The Treatment of Pernicious Anaemia

Pernicious anaemia has been defined by Wintrobe as a chronic disease of insidious onset, characterized by the development of a macrocytic anaemia with evidence of increased blood destruction, by achylia gastrica and by certain gastrointestinal and neurological disturbances. With increasingly precise criteria of diagnosis, several groups of megaloblastic anaemias previously included as pernicious have now been excluded from the disease.

In Edinburgh in 1822, Dr. J. S. Coombe discussed the history of a case of pernicious anaemia. Thomas Addison, colleague of Richard Bright at Guy's Hospital, described the disease as a clinical entity first in 1849 and again in 1855. Anton Biermer, of Zurich, in 1871 described 15 cases of severe anaemia under the title of progressive pernicious anaemia. Treatment throughout this period and until 1926 was uniformly unsuccessful. In 1926 Minot and Murphy showed that the daily ingestion of mammalian liver was an effective remedy. In the last 20 years extracts of liver have been obtained for oral use and for parenteral administration. In 1945 Spies showed that synthetic folic acid was effective in restoring normal blood levels in this condition. In 1948 the isolation of a new chemical compound, Vitamin $B_{12}$, was reported independently by Lester Smith in this country and by Rickes et al. in the United States. This substance is believed to be the anti-pernicious anaemia principle.

The basis of modern therapy is the intramuscular injection of a potent liver extract at regular intervals. In the past there has been no adequate laboratory method of assessing the potency of anti-anaemic preparations. The method finally adopted was the study of the effect produced on the blood of patients. The American unit represents the minimal amount of therapeutic agent which, when given daily in an uncomplicated case of pernicious anaemia produced a satisfactory or average reticulocyte response and so subsequent relief of anaemia and symptoms. For the average uncomplicated case of pernicious anaemia the equivalent of 30 U.S.P. units are given every four weeks. In this country each batch of liver preparation is tested in the recommended dose against a case of uncomplicated pernicious anaemia for an adequate response; but no unit has been adopted. With the isolation of vitamin $B_{12}$ microbiological assay of liver extracts can be carried out and their content reported in micrograms.

Liver extracts can be divided into two groups, crude and concentrated or refined extracts. Of the crude extracts 10 to 20 ml. are required for patients in relapse, 4 to 6 ml. weekly for maintenance. Of refined extracts 6 to 12 ml. are required for patients in relapse and 2 ml. at fortnightly intervals for maintenance. These amounts are average requirements. The response of individual patients varies considerably and in considering the dosage adopted it is pertinent to bear in mind Minot's remarks in his Nobel lecture in 1934, 'The grave error in treatment is to prescribe too little liver extract or potent substitute. When there is doubt, more rather than less should be given.' The objectives of treatment are the restoration of the blood count to normal, the reduction of the red cell size to normal and the relief of all symptoms. Higher dosage is required if there is associated neurological disease and in the presence of infection.

Of the oral preparations, raw liver has now been practically abandoned; the dose is $\frac{1}{2}$ to 1 lb. daily in relapse and 2 to 4 lb. weekly for maintenance. It is, however, interesting to note the case recorded in the American literature of the patient who preferred $\frac{1}{2}$ lb. of beef liver daily and who had already imbibed over a ton of raw liver in addition to liver by other routes. Preparations of hog's stomach are used in 30 gm. doses for cases in relapse and 4 to 10 gm. daily for maintenance. Wilkinson maintains that cord complications respond well to stomach extract therapy. Proteolysed liver, a papain digest of raw liver, has been used by Davidson in cases refractory to liver extract, a daily dose of $\frac{1}{2}$ to 2 oz. may be necessary. Oral therapy, however, suffers from the defect of uncertain absorption and maintenance over long periods is not so satisfactory.

When a diagnosis of pernicious anaemia is established a regular schedule should be followed.
It is essential that a reputable liver extract be used and it is wise to adhere to one brand. Initially 2 ml of a refined or concentrated extract is given daily for five to six days. This is followed by 4 to 6 ml weekly for six to eight weeks and until the red cell count has returned to normal. Daily reticulocyte counts should be made for the first ten days and a reticulocyte peak should be reached in five to eight days. Red cell counts and haemoglobin estimations should be carried out twice weekly until satisfactory levels are reached, and thereafter every month. If an adequate reticulocyte response does not occur and if the red cell count and the haemoglobin fail to rise at an adequate rate, the dose of liver extract should be increased. If there is still no response, provided that the extract is known to be potent, the diagnosis must be reconsidered.

With the initiation of liver therapy there will be a return of well-being and of appetite. The improvement produced affects the manifestations of the disease in the tongue, in the bone marrow and in the central nervous system, but it does not restore to the stomach the ability to secrete hydrochloric acid. The majority of patients have no gastric symptoms when in remission, but should these be present they may be relieved by the administration of dilute hydrochloric acid with meals. There are no accepted indications for transfusion in the severe case of pernicious anaemia. This procedure should be borne in mind when the red cell count is below 1,000,000 per c.mm. and the haemoglobin below 20 per cent. If there is not a symptomatic and a haematological improvement within 48 hours of adequate liver therapy, a slow transfusion (40 drops a minute) of 200 ml of packed cells may be life saving. It is, however, a hazardous procedure with this degree of anaemia particularly in the older age groups. During the period of rapid rise in the red cells, iron may be given with advantage particularly if the colour index or M.C.H.C. fall below normal levels.

A rare complication of liver therapy is the development of sensitivity. The manifestations are usually mild, consisting of pruritus, urticaria and oedema of the face; they occur about 30 mins. after the injection. The symptoms are usually quickly controlled by the subcutaneous injection of adrenaline. They can be prevented by the administration of one of the anti-histamine preparations 1 hour before the injection. Bauer has shown that this sensitivity is species specific and it is occasionally possible to replace the sensitizing extract with another liver extract. Desensitization can be carried out by commencing with minute doses (0.01 ml) of liver extract. It is in this complication that the temporary use of oral preparations of liver have an important role in therapy.

The administration of folic acid in pernicious anaemia has been largely abandoned. Adequate haematological response is obtained but neurological signs may develop when the blood picture is normal. Welch, in 1947, in discussing the role of folic acid, stated that the synthesis of red cells might be formed through the catalytic effects of either folic acid or the factor of refined liver extract. He suggested further that the refined liver extract factor could not completely replace the folic acid requirement in man. It is of interest, therefore, to note that in the last year there have been reports of megaloblastic anaemias refractory to vitamin B₁₂ therapy but which have responded to folic acid.

Vitamin B₁₂ is a crystalline chemical compound, of molecular weight approximately 1,600, containing cobalt as well as phosphorus and nitrogen. It is now available at a cost comparable to that of liver extracts. Ungley has found that a dose of 10 µg. produced the expected response of reticulocytes and red cells, as calculated from the formula of Della Vida and Dyke, in the uncomplicated case of pernicious anaemia. The dosage suggested by Ungley is 40 to 50 µg. initially, 20 µg. weekly for three months and 30 µg. every three weeks for maintenance. Should there be the least sign of relapse or if infection develops the dosage should be doubled or trebled. Neurological signs have improved in the majority of cases and as yet no case has developed neurological lesions while on therapy. From the above figures it would appear that the requirements for maintenance would be about 1 µg. a day; although it must be stressed that the vitamin B₁₂ requirement for maintenance over a long period of time is unknown. The protective action of vitamin B₁₂ against the develop-
ment of neurological complications over a long period of time is also undetermined.

In conclusion it may be said that modern therapy with potent liver extract relieves the patient of his symptoms, restores a normal blood level and prevents neurological disease. The treatment is not complete without periodical radiological examination of the stomach for neoplasia. Kaplan and Rigler in autopsy studies showed the presence of carcinoma of the stomach in 12 per cent. of their cases, an incidence three times as great as the average for the same age group.

D. G. T. Hicks, M.A., B.M., M.R.C.P.

LETTER: The Nursing Situation

Mr. Douglas Robb, in your last number, stated that the problem of the shortages of nurses in the English-speaking countries is in direct relation to the woman power. This may, to some extent, be true but surely he, like so many other people, is only looking at the problem from the number of new recruits available every year.

If every girl who trained as a nurse continued to nurse (other than those who married, and even they might be expected to nurse their own families) the shortage would be overcome.

If as a means of increasing the number of nurses the training is shortened, then more people than ever will be required to train so that even the existing standards of nursing care, carried out by student nurses, may be maintained.

It is amazing to think that medical men, who expect such a high degree of intelligence and knowledge from the people on whom they rely to help them care for their patients, should really seriously think that a nurse can be trained in less than three years. It is only towards the end of that time, by constant attendance on seriously sick people, that the nurse really begins to understand what she is doing, how to recognize the slight changes in patients which are so vitally important for their welfare and how at last to know how to make a patient comfortable and to make the doctor’s treatment and orders acceptable to the patient.

The principles of nursing care have to be learned while actually doing all the day to day and hour to hour duties for the patient. They cannot be learned in the classroom, although a sound theoretical knowledge is also essential. If it were otherwise, a short correspondence course would be excellent.

Hundreds of girls are training every year. They are doing excellent work while training but the tragedy is that having qualified they infinitely prefer to be receptionists, secretaries, dental attendants or nannies, and they are frequently encouraged to take these posts by doctors from whom they receive higher salaries than they would receive as nurses.

The solution surely lies in recognizing the position of the trained nurse, from the staff nurse up to the matron, and in giving them the responsibility and salary of the posts to which they are appointed. Then, and then only, will the right type of nurse remain in nursing.

Clare Alexander,
Matron, The London Hospital.

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D. G. T. Hicks

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