TREATMENT OF PERNICIOUS ANAEMIA BY LIVER.*

BY

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IN August, 1926, Minot and Murphy¹ reported that they had obtained good results in the treatment of pernicious anaemia by means of a generous diet rich in animal proteins and especially in liver, and a year later they published a further report² on a series of 105 cases. In their second report they confirmed the good results obtained and emphasized the importance of the liver in the diet, and they were further able to announce that a non-protein

CHART 1.—Case I.

fraction of liver had been prepared by Cohn that appeared to have the same influence as the whole liver in bringing about a remission in the symptoms and a striking improvement in the blood picture. They were led to try the influence of diet, and especially of liver feeding, for a number of reasons. The similarity of pernicious anaemia in many of its symptoms and signs to pellagra, sprue, and beri-beri suggested that, like these diseases, pernicious anaemia might be associated with a faulty diet. The improvement noted in cases of sprue when liver soup was administered, and the observations of Whipple^{3,4} and his associates that liver feeding exerted a striking influence on the regeneration of the haemoglobin in severe secondary anaemia produced by repeated bleedings in dogs, pointed to liver as likely to have a specially favourable influence, although it is probably a defect in the development of the cells rather than of the haemoglobin that is present in pernicious anaemia. At the meeting of the British Medical Association in Edinburgh last year a paper by Minot and Murphy⁵ was read reporting on the results in 125 cases, and a number of papers have appeared in the literature of other countries in the last few months. In this country

* This article is based on a paper by Professor Fraser opening a discussion on "The treatment of pernicious anaemia" at the Medical Society of London on January 23rd, 1928 (see p. 178).

Anderson and Spriggs⁶ reported that they had successfully treated two cases by liver feeding, and Spence,⁷ at a meeting of the Newcastle and Northern Counties Medical Society in November, 1927, reported the results in 20 cases.

We have been able to treat 19 cases of pernicious anaemia by the administration of liver, but in 6 of these the disease was in the remission stage, and in 4 others methods of treatment other than liver administration were employed in addition, or the observations were incomplete, so that a valuation of the treatment in them is not possible at present. Nine cases came under observation in the stage of relapse or before the first remission, and in them there were no other methods of treatment that interfere with the estimation of the value of treatment by liver.

Results.

CASE I (Chart 1).

A woman, aged 47. First attack in 1920. Admitted on August 25th, 1927, in the second relapse. Subjective and objective

CHART 2.—Case II.

evidence of involvement of nervous system. Achlorhydria present. Indirect van den Bergh test, 1 unit. Red blood cells numbered 1,470,000 per c.mm.; haemoglobin 32 per cent.; white blood cells 2,200. Megaloblasts present. Price-Jones curve positive.

Treatment: The patient was given $\frac{1}{2}$ lb. cooked liver daily. On the tenth day of treatment the percentage of reticulated red cells had risen to 18.0, and at the end of two months the blood count showed red blood cells 4,410,000; haemoglobin 98 per cent.; white blood cells 9,500.

CASE II (Chart 2).

A woman, aged 37, admitted on July 29th, 1927, in first attack. Subjective and objective evidence of involvement of nervous system. Achlorhydria present. Red blood cells numbered 1,320,000; haemoglobin 30 per cent.; white blood cells 4,500. Megaloblasts present.

Treatment: She was given $\frac{1}{2}$ lb. cooked liver daily. On the seventh day of treatment the percentage of reticulated red cells had risen to 13.0, and at the end of ten weeks the blood count was, red blood cells 4,850,000; haemoglobin 90 per cent.; white blood cells 6,600.

CASE III.

A man, aged 58, admitted on September 16th, 1927, in first attack. Subjective and objective evidence of involvement of nervous system. Achlorhydria present. Indirect van den Bergh test, 0.7 unit. Red blood cells 2,160,000; haemoglobin 69 per cent.; white blood cells 3,750. Megaloblasts present. Price-Jones curve positive.

Treatment: Patient was given $\frac{1}{2}$ lb. cooked liver daily. He had been receiving arsenic by the mouth for four days before admission; this was stopped for nine days before liver was commenced.

On the eighth day of treatment the percentage of reticulated red cells had risen to 5.0, and at the end of seven weeks the blood count was, red blood cells 4,530,000; haemoglobin 98 per cent.; white blood cells 7,000.

CASE IV.

A woman, aged 45. First attack commenced in 1921. Admitted on June 10th, 1927, in the fourth relapse. In the previous remissions there is no note of the haemoglobin reaching a higher figure than 75 per cent. The tongue showed atrophy of the mucous membrane. There was subjective and objective evidence of involvement of the nervous system. Spleen palpable. Achlorhydria present. Indirect van den Bergh test, 4 units. Megaloblasts present. Price-Jones curve positive.

On June 23rd she was given 200 c.cm. of blood intravenously, and on July 11th received a further 600 c.cm. On July 12th the blood count showed red blood cells 2,100,000; haemoglobin 45 per cent.; white cells 3,600. On July 15th the red cells numbered 1,700,000; haemoglobin 50 per cent.; white cells 3,000. On July 20th liver treatment was commenced— $\frac{1}{2}$ lb. cooked liver daily. On the seventh day of treatment the percentage of reticulated red cells had risen to 5.0, and at the end of seven weeks the blood count was, red cells 4,350,000; haemoglobin 96 per cent.; white cells 8,800.

CHART 3.—Case v.

Through the kindness of Dr. Minot and the committee on pernicious anaemia of the Harvard Medical School, who were controlling the preparation of a liver extract, we received a small supply of an extract prepared by Eli Lilly and Co., by the method devised by Cohn.⁸ The effect of this extract is seen in the next two cases.

CASE V (Chart 3).

A man, aged 60, admitted on September 29th, 1927, in the first relapse. Mental disturbances pronounced, and subjective and objective evidence of involvement of nervous system. Tongue smooth. Achlorhydria present. Indirect van den Bergh test, 0.6 unit. Red blood cells numbered 1,920,000; haemoglobin 53 per cent.; white cells 4,000. Megaloblasts present. Price-Jones curve positive.

Treatment: Extract (Lilly) equivalent to 500 grams of liver daily. On the eighth day of treatment the percentage of reticulated red cells had increased to 11.2, and the red cells and haemoglobin rose rapidly. The extract was stopped on the nineteenth day, and $\frac{1}{2}$ lb. of liver daily was substituted. After thirteen weeks of treatment the blood count was, red cells 4,290,000; haemoglobin 97 per cent.; white cells 7,100.

CASE VI (Chart 4).

A woman, aged 56, admitted on October 11th, 1927, in second relapse. Subjective and objective evidence of involvement of nervous system. Achlorhydria present. Indirect van den Bergh test, 1.5 units. Red cells numbered 2,310,000 haemoglobin 56 per cent.; white cells 3,400. Normoblasts present. Price-Jones curve positive.

Treatment: Extract (Lilly) equivalent to 500 grams of liver daily. On the eighth day of treatment the percentage of reticulated red cells had risen to 6.8. The extract was stopped after twelve days, and $\frac{1}{2}$ lb. of liver daily was substituted. After thirteen weeks the blood count was, red cells 4,810,000; haemoglobin 95 per cent.; white cells 5,400.

A small quantity of liver extract was prepared in the Medical Research Council's laboratories by a modification of Cohn's process, and the next case illustrates the effect of this extract.

CASE VII (Chart 5).

A woman, aged 34, admitted on November 14th, 1927, in first relapse. Subjective and objective evidence of slight involvement of nervous system. Achlorhydria present. Liver enlarged and spleen palpable. Indirect van den Bergh test, 1.2 units. Red cells 1,850,000; haemoglobin 38 per cent.; white cells 3,900. Megaloblasts present. Price-Jones curve positive.

Treatment: Extract (M.R.C.) equivalent to 500 grams of liver daily. On the thirteenth day of treatment the percentage of reticulated red cells had risen to 16.6. The extract was stopped

CHART 4.—Case VI.

after twenty-two days, and $\frac{1}{2}$ lb. of liver was substituted. After ten weeks of treatment the blood count was, red blood cells 4,660,000; haemoglobin 92 per cent.; white cells 11,200.

In a discussion such as this it is not possible to include many observations of interest that have been made in these cases, but the results in general agree with the reports of Minot and Murphy and their colleagues.^{9 10 11} They found that in a few days after commencing liver treatment the percentage of reticulated red cells began to rise, and that it reached a maximum a few days later and then declined rapidly, and that a little after the commencement of the rise in the number of reticulated cells the total red cells and haemoglobin began to increase, and continued to increase after the fall in the number of reticulated cells. The improvement in the general condition of the patients has been very striking, and commenced as a rule with the beginning of the rise in the reticulated cells. The feeling of weakness and depression quickly disappeared and the appetite returned, but the more definite symptoms, such as dyspnoea, palpitations, headache, cramps, and numbness, only gradually disappeared as the red cell count and the haemoglobin approached normal. In the cases with mental disturbances the improvement that occurred in a few days, and that amounted almost to a change in temperament, was remarkable.

In two cases in which it has not been possible to make any other diagnosis than that of pernicious anaemia, although there were reasons for uncertainty in making this diagnosis, the treatment by liver has failed.

CASE VIII.

A man, aged 48, admitted on October 18th, 1927, in the first attack. There was marked dental sepsis, but no history of sore tongue, nor did the tongue show evidence of previous glossitis. Apart from some tingling in the fingers there was no subjective or objective evidence of involvement of the nervous system. Achlorhydria present. Indirect van den Bergh test, 0.4 unit. Red blood cells numbered 980,000 per c.mm.; haemoglobin 19 per cent.; white cells 4,600. Megaloblasts present. Price-Jones curve positive. The teeth were removed and he was treated by liver extract equivalent to 500 grams daily, and for a few days 1,000 grams, and later whole liver ($\frac{1}{2}$ lb. daily) for three months without any response. Hydrochloric acid was given, and on two occasions he received blood transfusions. The red cells and haemoglobin rose after each transfusion, but there was no increase in the reticulated red cells. This patient is still under observation.

CASE IX.

A man, aged 61, admitted on July 12th, 1927, in first attack. No evidence of glossitis. Apart from occasional numbness in the fingers there was no subjective or objective evidence of involvement of the nervous system. There was considerable dental sepsis and pyorrhoea. Achlorhydria present. Indirect van den Bergh test, 0.7 unit. Red blood cells 1,000,000; haemoglobin 25 per cent.; white cells 8,600. Megaloblasts present. Price-Jones curve not typical of pernicious anaemia. There was a temporary response to each of three blood transfusions, but no response to $\frac{1}{2}$ lb. of liver daily. The liver treatment was continued for eight weeks and was stopped because of a recurrence of acute gout. He died on October 27th, 1927, and except for the absence of any degenerative changes in the nervous system the autopsy findings were compatible with a diagnosis of pernicious anaemia.

Of the remaining ten patients, who either commenced liver treatment in the remission stage or received other forms of treatment in addition, seven have remained well during the three to six months that they have been under observation, and four of them have red cell counts of over 5,000,000, two of over 4,000,000, and one of 3,500,000. One patient was not able to take satisfactory amounts of liver, but after five weeks of treatment felt well; the blood count showed red cells 3,140,000 per c.mm., haemoglobin 96 per cent. Another patient, who responded with a rise in the reticulated cells, was suffering from severe heart failure, and the treatment was abandoned. The last patient came under observation when on treatment with arsenic, and was entering on a remission with a raised percentage of reticulated red cells that dropped in a few days. Treatment with $\frac{1}{2}$ lb. of liver daily was commenced shortly after, and he remained well for four months. He then developed acute appendicitis with perforation and general peritonitis, and died. A blood count on his readmission two days before his death showed red cells 5,120,000; haemoglobin 95 per cent.; white cells 13,400.

COMMENT.

In view of the natural remissions that occur in this disease it is difficult to prove conclusively from the small series of cases reported here that liver treatment is of value. If, however, we consider these cases in conjunction with the 125 cases reported by Minot and Murphy, there is a remarkable uniformity in the improvement following this treatment. Above all, Cases I to VII confirm the reports of Minot and Murphy—that if treatment is commenced in the first attack, or in the stage of relapse, the reticulated red cells increase in a few days after the commencement of liver treatment with a striking regu-

larity, and this increase is followed by a steady rise in the total red cell count and in the haemoglobin. This characteristic response does not occur in patients with secondary anaemia or leukaemia. These facts seem to point to a therapeutic action of great value. The work of Cohn, and the discovery that a non-protein, iron-free extract of liver has the same action as whole liver, points to a therapeutic principle of which we have hitherto had no knowledge or suggestion. It is obviously too early to form any conclusions on the value of this treatment in maintaining the patients in this improved state or in preventing relapses, but the results obtained in America are most encouraging.

The studies of Peabody¹² on the bone marrow in the stages of relapse and of remission indicate that in the relapse stage the marrow is packed with megaloblasts, and that when the red blood cells increase in the circulating blood during the remission the number of megaloblasts in the marrow decreases, and the marrow approaches the usual normoblastic type. The reticulated red cells that appear temporarily in the circulation after commencing liver treatment are young cells,¹³ and are mainly larger than the normal erythrocyte, and Peabody suggests that liver acts by stimulating the immature megaloblastic cells that pack the marrow to develop to maturity. The approach to the normoblastic type of blood cell formation occurs later.

It is still uncertain what effect liver treatment has on the changes in the nervous system. It is not to be expected that objective signs of degenerative changes should disappear, and though in our experience evidence of progressive degeneration has appeared during liver treatment, it is possible that the process ceases after the treatment has been continued for some time, as Minot and Murphy believe.² There is less doubt as to the effect on the achlorhydria which is constantly present. There is no evidence that it disappears as the result of this treatment, and there is evidence that it persists in spite of liver treatment,² and that it is present

long before the development of the anaemia.¹⁴ It would appear probable, therefore, that liver treatment exerts a specific influence on the faulty development of the red cells, but there is no evidence that it affects the underlying abnormality that is present in those patients who develop pernicious anaemia, and of which the achlorhydria is a manifestation.

For this reason it is as important as it was formerly to pay attention to the general condition of the patient, to treat septic conditions, and to administer hydrochloric acid. Our patients have all been given hydrochloric acid after the immediate effects of the liver have been observed. Following the advice of Minot and Murphy we have given the patients a generous, well balanced diet, with plenty of vegetables and red meat, in addition to the liver. Considerable difficulty has been experienced in producing an active extract on a commercial scale, and until an efficient extract can be put on the market in considerable quantity, and at a suitably low price, treatment by whole liver must be continued. Most of the patients have taken the rather large quantities of liver ($\frac{1}{2}$ lb. daily) without difficulty, and have, as a rule, preferred it stewed, though fried liver and liver soup are agreeable variations. The raw juice mixed with orange juice has proved useful, especially in the more seriously ill patients. "Cooked liver," as Minot and Murphy² state, "may be served in any way that pleases

CHART 5.—Case VII.

the patient, but prolonged boiling is to be avoided." There is evidence that a smaller quantity of liver is sufficient to maintain the improved condition, and that the dose should be reduced when the blood picture approaches the normal.

SUMMARY.

Nineteen patients with pernicious anaemia have been treated with whole liver or a liver extract. Nine of them were in the first attack or in a relapse, and seven of these showed a prompt response to treatment, with a temporary rise in the percentage of reticulated red cells in the circulating blood, and a steady increase in the total red cells and the haemoglobin. The reason for the failure of the treatment in the other two patients is not clear.

Ten patients commenced treatment during the remission stage or received other forms of treatment in addition, so that observations on the immediate effects of the treatment were not possible. The condition of these patients at the end of varying periods of treatment (up to six months) affords confirmatory evidence of the value of this treatment.

Our thanks are due to the physicians of St. Bartholomew's Hospital and others who kindly enabled us to make these observations on their patients.

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THE TREATMENT OF GASTRIC ULCER.*

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It is possible to-day to cure the majority of cases of gastric and duodenal ulcer without having recourse to surgical intervention, and since the surgical treatment of this disease is attended by a definite, if small, immediate mortality, and by an even more definite percentage of subsequent relapses and complications that are often of a nature far more serious than those encountered in patients treated by purely medical methods, the present position is a grave one. The frequency of these cases is greater every year, and the problem of treatment one upon which practitioners as a whole remain in considerable doubt. I do not propose to bring before you any statistics, nor to go deeply into theories of causation or into experimental work bearing upon the etiology of peptic ulceration, but I am going to outline the treatment which ten years' experience has shown me to yield excellent results in a very large proportion of cases.

Removal of Septic Foci.

The first step in the treatment of gastric ulcer is one which must be adopted in every case, whatever the decision may be as to whether the general treatment is to be on medical or surgical lines. I refer to the eradication of septic foci in the mouth and elsewhere.

Oral sepsis is probably the most important cause of gastric and duodenal ulcer, bacterial emboli being carried from the region of the dental roots by the blood stream to the region of the pylorus and lesser curvature. The work of Rosenow, of Haden, of Christophe, and a score of others, may be quoted as supporting this view, which

* An address to the Hampstead Division of the British Medical Association on January 12th, 1928.

is very widely held in all countries at the present day. In addition to dental sepsis, or in its absence, chronic sepsis of the tonsils, nasopharynx, and nasal sinuses must be eliminated. Cases have been observed by many clinicians in which the recurrent attacks of pain in patients with chronic ulcer have corresponded with acute exacerbations in chronically infected tonsils. In a few cases chronic appendicitis and chronic disease of the gall bladder appear to be important factors, and I have on more than one occasion received the assistance of my surgical colleagues in removing a factor of this type without any surgical treatment being applied to the ulcer, which has subsequently responded well to purely medical treatment. It often, perhaps usually, happens that the removal of these septic foci is better effected after a few weeks' treatment rather than at once. It would, for example, be foolish to subject a patient recovering from a severe haematemesis to the risk of extensive dental extractions; but in all cases focal sepsis must be eliminated at some stage if a permanent successful result is sought, and I place it in this early and prominent position in order that its importance may not be overlooked.

Choice of Cases Requiring Surgical Treatment.

In spite of my opening words concerning the efficacy of medical treatment, I do not wish it to be imagined that such treatment is to be applied without restriction. On the contrary, I feel that in every case seen for the first time the physician should ask himself whether surgical treatment should be employed immediately. For whereas to-day hundreds of cases are sent to the surgeons without any real attempt at medical treatment ever having been made, others are allowed to linger in the hands of physicians when nothing but surgical treatment can help them.

The following cases call for surgical treatment as soon as it is safe for it to be undertaken:

1. All cases with a high degree of pyloric or duodenal stenosis, or with marked hour-glass deformity of a permanent nature.
2. All cases with deep ulceration involving adherence to or excavation of neighbouring structures, such as the pancreas or liver.

In the first of these groups there is mechanical defect which can only be put right by mechanical means. In the second group there is evidence of ulceration so deep that healing can hardly be expected, and amputation—that is, surgical treatment—is called for.

We now come to four further groups of very different type:

3. Cases which have relapsed after a thorough course of medical treatment.
4. Cases which have recurred in spite of treatment during many years.
5. Cases in which there has been recurrent and dangerous haemorrhage in spite of careful medical treatment.

To fall into one of these groups a case must have had previous and unsuccessful medical treatment, and it requires considerable judgement for a physician to decide whether the previous medical treatment has been such as to justify the abandonment of all but operative intervention at the time when the patient comes under his care. If a patient has been properly treated and still relapses, a new line of treatment must be adopted. If a case has gone on relapsing for many years the ulcer will probably be so callous that healing is problematical, but increasing experience has taught me that it is so rare for these cases to have received what, in my opinion, can be described as thorough treatment that I hesitate more and more to ask for surgical intervention until I have satisfied myself that they are incapable of healing when given drastic treatment on the lines I shall indicate.

6. Cases in which proper medical treatment is impossible, owing to the patient's habits and economic position.

This is an important group, but it is certainly less numerous than I used to believe. We are too ready to assume that the working man cannot devote the time and effort necessary for dieting himself on proper lines, and many such patients, if they can be got to grasp the seriousness of the position, will carry out medical treatment