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Eponymous signs in toxicology and poisoning in the nineteenth and early twentieth centuries

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ABSTRACT

Toxicology emerged as an independent discipline in the early nineteenth century and has been aided by the development of numerous sophisticated tests that allow physicians and scientists to identify, quantify, and quantitate elements, chemicals, compounds, and toxins and to sort them into their component parts. These developments also contributed to enrich toxicological terminology with many new terms and eponyms in particular. Eponyms are ascribed to a variety of phenomena including attributing, in many cases, to the person who first identified or described a particular phenomenon and are named for the variety of findings found during the medical, surgical, pathological, or laboratory evaluation. Focusing on eponymous signs caused by poisons and toxins, the purpose of this paper is to honor the eponymous persons who first discovered, described, or more fully elaborated the finding. Nearly 30 associated eponyms have been identified in the literature, half of which were named for persons (e.g., Anstie sign, Billard sign, Blyth sign, Burton sign/line, Corrigan sign, Hertoghe sign, Peary sign). We believe that they are important to learn as they impart an in-depth appreciation of their role and application during the clinical examination. Knowledge of the person's biographical accomplishment(s) and character imparts a personalized and humane qualities to these signs from a medico-historical perspective. Understanding these signs and how to recognize them provides a method applying the bedside clinical examination to further support clinical suspicion or diagnose disease.

1. Introduction

A long-standing tradition in medical nomenclature, the eponym, is an honorific term that entered into mainstream use after the nineteenth century. *Oxford Medical Dictionary* (2020) defines the term as "a disease, structure, or species named after a particular person, usually the person who first discovered or described it." [1]. In a broader sense, an eponym is bestowed on individuals who identified or discovered an anatomical part, disease, finding, sign, symptom, syndrome, or test, or who create an algorithm, classification, device, prediction rule, principle, procedure, treatment, or view [2]. The term originally comes from the Greek επωνυμος (epónumos), which means "having a surname; that gives its name to – receiving its name from." [3].

With their extensive and rich history, eponyms also occur in different branches of medicine including toxicology. There is, however, a certain lack of information not only about the original definition of eponyms in this field, but also concerning the history of their emergence as medical terms and the biographies of their namesakes. To investigate this gap in the literature, the current paper is aimed at exploring the history of eponymous terms in toxicology and poisoning in the nineteenth and early twentieth centuries.

Indeed, milestones of this period vary widely and are exemplified as follows: Considered as the founder of modern toxicology, Mathieu Orfila (1787–1853) described the symptoms of poisons and systematized toxic substances in his famous work *Traité des Poisons* (Treatise of Poisons) in 1814. Lewis Lewin (1854–1929) classified alcohols, hallucinogenic plants, and psychoactive compounds in 1854. Claude Bernard (1813–1878) described the toxic effects of carbon monoxide in 1857. Sir William Crookes (1832–1929) discovered thallium in 1861. Harvey Wiley (1844–1930) formed the Poison Squad in the United States in 1883 to determine the toxicity of food additives. Arsenic-based drug Salvarsan was used as the first modern antimicrobial agent as a remedy for syphilis in 1910. Harrison Narcotic Act enacted in 1914 and Fritz Haber (1868–1934) developed blistering agents and poisoning gases

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used in World War I a year later [4,5].

Focusing on eponymous signs caused by poisons and toxins, the purpose of this paper is to honor the eponymous persons who first discovered, described, or more fully elaborated the finding. Herein, we provide biographical information about the person, the sign as originally described, and other contextual information about the finding.

2. Material and methods

PubMed, Medline, online Internet word searches, and bibliographies from source text and textbooks were used. PubMed was searched using the Medical Subject Headings (MeSH) of the name of the eponyms and text words associated with the sign. Inclusion criteria consist of only those eponyms named for a person in order to narrow the list and focus of the paper.

We limited our research to the nineteenth and early twentieth centuries because it was during this period that a number of remarkable developments occurred such as of the rise of toxicology's importance as an applied science in parallel with the rapid development of research methods, laboratory techniques, and specializations contributing to this disciplines capacity to recognize and minimize causes that danger human health and well-being (i.e., alcoholism, insecticides, occupational poisoning, and pollution) [5].

3. Results and discussion

Nearly 30 eponyms associated with toxicology and various poisonings have been identified in the literature. In many cases the name reflects the type of poisoning or toxin (e.g., aconite sign for aconitine poisoning), syndrome (e.g., Minamata syndrome), disease (e.g., Feer disease), occupation (e.g., Plummer disease) or location (e.g., Devonshire colic). Almost half of these eponyms, however, have been named for persons between 1831 and 1910 (Table 1).

3.1. Billard sign

Charles-Michel Billard (1800–1832) was born in Pellouailles-les-Vignes, near Anger, France, received his medical training at École Secondaire de Médecine (Secondary School of Medicine) in Anger from 1819 to 1823, and subsequently in Paris beginning in 1824 [6–9] (Fig. 1a). He served as an intern at the Hôpital des Enfants Trouvés (Hospital for Foundlings) from 1826 to 1828 and received his medical degree from the Faculty of Paris in 1828 [6,9]. He returned to Anger and opened a general medical practice [7]. Despite his relatively short medical career, he published his acclaimed book titled, *Traité des maladies des enfants nouveau-nés et à la mamelle* (A Treatise on the Diseases of New-born Infants and those at the Breast) in 1828 while at the Hôpital des Enfants Trouvés de Paris [10]. The book was considered the most influential text of pediatrics in the early nineteenth century and the first text that took a pathological approach to the classification of disease based on organ system, correlating pathologic with clinical findings in infants and children [6,8–11].

Billard described a finding in a 16-year-old female who:

> [p]resented with a beautiful blue colour primarily on her face, neck, and upper chest spreading to involve the ala of the nose and perioral regions. The blue material stained a white cloth when the face was wiped, leaving the skin a white colour (p.454) [12]. (…) The treatment, far from being successful, was followed in 12 days by profuse sweating, decreased urine output, and an increased intensity of blue involving the forehead, face, neck, chest, and abdomen. The skin was colored with an azure blue which increased or decreased in intensity based on whether the subcutaneous circulation was fast or slowly moving. When the patient was asked an embarrassing question her face turned blue instead of red. The sudden changes in tint resembled that of a chameleon. It should be noted that the anterior part of the face, trunk shoulders, arms, thighs and posterior aspect of the knee were not colored. The patient's linen was stained blue (p.455) [12].

Table 1
Eponymous signs related to toxicology and poisoning (1831–1910).

Eponymic sign	Year described	Description	Toxic agent
Billard sign [12]	1831	blue discoloration of the skin caused by toxic exposure to indigo	indigo
Burton sign/ line [17]	1840	blue-grey line on the gum in lead poisoning	lead
Corrigan sign [23]	1854	purple to reddish-purple line occurring on the margins of the gum or incisor, canine and bicuspids in copper poisoning	copper
Anstie sign [31]	1865	systemic affects caused by alcohol poisoning	alcohol
Russ sign [36]	1868	loss of speech caused by the bite of a venomous snake	snake venom
Gubler sign [42]	1868	gout occurring in lead poisoning	lead
Clapton sign [51]	1869	green line occurring appearing at the margin of the gum and partially involving the teeth occurring in copper poisoning	copper
Tomaselli sign [53]	1874	fever, hemolytic anemia and hemoglobinuria caused by quinine	quinine
Andouard sign [58]	1877	blue bile occurring in copper sulfate, antiseptic or paraquat poisoning	copper sulfate
Blyth sign [67]	1884	method for identifying lead in water	lead
Hertoghe sign [72]	1900	loss of the lateral or outer-third of the eyebrow in severe hypothyroidism. It has also been used erroneously in other conditions including thallium and lead poisoning.	lead, thallium
Danysz sign [80]	1902	difference found in neutralization occurring during a toxin-antitoxin reaction based on the method of aliquoting these substances	unspecific to a particular toxic agent
Mondonesi sign [81]	1905	maneuver involves asking the patient to close his/her eyes and compress the eyeball with the fingertips above the corneal margin. Normally results in contraction and pain involving the ipsilateral facial muscles.	unspecific to a particular toxic agent
Peary sign [89]	1910	symptoms caused by vitamin A intoxication	vitamin A

Chromhidrosis is the name given to conditions which cause pigmented sweat [13]. Billard referred to the condition as *cyanopathia cutanea* (cutaneous blue) disease caused by azure blue cutaneous hue later recognized to be caused by toxic exposure to indigo [14].

3.2. Burton sign/line

Henry Burton (1799–1849) was born in London, England, received his medical degree in 1826 and served as assistant physician and later senior physician at St. Thomas's Hospital, London [15]. He was elected Fellow of the Royal College of Physicians in 1832, Censor in 1838, and Consiliarius in 1843 [16]. Burton described findings in patients with lead toxicity caused by the ingestion of lead acetate in 1834:

> [p]eculair discolouration was observed on their gums, which I could not discern on the gums of several hundred patients, who were not under the influence of lead (p.65) [17]. (…) The edges of the gums attached to the necks of two or more teeth of either jaw, were distinctly bordered by a narrow leaden-blue line, about the

Fig. 1. **(a)** Charles-Michel Billard (Académie nationale de médecine, Paris). **(b)** Francis Edmund Anstie (Wellcome Trust Library, London). **(c)** Adolphe-Marie Gubler (Bibliothèque nationale de France, Paris). **(d)** Salvatore Tomaselli (https://nicolosietna.it/it/dr-salvatore-tomaselli.html). **(e)** Alexander Wynter Blyth (http://glascoed.com/alexander_wynter_blyth.html). **(f)** Robert Edwin Peary. (Bibliothèque nationale de France, Paris).

> one-twentieth part of an inch in width, whilst the substance of the gum apparently retained its ordinary colour and condition (p.66) [17]. (…) For the discolouration is very permanent; it has endured through months and until death, and having been once observed may be afterwards easily recognized (p.68) [17]. (…) The time required to produce the blue line varies in general with the amount of the dose, but not always; and *coeteris paribus*, large doses affect the gums sooner than small (pp.77–78) [17].

Thus, Burton sign refers to the blue-grey line on the gums in persons with chronic lead poisoning.

3.3. Corrigan sign

Sir Dominic John Corrigan (1802–1880) was born in Thomas-Street, Dublin, Ireland, completed his medical studies in Dublin and Edinburgh, receiving his medical degree from Edinburgh University in 1825 [18–20]. After graduation, he commenced medical practice in Dublin followed by physician appointments at the Meath Dispensary, Cork-Street Fever Hospital, and in 1830 the Charitable Infirmary in Jervis-Street (Jervis-Street Hospital) [18–20]. He was appointed physician to the College of Saint Patrick at Maynooth, the place where he received his undergraduate education in 1831 [18]. He served as professor of medicine at Digges Street School, Peter Street School, and lastly from 1840 to 1860 the House of Industry Hospitals [Richmond (Carmichael School of Medicine), Hardwicke Fever Hospital, and Whitworth Hospital] [18,20].

Corrigan founded the Dublin Pathological Society in 1838, later serving as its president [19]. At Queen's University, he was appointed member of the University Senate in 1841, representative of the Medical Council in 1858 and lastly vice-chancellor in 1871 [18,20]. He was a member of the Royal College of Surgeon (MRCS), London, in 1843 and received an honorary Doctor of Medicine degree by the University of Dublin in 1849 [18]. He served as President at King's and Queen's College of Physicians and was bestowed the title Baronet in 1866 [18–21]. Corrigan was appointed physician-in-ordinary to Queen Victoria, Commissioner of National Education, Ireland, in 1870, and elected a member of parliament for the City of Dublin in the British House of Commons from 1870 until 1874 [18–20]. He was a member of a number of organizations including Dublin Pathological Society where he also served as President, Royal Zoological Society, Ireland, Royal Irish Academy, Academy of Medicine, Paris, Harveian Society of London [18,21] and the Pharmaceutical Society of Ireland in 1875 [18,21]. His name is undoubtedly best recognized in association with the visible pulse (Corrigan pulse or sign) occurring in patients with severe aortic insufficiency as described in his paper, "On permanent patency of the mouth of the aorta or inadequacy of the aortic valves" published in 1832. His name is also associated with a number of other eponyms including Corrigan cirrhosis (fibroid disease of the lung) [18,22].

As a description of his character, "As a practitioner, he exhibited in a

striking manner the distinguishing traits of his character, decision and boldness; tempered, however, with kindness and tenderness towards the sick, and guided by the most scrupulous honors in his professional relationship." [21]. Corrigan described in 1854 an unusual finding seen in patients with copper poisoning:

> [a]n edging of rich purple on the margin of the gums of the incisor, canine, and bicuspid teeth of both jaws. This purple colouring of the margin of the gums coincides in situation precisely with the colouring produced by lead, but the tint of colour is so different as at once to decide whether it has proceeded from copper of from lead; for while the colour produced by lead is of a pure blue, that from copper is a well-marked purple and even sometimes a reddish purple (p.229) [23].

Corrigan recognized that both lead and copper originate from their respective salt carbonate. Copper toxicity was believed to have occurred by prolonged exposure through skin absorption due to handling copper or its alloy brass.

3.4. Anstie sign

Francis Edmund Anstie (1833–1874) was born in Devizes, Wiltshire, England, attended King's College, received his diploma from the Royal College of Surgeons (MRCS) and the Apothecaries Company in 1856, and Bachelor of Medicine (MB) from the University of London in 1857 [24–27] (Fig. 1b). He was appointed physician to the Chelsea Dispensary in 1859, and member of the Royal College of Physicians in 1859 [26, 28–30]. He served as a pathologist at the Westminster Hospital and in 1860 was elected co-lecturer and assistant physician on forensic medicine and subsequently Materia Medica [26–28]. Anstie published his book *Stimulants and Narcotics, Their Mutual Relations: With Special Researches on the Action Alcohol, Ether, and Chloroform on the Vital Organism* in 1864 [31], *Notes on Epidemics for the Use of the Public* in 1866 [32], *On the Uses of Wines in Health and Disease* in 1870, and *Neuralgia and the Diseases that Resemble It* in 1871 based on his research while at Westminster Hospital [28,29,33]. Regarding these and other books and manuscripts:

> [t]he works that he published cost him enormous toil, and in each there was set before him, not the fame of literary distinction, not the pleasure of advancing new theories because they were new, but the direct practical good he could affect in the relief of suffering, and the happiness of mankind. (…) Anstie was one who never relaxed his grip upon a piece of work until he had finished it, and so, night and day, week after week, through the summer and autumn of 1863, he toiled in library and laboratory, at bedside and in out-patient room, gathering the materials for his book (pp.95–96) [29].

In addition to this appointment at Westminster Hospital, he also served as a physician at the Belgrave Hospital for physician and consulting physician to the Royal South London Ophthalmic Hospital [28,30]. He was elected Fellow of the College of Physicians 1865 and served as editor of the London *Practitioner* in 1869, a journal devoted to the study of therapeutics [27–29,34]. It was not until 1873, that he became full physician at Westminster Hospital, and the following year participated in the foundation of the medical school for women, serving as its first dean [24,34]. He also contributed to issues involving public and social health and occupational conditions including homes of the working classes in large towns displaced by the railroad companies, and those involving paupers in London workhouses [29]. As a description of his character:

> Dr. Anstie combined with his versatile and unflagging industry a singularly affectionate and enthusiastic temperament, and a kindness of heart that never varied. He had no enemies but those whose enmity was a tribute to his worth. It was well said of him by the 'Times', that his hatred of oppression or wrongdoing, his love of truth for its own sake, his generous and chivalrous character, had endeared him to all who were brought within the range of his personal influence. Of a warm heart and somewhat combative temperament, he was engaged in many controversies, but he never suffered his share in them to degenerate into personality, and never forgot to distinguish between the abuses he condemned and the possibly innocent persons who administered them. He was, indeed, *sans peur et sans reproche* (p.467) [28].

In an inscription engraved on a tablet at the Chapel of King's College London as written by Mr. John Simon:

> In memory of Francis Edmund Anstie, MD, London, FRCP, Physician to the Westminster Hospital, Honorary Fellow of this College. Laborious in study, accomplished in practice, ardent in love of truth and justice, strenuous in efforts for the poor and friendless, he was steadfast, gently, and affectionate in all personal relations, and dearest to those who knew him best. His death, which took places on September the 12th, 1874, in his 41st year, was caused by blood-poisoning incurred in the discharge of his duty [35].

Anstie described the effects of alcohol poisoning:

> In alcohol poisoning, the watery element of the urine is constantly much increased, and it has now been demonstrated that a small quantity of the poison passes off in the urine, the breath, and the skin perspiration (p.200) [31]. (…) Under the head of circulatory phenomena, we may notice all the flushing of the skin, which is an early sign of poisoning with alcohol and with several other narcotics (p.204) [31]. (…) Thus, in poisoning with alcohol or aether, we have numbness of the lips and face, and in poisoning with alcohol, aether, or chloroform, we have loss of the muscular sense of the extremities, before or coincident with the very earliest symptoms of palsy of brain or spinal cord (p.398) [31].

Thus, Anstie sign refers to the symptoms and physical findings found in alcohol intoxication.

3.5. Russ sign

We were unable to identify any historical information regarding M. Russ. Russ described a finding occurring in persons after a venomous snake bite:

> I have seen, says M. Russ, many persons who had lost their speech from being bitten by the fer-de-lance snake. This strange symptom is sometimes instantaneous; in other instances, it only appears after an interval of several hours. In those who survive the effect of the venom it lasts for an indefinite period. It is altogether independent of the particular situation of the bite. One man I have seen who had not only lost his speech in consequence of this accident, but had become, and still remained, hemiplegic; but in the rest speech alone was abolished. The intelligence was altogether intact. Sensibility and power of motion were unaffected. The persons in question continued to follow their ordinary occupations in silence. One woman who had been thus for a long time condemned to silence, all of a sudden, under the influence of strong excitement, recovered her speech; but when the emotion had passed away, speech again left her. I never had an opportunity of making a post-mortem examination in one of these cases. I therefore do not know what the condition of the brain is (p.169) [36].

Thus, Russ sign refers to the loss of speech occurring in a person after a venomous snake bite.

3.6. Gubler sign

Adolphe-Marie Gubler (1821–1879) was born in Metz, France, and

received his medical degree in Paris 1849 [37,38] (Fig. 1c). He was appointed Director of the Clinique de l'École in 1850, Associate Professor of the Faculty of Medicine in 1853, and Professor of Therapeutics at the Faculty of Medicine, Paris in 1868 [37,38]. In addition to his academic appointments, he served as member of the Society of Biology and Anatomical Society, Laureate of the Institute in 1852 and 1875, Vice-President of the Biological Society in 1852, Vice-President of the Society of Botany in 1862 and 1866, Member of the Academy of Medicine in 1865, Corresponding Member of the Metz Society of Medical Sciences, and President of the International Hygiene Congress in Paris in 1878 [38,39]. He was anointed knight of the Légion d'honneur in 1865 [37,38]. Gubler's scientific work spanned multiple therapeutic areas from the biologic to the clinical and pathologic sciences [38]. His other appointment as a physician included the municipal house of nurses in 1853, Saint-Antoine Hospital in 1853, and Beaujon Hospital in 1854 [38]. He founded with Bordieret and Labbé, the *Journal of Therapeutics* in 1874 [39]. As a description of his character as communicated by J. Renaut:

> Gubler possessed to the highest degree the hallmarks of the public figure. His politeness, his kindness to all who approached him, were extremely important. His memory will remain in the memory of those who knew him as that of a great doctor and a good man; he will remain in that of those he loved, received and celebrated in his house, like that of an always benevolent, affable and devoted friend. When such men disappear, moreover, they leave behind something of the deep charm which they radiated during their life, a charm which was exercised on all, and which makes them never forgotten (p.354) [40].

Gubler recognized the relationship between extensor tendon swelling and gout secondary to lead poisoning. He also reported a case of left hemiplegia with paralysis of the extensor tendons with similar symptoms not due to gout:

> [a]n unusual type of deformity that involved a lesion of the tendinous apparatus which he first observed in a person with gout. This lesion consists of a sort of plastic, fungous synovitis located in the extensor sheath on the dorsum of the hand. He thinks that he can relate it to a nutritive disturbance caused by lead poisoning rather than to the action of the poison itself (p.566) [41].

> Until now, the facts recorded in science allowed us to believe that the dorsal tumor of the hand, mainly formed by the swelling of the extensor tendons and their sheaths, was a lesion peculiar to lead palsy. In fact, my first observations, communicated to the Medical Society of Hospitals, in the meeting of March 27, all related to cases of lead poisoning. Here, however, is a fact, unfortunately not well known, which proves that the lesion of the tendon apparatus has also been found in cases of paralysis of the extensors caused by a trivial cause such as an alteration of the nervous centers devoid of all toxic complication (p.334) [42].

Thus, Gubler sign refers to the swelling involving the extensor tendon of the dorsum of the hand caused by gout in patients with lead poisoning.

3.7. Clapton sign

Edward Clapton (1830–1909) was born in Stamford, London, England, and received his medical degree from the University of London and Fellowship to the Royal College of Surgeons in 1857 [43,44]. After graduation, he was appointed Assistant Physician at St. Thomas Hospital Medical School, lectured on Botany in 1860 and Materia Medica at the same institution in 1861 [43,45]. He also served as a visitor of Lunatics for Surrey [46]. He was appointed member in 1858 and Fellow in 1870 of the Royal College of Physician [45,47]. Due to poor health conditions, he resigned from St. Thomas in 1875, but continued his practice as a physician in various capacities at a number of facilities (Magdalen and Miller Memorial Hospitals), St. John's Blackhealth Cottage, as well as the London Assurance Company and Royal Kent Dispensary [45]. He also served as a member of the Medico-Psychological Association and the Clinical Society of London [46,48]. His strong conservative values from his father as well as evangelical principles of his parents was presumably the foundation driving his deep religious belief and involvement in church and missionary work [44,47]. His avocation involved biblical studies culminating in the publication of two books *The Precious Stones of the Bible* and *The Life of Saint Luke* [49,50]. As a description of his character:

> Dr. Clapton was a devoted husband, an affectionate father, and a faithful friend to all who had the privilege of coming into close touch with him. Modest and retiring by nature, he exercised a remarkable influence, and has left behind him a fragrant memory which belongs only to those who have faithfully served both God and a throughout a long and useful life (p.1201) [47].

Edward Clapton described in 1869 the effects of excessive copper accumulation:

> [f]requent vomiting, purging, and griping, a patchy tongue partly furred and partly morbidly red, a feeling of constriction in the throat, coldness and numbness of extremities, a small frequent pulse, constant headache, and frequent cramp of legs. One peculiarity which I made a particular note of at the time was the existence of a most marked green line on the margin of the gums and for some little distance on the teeth (pp.8–9) [51].

He also noted in sixteen men working in a coppersmith:

> Their perspiration too, had a bluish-green tinge. I examined the shirts and flannel vests of several, and found some very deeply stained, especially under the arms. I thought at first it might have been the copper particles or fumes which had lodged in the skin and garments, and so by its direct action caused the discoloration; but on careful examination I was convinced it was not so. Even after a hot bath and a thorough washing with soap, a clean shirt will be quickly stained with the green perspiration, especially after a brisk walk on a hot day (p.8) [51]. (…) The hair of several old workmen had also a distinct greenish tinge, and I was informed that it remained permanently so, even after they had left work altogether, but there is no instance of its occurring under 20 years' service (p.8) [51]. (…) [m]any of the men complain of habitual lassitude and giddiness (…) some of them were exceedingly thin and had very unhealthy complexions (p.9) [51].

Thus, Clapton sign refers to the green line appearing at the margins of the gums and partially infiltrating the teeth due to copper poisoning.

3.8. Tomaselli sign

Salvatore Tomaselli (1830–1906) was born in Nicolosi, Sicily, Italy, and received his medical degree at Naples (Fig. 1d). He served as a private lecturer on medical diagnosis in 1857 and Professor of Medical Pathology followed by Professor of Clinical Medicine at the University of Catania in 1880 [52]. He was Nestor of clinical teachers in Italy [52]. Tomaselli initially reported in 1874 in a memorandum read by him at the Academy of Catania his observation regarding the toxic effect of quinine used in the treatment of malaria [53]. At the First Congress of the Italian Society of Medicine held in Rome from October 20–23, 1888, Tomaselli presented his findings on quinine poisoning:

> For the past several years I have observed repeatedly that quinine in some individuals with malaria did not resolve the infection but produced an intoxication characterized primarily by fever and hematuria. (…) This state is due to the quinine preparations which exert a dissolving action on the blood; causing rapid deterioration

and circulatory collapse; there is destruction of red blood cells and hemoglobin in the urine. Thus, in some patients with malaria, quinine administration can be harmful, even if the drug is ingested in low doses. In these cases, it is necessary without saying that you must stop giving this drug and use a substitute [54].

Thus, Tomaselli was the first to recognize an adverse drug effect caused by quinine ingestion used in the treatment of malaria with laboratory findings including hemolytic anemia and hemoglobinuria.

3.9. Andouard sign

Ambroise Pierre Andouard (1839–1914) born in Nantes (Loire-Inférieure) and served as Professor and Chair at the School of Medicine in Nantes, France [55,56]. This was followed by an appointment as Professor and Director of the Loire-Inférieure Agronomic Station where he was involved in the study of agricultural food chemistry [55]. He published *Nouveaux éléments de pharmacie* in 1874 [57]. Among his accolades he was elected corresponding member of the National Academy of Medicine and National Correspondent for the Division of Medical Physics and Chemistry in 1883 and the National Association in 1900 [55,56]. As reported by Ferrand and as described by Andouard:

> At various times predominately in animals, secretions primarily from sweat and suppuration and occasional bile were stained blue. In all cases the pigment had an identical composition. M. Professor Andouard, from Nantes, was recently called upon to examine spots of vomit which showed an intense blue colour. These unusual findings had attracted the attention of his assistant which aroused their suspicion since it was a woman and public rumors accused the husband of the attempted poisoning. The police believed that they saw copper salts in the spots and requested further analysis. M. Andouard had at his disposal five large linen sheets, three of which were half covered and more or less stained dark, ranging from sky blue to indigo. The first tests demonstrated that there was no trace of copper in these droppings. On the other hand, the microscopic study could not reveal a particular cause to which could be attributed to the coloring. The expert thought, in the end, that it was a pathological secretion, and subsequent experiences brought it, in fact, to conclude that it was in the presence of bile, the ordinary pigment was found to be altered. (p.788) [58].

Thus, Andouard sign refers to the presence of blue bile believed to be caused by the oxidation of bilirubin and biliverdin. It has also been reported in association with copper sulfate poisoning (blue vitriol) or boric acid containing compounds such as antiseptics or pesticides (paraquat) [59,60].

3.10. Blyth sign

Alexander Wynter Blyth (1844–1921) was born in Woolwich, London, England, and received his medical degree from King's College in London, qualifying in the Royal College of Surgeons in 1870 [61–64] (Fig. 1e). He also studied law and served as barrister-of-law at Lincoln's Inn [61–63]. After practicing medicine for several years in Devon, he served as Public Analyst and Medical Officer for Totnes followed by Devon counties in 1878, Tiverton in 1879, and as Medical Officer of Health and Public Analyst St. Marylebone Burrough in 1882 [61,63,64]. He remained in the latter position for a period of 30 years, subsequently relinquishing the medical officer position and continued as Public Analyst throughout the remainder of his career. His passion was in the fields of chemistry and public health. In the public health realm, he was elected Fellow of the Institute of Chemistry in 1877, served as President of the Incorporated Society of Medical Officers of Health and the Registrar of the Royal Sanitary Institute and Fellow of the Société Française d'Hygiène and Italian Society of Hygiene, Milan [61–65]. He was editor of the journal *Public Health* and authored several well-known analytical books including *Dictionary of Hygiene and Public Health* 1876 [66], *Poisons: Their Effects and Detection*, in 1884 [61,63] and *Foods: Their Composition and Analysis* in 1888 [63]. His ingenuity led to the discovery of new methods and devices as well as refinement of previous procedures in analytical chemistry involving foods and public health issues [64].

As a description of his character as told by JKC:

> [a] man of great ability and untiring energy. (…) He leaves a son and two daughters and a large number of friends to mourn his loss, amongst the latter being many who were much indebted to him for the help and kindness he was ever ready to extend (p.547) [61].

Blyth discovered a method for testing lead in water:

> A solution of cochineal produce by digesting one part of cochineal in a hundred parts of proof spirit is first made. An ounce of distilled water is next placed in a white porcelain dish, and ten drops of the cochineal solution are added and mixed so as to give the water a distinct rose-red colour. An ounce of the suspected water is then treated in another white porcelain dish in precisely the same manner, when, if lead be present, a purple-blue tint is truck, varying, according to the dilution, from a purple-blue to a light pink-purple. One part of lead in seventy thousand parts of water, or one grain in a gallon, gives a most distinct purple-blue colour under the test. With careful manipulation, one part of lead in seven hundred parts of water, or one grain in ten gallons, gives a characteristic purple-pink [67].

Thus, Blyth sign describes the method for identifying lead in water.

3.11. Hertoghe sign

Eugène Lois (Ludovic) Chrétien (Christian) Hertoghe (1860–1928) was born in Anvers, Belgium, elected corresponded of the Royal Academy of Medicine of Belgium in 1901, became a full member in 1919, eventually rising to the rank of Vice-President in 1928 [68–70]. He is best recognized for his extensive work on aspects of myxedema and hypothyroidism, the latter term coined by him and which has been referred to in the French literature as "maladie d'Hertoghe" (Hertoghe disease) [70,71]. Among his other accolades, he was bestowed the Doctor of Science degree from Lincoln Memorial University, Foreign Member of the Paris Neurological Society, Chairman of the Society of Medicine in Anvers, and President of the Association of Former Students of the faculty of Medicine of Louvain. He served on rector council at the University and was an Officer of the Order of Leopold [71]. He founded the Zander Institute in Anvers in 1897 as well as the Institute St. Henri [71]. A description of his character as described by van Ermengem:

> He was a first-rate clinician, honest and perspicacious observer, who did not shy away from the boldness of the conclusions to which his findings led him. The writings of our late colleague abound in original ideas and suggestions are only waiting their time to become fruitful truths. He was keen and open-minded, welcomed lofty thoughts, and searched for the good of all things. He spent time doing good and earned the reward promised to his Faith! The numerous sick whose ailments he cured or relieved, the unfortunate people he helped, and his colleagues who highly appreciating his professional merits elevated him to the presidency of their Societies. Finally, all his friends dismayed by his sudden loss, will never forget him (pp.6–7) [70].

Hertoghe in his paper, "Le myxœdème franc et le myxœdème fruste de l'enfance" published in 1900 described the physical features found in children with cretinism and their mothers and children with myxedema. In a 21-year-old male he found "numerous patches of alopecia areata, hidden by the rest of the hair which was left long purposely" (p.411) [72]. In the 41-year-old mother he keenly observed when he compared

her facial features compared to an earlier photograph, "puffiness of features. The eyelids, especially the upper ones, are drooping. The outer third of the eyebrow is absent. Graying is clearly visible" (p.413) [72].

Thus, loss of the lateral or outer one-third of the eyebrow in severe hypothyroidism is referred to as Hertoghe sign. The sign has also been used erroneously to describe hair loss involving the outer two-third on the eyebrow in persons with thallium [73,74]. It has also been identified in whole or in part in cases of lead poisoning, systemic lupus erythematosus, leprosy, normal aging, and secondary syphilis [75,76].

3.12. Danysz sign

Fonds Jean Danysz (1860–1928) was born in Chylin, Poland, and completed he scientific training at the Faculty of Sciences in Paris and Caen where he obtained his Bachelor of Science degree [77,78]. At the Museum of Natural History, he was involved in the study of the parasite *Taenia fenestrate* and life cycle and structure of the genus *Gymnodinium musei* n. sp a new Peridinian of the order Dinoflagellata [77,79]. He was editor of *Journal de la Meunerie* and director of the Parasitology Laboratory at the Bourse of Commerce followed by an appointment at the Pasteur Institute beginning in 1893, later rising to the position of director until the time of his death [77,78]. Danysz was involved in a number of important investigations and discoveries including the control of rinderpest in southern Africa, Australia's rabbit plagues, passive immunization, horse sickness, isolation of *Salmonella typhimurium*, and radium in the treatment of malignancy, and what became eponymously named the Danysz phenomenon [79].

A description of his character as enumerated by E. Pozerski:

> Artist as much as scholar, Jean Danysz leaves in all those who knew him the memory of a superior mind that has extended itself in the most diverse direction in search of the truth in the fields of science as well as in philosophy [77].

Danysz studied the interaction between toxin and antitoxin and found the following:

> 1. The formation of precipitates in mixtures based on different proportion of ricin and antiricin, the variable properties of mixtures containing identical amounts of toxin and antitoxin, and finally the properties of both antitoxic and toxoactive compounds of toxins and antitoxins mixed in any proportions, indisputably prove that these two substances bind or fix each other in varying proportions. When mixed together, toxins and antitoxins therefore do not form a single compound, but a series of compounds in which one of the two substances is fixed by the other which remains active to various degrees.
> 2. Antitoxins bind to toxins in vitro and saturate their binding sites without destroying them (p.345) [80].

Danysz found that neutralization of the toxin by the antitoxin occurs faster if the antitoxin is added at once rather than in sequential incremental doses. Furthermore, the amount of free toxin available was greater if the total toxin was added to the antitoxin in fractional concentrations compared to all at once. This has also been referred to as the Danysz effect, Danysz phenomenon, or Bordet-Danysz phenomenon.

3.13. Mondonesi sign

There is limited information on Filippo Mondonesi. He practiced medicine at the Maggiore Hospital in Bologna, Italy. Mondonesi described the findings in a woman with previous left hemiplegia caused by a cardioembolic stroke who was now in a coma:

> I then observed that by strongly compressing her eyeballs with my thumbs, a certain motor reaction in the facial region was elicited on the left side of the face, while the other side of her remained completely unchanged. This fact led me to reject the hypothesis of a new lesion of the previously injured hemisphere and to admit that that facial reaction was caused by a process that arose in the left hemisphere in a patient with right-sided hemiplegia (p.619) [81].

He further described the method for performing the test:

> The phenomenon is best determined by compressing the eyeball above the corneal margin with the tip of the fingers, with the eyelid lowered. When the compression reaches a sufficient degree, the contraction of the facial muscles of the same side is aroused, which assume the characteristic attitude of pain: especially the contraction of the muscles innervated by the upper and middle branches of the facial and especially the orbicularis of the eyelids and the elevators of the lip and corner of the mouth. For even greater compression the motor reaction spreads to the opposite side (p.620) [81].

He referred to this phenomenon by the shortened name "bulb reflex" which best described its characteristic features and highlights its clinical utility as a: 1) reflex which is present in patients with coma while its absence is a poor prognostic finding, 2) means to identify the location of an organic hemispheric lesion once peripheral nerve lesions have been excluded 3) if the reflex is present bilaterally than a systemic encephalopathic process (e.g., uremia, toxic) should be considered.

3.14. Peary sign

Admiral Robert Edwin Peary (1856–1920) was born in Cresson, Pennsylvania, US, and graduated from Bowdoin College in Brunswick, Maine with the Computer Engineering (CE) degree in 1877 [82–84]. He served from 1877 to 1879 as a civil engineer in Fryeburg, Maine, a draftsman at the Coast and Geodetic Survey offices in Washington, DC, and in the Engineer Corps with the rank of Lieutenant in the US Navy in 1881 [85]. Peary was assistant engineer in the Nicaragua ship canal which was tasked to identify an alternative route around the Panama Canal from 1884 to 1885, and engineer overseeing the canal surveys from 1887 to 1888 [83–86]. He was awarded the ScD degree in 1894 and LLD in 1910 from Bowdoin College as well as the later degree from Edinburgh and Tufts Universities [83]. He was promoted to Lieutenant Commander in 1901, rank of Commander of the US Navy in 1902, and Captain of the Civil Engineer Corp in 1910 [87]. He began his Arctic exploration in 1886 eventually culminating along with Matthew E Hanson and four Eskimos as being the first persons to reach the North Pole on April 6, 1909 [82]. It is because of this significant accomplishment that he was promoted to the rank of rear admiral in 1911 [86,87]. Among his other accomplishments, awards, and accolades, he was a member of the Board of Overseers of Bowdoin College in 1917, served as President of the American Geographical Society from 1903 to 1907, and President of the International Geographical Congress in 1904 [83]. He was anointed officer of the légion d'honneur, France in 1914 [85], and authored five books including *Northward Over the: Great Ice*, *Snowland Folk*, *Nearest the Pole*, *The North Pole and Secrets of Polar Travel* from 1898 to 1917 [83].

This passage best exemplifies Peary's character as articulated by him in reply to President Roosevelt during the presentation of the Hubbard Medal by the National Geographic Society on December 15, 1906:

> The true explorer does his work for any hopes of record or honor, but because the thing he has set himself to do is part of his being and must be accomplished for the sake of the accomplishment. And he counts lightly hardships, risks, obstacles, if only they do not bar him from his goal. To me the final and complete solution of the Polar mystery which has engaged the best though and interest and some of the best men of the most vigorous and enlightened nations of the world for more than three centuries, and to-day quickens the pulse of every man or women whose veins hold red blood, is the thing which should be done for the honor and credit of this country, the thing which it is intended that I should do, and the thing I must do (p.ix) [88].

Peary described the symptoms of Arctic hysteria, also known as *piblokto*, later found to be due to vitamin A toxicity caused by consumption of polar bear liver:

> The patient, usually a woman, begins to scream and tear off and destroy her clothing. If on the ship, she will walk up and down the deck, screaming and gesticulating, and generally in a state of nudity, though the thermometer may be in the minus forties. As the intensity of the attack increases, she will sometimes leap over the rail upon the ice, running perhaps half a mile. The attack may last a few minutes, an hour, or even more, and some sufferers become so wild that they would continue running about on the ice perfectly naked until they froze to death. If they were not forcibly brought back. When an Eskimo is attacked with piblokto indoors, nobody pays much attention, unless the sufferer should reach for a knife or attempt to injure someone. The attack usually ends in a fit of weeping, and when the patient quiets down, the eyes are bloodshot, the pulse high, and the whole-body trembles for an hour or so afterward (p.167) [89].

Thus, Peary sign refers to vitamin A toxicity caused by the consumption of polar bear liver which contains high concentrations of vitamin A. The link between these symptoms and vitamin A intoxication have been called into question given that the symptoms more closely resemble that due to vitamin D and calcium deficiency [90].

4. Conclusion

A variety of clinical and laboratory-based findings became increasingly recognized beginning in the nineteenth century and later eponymously attributed to the person who first discovered or more thoroughly described the sign. These signs recognized during the clinical or laboratory examination provided further evidence to support the association between various elements, vitamins, toxins, drugs, and their toxic effects. Many of these signs are identified through the meticulous observation and application of various maneuvers during the physical examination, thus reemphasizing the importance of this step in clinical diagnosis.

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Declaration of Competing Interest

None.

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