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

BY

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AND

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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

TABLE I.—S. D., male, aged 58

Date	Days from 1st Intrad. Treatment	Haemoglobin, per cent.	Red Cells, per c.mm.	Colour Index	Reticulocytes		Leucocytes, per c.mm.	Polymorphs, per c.mm.	Lymphocytes, per c.mm.	Monocytes, per c.mm.	Eosinophils, per c.mm.	Basophils, per c.mm.	Platelets, per c.mm.	Arneth Lobes, per 100 polys.	Van den Bergh, Indir.
					Per c.mm.	Per cent.									
22/6/31	-45	38	1,150,000	1.65	—	—	3,100	2,588	496	16	0	0	—	312	—
15/7/31	-22	22	875,000	1.29	42,900	4.9	4,800	3,437	1,267	77	19	0	16,000	270	Pos.
30/7/31	-7	21	712,000	1.5	62,000	8.8	3,400	—	—	—	—	—	—	—	—
9/8/31	5	20	704,000	1.44	—	—	3,900	—	—	—	—	—	—	—	—
18/8/31	14	40	1,750,000	1.14	—	—	3,400	—	—	—	—	—	—	—	Neg.
27/8/31	23	55	2,825,000	1.0	—	—	—	—	—	—	—	—	—	—	—
12/9/31	39	65	4,025,000	0.81	—	—	—	—	—	—	—	—	—	—	—
24/9/31	51	63	3,537,000	0.89	—	—	—	—	—	—	—	—	—	—	—
13/10/31	70	72	3,870,000	0.93	45,000	1.2	4,500	2,430	1,620	360	67	23	83,000	282	Neg.
13/11/31	101	80	4,475,000	0.9	—	—	4,300	—	—	—	—	—	—	—	—
7/12/31	125	82	4,862,000	0.85	82,000	1.7	5,400	2,835	2,133	297	108	27	150,000	296	Neg.

22/6/31: Megalocytes present. 15/7/31: Megalocytes, megaloblasts, and Howell-Jolly bodies present.

TABLE II.—A. H., female, aged 38

1/10/31	-1	21	775,000	1.4	106,000	13.7	9,200	5,042	3,238	626	55	18	38,000	238	Pos.
5/10/31	4	32	1,275,000	1.28	574,000	45.0	7,000	4,060	2,275	385	140	35	72,000	289	Pos.
7/10/31	6	38	1,500,000	1.27	660,000	44.0	3,000	1,350	1,350	120	165	0	130,000	294	Pos.
9/10/31	8	46	2,212,000	1.05	662,000	29.0	3,600	1,764	1,332	414	90	0	175,000	314	Neg.
12/10/31	11	45	2,162,000	1.05	324,000	15.0	3,300	1,897	1,074	231	49	49	195,000	282	Neg.
20/10/31	19	55	2,637,000	1.04	122,000	3.0	3,600	2,106	1,008	270	198	18	93,000	275	Neg.
28/10/31	27	63	3,000,000	1.05	24,000	0.8	3,600	2,070	1,116	180	198	36	96,000	269	—
7/12/31	67	81	4,387,000	0.92	4,400	0.1	5,700	3,847	1,340	171	313	29	110,000	264	Neg.

1/10/31: Myelocytes, 221 per c.mm.; nucleated reds, 11,000 per c.mm.; megalocytes, megaloblasts, punctate basophilia, Howell-Jolly bodies.
5/10/31: Myelocytes, 105 per c.mm.; nucleated reds, 400 per c.mm. 7/10/31: Myelocytes, 15 per c.mm.; nucleated reds, 60 per c.mm.

for the previous five weeks, of shortness of breath, and of yellowness of his skin. There was an icteric tinge in skin and conjunctivae, and also some albuminuria. Abdominal examination revealed an indefinite resistance below the right costal margin. A blood count made the same day suggested a primary anaemia. The man reported again on July 13th, and was admitted to the wards, his appearance being much the same as when first seen. The liver and spleen were not enlarged, and the indefinite resistance below the costal margin could not be detected. The blood condition had deteriorated (see Table I). Radiological examination showed a slight delay in the passage of the barium meal into the stomach, and a growth at the lower end of the oesophagus was hinted at. On July 23rd a fractional test meal showed an absence of free hydrochloric acid in the stomach. On account of the blood picture he was put on 40 grams of desiccated hog's stomach daily, and 1 drachm of dilute hydrochloric acid three times a day. This treatment failed to produce any improvement in the blood picture, and after a few days he began to refuse his food and vomited both food and hog's stomach once or twice a day.

On August 5th treatment with hepatex P.A.F., 5 c.cm. intravenously each day, was begun. On August 15th the injections were given by the intramuscular route, and on the 18th they were altered from daily to every other day, with an oral liver extract (hepatex), in amount equivalent to 172 grams of fresh liver, on the intervening days. On August 30th the injections were stopped and oral treatment as above was given daily. The immediate effect of the intravenous injections was dramatic. Within forty-eight hours of the commencement of the treatment the man was hungry, and could eat his meals well. He was discharged on September 24th, and has continued taking the oral extract and dilute hydrochloric acid in the above doses ever since. The blood picture on December 7th was approaching the normal (see Table I). The man now looks well, and he states that he is putting on weight and feels fit.

Although this case had failed to react to the oral treatment administered, it is not claimed that no response

would have occurred if the preparation given had been retained. We have not yet encountered a case of uncomplicated pernicious anaemia with the complete picture in the blood and gastric juice and without atypical features, which has failed to react to liver extract or hog's stomach by the mouth, where doses larger than those generally required have been employed when necessary, and retained. Our experience differs from that of Wilkinson, whose results with liver treatment⁹ appeared to be very much inferior to those with hog's stomach.¹⁰ We have seen cases which failed to do well on the usual 230 grams of liver per day, or its equivalent as extract, given orally; but on increasing the dose satisfactory results have always been obtained, and we feel, therefore, that Wilkinson's poor results with liver may have been due to inadequate dosage or that many of his cases were atypical. Our more limited experience agrees with the findings of Minot and Murphy,⁴ who stated that "it is highly probable that if a patient, supposed to have pernicious anaemia, has shown no improvement after taking liver in adequate amounts for about four weeks, the diagnosis has been incorrect." We exclude from these remarks atypical cases, such as those complicated by septic conditions, which have been regarded as less likely to react to liver therapy. Such has been our experience, although some cases have responded.

CASE WITH SEPSIS

Our second case is of interest, because a septic condition was present, as shown by the pyrexia, the condition of the mouth, and the leucocyte count with Arneth shift to the left instead of the usual shift to the right.

A. H., female, aged 38. Admitted September 29th, 1931, with a history of "falling off for the previous three years and progressive anaemia." On admission, she was well

nourished, but the skin was pale and lemon-tinted. She was dyspnoeic on slight exertion, the tongue pale and glazed, the lips blanched, and the teeth and gums septic. The liver was palpable three fingerbreadths below the costal margin, and was tender. The spleen was palpable two fingerbreadths below the costal margin, and was also tender. The blood picture (Table II) was that of a severe pernicious anaemia with a polymorph leucocytosis. A fractional test meal done on admission showed an absence of free hydrochloric acid in the stomach. The temperature was 101.2° F. On October 2nd daily injections of 5 c.cm. of hepatex P.A.F., intravenously, were commenced. Within three days the appearance of the patient had altered. She stated that she felt much better, and the spleen and liver were smaller and less tender. By October 5th the temperature was normal, and remained so while she was in hospital. The injections were continued for ten days, by which time the red blood cells had risen from 775,000 to 2,212,000 per c.mm., and the spleen and liver had become normal in size. Liver extract (hepatex) orally in dosage equivalent to 172 grams of fresh liver daily, and 1 drachm of dilute hydrochloric acid three times daily, were commenced, and on November 2nd she was discharged at her own request. The red blood cells at the time of discharge had risen to 3,000,000 per c.mm., but the colour index was still just above 1.

Since discharge she has taken desiccated hog's stomach (Benger's), 10 grams daily, and on December 7th the red blood cells were 4,387,000 per c.mm., and the colour index 0.92. She stated that she felt well and could do her own housework easily.

It is of interest that the septic condition rapidly subsided with the treatment, and it seems not improbable that here the sepsis was merely secondary to the pernicious anaemia. In those cases which do not respond the opposite may possibly hold good, but the relation of the sepsis to the anaemia will generally be difficult to determine. With the subsidence of the sepsis here, the leucocytic picture was converted from one atypical of pernicious anaemia to one typical of it, the Arneth becoming right-handed, with a polymorph leucopenia in place of a leucocytosis. The Arneth count subsequently became normal, and the following three counts are given to show the changes in detail. (Cooke's¹¹ technique was used.)

Oct. 1st.—Arneth count: 27, 30, 26, 12, 5—238 lobes per 100.

Oct. 9th.—Arneth count: 6, 12, 44, 28, 8, 2—314 lobes per 100.

Dec. 7th.—Arneth count: 8, 34, 46, 10, 2—264 lobes per 100.

The polymorph leucopenia in pernicious anaemia is not due to the inability of the bone marrow to react to stimuli. It is of interest, therefore, in view of the work of Ponder and others,^{12 13} who showed that the subcutaneous injection into animals of a wide variety of substances produced an Arneth shift to the left by increasing the output of polymorphs, that in this case the intravenous injections of a potent liver extract were followed by no such effect, although the first count showed the capacity of the bone marrow to react.

No conclusions are to be drawn as to the probable effect of such treatment in other similarly septic cases, but there is no doubt that the method is a very effective one, the response being obtained much more rapidly than with the oral route. The treatment would appear to be somewhat costly, but when the more rapid response and earlier return of the patient to normal is considered, and the cost of maintenance in hospital is taken into account, this is not necessarily so. One of the above cases was discharged from hospital thirty-one days after commencing intravenous treatment. Owing to the great variation in dosage required by individual cases, however, exact comparison of the cost of the oral and parenteral methods of treatment is impracticable, except with large groups of cases.

SUMMARY

Two cases of pernicious anaemia treated intravenously with liver extract are described.

Both responded rapidly, although one had previously failed to respond to oral treatment owing to vomiting, while the other was complicated by sepsis.

We are indebted to Dr. Franklyn for the radiological report quoted.

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THE RADIOGRAPHIC DISSECTION OF CHRONIC RHEUMATIC ARTHRITIS*

BY

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The following is a brief outline of the radiological investigation upon which I am at present engaged at the British Red Cross Clinic for Rheumatic Diseases in London. The objects in view are to simplify the classification and identification of rheumatic arthritic conditions by a radiographic dissection. If it is realized that a radiograph will depict pathological changes or processes in terms of shadows, it is obvious that it is only necessary to interpret these properly for a correct diagnosis to be reached.

In 1907 Dr. Strangeways carried out some important and painstaking research in this complex subject. Though it covered the clinical, radiographic, and morbid-histological aspects, and though many specimens of arthritis were dissected, his final deductions were inconclusive. He even remarks that it was not possible at that time to distinguish between the various types of rheumatic arthritis. This statement might have been true twenty-four years ago; I do not consider it will stand to-day. Two reasons why fuller value was not obtained from his radiographic examination in those days were the inability, owing to inefficient x-ray apparatus and technique, to detect the early and slight diminution in bone calcium and other minute alterations in bone construction, and the fact that the clinical diagnosis was often regarded as infallibly correct.

TECHNIQUE

The technique which I have adopted at the Rheumatism Clinic, and which I consider essential to the investigation and identification of chronic rheumatic arthritis, is as follows. A "standard" radiograph of the hand is taken of every case accepted for treatment. "Standard" refers to the conditions under which the radiograph is taken. The hand, for instance, has been taken to be of standard thickness and density in the adult male and female, and is therefore used as the standard tissue. One particular wave-length and a definite time of exposure is decided upon, while a set distance of tube from film and a uniform time and temperature for development will ensure all these radiographs of the hand being taken under uniform

* The substance of a paper read at the Third International Radiological Congress, held in Paris in July, 1931.