Historical eponyms of vitamin A (1863–1954)

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ABSTRACT

The discovery of vitamin A by Socin in 1891 and its isolation in crystalline form by Holmes and Corbet in 1937 paved the way for further discoveries involving its role in storage, photoreceptors in the eye, the cornea, epithelium, and normal immune function. Various symptoms and physical findings have been recognized and eponymously named a syndrome in honor of the person(s) who first reported those clinical entities about vitamin A. Seeking to fill the historical gap in the literature, the focus of this paper is to describe the eponymic cells, diseases, observations, syndromes, or tests ascribed to hypovitaminosis and hypervitaminosis A. In a chronological sequence based on the initial publication year of related reference, we presented concise biographical data concerning the scientist(s) responsible for recording the eponym, along with the presentation of the original depiction of the sign. We identified 12 eponyms related to vitamin A that were described between 1863 and 1954. These eponyms were named after 17 scientists from nine countries. Among them, Marie and Sée described the phenomena occurring in infants with hypervitaminosis A. The detailed and comprehensive description of the cornea or retina in vitamin A deficiency by Bitot, Lobo, Petzetakis-Tzakos, and Uemura remains relevant today.

Keywords: avitaminosis, biography, deficiency disease, eponyms, vitamins
INTRODUCTION

The discovery of vitamin A by Carl A. Socin in 1891, its isolation in crystalline form by Harry N. Holmes and Ruth E. Corbet in 1937, and synthesis by Otto Isler and colleagues in 1947 paved the way for further discoveries involving its role in storage, photoreceptors in the eye, the cornea, epithelium, and normal immune function\(^1\). Additionally, various symptoms and physical findings have been recognized and, in some cases, eponymously named a syndrome in honor of the person(s) who first reported those clinical entities about vitamin A. Seeking to fill the historical gap in the literature, the focus of this paper is to describe the eponymic cells, diseases, observations, syndromes, or tests ascribed to hypovitaminosis and hypervitaminosis A. Included is a brief overview of the discovery of vitamin A and the refinement of the nomenclature surrounding the vitamins in general.

Historical background

Physicians have long recognized the relationship between diseases, including night blindness and scurvy, and their treatment by consuming raw beef liver by Hippocrates (460-370 BC) and lemon juice by the Dutch and Portuguese in the 16th century\(^4,5\). Little was known about vitamin A and other vitamins before the early twentieth century. Carl Andreas Socin (1966–1933) in 1891 and Wilhelm Otto Stepp (1882–1964) in 1911 identified an unknown substance or fat soluble factor necessary for growth\(^6\). Sir Frederick Gowland Hopkins (1861–1947) recognized the deficiency of a “dietetic factor” and the onset of diseases including scurvy and rickets and presented those findings at the meeting of the Society of Public Analysts in 1906\(^7\). Hopkins in 1912 also demonstrated that rats fed a mixture of pure protein, fats, carbohydrates, and salts did not grow\(^8\). Growth occurred when the rats were fed small quantities of raw milk, suggesting that a substance or “accessory factor” in the milk promoted growth\(^8\). Casmir Funk (1884–1967) introduced the general term “vitamine” to define a substance deficient in scurvy and beriberi and preventing the onset of disease\(^9\). Elmer Verner McCollum (1879–1967) and Marguerite Davis (1887–1967) in 1913 found that laboratory rats grew when ether-soluble egg yolk or butter extracts were added to a diet containing purified proteins, carbohydrates, fats, and salts contained accessory factors that are essential for promoting normal growth and development\(^10\).

McCollum and Cornelia Kennedy (1881–1969) in 1916 challenged the use of the term “vitamine” by Funk based on their view that it did not accurately describe the underlying substance\(^11\). Their opinion was based on the lack of evidence that these substances contained an amino group and that the prefix “vita” refers to that the substance is essential and thus confers a mistaken impression
that they supersede other essential and relevant biological processes. In lieu of the word “vitamin” they suggested that the term fat-soluble and water soluble be used in reference to those unknown substances necessary for growth. Furthermore, based on this classification, alphabetical letters can be assigned and added as fat-soluble and water-soluble are recognized in each class. In 1920, Drummond recommended a revision of the nomenclature to address the discrepancy within the literature regarding the naming of these substances. He recommended dropping the “e” in “vitamine” such that the term “vitamin” now be recognized as the standard nomenclature used by the Chemical Society with the letter designation (A, B, C) to follow.

**METHODOLOGY**

We conducted word searches in PubMed, Medline, Internet search engines, medical dictionaries, and bibliographies from textbooks, using specific Medical Subject Headings (MeSH) related to the names of eponyms and keywords associated with vitamins. Our inclusion criteria focused on eponyms associated solely with vitamin A, including studies on the cell, observations, syndromes, and tests, narrowing the focus of the content of this paper. In a chronological sequence based on the initial publication year of related reference, we presented concise biographical data concerning the scientist(s) responsible for recording the eponym, along with the presentation of the original depiction of the sign.

**RESULTS and DISCUSSION**

We identified 12 eponyms related to vitamin A named after 17 scientists from nine countries: Brasilia, Canada, Denmark, England, France, Greece, Japan, Spain, and the United States between 1863 and 1954 (Table 1). Only two eponyms (Bitot spot and Brazilian ophthalmia) were identified before the 20th century. Dorothy Hansine Andersen (1901-1963), an American pediatrician and pathologist, is the only female eponym namesake.

**Bitot spots**

Pierre Alain Bitot (1822-1888) was born in Podensac, France, completed medical school in Bordeaux, France, and received his medical degree from the Faculty of Paris, France, in 1848. He served as head of anatomy at the Bordeaux School of Medicine in 1848 and professor of anatomy the following year. He was appointed doctor at the Charité in 1849, an assistant surgeon in 1852, professor and chair of anatomy at Bordeaux School of Medicine in 1854, titular surgeon of hospitals in 1856, chief of the surgical services at the Military Hospital in 1865, medical inspector of the department services for the mentally ill, head of the children’s surgical clinic in 1878, and honorary professor of
the faculty of medicine, Bordeaux in 1879\textsuperscript{13,14}. He was named to the Medical Society of Bordeaux in 1850. He co-founded the Medical and Surgical Society of Bordeaux in 1866\textsuperscript{13}.

While professor of anatomy at the Bordeaux School of Medicine and honorary surgeon of the Hospital of Bordeaux, Bitôt identified a collection of bright white dots producing a pearly or silvery spot on the epithelial layer of the conjunctiva adjacent to the cornea in patients with night blindness\textsuperscript{15}. Bitôt in 1863 provided a detailed description of the characteristics of these spots. Included are some of the following excerpts:

> While standing in front of the patient, we can distinguish them quite well when the eyes are converged. (...) They appear as an aggregate of small dots or thin, short lineaments resembling a half-frozen white foam patch. When the spots are observed, their color varies slightly and is apparent in each person. As they disappear, their whiteness fades. (...) The spots are generally triangular, with an external vertex; the base close to the cornea is slightly concave but may be circular, oval, or linear. The particles composing it are often agglomerated to constitute a punctuated, rough surface. They are frequently arranged in series or flexuous, parallel lines, making them appear wavy or wrinkled. These various forms can be modified by applying pressure using one or two fingers on the eyelids. These changes in form appear to give the impression that the spots are not conjoined but juxtaposed and displaceable by reducing a spot to a simple line or a vertical or horizontal bundle, then reforming it immediately by flattening this beam by moving the eyelids in the opposite direction (p. 287)\textsuperscript{15}.

Bitôt is credited for providing the first comprehensive clinical description of the ocular findings in nyctalopia (night blindness), the condition later known to be caused by vitamin A deficiency (Table 1).

**Brazilian ophthalmia**

Manoel da Gama Lobo (1831-1883) was born in the province of Monte Alegre, Pará, Brazil, and received his medical degree from the Faculty of Medicine in Rio de Janeiro, Brazil, in 1858\textsuperscript{16,17}. He was a physician in the War Arsenal of the Court in Rio de Janeiro and pursued ophthalmology training in Germany. He returned to Germany in 1872, seeking additional training in ophthalmology and histology\textsuperscript{16}. He served as head of the eye service at Santa Casa da Misericórdia, Brazil, and was a member of the Imperial Academy of Medicine in 1863\textsuperscript{17}.

Gama Lobo, in 1865, described the ocular findings of enslaved children aged two to seven, which he referred to as “Brazilian ophthalmia”: 
In my opinion, is one of the manifestations of a general condition and is only present when the person is already in an extremely deteriorated state. In addition to chronic bronchitis, liver congestion, and large voluminous diarrhea, the patient presents in a cachectic state, succumbing to marasmus. (...) It is a chronic type of disease that begins to manifest itself in the conjunctiva extending to the choroid and retina (p. 16).\textsuperscript{18}

He described three stages of the disease. Salient features reported during the second stage of the disease are as follows:

The palpebral conjunctiva is of a deep reddish-purple color and covered with small elevations. The ocular conjunctiva is grayish-white due to the movements made by the eye. It is covered with rugosities, giving the appearance of small ripples on the surface like water driven by the wind. From the sclerocorneal insertion until the palpebral reflection, the conjunctiva is devoid of vessels, and the one or two observed, exist on the surface of the sclera. From the beginning of the oculo-palpebral reflection, the vessels resemble the deep purple-reddish soil color. The papilla is normal and well-defined during ophthalmoscopy, and the vessels can be followed to their last branches. However, its color is a whitish red. In this period, secretions of tears pass over the eye but fail to moisten it, and thus it appears smeared with very fine globes of fat (p. 17).\textsuperscript{18}

During the third stage, the conjunctiva is dry and grayish, with wrinkles on the bulbar conjunctiva occurring during eye movement. The cornea contains a round ulcer with a hypopyon in the eye’s anterior chamber.\textsuperscript{18} Gama Lobo was unaware of the etiology of the ocular finding but keenly observed that the diet provided to enslaves people in different Brazilian provinces accounted for disparities in their overall health and mortality, corneal ulceration, and night blindness (nyctalopia) (Table 1). Thus, Brazilian ophthalmia, also known as xerophthalmia, occurs secondary to vitamin A deficiency or hypovitaminosis A.

Carr-Price reaction

Francis Howard Carr (1874-1969) was born in Croydon, England, and received his education at Finsbury Technical College from 1889 to 1892 and Guilds College, London\textsuperscript{19}. He served as a research assistant to Wyndham Rowland Dunstan (1861-1949) at the Pharmaceutical Society between 1892 and 1896, then at the Imperial Institute\textsuperscript{20}. Carr received the Salter’s Research Fellowship from 1894 to 1898\textsuperscript{19,20}. He was chief manufacturing chemist at Burroughs, Wellcome & Company from 1898 to 1914 and Director and Chief Chemist at Boots Pure Drug Company from 1914 to 1919. He assisted in establishing the Associa-
tion of British Manufactures in 191620. Carr was awarded the Commander of the Order of the British Empire in 1920. He was a Fellow of Imperial College, Chairman of the British Drug Houses, and President of the Society of Chemical Industry and Association of British Chemical Manufacturers in 192619. He received a D.Sc. degree from Manchester University in 192920.


Carr and Price, in 1926, described a quantitative method for measuring vitamin A using a colorimetric technique:

We were naturally led, therefore, to make experiments with a view to improving the technique of the colour tests in order to find conditions whereby quantitative and strictly comparable readings may be obtained. This work has resulted in our utilizing for the purpose yet another reagent of a similar character, namely, a solution of antimony trichloride in chloroform. By its use we have been enabled to determine standard conditions whereby direct readings of the intensity of the colour may be taken with the help of tintometer (p. 497)22. (...) [w]e found a 30% solution of antimony trichloride in chloroform (weight in volume), decidedly the most suitable and convenient. Its advantages are: 1) the oil and solvent do not need to be perfectly dry or entirely free from alcohol. (In many of the tests either water or alcohol interferes with the colour). 2) the colour is an intense blue, slightly more intense and more permanent than that produced by arsenic trichloride. It is very much better in this respect than the colour produced by any other reagent we have tried. 3) it may be depended on to produce the same intensity of colour with the same oil on very occasion. 4) as compared with arsenic trichloride the reagent is innocuous; it is, however, somewhat corrosive to the skin (p. 499)22.

Thus, the Carr-Price reaction was a quantitative method for measuring retinol or vitamin A (Table 1). Current analysis of vitamin A includes measurement of serum retinol alone or in combination with B-carotene23.

**Uemura disease**

Misao Uemura (Uyemura) (1900-1997) received his medical degree from the Faculty of Medicine, Keio University, Japan, in 1925 and his MD degree in 192924. At Keio University, Tokyo, he served as an assistant professor from 1931 to 1941 and as professor and chair of the department of ophthalmol-
gy from 1941 to 1961. He was director of the University Hospital from 1957 to 1959, dean of the School of Medicine from 1959 to 1961, director of Tokyo Second National Hospital from 1961 to 1971, and director of Ryuky University Hospital, Nishihara, Okinawa, from 1971 to 1975. He also served as executive director of the Japanese Ophthalmology Society.


Uemura, in 1928 described the fundoscopic findings in two patients with hemeralopia. One patient had Bitot spots on the bulbar conjunctiva while in both, as fully described in one case during ophthalmoscopic examination:

The delicate gray-white clouded background is densely dotted with innumerable yellowish-white dots on both sides except for the macular regions and in the vicinity of the papilla. These dots are most dense in the equatorial region and look somewhat elongated, as if short rods had been driven obliquely into the retina. Toward the periphery, their number gradually decreases, and at the same time, they appear more prominent and polygonal (p. 472).

Uemura disease refers to reversible white spots in the deep retinal layer, occurring in patients with avitaminosis caused by vitamin A deficiency (Table 1).

**Friderichsen test**

Carl Friderichsen (1886-1979) was born in Copenhagen, Denmark, and received his medical degree from the University of Copenhagen in 1912. He served as a physician at the Children’s Department of the Rigshospitalet and was a superintendent of the children’s department at Sundby Hospital, Copenhagen, Denmark. Friderichsen was chair of the Danish Pediatric Society from 1828-1934. His name is best recognized eponymously along with Rupert Waterhouse (1873-1958), who described the findings of bilateral adrenal hemorrhages and degeneration of the adrenal glands associated with cutaneous hemorrhages (Waterhouse-Friderichsen syndrome).

Friderichsen, in 1937, devised a bedside clinical test to determine whether there are adequate stores of vitamin A in children less than two years of age. The method measures the reflex irritability of the eyes to light and involves:
Flashing a light in a child’s eyes after it has been in the dark for at least half an hour, the “minimum relexibile” (m.r.) being the smallest light irritation capable of provoking certain reflex movements through the child’s eyes, wrinkling of the forehead, and an upward movement of the eyebrows when the light comes from above. Or the movements may be prompted by an oculomotor reflex, the eyes moving very quickly in the direction of the source of light. Or there may be other movements such as rotation of the head in the direction of the light or snatching at the light.

Friedrichsen and Edmund in 1937 found that a low minimum relexibile may be associated with either a low absorption or dietary insufficiency of vitamin A (Table 1). Moreover, through this test, they were able to quantitate the international units of various preparations of vitamin A.

**Andersen syndrome**

Dorothy Hansine Andersen (1901-1963) was born in Asheville, North Carolina, and received her medical degree from Johns Hopkins University School of Medicine in 1926. She was an assistant in anatomy at Rochester School of Medicine from 1926 to 1927 and completed a surgical internship at Strong Memorial Hospital, Rochester, New York, from 1927-1928. Andersen was a faculty member of Columbia University College of Physicians and Surgeons (currently Columbia University Vagelos College of Physicians and Surgeons) as an instructor in pathology in 1929. She received a doctorate of medical science degree in endocrinology. She was appointed assistant pathologist at the Babies Hospital Columbia-Presbyterian Medical Center in 1935, ascending to the rank of chief of pathology in 1952 and professor of pathology at Columbia University College of Physicians and Surgeons in 1958. Her active medical and research interest was in the area of cystic fibrosis.

Andersen was a member of several national organizations, including the American Board of Pathology, the American Association of Pathologists and Bacteriologists, the American Academy of Pediatrics, the American Society of Experimental Pathology, and the College of American Pathologists. She served as honorary chair of the National Cystic Fibrosis Research Foundation on the general medical and scientific advisory council. She was the recipient of several awards and accolades, including the Edward Mead Johnson Award of Pediatrics in recognition of her discovery of cystic fibrosis, and Borden Award for research in nutrition in 1948, and a citation from Mount Holyoke College in 1952, Elizabeth Blackwell for Women in Medicine, New York Infirmary in 1954, and a posthumous distinguished service award from Columbia-Presbyterian Medical Center in 1963.
Cecil Clarke (1886-1925) and Geoffrey Hadfield (1899-1968) were the first to report the postmortem findings in a four-year-old with steatorrhea and atrophy of the pancreas in 1924:

The gland was represented by fat, and a fraction of normal gland tissue estimated at one-twentieth. The surviving pancreatic tissue was active but appeared to be undergoing slow replacement fibrosis; it contained islet tissue in more than the normal amount; there was no clear evidence of pancreatitis (p. 364)\(^38\).

Andersen, in 1938, identified in 44 cases of cystic fibrosis of the pancreas that 23% had severe vitamin A deficiency, and more mild degrees may have been present in the remainder\(^39\). She found that:

The frequent occurrence of vitamin A deficiency was probably due to the failure of absorption of this vitamin. It is suggested that the pulmonary infection was possibly secondary to vitamin A deficiency (p. 382)\(^39\). (...) There is a good deal of evidence to show that, at least in the majority of cases, the pancreatic lesion comes first. (...) The evidence at hand suggests that the pancreatic lesion prevents the normal digestion and absorption of fats, the poor absorption of fats results in poor absorption of the fat-soluble vitamin A, and epithelial metaplasia, bronchiectasis, and bronchopneumonia are consequences of vitamin A deficiency (p. 399)\(^39\).

Andersen not only identified and named the disease cystic fibrosis but recognized the deficiency of vitamin A in this disease secondary to malabsorption and the essential role of vitamin A in epithelial development and the immune response (Table 1)\(^39\).

**Vilanova-Cañadell syndrome**

Xavier Vilanova i Montiu (1902-1965) was born in Barcelona, Spain, and received his medical degree from the Central University of Barcelona in 1923 and doctorate in 1928\(^40\). He continued his training at St. Louis Hospital in Paris; Pasteur Institute and Curie Institute in Strasbourg; and Milan, and finally, Aguas de Dios leprosy clinic in Colombia in 1936\(^40\). He was appointed professor and first chair of dermatology and venereology at the University of Valladolid, Spain, in 1942, chair at the University of Valencia, Spain, in 1942, and chair of dermatology at the Faculty of Medicine at the University of Barcelona, Spain in 1947\(^40\).

He was president of the Spanish Academy of Dermatology and Venereology, a member of Valencia and Catalonia Royal Academies of Medicine in 1944 and 1950, an officer of the Order of Public Health, and a corresponding member of
Josep Maria Cañadell (1915-1997) was born in Reus, Spain, and enrolled at the University of Barcelona Medical School from 1933 to 1934, which was interrupted because of the Spanish Civil War (1936-1939)\textsuperscript{42}. During that time, he was a lieutenant in the Military Health Corps in Husca and Manresa in Spain. He completed his medical studies graduating from the University of Barcelona in 1941\textsuperscript{42}. He continued his studies in Boston, Massachusetts, and Rochester, New York, from 1947 to 1948 and in London, Oxford, and Paris the following year\textsuperscript{42}. He served as a professor of medicine in the Faculty of Medicine as director of the endocrinology department in Clínica Médica B at the University of Barcelona. He taught postgraduate courses in endocrinology beginning in 1948\textsuperscript{42}.

Cañadell was a corresponding academic member of the Spanish Academy of Medicine, an honorary member of the Academy of Medicine, Turin, and an elected member of the Royal Academy of Medicine, Balearic Islands\textsuperscript{42}. He was an Officer of the Order of Public Health, France. He co-founded with Mário Cardia and was co-Editor-in-Chief of the journal *Acta Endocrinologica et Gynecologica Hispano-Lusitana* which later became *Acta Endocrinologica Iberica*\textsuperscript{42}. He also served on the editorial board as its editor from 1943 to 1956. He was the recipient of the Order of the Star of Italian Solidarity\textsuperscript{42}.

Vilanova and Cañadell, in 1949, reported on the relationship between hypothyroidism, vitamin A deficiency, and dermopathy:

> Among our cases of severe and untreated thyroid insufficiency, especially in infantile and juvenile hypothyroidism, we have frequently observed cutaneous findings corresponding to those caused by avitaminosis A. Clinically, these alterations manifest in the form of xeroderma, starting with dermatosis due to dryness and roughness of the skin, which is better felt than seen during its early stage. Furthermore, an eruption of perfectly delimited elements, with a horny appearance, the size of pinheads, sits on the opening points of the pilosebaceous follicles corresponding dermatologically to keratosis pilaris. It is typically located on the back of the forearms and the anterior and lateral aspects of the legs. Only in the most severe cases do the lesions extend to the arms, shoulders, back, thighs, and the remainder of the body. The lesions are almost always absent on the face, neck, and scalp. When looking at
these patients, it could be difficult to determine if the dermopathy is due to the thyroid or a vitamin A deficiency. The majority of subjects with these skin lesions heal slowly with thyroid opotherapy or even faster by administering vitamin A, even when the corresponding provitamin is completely ineffective.

Thus, they identified the permissive effect of thyroid hormone on converting provitamin A to the active form of vitamin A (Table 1).

**Bassen-Kornzweig syndrome**

Frank Albert Bassen (1903-2003) was born in St. George, Nova Scotia, Canada, and received his medical degree from McGill University in 1928. He interned at Jersey City Medical Center, New Jersey, from 1928 to 1930 and was a medical resident at Sinai Hospital, Maryland, Baltimore, from 1930 to 1933. He served as an adjunct professor in hematology and was appointed clinical assistant in medicine at Mt. Sinai Hospital, New York. During World War II, he served as Captain and Lt. Colonel Marine Corps, returning to Mount Sinai Hospital in 1946.

Abraham Leon Kornzweig (1900-1982) was born in New York City, New York, and received his medical degree from New York University (NYU) Medical School in 1925. He completed an internship at Mount Sinai Hospital from 1925 to 1928 and returned for additional residency training in ophthalmology. He served at NYU-Bellevue Postgraduate Medical School, where he taught embryology of the eye, achieving the rank of associate clinical professor, followed by appointment as a clinical and emeritus professor of ophthalmology at Mount Sinai School of Medicine, New York. He was chief of ophthalmology and director of research at the Jewish Home and Hospital for the Aged in New York. His research interests were ocular problems in older adults. He was instrumental in founding The Society of Geriatric Ophthalmology.

Bassen and Kornzweig in 1950 described the case of an 18-year-old female with atypical pigmentary degeneration of the retina with macula involvement, oscillating nystagmus, ataxia, sensory neuropathy, high arch palate, epicanthal fold and male-type of pubic escutcheon. An unusual finding which had not been previously reported was identified on a peripheral blood smear in the patient and her brother:

The count, in general, was quite normal except for a slight anemia. Great numbers of the stained red cells, however, revealed unusual abnormalities in shape and, to some extent, in size. (...) No two cells looked exactly alike. In general, they presented a crenated appearance but of such
that they took on bizarre shapes, stimulating small beetles, crabs, and turtles. Others were star shaped. The variations depended on the number and length of what appeared to be appendages growing out of the cells. Some of the cells appeared small and deeply stained. They resembled spherocytes from which buds or pseudopods were protruding, and these cells in particular varied from ordinary crenation (p. 385). The unusual shape of the erythrocytes is referred to as acanthocytosis. The red cell membrane appeared rough or prickly; hence it was called a “burr cell.” The syndrome is also referred to as abetalipoproteinemia in recognition of the lack of serum B lipoprotein resulting in defective intestinal absorption and transport of fat and fat-soluble vitamins, including vitamin A. The principal clinical manifestations of this syndrome include ocular and central nervous system defects and steatorrhea (Table 1).

**Petzetakis-Tzakos syndrome**

Limited historical information is identified on Michel Petzetakis (1899-1975). He was an associate professor of pathology at the University of Athens, Greece. At the time of his publication, he was chief physician at the General Hospital in Athens.

Konstantinos Tzakos (1903-1984) was born in Pogoni, Greece, and relocated to Istanbul with his family in 1908. He completed his education at the Phanar (Fener) Greek Orthodox College in Istanbul before pursuing a medical degree at Athens University. Under the supervision of Benediktos Adamantiadis (1875–1962), he gained practical experience at the trauma clinic of Polygonos and the Hippocrates Hospital. As a recipient of a national scholarship, Tzakos studied at the Military Medical School in Lyon, France, with the understanding that he would later serve as a military doctor in the Greek army. While in Lyon, he specialized in ophthalmology and completed his dissertation. From 1929 to 1930, he served as an assistant at the Ophthalmology Clinic of the University of Lyon. Subsequently, he underwent further training at the Ophthalmology Clinic of the Val-de-Grâce Military Hospital in Paris. Following his return to Greece, he fulfilled his mandatory service obligations.

In 1941, Tzakos established and organized the Ophthalmology Clinic at the General State Hospital of Athens, where he served as Director until his retirement in 1968. In 1947, he was appointed a professor of ophthalmology at the University of Athens. His considerable research on “Ocular changes during pellagra” is widely regarded as a seminal work. His studies entitled “Ocular changes due to edema and pellagra” as “Traumatic lachrymalitis” gained inter-
national recognition and are regarded as classic texts in the field of ophthalmology. However, his most significant contribution to Greek ophthalmology was his four-volume publication titled *Ophthalmology* (1954–1962), which included his illustrations.\textsuperscript{52}

Referring to Tzakos’s previous work, Petzetakis, in 1950 described in patients, ocular and systemic symptoms following the famine during the Nazi occupation of Greece from 1941 to 1944:

These ocular disorders, which we noted from the beginning of the famine, prompted us to study them more methodically with M. Tzakos, and it is in this way that we have described a particular form of keratitis, which I studied first from an anatomo-pathological point of view, under the name of superficial trophopenic keratitis. It was found in 85% of cases with generalized edema and 15% in dry forms (p. 1082).\textsuperscript{51}

He identified in superficial trophopenic keratitis (epithelial keratopathy), the following symptoms caused by vitamin deficiencies:

1) Palpebral edema, 2) Edema of the bulbar conjunctiva, 3) Hypoesthesia of the cornea, 4) Decreased iris reflexes, 5) Decreased tear secretion, 6) Alterations of the precorneal layer of Rollet; 7) Corneal disorders. These findings, studied using different instruments, are as follows: i. frequent edema of the anterior layers of corneal epithelium; ii. very fine granulation, which are of different shapes and sizes and sometimes raised (bulged) from the surface cornea; iii. small ulcerations of different shapes and sizes which are predominately superficial and polymorphic. The combination of several lesions sometimes gives a meandering or geographical map of these superficial ulcerations (p. 1082).\textsuperscript{51}

In addition to vitamin A, B, and C deficiencies, he observed hypoproteinemia, hypolipidemia, hypoglycemia, and alterations in the central and peripheral nervous system (Table 1).\textsuperscript{51}

**Jacobs syndrome**

Eugene Coryell Jacobs (1905-2000) was born in Schenectady, New York, and received his medical degree from the University of Michigan Medical School in 1929.\textsuperscript{53,54} He served in the Army Medical Reserve Corps in 1934 at Walter Reed Hospital as Chief of the Gastrointestinal Section.\textsuperscript{55,56} During World War II, he was Captain and Commanding Officer of Camp John Hay, Philippines.\textsuperscript{54} He was the chief of medical service in the Japanese Prisoner of War (POW) Camp No. 1 Hospital in Cabanatuan province of Nueva Ecija, Philippines, from
1942 to 1944. He was a prisoner of war at Moji Military Hospital in Fukuoka, Japan, and later at Camp Hoten in Mukden, Manchuria prison camps in 1945 and liberated from the camp that same year. He achieved the rank of Colonel, Medical Corps, US Army, Washington, DC, by 1965.

Jacobs was the recipient of the Medical Combat Badge, the Distinguished Unit Citation, the Legion of Merit, the Bronze Star, the Army Commendation Pendant, the Purple Heart, the Philippine Presidential Unit Citation, the George Washington Honor Medal, and US Army and Medical Service Medallion. For his research, he was recognized and received the Henry Wellcome Medal and Prize for “the most useful original investigation in the field of military medicine.” He also published *Blood Brothers: A Medic’s Sketch Book* in 1985.

Jacobs described the constellation of symptoms among prisoners of war in the Cabanatuan Prison Camp in 1942. He coined the term oculo-genital syndrome to define this entity which consisted of:

1) A deficiency disease comprised of an exfoliating dermatitis of the scrotum, stomatitis, and conjunctivitis insidiously appeared in more than 75 percent of 8,000 American prisoners-of-war after six months of an inadequate rice diet.

2) The syndrome was quickly and markedly improved by two months of an adequate diet.

3) On return to an inadequate rice diet, the syndrome was far less prevalent, indicating some adaption of the body to lowered caloric and vitamin intake.

4) The vitamin requirements of the body appeared to be less after a loss of considerable body weight.

5) The syndrome did not develop on a minimal diet composed of corn and soybeans.

6) The syndrome is thought to be closely associated with pellagra but not pellagra per se (p. 1053).

In addition to the symptoms mentioned earlier, some prisoners also developed amblyopia (optic atrophy) and burning of the feet (sensory peripheral neuropathy). He attributed the amblyopia to vitamins A and B₆ deficiency (thiamine) and sensory peripheral neuropathy to vitamin B₃ deficiency. Even though he recognized scrotal dermatitis, angular cheilitis, and stomatitis were caused by deficiencies involving the vitamin B complex, Jacob was unable to determine the specific deficiencies involved. This may be attributed to multiple vitamin...
deficiencies caused by malnutrition and overlapping symptom presentations. The oculo-oro-urogenital syndrome has since been recognized to be caused by a polyhypovitaminosis due to deficiencies involving $B_2$ or riboflavin and $B_6$ or pyridoxine deficiencies and manifesting as angular cheilitis, stomatitis, conjunctivitis, and scrotal dermatitis\textsuperscript{59}. Amblyopia from optic atrophy can be caused by vitamin A and B\textsubscript{1} deficiencies\textsuperscript{59}.

**Ito cells**

Toshio Ito (1904-1991) was born in Aichi, Japan\textsuperscript{60}. He completed postgraduate studies in anatomy at Keio University Faculty of Medicine and received his doctorate in 1936\textsuperscript{61}. He was an assistant from 1930 to 1932, an instructor from 1932 to 1941, and an assistant professor from 1934 to 1941 at Keio Medical School\textsuperscript{62}. Ito was a professor of anatomy at Tokyo Women’s Medical College from 1941 to 1947 and at Gunma University School of Medicine, Mayebashi, from 1954 to 1970, serving as dean from 1961 to 1963\textsuperscript{60-62}.

Ito and Nemoto in 1952 identified cells in the blood capillary wall in the human liver, which was later recognized to be the fat storage cell containing vitamin A (Table 1):

In 1950, while studying stellate cells, one of us accidentally discovered hitherto unknown cells in the capillary wall, and due to the fact that they mostly contained small fat globules in varying numbers, he named them “fat-storing cells” and published about it in 1950 in the \textit{55th} Assembly of the Japanese Anatomical Society. Through further investigation of these cells, we have come to the conclusion that morphologically they represent a quite distinct type of cell from the stellate cells (p. 243–4)\textsuperscript{63}.

As to the morphological location of these cells, they are located within the latticework of the capillary wall on the surface facing away from the liver in a depression between the surface of the adjacent neighboring liver cells toward the capillary lumen or in a shallow indentation on the surface of the liver cell. They are primarily spindle-shaped and contain small fat globules. As to the properties of these cells, the authors believed that:

The fat-storage cells probably represent functionally important cells in the liver, which secrete lipids from the blood and store them as neutral fat to release them back into the blood when needed. The fat in fat storage cells is nothing other than a reserve nutrient. In this way, the fat storage cells most likely participate in the lipid metabolism of the liver (p. 256)\textsuperscript{63}.
Thus, their primary function involves the storage of vitamin A (Table 1). In pathological conditions, Ito cells are also involved in collagen deposition and fibrosis\(^6^4\).

**Marie-Sée syndrome**

There is limited historical information on Julien Marie (1899-1987) and Georges Sée (1904-2000). Marie was a professor of infant medical clinic and social pediatrics in the Faculty of Medicine, Paris, and a physician in the Hôpital des Enfants Malades (Hospital for Sick Children), Paris\(^6^5\).

Marie and Sée first reported the cases and published a series of three cases of acute hypervitaminosis A in infants presented to the Society of Pediatrics, Paris, on February 20, 1951:

> We aim to draw attention to the acute events that may follow the administration of vast quantities of vitamin A in infants. These incidents are mainly characterized by acute hydrocephalus, spontaneous and intensive fontanel bulging, frequent vomiting, agitation, or insomnia, without any meningeal signs or other general disorders. The disorder begins 12 hours after ingestion of the drug and ends 24 to 48 hours later, either spontaneously or after a lumbar puncture (p. 731)\(^6^5\).

They identified that an increased cerebrospinal fluid and pressure was associated with the increased vitamin A concentration (Table 1).

In conclusion, eponyms related to vitamin A have been named for syndromes, cells, diseases, or qualitative or quantitative tests. Syndromes have been primarily described concerning conditions leading to inadequate intake or those interfering with vitamin A’s absorption or metabolism. In contrast, Marie and Sée described the phenomena occurring in infants with hypervitaminosis A\(^6^5\).

The detailed and comprehensive description of the cornea or retina in vitamin A deficiency by Bitôt, Lobo, Petzetakis-Tzakos, and Uemerua remains relevant today. It is important to recall that many of these physicians recognized, through their astute insights and observations, the relationship between the deficiency of certain substances contained within certain foodstuff and the emergence of disease (e.g., Gama Lobo and Jacobs)\(^1^8,5^8\).

A deficiency of vitamin A causes primarily ocular and cutaneous manifestations. Xerophthalmia is the term used to describe the ocular spectrum of signs and symptoms found in vitamin A deficiency, including Bitot spots, nyctalopia (night blindness), conjunctivitis, and keratitis\(^6^6\). Although the specific cause was unknown at that time, these ocular findings were first recognized by Pierre
Alain Bitôt and Manoel de Gama Lobo in the mid-19th century, prior to the isolation and synthesis of vitamin A in the early twentieth century.\textsuperscript{15,18}

Eponyms have been ascribed to physicians and scientists who made substantial contributions recognizing and describing the constellation of clinical manifestations of vitamin A deficiency occurring in isolation (Anderson, Vilanova-Cañdell, Bassen-Kornzweig, Petzetakis-Tzakos), a hypervitaminosis A (Marie-Sée), a general hypovitaminosis (Petzetakis-Tazkos, Jacob) or as a method to measure and quantitate its level (Friedrichsen). Deficiencies of vitamin A were caused by conditions fostering malnutrition (Jacob) or mechanisms interfering with absorption (Andersen) or absorption and transportation (Bassen-Kornzweig) and storage (Ito). With further discoveries, investigators identified that the synthetic and natural analogous of vitamin A or retinoids are useful in treating conditions including acne and psoriasis and in the cosmetic industry being promoted because of their anti-aging process.\textsuperscript{57,68}

Table 1. Eponyms related to vitamin A, described between 1863 and 1954

<table>
<thead>
<tr>
<th>Year described</th>
<th>Eponym</th>
<th>Related person(s) or namesake(s)</th>
<th>Definition</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1863</td>
<td>Bitot spots (patches)\textsuperscript{15}</td>
<td>Pierre Alain Bitôt\textsuperscript{9} (1822-1888), French anatomist, physician, and surgeon</td>
<td>Small, circumscribed, triangular shiny gray deposits on the bulbar conjunctiva. Seen in vitamin A deficiency and other conditions.</td>
<td>observation</td>
</tr>
<tr>
<td>1865</td>
<td>Brazilian ophthalmia\textsuperscript{18}</td>
<td>Manoel da Gama Lobo (1831-1883), Brazilian physician</td>
<td>Degeneration of cornea, secondary to vitamin A deficiency (syn: xerophthalmia)</td>
<td>observation</td>
</tr>
<tr>
<td>1926</td>
<td>Carr-Price reaction\textsuperscript{22}</td>
<td>Francis Howard Carr\textsuperscript{7} (1874-1969), English chemist; Ernest Arthur Price\textsuperscript{7} (1882-1956), English biochemist</td>
<td>A quantitative method for measuring retinol or determination of vitamin A using a colorimetric technique.</td>
<td>test</td>
</tr>
<tr>
<td>1928</td>
<td>Uemura (Uyemura) disease\textsuperscript{25}</td>
<td>Misao Uemura (Uyemura)\textsuperscript{7} (1900-1997), Japanese ophthalmologist</td>
<td>Reversible white spots in the deep retinal layer occur in patients with vitamin A deficiency. (syn: night blindness syndrome)</td>
<td>disease</td>
</tr>
<tr>
<td>1937</td>
<td>Friderichsen test\textsuperscript{23}</td>
<td>Carl Friderichsen\textsuperscript{9} (1886-1979), Danish pediatrician</td>
<td>Indicator of vitamin A deficiency. The smallest light causes oculomotor reflex, in which the eyes or head move in the direction of the light source. Other findings include wrinkling of the forehead and upward movement of the eyebrows.</td>
<td>test</td>
</tr>
<tr>
<td>Year</td>
<td>Syndrome</td>
<td>First Author</td>
<td>Second Author (if applicable)</td>
<td>Description</td>
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<td>------</td>
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<tr>
<td>1938</td>
<td>Andersen Syndrome (triad)</td>
<td>Dorothy Hansine Andersen</td>
<td>American pediatrician and pathologist</td>
<td>A triad of cystic fibrosis of the pancreas, vitamin A deficiency, and steatorrhea. (syn: pancreatic infantilism)</td>
</tr>
<tr>
<td>1949</td>
<td>Vilanova-Caladell Syndrome</td>
<td>Xavier Vilanova i Montiú</td>
<td>Spanish dermatologist; Josep Maria Cañadell</td>
<td>A combination of phrynoderma, hypothyroidism, and vitamin A deficiency. (syn: hypothyroid phrynoderma)</td>
</tr>
<tr>
<td>1950</td>
<td>Bassen-Kornzweig Syndrome (disease)</td>
<td>Frank Albert Bassen</td>
<td>Canadian hematologist and internist; Abraham Leon Kornzweig</td>
<td>An autosomal recessive condition, with onset at 6-16 years of age. Marked by neuromuscular abnormalities, retinitis pigmentosa, defective intestinal absorption and transport of fat and fat-soluble vitamins, including vitamin A, and burr shaped red blood cells (syn: abetalipoproteinemia or acanthocytosis).</td>
</tr>
<tr>
<td>1950</td>
<td>Petzetakis-Tzakos Syndrome</td>
<td>Michel Petzetakis</td>
<td>Greek pathologist; Konstantinos Tzakos</td>
<td>Keratitis, eyelid edema, and other eye ailments caused by severe malnutrition, including insufficient vitamin A intake, and poor hygiene. (syn: trophopenic superficial keratitis)</td>
</tr>
<tr>
<td>1951</td>
<td>Jacobs Syndrome</td>
<td>Eugene Coryell Jacobs</td>
<td>American military physician</td>
<td>A deficiency disease observed in American prisoners of war who were fed a rice diet. Characterized by the ocular findings (e.g., keratitis and conjunctivitis), oral (stomatitis and angular cheilitis and cutaneous (scrotal dermatitis) findings. Manifested with deficiency of riboflavin B2 and vitamin B6. Amblyopia (optic atrophy) caused by vitamin A and vitamin B1 (thiamine) deficiencies.</td>
</tr>
<tr>
<td>1952</td>
<td>Ito cells</td>
<td>Toshio Ito</td>
<td>Japanese anatomist and physician</td>
<td>Fat storage cells containing vitamin A lining hepatic sinusoids.</td>
</tr>
<tr>
<td>1954</td>
<td>Marie-Sée Syndrome</td>
<td>Julien Marie</td>
<td>French pediatrician; Georges Sée</td>
<td>An increased cerebrospinal fluid and pressure associated with hypervitaminosis A. syn: hypervitaminosis hydrocephalus syndrome pseudotumor cerebri or idiopathic intracranial hypertension.</td>
</tr>
</tbody>
</table>
STATEMENT OF ETHICS

This study, focusing solely on the analysis of historical materials, does not require ethical approval or consent, as it involves no human or animal participants, and all sources used are in the public domain or have been properly cited in accordance with academic standards.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest regarding the publication of this paper. This includes, but is not limited to, financial, personal, or professional affiliations that could be construed as influencing the objectivity, integrity, or interpretation of the research findings.

AUTHOR CONTRIBUTIONS

All authors have contributed equally to the conception, drafting, and critical revision of the manuscript, and approve of the final version to be published.
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