SOME NINETEENTH-CENTURY PIONEERS OF HAEMATOLOGY*

by

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In the course of the nineteenth century, the foundations of our modern understanding of the blood were laid. The part played by the cell in the body's economy was worked out, particularly by Virchow,[1] and this permitted a rational understanding of the nature and role of blood cells. Technological advances such as the refinement of microscopes and the development of staining techniques enabled the morphology of the three formed elements of the blood to be described precisely, both in health and disease. Quantitative methods of blood examination were devised including techniques for counting erythrocytes and leucocytes and for determining the iron concentration, oxygen and carbon monoxide capacity and haemoglobin content. Variations in the ratio of haemoglobin content to red-cell numbers in disease were studied and the correlation of these variations with morphological changes in the cells were defined. Classical descriptions of a number of haematological syndromes were published.

It was, in fact, an exciting period in the development of haematology as well as of medicine as a whole. However, I do not propose to tell here the history of the discoveries themselves. My purpose is to tell the stories of a select few of the many hundreds of people who made significant contributions to haematology in the nineteenth century.

Naturally, any such selection is a matter of personal judgment and preference and I have chosen those workers whose contributions lay in general haematology and in the laboratory study of blood rather than those who described specific haematological syndromes. One other factor has influenced the selection. Preference has been given to those whose contributions to haematology are less well known but equally praiseworthy, rather than to those about whom a great deal has been written. For convenience, I have grouped the various people to be discussed according to their nationalities and as it was the French group who first studied the blood on a large scale, it is with workers from that country that we shall begin.

GABRIEL ANDRAL (1797–1876)

To assess the place of Gabriel Andral in haematology, some understanding of the state of medicine in France in his day is needed. In the first thirty years of the nineteenth century, French medicine enjoyed a high reputation and we need only mention such names as Bichât, Corvisart, Larrey, Laënnec, Dupuytren and Magendie to realize the tremendous contributions to medical science made by Frenchmen at that time.

On the other hand, there was a dominating personality in France in those days

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whose effect on French medicine was anything but progressive. Ex-Army Sergeant and Professor of Medicine at Paris, François Joseph Victor Broussais imposed on his contemporaries the dogma that most diseases were the result of irritation and he laid particular stress on irritations of the gastrointestinal tract. His theories had practical implications because he believed that irritation should be counteracted by depletion, either by purging, by general blood-letting or by leeches. As a result of his teaching, the sale of leeches in France reached astronomical figures. The net imports of leeches into France in 1834 were 21,000,000. In considering the forces that moulded Andral's thinking, Broussais' teaching must be given pride of place.

Andral,[2] twenty-five years Broussais' junior and his successor to the Chair of Medicine, was first a follower of Broussais, but later reacted against his views and became an adversary. He described himself as an 'eclectic'. This meant, by his definition, that he believed in selecting the best features of all past schools of medical thought and incorporating them in his own theory and practice. In other words, he did not want to be bound to any particular school or system. Andral achieved fame in both clinical medicine and pathology. Passing his 'concours d'agregation' in 1823, he was elected to the Academy of Medicine in the same year. In 1828 he was elevated to the Chair of Hygiene and in 1830 became Professor of Internal Medicine in Paris. Among his contributions to medical literature his *Clinique médicale* appeared in 1824 and his *Précis d'Anatomie pathologique* in 1829. The article on blood in the *Dictionnaire de Médecine et de Chirurgie pratique* of 1835 was written by Andral in association with his colleague, C. Forget of Strasbourg, and in 1843 a considerable portion of the material in this essay appeared as a definitive work on haematology, *Essai d'Hematologie pathologique*.

Not only did Andral oppose exclusive systems of medicine such as that of Broussais. He also reacted against another tendency, good in itself, but harmful when taken to extremes to the exclusion of other aspects of medical science.

The work of Morgagni, Baillie and Bichât in particular, had focussed attention on the structural changes in disease. Andral felt that the emphasis on these changes in the 'solids' had overshadowed important studies on the variations in the body fluids in health and disease. He set out to rectify this situation and devoted considerable attention to what he called 'neo-humoralism'. Unlike the ancient humoral theories, his neo-humoralism was based on scientific chemical studies of the body fluids. The fluid that he paid particular attention to was the blood and so he became an important pioneer of haematology.

Space prevents a detailed account of his contributions to the study of the blood which has been the subject of an earlier paper.[3] Before leaving Andral, I would like to mention a strange twist of fate. In 1868, Louis Pasteur, while addressing a scientific meeting, was stricken with paralysis. Andral was called and prescribed the application of sixteen leeches behind the ears, thus rendering belated homage to his old antagonist, Broussais.

ALFRED DONNÉ (1801–1878)

A contemporary of Andral's was Alfred Donné, who made a number of contributions to medical science, including some that have become so much a part of everyday

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practice that we have largely forgotten their origins.[4]

He was born on 13 September 1801, at Noyon in the Department of the Oise. When he was twenty, the family moved to Paris where he commenced the study of law, but, developing a dislike for that discipline, he turned to the study of medicine at the age of twenty-five. At the age of thirty he presented his thesis for his doctor's degree. Donné came from a well-to-do and well-connected family, and in the course of time, won the favour of the royal family. Because of this, the post of Inspector General of Medicine was created for him. Later, he became Rector of the University of Strasbourg for ten years and then transferred to Montpellier for nineteen years.

Of Donné's many contributions to medicine, undoubtedly his greatest was the work he did in promoting the use of the microscope in medical practice and more particularly in medical teaching. He established a course on the microscope. In his classes he would set up twenty microscopes, each labelled with the objects on the stage, which the students could examine in turn. He also was active in promoting the use of the microscope at the bedside.

It should be mentioned that in the early nineteenth century, many of the leading figures in medicine looked on the microscope more or less as a toy. Thus, Bichât, the founder of the science of histology, had relied on naked-eye examination of the tissues and their chemical treatment, while Magendie, until he was finally convinced to the contrary, had regarded the appearances seen under a microscope as optical illusions. Thus, Donné had a certain amount of prejudice to overcome in his popularization of the microscope.

Donné devoted a considerable part of his microscopic researches to the study of body fluids, including blood, pus, mucus and milk. In 1844 he published his *Cours de microscopie*, along with an atlas that he produced in association with Léon Foucault which was of considerable importance in the history of haematology and of book illustration. In this atlas, he took advantage of a new invention in which he was intensely interested.[5] When on 19 August 1839 the astronomer, François Arago,[6] presented Daguerre's discovery of photography to the Academy, one of the people who embraced the new art with enthusiasm was Donné, who saw in particular, its possibilities in photomicroscopy. He suggested a fairly accurate theory of the nature of the photographic process.[7] He produced the first successful etched photographic plates,[8] the first portrait photograph[9] and the first photomicrograph.[10]

He used photomicrographs to illustrate his atlas but as his photo-engraving process was not adequate for the purpose, he had to employ an engraver, Monsieur Oudet, to produce the blocks from them by a conventional engraving process.

His microscopic studies led him to the study of milk, seminal fluid, urine and vaginal discharges. He described trichomonas vaginalis and milk globules and thought he had discovered the causative organism of syphilis. He invented a lactoscope and in association with the optician, Monsieur Soleil, he constructed a pocket microscope for bedside use. [11] His was one of the early descriptions of blood platelets.

The credit for the first description of leukaemia is generally attributed either to John Hughes Bennett (once a postgraduate student of Donné's) or Rudolf Virchow. Both published reports in 1845. However, in 1839, Donné had examined a case at the Hôtel-Dieu with hypertrophied spleen but had not published anything about it until

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much later. Moreover, in 1844, one year before Bennett or Virchow, he had described a case in the following words:

> The patient's blood presented such a quantity of white blood cells that considering the nature of the affection, I was led to believe that the blood was actually mixed with pus, but in fact it was not possible for me to determine any significant difference between these globules and the white globules and indeed one could not find at autopsy, any trace of pus in the vessels or in the clot. In recalling that I have frequently observed an analogous condition in the blood of individuals in whose blood one could not suspect the presence of pus, I am led to believe that the excess of white globules is mainly the result of a defect in their transformation to red globules, a sort of arrest in the evolution of the blood, which results in the presence of foreign globules like those of pus. It is, in fact, in patients affected by severe enfeebling lesions deteriorated by a prolonged morbid process which disseminated the trouble throughout the whole economy, but in particular, on the processes of nutrition and assimilation where one meets these white globules in excess. According to the theory I have just propounded on the origin and mode of formation of the blood globules, the superabundance of white globules is only natural in the circumstances; it will then only be, I repeat, the result of an arrest of development in these transitory particles.

Enough has been said to show that Alfred Donné is to be numbered among the great medical discoverers of the nineteenth century and that posterity is in his debt for many everyday pieces of knowledge that we take for granted.

LOUIS CHARLES MALASSEZ (1842–1909)

One of the most energetic workers in the field of laboratory haematology in the mid-nineteenth century was Louis-Charles Malassez. He devised two methods of blood counting,[12] invented a haemoglobinometer and studied the haemoglobin content of erythrocytes as well as the spleen and tumours. His name is perpetuated in Malassez's Disease, a cystic anomaly of the testis.

Apart from his personal contributions to haematology, an account he has left of earlier work[13] is an important contribution to the history of the subject.

Malassez was born on 21 September 1842, at Nièvre. He studied in Paris where he was a pupil of Claude Bernard and of Ranvier and received his doctorate in medicine in 1873. In 1875 he became Associate Director of the Histological Laboratories of the Collège de France. He died in Paris on 22 December 1909. A dedicated and unobtrusive laboratory worker, he has been likened to the artisans of the middle ages and the renaissance who spent their lives perfecting and polishing some masterpiece with their own hands.

GEORGES HAYEM (1841–1933)

Of all the French haematologists of the nineteenth century, there was none greater than Georges Hayem. Indeed, it is difficult to think of anybody else in the nineteenth century in any country, who more fulfilled our modern ideas of a general haematologist. Others made important contributions to the subject but Hayem was the complete laboratory and clinical haematologist and as such, was unique in those days. He did more than anybody else to father the discipline. Yet, such is the way of history that his name has only recently been rescued from comparative oblivion even though laboratories throughout the world have used 'Hayem's solution' as a diluting fluid for blood counts ever since his day.

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This position was rectified some years ago by the appearance of Dreyfus' book, *Some Milestones in the History of Haematology,* in which the author devoted a chapter to Hayem.[14]

Hayem, the son of a successful Jewish businessman, was born in 1841. However, the family had a strong medical tradition and preserved with pride the portrait of an ancestor of Hayem's, Isaie Ulman, medical practitioner of Metz, who had treated Louis XV for severe dysentery and while doing so had gained improved conditions for the Jews in Lorraine.

Georges Hayem commenced his medical course in 1861 and completed the two-year course in one year. He commenced his internship in 1863. In 1867 he received the Gold Medal of the Academy of Medicine and in 1872 he was accepted as a physician and licensed to practise. He became titular professor in 1879. He first made his reputation in the cholera epidemic during the siege of Paris when he treated and saved many patients by the use of intravenous infusions and won for himself the name of 'Dr. Cholera'.

As mentioned above, Hayem's contributions to haematology embraced every facet of the subject but certain aspects of his work deserve special attention. He invented a haemocytometer for counting blood cells. In this instrument he relied on a ruling in the eye-piece of the microscope as in the original counting chamber devised by the Dutchman, Cramer, and not in the counting chamber itself. He used 'Hayem's solution' for diluting the cells. He also used a similar type of apparatus as a haemoglobinometer in which the colour of the diluted blood was compared with papers of graded colours. He studied microscopically the size, shape and colouration of blood cells in health and disease and correlated their appearances with the red cell count and haemoglobin.

In emphasizing the importance of the variations in the ratio of the red cell count to the haemoglobin, he put forward for the first time, the concept of the colour index.

Hayem also identified the platelets and their role in coagulation. Apart from his laboratory work he left a number of clinical descriptions of blood disorders and in particular, he classified a number of haemorrhagic states. He has left two major works on haematology, *Du Sang et ces alterations anatomiques* which appeared in 1889 and *Leçons sur les Maladies du Sang* which appeared in 1900.

Thus, he was a giant among the haematologists in his day, but he also contributed to other branches of medicine including gastrointestinal disorders.

In his later years, Hayem had two absorbing hobbies, modelling medallions and painting.

In assessing the work of Hayem, one can do no better than read the following quotation from Dreyfus. 'At every instant, in the practice of treating diseases of the blood, we draw on his experience; at every step we utilise what we inherited from Hayem. But this heritage became classical and therefore anonymous. Many valuable procedures in haematology were introduced by Hayem, but we have forgotten their origin as we have forgotten who taught us to walk'.

WILHELM THIERRY PREYER (1828–1897)

We now come to a consideration of haematologists who worked in Germanspeaking countries. The first deserving of mention is Wilhelm Thierry Preyer who owes his place in the history of haematology to the fact that he wrote the first two definitive monographs on haemoglobin. These were *Über einige Eigenschaften des Hämoglobins and Methämoglobins* (Bonn, 1868) and *Die Blutkrystalle* (Jena, 1871) He also published an impressive list of books on a variety of subjects.

Preyer was born on 4 July 1828, at Moss-side near Manchester and studied at Bonn, Heidelberg, Berlin and Vienna. Even as a student, he devoted his main effort to physiological and clinical studies. He obtained the degree of Doctor of Philosophy in 1862 and worked for a time with Claude Bernard in Paris. He succeeded J. N. Czermak as Professor of Physiology in Jena in 1869. He retired in 1888 and died in 1897.

His scientific career was divided into a number of distinct phases. In his earlier years his main interest lay in physiological chemistry and he worked on such things as blood pigments and blood gases. Next he turned to the physiology of muscle and of the sensory organs and this led him gradually to the study of predominantly psychological topics such as suggestion and hypnosis. His lactic acid theory of sleep achieved considerable prominence and his popular writings aroused an interest in scientific and psychological questions throughout a wide circle of readers.

ERNST FELIX HOPPE-SEYLER (1825–1895)

Ernst Felix Immanuel Hoppe was born at Freiburg-in-Thuringen on 26 December 1825, the son of a pastor. He became one of the leading physiological chemists of the nineteenth century and a pioneer in the study of haemoglobin and its functions. In 1864 he changed his name to Hoppe-Seyler out of regard for his brother-in-law, Dr. Seyler, who had sheltered him as a child after his parents had died.

He received his training in the universities of Halle, Leipzig, Berlin, Prague and Vienna. Among his teachers was Johannes Müller. He obtained his doctorate in Berlin in 1850. Among the positions he held in his early career was that of Assistant in the Pathological Institute in Berlin under Virchow. He became Professor of Applied Chemistry at Tübingen in 1861 and later, in 1872, Professor of Physiological Chemistry in Strasbourg, where he remained until his death in 1895.

He was one of the founders of the discipline of physiological chemistry which he promoted through his own prolific researches as well as his energetic teaching and guidance of other workers. His researches included investigations on the colouring matter of blood, on proteins and on the oxygenation of tissues. In connection with the blood pigments he studied gaseous exchange and the relationship of blood and bile pigments. He also laid down several important principles in haemoglobinometry which such people as Haldane (see below) were to develop. Apart from a large number of contributions to journals, the fruits of Hoppe-Seyler's labours are to be found in three important books: *Handbuch der physiologisch- und pathologisch-chemischen Analyse,* of which five editions appeared between 1858 and 1883 *Physiologische Chemie* (1877 and 1881) and *Medicinisch-chemische Untersuchungen* which appeared in four volumes between 1866 and 1871.

KARL VIERORDT (1818–1885)

However, the man I want to deal with in more detail is Karl Vierordt, who made

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contributions to many branches of physiology and who, like Alfred Donné and Georges Hayem, made discoveries that are today such an integral part of everyday knowledge that their discoverer tends to be forgotten.

Vierordt was born at Lahr in Baden in 1818, the son of a clergyman who later became Director of the Lyceum at Karlsruhe. In 1836 he entered Heidelberg University but also studied at Göttingen, Berlin and Vienna prior to returning to Heidelberg where he received his doctor's degree in 1841. During his student days he sat at the feet of teachers who have left a permanent mark on medical science. At Heidelberg there was Gmelin and Tiedemann (the chemists), Bischoff (the embryologist), Naegele (the obstetrician) and Chelius (the surgeon). In Göttingen he attended the lectures of Langenbeck and of Wöhler, the first person to synthesize urea. In Berlin there was Schönlein and Johannes Müller, the physiologist. In Vienna there was Skoda and Rokitansky. After graduation, Vierordt, at the wish of his father, settled in Karlsruhe as a general practitioner but the passion for physiological experimentation was strong within him and in the following year (1842) he published his first paper. It dealt with the pathology and therapy of strabismus.

In 1843 he became surgeon to the Grand Duke's own regiment and also published the first of a series of papers on the physiology of respiration. In it he demonstrated the role of carbon dioxide in controlling respiratory rate—a piece of physiological knowledge so fundamental that its origin has been almost forgotten. His experiments were carried out in his home with the simplest of apparatus and without a proper laboratory.

In 1852 he made his first contribution to haematology with three articles on blood counting. His were the first attempts to make any sort of quantitative laboratory measurements in haematology. He took up an academic career in 1849 when called to Tübingen as Extraordinary (or Associate) Professor of Theoretical Medicine and for the next thirty-five years his fortunes were bound up with those of that university. He lectured there in general pathology, therapy, materia medica and the history of medicine. Later, he was placed in charge of physiological teaching. He invented the sphygmograph and wrote a monograph on the pulse which was the first treatise in which a normal and pathological pulse was studied. He also attempted to measure the blood pressure by adding weights to the pan of that instrument. Later, he invented a haemotachometer with which he tried to measure the rate of flow of blood. Thus, he pioneered a field that was to be refined by E. J. Marey, twenty-five years later and by James Mackenzie, fifty years later.

In passing, it is of interest to note that Mackenzie, like Vierordt and like Robert Koch, was also a general practitioner turned scientific experimenter.

Vierordt's famous work, *Grundriss der Physiologie des Menschen* first appeared in 1860 and went into five editions. In 1864 he became Rector of the University and in 1868, Director of the Institute of Physiology. In that year he began experiments on a new field of physiology in which he investigated the sense of time, errors in time perception and the speed of voluntary movement. These experiments were, in fact, in the field of experimental psychology.

Vierordt next turned his attention to haematology once again and made a contribution to the subject on a par with his earlier work on blood counting. In 1873 there

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appeared his classic monograph, *Die Anwendung des Spektralapparat zur Photometrie der Absorptions-spektren und zur quantitaven chemischen Analyse,* which was followed in 1876 by a further work on the same topic, *Die quantitave Spektralanalyse in ihrer Anwendung auf Physiologie, Physik, Chemie und Technologie.* In these works he studied the spectral absorption curves of the pigments of blood, bile and urine. In particular, he demonstrated the spectral curves of haemoglobin and made quantitative measurements of it by a spectrophotometric technique. He showed that to get a true estimation one should take readings at two places on the absorption curve. It is apt to be forgotten that to meet the definition of a spectrophotometer, a piece of apparatus does not need to be a complex device depending on photoelectric cells, electric currents and sensitive galvanometers. Even fairly simple equipment for measuring optical densities at different wave lengths of light by visual means can meet the definition.

Vierordt's apparatus was quite simple but from his experiments with it he foreshadowed the possibilities of spectrophotometric methods long before optics, lighting technique and refinements of instrumentation were developed sufficiently to make it a practical proposition for general use. His chief contribution to haematology was, in fact, his study of the absorption curves of haemoglobin and their application to the quantitative estimations of that blood pigment.

His work was pursued further by Hüfner, [15,16,17,18] with improved instruments, and the principles Vierordt and Hüfner laid down are still applied to the spectrophotometric determination of blood pigments. In his later years, Vierordt busied himself with the study of the physiology of sound. He died in 1885—one of the supreme pioneers of laboratory haematology and of physiology generally. A more detailed account of his life has been given by Major.[19]

RICHARD THOMA (1847–1923)

The name of Richard Thoma has been a 'household' word in clinical laboratories for the last eighty years as a result of his invention of the Thoma counting chamber and Thoma diluting pipettes. The latter are still the standard type of blood diluting pipettes in common use.

Thoma was born at Bonndorf in Baden on 11 December 1847, and studied in Berlin and Heidelberg where he became Assistant at the Pathological Institute after his graduation in 1872. In 1877 he became Associate Professor and in 1884 he was called to Dorpat as full Professor. He retired in 1894 to teach privately and died in 1923. Like several others who worked in the same field, his work on blood counting arose from studies in climatology. Apart from his work in haematology, his main interests were the problems of blood flow, bone development and inflammation.

SIR WILLIAM GOWERS (1845–1915)

Now we come to some British pioneers of haematology, the first of whom, William Richard Gowers, is remembered mainly as a neurologist. This, indeed was his life's work, but he made two important contributions to laboratory haematology.

He invented a haemocytometer that incorporated an important new feature, for the ruling was on the floor of the counting chamber and not in the eyepiece of the microscope as in earlier instruments. He also invented a haemoglobinometer in which blood was diluted until it matched a picrocarmine standard. This instrument was very popular but it had some serious faults and was ultimately superseded by a modification introduced by John Haldane, whom we shall mention later.

Gowers' haemoglobinometer tends to be regarded as the first clinical instrument of this nature. This was by no means so, as a number had been devised on the continent earlier. The impression probably arose because of the failing Gowers had of not always putting references or acknowledgements in his writings.

But what of the man himself? He was born on 20 March 1845, at Church Street, Hackney, where his father had a shop as a maker and retailer of shoes. When William was aged eleven, his father died and his mother took him to live with her family at Headington. In 1861 he was offered an apprenticeship by Dr. Thomas Simpson. The offer was accepted and on payment of £150, young Gowers commenced work. During his apprenticeship he studied for his London matriculation which he passed in 1863 and entered University College Hospital as a medical student. On qualifying in 1867 as M.R.C.S. he commenced work as assistant and secretary to Sir William Jenner, Bart., the President of the Royal College of Physicians. In 1869 he achieved the degree of M.B.(Lond.) and the M.D. with the Gold Medal the following year. In 1888 at the age of forty-three, Gowers resigned his Chair of Medicine and his appointment as Physician to University College Hospital to devote more time to private practice. However, he continued to serve at the National Hospital.

Gowers wrote extensively on his chosen field of neurology but a detailed account of his neurological writings is outside the scope of the present account. His diagnostic skills were uncanny and in a day when ancillary aids were scarce he made the best possible use of those available. In particular, he did much to promote the use of the ophthalmoscope. Outside his professional life, he had a number of other interests. He was a talented artist, the delicate techniques of etching and engraving appealing to him most. He also did pencil drawings but watercolours appealed to him less and he never attempted oils.

From the days of his apprenticeship, he was absorbed with the value of shorthand, particularly as an aid to medical note-taking. In 1894 he founded and became the first President of the Society of Medical Phonographers and wrote a number of articles on the value of shorthand. Gowers, throughout his career, had a fondness for gadgets. This was illustrated by his first contribution to medical literature, the description of a safety syringe to avoid overdosage and in his two contributions to haematology, his haemocytometer and his haemoglobinometer. He also carried this gadgeteering into his private life. He invented a reading lamp so that he could read on long train journeys and at a time when electricity was a rarity, he illuminated his house from a battery in the sideboard. He was also interested in natural history and antiques.

In appearance, he was of slight physique but distinguished appearance. He wore his hair long and had an abundant square beard. He had an awkward gait and a strident voice. His personality was cold and aloof and he could be caustic. As a result, his colleagues and assistants held him in respect rather than affection, but to the few who got beneath this exterior, he was a warm friend.

In 1914 both Sir William and his wife developed pneumonia and Lady Gowers died. Sir William recovered from the attack but never regained his former health and died the following year. A biographical appreciation of Gowers has been published by Macdonald Critchley.[20]

JOSEPH LOVIBOND (1833–1918)

One of the most interesting characters in the history of laboratory technology was Joseph Lovibond, the inventor of the Lovibond Comparator. Although he was not a doctor and had no academic qualifications, he deserves a place among the pioneers of haematology because of the principles of colour comparison he laid down and because of his comparator which continues to be used to the present day in the estimation of haemoglobin. The methods of Oliver and Harrison and the neutral grey step-photometer method were specifically designed for use with Lovibond apparatus. In addition, the Lovibond comparator has been employed for the estimation of haemoglobin by adaptations of the acid haematin, alkaline haematin, cyan-methaemoglobin, oxyhaemoglobin and carboxyhaemoglobin methods.

Lovibond began his career by running away from home and shipping as cabin boy at the age of thirteen. He jumped ship in Australia and later went to California for the 1849 gold rushes, but eventually he returned to England and settled into the family brewing business. He opened a branch at Salisbury where he eventually became Mayor, Magistrate and County Councillor. Among his interests were meteorology, a cottage industry for the cloth weavers of Salisbury Plain, reinforced concrete, the study of camouflage during the 1914–18 war and scientific trout breeding.[21]

His investigations on colour measurement arose directly from his livelihood as a brewer.[22] The colour and flavour of beer in those days were both dependent on the degree of roasting of the malt. The finest flavour in beer was always associated with a colour technically known as 'golden amber' and as the flavour deteriorated the colour assumed a reddish hue. In an attempt to define the colour scientifically, he first used liquid standards but later changed to coloured glass wedges with regular tapers. He soon met with the usual difficulty that a glass wedge matching at one dilution at a certain point did not match as expected at another dilution. In the course of his investigations he worked out the principles of analytical absorption of colours and devised scales of three primary colours with which he could make about nine million different colour combinations. To facilitate colour matching he devised his well-known comparator, the first model of which he made by drilling holes in his wife's tea caddy. The principles he laid down and the apparatus he devised found application in innumerable fields of technology as well as in haematology, and from his first 'factory', a shed at the bottom of his garden, has grown a vast enterprise.

GEORGE OLIVER (1841–1915)

The man first responsible for applying Lovibond's principles to haemoglobinometry was George Oliver who made a number of contributions to the study of the blood and circulation as well as to other branches of physiology. Besides his haemoglobinometer, he invented a haemocytometer depending on turbidometric readings, an arteriometer and testing papers that bear his name.

He was born at Middleton-in-Teesdale, Durham, the son of Mr. W. Oliver, a surgeon. He was educated at Gainford School and received his medical training at University College, London, where he qualified in 1863. After a few years in general practice, he settled at Harrogate and concentrated on consulting work. In his later years he divided his time between Harrogate, London, Sidmouth and Farnham and managed to indulge in his love for physiological research.

In 1883 he published his *Bedside Urine Testing* and in 1901 his *Studies on Blood Pressure* which went into a third edition. In 1896 he delivered the Croonian lectures under the title of 'A Contribution to the Study of the Blood and Circulation' which described his haemoglobinometer, haemocytometer and arteriometer[23] and which were subsequently published in book form. His work with Sir Edward Schäfer on the adrenalin glands paved the way for the discovery of adrenalin. In memory of his former teacher he established the Oliver-Sharpey Lectureship for the promotion of physiological research.

JOHN SCOTT HALDANE (1860—1936)

An important figure in laboratory haematology at the close of the nineteenth century and the beginning of the twentieth was John Scott Haldane.

He was born in Edinburgh and after graduation there in medicine in 1884 he went to Dundee and studied the bacterial and chemical contamination of the air in stores and schools under Professor Connelly. This work overthrew the erroneous idea that 'sewer gas' was the cause of diphtheria, scarlet and typhoid fevers. Next, he went to Oxford as demonstrator in physiology where he worked for the remainder of his life.

He was interested in the gases of coal mines and determined their composition and studied their physiological effects, thus giving great service to industrial hygiene. He showed that 'black damp' was air diluted with an inert gas, 'fire damp' was the explosive gas methane, and 'after damp' was carbon monoxide. He showed that carbon monoxide was the gas responsible for most cases of asphyxiation in mines.

From 1905 to 1915 he devoted himself to studies on respiration and stressed the role of carbon dioxide in the initiation and control of breathing.

Haldane's contributions to haematology were in the field of haemoglobinometry and arose directly from his interest in respiratory physiology and gas analysis. In 1898 he introduced an improved method for determining the oxygen and carbon monoxide capacities of blood and hence deducing the haemoglobin value. Most earlier methods had depended on withdrawal of the gas from combination with haemoglobin by means of a vacuum prior to measurement and analysis of the gas—a procedure requiring considerable time, apparatus and skill. Haldane found that releasing the oxygen by the addition of potassium ferricyanide simplified the procedure considerably. His technique was later improved considerably, particularly by Van Slyke and his co-workers.

But it was a much simpler technique that won Haldane eponymous immortality in clinical laboratories throughout the British Empire. One of the difficulties with Gowers' haemoglobinometer was that if oxyhaemoglobin was used as a standard it was unstable and artificial standards had to be used. Based on the work of Hoppe-Seyler, Haldane devised a haemoglobinometer on the principle of Gowers' instrument, except that the haemoglobin solution was transformed to carboxyhaemoglobin by exposure to coal gas and the standard solution consisted of a 1 per cent solution of carboxyhaemoglobin from blood with an oxygen capacity of 19.1 per cent. This solution was quite stable and gave a permanent standard. Based on the mean of the readings of twelve healthy males, the mean normal oxygen capacity was found to be 18.5 per cent which was equivalent to a haemoglobin capacity of 13.8 grams so this value was taken at 100 per cent. The Haldane-Gowers or Haldane haemoglobinometer became the standard instrument in laboratories throughout the British Empire for some forty years.

At a later stage, precise specifications were laid down for the standards employed and the instrument was used for nutritional surveys right up to the period of World War II.

Then an astonishing discovery was made. For many years it had been found that average British haemoglobin values were lower than American or Continental means. Then it was shown by workers at Hammersmith that the B.S.I. Haldane Standard was equal to that given by blood of 19.8 per cent oxygen capacity (equivalent to 14.8 gm. haemoglobin) and not to 18.5 per cent. Thus, British workers had operated on the wrong calibration for some forty years.

Besides inventing his haemoglobinometer, Haldane, in his original paper, gave an excellent account of the problems involved in clinical haemoglobinometry and in the designing of clinical haemoglobinometers.

Haldane's work coincided with the close of the nineteenth century and the beginning of the twentieth. This, therefore, is an appropriate point to end this account of the people who pioneered the scientific study of the blood and who, in so doing, laid the foundations of a discipline that has assumed continually increasing importance in modern medicine. It was their fundamental studies that made possible the advances that have taken place in the present century.

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