SOME PRACTICAL POINTS IN THE DIAGNOSIS AND TREATMENT OF ANÆMIA.*

By GEOFFREY BOURNE, M.D., F.R.C.P.

*(Physician with Charge of Out-patients, and in Charge of the Cardiographic Department.
St. Bartholomew's Hospital).*

The understanding of the problems concerned in the diagnosis and treatment of various forms of anæmia has been greatly helped by the work that has been done in that subject during the past ten years. The origin of this new activity in hæmatology was the work of Minot and Murphy in Boston. Their observations, which have since been confirmed and amplified by Castle's most able researches, prove the underlying factors causing pernicious anæmia. A subsidiary result was the proof that the reticulocyte count provided definite evidence as to the effect on various anæmias of certain therapeutic experiments. It could be deduced, for instance, that if a definite reticulocytosis followed the administration of liver or of iron, proof was thereby available as to the specificity of these methods of treatment in the particular cases.

CAUSATION.

It is essential that a clear conception be held as to the normal course of blood formation. The endothelium of the sinusoids in the bone marrow gives rise to megaloblasts. These produce normoblasts, which in turn produce reticulocytes which are the youthful form of the normal red blood corpuscles. This developing series of cells has been named by Witts the erythron, and it is useful to consider it as a unit. Factors may be active at various stages of this chain of development and may give rise to varying types of anæmia. If there is a severe interference with the activity of the sinusoidal endothelium a hypoplastic or an aplastic form of anæmia develops. For the transformation of megaloblast into the normoblast a substance known as the hæmatinic principle is necessary, and its absence so interferes with the normal erythropoiesis that the megaloblast itself gives rise to abnormal red blood cells, somewhat increased in size, with the result that a megalocytic type of anæmia is produced. The hæmatinic principle is formed in the stomach by the inter-action of two factors, the extrinsic factor which is present in the proteins of the food, and which is thought by some people to be vitamin B₁₂, and an intrinsic factor, which is present in normal gastric secretion. It is highly improbable that food is in this country so deficient as to produce a megalocytic anæmia from the deficiency of the extrinsic factor, and it is therefore to a deficiency of the intrinsic factor that most cases of megalocytic anæmia must be ascribed.

The intrinsic factor can be deficient in various ways. Firstly, it may be absent for no known reason, generally in middle-age in those individuals who already have a hypochlorhydria. This deficiency appears quite often to be familial. Secondly, destruction of the prepyloric part of the stomach where this factor is produced may occur from carcinoma or as a result of surgical operation, and an anæmia of the pernicious type may follow. Thirdly, gastro-intestinal disease, as in sprue, may interfere with the absorption of the hæmatinic principle. A further reason for deficiency in the hæmatinic principle is occasionally found

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in advanced disease of the liver, such as cirrhosis, when there is a sufficient deficiency in the store of this principle to produce an anæmia. The treatment of magalocytic anæmia therefore to some extent depends upon a recognition as to where this mechanism is at fault. When pernicious anæmia has been diagnosed it can be symptomatically cured by the administration of liver extract which is now most efficiently and easily given in the form of an intramuscular injection of the concentrated product. Pernæmon, campolon and anahæmin are all potent therapeutic agents. The latter is the one that I am using at present. It produces very little local discomfort and its results are satisfactory. It should be given at first in doses of 4 ccs. at weekly intervals for two or three doses. Subsequently a maintenance dose of 2 cc. per month is generally sufficient. The other two preparations are used in a similar manner but in the case of campolon somewhat larger doses are generally given.

Normocytic anæmia, that is anæmia in which there is no excess of unduly large or unduly small red cells, is found either when there is interference with the sinusoidal endothelium, or when the anæmia is the result of mechanical destruction or loss of red blood cells, as in malaria or in chronic bleeding from peptic ulceration, piles, or in menorrhagia.

There are two main types of microcytic anæmia, according to Witt's classification. Simple microcytic anæmia is found in acute or chronic infections, whether pyogenic or tuberculous, and in carcinoma. Here there is no severe depletion of the hæmoglobin in the cells. The second form, hypochromic anæmia, is apparently definitely due to iron deficiency, and it is frequently associated with achlorhydria. It should be remembered here that iron theoretically is only found in solution and absorbed satisfactorily in the presence of an acid medium, and furthermore, it should be borne in mind that the rapidity of absorption of iron in dilute hydrochloric acid is increased in proportion to the concentration of the iron solution. Therapeutically iron seems to produce its best effect in the form of Ferri et Ammon. Cit. in large doses, such as 20-40 grains t.d.s. in solution, or as Blaud's pill grains 10-15, t.d.s. This is the conclusion of Murphy who has done careful work on the subject, and has compared it with the intravenous administration of iron. He finds that the iron is apparently more rapidly absorbed if it is given in association with periodic intramuscular injections of liver extract. It has been found experimentally that the production of an acidity in the contents of the small intestine, by tying the pancreatic duct, results in an excessive absorption of iron. A similar result has been produced experimentally by excessive dosage with ammonium chloride. It is a fact clinically, however, that an achlorhydria does not always produce an anæmia, and that therefore some other factor must be concerned in this process of iron absorption. Two further theoretical points need to be remembered. Firstly, that the reticulocyte count is evidence not only of the activity of the therapeutic agent but that the reticulocyte response is generally in proportion to the speed and ultimate extent of the blood recovery. The second point is the amount of hæmobilirubin present in the blood serum, as shown in Van den Bergh's test. In certain anæmias, particularly pernicious anæmia and acholuric jaundice, there is a marked increase in the bilirubin content of the blood serum. This may be partly due to blood destruction but it is possibly also due to the fact that some of the bilirubin goes astray in abnormal blood formation.

DIAGNOSIS.

Difficulties may arise in the diagnosis of anæmias in two ways. First it may be obvious that an anæmia is present, but there may be some difficulty as to determining its cause. Secondly, the anæmia itself may pass unnoticed so that its clinical manifestations give rise to a suspicion of the presence of some other disease. Pallor does not necessarily mean anæmia. There is a definite type of individual whose skin vessels are generally in a state of contraction and who therefore nearly always looks abnormally pale. One frequently finds in such cases a hæmoglobin percentage of nearly 100. It is also true that patients of good colour are fairly frequently definitely anæmic. This class of case is frequently difficult to diagnose as a result of the use of cosmetics. The only certain way of determining whether a patient is anæmic or not is by the use of a hæmoglobino-meter. Sahli's apparatus is probably the most convenient. Its chief advantages are that it can be used by daylight or by artificial light and that no carbon monoxide or coal-gas is necessary, the hæmoglobin being transformed to methæmoglobin by the use of $\frac{N}{2}$ hydrochloric acid. An accurate hæmoglobin determination with this apparatus need not take more than three or four minutes from start to finish.

Should a patient be obviously anæmic certain points will arise in the differential diagnosis.

Primary Anæmias.

Pernicious anæmia will be suggested by the following clinical findings. The classical lemon-yellow colour is frequently so striking as to give the clue straight away. The state of nutrition tends to be good, and this is in marked contradistinction to such conditions as carcinoma of the stomach, or chronic infective conditions which may produce a marked anæmia. The sore tongue is not invariably complained of as an outstanding symptom by the patient, but if enquiries are directed towards this point it is found in many cases of pernicious anæmia. Further points on examination are that there is a marked superficial glossitis, the surface of the tongue appearing smooth, shiny and with very atrophic papillæ; in addition the early symptoms and signs of postero-lateral sclerosis may be present. The patient will often admit to having some tingling or numbness of the feet and hands. The earliest physical sign of this common complication of pernicious anæmia is the absence of vibration sense, as tested by the tuning fork.

The most essential points of laboratory diagnosis are first that the Colour Index is above 1, secondly, that there is a leucopenia, thirdly that the hæmoglobin is increased in an untreated case, and finally, that the gastric test meal shows a complete achlorhydria.

Microcytic hypochromic anæmia is typically found in women between the ages of forty and fifty. Here, too, there is frequently a chronic glossitis. The nails are often brittle and sometimes spoon-shaped. The symptoms are generally those of a simple anæmia, such as tiredness, headache, palpitation and giddiness. Although this type of anæmia is far commoner in women it is found also in men, as the following case report shows.

The man, aged twenty-seven, was admitted under my care to St. Bartholomew's Hospital with a history of palpitation, shortness of breath and headaches. He was obviously pale and his blood count was as follows:—Red blood cells 5,300,000, Hæmoglobin 60 per cent., White blood cells 10,200. His blood serum contained more than twice the normal amount of hæmobilirubin. The sputum and X-ray examination of the chest showed no sign of tubercle. Examinations of the stools for occult blood were negative. The Wassermann reaction was negative. He was given full doses of Ferri et Ammon.Cit., 90 grains a day, and four days after the start of this his reticulocyte count rose from the normal of .7 per cent. to 7.2 per cent. He made a progressive and rapid recovery. This man had a marked hypochlorhydria, which is of interest in view of what is known with regard to iron absorption.

There are certain somewhat rare types of anæmia which are associated with **splenic enlargement**. The splenomegaly is sufficient to suggest a complete blood count, and as a rule the diagnosis is fairly straightforward. This group of patients is therefore eliminated from the present discussion.

Secondary Anæmias.

Anæmia must always be regarded as a symptom whose causes are various. The label secondary anæmia can usefully be reserved for those cases in which some other well-known disease is the cause of the anæmia. Gastric or duodenal ulcer may sometimes remain comparatively unnoticed until the resulting anæmia produces palpitation, faintness or undue fatigue, and the following two cases bring out this point. They had both been admitted to local hospitals outside London and I was asked to admit them to St. Bartholomew's Hospital for further investigation as to the cause of an unexplained anæmia.

The first case was a woman of sixty-six who had been suffering from loss of appetite and lassitude. Her blood count was as follows:—Red blood cells 3,600,000; Hæmoglobin 30 per cent.; White blood cells 16,400. It was only when a careful history was taken that she would admit to having suffered from dyspepsia for two or three months, which was worse from half an hour to an hour-and-a-half after food. These symptoms had been present three years previously, had recurred one year ago, and had again been present six months before her admission. Examinations of the stools for occult blood were negative, and the test meal showed no achlorhydria and no blood, but X-ray examination of the stomach revealed the presence of a large gastric ulcer, for which she received medical treatment. On her discharge the hæmoglobin had risen to 62 per cent., and she made a good recovery.

The second patient gave a similar type of history, the chief symptoms being weakness, headaches and fainting. His blood count was:—Red blood cells 1,460,000; Hæmoglobin 32 per cent.; White blood cells 11,200. Here again it was only on taking a careful history that he admitted having suffered from pain which was worse from one to one-and-a-half hours after food, and which was relieved by alkalis. He had suffered from this, on and off, for five years. An X-ray examination of the duodenum proved the presence of a duodenal incisura. He was treated for this medically, and on discharge his blood count was normal, the hæmoglobin having risen to 96 per cent.

The anæmia associated with carcinoma of the stomach may be of a similar type, and due to persistent loss of blood rather than to destruction of that area of the stomach which produces the intrinsic factor. The megalocytic type of anæmia due to carcinoma of the stomach has already been mentioned. Intra-thoracic tuberculosis may occasionally produce a severe secondary anæmia. This is most frequently seen in girls between the ages of seventeen and twenty-five. The following example is a good illustration.

A girl, aged 18 years, was employed as a house-maid. She was of a very fair complexion and her pallor was at first therefore unnoticed. She had no symptoms until one day she had a fainting attack during her work, and on critical examination it was obvious that her mucous membranes were unusually pale. Full clinical examination revealed no physical abnormalities, but examination of the blood showed that the hæmoglobin had fallen to about 40 per cent. It was only after an X-ray examination of her chest that a definite zone of tuberculous infiltration was found. This was quite an early lesion, for after six months' treatment, the first four in a sanatorium, she became perfectly well and has remained so for the last seven or eight years.

I have seen two similar cases to the above in hospital nurses, both of whom were about the same age. Myxœdema is another disease which has to be considered in the differential diagnosis of anæmia. A woman of thirty-five was sent up to my out-patient department with the diagnosis of pernicious anæmia. She had a pale, somewhat earthy complexion, and at first sight suggested the diagnosis. She was, however, a brunette, and it had been pointed out to the writer by Dr. Murphy that nearly all of his cases had occurred in blondes. As a result a full investigation was undertaken and she was found to be suffering from myxœdema, the symptoms of which, including the anæmia, cleared up completely on treatment with thyroid extract.

In certain cases, owing to the fact that the patient does not appear to be unduly pale, or because the general appearance suggests that pallor is the patient's natural state, the presence of anæmia may pass unnoticed. The commonest symptoms under such circumstances suggest at first a diagnosis of some cardiac trouble. In anæmia, as in hyperthyroidism, there is a definite increase in the circulation rate as well as a deficiency of hæmoglobin. This manifests itself by the symptoms of lassitude, palpitation, shortness of breath and by the signs of increased pulsation in the vessels of the neck, tachycardia, more or less cardiac dilatation, and systolic murmurs of various types. A very interesting case belonging to this group was the following.

A woman, aged 28 years when she came under observation, gave the history that, in April, 1935, after her second pregnancy, a tumour appeared on the right side of the neck. This was diagnosed as an aberrant thyroid, and the diagnosis was confirmed after the tumour had been removed. The heart remained rapid and irregular after this for some time. From January to August, 1936, she had a third pregnancy and a similar lump appeared, associated with tachycardia, tremor and exophthalmos. Furthermore, the thyroid itself swelled somewhat. The lump in the neck and the thyroid were both removed, the first completely and the latter partially, and her symptoms of hyperthyroidism disappeared. She remained fairly well until early in September, 1936, when tachycardia, some lassitude and some palpitation were again noticed. On examination the colour of her cheeks was reasonably pink, and this was not due to

artificial causes. The heart showed no enlargement and no abnormality, except for an impure first sound, was noted. Her lips, however, were not as red as they should have been, and a hæmoglobin estimation was therefore done which gave a result of 50 per cent. She was treated with full doses of iron and within three or four weeks was almost completely restored to health.

In this case it is probable that the metabolic strain of two closely successive pregnancies was the cause of the anæmia.

It is also well known that anæmia may accentuate the symptoms of coronary disease, and the following are good examples.

A man came under observation on account of symptoms of angina of effort, but on examination he was seen to have the typical pallor of pernicious anæmia, and the history revealed symptoms of tingling and pins and needles in the feet, and hands. Treatment of his pernicious anæmia was very successful, the hæmoglobin rising within a month to 90 per cent, and his angina pain nearly completely disappeared, but could still be evoked by rather rapid walking.

The other patient, also with angina of effort, associated with aortic stenosis, was found to be very pale and on investigation he proved to have a severe anæmia of the secondary type, the hæmoglobin being 54 per cent.

In both of the above cases the cardiac symptoms were very greatly accentuated although not caused by the hæmoglobin deficiency. Some patients with an exceedingly severe degree of anæmia, in addition to shortness of breath and lassitude, have marked oedema of the feet and legs and occasionally even some free fluid in the abdomen. One such patient, whom I saw and who was suspected of having a cardiac lesion was proved to be suffering from a very severe secondary anæmia due to carcinoma of the rectum. The striking clinical feature here is that such patients prefer to lie flat as the upright position tends to accentuate their cerebral anæmia. This is a simple but certain way of differentiating them from patients whose oedema and ascites are due to congestive heart failure, and who invariably prefer a more or less upright position of the thorax.

One final condition is occasionally thought of in cases where the true diagnosis is really that of anæmia. I saw such a patient a few months ago. She was a woman of fifty who for about a year had been suffering from increasing lassitude, and who, for the preceding few weeks, had had persistent vomiting. During this latter period her body had become definitely pigmented and this pigmentation was more of a brown than of a yellowish hue. The blood pressure also was noticed to be somewhat low. I found on examining her, however, that there was no pigmentation of the buccal mucous membrane, that a superficial glossitis was present, and that the excitement of a visit from a strange doctor had sent the systolic blood pressure up to 130. This, to my mind, eliminated the possibility of Addison's disease, and a subsequent blood count proved the presence of pernicious anæmia which responded rapidly to treatment. The marked brownish pigmentation here was the cause of the mistake in diagnosis and it is interesting, for this was probably the reason why Addison in his first account of his disease included certain cases of pernicious anæmia, which in his latter work he subsequently separated out. In these cases, as occurred here, the pigment leaves the skin in two or three days after the institution of the intramuscular liver therapy.