clinical phenotype of APECED, as a variable mixture of autoimmune reactions in diverse endocrine and nonendocrine organs, may include various failures of parathyroid glands, adrenal cortex, pancreatic β-cells, gonads, and gastric parietal cells. These clinical signs may be connected with ectodermal appearances, including dystrophies of dental enamel and nails. The syndrome is quite rare, and only about 500 patients have been identified worldwide. The highest prevalence was reported in the Iranian-Jewish community, Sardinia, and Finland.

Essentially, there are two types of polyglandular autoimmune syndrome: type I (**Whitaker syndrome**) and the more common type II (**Schmidt syndrome**). A third type occurring in adults, however, also has been suggested. This type III does not affect the adrenal cortex but should include 2 symptoms: thyroid deficiency, type 1A diabetes mellitus, pernicious anemia, vitiligo, or alopecia. PGA syndrome also may be linked with other condition—for instance, pulmonary hypertension associated with PGA syndrome type II.

Historically, many of these related syndromes associated with the adrenal cortex were described in the nineteenth century. In 1849, ***Thomas Addison*** first reported the clinical and pathological characteristics of adrenocortical failure in patients with coexisting pernicious anemia. In the following 150 years, a great deal of new data on the pathogenesis of the polyglandular autoimmune syndromes and their modular disorders have been generated by clinical geneticists, immunologists, and endocrinologists.

The autoimmune etiology of Whitaker syndrome is supported by the existence of chronic-inflammatory lymphocytic infiltrates in the affected organs and by the occurrence of autoantibodies recognizing the tissue-specific antigens. Adrenal cortex is one of the distinguishing target organs for tissue destruction in Whitaker syndrome, and both adrenal autoantibodies and steroidal cell autoantibodies have been isolated from the serum of affected individuals. Although adrenal antibodies bind only to the adrenal cortex, steroidal cell antibodies also bind to ovary, testis, and placenta. Therefore, both these autoantibodies have an important prognostic significance as they may predict the development of adrenal and ovarian failure.

In Whitaker syndrome, all known adrenal cortex and gonad autoantigens are cytochrome P450 and cholesterol side-chain cleavage enzymes involved in steroid synthesis and catalyzing conversion of cholesterol to sex hormones. For instance, steroid 17α-hydroxylase (P450c17), cholesterol side-chain-cleaving enzyme (P450scc), and steroid 21-hydroxylase (P450c21) were proven to react with serum specimens obtained from the patients. Interestingly, P450c21 associates with the detection of adrenal antibodies, suggesting its role as the major antigen in adrenal autoimmune diseases. On the contrary, autoantigens in P450c17 and P450scc complexes induce the formation of steroidal cell antibodies.

Another common target in Whitaker syndrome is the Langerhans' islets of the pancreas. Autoantibodies targeting aromatic L-amino acid decarboxylase and glutamic acid decarboxylase (Gad65) and pancreatic cytoplasmic islet cell antibodies (ICA) often are seen in Whitaker syndrome with high titers. Furthermore, patients with Whitaker syndrome, and also suffers from chronic hepatitis, produce

autoantibodies to the major hepatocellular autoantigens (e.g., cytochrome P450 enzymes 1A2 and 2A6). Detection of these autoantibodies has been reported to be useful in the monitoring of hepatitis activity and the response to immunosuppressive therapy.

The Whitaker syndrome is unique in the group of known autoimmune endocrine disorders because it has no HLA-antigen association—that is, genetic susceptibility. Still, some data may suggest an increased frequency of HLA-A28 and HLA-A3. Anyway, this disease is inherited in an autosomal-recessive fashion. Unlike other autoimmune diseases, Whitaker syndrome is linked to a genetic defect in a single gene. This gene was cloned in 1997 and is known as an autoimmune regulator (*AIRE*) gene. To date, 45 diverse mutations of the *AIRE* gene have been identified and are distributed throughout the entire coding region. It is a 13 kb gene on chromosome 21q22.3. *AIRE* is a transcription factor expressed in cells participating in induction and maintenance of immune tolerance and can be found in the thymus, lymph nodes, spleen, and fetal liver. In the thymus, *AIRE* is part of the selection pathway that eliminates self-reactive T cells that would cause autoimmune reactions.

The presence of chronic mucocutaneous candidial infections in patients with Whitaker syndrome suggests an additional defect in the T-cell activity. Yet, the patients display high titers of protective antibodies against major *Candida* antigens despite the proven cutaneous anergy to these antigens and the incapacity to eliminate *Candida albicans* from body surfaces.

JoAnne Whitaker (Feb 8, 1927–Dec 5, 2008) was a US physician. She was born in Bartow, Florida. She was a graduate of the Bowman Gray School of Medicine at Wake Forest University. After obtaining her medical degree, she finished several fellowship programs in pediatrics, oncology, hematology, nutrition, and psychiatry. She worked and taught in 7 different medical schools and various hospitals, including the Sloan Kettering Institute and Bellevue Hospital (New York), the Cincinnati Children's Hospital, and the Parkland Memorial Hospital and Children's Medical Center (Dallas, TX). She also worked in Southeast Asia for 9 years, developing a medical school and nutrition laboratory in Thailand and establishing research and clinical training programs in the Children's Hospital in Saigon, Vietnam.

Whitaker published more than 70 papers and accumulated many awards and honors. Lyme disease testing and research is one of the activities of the institute, and Whitaker worked a lot on development and testing of new diagnostic tests for **Lyme disease**. Whitaker's favorite sport was golf. She was a very good athlete I college and finished her sports activities by being a second-time winner of the Florida Amateur Golf Championship.

(**Publ**.: Whitaker J, Lamding BH, Esselborn VM, Williams RR. The syndrome of familial juvenile hypoadrenocorticism, hypoparathyroidism and superficial moniliasis. *J Clin Endocrinol Metab* 1956; 16(10):1374–1387.)

Widal syndrome see **Hayem-Widal syndrome**

Widal's syndrome see **Samter's syndrome**

Widal test (**Gruber-Widal reaction, Gruber reaction, Widal reaction**) is a method that may be used to help make a presumptive diagnosis of enteric fever, also known as typhoid fever—a life-threatening infection with the bacterium *Salmonella enterica* serotype Typhi (*S. typhi*). The disease usually is transmitted through food and drinks contaminated with fecal material. Even though this diagnostic test is no longer used in the US and other developed countries, it still is performed in many developing countries where typhoid, or paratyphoid feve,r is endemic and quite limited resources necessitate the selection of fast and inexpensive testing alternatives.

Developed in 1896 and named after ***Georges Ferdinand Widal***, who introduced it, the method relies on a reaction between antibodies present in the infected person's blood sample and specific antigens of *S. typhi*, which produce visible agglutination in a test tube or on a slide. Widal presented his test to the Medical Society of the Hospitals of Paris in 1896 and published a description of the test a few months later in *The Lancet*. The test reveals the occurrence of somatic (O) and flagellar (H) agglutinins to *Salmonella typhi* in the patient's serum using suspensions of O and H antigens. ***Salmonella*** *paratyphi* A and ***Salmonella*** *paratyphi* B antigens are included in all commercial kits. The common method of executing the Widal test is by the tube agglutination technique, where serial twofold dilutions of tested serum from a patient from 1:20–1:1280 are evaluated. Even though the method is easy to perform, there are various concerns about the reliability and sensitivity of the **Widal test**. In addition to cross-reactivity with other *Salmonella* species, the assay cannot differentiate a current infection and an earlier one, or a vaccination against typhoid.

Widal was not the first scientist who defined the phenomenon of agglutination. It was demonstrated earlier by Charrin and Roger. Furthermore, animal studies by ***Max von Gruber*** have indicated its utility for typhoid testing. Thus, there is controversy about who should be credited for the test, which is often referred to as the "**Gruber-Widal reaction**," or just "the agglutination reaction."

Georges-Fernand-Isidor Widal (Mar 9, 1862–Jan 14, 1929) was a French physician. He was born into a Jewish family in Dellys, Algeria. He was the son of a distinguished doctor who served as the medical inspector of the army and the nephew of Mathieu Hirtz, the dean of the Department of Medicine at Strasbourg. Widal followed in his father's footsteps and studied medicine at the University of Paris. He was an outstanding student and easily attained a position of *interne des hôpitaux*, or assistant physician. Widal became a doctor of medicine in 1889. He remained in Paris for all his professional and was in charge of a course in bacteriology. In 1904, he became an instructor at the Department of Medicine; then, in 1905, he became a physician at the Hospital Cochin. He was also in charge of the medical clinics at the same institution. He was professor of internal pathology from 1911 and of clinical medicine from 1918 onward; he was in office until 1929. Widal was a member of the National Medical Academy starting in 1906 and the National Academy of Science from 1919. During World War I, he generated an antityphoid–paratyphoid vaccine that noticeably decreased typhoid infections among the allied armies.

Widal published many clinical and research papers and essays on infectious diseases; diseases of the heart, liver, and nervous system; and other topics. Together

with G. H. Roger and P. J. Teissier, he edited 22 volumes of a medical textbook. In addition to developing the **Widal test**, he also recognized the body's retention of sodium chloride as a feature of nephritis (i.e., inflammation of the kidney) and cardiac edema (i.e., accumulation of excessive fluid in tissues because of heart disease), recommending salt deprivation in the treatment of both diseases. He demonstrated the increased fragility of red blood cells in cases of hemolytic jaundice, and, with hematologist ***Georges Hayem***, he described acquired hemolytic anemia—a disease that was historically referred to as **Hayem-Widal syndrome**.

Widal was a brilliant speaker and lecturer and was described as an accurate, stout, handsome man who was not self-centered and greatly admired his colleagues' abilities. He was married, but they did not have any children. He died of a cerebral hemorrhage in Paris after an acute gout attack. After his death, his statue was erected at the Hospital Cochin in memory of this great serologist and his agglutination test.

Maximilian Ritter von Gruber (Jul 6, 1853–Sept 16, 1927) was an Austrian scientist. He was born in Vienna into a Jewish family, the youngest son of Ignaz Gruber, a general practitioner and the first specialist in otology in Austria, and his wife Gabriele Edle von Menninger. His parents awakened Max's interest in medicine and natural science. Gruber studied medicine at the University of Vienna, receiving his medical doctorate in 1876. He then studied chemistry and physiology in Munich and Leipzig and concentrated on bacteriology. In 1882, Gruber was habilitated as a lecturer in Vienna. In 1886, he received a position of associate professor and head of the recently established Institute for Hygiene at the University of Graz. He worked a good deal on public health and successfully assisted with the cholera epidemic that was spreading in southern Austria in 1885–1886.

In 1891, Gruber was appointed to the chair of hygiene at the University of Vienna. It was while in Vienna that he, with his English student Herbert Edward Durham, discovered the agglutination that gained him international fame. These results were reported by Durham in January 1896 in *Proceedings of the Royal Society* and by Gruber in February 1896 at the Society of Physicians in Vienna. Shortly, these new findings were published in several medical journals, including *Münchener Medizinische Wochenschrift* (March 1896), *Semaine Médicale* (March 1896), and *Wiener Klinische Wochenschrift* (March 1896).

Gruber left Vienna in 1902 and became a director of the Hygiene Institute in München (Munich). He directed the institute until his retirement in 1923 on his 70th birthday. After that, he focused totally on his duties as president of the Bavarian Academy of Sciences. He worked on social hygiene and dealt with sexual behavior, alcoholism, education of children and adults, and racial hygiene. Although later the Nazis initially tried to introduce him as one of the German authorities on racial hygiene; however, Max von Gruber never was a racial hygienist. No wonder, he was a Jew himself, although he never practiced as one or declared himself in public. Gruber died in Berchtesgaden, Germany.

(**Publ**.: Widal GFI. On the sero-diagnosis of typhoid fever. *Lancet* 1896; ii:1371.

Widal F. Serodiagnostic de la fiévre typhoide a-propos d'uve modification par MMC Nicolle et al. Halipie. *Bull Soc Med Hop* 1896; 13:561–566.

Gruber M. Über active und passive Immunität gegen cholera und typhus, sowie über die bacteriologische: Diagnose der cholera und des typhus. *Wien Klin Wochenschr* 1896; 9(11–12):183–186, 204–209.

Gruber M. Theorie der activen und passiven Immunität gegen cholera, typhus und verwandte krank heitsprozesse. *Münch Med Wochenschr* 1896; 44(9):206–207.

Gruber M, Durham H. 14th Congress für Innere medizin, Wiesbaden. In: Verhandlungen des Kongress für Innere Med; 1896; pp. 207–227.)

Widal-Abrami disease (**Widal-Abrami syndrome**, **Abrami's disease**, acquired hemolytic jaundice, immune hemolytic anemia) is a variable set of clinical signs and symptoms caused by hemolytic anemia, which is now recognized as having an autoimmune substrate.

Georges-Fernand-Isidor Widal see **Widal test**

Pierre Abrami see **Samter's syndrome**

Widal and Abrami test is a modification of the **Donath-Landsteiner test** for paroxysmal hemoglobinuria.

Georges-Fernand-Isidor Widal see **Widal test**

Pierre Abramisee **Samter's syndrome**

Widal-Abrami-Lermoyez triad see **Samter's syndrome**

Widal-Lermoyez syndrome see **Samter's syndrome**

Winiwarter-Buerger syndrome see **Buerger's disease**

Wiskott-Aldrich syndrome is a rare X-linked recessive disease characterized by eczema, thrombocytopenia, and immune deficiency. The immune deficiency is caused by decreased antibody production and the inability of T cells to reorganize their actin cytoskeleton and thus become polarized. This leads to increased susceptibility to infections, particularly of the ears and sinuses. Recurrent bacterial infections develop by 3 months of age. Almost 30% of affected children develop at least a single autoimmune disorder and cancers (mainly lymphoma and leukemia). Typically, IgM levels are low, IgA levels are elevated, and IgE levels also may be elevated; paraproteins (i.e., monoclonal immunoglobulins) are occasionally observed. Skin immunologic testing (i.e., allergy testing) may reveal hyposensitivity. The platelets are small and not fully functional. They are removed by the spleen, leading to thrombocytopenia.

Wiskott-Aldrich syndrome (WAS) has been linked to mutations in a gene on the short arm of the X chromosome, which was termed the Wiskott-Aldrich syndrome protein gene (*WASp*). The *WASp* gene encodes for the protein WASp, which is expressed primarily in hematopoietic cells and is responsible for activation of actin polymerization. In normal T cells, WASp is activated through T-cell receptor

signaling pathways to induce the actin cytoskeleton rearrangements required for the immunological synapse formation.

The syndrome is named after ***Robert Aldrich***, who described the disease in a family of Dutch-Americans in 1954, and ***Alfred Wiskott***, who first noticed the syndrome in 1937. Wiskott characterized a family with 3 brothers who had had eczema, hematorrhea (i.e., moderate hemorrhage, bleeding), and recurrent ear infections since early infancy. He noted that, although these brothers died early because of bleeding and infection, their sisters were healthy. Wiskott proposed that this disease is caused by a defect in the platelets and called it "hereditary thrombopathia," speculating that it as a familial congenital form of **Werlhof's disease**. The condition came to be known as "Wiskott-Aldrich syndrome" based on the suggestion of Lenz, and as a consequence of a paper by Gelzer and Gasser in 1961 (Gelzer and Gasser, 1961). Since then, the acronym WAS has become common.

Robert Anderson Aldrich (Dec 13, 1917–Sept 16, 1998) was a US pediatrician. He was born in Evanston, Illinois, a son of ***Charles Anderson Aldrich***, professor of pediatrics at the Mayo Clinic eponymously remembered for **McClure-Aldrich's test**. Aldrich was educated at Amherst College in Amherst, MA, and at the Northwestern University Medical School in Chicago. After graduating in 1944, he spent 2 years serving with the US Navy as a medical officer in the South Pacific. After military service, Aldrich was trained in pediatrics at the University of Minnesota before he went to consulting staff of the Mayo Clinic in 1950.

When an attending on the inpatient service at St. Mary's Hospital in Rochester, MN, Aldrich saw a little boy in serious condition with the clinical presentation he had never seen or read about. Talking with the mother about relatives, he learned that many of them suffered from a similar disease. Analysis of each male death in the family revealed the sex-linked origin of the syndrome. Aldrich could trace the female carrier, who came from the Netherlands, to Iowa using help from pediatricians in her area of the Netherlands. Soon, together with his colleagues, Arthur Steinberg and Donald Campbell, Aldrich published the data in *Pediatrics*. In several months later, he received a letter from a German pediatrician who directed his attention to the abstract in a journal by ***Wiskott*** (1937) that reported a very similar clinical case in 3 brothers whose sisters were unaffected.

By then, Aldrich was a clinical faculty member at the University of Oregon in Eugene, OR. In 1956, he became professor of pediatrics at the University of Washington in Seattle. In 1962, President John F. Kennedy invited Aldrich to establish a new National Institute of Child Health and Human Development at the National Institutes of Health (NIH) in Washington, DC. He also created a Division of Human Ecology at his own university. In 1980, he returned to the University of Washington and died in Seattle.

Alfred A. Wiskott (Mar 4, 1898–1978) was a German pediatrician. He was born in Essen and studied medicine after World War I, where he had been injured seriously in 1916 at the Battle of Verdun in France. After the war, he received his medical education in Munich and then continued his training in pediatrics at the University Clinics there. From 1939 on, he was a director of this clinic. After the

World War II, he was directly involved in the reconstruction of this hospital, which had been seriously damaged by Allied bombing. Wiskott retired in 1967.

(**Publ**.: Wiskott A. Familiärer, angeborener morbus Werlhofii? [Familial congenital Werlhof's disease?]. *Montsschr Kinderheilkd* 1937; 68:212–216.

Aldrich RA, Steinberg AG, Campbell DC. Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. *Pedia* 1954; 13(2):133–139.)

Witebsky's criteria/postulates are criteria for recognizing the autoimmunologic pathogenesis of a human disease. In 1957, ***Witebsky*** with his colleagues formulated "Witebsky's postulates" that govern whether a particular disease entity can be considered an autoimmune disease. These criteria were improved in 1993. Witebsky's original (1957) postulates were the following: direct demonstration of free circulating antibodies active at body temperature; recognition of the specific antigen targeted by this antibody; generation of antibodies recognizing the same antigen in experimental animals; and experimental animals that display the same tissue alterations as seen in humans. The following are the amended postulates: autoantibodies demonstrable in all cases of disease; experimentally reproducible by immunization with antigen; experimental disease that must show immunopathological lesions that parallel those in the natural disease; and transferable by serum or lymphoid cells. The modern amendments reflect 3 types of evidence: (1) direct evidence from transfer of pathogenic antibody or pathogenic T cells; (2) indirect evidence based on reproduction of the autoimmune disease in experimental animals; and (3) circumstantial evidence from clinical signs.

Ernst* (*Ernest*) *Witebsky (Sept 3, 1901–Dec 7, 1969) was a German-Jewish-US immunologist. He was born in Frankfurt am Main, Germany. He received his undergraduate and graduate education in Frankfurt, Heidelberg, and Berlin and got his doctorate degree in Heidelberg in 1925. In 1929, he successfully passed his qualification exams for serology and immunology research in Heidelberg and began to work there as an assistant in the University Institute for Experimental Cancer Research. There he worked primarily with brain and organ tissue, as well as blood group antigens.

When the Nazis came to power in Germany in 1933, Witebsky worked with Hans Sachs who was the director of the Kaiser Wilhelm Institute for Medical Research. Both Sachs, well known as "Germany's first serologist," and coworkers Ernst Witebsky and Alfred Klopstock, all Jews, were required to leave their jobs and afterward emigrated. Witebsky went to the State University of New York at Buffalo in 1935, where his professional career was outstanding. In collaboration with Niels Klendshoj, he discovered and isolated the B antigen from human blood. He worked on the development of a methodology for the separation and characterization of A and B blood antigens. He also initiated testing neutralization of specific antibodies in the blood of universal donors.

Witebsky was professor and chair (1941–1967) of the Department of Bacteriology—now the Department of Microbiology. The Witebsky Center for

Immunology was founded in 1967 for the purpose of enhancing research in immunology in Buffalo, NY. In 2000, the Center for Microbial Pathogenesis and the Witebsky Center for Immunology merged making it the Witebsky Center for Microbial Pathogenesis and Immunology.

Witebsky published more than 300 papers in European and US medical journals that dealt with problems focusing on specific aspects of clinical immunology and bacteriology. He was consulting editor of 4 professional journals—*Transfusion*, *Clinical and Experimental Immunology*, *Blood*, and *Blut* in German. He was an editor of the *Journal of Immunology* and a member of various local, regional, and national professional societies, including the following: American Association for the Advancement of Science, American Academy of Microbiology, American Public Health Association, New York Academy of Sciences, and Royal Society of Health. He was an honorary member of the Royal Society of Medicine starting in 1958 and the British Society for Immunology from 1960 onward. In 1964, he became a diplomate of the Pan American Medical Association.

(**Publ**.: Witebsky E, Rose NR, Terplan K, Paine JR, Egan RW. Chronic thyroiditis and autoimmunization. *J Am Med Assoc* 1957; 164(13):1439–1447.

Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 1993; 14(9):426–430.)

Witebsky substances are substances specific for ABO blood groups extracted from horse and pig stomachs. Witebsky and associates did a lot of the work with group-specific substances A and B and reported adding these substances to Group O blood intended for transfusion to neutralize the A and B isoagglutinins—isoantibodies capable of agglutinating cells of other individuals of the same species. Witebsky helped develop procedures for the isolation and partial characterization of A and B blood antigens. He also began the practice of neutralization of certain antibodies in the blood of universal blood donors. Witebsky's work was vital to the development of successful techniques for both emergency blood transfusions and organ transplantation. Witebsky received the Karl Landsteiner Award in 1959 for his work with blood antibodies.

Ernst Witebsky see **Witebsky's criteria/postulates**

(**Publ**.: Witebsky E, Klendshoj NC. The isolation of an O-specific substance from gastric juice of secretors and carbohydrate-like substances from gastric juice of non-secretors. *J Exp Med* 1941; 73(5):655–667.

Witebsky E, Klendshoj NC, Swanson P. Preparation and transfusion of safe universal blood. *JAMA* 1941; 116:2654–2656.

Witebsky E, Klendshoj NC, Swanson P. Reduction or elimination of anti-A antibody in O blood bv means of addition of "A" specific substances. *J Infect Dis* 1940; 67:188–192.)

Letter Z



Zuelzer syndrome (famili al eosinophilia) is an autosomal recessive trait characterized by the association of eosinophilia, leukocytosis, and hypergammaglobulinemia in infants and young children described by ***Wolf Zuelzer*** in 1949. After that initial observation, many patients were detected with it, and many new studies have been carried out to understand congenital neutropenia. In 1964, Wolf Zuelzer first used the term "myelokathexis" to describe a 10-year-old girl with severe neutropenia who had abundant mature and hypersegmented neutrophils in the bone marrow but severe peripheral neutropenia. Thus, occurrence of neutropenia and retention of bone marrow neutrophils has been called myelokathexis (*kathexis* = retention). This initiated the appearance of a new term—WHIM syndrome.

WHIM stands for **w**arts, **h**ypogammaglobulinemia, **i**nfections, and **m**yelokathexis. Even though hypogammaglobulinemia and verrucosis (warty elevations) are not seen in all patients, neutropenia and a hypercellularity in the bone marrow are usually seen in WHIM syndrome. In addition to neutropenia, patients with **Zuelzer syndrome** often develop a slight reduction of lymphocyte numbers and abnormal distribution of subpopulations of T and B lymphocytes, which reflects an atypical trafficking and homing of lymphoid cells in the lymphoid tissues. Nearly all patients with WHIM syndrome are truly panleukopenic (i.e., a decrease in the number of all the white blood cells) and show a significant decrease in peripheral blood B cells and a small reduction of peripheral blood T cells and monocytes.

Lately, heterozygous mutations of the chemokine receptor CXCR4 have been reported, which may cause WHIM syndrome. WHIM mutations of CXCR4 upregulate intracellular signaling because they interrupt negative regulatory elements amplifying the common hematopoietic functions of the receptor. CXCR4 normally is expressed by all leukocytes and has one ligand, CXCL12 (i.e., a stromal cell-derived factor 1 or SDF1). CXCL12 is expressed at high levels by stromal cells in the bone marrow, and its signaling via CXCR4 mediates hematopoietic stem cell maintenance in bone marrow niches. Lymphocytes and neutrophils from WHIM

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patient blood demonstrate enhanced chemotaxis, adhesion, and transendothelial migration in response to the SDF1.

Expression of the truncated form of CXCR4 results in upregulated responsiveness of mature leukocytes to the chemokine and precludes their marginalization to the bone marrow and consequent release to the bloodstream. Still, in inflammation, leukocytes may be released from bone marrow to the circulation as a result of the raised levels of CXCL8 and CCL2, which can neutralize the intensified functional activity of CXCL12. Thus, WHIM syndrome is an inherited immunodeficiency condition induced by hyperactivity of CXCR4 signaling that controls homing and circulation of leukocytes in the bone marrow and blood.

The common pathogen in WHIM syndrome-associated infections is human papillomavirus (HPV) that produces warts, which cannot be controlled by traditional treatment and may progress to malignant lesions. Recurrent bacterial infections are also common in patients with WHIM syndrome, usually in the sinopulmonary tract (i.e., the paranasal sinuses and the lungs), oral cavity, ear, skin, and soft tissue, where chronic complications, such as bronchiectasis and hearing loss, may occur.

Wolf William Zuelzer (***Zülzer***) (May 24, 1909–Mar 20, 1987) was a German-American hematologist. He was born in Berlin to Edith and Georg Ludwig Zuelzer-Wolff of Jewish descent. His father was a physician, professor in Berlin, and himself the son of the physician Professor Wilhelm Zuelzer. Wolf's father was a pioneer in the search for antidiabetic therapy. In 1908, he was the first to bring moribund patients out of diabetic coma using a pancreatic extract he had prepared. Overall, almost every member of the family for 2 generations had been physicians, medical scientists, or biologists of some distinction. Wolf's grandfather, Wilhelm Zuelzer, had been offered the directorship of the Reich Health Department by Bismarck, but he declined the position because it would have required that he convert from Judaism to Protestantism. The position was eventually filled by ***Robert Koch***.

Wolf maternal grandfather, Herman Wolff, was the founder of the Berlin Philharmonic Concerts, a friend of a great German composer, pianist, and conductor Johannes Brahms, and **a great Hungarian composer and pianist** Franz Liszt. Wolf studied French literature at Sorbonne in 1927–1928 and then in 1929–1930 philosophy and romance languages at the University of Heidelberg and completed his PhD degree. Then, he suddenly switched to medicine and studied it in Bonn and Berlin but was excluded from the university in 1933 for being a Jew when thevNazis came to power in Germany. He completed his medical education at the German University in Prague earning his MD degree in 1935. Afterward, he immigrated to the US.

Zuelzer did his pediatric internship at the Massachusetts General Hospital and worked as a volunteer in the Boston Children's Hospital for Sidney Farber for a year, and then in 1941 he moved to the Chicago Children's Hospital to finalize his training in pathology and pediatrics. In 1945, he received a position of assistant professor of pathology and pediatrics, and, in 1947, he became professor of pediatric research. In 1949, he got the Mead Johnson Award from the American Academy of Pediatrics for the first description and characterization of megaloblastic

childhood anemia. He directed the Child Research Center and the Michigan Community Blood Center in 1955–1975. In 1976–1979, he was a director of the Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute of NIH in Bethesda, MD. In 1976, he received the Grove Rasmussen Award of the American Association of Blood Banks.

Zuelzer had 2 daughters with his first wife, Margery Jenks, whom he married in 1938. He died of leukemia in Washington, DC. Zuelzer's name also is associated with Crosby's syndrome (Zuelzer-Kaplan syndrome I), Jirásek-Zuelzer-Wilson syndrome, Zuelzer-Kaplan syndrome II, and Zuelzer-Ogden syndrome (i.e., megaloblastic anemia in infants).

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