to obtain such a result by the intramuscular introduction of the active principle. Gänsslen states that he has never failed by this method in any liver-resistant case in which the diagnosis of pernicious anaemia was undoubtedly correct.

CONCLUSIONS

1. Gänsslen's liver extract for intramuscular injection is shown to be a highly potent preparation. Its effectiveness is about one hundred times that of raw liver given by the mouth. No undesirable local or general manifestations occurred as a result of its injection.

2. (a) Intramuscular liver extract therapy is of particular value in cases of pernicious anaemia which are critically ill, with marked nausea and vomiting. The necessity for blood transfusion is reduced to a minimum if adequate quantities of liver extract are given intramuscularly. (b) The so-called liver-resistant cases of pernicious anaemia should be treated by intramuscular injection of liver extract.

3. In patients in the remission stage the fortnightly injection of liver extract enables the maintenance dose of

liver to be reduced to limits which can be easily tolerated even by persons who have an active dislike for the consumption of this organ. The importance of maintaining a normal blood level in such patients, for the prevention and treatment of subacute combined degeneration of the cord, is discussed.

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RESISTANT SPRUE ANAEMIA YIELDING TO INTRAVENOUS LIVER EXTRACT

BY

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The patient, a European male aged 47, has been under the care of one of us (L. R.) at the London Hospital for Tropical Diseases, at intervals since 1926, for relapsing sprue contracted originally in Burma in October, 1923, and complicated by severe anaemia. At first he responded well to a milk diet and returned to Burma, only to come home again in 1925 with a recurrence of his sprue, with sore tongue, fatty stools, and anaemia. In 1926 he was again treated with milk diet (and was also given small doses of novarsenobillon, as a positive Wassermann reaction had been obtained), with good effect on the anaemia. In addition, he had injections of an autogenous oral streptococcal vaccine, which resulted in the clearing up of the soreness of his tongue. In December, 1928, he was readmitted with severe anaemia; red blood cells 1,470,000, haemoglobin 50 per cent., and colour index 1. A transfusion of 500 c.cm. citrated blood was given (causing rather a severe reaction), together with liquor arsenicalis orally, and a milk diet. Once more good results occurred, and the blood was restored to about normal. In July, 1929, he was readmitted with sprue symptoms and moderate anaemia, and was treated with 1 lb. of liver extract and Fairley's high protein diet. By January, 1929, he had gained a stone in weight, and his blood was practically normal again, but he relapsed

once more in July, 1930, to pick up yet again on liver extract and high protein diet. He continued taking one to three tubes of liver extract daily after leaving hospital, but had to be readmitted in February, 1931, when the liver treatment failed to have as good an effect as previously.

On July 29th, 1931, he was again admitted to the hospital with severe anaemia, but freedom from the former sprue symptoms of diarrhoea and sore tongue. Red blood cells were 1,940,000, haemoglobin 40 per cent., and colour index 1, and there were signs of megalocytic anaemia, including the presence of scanty normoblasts and of megalocytes. On admission, in view of the good effects of the previous blood transfusion, 600 c.cm. of citrated blood were injected intravenously. This was followed by

Therapeutic failure of blood transfusion with subsequent adequate haematological response to hepatex P.A.F. intravenously and full dosage of liver extract and iron per os. (July 29th to October 22nd, 1931.)

a temperature of 104° F. on the next day, accompanied by vomiting of bile-stained fluid, and the passage of dark urine. There was drowsiness for three days and slight jaundice, while at the same time the liver became somewhat enlarged and tender, the reaction being thus a severe one. Unfortunately, instead of the hoped-for improvement in the condition of his blood, it steadily deteriorated, until on September 1st it showed red blood cells 1,000,000 and haemoglobin 20 per cent. His condition caused grave anxiety, for in the meantime both Parke, Davis and Co.'s ventriculin orally, and the same company's liver extract subcutaneously, had failed to check the downward course of the blood changes. Dr. Donald Hunter was now asked to see the patient with us, and he suggested iron orally in the form of Bland's pills, and the trial, if available, of intravenous injections of the new form of liver extract recently used by Professor Minot and his colleagues in Baltimore. A cable to Professor Minot informed us that this could be supplied by Evans Sons Lescher and Webb, in the form of hepatex P.A.F., so we decided to try it.

RESULTS WITH HEPATEX

This new preparation, sold in 5 c.cm. doses containing the equivalent of 100 grams of fresh liver, is said to produce an immediate reticular response. To be on the safe side, a 2 c.cm. dose was injected intravenously on September 2nd without any undesirable symptoms. Five c.cm. was given by the same route on each of the next four days, making a total of 22 c.cm. in six days. After the third dose of 5 c.cm. the patient felt better, though he had a restless night. On the afternoon of the fourth injection he first complained of discomfort in the upper abdomen, which became acute after the fifth dose, and there was vomiting of undigested food in the evening. On this day the pain began a quarter of an hour after the injection, with discomfort in the right hypochondrium spreading to the epigastrium, becoming severe for five hours, and being unrelieved by hot fomentations. On the following morning the liver was found to be enlarged to below the ribs, and its edge was very tender. As the red corpuscles had already risen from 1,000,000 to 1,800,000, a 5 c.cm. dose of hepatex was given intramuscularly on September 7th, the injections being omitted on the 8th and 9th, as the severe abdominal pain had recurred and the sickness continued. On the morning of the 9th, the edge of the liver was felt two inches below the ribs, and there was a tender spot over the region of the pylorus. A bismuth meal was given, and a radiological examination of the stomach and duodenum carried out, with negative results. A rise of temperature accompanying the abdominal reaction on September 9th subsided the next day, so between that date and October 7th ten doses of 2.5 to 3 c.cm. of hepatex were admin-

istered intramuscularly every second or third day without any further untoward symptoms. On the 13th the Bland's pills, which had been omitted on the 8th, were recommenced.

The blood response was very satisfactory, for a rapid and steady rise took place in both the red corpuscles and the haemoglobin, accompanied by a remarkable reticulate response up to 6.6 per cent. in three days, and up to 33 per cent. within six days of the commencement of intravenous hepatex. The red corpuscles and haemoglobin rose from 1,000,000 and 19 per cent. on September 3rd, to 1,800,000 and 20 per cent. on the 7th; 2,660,000 and 41 per cent. on the 18th; 3,590,000 and 55 per cent. on the 29th; 4,020,000 and 64 per cent. on October 6th; and 5,060,000 and 84 per cent. on October 22nd, by which time the patient had been discharged from hospital. Two months later his blood condition was well maintained and the general health good, except for the return of occasional watery diarrhoea, which he believes followed the intramuscular injections of hepatex.

The main points of interest in the case are: first, the remarkable and rapid recovery, after intravenous hepatex, from a dangerous condition of post-sprue pernicious anaemia, which had failed to respond to ordinary methods of liver extract administration; secondly, the severe abdominal symptoms following a few intravenous injections, due to rapid enlargement of the liver, and sufficiently acute to raise the question of serious gastric or duodenal disease. These symptoms subsided when the injections were made by the intramuscular, instead of the intravenous, route.

We are indebted to Dr. N. H. Fairley for the chart of the blood examinations carried out in his laboratory.

THE INTRAVENOUS LIVER TREATMENT OF PERNICIOUS ANAEMIA

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The intravenous use of liver extracts in pernicious anaemia was first reported by Castle and Taylor,¹ who showed that a much lower dose, in terms of liver, could be effective in treatment than was required by oral administration. The preparation used had the disadvantage of causing lowering of blood pressure. Wilkinson² recently employed an improved preparation made in the Evans Biological Institute; this is stated to have been prepared by a method similar to Cohn's,³ but the protein fraction was separated as completely as possible to remove all blood pressure depressants. This preparation is now available under the name of hepatex P.A.F., and is stated to contain no carbohydrates, lipoids, or proteins. The intravenous injection produced no alteration of blood pressure in pernicious anaemia cases.

We have used this preparation in the treatment of the following two cases, which present certain points of interest. Wilkinson refers to its advantage in severe cases, in rendering transfusion unnecessary owing to the rapid reaction obtained, and also in other cases where oral administration is impracticable on account of nausea, vomiting, or refractoriness on the part of the patient. He reports two cases of the latter type which were successfully treated, one intravenously, the other intramuscularly. Transfusion must be rarely necessary, and, owing to its various drawbacks, it has not been a practice in this hospital, even when the red cell counts were below

800,000 per c.mm. No patients have died since we commenced liver therapy in 1927, but some fatal cases have been reported⁴ in which transfusion might have been effective. Another probable advantage of intravenous liver therapy is that a larger effective dose can more readily be given by this route than by the mouth. Castle and Taylor claim success with a single intravenous dose derived from only 100 grams of liver, where oral administration of the equivalent of 3,000 grams of liver had been given in ten days without effect. Similarly, the work of Smith,⁵ who appears to have been the first to use the parenteral method, and, later, Gänsslen⁶ and Schottmüller,⁷ points in the same direction. These workers used doses equivalent to 1/2 to 30 grams of liver, and although only given intramuscularly, the efficacy of the parenteral route with Gänsslen's preparation is estimated at about fifty times greater than is the oral. Anderson⁸ reports a case "put on liver in the usual daily doses, and a little hog's stomach extract"; but the duration of time is not stated, the treatment apparently being discontinued owing to nausea. The blood condition had deteriorated one month after commencing treatment, and subsequent response was obtained with hepatex P.A.F., intravenously and intramuscularly. Whether oral treatment had failed owing to absence of response, inadequate dosage, or inability to continue it on account of nausea, is not clear.

UNCOMPLICATED CASE

The following case failed to respond to oral administration of 40 grams of desiccated stomach, for three weeks, owing to vomiting, subsequent response to intravenous hepatex P.A.F. being obtained. The dose used for each injection was 5 c.cm., stated to be equivalent to 100 grams of liver. No undesirable reactions occurred.

S. D., male, aged 58, first seen at the out-patient department on June 22nd, 1931, complained of feeling progressively weaker