THE TREATMENT OF PERNICIOUS ANAEMIA WITH LIVER AND LIVER EXTRACT,

by

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THE TREATMENT OF PERNICIOUS ANAEMIA WITH LIVER AND LIVER EXTRACT.

The scope of the present paper is defined in its title. It is intended to recount briefly the earlier views on the place of diet in the treatment of Pernicious Anaemia; to indicate the reasons which led to the supposition, on theoretical grounds, that a diet rich in liver might prove a valuable therapeutic measure; and finally to describe the results which have, in practice, attended the adoption of this mode of treatment. It is not proposed to discuss the question of aetiology, which, far from being clarified by this recent therapeutic advance, has been rendered, if possible, even more obscure than before.

I.

" Earlier Views ".

Diet, as a factor in the treatment of Pernicious Anaemia, has been referred to by most writers on the subject. Thus, in 1863, Habershon, describing what is apparently a case of this nature, writes that "many patients at an early stage completely recover under the influence of bracing air, and a nutrient and stimulating diet. No remedy, however," he states later, "is of any permanent benefit, and the patient very gradually, but with steady course, loses strength and power, till life ceases from simple exhaustion". What was appreciated at this time, evidently, was the desirability of prescribing easily digested foods, in a condition known to have, as one of its characteristic features, an unhealthy condition of the gastro-intestinal tract. Pepper (1875) draws attention to the fatty degeneration of the liver, and of the gastric
mucosa, found post-mortem, the consequently impaired state of the digestion during life, and hence the necessity for careful attention to the nutrition, and the administration of food in the most digestible forms. The atrophic state of the mucous membrane of the stomach is also referred to by Fenwick (1877), and the subject of diet is spoken of as one of great difficulty, on account of the patient's lack of appetite. A hint of some special importance attaching to diet is, perhaps, given by Osler (1885), when he speaks of cases "that appear to have got well with change of air and a better diet, after resisting all ordinary measures". It is natural that Hunter (1890), taking the view that Per-nicious Anaemia is a disease dependent on "the presence, under certain favourable conditions, of organisms of a specific nature within the gastro-intestinal tract", should attribute great importance to dieto-therapy in this condition. It is interesting to note that Hunter considered a farinaceous diet to be superior to a nitrogenous one. He lays stress on the fact that, while on an ordinary mixed diet the ratio of free sulphate in the urine to aromatic sulphate was 9:1, on a farin­aceous diet the ratio was 15:1----indicating a lessened production of supposedly "toxic" substances within the bowel. Of very great interest is a case recorded by Fraser (1894). This patient went downhill under treatment with iron and arsenic, but remarkable improvement occurred when he was given bone marrow (3oz. daily of ox, and later calf, marrow, taken raw). Soon after the administration of bone marrow was commenced, the blood platelets, which had stood at a very low level, greatly in­creased in numbers, and the red blood corpuscles (previously less than 1 million per cub. mm.) rose in a short time to 4 million, and the haem-
oglobin percentage to 85, by which time the number of blood platelets had returned to about a normal level. The possibility of spontaneous natural remission cannot, of course, be excluded in this case, but it is striking that such improvement should have followed the exhibition of a substance so similar in nutritional composition to liver and kidney, the strikingly beneficial effects of which are dealt with subsequently. This clue does not appear to have been followed up, for, so late as 1917, Barker and Sprunt (3), in outlining a scheme of treatment for cases of Pernicious Anaemia, discuss diet as relating simply to the general needs of the patient, and to the state of his gastro-intestinal tract. It is true, however, that, in advising "an abundant roborant diet, rich in protein", they may, in the light of recent work, have been not so wide of the mark. The same applies to the statement by Fitch (1922) that the inclusion of bone marrow, liver, and spleen in the dietary is to be advised (on the ground that these foodstuffs are rich in nucleo-albumens containing iron). The idea that any "specific" treatment is here intended is, however, negatived by the subsequent statement that, though "the life of the patient may be prolonged and a reasonable degree of comfort secured through careful supervision of digestion and elimination --- there in no specific evidence that diet per se modifies the course of the disease".

So far, then, it is evident that dietotherapy in Pernicious Anaemia has been regarded chiefly as part of the general treatment of a patient suffering from a debilitating condition, and exhibiting in particular a state of hypofunction of the gastro-intestinal tract. Diet, in fact, has been largely of the nature of "symptomatic" treatment. A period
now commences, however, in which diet begins to be studied with special reference to possible beneficial effects on the course of the disease itself. Thus, Mosenthal (1918) states that, whilst a negative nitrogen balance has been thought to be characteristic of Pernicious Anaemia, he has been able, by means of a forced diet, readily to produce a positive balance, and that further, in each of the three cases observed, improvement in the blood picture is to be noted. A further important paper on metabolism in Pernicious Anaemia is that of Gibson and Howard (1923). These observers tentatively suggest that an iron-rich and vitamin-adequate diet may be beneficial.

A series of researches was carried out under the auspices of the Carnegie Institute of Washington (1919), in which the effect of pronounced restriction of diet was observed in the case of 24 normal healthy individuals. A slight anaemia was produced in most of these cases, but the anaemia was of the secondary type. (These experiments were not, of course, designed with special reference to possible blood changes; the blood was examined merely as part of the general routine).

II.

"Reasons Leading to Adoption of Liver Diet".

The principal work to be dealt with in this section is that of Whipple and Robscheit and their associates. These observers (1920), working with dogs, determined, for each animal, the "available red cell pigment", by observations of the haemoglobin percentage and the blood volume. They then produced a uniform degree of anaemia by the removal, on each of two successive days, of one quarter of the already determined blood
The time taken for the "available red cell pigment" to return to its previous level was then observed, and the influence of a variety of diet factors noted. On an ordinary diet of mixed table scraps, the time taken for complete return to normal was 4-7 weeks. On a liberal diet of meat and beef heart, however, the time taken was only 3-4 weeks, while with cooked liver it was even less (2-4 weeks). Watery liver extract had a distinct, but only very slight, influence on blood regeneration—but of course the dosage may have been insufficient. Commercial meat extract was found to be inert. It was found that the active foodstuffs could be given either alone, or in combination with other foods, and that they "would stand the severe test of promoting definite blood regeneration when administered after long limited diet periods unfavourable to blood regeneration".

Studies on blood regeneration were also reported by Jencks in 1922. Regeneration was found to be more rapid "with protein than with either carbohydrate or fat, when fed as the sole nutrient, and a diet of vitamin-rich food gave somewhat more speedy regeneration than any other diet containing only one food factor".

In 1925, further experiments were reported by Whipple and Robscheit-Robbins. In this series, they produced a constantly maintained severe secondary anaemia, in place of the single post-haemorrhagic period previously described. The haemoglobin level was reduced to 40-50%, and maintained at this point by frequent bleedings of calculated amounts. Obviously, estimation of the total haemoglobin in the samples of blood, which it was found necessary to remove, gave a measure of the rate of blood regeneration. This could be measured with greater accuracy than...
could the "circulating" haemoglobin of the previous experiments. Again, the maintaining of the constant haemoglobin level meant that the stimulus to regeneration, dependent on this factor, was fairly constant, so that the value of the diet factor could be more properly appreciated. While, in the early "short anaemia" experiments, beef muscle, heart, and liver were found to be nearly equally efficacious, it was found that, in the "severe anaemia" experiments, beef liver feeding was associated with maximal blood regeneration, beef heart was distinctly less favourable, and beef muscle still less. The observers' final conclusion was that "liver feeding in these severe anaemias remains the most potent factor for the sustained production of haemoglobin and red cells. This favourable and marked reaction is invariable in our dog experiments, no matter how long continued the anaemia level, no matter how unfavourable the preceding diet periods may be, and regardless of the substances given with liver feeding".

Certain other work, which also contributed to the final resolve to try the effect of a special diet in cases of human Pernicious Anaemia, remains to be referred to.

Work published in 1912, on the general question of cell division, had shown that certain products of nucleo-protein hydrolysis appeared to have a definite stimulating effect upon the division rate, not only of the cells of the protozoon Actinobulus Radians (Stein), but also of the supposedly "fixed" cells of the glandular organs of rats. Some such effect from feeding with a tissue rich in nuclein compounds was at least a theoretical possibility.

Again, McCollum (1923) drew attention to the difference in dietary
properties between the leaves of plants and tissues concerned with storage, and stated that, in the case of animal tissues also, glandular organs were more "complete" foods than supporting or skeletal tissues. "Kidney, liver, and milk proteins" he said, "stand out as a group of foods containing proteins of unusual value".

The greater value of certain amino-acids than others, in promoting the regeneration of poisoned cells, was pointed out by Smith and Moise (1924).

The original choice of diet thought, on theoretical grounds, likely to be beneficial in cases of Pernicious Anaemia, was also influenced by the work of Baker and Carrel (1925), who showed that lipoids (both those occurring naturally in serum, and those extracted from various tissues) had an inhibitory action on the growth of fibroblasts in vitro.

Finally, a series of experiments on Vitamin A deficiency (1926) suggested an important connection between Vitamin A and blood regeneration, and emphasised the importance of a "rationally balanced" diet---[in the case both of rats suffering from experimental haemorrhagic anaemia and of humans suffering from anaemias of various types).

III.

"Effect of Liver Therapy in Pernicious Anaemia".

Minot and Murphy, in August 1926, reported on a series of cases of Pernicious Anaemia treated by a "special diet". This diet consisted of, daily, 120-240 gm. of cooked calf or beef liver; 120 gm. of red meat; not less than 300 gm. of vegetables; 250-500 gm. of fruit; 40 gm. of fat; an egg, if desired; 240 gm. of milk; dry crusty bread; potatoes;
cereals------to give a total calorific value of 2000-3000 (340 gm. carbohydrate; 135 gm. protein; not more than 70 gm. fat). Sugar was to be used sparingly; grossly sweet foods were prohibited. They reviewed briefly the reasons leading up to this choice of diet, mentioning especially the work of Whipple and Robscheit, and of Baker and Carrel, to which reference has already been made. They also stated that their own experience was to the effect that Pernicious Anaemia patients had often been in the habit of eating an excess of fat; and that, as Pernicious Anaemia tended to be rarer in regions where fewer starchy foods and dairy produce were consumed, the disease might depend on some nutritional excess or defect, or some vitamin deficiency. A possible importance attaching to fruit was also noted, and the beneficial effect of strawberries in Sprue pointed out. 45 cases were reported on as having received this diet (i.e. a diet rich in liver and red meat, relatively poor in fat, and containing an abundance of fresh fruit and vegetables) for periods varying from 6 weeks to 2½ years. A few, at first, had been unable to take the full diet, and, in them, liver alone was "pushed". Within a fortnight, all are stated to have been able to take the diet, and, indeed, to have exhibited a "ravenous" appetite. The bowels also became more regular. Four patients died, but all of these were so ill from the beginning that they could take no liver. The remainder all improved, irrespective of the length of time the disease had lasted before the inception of treatment, and all were "well" at the time of publication, though it was thought that patients who had had several previous relapses took on the whole longer to improve. By the end of the first week of treatment, the reticulated red cells of the blood
had risen markedly, returning to normal level by the end of the second week, by which time the red cell count and the haemoglobin percentage were beginning to show noticeable improvement. The rate of improvement was greatest in those cases who had had the lowest initial counts. After 4-6 months of treatment, no patient had less than 3½ million red cells, 81% had 4 million or more, and 30% had over 5 million. The icterus index had usually fallen to below normal by the time the red cell count had reached 2½ millions. Those patients who were most careful in taking the full amount of liver improved quicker than the more careless. Three patients relapsed, but this was evidently due to their not taking the diet satisfactorily, and they quickly improved when this was put right—showing, apparently, that the diet must be continued indefinitely if the patient is to remain well. In conclusion, the writers refer to the well known phenomenon of natural remission in this disease, but point out the great regularity (as measured by the reticulocyte increase in the blood) with which the remission in their cases had commenced within a week of treatment being begun; also that, while each natural remission tends to be less complete than the one before, they had had many patients who had had previous remissions, and during none of these had they reached the level attained to following liver therapy. As the experiment proceeded, it was found that a low fat content in the diet was apparently of less importance than the high protein (or, more probably, some special constituent of the protein foodstuffs employed).

The same authors, in a subsequent paper, gave more detailed directions as to the diet they advised, with actual sample menus. In a later paper, data were given as to the measurements of the red
blood corpuscles before and after treatment—along the lines suggested by Price-Jones—and it was stated that the mean and median diameters of the corpuscles might, during remission, fall to normal or less, while the dispersion of diameter might be well below the upper normal limit or might remain slightly above normal.

Work on the relation between Vitamin E and iron assimilation (April 1927) suggested a possible explanation of the beneficial action of liver in Pernicious Anaemia. It was shown that rats, when fed with iron in the form of ferrous salts, were unable to assimilate it properly in the absence of Vitamin E, and developed deficiency symptoms. The substitution of ferric salts, or the addition of Vitamin E to the diet, brought about recovery. It was suggested that the fact that liver fat contains Vitamin E in considerable amount, and liver itself a fair amount of iron, might account for the benefits derived from liver therapy in Pernicious Anaemia. Reference was also made to the work of Koessler already mentioned, and it was pointed out that the results this observer had attributed to vitamin A might equally well, from a consideration of the diets he had employed, be regarded as Vitamin E effects.

Murphy, in April 1927, published further special details of ten of the cases reported in his original paper, drawing attention to the "reticulocyte crisis"; fall in icterus index; rise in red blood corpuscle count and haemoglobin percentage; fall in colour index; increase in numbers of circulating leucocytes and blood platelets; disappearance of abnormal forms of red cell; fall of individual cell volume and diameter; rise of stroma index; increase of corpuscular and whole blood
volume, plasma volume remaining constant; constant level of non-protein nitrogen and protein nitrogen in the plasma; and increase of circulating protein to an extent accounted for by the increased quantity of haemoglobin. No estimation was made of nitrogen balance, or of total metabolism.

The next advance was the preparation by Cohn and others of a liver fraction, which had apparently a beneficial action in cases of Pernicious Anaemia comparable to that of liver itself. This fraction was soluble in water; ether-insoluble; alcohol-precipitable; free from lecithin and ordinary lipoids; and free from all but a trace of protein, sulphur, and iron. It was found to be free of blood-sugar reducing properties, and had no effect on blood-pressure (though such properties were possessed by other fractions obtained in the course of the experiments). It had been fed to several patients suffering from Pernicious Anaemia, and excellent results obtained.

In a further paper, Minot and Murphy reported on eight cases treated with this liver fraction, with satisfactory results in each case. They also pointed out that this negatived the idea that Vitamin E might be the factor in liver responsible for its action, Vitamin E being insoluble in water, and soluble in ether. Another theory as to the action of liver had been that it might supply material for the stroma of red cells—according to Whipple's conception of the disease, namely a lack of corpuscles in which to store the abundantly existing haemoglobin. This theory also appeared to be negatived by the nature of the active liver fraction. Cases satisfactorily treated with ordinary liver were also reported on, as well as three cases in which similar results
had been produced by feeding with large quantities of kidney. Attention was drawn to the work of Peabody, who had shown that, during the relapse stage of Pernicious Anaemia, the bone marrow is packed with primitive cells of the myeloid series (megaloblasts), with apparently little evidence of differentiation towards maturity; while, in the remission stage, the appearance of the marrow is fairly normal, there being few megaloblasts, and a great relative increase of normoblasts and mature erythrocytes. It was suggested that the beneficial action of liver in Pernicious Anaemia might be due to the presence of some factor having a stimulating action on the development and differentiation of the haemopoeietic marrow tissue. It had been found that, in cases of secondary anaemia, where no such collection of megaloblasts occurs in the bone marrow, the exhibition of liver did not produce the prompt rise in the numbers of circulating reticulocytes, so constantly seen in Pernicious Anaemia.

West reported apparently good results with an alcohol-ether soluble extract of liver, but his paper (which deals with five cases) is of the nature of a preliminary report, so that little can be said about his claims. Certainly, after the removal of the alcohol-ether soluble fraction in Cohn's process, what remained appeared to be as active as before.

It should be stated here that not all observers agree that Peabody's cells are megaloblasts. Pini regards them as 'macro-normoblasts,' and they have also been regarded as myeloblasts. In any event, they are 'primitive,' immature, cells of some sort, the appearance of the marrow being that of 'cellular hyperplasia with functional inefficiency' (Peabody).
In the most comprehensive paper yet published (September 1927), Minot and Murphy reported on further cases, bringing the total number of cases treated by them up to 105, some of whom had been under observation for as long as 3 years. Of these, only three had died, and in none of the cases could death be attributed to failure of the treatment—-one death was due to accident; one to cerebral thrombosis, at the age of 71; and one to an unknown cause, when the red blood count was 4,300,000. Of 90 patients who started treatment when the red count was below 2.7 millions, ten (who took the diet badly) averaged, after 4-6 months 3.5 millions; the remainder averaged 4.79 millions; and 44 had over 5 millions. The need for continuance of the diet, if health was to be maintained, was emphasised. Patients who had had repeated previous transfusions had not, as a rule, responded so well, and the presence of complications, such as infection, or cirrhosis of the liver, had also been associated with a less satisfactory response. The improvement in the state of the patients was described. In addition to the points noted in previous papers, attention was drawn to the following:—The disappearance of fever; the appearance of a pink flush in the cheeks, even before any changes in the blood were to be noted; the early loss of weight, from disappearance of oedema, with later rapid increase; the increased appetite and sense of well-being (in contrast to normal subjects, who were often nauseated by the diet); the occasional temporary looseness of the bowels, quickly followed by the establishment of normal evacuations; the disappearance of glossitis and oesophagitis, and of dyspeptic symptoms, in spite of the non-return of free hydrochloric acid to gastric juice; the diminution in size of the liver and spleen, if previously enlarged; the clearing up of scaliness, pigmentation,
purpura, and other skin lesions; and disappearance of cardiac pain, in those who had presented this rather uncommon symptom. Though those cases who had had a low blood pressure before treatment attained to a normal level, hypertension was not observed to develop in any case. Nor was any evidence of renal injury, attributable to the liver diet, detected. Bursitis, and a stiff and painful condition of the joints, was observed in some cases, but in others previously existing arthritis appeared to be improved. With regard to neural symptoms, no case was observed to show definite progression of symptoms, and many cases actually improved. Recently developed, mild, symptoms, such as paraesthesiae, improved the most, but even impaired bone vibration sense was bettered in some cases, as also was co-ordination of the extremities. In general, however, signs and symptoms referable to the nervous system were not so much improved as those referable to other systems, and usually not before treatment had been continued for about 4 months. The importance of early diagnosis and treatment was emphasised, together with the role of such symptoms as achlorhydria and glossitis in raising a suspicion of Pernicious Anaemia, even before the appearance of anaemia. The reasons leading up to the choice of diet, and the possible mode of action, were recapitulated. A case was reported which showed no response while treated with Vitamin E (in the form of wheat germ oil), but which later improved markedly on a liver diet. It was suggested that raw liver might be more efficacious than when cooked, but it had been found that, provided prolonged boiling were avoided, cooking did not markedly diminish its efficacy. Liver juice, to be efficacious, required to be given in large quantities. For patients too ill to take
liver in the ordinary way, the stomach tube was suggested. Some patients, after their blood had reached a normal level, had remained well on only 150 gm. of liver thrice a week. Possible harmful effects of too much liver had not been investigated. In spite of the efficacy of the liver extract, liver itself might contain additional substances of benefit, and might be taken in addition to extract, as also ought red meat and fruit. Excess of fat had not been found, as originally thought, to inhibit the rapid improvement in the condition of the blood. Excess of fats and starches might, however, upset the already impaired digestion, and, having no beneficial action, was better avoided. Patients who had received no hydrochloric acid had improved no less rapidly than those who had had it. Treatment apart from the giving of liver (rest, massage to muscles, etc.) was subsidiary, though still, of course, necessary. Finally, it was claimed that the success of this mode of treatment was such that, if a case showed little improvement after 6 weeks of treatment, the diagnosis of Pernicious Anaemia was probably wrong.

In a paper read at the British Medical Association Meeting at Edinburgh in July last, Minot stated that 20 cases had then been successfully treated with liver extract (including two who were so ill as to be comatose when treatment was commenced); two other patients, however, had died in spite of treatment, but they also had been comatose before treatment was begun.

Since then, many cases have been reported in this country—by Anderson (2 cases); Spriggs (22 cases); Spence (22 cases); Phillips (1 case); Brewer, Wells, and Fraser (19 cases); and East (3 cases). Meulengracht has
Of Spence's cases, one did not respond well. The reason is not clear, but faulty diagnosis is suggested by Spence. In view of the fact that, in some of Minot and Murphy's cases, "arthritis progressed, and the joints became painful", it is interesting to note that two of Spence's cases had attacks of "gout". Venous thrombosis occurred in a third case. Two of the successful results were obtained with liver extract. Two patients, who received "certain proprietary compressed liver tablets" did not do well.

Of Fraser's cases, two failed to respond to treatment, although no other diagnosis than Pernicious Anaemia appeared tenable. Three of the successful cases were treated with extract.

Meulengracht emphasised the necessity for adequate dosage with liver. Three of his early cases received less than 20 gm. of liver daily, and all three died. Two cases died from other causes, such as malignant disease. The remaining sixteen have all done well, and it is interesting to note that, in the case of two who had "paralysis and ataxia" of the legs, these symptoms have improved markedly. Gastric achylia persisted, however, in all cases examined. Calf's liver was more acceptable to the patients than pig's, and some preferred to take it raw, either in fluid form with orange, or "in lumps of 5-10 gm., wrapped up in paper, swallowed whole, and washed down with a little water".

An official investigation into the efficiency of liver extract was undertaken by the Medical Research Council, and the report was recently published. 34 cases were dealt with, and all but two
The present writer has been fortunate enough to have been associated with Professor G. L. Gulland and Dr. L.S.P. Davidson in the investigation of 45 cases of Pernicious Anaemia, all of whom received treatment with liver or liver extract—the period of investigation covering the past year, and corresponding roughly with the period during which this mode of treatment has been on trial in this country. The majority of the cases received a liver diet; in others, an extract was substituted, in whole or in part, for the liver in the diet. The various extracts used comprised those manufactured by Boots Pure Drug Co., Ltd.; British Drug Houses, Ltd.; Burroughs Wellcome and Co.; Eli Lilly and Co.; the Promonta Co., Ltd.; and Messrs. Nordmark. The liver, or liver extract, was given in conjunction with ordinary diet, no special attempt being made to limit the fat or carbohydrate intake, though the patient was encouraged to take as much fruit as possible. Kidney was sometimes included in the diet, but the effect of kidney feeding alone was not tried. The investigation of each patient included red and white blood counts; haemoglobin estimations; reticulocyte counts;
examination of blood films; test meal (for diagnosis); examination of the nervous system; in some cases, a second test meal, after improvement had occurred as regards the blood condition; and, in some cases, before and after treatment, examination of the blood serum for its bilirubin content, and actual measurement of the red blood corpuscles as seen in films.

An account of the results obtained in 42 of these cases is at present in the hands of the Editor of "The Lancet", with a view to early publication, and it is not proposed to repeat the details of the cases here. By way, however, of illustration, details are given (in Appendixes I and II) of 11 of the cases, which came under the special notice of the writer.

In general it may be said that the results of treatment were in accord with those of Minot and Murphy. It appears unnecessary to recount here the subsidence of fever; the malar flush; the reticulocyte rise; the fall in icterus index; the rising blood count, etc., of which a description has already been given. The claims of Minot and Murphy appeared to be borne out, no case failing to respond to the treatment, although in two cases (Appendix I, cases 9 and 10) the response was slow.

The following points, however, may be specially noted. Patients who had had previous relapses appeared to do just as well on this treatment as patients in a first attack, and the blood in several such cases reached a level higher than that attained in any previous remission. With regard to nervous symptoms, improvement occurred in most instances. The impression formed was that, while cases of the tabetic type of subacute combined degeneration of the cord tended to be improved, symp-
toms of the spastic type were not benefited. In one case, they actually became worse; it was suggested (Gulland) that this might be due to the increased muscular tone.

In none of our cases were any "gouty" or "arthritic" symptoms observed. Minot and Murphy found no evidence of renal damage in any of their cases. One of our cases, however, died from uraemia (a private case of Professor Gulland's), and another developed an acute nephritis while on the treatment. Admittedly, this latter case was of the pregnancy-puerperal type, and had suffered from nephritic toxaemia during the pregnancy, but it would appear that cases with any suspicion of kidney damage should be treated with caution—liver extract probably being more suitable than the liver and red meat of the original diet.

We are also inclined to differ from Medearis and Minot in their statement regarding the complete return of the blood to a normal type, as shown by direct measurement of the cells. Abnormally large cells appear to be present even during the most complete remission. Figures in support of this contention are given in Appendix II.

The persistence of achylia gastrica during remission was confirmed in several cases.

CONCLUSIONS.

1. Treatment of patients suffering from Pernicious Anaemia with liver, or a suitable extract of liver, appears to bring about, in practically all cases, a prompt and complete remission.

2. The commonest cause of an unsatisfactory result is the use of an insufficient quantity of liver. Complications, such as infection,
may retard the improvement, as also may previous repeated blood transfusions. Very rarely, a case may fail to respond to liver for no obvious reason, even although the diagnosis of Pernicious Anaemia appears to be correct.

3. Neural Symptoms usually improve, but to a less extent than those referable to other systems.

4. The condition brought about by adequate liver treatment is one of "remission", not "cure". Apart from the fact that relapse occurs if the treatment is discontinued, the patients (though symptomatic-well) continue to exhibit gastric achylia, and a somewhat abnormal condition of the blood as shown by measurement.

The writer's thanks are due to those Physicians of the Royal Infirmary who kindly allowed him to make observations on their cases.
APPENDIX I.

Details are here given of 11 cases treated with Liver or Liver Extract. In all cases, gastric achlorhydria was present, and the appearance of the blood film was typical of Pernicious Anaemia, no case being included in the series unless the diagnosis was unequivocal. In cases 6, 7, and 8 (in whom alone it was tested for at this time), free acid was found still to be absent from the gastric juice, at the close of the period of observation. In cases 1, 2, 3, 4, and 6, hyperbilirubinemia was noted at the beginning of treatment, and to have disappeared by the time the blood count had reached a normal level.

Case 1. M. 56. 3rd attack.

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<th>Date</th>
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<th>Hb.</th>
<th>C.I.</th>
<th>W.B.C.</th>
<th>Reticulocytes</th>
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<td>2,800</td>
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<tr>
<td>12-12-27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
14-12-27. 6.0%
16-12-27. 3.5%
20-12-27. 0.5%
5-1-28. 3,030,000. 60% 1.0 6,000.
12-1-28. 3,020,000. 65% 1.1 4,000.
Liver Diet increased.
21-1-28. 3,700,000. 85% 1.1 5,400
30-1-28. 4,100,000. 90% 1.09 4,000.
This is the first case in which Liver Extract was tried. As we had no certainty, at that time, that the extract was active, and as the patient, at first, continued to go downhill, extract was stopped on 28-11-27, and ordinary liver given. The next day, however, the reticulocyte count began to rise. It is clear that this occurred too soon to be attributable to the liver. The Extract must be held responsible for the initial improvement, and the liver diet for the continued progress thereafter. The comparatively slow progress is probably due to the fact that the patient was unable to take the full quantity of liver, owing to the recent extraction of teeth. He commenced eating liver satisfactorily and regularly about 12-1-28, after which, as will be seen, improvement was much more rapid.

Case 2. F.45. 1st attack.
14-11-27. 1,240,000. 32% 1.3 0.5%
Boot's Liver Extract, 10 gm. daily, commenced.
21-11-27. 9.0%
23-11-27. 12.0%
24-11-27. 16.5%.


1-12-27. 4.0%.

15-12-27. 2,930,000. 62%. 1.1. 4,600.

Liver Extract, 3 gm. daily, given in addition to Liver Diet.

24-12-28. Daily dosage of Extract increased to 5 gm.

4-1-28. 3,800,000. 70%. 0.92. 4,000.

18-1-28. 4,380,000. 80%. 0.91. 4,600. 0.5%.

On account of shortage of material, extract here was discontinued as soon as the reticulocyte rise had demonstrated its activity. Later, as the patient did not appear to be able to take sufficient liver, extract (in smaller dosage) was given in addition, and improvement was accelerated.

Case 3. M. 52. 3rd attack.

21-11-27. 740,000. 20%. 1.3. 3,600. 1.0%.

Patient very gravely ill; delirious; vomiting constantly; had really been sent into hospital to die. Had been on Liver-juice since 16-11-27.

26-11-27. 4.0%.


1-12-27. 3.4%.

2-12-27. 15.2%.

3-12-27. Daily dosage reduced to 10 gm.

5-12-27. 9.4%.

6-12-27. 4.5%.
<table>
<thead>
<tr>
<th>Date</th>
<th>Count</th>
<th>%</th>
<th>Unit</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12-27</td>
<td>1.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-12-27</td>
<td>2,150,000</td>
<td>40%</td>
<td>1.0</td>
<td>4,000</td>
</tr>
<tr>
<td>19-12-27</td>
<td>Daily Dosage reduced to 5 gm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-12-27</td>
<td>3,050,000</td>
<td>60%</td>
<td>1.0</td>
<td>4,000</td>
</tr>
<tr>
<td>(23-12-28. Daily Dosage increased to 10 gm.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-1-28. 22 teeth extracted.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-1-28. 3,290,000</td>
<td>60%</td>
<td>0.94</td>
<td>6,600</td>
<td></td>
</tr>
<tr>
<td>10-1-28. 3,600,000</td>
<td>65%</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23-1-28. 4,580,000</td>
<td>85%</td>
<td>0.94</td>
<td>7,000</td>
<td></td>
</tr>
</tbody>
</table>

*Initial reticulocyte rise probably due to the liver juice; extract, however, responsible for the subsequent steady improvement.*

**Case 4. F, 67. 2nd attack.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Count</th>
<th>%</th>
<th>Unit</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-12-27</td>
<td>850,000</td>
<td>20%</td>
<td>1.2</td>
<td>2,600</td>
</tr>
<tr>
<td>11-12-27. &quot;Hepatopson,&quot; a decicated liver preparation made by the Promonta Co., commenced (100 gm. daily).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticulocytes rose steadily, reaching 30% on 20-12-27 and returning to normal by 3-1-28.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-1-28. 2,450,000</td>
<td>60%</td>
<td>1.25</td>
<td>5,200</td>
<td></td>
</tr>
<tr>
<td>11-1-28. 2,300,000</td>
<td>60%</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-1-28. Daily dosage increased to 125 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-1-28. 2,440,000</td>
<td>60%</td>
<td>1.3</td>
<td>3,600</td>
<td></td>
</tr>
<tr>
<td>24-1-28. 3,050,000</td>
<td>75%</td>
<td>1.16</td>
<td>3,600</td>
<td></td>
</tr>
<tr>
<td>1-2-28. 4,000,000</td>
<td>80%</td>
<td>1.0</td>
<td>3,600</td>
<td></td>
</tr>
</tbody>
</table>

**Case 5. F, 51. 1st attack.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Count</th>
<th>%</th>
<th>Unit</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-10-27</td>
<td>1,000,000</td>
<td>25%</td>
<td>1.25</td>
<td></td>
</tr>
</tbody>
</table>
Liver Diet begun.

22-11-27. 2,500,000. 62%. 1.1.
9-12-27. Teeth extracted.
16-12-27. 2,280,000. 58%. 1.3.
17-12-27. Boot's Liver Extract, 5 gm. daily, added to diet.
30-12-27. 3,700,000. 60%(?). 0.78(?).

Patient, a slight frail woman, could not eat more than 4 oz. liver and 4 oz. liver juice per day. The improvement, on adding extract to this diet, is apparent.


11-1-28. 1,100,000. 26%. 1.18. 2,600. 0.5%.
20-1-28. 1,060,000. 28%. 1.33. 2,000. 4.0%.
21-1-28. 9.0%.
24-1-28. 1,470,000. 35%. 1.21. 3,600. 8.0%.
28-1-28. 1,620,000. 40%. 1.25. 2,600. 0.5%.
7-2-28. 2,600,000. 62%. 1.20. 4,100. 0.5%.
28-2-28. 4,040,000. 85%. 1.05. 5,800. 0.5%.

Case 7. M. 66. 2nd attack.

19-12-28. 890,000. 26%. 1.5. 4,600. 6.5%.
23-1-28. 16.0%.
25-1-28. 1,290,000. 36%. 1.5. 9.0%.
28-1-28. 1,610,000. 40%. 1.25. 6,000. 3.0%. 
During week previous to admission, this patient had eaten 1½ lbs. of liver, so that treatment may be said to have begun then----hence high initial reticulocyte count and quick response.

Case 8. M. 51. 1st attack.
26-1-28. 2,540,000. 60%. 1.18. 4,200. 0.5%.
2-2-28. 2,690,000. 65%. 1.15. 5,400. 9.0%.
7-2-28. 3,250,000. 75%. 1.15. 7,000. 2.0%.
29-2-28. 4,240,000. 90%. 1.07. 10,200. 0.5%.

Case 9. F. 50. 1st attack.
18-2-28. 1,120,000. 30%. 1.36. 4,000. 4.0%.
1-3-28. 1,360,000. 34%. 1.26. 5,400. 5.5%.
3-3-28. 
5-3-28. 
6-3-28. 
10-3-28. 
15-3-28. 1,760,000. 45%. 1.29. 4,000. 10.0%.
17-3-28. 
26.
7-2-28. 2,760,000. 65%. 1.18. 6,400. 0.5%.
22-3-28. 4,080,000. 82%. 1.01. 4,600. 0.5%.
27-3-28. 2,380,000. 52%. 1.11. 4,200. 2.0%.

This is one of the cases, previously referred to, where progress has been unaccountably slow.

Case 10. M. 40. 1st attack.

1-3-28. 1,390,000. 35%. 1.3. 2,000. 4.0%.


Reticulocytes continued about 2-4%.

14-3-28. 1,780,000. 35%. 1.0. 2,200. 3.0%.


24-3-28. 9.0%.

27-3-28. 2,340,000. 55%. 1.19. 6,800. 5.0%.

This is another case which has improved somewhat slowly, though the results have been better on the fluid preparation than on the dry.

Case 11. M. 33. 2nd attack.

24-3-28. 1,580,000. 36%. 1.16. 2,000. 0.5%.

Boot's Extract (= 500 gm. Liver daily) begun, along with (owing to a mistake) ½ lb. liver.

29-3-28. 5.0%.

31-3-28. 24.0%.

2-4-28. 25.0%.

Obviously, the beginnings of a very good result are seen in this case.
APPENDIX II.

The following Table gives the results of measurement of the red cells in some of the cases, after the method of Price-Jones. It will be seen that the cells are divided into groups (e.g. those between 4μ and 5μ in diameter), and the percentage of cells falling into each group is given.

<table>
<thead>
<tr>
<th>Patient</th>
<th>4-5μ</th>
<th>5-6μ</th>
<th>6-7μ</th>
<th>7-8μ</th>
<th>8-9μ</th>
<th>9-10μ</th>
<th>10-11μ</th>
<th>11-12μ</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Blood</td>
<td>0</td>
<td>0</td>
<td>4.4</td>
<td>74.9</td>
<td>20.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Normal Blood</td>
<td>0</td>
<td>0</td>
<td>4.0</td>
<td>69.5</td>
<td>26.0</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case 3 21-11-29</td>
<td>0</td>
<td>4.1</td>
<td>8.2</td>
<td>14.8</td>
<td>36.3</td>
<td>25.2</td>
<td>8.2</td>
<td>3.0</td>
<td>99.8%</td>
</tr>
<tr>
<td>Case 3 23-1-28</td>
<td>0.9</td>
<td>2.3</td>
<td>18.4</td>
<td>61.3</td>
<td>15.3</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
<td>99.9%</td>
</tr>
<tr>
<td>Case 6 20-1-28</td>
<td>2.7</td>
<td>8.0</td>
<td>9.3</td>
<td>26.0</td>
<td>35.3</td>
<td>12.0</td>
<td>4.0</td>
<td>2.7</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case 6 28-2-28</td>
<td>0.5</td>
<td>2.0</td>
<td>4.5</td>
<td>35.5</td>
<td>55.5</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case 1 11-11-27</td>
<td>0</td>
<td>2.5</td>
<td>1.5</td>
<td>27.0</td>
<td>38.5</td>
<td>27.5</td>
<td>3.0</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case 1 30-1-28</td>
<td>0</td>
<td>0.8</td>
<td>2.0</td>
<td>55.2</td>
<td>40.8</td>
<td>0.4</td>
<td>0.8</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case 7 19-1-28</td>
<td>0</td>
<td>2.4</td>
<td>7.6</td>
<td>15.2</td>
<td>20.4</td>
<td>37.2</td>
<td>10.8</td>
<td>6.4</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case 7 22-3-28</td>
<td>0</td>
<td>1.5</td>
<td>1.0</td>
<td>39.5</td>
<td>46.5</td>
<td>9.5</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case A</td>
<td>0</td>
<td>0</td>
<td>3.0</td>
<td>54.0</td>
<td>33.5</td>
<td>9.5</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
</tr>
<tr>
<td>Case B</td>
<td>0</td>
<td>0</td>
<td>4.6</td>
<td>57.0</td>
<td>36.0</td>
<td>2.4</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

It would appear from these figures that, even in remission, the blood of a pernicious anaemia patient does not conform quite to a normal type. Lest it should be thought that, in none of the cases quoted, was the red count high enough to justify the term "complete remission", figures are given from two additional cases ("A" & "B"). In case A,
when the measurements were made, the r. b. c. count was 6,100,000 per cub. mm. and the Hb. 100%. In case B, the figures were 5,740,000 and 95%.
REFERENCES.


13. Fraser, T.R. "Bone Marrow in the Treatment of Pernicious Anaemia". B.M.J., I, 1172, (June 2) 1894.


