TREATMENT IN GENERAL PRACTICE

This article is one of a series on the management of some diseases of the blood and blood-forming organs met with in general practice.

PERNICIOUS ANAEMIA AND OTHER MACROCYTIC ANAEMIAS

BY

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It is necessary to emphasize that there are many types of macrocytic anaemia which differ widely one from another in their aetiology, response to treatment, and their blood picture, excluding the common factor of increased diameter of the erythrocyte. For convenience, however, it is possible to divide all macrocytic anaemias into two groups.

Group I contains the macrocytic anaemias which develop from a megaloblastic bone-marrow consequent on a deficiency of the factor necessary for the continuation of normal blood formation. This factor, often described as the "specific anti-anaemic factor," is produced in the stomach as the result of the action of a gastric enzyme on food, and is absorbed from the intestine, stored in the liver, and supplied as required to the bone-marrow. Anaemias developing consequent on a deficiency of the specific anti-anaemic factor belong to the category of megalocytic anaemias.

Group II consists of those anaemias in which the macrocytosis results from causes other than a deficiency of the specific anti-anaemic factor; it is a more ill-defined and heterogeneous group of relatively rare macrocytic anaemias resulting from widely differing causes. The macrocytosis is secondary, in the majority of cases, to prolonged stimulation or irritation of the bone-marrow. Blood formation proceeds on a normoblastic basis, but owing to its excessive activity the parent cells in the bone-marrow are primitive normoblasts, and as a result many of their offspring entering the peripheral circulation are larger and more immature than normal erythrocytes. Macrocytic anaemias belonging to Group II are present in (a) some cases of haemolytic anaemia—for example, acholuric jaundice, sometimes of the congenital but more usually of the so-called "acquired" type; (b) occasionally in malignant malaria and lead poisoning; (c) not infrequently in leucopenic leukaemia and in the terminal stages of leukaemia; and (d) in cases of Hodgkin's disease and malignant disease, in which the bone-marrow is irritated by metastatic deposits. These macrocytic anaemias are differentiated from the true megalocytic anaemias on three main grounds: (1) the finding of the aetiological factor; (2) by full examination of the blood picture, which differs in important details in regard to red cells, white cells, and platelets; and (3) by their failure to respond to the ingestion or the injection of the specific anti-anaemic factor, and by their response to appropriate treatment (splenectomy, x rays, etc.).

It is hoped that the preceding remarks make it clear that all megalocytic anaemias are macrocytic but that all macrocytic anaemias are not megalocytic. This paper will be restricted to the treatment of pernicious anaemia and other megalocytic anaemias.

Classification of the Megalocytic Anaemias

It is obvious that a deficiency of the specific anti-anaemic factor may arise in one of three ways: (A) by a failure in its manufacture in the stomach; (B) by defective absorption; and (C) by ineffective storage, mobiliza-

tion, or utilization. On this basis a simple classification of the megalocytic anaemias can be produced.

Under (A) are included: (1) Addisonian pernicious anaemia and the pernicious anaemia of pregnancy. In the former the loss of the specific gastric enzyme is permanent, while in the latter it is temporary. (2) The megalocytic anaemias, which result occasionally from extensive resection of the stomach or its widespread destruction by cancer. (3) The tropical macrocytic anaemias of Indian women (Wills), which arise from nutritional deficiency and not from a failure of gastric secretion.

Under (B) is included the megalocytic anaemia which occurs in many cases of tropical and non-tropical sprue, and in some cases of pellagra. In certain instances dietary deficiency and impairment of gastric secretion are factors to be considered in addition to a failure in absorption. Occasionally absorption is so seriously affected in individuals suffering from intestinal stenosis, from multiple anastomoses, and from prolonged diarrhoea as to result in a megalocytic anaemia.

Under (C) are included cases of severe liver diseases, particularly cirrhosis, in a proportion of which, estimated by various authors at from 5 to 25 per cent., a megalocytic anaemia occurs. In some of these cases cell-volume measurements show that this is really a false macrocytosis, due to a flattening of the cells produced mechanically during the spreading of the blood film. It is suggested that the physical state of the plasma in cirrhosis conduces to this effect. In other cases, however, cell-volume measurements are in agreement with cell-diameter measurements, and it is presumed that the damage to the liver prevents it from functioning efficiently as a storage organ for the specific anti-anaemic factor, thus allowing a megaloblastic blood picture to occur. In such cases the administration of the specific anti-anaemic factor, by mouth or by injection, will cure the anaemia but will not alter the underlying disease of the liver. Lastly, it has been suggested that a failure in the mobilization or utilization of the specific anti-anaemic factor arises occasionally, since in certain cases of megalocytic anaemia production and storage of the active principle has been shown to be satisfactory and yet the bone-marrow fails to respond to the naturally produced factor or to its parenteral administration. Before this group of megalocytic anaemias, called by Wilkinson the "achrestic" anaemias, can be finally accepted and its clear demarcation from partial aplasia of the bone-marrow be fully distinguished, further studies of the bone-marrow are required.

The value of such a classification lies in the fact that all cases of megalocytic anaemia falling under (A) and (B), and some under (C), are examples of anaemias due to a specific deficiency, and as such can confidently be expected to be relieved by supplying the missing factor. Since Addisonian pernicious anaemia is the most common and the most important of the megalocytic anaemias, it will be used as the therapeutic example on which treatment of all the megalocytic anaemias can be modelled, with minor modification.

Necessity for Accurate Diagnosis

It might appear unnecessary to emphasize the fact that treatment should be preceded by adequate diagnosis. Those of us who are accustomed to seeing large

numbers of cases of anaemia realize only too well that the technical difficulties which the majority of doctors experience in making a blood examination frequently result in treatment being instituted without this essential diagnostic procedure being undertaken. In consequence, there are large numbers of persons taking liver extract who require either no anti-anaemic remedy or only a simple iron preparation; and, vice versa, there are other individuals who reach hospital desperately ill in the severe relapse stage of pernicious anaemia, or crippled with advanced neurological disease, who have been taking iron pills for months or have received no treatment at all owing to wrong diagnosis. The last three cases of pernicious anaemia with a blood count of one million red cells or less seen by the writer had been diagnosed as inoperable cancer of the stomach; no blood examinations had been made and hence no treatment instituted.

The treatment of the anaemias with a "shot-gun" prescription of iron and liver extract, without full investigation, is becoming increasingly common, based on the presumption that one or other of these constituents must be required. If the patient's blood condition fails to respond serious organic disease is generally responsible and a fatal delay in diagnosis may result. If the patient improves the diagnostic criteria obtained from blood examination will disappear, and after a few weeks the doctor will not be able to know which of the substances should be continued for maintenance purposes. For the adequate control of treatment regular blood examinations are essential because of the great variation which occurs not only in the potency of different anti-anaemic preparations available, but also in the individual's response to treatment. As much as five to ten times the amount of liver extract may be required in one case compared with another apparently similar in regard to age, blood level, and the absence of inhibiting factors such as arteriosclerosis or infection. Lastly, for estimating the amount and the frequency of dosage needed for the maintenance of a normal blood level no alternative to regular blood examinations is available. If these facts are accepted it is obvious that so long as such procedures are beyond the scope of the majority of the practising members of the profession, central blood clinics must be established in suitable localities for the benefit of both doctors and patients alike.

Objects of Treatment.

The aim of treatment is (1) to restore the blood picture, qualitatively and quantitatively, to normal as quickly as possible; (2) to maintain a normal blood level; and (3) to replenish and stock adequately the depots of the body with the factors necessary for blood formation. Minot has rightly pointed out that the individual who receives only just enough of a nutritional factor, such as a vitamin or a mineral, to maintain health may be precipitated into the zone of partial deficiency with the advent of infection: hence the importance of adequate reserves.

It would appear advisable to consider the treatment of pernicious anaemia according to the stage of the disease present when the patient is first seen.

The Severe Relapse Stage

The patient is critically ill and in a collapsed state, with a blood count of approximately one million red cells and a haemoglobin content of 20 to 30 per cent. Before 1926 patients were frequently seen in this terminal stage, but to-day there can be no possible excuse for allowing such a state to develop. The question of blood transfusion immediately arises: the clinical state of the patient, as judged by the degree of circulatory failure rather than by the blood level present, must be the deciding factor. If the blood pressure is very low (diastolic pressure of 55 mm. Hg or less), the pulse fast

(120 or more), the heart dilated, dyspnoea present at rest, and oedema severe, it may be decided that the delay of four or five days which must elapse before improvement can occur as a result of treatment entails a risk to life which cannot be taken. In which case a blood transfusion should be given at once.

Blood Transfusion.—One pint of blood from a suitable donor should be run into the recipient's vein, very slowly in order to avoid a reaction which the weakened system may be unable to tolerate. At least half an hour should be taken for the transfusion of blood. Five c.cm. of a liver extract specially prepared for intravenous injection (hepatex P.A.F.) should be added to the blood, and 5 c.cm. of an extract suitable for intramuscular injection should be injected into the gluteal region (campolon, hepastab, pernaemon forte, Lilly, etc.). In less urgent cases, in which some doubt exists regarding the need for immediate transfusion, a suitable donor should be procured and arrangements made to keep in touch with him should an emergency arise. The intramuscular injection of 5 c.cm. of liver extract should be continued daily for three or four days, by which time the reticulocyte increase will have started and a marked subjective improvement will be noted. Within ten days the blood count should have risen by nearly one million red cells, and the patient should be out of all danger.

Iron.—Iron and ammonium citrate, 30 grains three times a day, or one tablet of ferrous sulphate (Glaxo) or ferrous carbonate (Oppenheimer's bipalatinoids 501A), twice or three times a day after food, should be started after the first week and continued for two months. In all cases receiving treatment by the parenteral route, since an iron shortage is apt to arise owing to the exceedingly rapid production of erythrocytes.

Diet.—For the first week a light fever diet should be given, owing to the impairment of gastric digestion.

Drugs.—Hydrochloric acid, combined with glycerin of pepsin, according to the following prescription, is of value if dyspepsia or diarrhoea is present.

R. Acid. hydrochlor. dil. ... 3 ij
Glycerin. pepsin. ... 3 iv

One to three teaspoonfuls to be added to a large tumbler of water flavoured with orange juice and sipped during meals.

It should be pointed out that the most efficacious treatment for all the symptoms of pernicious anaemia, and for the prevention of such serious complications as spinal cord degeneration and gall-bladder inflammation, is the adequate administration of the anti-anaemic factor. Dyspepsia, diarrhoea, sore tongue, and general weakness all rapidly disappear in the majority of cases without any symptomatic treatment.

Stage of Moderate Relapse

The patient complains of weakness, palpitation, exhaustion, dyspepsia, and dyspnoea on effort, but there is no danger to life. The blood count may be from $1\frac{1}{2}$ to $2\frac{1}{2}$ million red cells and the haemoglobin 40 to 60 per cent. In such a case a choice must be made between parenteral and oral treatment.

PARENTERAL TREATMENT

An intramuscular injection of 5 c.cm. of a liver extract should be given on three or four consecutive days deeply into the gluteal region, alternating daily from side to side. Following the injection firm massage should be applied at the site of injection for a few minutes. By this means subsequent pain and stiffness are greatly reduced. Thereafter a weekly injection of 5 c.cm. must be given until the blood count is normal. It not infrequently happens that the blood level tends to become stationary around $3\frac{1}{2}$ to 4 million red cells and 80 to 85 per cent. haemoglobin and the patient looks and feels

perfectly well. It is essential to restore the blood level completely to normal (5 million red cells and 100 per cent. haemoglobin), as this is an important factor in preventing degenerative changes in the spinal cord. It may be necessary to double or treble the number of weekly injections before normality is obtained.

No special diet is required. The patient should take a plentiful, well-balanced mixed dietary, containing red meat and green vegetables in at least one meal a day. Drugs: iron and hydrochloric acid as already indicated.

ORAL TREATMENT

Liver extract by mouth was the treatment of choice till about three years ago. The extract from 500 grams of liver daily is generally needed to obtain the maximal regeneration of blood. As the cost of treatment works out at from 20s. to 30s. weekly, compared with approximately 2s. 6d. to 3s. when parenteral treatment is given, liver extract by mouth can no longer be recommended, for economic reasons. In addition, in resistant cases and in those in whom absorption is poor, oral treatment does not compare with parenteral, on the grounds of efficiency. Half a pound daily of lightly cooked liver is the average dose required if liver is taken in the crude state. Since the specific anti-anaemic factor is moderately heat-stable there is no point in prescribing raw liver. There are several reasons why the ingestion of liver cannot be recommended as the treatment of choice: first, there is an ever-increasing difficulty in obtaining regular and adequate supplies; secondly, the cost of liver has risen very greatly; and, thirdly, many persons fail to continue to take the requisite amount required to attain and maintain a normal blood level, owing to the nausea and disgust engendered by the constant sight, taste, and smell of the article.

Hog's Stomach Preparations.—These preparations are insoluble and contain the gastric enzyme, which is thermolabile; hence they must not be heated. Excellent results can be obtained from the use of such preparations as ventriculin, pepsac, ektomak, etc., in doses of a tablespoonful three times a day, in water, milk, orange juice, etc. English preparations, such as pepsac, are cheap (8s. 6d. a pound), but they have an unpleasant taste and smell, which can be improved by exposing the next day's ration in a saucer to the air for twelve hours.

GENERAL AND PRE-OPERATIVE MEASURES

Patients should be kept in bed until the haemoglobin has reached approximately 60 per cent. Chronic focal sepsis (tonsils, teeth, or accessory sinuses) should not be treated radically until there has been an adequate response to specific anti-anaemic therapy. On the other hand, localized and easily accessible collections of pus should be evacuated, since they tend to inhibit or retard the therapeutic response.

Should an emergency arise during the relapse stage of pernicious anaemia, requiring an operation which cannot be delayed, intensive parenteral treatment should be undertaken immediately (10 c.cm. of liver extract intramuscularly, repeated in six hours), and a suitable donor should be procured in order that blood transfusion can be immediately given if required. Patients in the remission stage of pernicious anaemia, particularly if they show signs of neurological disease, should receive double or treble the usual quantity of liver extract for a few days before undergoing any major operation, since the blood level tends to fall and neurological degeneration to progress, after serious surgical procedures.

Maintenance Treatment

The amount of material required to maintain a normal blood level varies greatly in different individuals, often for no apparent reason. Only by trial, checked by blood

examination, can the problem of dosage be satisfactorily settled. In parenteral treatment the necessary number of intramuscular injections of 5 c.cm. of liver extract varies in different individuals from one a week to one every six weeks. In my experience, 5 c.cm. of campolon, given once every two or three weeks, is an average dose. Iron is not required if it has been prescribed during the first two months of treatment. Hydrochloric acid and pepsin are necessary only for the purposes already mentioned. An ordinary mixed diet is all that is required. The maintenance dose of liver and hog's stomach preparations is also extremely variable in different individuals: on the average, it may be said to be two pounds of liver or four ounces of dried hog's stomach preparation weekly.

The depot storage method of treatment, whereby 5 to 10 c.cm. of a liver extract is injected intramuscularly on two consecutive days, is of value to patients proceeding on holiday or on business to places where facilities for treatment are not available. By this method a satisfactory blood level may be maintained over periods up to two months.

In my experience parenteral treatment is the method of choice at all stages of the disease, on the grounds both of efficiency and of economy. Should the patient object to injections, however, cooked liver and hog's stomach preparations on alternate days, in the doses mentioned above, should be advised, as by this means the distaste engendered by both articles, if continuously taken over long periods, is reduced.

MEGALOCYTIC ANAEMIAS OTHER THAN ADDISONIAN ANAEMIA

The scheme of treatment outlined above is satisfactory for the treatment of the anaemia present in the other conditions mentioned, with the following modifications.

PERNICIOUS ANAEMIA OF PREGNANCY

In the majority of cases treatment can be discontinued after parturition.

TROPICAL AND NON-TROPICAL SPRUE AND PELLAGRA

In the above conditions multiple deficiencies are present which must be corrected. In addition to supplying the anti-anaemic factor, the deficiency of vitamins and minerals must be repaired by the administration of marmite (one teaspoonful in water or in a bread-and-butter sandwich thrice daily); radiostoleum or adexolin (5 minims thrice daily); calcium (calcium lactate, 30 grains thrice daily); and iron (as above). For the control of the fatty diarrhoea restriction of fatty foods, especially cream, butter, milk, bacon, and fatty meat, must be made. A high intake of Grade A protein—for example, liver and butcher's meat—is recommended, while starchy food should be taken in small quantities only. For details the reader is referred to the literature dealing with the dietary problems in the above deficiency diseases. When the condition has been cured by diet and anti-anaemic treatment the maintenance dose of the specific anti-anaemic factor may be steadily reduced, many cases being able thereafter to maintain a normal blood level by diet alone.

With regard to the megalocytic anaemias occurring in cases of severe liver disease, the results of anti-anaemic treatment are less satisfactory, since prognosis depends on the degree and progress of liver damage. Lastly, in the so-called "achrestic" and semi-aplastic anaemias with a megalocytic blood picture the response of the formative tissues to the treatment outlined above is absent or very poor. Repeated blood transfusions can, however, maintain the patient alive, but in a poor state of health, for long periods.