HAEMATOLOGY IN MY TIME*

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De Solla Price[1] and others have pointed out that 80 - 90% of all the scientists that have ever lived are alive now; in other words, more than 80% of our knowledge is contemporaneous. The latest edition of Wintrobe's *Clinical Haematology*[2] weighs 6 lb. and it makes no pretence to be an encyclopaedia. It would therefore be hopeless for me to attempt to review the whole development of haematology in my lifetime, and I shall confine myself to haematology as I have seen it. I shall also be influenced by the extent to which discoveries have reduced the total sum of human misery.

When I was a medical student in Manchester immediately after World War I, one of the physicians for whom I acted as ward clerk, the late Dr E. M. Brockbank, was interested in the blood. He was a tall, handsome physician of the old school, with silver-white hair and elegant hands, on one of which he wore an agate seal-ring, and I can still see those hands as he stained a blood smear in the side room after the ward round.

The effect of the personality and interests of a teacher on the student at an impressionable age is often long lasting, and so it was with me. At that time haematology was for me a pictorial study and I delighted in Pappenheim's atlas[3] and the plates in Naegeli's *Blutkrankheiten und Blutdiagnostik*.[4] These pictures have never been surpassed, though some of the modern colour transparencies with their stereoscopic effect may rival them.

What I have called pictorial haematology fell into some disrepute with the development of physicochemical methods of examination of the blood, but it was restored to favour by the introduction of marrow puncture by Arinkin[5] in 1929. The time lag was longer in those days and I did not do my first sternal puncture until 1934. The delegation of much haematological routine to technicians and the increasing adoption of automation have increased the importance of the examination of the stained smear by the haematologist. Ovalocytosis and hypersegmentation in folic acid deficiency, rouleaux formation in myelomatosis, and fragmentation and distortion of the red cells in renal and micro-angiopathic disease are only three examples of diagnostic indications which may be detected by the expert.

In 1924 I had the opportunity to go to the USA as research assistant to F. M. Allen. Allen was one of the most remarkable men I have ever met. He was then in his early forties, a man with a strong physique and a jutting jaw, who would have made a first-class general, as he had a powerful intellect, supreme self-confidence and the ability to make people carry out his orders under difficult conditions. After working at Harvard and the Rockefeller Institute, he had founded his own clinic and research institute in New Jersey and it was there that I learnt to assist in operating on animals at all hours of the day and night, and to understand colloquial German, for the laboratory was largely staffed by German doctors and medical students who had come there to escape the post-war inflation in their own country.

Allen will always be remembered for his work on the islets of Langerhans and the fasting treatment of diabetes.[6] He was not only a gifted experimental pathologist but a superb dietitian, and his work on salt-free diets was years ahead of its time. He conceived the idea that just as the pancreas could be damaged by excess of carbohydrate in diabetes, and the heart and the kidneys by excess of salt in cardiorenal disease, so also the megaloblastic degeneration of the bone marrow in pernicious anaemia might be due to the excess or deficiency of some principle in the diet. We therefore began treating patients with diets rich in vitamins and proteins, but with only inconstant success, and just as he had been beaten by Banting and Best in the race for insulin, so now he was to be beaten once again in the race for the liver principle. No wonder he died a disappointed and embittered man.

When I visited Boston in 1925, the Thorndyke Memorial Institute was headed by Peabody, a man still remembered for his charm and his unique combination of ability at the bedside and in the laboratory. Peabody[7] showed that the haemopoietic marrow extended down the shaft of the long bones during relapse in pernicious anaemia as a result of what we now know to be ineffective erythropoiesis. Peabody died of malignant disease in 1927 at the early age of 46 years, and he was succeeded by Minot, who, with Murphy, had discovered the liver treatment of pernicious anaemia in 1926.[8] Their success was largely due to the use of the reticulocyte crisis as the first indication of remission. The inspiration for their work came from Whipple, who had established a method for measuring the haemopoietic value of different foods and nutrients in the dog. Dogs were given a basic diet and were maintained in a state of anaemia by bleeding them at intervals. It was thus possible to measure the production of haemoglobin on the basic diet and the effect of the addition of different nutrients. Liver was found to make a great contribution to haemoglobin formation in the dog, and it was this that led Minot and Murphy to try it in pernicious anaemia, a good example of what Robb-Smith[9] has called the importance of false assumptions.

The success of liver therapy in pernicious anaemia took Europe by surprise. Pernicious anaemia was by definition an incurable disease, and Naegeli,[10] the best-known European haematologist, was deeply sceptical. I remember being on a ward round at Guy's Hospital in London in 1927, which was being taken by John Ryle, perhaps the best English clinician of his time. We were looking at a patient with pernicious anaemia, and one of those present said that he had heard that in the USA it was being treated with liver. 'Whatever will those Americans do next!' said John.

For me, as for most of my generation, haematology had ceased to be a purely visual study and had become quantitative. The papers of Whipple and Robscheit-Robbins[11] and the textbooks of Abderhalden[12] and Graham

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Lusk[13] replaced the atlases of haematology, and we began to think of anaemia as a disturbance of nutrition and metabolism. Quantitative methods spilled over into the examination of the blood itself. Fahraeus[14] had introduced the erythrocyte sedimentation reaction into the clinic in 1921, and Haden,[15] Wintrobe and others showed the value in the diagnosis and classification of the anaemias of the constants derived from the use of the haematocrit and the measurement of the haemoglobin in G/100 ml., in particular the size and mean corpuscular haemoglobin concentration of the red cells.

One of my tasks with Allen had been to carry out some experimental work on the spleen, and, expecting to continue this, I spent the summer of 1926 in Prague, where Kaznelson,[16] while still a student, had introduced the treatment of idiopathie thrombocytopenic purpura by splenectomy. The German university medical school in Prague was at this time the seat of a brilliant school of haematologists which had grown up around the pharmacologist Starkenstein and which was later, alas, to be destroyed by the Nazis. Starkenstein[17] had done a great deal of work on iron metabolism and it was in Prague that I first learnt of the superiority of ferrous over ferric iron and of the existence of achylic chloranaemia. When I returned to England I went to the pathology department in Cambridge for a time, working on the cytology of the monocyte by the methods of Sabin[18] and her school, and it was not till I resumed clinical work in London in 1928 that I took up the study of hypochromic anaemia and iron deficiency, another example of the more leisurely pace of research 40 years ago.

At Guy's Hospital in London I came under the influence of Sir Arthur Hurst, who was one of the outstanding personalities in British medicine between the two wars. Despite a frail physique, deafness and persistent asthma, he radiated lines of force, and whether the effect was positive or negative he was always stimulating. Hurst's life should be a lesson to us today on the value of allowing young people in medicine to develop freely, instead of labelling them and confining them within a particular career structure to suit the requirements of examining bodies and boards of selection. He began his medical life as a neurologist, a pupil of Janet, and he achieved great success in the treatment of neuroses in World War I. He was a pioneer in the study of the alimentary tract by X-rays in health and disease, and he became the leading gastro-enterologist in the country. He was one of the first to stress the invariable occurrence of achlorhydria in pernicious anaemia and subacute combined degeneration.[19] Through him I got to know Knud Faber, whose work on the stomach stretched back into the 19th century, and whose lectures in 1935, entitled *Gastritis and its Consequences*, are still topical because Faber studied the whole stomach which had been fixed immediately after death.[20] Through association with these two men and with Meulengracht,[21] who was Faber's successor, I acquired an interest in the relation between the stomach and anaemia which has been one of the main themes of my life.

One of many other things I learnt from Hurst was the importance of pushing the dose of a drug till one got an effect, either therapeutic or toxic. For years people had been treating anaemia ineffectively with iron and ammonium citrate in doses as small as gr. 5 three times a day, whereas to obtain satisfactory improvement it was sometimes necessary to give gr. 90 a day of this particular preparation, as it is a ferric complex from which the iron is poorly absorbed.

It was in 1927 that W. B. Castle, who had been assisting Minot in some of the work on liver fractions, while descending in the back elevator from the fourth floor of the Thorndyke Memorial Institute in Boston, suddenly conceived the idea of digesting beef steak in the human stomach and administering it in pernicious anaemia after a control period on beef muscle alone.[22] These unexpected moments of inspiration, which usually follow a long period of preparation and often unconscious association of ideas, are of perpetual interest to the student of discovery. At any rate, this was the unlikely place in which Castle conceived the hypothesis that pernicious anaemia was due to the absence from the gastric juice of an 'intrinsic factor', which was necessary for the absorption of an 'extrinsic factor' from the diet, a hypothesis which still survives intact 41 years later.

What an exciting time this was! As one progressed further in the study of idiopathic hypochromic anaemia, as it came to be called, it soon became apparent that achlorhydria was not a *sine qua non* for the disease, as it was for pernicious anaemia, and that intrinsic factor was still present in the gastric juice despite the achlorhydria. The common factor in conditions so diverse as hypochromic anaemia in infancy and the Plummer-Vinson syndrome in middle-aged women was not achlorhydria but iron deficiency. Now, after 40 years, we still do not know the exact relationship between iron-deficiency anaemia and the epithelial lesions which so often accompany it, and we do not know how often iron deficiency precedes the anaemia and vice versa.

Both Castle and Wintrobe visited London round about 1930, and the friendships we made have lasted through the years. At the combined meeting of the American and London Colleges of Physicians in Boston in April 1968 I was asked by a friend and former pupil where I was staying. 'With Bill Castle,' I replied. 'What?' he said, 'is he still alive?' I am reminded of an international symposium on iron metabolism in 1963, when one of the participants referred to me as one of the earlier workers in this field, and of a lecture on the adrenal gland in San Francisco in early 1968 by George Thorne, when a younger member of the audience irreverently remarked that it was like hearing Jesus Christ lecture on the New Testament. How brief is mortal sovereignty!

Another friend in London at this time was Lucy Wills, who made the classical studies in India and at home which suggested that liver contained two haemopoietic factors, the Wills factor and the Cohn factor, later to be identified as folic acid and vitamin B_{12}. It was deficiency of the Wills factor, or folic acid, which was responsible for tropical macrocytic anaemia.[23] The dramatic quality of this work for a time distracted attention from other causes of nutritional anaemia in the tropics and subtropics. As in temperate climates, iron deficiency is much the commonest form of anaemia and it is often associated with infestation with hookworms. Recent work by Lay-

risse and Roche[24] and others has convincingly demonstrated the relationship between hookworm load and haemoglobin levels in Venezuela and other countries, and the mechanism of action of the worm.

One of my colleagues at Guy's Hospital was J. M. H. Campbell, who wrote a striking statistical paper in 1923[25] on the great epidemic of chlorosis which filled the out-patient departments of Western Europe in the 19th century and which declined and disappeared in the first quarter of the present century. Another lifelong friend was L. S. P. Davidson, then at Aberdeen. I regard the study by Davidson and his colleagues[26] on the prevalence of anaemia in Aberdeen as one of the most important contributions to haematology made over this period. It related the incidence of anaemia to iron intake and introduced the concept of the vulnerable groups—infants, young children, and women of reproductive age, particularly in pregnancy.

Lucy Wills and Stanley Davidson pioneered the use of group studies in anaemia, and these remain of undiminished importance. It is useful to differentiate between surveys and screening. In surveys the object is to determine the prevalence of anaemia and relate it to possible aetiological factors. One of the chief uses of surveys is to provide the basis for prospective studies. In screening tests, the object is to identify individuals with unrecognized anaemia and refer them for diagnosis and treatment. Selective screening can be employed on vulnerable groups such as women of reproductive age, infants and old people. Current surveys show that anaemia is much commoner in Asia, Africa and South America than in the West. In the most severely affected areas just over half the men and two-thirds of the women may have haemoglobin values of less than 10 G/100 ml. In the vast majority the anaemia is of the iron-deficiency type and in theory could be simply remedied. The improvement of this state of affairs is one of the main preoccupations of the World Health Organization. The tropical anaemias have proved more complicated than we realized in the 1930s, a point I shall return to later.

BLOOD TRANSFUSION

I gave my first bood transfusion in the USA by the direct method in 1924 on one of the patients with pernicious anaemia Allen was studying. Transfusion had become practicable with the introduction of sodium citrate as an anticoagulant in World War I, but it was slow to become a routine procedure in clinical medicine. The London Blood Transfusion Service was founded in 1921, as the result of a telephone call from King's College Hospital to the late Percy Lane Oliver, who was then the Honorary Secretary of the Camberwell Division of the British Red Cross Society.[27] He was asked if he could find a donor to save the life of a patient who would otherwise die. Oliver and a number of his colleagues volunteered. One of them, a woman, was chosen and all went off well, with no untoward consequences to her and an excellent result for the patient. Oliver then conceived the idea of establishing a panel, to cover all London, with a record of the names of willing donors and their blood groups, so that any hospital, whether by night or day, could be assured of a donor of suitable type. After his death the Oliver Memorial Fund was established in 1945, from which annual awards are made 'to those persons whose work in or services to blood transfusion have been outstanding'. How fortunate we have been in the UK never to have employed paid donors!

In the early days apparatus was often primitive, and I remember a large brass syringe at the London Hospital with which it was only too easy to inject air into the veins. Marriott and Kekwick introduced continuous-drip blood transfusions in 1935[28] and they reported a series of massive blood transfusions in 1940.[29] This technique brought about a great reduction in the death rate from haematemesis and melaena and for a time biased treatment perhaps too strongly towards medical rather than surgical treatment of bleeding peptic ulcers. In spite of their work, it is extraordinary how long the idea persisted that a transfusion was one pint of blood. The shackles of convention are hard to discard. We still think of medicines in terms of the adult dose instead of the dose per kilogram of body-weight or square metre of body surface. We still tend automatically to give medicines three times a day, and it is only recently that we have begun to study the best schedules for the administration of antimitotic drugs in leukaemia so that they can attack the leukaemic cells when they are in the most vulnerable part of the mitotic cycle.

During World War II acid citrate dextrose was introduced as the anticoagulant and it became possible to store blood and to give massive transfusions relatively easily. It also became possible to give individual components of the blood, first by the relatively crude separation of the packed red cells from the plasma and later by more specific isolation of particular fractions of the cells or plasma. Platelet transfusions have now been in use for some years, using either platelet-rich plasma or platelet concentrates from fresh units of whole blood. More recently plasmaphaeresis has been employed, whereby a single donor may give up to 1·5 litres of plasma a week. Apparatus is being developed on the lines of a cream separator, whereby not only platelets but also white cells and if necessary even lymphocytes alone can be obtained by plasmaphaeresis. It is also possible to concentrate the antihaemophilic factor in plasma by a relatively simple process of cryo-precipitation. There is still much basic research to be done on the transfusion of platelets and white cells, but it is generally held that the treatment of leukaemia and the haemorrhagic diseases is being greatly advanced by these procedures.

In 1930 I became a member of the Association of Physicians of Great Britain and Ireland, and among others I got to know Claude Wilson, who had described the first cases of acholuric jaundice in England[30] (though not under that name) in 1890 when he was aged 30 years. These cases were followed up and confirmed by J. M. H. Campbell at Guy's Hospital in 1926.[31] At that time my knowledge of the haemolytic anaemias could probably have been summed up under the headings of typical acholuric jaundice and atypical acholuric jaundice. The vast expansion of our knowledge since is beautifully described in the four volumes of Dacie's *The Haemolytic Anaemias* (1960 - 1967).[32] In Europe the most important example of these anaemias is the haemo-

lytic anaemia of the newborn, for which effective treatment and prophylaxis are now available. Another important event has been the isolation of the immunohaemolytic anaemias in the adult. With the recognition that immunohaemolytic anaemia may be the result of the use of drugs such as methyldopa, we no longer dare to call these anaemias idiopathic or auto-immune.

I myself have done little work on the haemolytic anaemias except in a rather peripheral way. In Oxford during World War II we had to treat many airmen with burns, and I became interested in the anaemia of burns—which is, at any rate in part, haemolytic. In the course of this work we used the Ashby technique to measure the survival of the red cells in the circulation. I had previously been impressed by Schiodt's[33] observations on the regeneration of the blood after haemorrhage from peptic ulcer. Schiodt was the first person to treat such observations mathematically and to derive from them figures for the life-span of the red cell, the fraction of the cells destroyed daily and the contribution made by ageing and by random destruction. We were fortunate to interest a mathematical friend, Mr E. O. Powell, in the curves we had obtained by the Ashby technique, and he carried out the first, I think, of the mathematical studies of red-cell survival which have played such a large part in the development of the science of erythrokinetics.[34] As a result we have now reached the objective indicated in my Goulstonian Lectures[35] in 1932, which was to be able to measure the red cells which enter or leave the circulation in 24 hours with the same accuracy as we can measure the protein metabolism or the work of the heart.

The Ashby technique was subsequently replaced by the labelling of the red cells with radio-isotopes and by the use of scintillation counters to determine the fate of the labelled cells in the organism. It would indeed be difficult to conceive of haematology nowadays without radio-isotopes. Their applications extend from the minute details of cellular proliferation to absorption and retention in individual organs and in the body as a whole. Enormous advances have been made in the pathological physiology of the blood and in the dynamics of the three populations of red cells, white cells and platelets. The whole-body counter has greatly accelerated work on the metabolism of iron and vitamin B_{12}, but it is well to remember that the conditions of study are often highly artificial and we are still unable to measure the amount of iron absorbed from a mixed diet or the availability of the folic acid and vitamin B_{12} in such a diet.

Closely related to the haemolytic anaemias are the haemoglobinopathies, in the elucidation of which one of the protagonists in this history, W. B. Castle, was concerned. The story is worth retelling in Castle's own words, because it shows how much more important are people than plans in research, and how a great discovery may depend on the chance meeting of minds.[22]

'Linus Pauling and I were both members of a committee that eventuated in the publication of the book by Vannevar Bush, *Science, the Endless Frontier*, that, among other places, met in Denver I think in 1945. On the overnight train between Denver and Chicago, not long after leaving Denver, I had a conversation with Dr Pauling about the molecular relation of antibody and antigen, etc., which was very informative to me. I then sketched a little bit of the work that Dr Ham and I had been doing since 1940 on sickle cell disease and mentioned that, as stated by Dr I. J. Sherman in 1940, when the cells were deoxygenated and sickled they showed birefringence in polarized light. This, I stated, meant to me some type of molecular alignment or orientation, and ventured to suggest that this might be "the kind of thing in which he would be interested". I am equally clear that I did not make the further generalization that it was orientation of the haemoglobin that might be doing this.'

Strauss aptly remarks that this passage shows that committee meetings do occasionally, if inadvertently, produce something useful. In 1949 Pauling[36] showed that the haemoglobin of sickle-cell anaemia differed electrophoretically from the haemoglobin of normal subjects. In the same year Neel[37] showed that the disease was inherited in the manner of a single gene. Pauling[36] called sickle-cell anaemia a molecular disease, and thus was born the subject of molecular biology, i.e., the study of the synthesis and structure of proteins and nucleic acids, with special reference to their genetic basis. By the use of relatively simple methods of electrophoresis a variety of haemoglobinopathies and abnormal haemoglobins was discovered, of which S, C, D and E are the most common. Thalassaemia was shown to be due to a disturbance in the regulation of haemoglobin synthesis, as a result of which the formation of normal adult haemoglobin (HbA) is suppressed and abnormal amounts of foetal haemoglobin and haemoglobin A_2 are formed.

The normal haemoglobin molecule contains two alpha-peptide chains and two beta-peptide chains, each of which comprises a large number of amino acids in sequence. By breaking down the haemoglobin molecule into fragments and examining these by combinations of electrophoresis and chromatography it is possible to obtain characteristic pictures or 'fingerprints' from the different haemoglobins. It has further been possible to show that the differences may be due to the substitution of a single amino acid in one of the peptide chains. Clinical science, in the USA in particular, has tended to become dominated by molecular biology. The results have been particularly interesting in the study of the abnormal proteins of multiple myeloma and it has been necessary for even the oldest of us to learn something about heavy chains and light chains.

I must return to my history. I left Guy's Hospital for St Bartholomew's in 1934 and there met a number of young men who were later to make a name in haematology, including R. G. MacFarlane, Magnus and Robb-Smith. MacFarlane would be the first to admit that on a superficial view he was the least promising of the three. The reason presumably was that he could not take seriously subjects in which he was not interested. The position of demonstrator of pathology became vacant and both MacFarlane and Magnus, who were and remained great personal friends, were candidates. To most people's surprise the head of the department, Prof. E. H. Kettle, chose MacFarlane. His choice was amply justified by MacFarlane's career—the treatment of haemophilia with anti-anaemophilic globulin, the discovery of Christmas disease and the cascade theory of blood coagulations.[38] Magnus, of course, was no mean opponent and his work on the anatomy of the stomach in pernicious anaemia has now become classical.[39] Magnus would in any event have become a distinguished pathologist, but MacFarlane might have been lost to science but for Kettle's discerning

eye. The ability to pick people is one of the greatest gifts the head of a department can possess. I do not think there are any rules for it and I doubt whether it can be learnt.

Blood coagulation has now become a subject in its own right. Much of the literature is esoteric and concerned with rare diseases, but there have been great practical gains. In 1934, only about 20% of boys with haemophilia survived beyond puberty; today we should be seriously disturbed if we lost a patient. Equally important is the lead the new work may give in the problems of thrombosis and fibrinolysis. Deaths from venous thrombosis in both sexes and at all ages have increased considerably in the last 10 - 15 years, and coronary thrombosis and cerebral thrombosis are major causes of death. There is every hope that the tools forged in the study of the rare coagulation disorders may lead to a better understanding and treatment of thrombo-embolic disease, and, as I have written elsewhere, this may well prove to be another case in which the study of the exceptional leads to a better understanding of the common.

At the time I joined St Bartholomew's Hospital I was a member of a medical travelling club founded by Sir Arthur Hurst, and at one meeting Snapper and colleagues[40] showed cases of hypopituitarism associated with achlorhydria and anaemia. This afterwards became irreverently known as the Whipper-Snapper syndrome. The cases interested me, as I have always wanted to understand the aetiology of pernicious anaemia and the relation between achlorhydria and anaemia.

In 1938 Magnus and Ungley[39] described a clear-cut lesion—simple atrophy of the stomach—in pernicious anaemia, and this seemed to be the pathognomonic feature of the disease. In a reassessment of the gastric lesion 20 years later Magnus[41] gave reasons for believing that gastric atrophy was the end stage of chronic gastritis, but at the time it was tempting to think that it might be due to an endocrine deficiency. As a result Spence and I[42] treated a man with hypopituitarism, hypochlorhydria and gastric atrophy with thyrotrophic and gonadotrophic extracts of the pituitary gland, and observed restoration of secretion of acid and apparent regeneration of the mucosa. More than a quarter of a century later Jeffries[43] and others were to show recovery of gastric mucosal structure and function in pernicious anaemia during prednisolone therapy, but this is almost certainly the result of the non-specific anti-inflammatory action of corticosteroids.

The relations between pernicious anaemia and endocrine disease have proved difficult to unravel, not less because the pituitary and the other ductless glands work as a co-ordinated system. Another reason is that the demonstration of an association between diseases is an extremely difficult exercise beset with statistical fallacies. One of the rewards of schemes like the Oxford Record Linkage Study[44] will be to show which suspected associations are fact and which are fiction. There is an odd association between parathyroid disease and juvenile pernicious anaemia, and the adrenal gland also may be involved in this syndrome. There seems little doubt about the increased frequency of pernicious anaemia in diabetes mellitus, hypothyroidism and thyrotoxicosis, but the link here may be a tendency to auto-immune reactions involving both the stomach and the endocrine glands. A few years ago James Biggs,[45] in my department at Oxford, carried out an extensive study of the effects of experimental hypothyroidism and thyrotoxicosis in the rat, but he was unable to demonstrate any effect on the histology of the stomach or the secretion of hydrochloric acid and intrinsic factor.

When we resumed research work on pernicious anaemia after World War II, much that had been obscure was soon clarified by the synthesis of folic acid in 1945 and the isolation of vitamin B_{12} in 1948. Nevertheless, the nature of intrinsic factor and the aetiology of pernicious anaemia remained undetermined and we were still anxious to produce the disease in animals, to have what in modern jargon is called an 'experimental model'. It is impossible to reproduce the picture of pernicious anaemia in animals by dietary deficiency or by total gastrectomy, though we know that these procedures do in fact produce avitaminosis B_{12} if coprophagy is prevented and iron deficiency is treated. The only way anything like pernicious anaemia had been produced experimentally was by creating stenosis or blind loops in the small intestine. Cameron and Watson, who were working with us, successfully adapted these techniques to the rat, but the operations were difficult and the results capricious.[46] Radioactive vitamin B_{12} then became available, and when Watson moved across the road to work with Florey in 1955, they were able to demonstrate failure of absorption of vitamin B_{12} in gastrectomized rats.[47] So began what Castle subsequently called the 'years of the rat', years in which much has been learnt about the nature and mode of action of intrinsic factor.

During the same decade McCall, O'Brien and others associated with us[48] maintained a colony of iron-deficient rats in Oxford by methods that have since been widely copied, and though we found no epithelial changes or achlorhydria in the iron-deficient rat, the value of the rat in the study of iron metabolism was fully confirmed. There is still a great deal of work to be done with them in this field. Rats are easy to handle and very suitable for studies using isotopes, and one can carry out test-meals and similar procedures on the intact, unanaesthetized animal. I was almost as sorry to leave the rats as the patients when I retired in 1965. I believe every academic department of medicine should have facilities and staff trained for animal investigation. Far too often research is carried out on patients which would be better done in animals.

In 1955 Blackburn and others[49] demonstrated that patients with pernicious anaemia who were treated with preparations of vitamin B_{12} and intrinsic factor by mouth became refractory to the treatment unless the dose of intrinsic factor was greatly increased. In the course of investigating this phenomenon, Keith Taylor[50] in Oxford and others elsewhere discovered that in patients with pernicious anaemia who had not been treated with preparations of intrinsic factor—or indeed who had not been treated at all—a substance which blocked the absorption of vitamin B_{12} could be demonstrated in the serum. It is quickly realized that this was an auto-immune antibody, similar to those which were being contemporaneously studied in thyroid disease.

We now know that two gastric auto-antibodies may be found in the serum in pernicious anaemia, the intrinsic-factor antibody which is probably found only in pernicious anaemia and pre-pernicious anaemia, and parietal cell antibodies which are found not only in pernicious anaemia but in other forms of chronic gastritis, such as that associated with iron deficiency. It seems probable that an auto-antibody will tend to perpetuate the disease with which it is associated, but the problem remains: which comes first, the disease or the antibody? A practical gain from this work is that it is now possible to estimate quantitatively the amount of intrinsic factor in the gastric juice, because of the specific affinity between intrinsic factor and its antibody.

So far I have said nothing about leukaemia and the lymphadenopathies, though they have been of continuous interest to me, as they must be to any clinical haematologist. I became a member of the Scientific Advisory Committee of the Lady Tata Memorial Trust for research on leukaemia in 1936, I have sat on several other committees on acute leukaemia and I have been chairman of the MRC Working Party since 1958. Leukaemia has not suffered from neglect at the committee table. During these years an enormous amount of clinical and experimental work has been done in this field. We have learnt much about the prevalence, classification and life history of the leukaemias. We have seen the curve of incidence rise alarmingly, though now at last it appears to be flattening out for reasons which are just as obscure as the initial increase. Life can be prolonged for a year or two in the acute leukaemias. All this is to be welcomed, but it must be admitted that progress has been painfully slow.

At the end of World War II, as a result of such striking successes as the development of radar and the production of the atomic bomb, consciously or unconsciously people came to believe that the problems of medicine could similarly be solved if enough resources were devoted to the enterprise. In the USA, appropriations for medical research were greatly enlarged and the number of full-time workers in departments of medicine has increased at least fivefold. In the decade beginning 1955, the National Institutes of Health in the USA expended $214,000,000 on its cancer chemotherapy programme alone, much of it devoted to leukaemia. One now detects a feeling of disappointment that the results of all this expenditure have been rather small in terms of improvement of the public health.

It is right that continuous pressure should be maintained in the study of killing diseases, and there should be bodies of research workers with special knowledge of them, ready to pick up any useful clues to their understanding. However, it has been my experience, as recounted in this lecture, that primary, seminal discoveries are not the result of planning or project research. These have their place in the second stage, in the mopping-up operations and in the exploitation of ideas. The anaemias of the tropics and subtropics are in this phase at present, where the knowledge has been acquired and needs to be applied.

I have emphasized the importance of personal contact between research workers and of cross-fertilization of ideas. This becomes more and more important as the volume of printed material becomes so great. The speed with which ideas can be exploited is now so fast that it is necessary to travel to scientific meetings and to visit other laboratories and countries if one is to keep pace with the advancing front of knowledge. Nevertheless, it is easy to become too peripatetic, for nothing can replace work in the clinic and at the bench. I have been impressed by the contribution made by schools which go on for several generations: the Peabody, Minot, Castle dynasty at the Thorndyke; Faber, Meulengracht and Schwartz in Copenhagen; the plenitude of haematologists in Oxford during the last 30 years

Are there any important things we are missing as we missed the haemoglobinopathies in the past? Although it may sound overbold, I doubt it. Most fields in clinical medicine are too well tilled and are now subject to the law of diminishing returns. Are there any prevalent delusions, such as the exaggerated importance formerly attached to intestinal toxaemia, focal sepsis, allergy stress and the psychogenic factors in organic disease? It is probable that the auto-immune theory of disease is being overworked, but there is general realization of the dangers.

Are we, as clinical haematologists and pathologists, following the right lines in our research work? In 1967 clinical science came under heavy fire both from Lord Platt[51] in his Harveian Oration and from Paul Beeson[52] in his presidential address to the Association of American Physicians. Both stressed the preoccupation with minutiae and with laboratory techniques, and the poverty of the contribution to the health and happiness of mankind. There is disproportionate attention to molecular biology by men whose primary training was in clinical medicine. The cobbler should stick to his last.

One answer to that, I suppose, is that only molecular biology is likely to provide methods which will eliminate the haemoglobinopathies and the hereditary blood diseases; only work at the cellular and subcellular level will solve the riddles of leukaemia and malignant disease. Nevertheless, clinical work still continues to throw up the fruitful ideas which provide the stimulus to creative work. A relatively recent example is given by Burkitt's observations on lymphosarcoma in Africa.[53] There are still clinical topics about which there are confusion and controversy. Modern methods of record linkage and data processing have provided the clinical haematologist with new techniques for his work. There is no substitute for genius, and it is probable that the number of geniuses in medicine has not increased in the same ratio as research workers, but there is plenty of work for those who are prepared to accept the role of what T. H. Huxley called the honest hodmen of science.

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