# THE EARLY HISTORY OF CLINICAL PATHOLOGY IN GREAT BRITAIN*

*by*

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THE origins of clinical pathology are difficult to distinguish and depend upon one's definition of the subject. The examination of the urine, faeces, sputum, etc., may vary in complexity from simple naked eye inspection to the most complicated of chemical analyses. Simple inspection of excretions was an important part of the examination of the patient amongst the ancients, and defined in this way clinical pathology is as old as medicine itself. However, it is the advances over and above mere naked eye inspection that constitute modern clinical pathology and it was not until the latter part of the seventeenth century that a beginning was made.

The seventeenth century saw the birth of three things relevant to clinical pathology: scientific chemistry, the microscope, and the idea that disease might produce specific changes in the blood which could be detected and would be helpful in the management of the patient. The first man to whom we know this idea occurred was John Locke, the philosopher, who was also a physician deeply interested in his profession. As a result of conversations with his friend Robert Boyle,[1] in which the idea that the blood might show specific changes in disease was discussed, Boyle undertook the basic work of analysing normal blood chemically, but left it to those trained in medicine to investigate possible pathological changes. The techniques he employed were, of course, crude and consisted largely of a sort of fractional distillation with weighing at intervals. None the less, he was able to demonstrate accurately the presence of 'sea salt' in the blood using silver nitrate as his test reagent. Boyle also suggested that the urine might be similarly examined.

This work was not, however, taken up by others until some fifty years later when a country physician, by the name of Browne Langrish, who practised in Petersfield, Winchester and Basingstoke, published his *New practice of physic*, in which he recorded a series of chemical analyses on the blood of patients with various types of fever. Langrish states in his preface that he had been encouraged to pursue these methods in the hope that

> the proportions of the several principles of the blood and urine, both in a sound and diseased state, will be highly useful in investigating the causes of the phenomena of diseases and the most expeditious way of relieving them.[2]

The simple inspection of blood shed at phlebotomy had long been recognized as being diagnostically significant, and was always described as part of the clinical picture. Langrish went beyond this in the following ways: he weighed

* *Medical History* Prize Essay, 1958.

the serum and clot noting the proportion they bore to each other, and invented an instrument to measure the 'degree of cohesion' or toughness of the clot.[3] It consisted of a graduated glass tube blown to a bulb at one end. This was rested upon the surface of the clot, and then gradually filled with mercury until the weight forced the bulb into the clot. The 'degree of cohesion' was then read off on an arbitrary scale. He also performed chemical analyses after the manner of Boyle, with whose work he was familiar. This technique of fractional distillation divided the blood into the following components: Lymph, volatile salt, oil, caput mortuum before calcination, caput mortuum after calcination and fixed salt.[4] He thought that in acute continual fever the blood 'seemed to be more strongly charged with volatile salt and oil', but admitted that he had performed too few analyses 'to deduce any practical references from'.[5]

With regard to the urine, he describes in detail the various appearances such as colour, sediment, taste and smell 'which furnishes us with signs as well diagnostic, as prognostic'.[6] He goes on to say that

> If therefore a bare inspection of urines is of such advantage towards investigating the nature, state, progress and cure of diseases; most certainly the natural history of it, or a more curious search into the contents of the urine, in every period of the disease, will be of more moment in discovering the several dyscrasias of the blood, and in indicating the method of cure, than what we can meet with in the normal way.[7]

He employed the same technique of fractional distillation of the urine as he used with the blood, and, despite much work, obviously achieved no meaningful results, but the attempt, and the appreciation of the possibilities of chemistry as applied to diagnosis, entitle Browne Langrish to a significant place in the history of clinical pathology. The attempts of Langrish to utilize the techniques of chemistry in clinical medicine were premature, and he himself claimed little in the way of practical results and no doubt others were unable to confirm or extend his work.

It was not until about a hundred years after Langrish's publication that much further interest was taken in blood chemistry. In the early nineteenth century continental workers took up the study, and in 1843 G. Andral of Paris published his famous *Essai d'hématologie pathologique*. Andral's technique of blood analysis was both simpler and more meaningful than that of Langrish. He collected two six-ounce samples of blood, allowed one to clot and the serum separate, and whipped the other with twigs to collect the fibrin. By drying and weighing the constituents so separated he was able to calculate the weight of fibrin, red cells, the solid residue of serum and water in blood.[8] He was able to determine that the red cells were reduced in anaemia and increased in plethora, that the serum albumin was low in cases of albuminuria and famine oedema, and that in certain haemorrhagic diatheses the blood fibrin was reduced.[9]

About this time urine analysis was beginning to be extensively practised. This was technically somewhat simpler, and urine was available in the large quantities that the methods of the times required. Although albumen had been demonstrated in the urine in the seventeenth century by a Dutch physician,

F. Dekkers,[10] using heat and acetic acid as a test, its significance was unknown. The utility of testing for albuminuria was not widely appreciated until the contemporary but independent observations of two British physicians in the first decade of the nineteenth century, W. C. Wells,[11] an American colonial loyalist migrated to England and physician to St. Thomas's Hospital, and J. Blackall,[12] a west country physician. Both tested the urine for albumen in a large number of patients and observed that it was commonly present in cases of dropsy. The study of morbid anatomy was at that time beginning to revolutionize medicine, and both these men performed autopsies and reported cases of massive albuminuria and dropsy which were associated with diseased kidneys. It was, however, the careful studies of Richard Bright at Guy's hospital that firmly established the correlation of albuminuria with diseased kidneys. The detection of albumen in the urine was the first really useful procedure that may be fairly classed as 'clinical pathology', and the modern development of the subject starts at this point.

At about the time Bright published his celebrated 'Reports' (1827), a new influence was just beginning to be felt in medicine which was greatly to enlarge the scope of clinical pathology. This was the introduction of much improved microscopes, which were basically of the modern type. Bright did not possess a microscope, but he had access to one belonging to his friend Dr. Roget, whose famous *Thesaurus of English words and phrases* is still being reprinted. Without doubt many doctors possessed and occasionally used microscopes in their medical practice, but the first to publicly advocate the use of the instrument in everyday practical medicine and to teach its utility was John Hughes Bennett of Edinburgh.[13]

Bennett had spent the years of 1837–41 in postgraduate study on the continent, and was amazed at the advances being made in physiology and pathology with the aid of the microscope, particularly in Germany. There medical microscopy was enthusiastically studied, and courses of instruction given. Bennett had also attended the lectures and practical demonstrations on histology and medical microscopy given by A. Donné in Paris. Donné was an advocate of the microscope as a practical diagnostic tool. One of the examples of its use, with which he used to impress his students, was the occasion when he had detected an abnormality in the breast milk of the wet nurse to the Count of Paris, the heir to the French throne, to which he attributed the ailing princeling's symptoms. Bennett commented that

> In aristocratic or wealthy families where the preservation of an infant heir to noble titles or great wealth is at stake, the possession by the practitioner of another means of distinguishing the source of disease cannot be too highly appreciated.

Bennett, himself, whilst on his travels, met an Englishman in Heidelberg who complained of headache, vertigo and fainting. He had lead a dissipated life and he had had syphilis. No doctors, despite heroic treatment, had been able to do anything for him and he had been put on a low diet. Bennett did not know

what to advise until one day, examining some of his urine under the microscope, he found numerous spermatozoa. On questioning, the patient admitted to involuntary seminal emissions, so Bennett prescribed beef steak, beer and tonics and in six months restored the man to health.

In 1841 Bennett returned to Edinburgh, and started the first practical class in medical microscopy to be held in Great Britain. The stories just recounted doubtless added interest to his introductory lecture, but he was also able to give many examples of the real utility of the microscope in diagnosis. For example, in differentiating pus from amorphous deposit in urine, malignant from simple ulcers by examination of scrapings and cellular exudate (he was quite familiar with the modern criteria of malignant cells—large nuclei and nucleoli) and in detecting the fungus of favus and such frauds as birds' blood in sputum. This course appears to have been a success and continued for a number of years. Bennett considered that a microscope should be in the hands of every practitioner and recommended a portable model which could be taken to the bedside. Suitable models were available for from £2 2*s.* 0*d.* upwards.

The cause of clinical microscopy was taken up in London by L. S. Beale of King's College Hospital who gave a course in practical microscopy at his house in Carey Street, starting in 1853. Beale published the substance of his course in book form under the title of *The microscope in its application to practical medicine*. The book was popular, and ran through four editions between the years 1854–78. It included much more than the mere use of the microscope for diagnostic purposes, but Beale, like Bennett, stressed its value in everyday medicine.

The chemistry of disease, meanwhile, was receiving much attention and tests of diagnostic value were evolving in increasing numbers. Prominant among the workers in this field were four London physicians, John Bostock, Golding Bird, William Prout and Henry Bence Jones. John Bostock, the senior of these, had graduated at Edinburgh in 1798. He practised in Liverpool for nearly twenty years, and then moved to London and lectured on chemistry at Guy's Hospital. It was to him that Bright turned for biochemical investigations on his dropsy cases. He was probably the first man to demonstrate that the blood urea may be raised in renal failure as he was able to detect that substance in the blood of such patients but not in healthy persons.

Golding Bird was a physician at Guy's Hospital who wrote an eminently practical book on Urinary chemistry which was based on a course of instruction given at Guy's Hospital. *Urinary deposits, their diagnosis, pathology and therapeutical indications* first appeared in 1844 and went through several editions. It contains more than an exhaustive account of the various crystals that could be observed with the microscope in urine. In addition to the well established test for albumen, Bird used nitric acid to test for bile in the urine and a simple polarizer or alkaline copper reagent for glycosuria, and he recognized casts, which had been described by H. B. Jones, as diagnostic of Bright's disease. Quantitative analyses of twenty-four hourly collections of urine were done by a crude gravimetric technique which can have yielded little information of value in clinical pathology. The specific gravity of the urine was measured, but the concept of the capacity of

the kidneys to concentrate or dilute the urine, a valuable test within the technical capacity of the times, was not appreciated.[14]

William Prout graduated at Edinburgh in 1811 and settled in London at the end of the following year. He immediately commenced to study and teach chemistry, and made an important contribution to the atomic theory, being the first to suggest that the atomic weights of all elements were exact multiples of that of hydrogen. He was a pioneer organic chemist, and divided organic substances into carbohydrates, fats and proteins. In 1823 he discovered hydrochloric acid in the gastric juice. In 1831 he delivered the Goulstonian lectures on 'The application of chemistry to physiology, pathology and practice'.[15] He wrote much more on allied topics and was a most active and influential worker who played an important part in developing chemistry as applied to medicine.

Henry Bence Jones graduated with the M.B. at Cambridge in 1842. He spent some time in postgraduate study under the great organic chemist Liebig at Giessen. In 1845 he became physician to St. George's Hospital and delivered lectures there on chemistry. Part of this course of lectures was published in 1850 under the title *On animal chemistry in its application to stomach and renal diseases*. This work at once caused him to be recognized as an authority on the subject and in it he stressed the practical diagnostic value of chemistry, maintaining that in diseases of the stomach and urinary tract it gave information as valuable as did the stethoscope in diseases of the chest.[16]

By about 1860, the clinical pathology of the urine had reached a state of advancement beyond which it scarcely progressed until the deliberate attempts to measure renal function by urea concentration and clearance techniques in the second decade of the twentieth century.

Haematology had its beginnings in the 1840's, indeed, one of the first fruits of medical microscopy was the recognition of the condition of leukaemia in 1845 by Bennett, Virchow and Donné,[17] independently and almost simultaneously. These observers noted the great increase in the number of leucocytes in the peripheral blood, and appreciated its diagnostic importance. Virchow even distinguished between myeloid and lymphatic leukaemia. Actual counts of leucocytes were not done but their increase in relation to the red cells was noted.

In the eighteenth century, a French physician, de la Mettrie, had noted that the blood of chlorotic patients did not colour water as deeply as that of healthy persons, but did so after they had been treated with an iron preparation. However, the first to suggest that a quantitative estimate of the red cells might be made was P. A. Piorry, an enthusiast for the use of accurate instruments in medicine, who is best remembered for his obsolete pleximeter. He was also a keen microscopist, and suggested examining a drop of blood diluted in a salt solution to preserve the red cells which could then be counted.[18] The first to actually perform and report red cell counts was a German, Karl Vierordt, a modest professor at the small university of Tubingen. In 1852 he reported the results of red cell counts done on himself, and found that the normal figure was just over five million per cu. mm. His method was to measure a small volume of

blood in a capillary pipette, dilute it with egg albumen, spread it over a glass slide ruled into squares and then count the cells under the microscope.[19] His method was, however, regarded as too difficult for routine use, and although done to some extent on the continent, never seems to have been taken up in this country. The beginning of the study of red cell counts in this country dates from the publication in the *Lancet* in 1877 of a paper by W. R. Gowers, the famous neurologist, entitled 'On the enumeration of red cells', in which, after reviewing the various methods suggested in the past, he described his ruled counting chamber, which was, in principle, exactly like those used today.[20]

The study of parasitology made considerable advances in the middle years of the nineteenth century and helped to extend the scope of clinical pathology. By 1880, the appearance of the eggs of various intestinal parasites was known, trichomonads had been observed in vaginal discharges, microfilariae had been found in the blood and their associations with lymphatic obstruction was known. The fungal cause of the various types of ringworm was known. In all these conditions microscopy offered the most accurate means of diagnosis.

Knowledge of pathological histology was rapidly accumulating, the value of the microscope in distinguishing a simple from a malignant tumour or ulcer was known and utilized. Modern methods of section cutting had not yet been introduced, and diagnosis rested largely on cytological differences as seen in scrapings or discharges, but these were well understood.[21] Sections were cut either free hand, or with the aid of Valentin's knife, a scalpel like instrument with two parallel adjustable blades which removed a thin slice of tissue between them.

The year 1880 is a good point at which to pause in the review of the development of clinical pathology, for the discoveries made during the next few years in bacteriology were to be a powerful stimulus and give rise to important changes in the subject. In 1880 there were no professional clinical pathologists, nor were there laboratories for clinical pathology even in the large teaching hospitals. These were not generally established till the late 1890's. However, the methods of clinical pathology in the form of medical microscopy and urine chemistry were widely used by the better sort of doctor in the wards and consulting room.

The history of the development and ultimate acceptance of the germ theory of disease cannot be detailed here. In the 15–20 years prior to 1880 much work had been devoted to it, and sufficient evidence accumulated to convince an impartial observer that infectious diseases were indeed caused by living micro-organisms. This is not to say that the germ theory had yet made much impact on the medical profession as a whole, or had had much practical effect, with the notable exception of antiseptic surgery. Even a man so up to date as William Osler in writing about the International Congress of Medicine in London in 1881 could dismiss the matter with 'there was abundant discussion on germs'.[22] However, a leading article in the *Lancet* of 15 October 1881, suggested that the progress of bacteriology might eventually enable diseases to be distinguished which had hitherto been confounded.[23]

In fact, by this time, the causative micro-organisms of several important diseases such as relapsing fever, leprosy, gonorrhoea, typhoid fever and anthrax had been discovered, but this had made no difference to the diagnosis of these diseases which were either easily diagnosed clinically, or else the causative organism, as in the case of typhoid fever, was too difficult to isolate from the patient to be of practical use.

The case was, however, different with tuberculosis. R. Koch announced his discovery of the tubercle bacillus in March 1882 and within a remarkably short time Ehrlich had discovered the principle of the staining technique used to differentiate this organism from others in the sputum. Here was a disease, often difficult to diagnose, which could be diagnosed with certainty by a simple laboratory procedure. This discovery was of great importance as a stimulus to the rise of clinical pathology. Nor did it stop at this point, because before long it was appreciated that other bacteria which were non-pathogenic might stain in the same way as the tubercle bacillus. They were not common and did not render the test useless, but it became necessary to proceed further in many cases, make cultures and perhaps resort to animal inoculation before a firm diagnosis of tuberculosis could be made.[24] Such work was beyond the scope of the clinicians. During the next twenty years, the causative organisms of most of the important infectious diseases were discovered. Sometimes they could be readily seen by simple microscopy, providing a valuable diagnostic aid. The vibrio of cholera and the bacillus of diphtheria are examples. However, for certain diagnosis, and it was soon appreciated that the microscopic appearance was seldom an infallible guide, culture and further testing were usually required.

In these early days some private practitioners endeavoured to do their own bacteriology, but it was time consuming, expensive and demanded special training which was only to be had abroad. The value of bacteriological diagnosis, especially in diphtheria, was soon widely appreciated, but the problem was to provide the trained men and the laboratory facilities. Oddly enough, it was not the great hospitals which gave a lead in these matters by appointing bacteriologists and setting up laboratories, badly though they needed their services. Amongst the reasons for this, one was the excessively 'clinical' bias of British medicine, there being few openings for laboratory work of any kind in medicine, a situation which contrasted sharply with the continent. Beale put his finger on another point of importance. The hospitals of England were charities for the relief of the sick poor, and their governors thought it no part of their business to spend the funds of their charities on building and staffing laboratories.[25] Beale's view, which had been expressed in 1878, was confirmed by several speakers at the ceremony of opening the clinical laboratory at the Westminster hospital as late as 1899. Then much stress was laid on the practical utility of laboratories in hospitals, on their being a 'good return' for hospital subscribers, and 'relieving the suffering poor'.[26]

In 1876 Watson Cheyne, Lister's house surgeon, attempted to study the bacteriology of his chief's cases 'in a little passage behind the operating theatre in the old Edinburgh Infirmary' but did so with 'no staining of bacteria, no

oil-immersion lenses, no solid cultivating media, no proper incubators'.[27] The first bacteriological laboratory in this country seems to have been founded in Edinburgh about 1883 by John Chiene, the professor of surgery.[28] He was convinced of the necessity for bacteriological investigations on his patients and read a paper at the B.M.A. annual meeting in 1884 on 'The desirability of establishing bacteriological laboratories in connection with hospital wards'.[29] In 1887 the Royal College of Physicians of Edinburgh decided to found a laboratory for medical research, but from the outset it was agreed that the laboratory might be used by Fellows for 'the examination of specimens met with in practice, and the making of such analyses as practitioners could not conveniently carry out at home'.[30] It was also laid down as a definite part of the superintendent's duties to report on specimens submitted to him. The volume of work on reporting on routine specimens soon became something of a problem, tending to interfere with the laboratory's primary function of research.

In England as late as 1887 there were almost no facilities for bacteriological work, and indeed, without going abroad, there was nowhere where training might be had in technique. E. Klein had been working at the Brown Institution, a veterinary establishment, since 1872, and though originally a histologist, had taken up bacteriology. A few people were able to turn to him for bacteriological diagnosis. He undertook the bacteriological diagnosis of cholera on quite a large scale, but, curiously enough, although admitting the constant association of Koch's comma bacillus with cholera did not regard it as the cause.[31]

The first professional bacteriologist in London was E. M. Crookshank who qualified at King's College in 1881. He decided to become a bacteriologist, studied under Koch and Pasteur, and in 1886 published a comprehensive *Manual of Bacteriology*, which proved very popular. He was made professor of bacteriology at King's College. In 1886 at a B.M.A. meeting at Brighton he gave a lecture and some demonstrations in bacteriology and in 1887 started a course in the subject at King's College. This was open to practitioners and senior students, and consisted of 15 lectures and practical classes, and lasted for four weeks. The laboratory was well equipped, and also provided facilities for private research.[32]

At this time, laboratories for clinical bacteriology were organized by enthusiastic individuals who felt the need for them, and their distribution was accordingly patchy. C. B. Lockwood deserves mention as an early worker in this field. He was a surgeon at the Great Northern Hospital and also at St. Bartholomew's Hospital, He had a small museum at the former hospital fitted up as a laboratory. In 1890 he gave what was probably the second course in London on bacteriology at St. Bartholomew's Hospital, which led to the establishment of a laboratory there.[33] About the same time J. W. Washbourn, who had recently been appointed assistant physician to Guy's Hospital, organized the first bacteriological laboratory there.[34]

The need for bacteriological diagnosis seems to have been most acutely felt by workers in public health, and some of the earliest laboratories were fitted up on their behalf. The sort of arrangement made varied in different parts of the

country. Some local authorities paid to have the work done by someone on a local university staff, others made arrangements for the work to be done in the local public analyst's laboratory and sometimes special institutions were founded. One such was at Leicester, founded in 1895. This was under the medical officer of health, and reports were issued to local practitioners who sent in specimens. Although, by this time, most universities had some sort of bacteriology department, this was the first in a non-university town in the Midlands.[35]

For the most part, laboratories were founded by the enterprise of individuals rather than institutions. Many practitioners ran their own laboratories. At one point, they were numerous enough for the question of government control of them to be raised.[36] An organization known as the Clinical Research Association, started in 1895, undertook the examination of specimens for practitioners for a fee. By 1897 the organization was examining over 3,800 bacteriological specimens a year.[37]

In London the Royal Colleges of Physicians and Surgeons had established a Conjoint Laboratory on the lines of the Edinburgh laboratory and a good deal of diagnostic work was undertaken there.

By the end of the nineteenth century, small but well equipped laboratories for clinical pathology had been established in the teaching hospitals. The staffing was always meagre, and rarely consisted of more than the director, a man of very junior status compared with his clinical colleagues, one or two technicians and perhaps some voluntary student helpers. Provincial hospitals were by no means up to this standard. As late as 1914 Sir William Osler stressed the need for more laboratories, but considered that the clinician should be in a position to undertake his own clinical pathology, the idea of a professional clinical pathologist on a whole time or even a part time basis scarcely developing until after the first world war. Osler also remarked that, when he inspected a hospital, he was in the habit of telling his guide not to bother showing him the wards, he was certain they would be all that they should be, but to show him the laboratory. This commonly led to a good deal of embarrassment and his being conducted to some ill-equipped, ill-lighted room in the cellars.[38]

The techniques of clinical bacteriology developed steadily. Koch had demonstrated his technique of using solid media at the International Congress of Medicine in 1881, which earned a 'C'est un grand progrès, monsieur', from Pasteur. The easy separation of individual organisms which this technique made possible was an essential prerequisite to clinical bacteriology which was concerned with the isolation of pathogenic organisms from sites in the body with a normal flora. The original technique of Koch was rather clumsy, involving the pouring of molten medium on sterile slides and smearing it out evenly. Inoculation was performed by streaking a needle dipped in infected material several times across the agar. The slides had then to be incubated under the cover of a bell jar. The method was not wholly satisfactory, and in 1883 Koch introduced his 'pour plate' technique, which was regarded as an improvement.[39]

Petri, working in Koch's laboratory, introduced in 1887 what he called a

'slight modification', when he described his well known 'Petri dish'.[40] Although the advantages of the 'slight modification' must have been easily apparent, it does not seem to have immediately supplanted the original technique. Inspissated serum was introduced by Koch in 1882 and the cut surface of a sterilized potato was also a favourite medium.

The aniline dyes had been in use for some time before the beginning of clinical bacteriology, and the standard techniques used today were rapidly developed. In 1882, Ehrlich described a way of specifically staining the tubercle bacillus. Soon after Ziehl, during his brief bacteriological career, and Neelsen, a Dresden morbid anatomist, suggested minor modifications which, because of their greater convenience, soon became the standard method.[41] Gram of Copenhagen introduced his famous technique in 1884.[42]

In those early days, the identification of pathogenic organisms depended very much on observing their stained appearance, and the appearance of growth on agar, gelatine and potato. It was soon noticed that some organisms liquified gelatine, and a good deal of stress was laid upon the appearance of the liquification in gelatine stab cultures. It was also noticed that some organisms produced gas in the gelatine. The production of gas in the gelatine was found to depend upon the presence of a fermentable carbohydrate in the nutrient gelatine, and it became the practice to add glucose deliberately. Gradually, the idea of adding other substances to the nutrient gelatine to observe gas production developed, but it was not until 1898 that H. E. Durham described liquid sugar media containing a small inverted tube for the detection of gas. He also suggested that it was desirable to add a little neutral litmus to detect any change of reaction as well. This simple technique rapidly led to a great extension of the study of bacterial powers of fermentation and methods of distinguishing between pathogenic and non-pathogenic organisms on this basis were soon evolved.[43]

Animal pathogenicity tests were also much relied on and the rather elaborate 'Pfeiffer's phenomenon' which had been discovered in 1894 was shown to be a highly specific method of distinguishing pathogenic organisms. However, in England, with its peculiar anti-vivisection laws, animal work was not easy to perform. Durham's discovery, whilst investigating the mechanism of Pfeiffer's phenomenon, in 1896, of specific agglutination, was at once recognized as a simple and accurate method for distinguishing between micro-organisms,[44] and the test in reverse, the examination of the patient's serum for specific antibodies in typhoid fever, was introduced by Widal in the same year. This test soon became one of the commonest clinico-pathological investigations.

During the last two decades of the nineteenth century there were considerable advances in haematology. The use of the haemoglobinometer and haemocytometer gradually became general. Numerous patterns of haemoglobinometer were introduced, but many were too complex for routine use. The simple haemoglobinometer, in which a measured volume of blood was diluted in a calibrated tube until it matched an artificial colour standard was introduced by Gowers in 1878[45] and became the most popular; and instruments on this

principle have only been displaced within very recent years. With instruments of this kind anaemia gradually became clearly defined as a reduction in circulating haemoglobin rather than the pallid condition of the skin and weakness that it had been in Addison's day. The importance of doing both a red cell count and haemoglobin estimation at the same time had first been pointed out by Duncan in 1867.[46] The distinction between the high and low colour index anaemias with their different therapy and prognosis was made. Although Addison had described the clinical features of pernicious anaemia in 1855,[47] it was the account of the condition by the Swiss physician Biermer in 1872[48] which renewed interest in the disease.

The most important advance in the study of the leucocytes was their classification by staining reaction by Ehrlich in the early 1880's. In healthy men the white cells were thought to be almost entirely of the polymorphonuclear type, and, although variation in type as well as number had been noted in leukaemia, no detailed analysis had been made. Ehrlich's classification of leucocytes according to the affinity of their cytoplasmic granules for acid, basic or neutral aniline dyes is well known, and has stood the test of time. Many staining mixtures were tried. Ehrlich recommended his 'Triacid stain' composed of a mixture of orange G, acid fuchsin and methyl green.[49] Of the many other mixtures tried, none are even of historic interest, except that of Romanowsky of St. Petersburg who, in 1891, introduced a mixture of methylene blue and eosin for staining malaria parasites.[50] It was soon found to be equally useful as a general blood stain. Modifications of this stain were introduced by Louis Jenner, Leishman and others and stains of this type have remained the routine stain for blood films ever since.

Although the blood platelets had been discovered by William Addison in 1842,[51] studied by the young William Osler in 1873[52] and clearly described by Norris in 1878,[53] it was the work of Bizzozero in the early 1880's which revived interest in them.[54] It was appreciated that they were of importance in controlling haemorrhage and were a constituent of thrombus, and that their normal number in the blood was about 300,000 per cu. mm. That they were reduced in number in purpura haemorrhagica which had been described by Werlhof in 1735 was not known.[55]

Despite an enormous amount of work, the mechanism of blood clotting remained completely mysterious. Vierordt, in 1878, had first described a method for measuring the coagulation time of the blood, but interest in the subject from the clinical point of view waited upon Sir A. E. Wright's description of his simple methods.[56] Although James Miller of Edinburgh had recognized the coagulation defect in haemophilia in 1842,[57] it was not widely appreciated that this was the fundamental defect, an abnormality of the blood vessels being more widely accepted as its cause.

The development of clinical pathology up to the close of the nineteenth century has now been described. By that time clinical pathology existed in the form which we have it today, albeit on a diminutive scale. Laboratories for clinical pathology were in existence, and some few men made it their profession,

Kanthack, appointed at St. Bartholomew's in 1893, being probably the first in London.[58]

The growth of the basic knowledge upon which clinical pathology is founded has been outlined, but it is perhaps worth considering just what part clinical pathology did play in the medical practice of the times. Evidence on this point may be found in the St. Thomas's Hospital reports for 1898, in which a statistical account of the work actually done during the year at the recently founded clinical laboratory of St. Thomas's Hospital is given. During the year 1898, 1,664 specimens were reported on. These included the histological examination of 535 operation specimens, 175 Widal reactions, the examinations of 266 swabs for diphtheria bacilli, 52 red cell counts, 36 haemoglobin estimations, 32 white cell counts, but only four differential counts, the general examinations of 47 stained blood films, the examination of 110 samples of urine including 34 for tubercule bacilli and the examination of 40 specimens of sputum for tubercule bacilli.[59]

During the next twenty-five years, two developments in medicine in particular influenced clinical pathology. One, transient, but an important influence in its day, was vaccine therapy, and the other the development of biochemistry.

The introduction of vaccine therapy played a significant part in moulding the relationship between the bacteriologist, and indirectly other medical laboratory workers, the patient and the clinician. It had been possible for the clinician to delegate his bacteriological diagnosis to a laboratory worker who did not come in contact with the patient, but merely examined and reported upon material submitted to him. This was, as Sir A. E. Wright pointed out, not satisfactory, and might even be scarcely ethical.[60] The clinician was not in a position to assess the reliability of the laboratory diagnosis or properly to interpret it. The advent of vaccine therapy in the first decade of the twentieth century had made the existing system even less satisfactory. Vaccine therapy made bacteriological work necessary on a vastly increased number of patients. The infecting microbe had to be isolated, separated from various members of the normal body flora, the vaccine prepared from the organism and its injection into the patient controlled as to frequency and dosage by a fairly complicated blood test, the opsonix index. Inoculation departments were established at the larger hospitals, the most celebrated being that at St. Mary's Hospital, and various more or less reputable private and commercial departments were organized. The clinician faced with cases of chronic acne, recurrent boils, lupus vulgaris, rheumatoid arthritis and other chronic diseases whose course he seemed powerless to influence referred them to the bacteriologists who perforce must be treated as a consultant colleague of equal status. Harmony was not achieved without considerable wrangling and bad feeling on both sides, but the outcome was undoubtedly to further entrench and to raise the status of the clinical pathologist.[61] This little chapter is surely one of the curiosities of the history of medicine, for here was a method of treatment and a laboratory test, probably valueless and meaningless respectively, which, none the less, exerted an important influence on the development of clinical pathology.

The early attempts at blood analysis have been referred to, but they were of little or no practical value. At the end of the nineteenth century there was not a single chemical test on the blood, except perhaps the occasional detection of abnormal haemoglobins by spectroscopy that was in routine use in clinical pathology. The development of modern clinical chemistry depended upon the introduction of colorimetric methods of analysis, which were at the same time simple and accurate, and upon the free use of venepuncture to obtain adequate blood samples. Venepuncture for diagnostic purposes was but slowly taken up. None the less, about this time blood culture was recognized as a valuable diagnostic measure, particularly in typhoid fever, and its use for this purpose no doubt lead to its use for other diagnostic purposes. It was, however, by no means the routine procedure it has become today. For many years it was an operation to be avoided if possible and Sir A. E. Wright's celebrated book on *The technique of the teat and capillary glass tube* which was published in 1912, described an elaborate and ingenious system for performing blood tests on the quantity of blood which could be obtained by pricking the finger. Colorimeters had been invented by Jules Duboscq in 1854, and the British firm of Lovibond was in the field in 1899 with a colorimeter for haemoglobin estimation. It was, however, Folin's method of estimating creatinine in the urine colorimetrically in 1904 that gave a great impetus to the use of colorimeters in medical chemistry. Over the next ten years colorimetric methods of estimating such important constituents of the blood as cholesterol, urea, uric acid, glucose and creatine were introduced. Ambard in 1910 studied the relationship between the blood urea level, the urine volume and urine urea concentration,[62] MacLean introduced the urea concentration test in 1920[63] and Van Slyke reported the concept of 'urea clearance' in 1928.[64] Likewise the accurate study of acid-base balance dates from the same worker's relatively simple technique brought out in 1917.[65] The development of micro-analysis of blood was very largely of American origin and the system of Folin and Wu of precipitating the blood proteins with tungstic acid and then performing a number of analyses on the protein free filtrate, had that simplicity and convenience which more than anything else leads to the diffusion of a technique.[66]

The standard which clinical pathology had attained in the years just prior to the first world war can be appreciated by examining the first edition of P. N. Panton's celebrated text-book of clinical pathology. Blood examination consisted of cell counts and examinations of stained films, agglutination reactions, Wassermann tests, examination for parasites such as malaria and blood cultures. Blood chemistry consisted of spectroscopic examination, the detection of bilirubinaemia by noting the increased yellow colour of serum and confirming it by Gmelin's qualitative test, the demonstration of excess uric acid by Garrod's time honoured technique and Wright's estimation of the alkalinity of the blood which can hardly have yielded any worthwhile information. Bacteriology was relatively advanced, and the usual simple staining and culture methods used today were available. The chemistry of the urine showed no advance upon the methods available 50 years previously, simple examinations for pus, red

cells, albumen and sugar comprising the only really useful investigations. Various other miscellaneous investigations were available. Test meals had been introduced about 30 years previously and there was a fair appreciation of their value. Faecal examination consisted of little more than simple inspection, with a few simple qualitative tests for such things as fat and stercobilin marking the only advances since the days of Hippocrates. Histological techniques were much as they are today, and included rapid diagnosis by means of frozen sections as well as paraffin embedding.

By this time the early phase of the history of clinical pathology was over, and it was established as a speciality essential to the practice of modern medicine. The story of its subsequent development would fall into two clearly defined chapters devoted to the inter-war years and the foundation of the Association of Clinical Pathologists, and the great expansion of the speciality that followed the introduction of the National Health Service in 1948. There are some clinical pathologists whose working lives have spanned this period, and we look to one of them to bring this history of clinical pathology in Great Britain up to date.

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