HAEMATOLOGICAL HERESY*

BY

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One of my teachers used to say that every so often there should be proclaimed a kind of sabbatical year. For this time, firm in the resolve to add nothing to medical writing, we should sift what had already been written and try to formulate principles. Whether we like it or not, the war has given some of us several such years, though I doubt if we have made the most of them; for military life, even when leisurely, is little suited to calm reflection, and libraries are often inaccessible.

A cursory acquaintance with haematological writings before the war of 1914-18 is enough to show that studies of a basic nature were interrupted by that war and some have never been resumed. A few years later the world of haematology, and indeed of medicine, was dazzled by the finding of a cure for pernicious anaemia and by the admirable experiments of the Boston school that soon afterwards revealed the source of the liver factor. I mean no disrespect whatever to the authors of these entirely brilliant discoveries when I say that their work seems in some ways to have continued to dazzle the world of haematology from that time on. It is odd, for instance, that there is almost no mention in English medical textbooks of the artificial synthesis by Hans Fischer of a near relative of the pigment portion of haemoglobin—another event of the same period which must surely one day take its place as an achievement of the first rank; and I cannot help thinking that the theory of anaemia due to arrest of maturation in the bone marrow has enjoyed an undeserved immunity from criticism because it saw light as an explanation of one of the two or three most dramatic discoveries in medicine of the century. It is this theory that I am going to indict with such vigour as I can muster. But should this heresy, which, like many others, is only the revival of an older doctrine, one day become orthodox, I would be the first to say that the theory in its day appeared to bring order out of disorder, and did excellent service as a scaffolding on which haematological teaching could be based.

The theory of arrest of maturation as a cause of anaemia holds that, in the absence of a factor necessary for a particular stage in the ripening of red cells in the marrow, there may be an accumulation of cells which cannot develop further and a useless hyperplasia of the marrow. As one author put it, "it is as if a mass-production motor factory were unable to obtain an essential manufacturing part. Soon the assembly hall is crowded with unfinished cars, but outside the street is empty of vehicles." A simile from military life might here seem appropriate. It is as if recruits were poured into a training area but no trained troops emerge. When, however, to carry the simile a little further, it is discovered that the area is full of soldiers who have been equipped only with left-sided boots, and right-sided boots are supplied, troops pour forth into battle.

The Hopper Theory

At the height of its glory the theory of arrest of maturation (more intimately known as the "hopper theory," from the resemblance in diagrams of stored-up cells to grain in hoppers) included the liver factor, thyroxine, ascorbic acid, iron, and copper as factors necessary for different stages in the ripening of the red cell.

Thyroxine and ascorbic acid were never perhaps very strong members of the team, but they held a humble place. I like to think, though others might not agree, that some observations I made on anaemia in myxoedema (Bomford, 1938) first lost thyroxine its place. Briefly I showed that when hypothyroidism with liver deficiency and hypothyroidism with iron deficiency were excluded there remained some cases of moderate anaemia which could be cured, but very slowly, by thyroid alone, and only by this means. The blood picture in these cases resembled fairly closely that which had been produced in animals by exposing them to atmospheres richer in oxygen than the normal; and I suggested that the anaemia should be regarded as a com-

pensation—in itself physiological—to the diminished needs of the body for oxygen. Unfortunately I did not examine my patients' bone marrow, but, collecting what scanty information there was available about the bone marrow in other hypothyroid states, I suggested that the bone marrow in myxoedema was relatively hypoplastic. That this is indeed the case was confirmed a year or so later (Jones, 1940). The uncomplicated anaemia of myxoedema appears, therefore, to be a partial atrophy of the erythron (a term that has been used to indicate the blood and the bone marrow considered as a single organ) as an adaptation to the diminished need of the body for oxygen, the bone marrow is relatively hypoplastic, and there is no evidence of an arrest of maturation.

Erythropoiesis in scurvy has also been the subject of a recent paper (Israëls, 1943). The existing knowledge was again scanty, and that author writes about three cases of his own, which appear to be the first in which the marrow was examined both before and after treatment. Briefly, Israëls found that before treatment there was diminished erythropoiesis in two patients, while in the third erythropoiesis was within the range of normal. After treatment with ascorbic acid the marrow showed increased erythropoiesis in all three cases. The effect of ascorbic acid deficiency seemed to be a depression of erythropoiesis rather than a failure of maturation at any particular stage.

I do not propose to say much about anaemia due to lack of iron or copper. There is no known human anaemia due to a deficiency of copper, but there is evidence that small traces of copper sometimes assist in cure of iron-deficiency anaemia. This may well be as a catalyst in some as yet unknown stage in the formation of haemoglobin. The normoblastic hyperplasia of the marrow in iron deficiency may simply be due to the fact that this particular part of the marrow is working overtime at the production of small and ineffective cells. Since, however, iron is the only one of the so-called maturation factors which is known to be a constituent of red cells an arrest of maturation of some kind is more plausible in this instance.

The Liver Factor in Anaemia

There is left for consideration the corner-stone of the theory—anaemia due to deficiency of the liver factor. Just before the war I travelled rapidly from the West Coast of America to London. In San Francisco I heard the theory roundly criticized—it has, I think, never really taken root in Western America (Dock, 1936). In Eastern America the subject was at least a proper one for discussion, but in London I found that to question the hopper theory in pernicious anaemia was to risk being cut in the corridor or common room. So from time to time in my enforced sabbatical years I have returned to ponder on this subject.

In morbid anatomy pernicious is distinguished from other anaemias by its association with changes in the alimentary tract, particularly atrophy of the gastric mucosa; by an increase in the amount of red marrow, which is of the type known as "megaloblastic"; by haemosiderosis of the liver and other organs; and by histological evidence of active phagocytosis of red cells by the reticulo-endothelial system. It is distinguished biochemically by gastric achlorhydria, by an increase of the bilirubin in the plasma, and by an increase in the urobilinogen or similar substances excreted, mainly in the faeces. It has a characteristic blood picture, in which the number of red cells is decreased more in proportion than is the percentage of haemoglobin, and the cells are mostly large, well stained, and unduly irregular in size and shape. Finally, it is distinguished therapeutically by the fact that it is completely relieved by the injection of small quantities of the liver principle, and that the onset of the remission is accompanied by a reticulocyte response of a particular kind.

How are these various features of the disease to be interpreted? Is the anaemia due to haemolysis, for which an accelerated rate of erythropoiesis is unable to compensate, as was generally thought until the last two decades? Or is it due to a diminished rate of erythropoiesis, brought about by an arrest in the process of maturation?

Consider first the increase of bilirubin in the blood, the increased excretion of urobilinogen, the haemosiderosis, and the histological evidence of active phagocytosis of red cells. An increase in the bilirubin of the plasma used to be thought to indicate an increase in the rate of blood destruction,

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but it is now regarded more as evidence of impaired liver function—of the liver's inability, that is, to deal rapidly enough with products of haemolysis. It can be neglected in this argument. The other features mentioned are regarded as indications that the rate of destruction of red cells is greater than normal in other anaemic states, and it is difficult to account for them otherwise in pernicious anaemia. Upholders of the theory of arrest of maturation usually say, therefore, that though a diminished rate of erythropoiesis is the chief cause of the anaemia, there is also present some increase in the rate of haemolysis, due to the easy breaking up of abnormal cells. But this, surely, is impossible, for simple calculation will show that the combination of a rate of erythropoiesis noticeably below normal with a rate of haemolysis noticeably above normal must lead to a rapidly progressive anaemia and an early exit.

The Part played by Haemolysis

A main argument against the haemolytic theory was that the rate of haemolysis, if the daily amount of urobilinogen excreted was in fact derived from the breakdown of haemoglobin, was so high as to be incredible. An example of an increase to thirteen times that found in health was quoted. It was therefore suggested that the urobilinogen was derived from precursors of haemoglobin, which had not been utilized because of the arrest of maturation at a stage, presumably, before the red cells acquire haemoglobin. But if it is incredible that haemolysis should be going on at thirteen times the normal rate, it is surely equally incredible that, in the presence of diminished erythropoiesis, the body should go on producing precursors of haemoglobin at thirteen times the normal rate? In point of fact, methods of estimating the daily excretion of urobilinogen in the stools and urine have improved since the time of these observations, and recent measurements show that the daily excretion in pernicious anaemia is usually not more than three or four times that in health. Such a rate of haemolysis is not incredible, and is little if at all greater than is found in other indubitably haemolytic conditions. My biochemist friends tell me that the supposition that these large quantities of urobilinogen are derived from hypothetical precursors of haemoglobin involves serious difficulties. So far as is known, urobilinogen can be derived only from the breakdown of porphyrin ring compounds, and the porphyrin ring compound of haemoglobin is formed only in developing red cells. It is difficult to see, therefore, how this increased amount of urobilinogen can be derived from anything but the breakdown of red cells, unless, indeed, it comes from some other respiratory pigment, and this seems unlikely. Further, if unused precursors of haemoglobin are excreted as urobilinogen, an increased excretion of this substance would be expected in iron-deficiency anaemia, for the response to treatment with iron suggests that there is no shortage of pigment in this disease. In fact, the excretion of urobilinogen is diminished.

The interpretation of the bone-marrow picture is linked with that of the reticulocyte response. For, according to the theory of arrest of maturation, the cells held up in the bone marrow pour into the circulation when the missing factor is supplied and give rise to the reticulocyte response. Or, to use the car factory simile, the missing part is supplied and the cars accumulated in the assembly hall pour into the street. If not this, what is the explanation of the reticulocyte response? It has been suggested by those who favour the haemolytic theory that reticulocytes, being young and tender, are more easily lysed than are mature cells. In other words, that the low count of reticulocytes before treatment is due to a selective lysis of reticulocytes. (There is a little evidence that a selective lysis of reticulocytes occurs in some forms of malaria.) When this process is brought to an end by treatment the reticulocyte count rises rapidly, and falls again slowly as matters readjust themselves. I am not sure that there is not an even simpler explanation. Let us return, admitting the fallacy of similes, to the car factory. On the haemolytic theory we must assume that the demand for cars is three or four times that which the moving belt was designed to produce. There is some acceleration, but this is not enough to supply the demand. Congestion then occurs in the early part of the assembly chain—not because the rate of production is diminished, but because cars cannot be fitted fast enough with necessary parts. When the demand falls rapidly and suddenly the moving belt, geared to the faster

rate, does not at once adjust itself to a slower rate, and pushes a number of very new cars into the street. This kind of explanation would account for the fact that there is in some cases a shower of nucleated red cells as well as an increase of reticulocytes for a short period at the beginning of treatment.

Finally there is sometimes a reticulocyte response when anaemia with malaria is treated with quinine. This must surely be due to a sudden slowing of the rate of haemolysis, and it is polemical to suggest, as I have heard done, that anaemia in malaria is due to an arrest of maturation brought about by the malign influence of malarial toxins.

Of the bone marrow I will say only that Miller and Rhoads (1934) have produced a marrow picture in animals that in essentials appeared to resemble quite closely that of pernicious anaemia. This they did by bleeding the animals regularly, separating off the haemoglobin that had been removed, and re-injecting it as a solution—a manoeuvre which reproduced some of the features of continued haemolysis.

Synthesis of Haemoglobin

Recent studies in the metabolism of pigments have possibly provided a means—though a difficult and very arduous one—of measuring biochemically and roughly quantitatively the rate of synthesis of haemoglobin (Dobriner and Rhoads, 1938, 1940). Briefly, the porphyrins of the animal body can be divided into types I or III according to whether they could theoretically be derived from types I or III of the four possible aetioporphyryns, or pattern types of porphyrin. All respiratory pigments, including haemoglobin, have a pigment portion which consists of a type III porphyrin. But normal persons excrete minute quantities of a type I porphyrin. It has been suggested that the type I porphyrin is formed as a by-product in the synthesis of the type III porphyrins needed by the body, and thus that the amount of this pigment excreted daily provides an indication of the rate of formation of haemoglobin. The rate of excretion of type I porphyrin is increased in haemolytic jaundice, in polycythaemia vera—conditions in which no one presumably would deny that the rate of erythropoiesis also is increased—and in pernicious anaemia. So far as this work has gone it seems to confirm that erythropoiesis is accelerated in pernicious anaemia, and this finding is of course incompatible with an arrest of maturation.

Suppose for a moment that the haemolytic theory is the correct one, and see in what other ways current views about the disease would need to be modified. The conclusions of the Boston school as to the source of the liver principle and its storage in the liver would of course stand unaffected. That the liver factor was in any sense utilized in the bone marrow was never more than supposition. We should have to assume that this factor in some way prevents a particular kind of haemolysis, possibly—and there is a little evidence for this—by altering the conditions of absorption from the intestinal tract. Now the multiplication of hypothetical toxins should probably be regarded as one of the cardinal sins of medicine (and will probably, like heresy in any form, be forbidden in organized services of the future by a medical administrative instruction), but it must be admitted that a return to the older theory of a haemolytic toxin, absorbed perhaps from the intestine, might help to solve some difficulties. It would help to explain those rare cases in which the presence of a small stagnant loop of intestine—too small to be expected seriously to interfere with absorption—is associated with an anaemia of the pernicious type (Barker and Hummel, 1939). Further, if the toxin had an avidity for lipids, it might explain not only the haemolysis but the particular type of red cell found in pernicious anaemia, for the shortage in this disease would appear to be of stroma or its constituents rather than of materials necessary for the formation of haemoglobin. And, finally, a toxin with a taste for the lipids of nerve cells as well as those of red cells might help to explain the association of this anaemia with subacute combined degeneration of the spinal cord.

Conclusion

To return to more practical things; since a near relative of the pigment portion of haemoglobin has been synthesized artificially, it should not be beyond the wit of man to discover how haemoglobin is synthesized naturally and what constituents

are actually necessary for the formation of red cells. There are signs that such inquiries are being pursued actively at the present time, and advances of this kind might well open the way to much new knowledge about the workings of the erythron.

I have stated the case for a reconsideration of the part played by haemolysis in pernicious anaemia in a provocative and, some may think, tendentious manner. There is, however, a case to be considered, as was realized in America before the recent war (Minot and Castle, 1939), and my object will have been achieved if some British haematologists are induced to give their minds to it.

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MENTAL DEFICIENCY IN NORTHERN IRELAND

A colony for mental defectives, providing ultimately for a thousand beds, within 20 or 30 miles of Belfast is recommended by the Mental Health Services Committee, whose report to the Minister of Health and Local Government is obtainable from H.M. Stationery Office (price 1s.). In a foreword the Minister (the Rt. Hon. William Grant) says: "The report gives a clear picture of the problem to be solved and contains many valuable recommendations as to the action which we in Northern Ireland might usefully take. It has been endorsed in its entirety by the Health Advisory Council. New legislation would be necessary to bring into operation a mental deficiency scheme, and this aspect of the matter is receiving consideration. I feel, however, that before the Government presents proposals to Parliament it is desirable that the committee's report should be made available to the public."

In Northern Ireland, says the report, there is no Mental Deficiency Act, no institution, no community supervision, and there is only one special school (in Belfast), which is unable to meet even local needs. Apart from the inadequate provision made by the Education Acts and the Poor Relief Acts, the responsibility for dealing with mental defectives has not been placed by statute on any authority, and for the most part these unfortunate people, estimated on the basis of parallel figures for England (Wood Committee) to number about ten thousand in the whole Province, lead a hopeless existence at home, in Poor Law institutions, or in mental hospitals. The problem of mental deficiency has, by years of neglect, developed into a grave social evil.

Four Classes of Defectives

The committee is of opinion that the education authorities should accept responsibility only for those backward children who are educable and socially efficient, and that all mental defectives should come under the aegis of the mental deficiency authorities. "It follows, therefore, that any definitions of mental defectives for the purpose of a Mental Deficiency Act should be based on the conception of social inefficiency rather than of educational inefficiency." Mental defectiveness is defined by the committee as meaning a condition of arrested or incomplete development of mind existing before the age of 18 years, whether arising from inherent causes or induced by disease or injury. It divides mental defectives into four classes:

Class 1: Persons in whose case there exists mental defectiveness of such a degree that they are unable to guard themselves against common physical dangers.

Class 2: Persons in whose case there exists mental defectiveness which, though not amounting to that of Class 1, is yet so pronounced that they are incapable of managing themselves or their affairs or, in the case of children, will when older be incapable of doing so.

Class 3: Persons in whose case there exists mental defectiveness which, though not amounting to that of Class 2, renders them socially inefficient to such a degree that they require care, supervision, and control for their own protection or for the protection of others, and in the case of children special training also.

Class 4: Persons in whose case there exists mental defectiveness of such a nature that their behaviour is strongly antisocial and they require care, supervision, and control for the protection of others.

Ascertainment and Executive Powers

As mental deficiency is most often discovered during the school years the initial task of ascertainment will fall on the health services operating under the Education Acts. The committee recommends that where a medical practitioner is of opinion that a person is a mental defective it should be compulsory for him to notify the mental deficiency authority, with whom should rest the final responsibility of ascertaining whether there is disability of mind amounting to mental deficiency. It should be a statutory requirement that when, as a result of conducting mental tests, a teacher, educational psychologist, or school medical officer has reason to suppose that a person is a mental defective, a notification, with reports, must be sent to the mental deficiency authority to enable the case to be reviewed by the authority's psychiatrists.

The committee recommends that in Northern Ireland the Ministry of Health and Local Government should be the central authority and that a regional authority should be established rather than that the task of administration be thrown on the county and county borough councils. The regional authority should be composed of representatives from the county and county borough councils and other interested bodies. It should be responsible for ascertainment, the provision and administration of institutions, and the supervision of defectives in the community. In addition local mental health committees should be formed to advise the regional authority and co-ordinate the activities of persons interested in the problem. The committee believes that the duties of the authorities relating to mental deficiency would be most efficiently carried out as an integral part of a general mental health service for the Province. In order to bring this about there should be either an actual amalgamation of, or the closest possible co-operation between, the mental deficiency authorities and the authorities administering all the other mental health services.

Other recommendations are that it should be permissive for all classes of defectives to be submitted for treatment to the regional authority at the instance of a parent or guardian; that in any Northern Ireland legislation the mental deficiency authority should be given powers to deal compulsorily with all ascertained defectives, and it should be obligatory for appropriate care, supervision, and training to be provided; and that persons who suspect they are mental defectives should, if over 18, have the right to submit themselves for examination and appropriate treatment by the mental deficiency authority. "It is wrong to wait until the defective gets into trouble or runs foul of the law before affording him the care, supervision, and training which his mental condition requires and which it is in his own interests to receive. Mental deficiency is often hereditary, and we consider it wrong to leave any power in the hands of mentally defective parents. . . . Each case would be carefully examined by the competent authorities, and many would be allowed to remain at home or elsewhere in the community if adequate care and supervision could be provided there."

MEDICAL FOUNDATION OF EPSOM COLLEGE

The Royal Medical Foundation of Epsom College appeals to all members of the medical profession who do not already do so to subscribe to the Foundation, the object of which is to help the families of less fortunate colleagues. The Foundation in 1946 has provided more than £15,000, as follows:

	£
50 ordinary pensions	1,500
41 Foundation scholarships for boys (educated, clothed, and maintained entirely free of cost)	6,748
13 scholarships for girls	570
25 Council exhibitions for boys	1,541
138 pensions and annuities of varying amounts	3,023
Grants towards education of 51 boys and girls	1,408
Grants to widows and spinsters	335

In order to maintain this assistance the Foundation has to rely upon the generosity of subscribers and donors for over £10,000 a year. Without sufficient help from them the existing benefactions would have to be curtailed. Owing to lack of funds, many deserving applicants—medical men, widows, and children of school age—remain unassisted. The Sherman Bigg Fund enables the Foundation to make educational grants for those who cannot obtain scholarships. Donations to augment the income of this Fund would be most welcome. Subscriptions and donations for whatever aspect of the work may be sent to the Secretary, Epsom College, Surrey.