Historical Review

DESCRIPTIONS OF BLOOD AND BLOOD DISORDERS BEFORE THE ADVENT OF LABORATORY STUDIES

BACKGROUND HISTORY

Since antiquity, blood has been recognized as the essential component of life. Without knowledge of the circulation, ancient Egyptian religion recognized the heart as the seat of the soul and entry into the afterlife depended upon Osiris weighing the heart on the scales of justice. In the New World, the supreme offering to the Incan gods was the beating heart of a human sacrificial victim. In the Holy Bible, Leviticus 17: 11 contains a universal truth about blood, ‘the life of the flesh is in the blood’. Ancient Egyptians believed that bathing in blood was a tonic for rejuvenation and recuperation and, in contrast to this, ancient Hebrew dietary laws were probably based on the knowledge that animal blood could transmit disease to humans. Some Roman gladiators, by drinking the blood of their fallen adversaries, hoped to acquire additional strength and valour. The Christians forbade their followers to ingest blood, and religious hospitals in mediaeval England excluded haemorrhaging, menstruating and pregnant patients. In the fifteenth century, blood was recommended for fits, melancholia, lunacy, palsy and bad disposition, but it was not used for bleeding or pallor.

Greek mythology and blood

In Greek mythology, the Gorgons were horrendous creatures who had serpents sprouting from their heads and whose stare turned beholders into stone. Perseus beheaded their leader Medusa and presented the severed head as a trophy to Athena (Minerva), the Goddess of Wisdom. She had learned that the blood from the right side of the Gorgon could revive the dead while blood from the left side would be the scourge of mankind. Athena favoured Asclepius, the God of Medicine, and gave him some of the Gorgon’s blood (Fig 1). This gift of blood became ‘the gift of life’ and empowered him to revive the dead. Ancient Greek mythology anticipated the future place of blood transfusion in medical care but foresaw that improper blood would inflict suffering (a possible ancient anticipation of transfusion reactions and acquired immune deficiency syndrome). Following the Renaissance, many physicians, polymaths and enthusiastic experimenters attempted various methods in order to administer blood directly or indirectly from animal and human sources into the circulation in order to treat human disease. Louis K. Diamond (1980) summarized the many unsuccessful empirical attempts at transfusion prior to 1901–2 when Karl Landsteiner identified in his laboratory the four basic human blood groups.

The Talmud and the earliest modern haematological treatise

Since antiquity, Rabbis have circumcised all the newborn boys in their congregations; they had a unique opportunity to observe the presence of operative and postoperative bleeding. Dr F. Rosner (1977) reviewed haemophilia in the Talmud and reported that Rabbi Judah (?135–?220) taught in the Babylonian Talmud that if two successive brothers bled to death following circumcision then the third son of the same mother is excused from circumcision. This led to the development of formal laws allowing rabbinical exception from circumcision for new offspring whose brothers had died from post-procedural haemorrhage. Maimonides (Moses ben Maimon 1135–1204), a physician and talmudist from Cordova, Spain, recognized that a mother bearing children with the disorder would transmit the disease to all male offspring, even if conceived by different fathers. Rabbis had identified the carrier state of haemophilia, two millennia before Mendel and the clotting time.

Greek philosopher physicians

The study of nature by ancient Greek physicians included the study of both medicine and philosophy. Aristotle observed that one might begin with philosophy but would end with medicine or begin with medicine and end with philosophy. Pythagoras, Empedocles, Alcmaeon, Hippocrates, Plato, Aristotle and Socrates are just a few of the philosophers. Some were more clinical in their interests while others were more concerned with philosophy. Their studies attempted to explain disease as a result of the forces of nature rather than displeasure of the gods. However, a surviving text of each paradoxically recorded their simultaneous belief and worship of Asclepius, the Greek god of medicine (Hart, 2000).

Pythagoras and favism

Pythagoras was a polymath who established his school at the Dorian colony of Croton in Southern Italy c. 529 BC. He believed that illness was the result of an imbalance between body and soul. Diet and music created a favourable disposition but gluttony adversely affected harmony and health. He and his followers adopted strict dietary regimens for the maintenance of health and they specifically forbade the eating of beans. Today, residents of this same area of Southern Italy have the highest incidence of Mediterranean-type G6PD enzyme deficiency. It is probable that this genetic
trait was present in ancient times and Pythagoras witnessed attacks of explosive haemolytic anaemia occurring in local residents who had ingested fava beans. Unfortunately, no written clinical descriptions survive. This dietary observation probably influenced followers of the Cult of Demeter (goddess of the harvest) to restrict the eating of beans.

**Malaria in the ancient world**

Empedocles of Acragas in Sicily (≈490–430 BC) was a disciple of Pythagoras. His philosophy was based on all matter being formed from fire, water, air and earth. Each of these basic elements possessed the characteristics of opposites, namely hot and cold, dry and moist. Empedocles is credited with relieving the recurring epidemics in the Sicilian city of Selinus located on the banks of the Selinus and Hypsos rivers. He recommended joining the rivers surrounding the city so that the marshes would be drained and the recurring epidemics (undoubtedly malaria) relieved. This major public health measure was recorded and celebrated on beautifully illustrated coins (Fig 2.). The circulation of these coins around the Mediterranean world would have spread the public health message.

The writings ascribed to Hippocrates are in reality the thoughts of not only Hippocrates but also various Hippocratic practitioners from his school on the island of Cos. These were written from the fifth to fourth century BC, and 70 or so of these were compiled into the *Hippocratic Corpus* at Alexandria around 200 BC. The Treatise of *Airs, Waters and Places* translated by W. H. S. Jones (1984) stated that people living near marshy water were noted to have large stiff spleens, protuberant abdomens, emaciated facies and shoulders: they were noted for suffering summertime epidemics of dysentery and long quartan fevers. With dry summers the disease ceased more quickly, but with rainy summers the fevers were more protracted.

The airs associated with the waters were thought to be responsible for the epidemics, but they ignored the mosquitoes inhabiting the air (anyone living in mosquito-infested areas is familiar with the effects of climate on the mosquito population).

The fevers were described as intermittent and remittent. The intermittent variety occurred in quotidian, tertian or quartan patterns. The remittent pattern was accompanied by a sensation of intense heat, pain in the hypochondrium and delirium. Patients with cachexia and enlarged spleens were noted to have a dark complexion and suffered from weakness. The treatises do not have any specific treatment recommendations.

The lowly mosquito defeated Alexander the Great, the conqueror of the ancient world. A few days before his death he became lost in the swamps around Babylon where he acquired a febrile illness, became delirious and died. The probable cause of death was cerebral malaria.

Marcus Terentius Varro (≈100 BC), a Roman scholar, postulated that tiny animals inhabiting the marshes entered the body and caused the disease. There were many marshes and landlocked lakes around Rome. Over the years attempts were made to drain them and make the land habitable and healthy. This public health manoeuvre was commemorated on coins. One of these minted by Emperor Trajan (98–117 AD) commemorated draining a portion of the Pontine Marshes, and Emperor Hadrian (117–38 AD) celebrated early efforts to drain Lake Fucinus by minting a coin depicting a farm labourer standing upon a pump. These two coins minted by successive emperors suggest a coordinated long-term public health project.

**Hippocrates and the physiological basis for blood-letting**

Hippocrates incorporated the four qualities of universal matter (hot/fire; cold/earth; moist/water; dry/air) with the concept of the balance of opposites in order to explain the physiology and pathology of health and disease. The four essentials of life became the four humours, which were blood (hot/moist), black bile (cold/dry), yellow bile (hot/dry) and phlegm (cold/moist). Illness occurred when an external cause upset the balance of the humours. The body reacted to this alteration and attempted to correct the imbalance by mixing (physically and chemically blending) the constituents in order to recreate a perfect fusion of all the humours without any excesses remaining. The process was called ‘coction’ and its occurrence was accompanied by a crisis whereby the remaining excesses were expelled by means of fever, sweating, urination, defaecation, expectoration and vomiting. Sometimes the usual means of evacuation were not successful and the excesses accumulated locally.
Haematological knowledge in ancient medical practice

The ancient philosophers agreed about blood and its function and their views were upheld for nearly two thousand years. Galen (on Natural Faculties translated 1952) and Celsus (De Medicina translated W. G. Spencer, volume I, reprinted 1960) summarized these beliefs. Haematopoiesis occurred in the veins in which nutrients in proper balance were converted by innate body heat into blood. The lack of body heat resulted in decreased production of blood, and severe chilling of the whole constitution produced dropsy (a possible clinical description of heart failure complicating severe anaemia). Galen (tr. 1952) argued that attention should be focused on the different kinds of foods suitable for blood production rather than on the process of its formation. A person’s complexion reflected the presence of thick and thin blood (polycystaemia and anaemia). The bone marrow was thought to nourish bone in the same way that blood nourishes flesh and muscle. Although the nourishing qualities of marrow were recognized, it was not associated with haematopoiesis.

Blood was purified by the spleen and gall bladder. The spleen had the power of altering and retaining all that it attracted (compatible with phagocytosis and antibody formation). In general, all nutrients belonging to the thick and earth-like portion of food were not altered by innate heat and were drawn to the spleen. The spleen of a healthy person wasted (atrophied), while the presence of suppuration in the body caused the spleen to enlarge and discharge evil humours (black bile). Jaundice associated with a malfunctioning spleen was darker in colour and the accompanying blood was darker and thicker. Liver disease was recognized as a cause of splenomegaly. Celsus (tr. 1960) made one reference to a rural method of reducing splenomegaly which was the taking of water in which the blacksmith from time to time had dipped his red hot iron († treatment of the splenomegaly that may on occasion accompany iron deficiency). The eating of ox spleen was beneficial to splenomegaly and it was recorded that animals raised by blacksmiths had small spleens. In autumn there were irregular fevers accompanied by splenic pain and a variety of local poultices were recommended for this. Caution needed to be taken in order to avoid burning the skin. Radiation of pain from the spleen to the clavicular area was recognized and a penetrating wound of the spleen was described with haemorrhage of dark blood, signs of peritoneal irritation, increased thirst and death.

\textbf{Plumbism}

Marcus V. Pollio Vitruvius was one of the greatest Roman architects of the first century BC. His work De Architectura was studied by the great architects of the Renaissance and continues to be studied today. He was interested in water supplies and recognized that the water from lead pipes was not as wholesome as that from clay pipes. He commented that lead workers had complexions affected by pallor occurring because the lead fumes robbed the limbs of the virtues of blood (compatible with mild hypochromic anaemia).

The Romans used lead in their plumbing, metallurgy and pottery; they also used sugar of lead (lead acetate) as a sweetener for desserts and an additive to wine.

Bone lead studies of excavated skeletal material show that plumbism was prevalent in the ancient world and Gilfillan (1965) speculated that the various effects of lead poisoning were responsible for the decline and fall of the Roman Empire. At the factual level of everyday life, bone lead levels were studied on skeletons from the Romano–British Cemetery excavated at Poundbury, Dorset. Molleson and Farwell (1993) and Waldron et al (1976) demonstrated that 50% of the bones studied had significantly high lead levels; some of the childhood lead levels suggested that this was the cause of death.

Celsus (tr. 1960) described the use of lead in various forms as an external medicament for bleeding, as an emollient for burns and ulcers, for cleansing wounds, for headaches and joint pains. Pliny stated that a cold plate of lead on the loins cooled the venereal passions and libidinous dreams. Although understanding its metallurgical properties, they ignored its toxic properties to the human body. Celsus’s only help for lead poisoning was to recommend mallow or walnut oil rubbed up in wine, but Galen and the great medical writers of the Roman Empire did not offer any advice about the prevention of plumbism.

Modern readers must not scold the Roman medical greats for turning a blind eye to preventative health; their inaction is reminiscent of the majority of modern physicians who up until recently ignored the known facts about the harmful effects of smoking!

\textbf{Asclepiades and anticipation of microscopic particles}

Asclepiades (first century BC) was the founder of the Methodists, who were one of several groups of post-Hippocratic medical practitioners. They believed that the healthy body was composed of moving atoms of various sizes imperceptible to the human senses. These flowed continuously in body fluids and through body pores. Themison, a pupil of Asclepiades, emphasized the importance of the body pores being either contracted or relaxed and stated that disease resulted from alterations in the size of their openings. Their system of therapeutics was directed at relaxing or contracting body pores by means of diet, heat,
cold, poultices, hot or cold air, styptics, medicines and bleeding.

Haematologists can readily relate to Asclepiades. His insensible atoms of varying size are compatible with the cellular constituents of the blood and could also include coagulation factors, proteins of various types and electrolytes. The contracting and relaxing pores may have extended beyond sweat pores in the skin to the capillaries and the continuous flow of the atom is compatible with the circulatory system!

Bleeding, cupping and leeches
Bleeding the patient became one of the mainstays of treatment for two thousand years. Physicians became blinded by the philosophical dogma of the Hippocratic School, which advocated bleeding as a method of restoring harmony of the humours and hence health. It was used especially with fevers in order to reduce body heat. The recommended site of incision was chosen from a background of astrological associations with body parts and the timing of the procedure coincided with the phase of the dog-star and other planets (Lazenby, 1993).

Galen (tr. 1952) was less enthusiastic in its use and recommended removal of only small volumes of blood. In recent times, Benjamin Rush (1745–1813), one of the signatories to the American Declaration of Independence, was profligate in its use during the 1793 Philadelphia yellow fever epidemic and contributed to the high mortality rate. The procedure had, at best, a placebo effect and often aggravated the underlying disease and decreased already borderline body iron stores.

Greek and Roman doctors used bell-shaped vessels of bronze or glass as well as animal horns with a hole in the pointed end. Cupping was performed by applying the heated bell over an incised vein or to an area of inflammation; with cooling, a negative pressure (vacuum) developed making it a suction apparatus. Dry cupping described its use as a counter-irritant without an incision. Wet cupping was used with an incision and the vacuum would remove blood or pus.

When a horn was used, the operator sucked through the narrow end in order to produce the necessary negative pressure for aspiration, then sealed the end with wax.

Cupping vessels became the symbol of the physician (Fig 3). Bleeding (venesection) involved an incision over a vein and the blood was collected into a bowl (Fig 4). In the eighteenth century this procedure was also called breathing a vein.

From the Middle Ages until the end of the nineteenth century, barber surgeons used specially designed bowls of pewter, silver or porcelain (the choice of material and artistic decoration varied with the wealth of the clientele). These bowls had a concave notch in the rim designed to fit the contour of the arm or neck and were used for either shaving or bleeding a client. This double use had limitless possibilities for transmission of infection!

Bleeding bowls for physicians and surgeons were marked with gradations; some had a capacity up to 700cc. These ‘professional bowls‘ did not have a notch in the rim.

Pliny was the first to record the use of leeches and sporadic use continues today. Carter (2001) reviewed their use in the nineteenth century when the demand for leeches almost depleted European supplies. Leeches were more useful in decreasing areas of inflammatory congestion rather than removing large volumes of blood and they had particular value in areas of limited access, such as the rectal and intratroital areas.

BONE MARROW BY EXCAVATION: CRIBRA ORBITALIA AND POROTIC HYPEROSTOSIS
Examination of an excavated skull in order to assess changes as a result of marrow hyperplasia is an essential component of modern osteology. This is the archaeologist’s counterpart to the physician’s marrow aspiration.

Cribra orbitalia (CO) are the earliest visible bone lesions of childhood marrow hyperplasia appearing as sieve-like...
openings (cribra) in the roof of the orbital fossa. They are produced by profound erythroid hyperplasia occurring around 6 months of age and become most marked at the age of 4 years. The marrow cells in the cancellous bone of the supraorbital plate hypertrophy making the depth of the roof greater than 3 mm and resulting in pressure atrophy with perforations of its external bone plate. The perforations are initially pinhead in size but may expand and coalesce producing lesions several mm in size, rendering underlying trabeculae visible. Stuart-Macadam (1989) classified the perforations into four groups (Fig 5). Continued increasing marrow hyperplasia results in similar lesions occurring in the cranial vault which are called porotic hyperostosis (PH) (Angel, 1967). These visible vault lesions result from hypertrophy of the diploë (hyperostosis) widening the diploic space and thinning the outer plate of the skull. The haemopoietic activity may spread under the periosteum and perforate it, allowing direct visualization of thickened trabeculae and expanded marrow spaces (Fig 6.). Trabeculae of bone grow along the course of blood vessels in a radiate fashion perpendicular to the outer plate of bone, causing the hair-on-end lines seen on X-rays.

The porosity of the surface of the skull (sieve- or coral-like appearance) is usually similar to the lesions in the orbit. It may be present in the frontal, parietal and occipital bones. Sometimes there is no accompanying cribra orbitalia, indicating healing of the original lesions or possible absence of haemopoietic tissue in the orbital plate.

PH also begins in infancy and is not initiated in adult life. When severe marrow hyperplasia continues into adulthood...
or only begins in adulthood, the medullary cavities of long bones are involved as well as extramedullary haematopoiesis. The lesions of PH are most severe in thalassaemia major, resulting in decreased pneumatization of the sinuses and secondary facial changes. Long bones are frequently involved with shortening and change of shape accompanied by invasion of the epiphyseal diploë. Vertebrae may be weakened with resulting disc herniation and collapse. Sickle cell disease and its variants also produce severe lesions and may have accompanying infarcts (visible when bones are held against a bright light). Other forms of congenital haemolytic anaemia may result in lesser degrees of bone change. If severe marrow hyperplasia begins in adult life, then CO and PH do not occur.

**Thalassaemia and malaria, an archaeological diagnosis from ancient Greece**

Angel (1966) demonstrated the social influences of thalassaemia and malaria in the Eastern Mediterranean. Skeletal remains from advanced hunter social groups (15000–8000 BC) had a 2% incidence of PH while those of early farmers (6500–2000 BC) had a 50% incidence. Skeletal remains of proto-city dwellers (2000–1200 BC) had a 12% incidence of PH and city state dwellers (650–300 BC) had a 2% incidence.

The incidence of PH among early farmers increased because they favoured low marshy soils, the habitat of malaria-carrying mosquitoes. Persons with thalassaemia, sickle cell anaemia and G6PD enzyme deficiency were resistant to malaria and had a selective survival. This conclusion is also supported by the rarity of PH in high dry areas unfavourable to mosquito populations and at low risk of malaria. Angel (1966) confirmed his conclusions by the 41% incidence of PH in the marshy areas of Catal Hüyük (Turkey) and 60% in similar areas of Macedonia, compared with the 9% incidence of PH in the dry rocky areas of Khirokitia (Cyprus) and the 11% incidence in Kephalaia.

**Geographic effects on dietary anaemia**

El-Najjar & Robertson (1976) found a 54% incidence of PH among Indians living in the canyons of Northern Arizona and New Mexico, whereas Indians living on the plains of Southern Arizona and New Mexico had a 14-5% incidence of PH.
The difference is explained by the availability of food. The canyon dwellers had iron deficiency owing to a diet containing little meat and consisting mostly of maize. This cereal is low in iron and the high phytate content of the husk inhibits iron absorption. The incidence was higher in children than in women and was lowest in men. In contrast, the plains’ Indians had ready access to additional animal food sources and their better diet resulted in a lower incidence of childhood anaemia.

Anaemia in Roman Dorchester (Durnovaria)
Between 1966 and 1982, 1450 skeletons were excavated from the Poundbury Romano–British cemetery located outside the western walls of Durnovaria (Molleson and Farwell, 1993). Stuart-Macadam (1989, 1991) studied bones from the initial 1000 excavations. Of these, 30·6% had PH and/or CO, indicating a high incidence of childhood anaemia probably as a result of iron deficiency. The author also felt that there was a high incidence of maternal and infant mortality.

There was a predominance of adult males with evidence of severe childhood anaemia. This was greater than expected and was not explained by the list of possible causes. A similar incidence of CO and PH with male predominance was found among Roman skeletons excavated at Cirencester. If iron deficiency in childhood produced these bone changes, Calvin Wells (McWhirr et al., 1982) made the suggestion that the increased incidence in males might be related to girls and women having more to do with food and ‘having opportunities to filch choice morsels from the stew-pot and to maintain a level of protein intake which gave them some protection against anaemia’.

Iron therapy during the fourth century at Lydney, Gloucestershire, England
At Lydney, Gloucestershire, there are the remains of an Asclepian style temple built in the fourth century AD. These are located on the summit of a hill formed from red ferruginous limestone; this was also the site of iron-mining activity in ancient times and is the location of the only intact Roman iron mine in Britain (Fig 7).

Wheeler and Wheeler (1932) excavated the temple in 1927 and concluded that it was a healing centre. They found an inscription that dedicated the temple to the Roman God Mars and the Celtic God Nodens. Mars was the Roman god of war and strength; iron was considered his gift to mankind. Red symbolized the element iron and rusty iron would impart its colour to water. It was believed that iron had acquired its strength from the god Mars and it was likely that pilgrims suffering from weakness believed that they would acquire some of Mars’ strength by ingesting the temple waters discoloured by the presence of iron.

During their excavation, the Wheelers excavated a unique bronze votive arm and hand. The arm was crude but the hand was detailed with the nails showing concavities in both the longitudinal and lateral axes (Fig 7). The nails are spoon-shaped (kollonychiae), a condition most commonly caused by severe tissue iron deficiency.

Votives depicting the diseased part were given to healing deities in order to focus attention to the diseased area or as a gift-offering indicating cure. Hart (2000) reviewed votives and divided them into mass produced and custom types. Would ancient artists have been asked to make a custom votive depicting kollonychia? If they had, then the probability of this occurring at Lydney would have been high.

A temple reputed to impart strength to its supplicants would attract pregnant women who desired strong healthy children and who themselves might benefit from some extra strength. Wheeler and Wheeler (1932) confirmed this conjecture from their excavated small finds that indicated a large female clientele. One of these depicted a bone figure with hands on her waist suggesting relief in childbirth. There were 320 votives of bronze and bone similar to those favoured by women in ancient Greece as a form of votive offering made to their special divinities at the time of childbirth. Other feminine ornaments, such as brooches and bracelets, were similarly used throughout the classical world and over 300 of these were also excavated at Lydney.

There is no doubt that the local water at Lydney and the iron-rich soil would treat iron deficiency. The votive depicting kollonychia is a unique archaeological find and by serendipity represents the earliest evidence of specific treatment of iron deficiency.

The osteological studies from Cirencester and Dorchester (supra) confirm the presence of iron deficiency in Roman Britain. Greek and Roman medicine did not consider the
Archives and Museum, St. Bartholomew’s Hospital, London.

Celsus stated that iron was used externally to arrest haemorrhage, to clean and heal wounds, and made one reference to it’s oral use as a rustic remedy for an enlarged spleen (Celsius, Spencer W.G. translation 1938, vol II xxxiii). In Owsei Temkin’s translation of Gynaecology (Gynaecia) written by the second century gynaecologist Soranus (Temkin, 1956), there is a description of what is recognized today as a rare complication of iron deficiency: ‘pica is an appetite for things not customary like earth, charcoal, tendrils of the vine and unripe and acid fruit’. Many of the female supplicants at Lydney might have experienced these symptoms and they may have taken some iron-laden soil home as an effective remedy for their geophagia. Unfortunately, although the ancient master of gynaecology recognized pica, he did not have any specific recommendations for treatment.

CHLOROSIS AND PALLOUR

Chlorosis, as a medical condition, was first described in the sixteenth century. The earliest reference to chlorosis (Latin for green) was the epithet applied to Emperor Constantius Flavius (Constantius Chlorus). He was born ≈ 250 AD of Illyrian origin and died at York 306 AD. Other descendants of his dynasty including his son Constantine the Great were not assigned this appellation. Constantius’s military career did not suggest he suffered from significant anaemia. He may have had a mild congenital haemolytic anaemia or even a mild benign hyperbilirubinaemia.

Historical support for the disease comes from Shakespeare’s numerous references to the ‘green sickness’ ‘...for thin drink doth so over-cool their blood, and making many fish-meals, that they fall into a kind of greensickness.’ Falstaff. 2 King Henry IV. iv. iii (1597). Many prominent clinicians discussed the condition and numerous artists portrayed it. Johannes Lange (1485–1566), a prominent Dutch physician, described the signs and symptoms of severe anaemia in 1554. His patient was a young girl whose complexion had become pale and suffered from palpitations and dyspnoea with exertion; there was no mention of a green complexion. She had anorexia and a loathing of meat. He called the disease morbus virgineus caused by retention of menstrual blood and recommended marriage with pregnancy as treatment. The anaemia described by Lange was often falsely described as chlorosis. Many subsequent physicians thought the disease was hysterical in nature and related to suppressed sexuality. Many others described the condition, including Osler (1892), who stated in the first edition of the Principles and Practice of Medicine:

‘the complection is peculiar; neither the blanched aspect of haemorrhage nor the muddy pallor of grave anaemia, but a curious yellow green-tinge which has given the name to the disease’. Contemporary 17th and 18th century artists recorded the chlorosis in clinical colour, especially those of the Dutch School, i.e. Di Haarlem’s grand classical scene Il Manigrismo depicting various nudes, including a young beauty with pallor and a faint greenish tinge in a somewhat neurotic pose beside two other nudes with normal skin colour. William Hogarth also supplied an illustration in his 1737 mural The Pool of Bethesda located above the Great Staircase at St. Bartholomew’s Hospital. Hogarth lived adjacent to the hospital and portrayed around his ‘Pool of Bethesda’ actual patients he had seen in and around the hospital. Many of them have recognizable diseases: the patient depicted in Fig 9 shows the signs of malnutrition and has a pale and sallow complexion faintly tinged by green.

The frequency of its diagnosis increased until the end of the nineteenth century. Crosby (1987) reported that, in the 1890s, this condition accounted for 16% of the admissions to St. Bartholomew’s Hospital, London, and to St. George’s Hospital, Hamburg, Germany. The incidence rapidly declined in the early twentieth century and disappeared over a span of 10 years. In the 1950s, most haematologists were sceptical of its existence. Fortunately for modern day haematology, Dr W. Crosby (1987), a well-known American teacher and researcher, confessed his doubts about the condition until he saw a case in 1955 at the Walter Reed Hospital, Washington, DC. The patient was a 35-year-old woman with severe iron deficiency as a result of menorrhagia. The heart was dilated, the legs were oedematous and her face was green. She was started on iron and the greenness rapidly disappeared before the iron had made any substantial improvement in her anaemia. Dr Crosby discussed the pathogenesis and, without this record, the existence of the condition would have continued to be doubted and no one would be able to give a factual explanation.

Dr Crosby concluded that chlorosis resulted from a diet low in both protein and iron. These deficiencies affected both the melanocytes of the skin and the haemoglobin of the red cells.

‘Melanin is not really black but is dark brown and very little melanin spread thin, might seem yellow, and that, combined with the pale, reduced haemoglobin in anaemic blood might produce green.’ A more wholesome diet and the ready availability of iron preparations is credited with the rapid disappearance of the condition in Western countries. Dr Crosby’s observation that the chlorosis disappeared before any substantial improvement in the
anaemia indicates that only a minute nutritional improvement erased the green complexion and relegated the condition to the history books and to art collections.

Chlorosis and Thomas Sydenham

Thomas Sydenham (1624–1689) was known as the English Hippocrates (Fig 10). He acquired this title by describing diseases as they presented at the bedside and by advocating that doctors rely upon their own observations and clinical experience. He accepted chlorosis as a manifestation of hysteria, but in 1681 advocated treatment by iron which ‘gave a spur or fillip to the animal spirits which are raised up and excited’ (Latham, 1850).

He practised gentle bleeding and purging with some patients, but for weak and worn out patients he recommended that this traditional therapy be omitted. After 30 d of ‘steel’, ‘the pulse gains strength and frequency, the surface warmth, the face (no longer pale and death like) a fresh and ruddy colour’.

This was the first prescription of iron as a specific oral medication for iron-deficiency anaemia. He made this recommendation 32 years before Lemery and Geoffy demonstrated the presence of iron in the ash of blood and 151 years before Faedisch demonstrated the deficiency of iron in chlorotic blood (in 1832).

Paradoxically, not only did the laboratory confirm that Sydenham was correct but also went on to offer pseudo proof that inorganic iron could not be absorbed or incorporated into haemoglobin. Such was the enthusiasm for laboratory medicine that Sir William Osler (1911), in his 1911 edition of Principles and Practice of Medicine, stated ‘since iron is present in the faeces of chlorotic patients before they are placed on treatment, it follows that the disease does not result from a deficiency of available iron’. It was not until the 1930s that the work of Castle and colleagues convinced the profession of the value of iron. After many decades of success with iron therapy, the laboratory was responsible for 60+ years of denying chlorotic patients specific therapy for their anaemia.

Sydenham’s foresight and inspiration was the first specific therapy for most common anaemia in the ancient and modern world. He did this unaided by the laboratory and deserves recognition as the Father of Clinical Haematology.

REFERENCES


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