REFRESHER COURSE FOR GENERAL PRACTITIONERS**DIAGNOSIS AND TREATMENT OF PERNICIOUS ANAEMIA**

BY

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Addisonian pernicious anaemia is the commonest and most important member of a group of diseases known as the megaloblastic anaemias. In pernicious anaemia the primary fault lies in a failure of gastric function. The mucosa of the stomach normally contributes a secretion (the intrinsic factor) which modifies, or combines with, a dietary factor to produce the anti-anaemic principle which is absorbed from the alimentary tract and stored in the liver. Pernicious anaemia arises when the glands of the gastric mucosa fail to secrete the intrinsic factor: its anatomical basis is an atrophy of the mucosal lining of the stomach.

Diagnosis

The importance of precise diagnosis before treatment is carried out cannot be overemphasized, for it may be impossible later. An incorrect diagnosis may mean that some other condition is overlooked until it has progressed beyond the possibility of cure; or, at best, that the patient is sentenced unnecessarily to regular injections for the rest of his life.

The logical steps in establishing a diagnosis of pernicious anaemia are to prove, first, that the anaemia in question is of the megaloblastic variety, and, secondly, that it has originated from failure of gastric function. Megaloblastic anaemias are characterized by a reduction of the red blood cell count proportionately greater than the fall in the haemoglobin level, and thus by a colour index greater than 1. Inspection of stained films of the blood will reveal variation in the size of the red blood cells, many of which will be abnormally large (megalocytes). This megalocytosis is shown by an increase in the mean corpuscular volume, an easily estimated index, of which the normal value lies between 75 and 95 μ^3 .

In pernicious anaemia the figure is almost always above 100 μ^3 and usually in the range 110–140 μ^3 . The leucocyte count is usually reduced, figures of 3,000 per c.mm. being common; the differential count shows no characteristic changes, but it is the rule to find some neutrophils whose nuclei have undergone abnormal segmentation to give rise to five or even six lobes. Complete proof that the anaemia is megaloblastic is given by examination of the bone marrow by puncture biopsy. Films of the aspirated material will show an increased cellularity with a predominance of megaloblasts. Although this investigation is always desirable, because its results are conclusive, it is not essential unless the diagnosis is in serious doubt.

Addisonian pernicious anaemia accounts for more than 90% of megaloblastic anaemias met with in this country, and is thus by far the most probable cause of any instance seen in practice. Probability is made virtual certainty by establishing the absence of other possible causes; by demonstrating gastric achlorhydria; and by the presence of signs indicating subacute combined degeneration of the spinal cord.

Megaloblastic anaemia occurs also as a result of tropical sprue, idiopathic steatorrhoea, and other variants of the sprue syndrome; it may be due to dietary deficiency (nutri-

tional megaloblastic anaemia), or to various disorders of the alimentary tract, such as intestinal stricture and regional ileitis. It may occur in pregnancy or the puerperium; it may follow operations on the stomach and particularly total gastrectomy; it has been reported in infants, probably due to nutritional causes. A few questions put when taking the history will help to exclude these uncommon conditions. Collateral evidence of impaired gastric function will be provided by the fractional test meal: the diagnosis of pernicious anaemia should never be entertained unless achlorhydria after injection of histamine is established. Finally, subacute combined degeneration of the spinal cord accompanies pernicious anaemia in 40–50% of cases, but it is very rarely associated with other megaloblastic anaemias; thus evidence of this disease provides strong support for the diagnosis.

In brief, it may be said that a megalocytic anaemia with achlorhydria is probably pernicious anaemia. The diagnosis is made more probable by the presence of signs indicating subacute combined degeneration of the spinal cord. It is established beyond doubt by the demonstration of a megaloblastic bone marrow or by the presence of megaloblasts in the circulating blood, and by the exclusion of other causes of anaemia of this type.

Initial Treatment

The patient with severe anaemia should be at rest in bed, and it is wise to insist that he should remain there until the haemoglobin level has risen above 65% (Haldane). An exception must be made of those patients in whom there is evidence of disease of the spinal cord, for their disability is increased by prolonged immobilization.

It has long been known that certain foods are particularly favourable to blood regeneration: highest in the list are liver and kidney; apricots, peaches, grapes, and apples have considerable potency; while in this respect green vegetables, dairy products, and the farinaceous foods rank low. The immediate importance of these foods in pernicious anaemia, for which a specific therapeutic agent exists, is not great; nevertheless, a well-balanced diet, containing a liberal supplement of vitamins and a representative selection of the articles mentioned, should be prescribed. Bread, cakes, pastry, potatoes, and fats should be taken only in moderation and to ensure an adequate calorie value, for in excess they diminish the appetite for more valuable foods.

Blood transfusion is now seldom required in the patient with pernicious anaemia. The indications are anaemia severe enough to constitute an immediate danger to life; the presence of an infection or other process likely to interfere with the adequate response to specific treatment; and the urgent necessity for raising the haemoglobin level rapidly when, for example, immediate surgical operation is necessary. It is not easy to give a precise figure for the haemoglobin level below which transfusion is essential. Some patients with a reading as low as 20% (Haldane) are obviously not in immediate danger, while others with a level of 30% (Haldane) as clearly require transfusion.

Mental disturbance due to cerebral anoxia, extreme venous congestion, and generalized puffy oedema afford the clearest indications for transfusion of blood. This must be undertaken with extreme caution, for circulatory overloading is particularly prone to occur in the gravely anaemic patient: not more than 1,200–1,500 ml. should be given at a time, and the rate of administration should not exceed 1 ml. per kg. body weight an hour.

Specific Treatment

The specific treatment of pernicious anaemia consists of the administration of the anti-anaemic principle. Many effective preparations are available. Of these, raw liver and the liquid extract of liver for oral administration have little more than historical interest.

Proteolysed Liver for Oral Administration.—This is a powder obtained after papain digestion of liver: 1 g. contains the product of about 5 g. of the original liver. It is believed to contain substances which are needed for the repair of some of the less common megaloblastic anaemias but are removed in the preparation of refined extracts. It is an active and satisfactory preparation, and the first choice in the treatment of pernicious anaemia when parenteral injection is refused or contraindicated. A dose of one teaspoonful two or three times daily is usually adequate.

Liver Extracts for Parenteral Injection.—In general, two varieties are available—crude and refined. Crude extracts have undergone the minimum of processing necessary to make them safe for injection, and contain a large amount of material other than the active principles. Each millilitre is derived from 2.5 to 10 g. of original liver. Refined extracts are derived from crude extracts by further purification, and the quantity of inert material they contain is less. Each millilitre is derived from 50 to 200 g. of liver. These definitions do not mean that the crude or refined extracts of different manufacturers are strictly comparable. It was long believed that crude extracts contained substances, removed during further purification, which made them more effective in some megaloblastic anaemias. It has often been stated that they should be employed when subacute combined degeneration is evident, but there is no foundation for this belief. Intramuscular injection of a refined liver extract of known potency is a completely effective method of treating pernicious anaemia, whether neural degeneration is present or not. Dosage varies with the product used. There is no indication for the use of crude extracts in treating pernicious anaemia.

Vitamin B₁₂.—Vitamin B₁₂ appears to be the anti-anaemic principle of liver; it has proved as effective in the treatment of pernicious anaemia and subacute combined degeneration of the spinal cord as liver extract. When *Streptomyces griseus* is grown in fluid media it elaborates a substance as active therapeutically as the vitamin B₁₂ obtained from liver and probably identical with it. This product of the *Streptomyces* metabolism is marketed as vitamin B₁₂.

It is probable that vitamin B₁₂ will replace liver extracts in the treatment of pernicious anaemia; it is cheaper, apparently as effective therapeutically, and never gives rise to the allergic complications which may follow prolonged use of liver extract.

The vitamin is given by parenteral injection: 20 µg. weekly is sufficient for the initial treatment of an average case; if signs of neural degeneration are present the dose should be raised to 40 µg. weekly.

Desiccated Hog's Stomach for Oral Administration.—This is, in a sense, the most logical remedy for pernicious

anaemia, because it contains the intrinsic factor which the patient lacks. It is prescribed as a dry powder with an unpalatable taste, and the dose required is one to two tablespoonfuls daily. Some authorities believe it to be particularly indicated in the presence of subacute combined degeneration of the cord, although this view has not gained general acceptance. It is fully effective in the treatment of pernicious anaemia, but it is not to be recommended as a routine method. It is useful, as an alternative to proteolysed liver, when parenteral injection is impossible.

Folic Acid.—Pteroylglutamic acid, or folic acid, is effective in raising the blood levels in pernicious anaemia, but it has been found to exert no control on the nervous degeneration. In fact, its administration is often followed by the explosive onset of nervous symptoms which progress rapidly even while the anaemia is improving. Further, it has been shown that folic acid is not always able to maintain the haemoglobin reading and red blood cell count at normal levels. For these reasons folic acid must in this respect be regarded as a dangerous drug which has no place in the treatment of pernicious anaemia.

Dosage

The problem of dosage in using liver extracts and related preparations has always been difficult. There is no officially recognized "unit" of activity in this country, although the *United States Pharmacopoeia* has attempted to define one. The practitioner is forced to take the recommendations of the manufacturer until he has used one preparation long enough to be familiar with its potency. Recently it has become the practice for preparations to bear a statement of the number of microgrammes of vitamin B₁₂ contained in a millilitre. This figure may well be fallacious because of technical difficulties in estimating the vitamin B₁₂ content of liver extracts. For these reasons it is unwise to accept such figures as indicating with any precision the potency of a liver extract.

At present the method to be recommended is the intramuscular injection of a refined liver extract of proved potency or of vitamin B₁₂. In the first case dosage varies with the product, but, on an average, 1–2 ml. at intervals of 7–14 days will procure a maximal effect. If vitamin B₁₂ is used, 20 µg. at intervals of 7–14 days is adequate. The response is easier to follow if daily reticulocyte counts can be made; a peak, the height of which is inversely proportional to the original red blood cell count, is reached between the fourth and ninth days after the initial injection. Thus a satisfactory response is indicated by a reticulocyte peak of about 40%, with an initial red blood cell count of 1,000,000 per c.mm.: with counts of 2,000,000 and 3,000,000 per c.mm. figures of 19% and 6.5% respectively would be anticipated. The increase in red blood cells follows hard on the reticulocytosis, and, whatever the initial count, a level of about 5,000,000 per c.mm. should be reached by the eighth week of treatment.

It is generally thought to be advisable to increase the dose of liver extract or vitamin B₁₂ if subacute combined degeneration of the spinal cord is present. It is reasonable to give twice the quantity which would otherwise have been prescribed.

Inadequate response raises three possibilities. First, the preparation may be inactive: this should not arise if a reputable product with which the practitioner is familiar is employed, for most manufacturers subject each batch to clinical trial before it is marketed. Secondly, the diagnosis may be incorrect: this will require careful revision, and further investigation may be necessary. Thirdly, some

condition known to impair the effect of the liver principle may be present. Infective processes are of particular importance in this respect. The most frequent is chronic infection of the urinary tract, which should always be excluded. Myxoedema and advanced arteriosclerosis are additional causes of an unsatisfactory response to liver.

Maintenance Treatment

When a normal blood picture has been restored the task of maintenance treatment is to preserve it. It is important to have exact criteria by which to judge normality, and the aim should be to keep the red blood cell count above 4,500,000 c.mm., the haemoglobin level above 90% (Haldane), and the mean corpuscular volume below $100 \mu^3$. Adequate control is possible only by means of regular examinations of the blood, and these should be made at least once in three months. At most clinics undertaking the treatment of pernicious anaemia a count once a month is the routine. The dosage required and the interval between injections vary with the patient; in the great majority 3-4 ml. of a refined extract or 40 μ g. of vitamin B₁₂ once a month will maintain a normal blood picture. If nervous symptoms are present it is advisable to give this quantity once a week for six months to a year. In any patient the dose should be increased if there is complaint of paraesthesia or sore tongue.

At the onset it is advisable to warn patients that they will require injections at regular intervals of a month for the rest of their days.

Complications of Liver Treatment

The only complication of parenteral injection of liver extracts is the occasional development of hypersensitivity. A small proportion of patients will complain, after a period, of collapse, sweating, vomiting, palpitation, skin rashes, or asthma immediately following an injection. When such symptoms appear parenteral injections of all liver extracts must be stopped, because hypersensitivity is seldom limited to one proprietary brand. Oral treatment with proteolysed liver or desiccated hog's stomach may be substituted. In some cases desensitization to liver extract is worth consideration; but the alternative, which will probably prove most satisfactory, is to continue with parenteral injections of vitamin B₁₂, to which no such reactions occur.

Adjuvant Treatment

It is rare to encounter patients in whom any symptoms, other than nervous, remain after effective liver treatment. The exceptions are those in whom some dyspepsia persists: in these, dilute hydrochloric acid (*B.P.*) in doses of 15-30 min. (0.9-1.8 ml.) three times a day in water or fruit juice is usually successful in relieving symptoms. Medication with iron is quite unnecessary unless a complicating iron-deficiency exists.

It should be noted that carcinoma of the stomach is at least three times as common in patients with pernicious anaemia as in the general population. The appearance of dyspeptic symptoms, loss of weight, or hypochromic anaemia should always arouse this suspicion. A radiological examination of the stomach once a year is a wise precaution.

Physiotherapy, and sometimes the assistance of the orthopaedic surgeon, will be needed in the treatment of patients with subacute combined degeneration of the spinal cord. It is usually found that symptoms and signs referable to peripheral neuritis improve rapidly, and usually vanish within two years of starting liver treatment. Damage to the cord becomes arrested, but little improvement is to be anticipated.

INCIDENCE AND TREATMENT OF NEUROSIS IN INDUSTRY

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It is becoming increasingly recognized that psychiatric and psychosomatic conditions comprise many of the recurring and chronic forms of illness, but their occupational aspects are still insufficiently appreciated. Characteristically, these disorders incapacitate rather than kill, so that morbidity statistics should provide the basic source of information. Unfortunately, emphasis in the past has been placed on mortality rather than morbidity as a criterion of national health, so that relevant figures are lacking. This paper is designed to bring some aspects of industrial neurosis to the general notice and to suggest measures for dealing with the problem.

The incidence of neurosis among working groups of the population has been investigated from time to time by different workers. Culpin and Smith (1930) examined 1,000 people, including factory, clerical, technical, and administrative workers, by means of a planned interview and specific psychological tests. They found the incidence of nervous symptoms or emotional maladjustment was not confined to any one group, sex, or age. Approximately 16% had serious emotional difficulties and a further 20% had minor difficulties. Comparable figures were found by Halliday (1935), Bashford (1940), Collier (1943), Stocks (1945), and Wyatt (1945). Figures of the incidence of neurosis in the Services are in general conformity with these findings. More recently, Russell Fraser *et al.* (1947) carried out a survey on a sample of 3,000 male and female workers employed in 13 light and medium engineering factories situated mainly in the Birmingham region. They showed that 9.1% of the men and 13% of the women had suffered from definite and disabling neurotic illness, and a further 19% of the men and 23% of the women from minor forms of neurosis during the course of six months. Neurotic illness caused between one-quarter and one-third of all absence from work due to ill-health.

Prevention of Neurosis in Industry

Clearly the incidence of neurosis in industry is influenced by working environment, both physical and psychological, so it is essential that both doctors and industrial management should have a satisfactory understanding of these problems. Evidence of the need for training at this level is shown in a recent report of a committee set up by the Minister of Education. The suggested syllabus of training includes such subjects as personnel selection, placement, health, welfare, and safety; general psychology and psychiatry; the measurement of intelligence, attainments, and special aptitudes; social psychology, including the human factor in industrial relations, rehabilitation, individual and group morale, and the psychological basis of morale.