If the invalid died it was through lack of confidence or want of belief. Dying patients were cast out and left to shift for themselves. The god had rejected them and no aid could be forthcoming. When the suppliant was healed, a thank-offering or payment had to be made. Often these offerings were in the form of a silver or terra-cotta model of the part that had been healed. The votive offerings thus made were preserved in the temple.

The Public Health. Hygieia, the Greek goddess, was not a healing deity, but the personification of the idea of Health. She was generally regarded as the wife or daughter of Asklepios, and said to have come to Athens with him from Epidauros in 420 B.C. She is usually shown on reliefs and statues as being in attendance on the god as at Athens, or as feeding and caring for the sacred serpents. The public recognized in Asklepios and Hygieia, ability to protect the health of the community as well as serving the individual. As neglect of the gods might result in disasters such as pestilence or famine, the State, in duty bound, supervised and controlled the rites of prayer and sacrifice. The Council at Athens is said to have brought Asklepios and Hygieia to Athens on account of a plague which was instantly stopped on their arrival. A sacred serpent representing Asklepios was sent from Epidauros to stop the pestilence at Rome. While the vessel was sailing up the Tiber, the serpent went ashore and was lost sight of among the rushes of the Insula Sacra. As the plague stopped almost immediately, the Romans built the great temple of Aesculapius at that spot.

REFERENCES.

The Healing Gods of Ancient Civilizations. W. A. JAYNE, Yale University Press.

Two lectures by DR. RICHARD CATON on the Temples and Ritual of Asklepios at Epidauros and Athens.

[*To be continued.*]

THE COMMON ANÆMIAS*

(With special reference to certain modern conceptions).

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Diagnosis of Anæmia.

Anæmia may be defined as lack of hæmoglobin or of red blood corpuscles and usually of both. The symptoms of anæmia, such as breathlessness on exertion, giddiness and a tendency to swelling of the ankles, are by no means pathognomonic as they are present in other conditions such as cardiac failure, toxæmia, etc., but when they are present anæmia should always be suspected. When anæmia is severe the characteristic pallor of the patient is usually a reliable guide, but minor degrees of anæmia often escape detection and pallor of course does not always indicate anæmia. It is true that pallor of the mucous membranes is a more trustworthy sign than is pallor of the skin, because these structures are less exposed to the varying influences which affect the skin. It must also be remembered that the colour of the skin or other structure depends, not only on the amount of hæmoglobin in the blood, but also on the amount of blood in the local vessels and, therefore, on the number of these vessels dilated and the degree

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of their dilatation. In this way constriction of blood vessels from various causes can mimic anæmia, and on the other hand their dilatation can mask an anæmia. In many cases, therefore, recourse must be had to hæmoglobin estimation and frequently to a full blood count. No reliance can be placed on methods which involve the comparison of blood absorbed by filter paper with standard colours as in Tallquist's method. A blood count usually gives a reliable answer to the question, "Is anæmia present?" We may, however, be led astray if the blood is concentrated as when loss of blood is coupled with loss of fluid, *e.g.* in ulcerative colitis. In these circumstances the hæmoglobin percentage may be normal, because of concentration of the blood; but a source of dessication such as diarrhœa is usually obvious. The likelihood of concentration should, however, be borne in mind when the question of blood transfusion arises in such a case.

Ætiology of Anæmia.

In our student days anæmias were classified into those due to hæmorrhage, those due to diminished blood formation and those due to increased blood-destruction. Apart from anæmias due to hæmorrhage, the teaching was that anæmia might be primary or idiopathic, due to unknown causes, or secondary or symptomatic due to some recognisable antecedent condition. The primary anæmias were chlorosis and pernicious and aplastic anæmia, all others were secondary. Chlorosis, perhaps as a result of improved hygiene and diet, has virtually disappeared. Pernicious anæmia, however, still prevails though it is slowly yielding its secrets to advancing enquiry, and it may be that in the not too remote future the term "primary" will not be so significant of our ignorance as it once was. For similar reasons, the term "secondary anæmia" is nowadays restricted to an anæmia which is not the predominant or essential part of the clinical picture. In infective endocarditis, for example, anæmia is usually present, but no one would believe that anæmia was anything but a subsidiary result of this disease.

To-day, when so much elaborate and fruitful research is being carried out on the "primary" anæmias, we should not forget that such causes as hæmorrhage, acute (*e.g.*, from a duodenal ulcer) or chronic (as in menorrhagia and from piles) and cachetic states (*e.g.*, infective endocarditis, nephritis and cancer) are potent causes of anæmia; in these cases treatment of the cause is usually, when practicable, of greater importance than direct treatment of the anæmia, except that in hæmorrhage a blood-transfusion may be necessary to tide the patient over an acute emergency and to give the bone marrow a chance to regenerate new red cells.

Boycott has pointed out that the red blood cells and their precursors in the bone marrow should not be regarded as separate entities, but rather as a single tissue for which he has proposed the name *erythron*. The erythron can suffer various disorders, most of which result in anæmia, although chronic oxygen lack causes polycythæmia. Polycythæmia may also arise without known cause (Vaquez-Osler disease), and is then regarded as a tumour of the erythron.

Anæmia may arise in any of the following ways. Part of the erythron may be lost by hæmorrhage; its roots in the marrow may be over-ridden and crushed by overgrowth of myeloid cells in leukæmia or by diffuse cancerous metastases; it may be injured by chemical poisons, hæmolysins and bacterial influences, as in hæmolytic (erythronoclastic) anæmia; it may for reasons both recognisable (*e.g.*, fevers) and obscure become hypoplastic or even aplastic, and it may suffer a lack of substances which are essential for blood formation, as in pernicious anæmia.

The adult red cell or erythrocyte develops within the blood-forming capillaries in the bone-marrow from primitive cells and passes through a series of stages. These stages include the megaloblast, the normoblast and the reticulocyte. The known hæmopoietic substances which are necessary for the full and healthy transformation of the megaloblast into the mature red blood corpuscle are the liver principle, iron, copper, vitamin C. and thyroxine, and if one of these is diminished or absent corresponding anæmia may result. In scurvy, for example, anæmia is a striking feature and the anæmia of myxœdema is well known. Continental work has shown the value of copper in minute doses in curing the anæmia which can be produced by the prolonged feeding of young animals on a milk diet. The scarcity of iron in milk is responsible for the relative anæmia which occurs in infants towards the end of the period of breast feeding. If weaning is unduly delayed a well-marked anæmia, curable by iron, develops. Iron preparations can now be obtained in palatable form for administration to infants.

The liver principle is necessary for the transformation of the megaloblast into the normoblast and when this principle is deficient the bone marrow undergoes a megaloblastic reaction and the red cells passed into the circulation tend to have a larger diameter than the normal, so that the anæmia is spoken of as megalocytic in type. The colour index is high, partly because of the increased size of many of the cells, and partly because there is a deficiency of stroma, so that each cell tends to contain a little more hæmoglobin than it should. Some of the nucleated red cells also tend to escape into the blood stream. Although the bone marrow shows a great proliferation of cells, these are of very immature type, and a decreased number of erythrocytes is thrown into the circulation. Anæmia due to deficient production of red cells is usually called an-hæmopoietic.

The liver principle is probably a substance of fairly simple chemical composition although its exact nature is unknown. The claim has been put forward that it is a dipeptide, or even an amino-acid. According to Castle it is produced by the interaction of an "intrinsic principle" in the gastric juice with an "extrinsic factor" in the food. This observer has shown that meat incubated with healthy gastric juice is capable of causing reticulocytosis and other evidences of blood-regeneration in cases of pernicious anæmia. The intrinsic factor, however, is probably not pepsin. The substance produced is stored in the liver, and to a less extent in the kidney and hence the value of liver as a therapeutic agent. Hog's stomach is likewise effective, either because it contains the intrinsic principle or because the intrinsic principle has already converted the proteins of the stomach wall into the liver principle during post-mortem autolysis. Wilkinson has done valuable work on this subject, and has brought forward evidence that the intrinsic principle is an enzyme, but it is beyond our present purpose to give more than the barest outline.

When there is a defective absorption of iron, hæmoglobin formation is sooner or later affected, as soon as the body's store of iron is depleted. An anæmia with a low colour index results, for the cells produced have a normal amount of stroma but deficient hæmoglobin. They are often smaller in diameter than in health, as in the so-called microcytic anæmias. The anæmias of scurvy and myxœdema have also a low colour index.

Some apology may seem necessary for this preamble, but the conceptions briefly outlined above, (of which an admirable account is given by Witts in the Goulstonian Lectures for 1932) help to make the subject of anæmia intelligible.

The various papers of Whipple, Minot and Murphy, Janet Vaughan, Castle, Wilkinson, Ungley, Helen Mackay, and others should also be consulted. We may now consider the practical application of our theoretical conceptions.

I.—Pernicious Anæmia.

The clinical features of this disease are well-known to you. The patient, who is usually over 35, complains of great weakness and a varying degree of breathlessness on exertion. When closely questioned, he (or less frequently she) can hardly define the date at which these symptoms were first noticed; in other words, the onset is insidious. Occasionally, if exceptionally, dyspepsia may be severe. When the patient is examined there is usually well-marked pallor, a few subcutaneous ecchymoses are occasionally found and retinal hæmorrhages may be observed. There is no wasting. The skin often shows a lemon yellow tint. This is due to excess of bilirubin, the result of blood destruction, but it is to be emphasized that the hæmolysis is entirely secondary to the production of abnormal red cells. In other words the anæmia is primarily "anhæmopoietic" and not hæmolytic and the turnover of red cells from the marrow is diminished. Indeed, part of the bilirubinæmia and hæmosiderosis of pernicious anæmia is due to the inability of the anhæmopoietic marrow to use again the products of blood-destruction. A hæmic systolic murmur is often to be heard. The tongue may be sore and red. The tip of the spleen is frequently palpable, while in rare cases the liver is enlarged and tender and causes considerable confusion in the diagnosis.

The fractional test meal shows an achlorhydria. A more complete examination will reveal that pepsin is absent also, *i.e.*, a condition of true achylia is present.

The blood count shows an anæmia, usually profound, with a high colour index. The red cells are often only 1,000,000 per cubic millimetre of blood, instead of the normal 5,000,000. The leucocytes and platelets are usually diminished in number. The red cells, on the average somewhat larger in diameter than in health (megalocytosis), show abnormal features such as gross inequality in size (anisocytosis), irregularities in shape (poikilocytosis) and in staining. Nucleated red corpuscles, both megaloblasts and normoblasts, are often present, but their absence does not exclude the possibility that pernicious anæmia is present. The occurrence of megaloblasts is always suggestive of pernicious anæmia, but they may occur in leukæmia and normoblasts are frequent in the anæmia which follows hæmorrhage. The reticulocyte count is low; indeed, an increase is one of the earliest signs of the effectiveness of liver treatment. Reticulocytosis occurs whenever there is active blood regeneration.

Blood counts resembling those of pernicious anæmia may occur in certain gastrointestinal conditions, such as fatty diarrhoea (coeliac disease and sprue), infestation with *Dibothriocephalus latus*, partial excision of the stomach, etc., but these conditions are rare in England at any rate, and the title of our lecture "Common Anæmias," absolves us from their detailed consideration and relationship with pernicious anæmia. An increase in cases of anæmia following partial gastrectomy is to be expected in view of the increasing popularity of this operation.

The **diagnosis** of pernicious anæmia, suspected on clinical grounds, is confirmed by a blood examination. When this is not practicable, a diagnosis may be made as the result of the administration of liver; this therapeutic test, however, is liable to fail in elderly arteriosclerotic people, who often show a poor or delayed reaction to liver treatment.

The various secondary anæmias are the chief source of difficulty in the clinical diagnosis of pernicious anæmia. Although the anæmia of leukæmia occasionally causes difficulty, a more common source of confusion is the anæmia which so often occurs in cancer of the stomach. In the absence of a palpable tumour, pernicious anæmia may be closely simulated. Wasting is more in evidence in gastric carcinoma than in primary anæmia, and on rare occasions the "sentinel" gland of Virchow beneath the lower end of the sterno-mastoid may be palpable. We may, however, note in passing that this gland, like other sentinels, frequently fails to give a timely warning of the approach of danger. In doubtful cases, the final court of appeal can be variously constituted by the barium meal, the blood count, the test meal or the mere ignominious lapse of time. Any one of these is usually conclusive. The barium meal shows an irregular filling defect in cancer of the stomach, the blood examination very rarely shows a high colour index and the resting gastric juice is foul, and the total gastric acidity high, although there is usually absence of free hydrochloric acid. In patients from the tropics, sprue should be thought of, as here there is sore tongue and often anæmia, but the presence of fatty stools serves to put the practitioner on the right track. The bloated anæmic appearance of a case of myxœdema may superficially resemble that of pernicious anæmia. The anæmia in this disease is rarely, however, profound and the dry skin and moderate falling of the hair are characteristic. Further, there is no lemon-yellow tint and the pulse rate is subnormal, rather than increased. The anæmia of chronic nephritis is readily differentiated from pernicious anæmia by examination of the urine and the general clinical picture, but in elderly arteriosclerotic patients a blood count may be necessary. On the other hand, breathlessness on exertion and the systolic murmur may suggest myocardial degeneration, but the presence of pallor and, in doubtful cases, a blood examination will, as a rule, enable a correct decision of pernicious anæmia to be made.

Treatment: The work of Whipple and of Minot and Murphy has transformed our attitude towards the treatment of pernicious anæmia from one of despair to one of hope. The essential of the treatment is the administration of liver or liver or stomach extract in adequate amounts. The dose at first must be large, half a pound of raw liver or its equivalent in lightly cooked liver or liver extract per diem. Raw or lightly cooked liver is fairly palatable as a puree with vegetables. A drachm of the sanctioned commercial liver extracts thrice daily is the equivalent of the half pound of raw liver, but it should be emphasized that raw or lightly cooked liver is the best initial treatment. Dried extract of hog's stomach is cheaper than liver extract, the adequate dosage being the equivalent of 100 gm. of fresh hog's stomach daily. Extract of hog's stomach is, however, less palatable than liver extract. Should the patient be unable to take anything by the mouth, on account of vomiting, a deproteinised liver extract should be given intramuscularly, for the first few days. In cases of great severity a blood transfusion is of value, but it is rarely necessary. In all cases rest in bed is advisable at first.

When dyspepsia is present, acid hydrochlor. dil. m XXX to LX t.d.s. should be given in water with meals. It is customary to give iron and arsenic to cases of pernicious anæmia, but the administration of these should not be continued indefinitely. Liver treatment must, however, be continued in moderate dosage for the rest of the patient's life. Any septic foci present should receive attention, usually after liver treatment is well advanced.

The immediate *prognosis* of pernicious anæmia is good. Recent statistics suggest that the remote prognosis is somewhat unfavourable, partly on account of neglect of treatment by the patients but partly also on account of intractable relapses of the disease.

Subacute Combined Degeneration of the Spinal Cord: This is the chief complication of pernicious anæmia. It can, however, occur in the absence of anæmia and, moreover, a case of well established pernicious anæmia rarely if ever develops progressive degeneration of the cord subsequently to the appearance of anæmia. In qualification of this statement it should be mentioned that cases of pernicious anæmia nevertheless do occasionally develop *minor* nervous symptoms during treatment.

In well marked examples the spinal cord is found post-mortem to be swollen, and not shrunk as in most other degenerative conditions. This peculiarity depends on the relative absence of condensing gliosis, and the presence of hydration in the degenerating myelin sheaths. The disease begins as translucent spots of myelin degeneration in the posterior and lateral columns, notably in the lumbar enlargement. These spots coalesce and spread up and down the long tracts or funiculi, constituting the so-called "funicular myelitis." The involvement of the posterior columns and spinothalamic tracts accounts for the sensory, and of the pyramidal tracts for the motor, symptoms. The ataxia depends partly upon the lesions in the posterior columns and resulting loss of joint and muscle sense and partly upon lesions of the spino-cerebellar fibres in the lateral column. The state of the deep reflexes depends upon the relative degree of damage to the posterior column, which tends to their abolition, and to the lateral column (with its contained pyramidal tract), tending to their increase. The degree of paralysis also depends upon the severity of the lesions in the pyramidal tract.

Classically subacute combined degeneration begins with paræsthesiæ, especially sensations of heat and cold in the lower limbs, girdle sensations and lightning pains and progresses through a spastic ataxia, with extensor plantar reflexes and brisk knee jerks, to a terminal condition of flaccidity in which the tendon reflexes are abolished, although the plantar reflexes still remain extensor in type. In contrast with most conditions in which the plantar reflexes are extensor, the abdominal reflexes are frequently retained until a late stage. It should be observed that occasionally the deep reflexes may be early abolished. In the late stages there is usually considerable wasting of the lower limbs. If anæmia is present the diagnosis of subacute combined degeneration is easy, if absent, other causes of spastic paraplegia *e.g.*, spinal compression and syphilis and disseminated sclerosis must be first excluded. If the deep reflexes are abolished peripheral neuritis may be suggested.

The value of liver treatment in subacute combined degeneration is not so definitely established as in pernicious anæmia, but it should always be tried. Larger doses are necessary than in pernicious anæmia. Ungley has recently suggested that brain extract may be of value and certain authors have insisted on the value of massive doses of iron.

2.—Chronic Microcytic Anæmia.

The chlorosis of young women, once so common, is now rare, but it is still seen from time to time. Attention has been focussed in recent years on the anæmia which is common in women about the age of forty. Witts, Daniel Davies and Vaughan have discussed this anæmia fully in their several papers.

The onset is insidious, with symptoms of pallor, breathlessness, weakness, etc. Sore tongue and dyspepsia are common features. Dysphagia may be well marked, when the term "Plummer-Vinson syndrome" is applied. Wasting is not prominent. The nails are brittle and may even be spoon-shaped, *i.e.*, concave on their free surface: to this hollowness of the nails the pompous term *koilonychia* has been applied. The spleen may be palpable.

The test meal usually shows achlorhydria, hence the term "simple achlorhydric anæmia." Even if free HCl is absent from the ordinary fractional test meal a small flow of HCl can often be excited by subcutaneous injection of histamine. Pepsin may be present or absent, but Hartfall and Witts have shown that the intrinsic principle of Castle is present, and that beef incubated with gastric juice can cause a reticulocytosis when administered to a case of pernicious anæmia. There is often an excess of mucus in the test meal, and it is not quite certain how far the gastric condition is a congenital achlorhydria or a gastritis. In any case, the dyspepsia coupled with economic factors leads to avoidance of iron-containing foods (the diet consisting mainly of tea and bread and butter) and the lack of HCl acts adversely on the absorption of what little iron is taken. As might be expected, a case of achlorhydric anæmia may later, through suppression of the intrinsic factor in the gastric juice, pass into one of pernicious anæmia.

The **treatment** consists in the administration of large doses of iron, in the form of Bland's pill gr. XV-XL thrice daily or iron and ammonium citrate gr. XL in a mixture t.d.s. Dilute hydrochloric acid should also be given. We may note here that the supervention of the menopause may result in spontaneous cure, when the strain of menstruation (often excessive menstrual loss) and of pregnancy is past, but I have seen cases in which the occurrence of the menopause apparently failed to influence the disease. In a refractory example liver should be given, for, although in most cases liver extract is not of much value, those verging on the pernicious type benefit by liver.

3.—Hæmolytic Anæmia.

This type of anæmia occurs when the erythron is damaged by various chemical poisons, *e.g.*, arseniuretted hydrogen, large doses of potassium chlorate, and also as a result of infection. In acholuric jaundice the abnormally fragile corpuscles are hæmolyzed easily, and the term chronic hæmolytic anæmia is the modern synonym for this disease.

In hæmolytic anæmia there is an excess of bilirubin in the blood serum from the excessive breakdown of red corpuscles. There is thus an icteric tinge of the conjunctiva and the blood serum shows a delayed direct and positive indirect van den Bergh reaction; the direct reaction is not present as the bilirubin has not been through the polygonal liver cells. When hæmolysis is rapid and excessive, there may be an escape of free hæmoglobin into the blood and urine; the substance present is more often methæmoglobin than hæmoglobin proper. Since the damage in hæmolytic anæmias is not always confined to the circulating

red cells, but often involves their precursors in the marrow also, the term *erythronoclastic* is often used as being more comprehensive. I propose to take two examples of hæmolytic anæmia, one acute, the other chronic, and describe them in some detail.

A.—Acute Hæmolytic Anæmia (Lederer type).

In 1925 Lederer in America described an acute hæmolytic anæmia, which occurred in both children and adults, characterised by sudden onset, fever, and severe anæmia. Alterations in the blood similar to those seen in pernicious anæmia were present, and there were evidences of "rapid and enormous blood destruction." Lederer regarded the condition as "an infection with selective action concentrated on the reticulo-endothelial system." An icteric tinge was noted, and sometimes hæmoglobinuria occurred. Cases have been recorded in this country by Parsons. There has been a case in this hospital recently. The importance of the condition is that a single blood transfusion saves the patient's life, and transfusion when a diagnosis of Lederer's anæmia has been made should always be carried out, even in the face of hæmoglobinuria.

We may note that some of the cases formerly described under the confusing heading "Leukanæmia" belong to this group, although others were probably examples of leukæmia. Probably many of the plastic (as opposed to aplastic) anæmias of childhood are examples of acute hæmolytic anæmia (Witts).

B.—Acholuric Jaundice.

Although this is not a common disease, it is mentioned because of the beneficial effect of splenectomy. The disease is usually familial and is characterised by chronic hæmolytic jaundice, usually slight, and an excess of urobilin but no bile pigment in the urine—hence the name *acholuric*. The spleen is moderately enlarged. High reticulocyte counts and increased fragility of the red corpuscles are usually found. The reticulocytosis represents active blood regeneration. The red cells hæmolyse in higher concentrations of saline than the normal. Thus hæmolysis may begin at 0.7 or 0.6 per cent. saline and be complete at 0.45, whereas normally the figures are 0.45 and 0.35 respectively. The health is usually good, but occasionally biliary colic occurs from the presence of pigment stones in the bile ducts and an exacerbation of the hæmolytic process may at any time result in a fatal anæmia. Dawson's paper gives an admirable account of the condition. The radical treatment is splenectomy. While admittedly splenectomy has a certain danger, the chance of a fatal anæmia developing in an untreated case is not to be lost sight of, and very careful consideration is necessary before dismissing the question of operation.

REFERENCES.

- Castle, W. B. and others,—*Amer. Jour. Med. Sci.*, 1929, clxxviii, 748; 1931, clxxxii, 741.
 Davies, D. T.—*The Lancet*, 1931, ii, 385.
 Dawson, Lord.—*Brit. Med. Jour.*, 1931, i, 963.
 Lederer, M.—*Amer. Jour. Med. Sci.*, 1925, clxx, 371; 1930, clxxix, 228.
 Linnell, J. W. and Dunlop, H. A.—*The Practitioner*, 1933, cxxxi, 288.
 Mackay, H.—*Med. Research Council, Spe. Rep. No. 157*, 1931.
 Minot, S. R. and Murphy, W. P.—*Jour. Amer. Med. Assoc.*, 1926, lxxxvii, 470.
 Ungley, C. C.—*The Lancet*, 1932, i, 227.
 Vaughan, J.—*ibid*, 1932, i, 122.
 Whipple, G. H.—*Arch. Inst. Med.*, 1922, xxix, 711.
 Wilkinson, J. F. and Klein, L.—*The Lancet*, 1933, ii, 629.