without discussion or other work, to medical graduates who have not entered for the full course, the fees being £5. 5s. for course, £2. 2s. for ten lectures, or 5s. for single lectures. Details are available from the honorary lecture secretary at the Institute.

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A Guide Book, giving details of how to reach the various London Hospitals by tube, tram, or 'bus, can be obtained from the Fellowship. Price 6d. (Members and Associates, 3d.).

A REVIEW OF ANÆMIA.*

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According to Price-Jones⁽¹⁾, the normal red cell count is from $4\frac{1}{2}$ millions to $6\frac{1}{2}$ millions per c.mm. in males, and from 4 millions to 6 millions in females. The normal range of the hæmoglobin percentage is from 95 to 117 and from 85 to 111 in the respective sexes. Anæmia exists when the figures are below the lower limits.

The Causes of Anæmia.

The red cell is not immortal. Its existence is limited to a few weeks. Hence the concentration of red cells in the blood at any time is principally conditioned by the balance which happens to be being struck between the births and deaths of the cells.

Modern classification of the anæmias rests upon the simple idea that anæmia in an individual is either because he is not making enough red cells or because they are being lost or destroyed too fast. Deficient formation on the one hand, and excessive loss or destruction on the other, are the primary ætiological categories.

*The substance of a Lecture-demonstration given at The National Temperance Hospital on Saturday, May 12th, under the auspices of The Fellowship of Medicine and Post-Graduate Medical Association.

1.—Deficient Formation :

The red cells are formed in the bone marrow. It is not generally realised what a large and important organ the bone marrow is. Its total volume is nearly that of the liver and thirteen times greater than that of the spleen⁽²⁾. Deficient output of cells from the marrow may be due to:—

- (a) *Depression of the marrow's function of hæmatopoiesis.* This is most commonly due to some general toxæmia which depresses the activity of the marrow along with the activity of all the other organs. Such toxæmias arise from chronic septic infection, the fevers, chronic nephritis, cancer, and other general diseases.

Infrequently, depression of hæmatopoiesis is due to the action of some agent specifically injurious to the marrow (secondary aplastic anæmia), e.g., lead, bismuth, benzol, arsphenamine, the rays of radium and X-rays.

Idiopathic depression of hæmatopoiesis is met with in aplastic anæmia (primary).

- (b) *A normal marrow being deprived of the substances essential for hæmatopoiesis*—a shortage of raw materials.

The important hæmatopoietic substances are:—

(i) Iron.

(ii) A factor present in mammalian liver (the hæmatin factor of Castle).

More than a dozen anæmic states belong to this group and the recognition of their true nature has been the main achievement of the enormous advances made in recent years in regard to the understanding of anæmia. Formerly, most of them were regarded as being hæmolytic anæmias. Now that their real causation is appreciated, they are termed the "nutritional" anæmias.

In all these conditions the bone marrow tends to be hyperplastic. It is more than willing to make red cells but cannot do so because of deprivation of essential ingredients. As soon as the missing ingredients are supplied, production is resumed.

Deprivation of the marrow may arise in two possible ways. The patient's diet may be lacking in one or more hæmatopoietic factors. Or the diet may be adequate, but some disease or defect of the alimentary canal may cause it to be improperly digested or absorbed. The latter is the commoner cause of the deficiency anæmias in this country.

Iron deficiency causes (i) nutritional anæmia of infants⁽³⁾, and (ii) idiopathic microcytic anæmia of adults⁽⁴⁾. The former condition is found in babies whose weaning has been unduly delayed, or in infants who were born prematurely. The essential cause is that milk is relatively poor in iron. Bunge demonstrated forty-five years ago that the milk of an animal is of the same proportional mineral composition as the body of its offspring except in regard to iron. The normal infant has enough stores of iron to carry it on till weaning; the premature infant has not, as the iron stores are mainly laid down in the last weeks of pregnancy.

Idiopathic microcytic anæmia has only received clear recognition as a syndrome in recent years. It occurs almost entirely in women between the ages of 20 and 50. Nearly every case shows *complete achlorhydria* which appears to be the principal cause of the condition since absence of hydrochloric acid hinders iron absorption. The sufferers tend to

aggravate their condition by living mainly on starchy foods poor in iron. Iron in adequate doses cures them in an almost miraculous manner.

Hæmatinic factor deficiency is the cause of pernicious anæmia and allied anæmias⁽⁵⁾. In normal persons an enzyme is present in the gastric juice termed hæmopoietin⁽⁶⁾ (the intrinsic factor). This enzyme acts upon some constituent found in protein foods (the extrinsic factor) and forms the hæmatinic factor which is essential to hæmatopoiesis. The cause of pernicious anæmia is absence from the gastric juice of hæmopoietin. The cause of tropical nutritional anæmias is absence of the extrinsic factor from the diet of the natives.

Hæmatinic factor, though elaborated in the stomach, appears to be stored in the liver and its discovery arose from Whipple's experiments with liver diets⁽⁷⁾.

Hæmatinic factor deprivation occasionally arises in extensive resections, disease or defect of the alimentary canal. It is the explanation of anæmia of the pernicious type arising in sprue and coeliac disease.

2.—Excessive Loss or Destruction of Red Cells :

Loss of red cells occurs with bleeding, and there is no need to enumerate all the causes of acute and chronic hæmorrhage. It is important always to remember how very frequent is chronic bleeding from the bowel and female genital tract, as patients do not always volunteer statements about these passages.

Destruction of red cells occurs in the hæmolytic anæmias. The importance of this group has greatly dwindled and it is now known that all forms of hæmolytic anæmia are rare.

Hæmolytic anæmia occurs in acholuric jaundice which appears to be a familial dystrophy of the red cells, and also in familial icterus gravis neonatorum. Hæmolysis is found in certain cases of poisoning by trinitrotoluene, chloroform, phosphorus, potassium chlorate and the arsenical preparations used in the treatment of syphilis. Septicæmia due to streptococci rarely causes hæmolysis but much more often does not. Infection with bacillus Welchii or malaria may cause hæmolytic anæmia.

The classification of the causes of anæmia is now complete. It is important for practical purposes to realise the relative frequency of the various causes as met with in practice in this country. The commonest causes are bleeding and non-specific depression of the marrow by a general disease. The other common causes are deficiency of iron or hæmatinic factor.

Pregnancy tends to aggravate any form of anæmia because the foetus abstracts hæmatopoietic factors from the mother especially during the last three months⁽⁸⁾.

Clinical Manifestations.

All the anæmic states manifest the symptoms and signs peculiar to anæmia *per se*, which explains their superficial resemblance to one another.

The anæmic patient complains of languor and weakness, and shortness of breath on exertion. He or she may also suffer from headaches, giddiness, palpitations and præcordial pain. Gastro-intestinal disturbance is common, especially in the achlorhydric anæmias, and loss of appetite, retching, vomiting, epigastric discomfort or pain may add to the patient's distress. Constipation is very common.

On examination, the most obvious feature is the pallor, although a malar flush is frequent. It is important to remember that pallor is misleading. Many people with a normal blood count have marked pallor due either to a naturally thick

opaque type of skin or to cutaneous ischæmia from lack of stimulation by sun and wind. Oedematous skin is pale. Even the complexion of the mucous membranes is a very rough guide. The blood count is the only accurate criterion.

The pulse of the anæmic patient is more rapid than normal and is easily compressible. The apex beat may sometimes be outside the nipple line due to dilatation of the flabby myocardium; a systolic murmur is frequent at both base and apex. Slight œdema of the ankles is common. The spleen may be palpable in any form of anæmia except aplastic anæmia.

Any severe anæmia may produce mental disturbance, and delusions of persecution are not unusual in such cases.

Diagnosis.

In dealing with a concrete case of anæmia one should always put to oneself the primary question: Is this patient anæmic because he or she is not making enough red cells, or is it because he or she is losing or destroying them too fast?

We know that the probability is that the case will be due to either some general disease depressing hæmatopoiesis or to bleeding. Hence the first step is to investigate these likely avenues. For this reason a complete history and a complete routine clinical examination of the patient (including a pelvic examination) are essential. Indeed, they are more important than the blood picture though this, of course, has its necessary place in the investigation.

The complete history and examination will in many cases suggest special investigations such as X-rays, the fractional test meal, various forms of endoscopy, bacteriological and bio-chemical investigations.

Supposing that no source of general toxæmia or bleeding is found, then the likelihood is that the case is one of deficiency of iron or hæmatinic factor and certain symptoms and signs may help to disclose the diagnosis. In idiopathic microcytic anæmia and in pernicious anæmia there may be complaint of sore tongue, and the tongue may be observed to be acutely inflamed or smooth and bald from previous inflammatory destruction of the filiform papillæ. In the former disease, but not in the latter, there may be complaint of dysphagia (Plummer-Vinson syndrome); and in idiopathic microcytic anæmia the nails are characteristically flattened or concave (koilonychia) and are painful and brittle. Parasthesiæ of the hands and feet, slowly spreading up the limbs or the organic signs of subacute combined degeneration, point to pernicious anæmia. In both diseases the fractional test meal demonstrates achlorhydria.

In aplastic anæmia whether idiopathic or due to specific bone marrow injury the tongue and gastric secretion are normal and there is a tendency to purpuric manifestations.

In the hæmolytic anæmias there is jaundice, and may be hæmoglobinuria, and the Van den Bergh reaction shows a positive indirect reaction.

The Blood Picture :

In any anæmia whatsoever, the following features may be observed:—

- (i) Anisocytosis, which means greater range of variability in the sizes of red cells than normally seen.
- (ii) Poikilocytosis, which means the presence of a number of oddly shaped small cells, pears, crescents, etc. They are merely senile red cells retained over-long in circulation because of the shortage.
- (iii) Reticulocytosis, basophilia, basophil punctation[®]. These terms are used when more than 2 per cent. of the red cells show reticulation or stippling. They are merely immature cells present in abnormal numbers.

There is nothing characteristic or pathognomonic in any of these findings. The only feature in the blood picture which may be diagnostically characteristic is the general average size of the red cells. Abnormal smallness (microcytosis) is found particularly in iron deficiency anæmia, and, to a lesser extent, in anæmias due to chronic toxæmia or chronic bleeding. Abnormal largeness of the red cells (megalocytosis) is pathognomonic of hæmatin factor deficiency anæmias of which the prototype is pernicious anæmia. In the remaining anæmias the cells are of normal size.

The size of the cells may be measured microscopically and plotted on a Price-Jones curve or they may be measured by the diffraction halometer, but the familiar colour index or amount of hæmoglobin per corpuscle can be made to serve since the hæmoglobin content runs roughly parallel with the size of the cell. The limits of the normal colour index are between 0.85 and 1.1; figures below and above represent microcytosis and megalocytosis respectively. In iron deficiency anæmia the colour index may be 0.3 to 0.7. In pernicious anæmia it may be 1.1 to 2.0.

The white cell count does not usually shed much light upon the diagnosis. A normal count or a leucopenia is usual except in anæmias due to sepsis in which a polymorphonuclear leucocytosis is the rule.

Treatment.

In any case of anæmia of such severity that life is in jeopardy the correct immediate treatment is transfusion of an amount of blood adequate to tide over the emergency.

It is not proposed to discuss the treatment of rare anæmias.

The commonest causes of anæmia are general toxæmia, depressing hæmatopoiesis, and bleeding. The correct radical treatment is to deal appropriately with the cause of the toxæmia or the source of bleeding. In addition administration of iron greatly hastens blood regeneration.

In the microcytic anæmias due to iron deficiency the obvious treatment is the administration of iron, and, indeed, it acts magically.

There are in existence over 600 preparations of iron⁽¹⁰⁾. The most potent and the cheapest is Bland's pill (pil. ferri) when given in adequate doses—gr. xx t.d.s., for an adult—it should be freshly prepared. The next most potent preparation is iron and ammonium citrate, for which the effective dose for an adult is about 40 grains t.d.s.; for babies, 3 grains thrice daily is adequate but this dose should be gradually approached as gastro-intestinal disorder may be provoked by the full dose given at once. It is an interesting fact that in adults and children iron in large doses is more likely to cause diarrhoea than constipation.

Preparations of iron meant for injection are relatively expensive and are useless or dangerous⁽¹¹⁾. The natural foods richest in iron are meat and green vegetables.

In hæmatin factor deficiency anæmias the sovereign remedy is also obvious. Hæmatin factor is useless in other than megalocytic anæmias. Much progress has been made since the days when it was necessary for pernicious anæmia patients to swallow masses of semi-raw liver. At present, the richest possible source of hæmatin factor is found in extracts of liver prepared, not by the older Cohn method, but by the technique of Gansslen by which liver is subjected to a pressure of several tons to the square inch. Paradoxically, the pressed juice from a given weight of liver is about fifty times as potent as the liver itself administered orally.

These new extracts have the merit of being many times cheaper than whole liver, the older oral liquid and powder liver extracts and desiccated stomach. However, they require to be administered intramuscularly, and so the cost of the doctor or nurse must be offset against the cheapness of the preparation unless the patient is taught to inject himself.

At the same time, these extracts of pressed liver for parenteral administration would appear to be *the* method of the future till something even better takes their place. As an initial dose in severe cases 10—14 c.c. has been found sufficient, and for maintenance dosage 2 c.c. once every 2 to 6 weeks has sufficed⁽¹³⁾. As the preparation is so cheap and there are no dangers in over-dosage it would seem wise to err on the safe side and to double these doses.

If oral administration of hæmatinic factor is to be used, the cheapest and best vehicle appears to be desiccated hog's stomach as prepared by the method of Wilkinson⁽¹³⁾. The dose is an ounce daily. It is important to remember that desiccated stomach must not be heated above body temperature if its potency is to be preserved.

There does not now appear to be any useful scope for the oral administration of whole liver or extracts of liver, or for the parenteral administration of Cohn extracts. The preparations mentioned above are so much more efficacious. It is important to bear in mind that proprietary preparations alleged to contain hæmatinic factor vary enormously in potency. Wilkinson made careful clinical tests of 16 proprietary preparations and found some completely inactive and those not among the cheapest⁽¹⁴⁾. It is essential to use a preparation guaranteed clinically tested.

In pernicious anæmia and the allied megalocytic anæmias one should not be satisfied with less than 5,000,000 red cells per c.mm. and 100 per cent. hæmoglobin as the patient's constant blood picture. Particularly in cases with subacute combined degeneration it is essential to keep the blood figures almost supra-normal, as has been shown by Carmichael⁽¹⁵⁾ and by Ungley⁽¹⁶⁾. If this is done, most remarkable recovery from nervous lesions takes place, and patients who have been incontinent and bed-ridden for months are restored almost to normal. To achieve these results it may be necessary to give ten times as much hæmatinic factor as would be needed by a case uncomplicated by nervous lesions. In regard to the prevention of subacute combined degeneration it is remarkable that Wilkinson has had 264 cases of pernicious anæmia under treatment for periods extending up to 3½ years and not one of them has developed subacute combined degeneration.

In all cases of anæmia it is important to eradicate foci of sepsis as sepsis appears to be definitely an hæmatopoietic. In cases of anæmia with achlorhydria the administration of hydrochloric acid is advisable, and 20 minims of acid hydrochlor. dil., should be taken in a tumbler of orangeade before meals.

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