TREATMENT OF PERNICIOUS ANAEMIA WITH HOG'S STOMACH

REPORT OF 108 CASES*

BY

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The successful results of some experiments upon the value of hog's stomach tissues in the treatment of pernicious anaemia were published in a preliminary report upon nine cases so treated in the laboratory.¹ It was found that very good results could be obtained either with uncooked fresh hog's stomach tissues or desiccated preparations of the same. By using such active products in cases of pernicious anaemia remissions were initiated more quickly and progress was better maintained than with the liver treatment. Subjective symptoms, such as glossitis, paræsthesiae, and gastro-intestinal disturbances, were much more rapidly and satisfactorily relieved without the aid of the mixture of hydrochloric acid and pepsin so often necessary in liver therapy. In 1929 Sturgis, Isaacs, and Sharp,² working independently along similar lines, reported remission in three cases, using a desiccated preparation. More recently they have made observations upon thirty-nine cases of pernicious anaemia for periods up to ten weeks.³ These results have been confirmed by workers in other countries, but the number of cases reported has been few, while the periods of observation have not been sufficiently long to indicate the real value of this form of therapy. Conner⁴ has reported six cases and Rosenow⁵ two where similar treatment was employed for pernicious anaemia. Meulengracht and Hecht-Johansen⁶ obtained satisfactory responses using desiccated preparations, but failed to get an active extract (one case) according to Cohn's method with liver. Ungley⁷ also failed to produce remissions in two cases treated with fresh sheep's stomach. I have confirmed this result using the desiccated preparation. Five cases have been recorded by Snapper and Dupreez⁸ as having been successfully treated with hog's stomach, while Hitzenberger,⁹ Faber,¹⁰ Winge,¹¹ and Lambin and Steenhoudt¹² have also obtained satisfactory results in a smaller number of cases.

GENERAL DESCRIPTION OF EXTENDED SERIES

During the last eighteen months I have extended considerably my own series. Since most of the patients on whom the treatment was first tried have continued to take it, its ultimate value can be estimated more exactly over these longer periods.

The present communication deals with a series of 108 consecutive cases of uncomplicated pernicious anaemia treated at the Manchester Royal Infirmary with preparations of hog's stomach. All these cases were typical for this condition, having reduced red cell counts and haemoglobin values, high colour indices, megalocytosis, achylia gastrica, etc.; a few of them had a less pronounced early postero-lateral involvement of the spinal cord.

For convenience of discussion and comparison the series is divided into three groups, although the cases constitute one consecutive series.

Group I consists of 52 cases, none of which had ever had liver or other special treatment for the condition prior to coming under observation.

Group II consists of 31 cases that had been given liver treatment at some time previously but had relapsed.

Group III consists of 25 cases that had been on liver treatment and complained of a return of symptoms.

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Two cases have been omitted from this series owing to other complications: both had relapsed on full doses of raw liver. In one an epithelioma had been removed from the tongue; later, a block dissection of the cervical glands was performed. The patient died from pneumonia and cardiac muscle failure after readmission to the Manchester Royal Infirmary. Necropsy confirmed the diagnosis of coexisting pernicious anaemia. The other died, while an in-patient, from broncho-pneumonia and acute colitis, having received treatment for only five days.

TREATMENT

The treatment given in this series of cases may be considered under two headings, according as the patients received fresh or desiccated preparations of hog's stomach.

Raw Tissue of Hog's Stomach

In the preliminary report already referred to¹ several cases were described that had been given uncooked fresh hog's stomach preparations. In all, about ten cases have been so treated, but the difficulty of continuing this treatment after the patient's discharge from hospital led to the replacement of the fresh by the desiccated preparations on transference to the out-patient department. These cases are marked with an asterisk in Table I.

One patient, however, was conveniently situated, so that it has been possible to continue the raw tissue therapy. This case was described in the earlier paper as Case III.

Case 1 (Table I)

It was a typical case of pernicious anaemia. The initial blood count showed: red blood cells 1,910,000 per c.mm., white blood cells 7,600; haemoglobin 50 per cent.; colour index 1.3. The patient was treated with 250 grams of uncooked fresh mucous membrane of hog's stomach daily, and very rapidly improved, so that by the seventy-eighth day the blood count was: red blood cells 5,072,000, white blood cells 8,300; haemoglobin 84 per cent. He returned to full-time work; since then he has been in normal health.

The dose has been gradually adjusted; at the present time he takes 1,000 grams of uncooked fresh tissue per month. For convenience this is divided into daily doses of approximately 350 grams, so that the whole of the month's supply is consumed in three days. He takes no more until the next month's supply is due. The tissue is carefully washed in cold water, examined macroscopically for parasites, and then minced. It keeps well in a refrigerator for long periods; the patient has not had any difficulty in keeping it the maximum of two and a half days before taking the last portion. By the administration of rather larger doses than this maintenance dose the blood picture can be kept at a somewhat higher level, but there has not been any noticeable difference clinically. He is perfectly well after sixty-four weeks on this diet; he is doing his full-time work, and has put on weight. The treatment is being continued.

During the treatment there was a marked eosinophilia, reaching its maximum (19 per cent.) at the twenty-seventh week, but was less than 5 per cent. after the forty-fifth week. The leucocytes have varied between 6,000 and 14,000, being high when he had a cold, and again when he had a septic finger.

Desiccated Preparations

In the earlier experiments, as reported previously, the desiccated hog's stomach was mixed with chocolate and lactose. This made a very palatable drink, but many patients have a distaste for milk—the medium chiefly used. I have therefore been using the preparation without these added constituents. This has certain advantages, in that the bulk of powder is less per dose, while it can be taken in milk or water as desired, or may be mixed with other foodstuffs *provided that heat is avoided*.

The preparation used for routine treatment is a desiccated whole hog's stomach ("extomak"), kindly prepared for me by Messrs. Benger's Food, Ltd., of Manchester. It is a very light, biscuit-coloured powder, insoluble in water and organic solvents; 25 grams are

equivalent to 100 grams of the fresh whole hog's stomach. It mixes well with milk and such media. Owing to its very powerful peptic activity (see below) it is advisable to mix the required dose just prior to its administration, otherwise it arrives before the patient as a junket-like mass—a much less palatable form to most patients.

The dose employed initially is 25 to 30 grams daily, divided into three portions. This is reduced to 10 to 20 grams daily as the blood picture becomes more normal, the average maintenance dose being about 10 to 12 grams daily. In some cases the maintenance dose is larger or smaller than this amount; the needs in each individual case have to be estimated by careful observation and regular blood counts. The dose may have to be increased or diminished according to the season of the year or the health of the patient, common colds and influenza having very profound effects on the blood counts in many of these cases.

An important practical point arises here. The dosage employed must be measured by *weight*. Owing to the very light, relatively bulky nature of the powder, the usual method of measuring by spoonfuls frequently leads to the ingestion of a dose which is much less than that prescribed, with obvious consequences.

Adjuvant Medicines

The use of hydrochloric acid in association with this form of treatment does not appear to be necessary or to have any marked effect. This is in contrast to its use in conjunction with liver, where it is often necessary for the complete relief of gastro-intestinal symptoms.¹³ During their period as in-patients a few of the cases were given certain iron preparations and occasionally arsenic, according to the prescription of the honorary physician in whose ward they happened to be. There was no noticeable difference in the speed of remission in any of these patients, compared with those who were not receiving such additional treatment. In this connexion it is interesting to compare the result obtained in Case 71 (see p. 87). It should be mentioned that in most cases after discharge from hospital these adjuvant medicines have been discontinued, only the hog's stomach preparations being taken regularly.

RESULTS OF TREATMENT

The results of treatment in 83 of the 108 cases contained in this paper are conveniently summarized in Tables I and II.

In Columns A the initial blood condition (red blood cells and haemoglobin) of each patient is shown before the commencement of hog's stomach therapy. The corresponding values obtained at the *last* blood count taken are recorded in Columns B, and do not represent the maxima obtained. In the last column are given the total periods of observation (in weeks) of each patient from the beginning of treatment until the last blood count was taken (Columns B). These periods do not represent the time taken to reach normal values in these cases. The leucocyte and differential counts have been omitted for economy of space, and are irrelevant to the present discussion.

The results may be classified in the three groups previously mentioned.

Group I.—No Previous Treatment

Table I, 52 cases. None of these had had any treatment before coming under my observation—apart from the usual tonics containing iron, arsenic, "phosphates," etc. They were treated with preparations of hog's stomach as above, but in Case 1 (see above) the uncooked fresh tissue has always been taken. The nine other patients, indicated by an asterisk, were similarly treated while in-patients, but continued on desiccated

TABLE I

Case	Sex	Erythrocytes		Percentage Haemoglobin		Period of Observation (weeks)
		A	B	A	B	
1*	M	See text page 85		—	—	64
2	F	600,000	4,900,000	20	86	21
3*	F	660,000	5,650,000	17	96	52
4	F	650,000	5,620,000	17	70	33
5	M	740,000	4,300,000	19	90	13
6	F	928,000	4,800,000	19	94	13
7	M	1,000,000	4,500,000	23	90	20
8	M	1,100,000	3,850,000	26	82	7
9	M	1,100,000	4,100,000	30	76	13
10	M	1,160,000	5,160,000	28	102	49
11*	M	1,160,000	4,900,000	38	94	40
12	M	1,200,000	5,950,000	37	96	22
13	M	1,240,000	5,000,000	40	90	20
14	M	1,200,000	5,000,000	45	110	52
15	M	1,290,000	4,700,000	35	100	50
16	F	1,290,000	5,100,000	27	96	41
17	F	1,300,000	4,800,000	46	96	37
18	M	1,400,000	5,220,000	46	104	49
19	M	1,500,000	4,200,000	40	78	13
20	M	1,600,000	4,800,000	34	80	25
21*	M	1,600,000	5,020,000	40	86	41
22	M	1,600,000	6,150,000	36	96	25
23	M	1,700,000	5,200,000	40	106	20
24	F	1,700,000	4,100,000	43	90	21
25	F	1,700,000	5,400,000	49	90	29
26	M	1,700,000	7,260,000	36	100	37
27*	M	1,700,000	5,400,000	46	106	37
28	M	1,790,000	5,110,000	40	98	23
29	F	1,890,000	5,980,000	42	86	24
30*	F	1,900,000	4,000,000	55	80	53
31	M	1,900,000	4,740,000	45	98	34
32	F	2,000,000	5,440,000	41	104	25
33	F	2,100,000	4,900,000	58	102	19
34*	M	2,180,000	5,100,000	50	100	59
35	M	2,350,000	5,870,000	52	80	27
36	M	2,400,000	4,500,000	52	88	19
37	M	2,700,000	5,320,000	56	108	44
38*	M	2,800,000	4,800,000	74	90	34
39	M	2,800,000	4,950,000	74	100	29
40	M	2,910,000	6,110,000	82	96	25
41	M	2,950,000	5,100,000	74	90	35
42	M	2,980,000	5,090,000	82	100	35
43*	M	3,000,000	4,800,000	82	100	48
44*	M	3,000,000	4,840,000	90	106	61
45	F	3,100,000	4,520,000	81	86	13
46	M	3,100,000	5,630,000	70	110	20
47	F	3,200,000	4,600,000	90	96	22
48	M	3,200,000	5,230,000	68	74	17
49	F	3,400,000	4,300,000	84	92	21
50	F	3,460,000	4,800,000	90	98	7
51	M	3,500,000	6,950,000	88	100	56
52	M	3,700,000	5,480,000	74	110	21

A = Blood count before treatment with hog's stomach.

B = Present blood count.

* = Received uncooked fresh hog's stomach while in-patients.

preparations after discharge from hospital. They are thus considered together with the remainder of the cases. Several patients were treated as out-patients, attending the laboratory daily for observation and treatment.

It will be observed that the periods of observation varied from seven to sixty-four weeks, giving an average of 32.4 weeks; seven cases have been under this form of treatment for more than fifty-two weeks, and fifteen for more than forty weeks.

The majority of the cases showed initial red cell counts less than 3 million, and thirty-one of them less than 2 million. The most recent counts are interesting, since they indicate a very marked tendency towards high red cell counts, but haemoglobin values of relatively less increment. This is not marked until the red cells become more numerous than approximately 5.5 million, after which the colour index shows a steady fall. Six cases have given higher counts, but at the present time only four are over 6 million, one of these being 7.25 million.

The haemoglobin tends to lie between 90 and 110 per cent., but where the dose is rather too small, or the patient discontinues the treatment for a time, it frequently falls to about 80 to 90 per cent. This rapidly improves with slightly increased doses.

The leucocytes showed an average initial count of 4,530, and an average final count of 6,500.

The following case illustrates this group very well, and is typical of the result obtained.

Case 18 (Table I)

A labourer, aged 49, was admitted to hospital complaining of anaemia, weakness, and paraesthesiae in the fingers for ten weeks before coming under observation. In the last few weeks the pallor had increased and numbness in the feet had developed. His appetite was good and the bowels were regular; there was no complaint of diarrhoea, sore tongue, indigestion, or loss of weight. Family and previous medical histories revealed nothing of note.

Examination.—Lower teeth were very septic; tongue was smooth but clean. He weighed 8 st. 8 lb. Spleen and liver were not enlarged, and there were no alterations in the reflexes. Wassermann reaction was negative. Fractional gastric analysis showed achylia gastrica. Blood count: red blood cells 1,400,000, white blood cells 6,500; haemoglobin 46 per cent.; colour index 1.6; platelets scanty; anisocytosis and poikilocytosis marked; polychromasia present; megaloblasts and nucleated red cells also seen.

The patient was given a desiccated preparation of hog's stomach equivalent to 280 grams of fresh tissue daily, reduced later to 15 grams of desiccated preparation, together with a hydrochloric acid¹³ mixture. There was a very prompt response to this treatment, the blood picture rapidly improving, so that one week after discharge from hospital—the sixty-fifth day of treatment—it showed: red blood cells 5,060,000, white blood cells 9,200; haemoglobin 104 per cent.; colour index 1.04; platelets abundant; and slight anisocytosis. The present condition, after forty-nine weeks of treatment, is indicated in Table I.

Results.—All the patients in this group are well after an average period of thirty-two weeks, and none have shown any indication of relapse at the time of writing.

Of these 52 cases, 46 (88.5 per cent.) are now in normal health, free from symptoms, and doing their original full-time work. (Included in this figure are a few male patients now perfectly fit but unable to get employment.)

Three patients are quite well, but still have symptoms of early postero-lateral sclerosis; one suffers from paralysis agitans, but is otherwise well (Case 15); the remaining two patients (Cases 8 and 19) are progressing very well, but have only recently been discharged from hospital, so that their blood counts are not yet normal. The latter patient took no treatment for two weeks, but is also rapidly improving; both will be fit for work in a very short time, as there are no signs of nervous involvement.

Twenty-seven of these patients complained of various

paraesthesiae affecting their hands and feet; after treatment with hog's stomach only one has definite numbness in the fingers, the remainder being cured or suffering only from occasional attacks.

Six patients had definite postero-lateral involvement of the spinal cord; three are so much improved that they have returned to full-time heavy manual work; two are much improved but are not working; one is unchanged as regards the nervous condition.

Group II.—Relapsed Cases after Liver Treatment

Table II summarizes the 31 cases in this group. All the patients had taken liver at some period before coming under my observation and had had definite relapses, as shown by the clinical conditions and the blood counts (Columns A). In most cases the relapse was caused

TABLE II

Case	Sex	Erythrocytes		Percentage Haemoglobin		Period of Observation (weeks)
		A	B	A	B	
53	F	920,000	4,920,000	21	93	43
54	M	976,000	5,720,000	24	93	25
55	M	1,070,000	5,000,000	25	88	13
56	M	1,090,000	4,200,000	22	92	20
57	F	1,100,000	5,750,000	24	102	41
58	M	1,200,000	5,100,000	26	102	70
59	M	1,250,000	5,790,000	40	86	19
60	F	1,300,000	4,700,000	25	104	49
61	M	1,300,000	5,400,000	34	92	28
62	M	1,440,000	6,100,000	50	102	16
63	F	1,470,000	4,600,000	37	72	19
64	M	1,700,000	4,300,000	40	84	34
65	F	1,700,000	4,500,000	48	90	14
66	M	2,400,000	5,200,000	65	112	25
67	F	2,620,000	5,450,000	72	102	21
68	M	2,900,000	5,112,000	72	98	12
69	M	2,900,000	4,000,000	93	78	18*
70	M	3,080,000	4,400,000	70	100	32
71	M	3,200,000	5,220,000	102	98	19
72	F	3,300,000	4,450,000	76	76	11†
73	M	3,400,000	4,400,000	100	94	23
74	F	3,400,000	4,350,000	86	70	11
75	F	3,420,000	5,200,000	90	94	9
76	F	3,500,000	4,540,000	92	96	8
77	F	3,600,000	5,180,000	80	82	38‡
78	F	3,700,000	4,950,000	94	94	26
79	F	3,700,000	5,060,000	96	91	20
80	F	3,700,000	5,860,000	100	102	17
81	F	3,750,000	4,450,000	80	92	6
82	F*	3,900,000	5,400,000	86	108	25
83	F	3,900,000	4,100,000	82	72	18§

* Discontinued treatment for 8 weeks.

† Discontinued treatment for 4 weeks.

‡ See text.

§ Discontinued treatment for 8 weeks.

either by discontinuance of the treatment or by the ingestion of inadequate active doses, due partly to excessive cooking of the raw liver. These cases were reinvestigated in this laboratory, and treated according to the routine followed in Group I.

Results.—In this group the results are not so striking as the previous ones, since the patients usually came under observation earlier, and hence the initial blood counts were on an average higher than in those cases

diagnosed for the first time. The average initial blood picture showed: red blood cells, 2,500,000; haemoglobin, 63 per cent. These patients have been under observation for a period of eight to seventy weeks, with an average of 23.5 weeks. During this time none has shown any signs of relapse, or developed postero-lateral involvement of the spinal cord.

Twenty-one patients (67.7 per cent.) are very well and doing full-time work; eight (25.8 per cent.), although not working, are also well and have no symptoms, making a total of twenty-nine patients (93.5 per cent.) in normal health again; two (6.4 per cent.) are well except for slight postero-lateral involvement, which is very much better than before treatment; none has failed to respond satisfactorily to the treatment.

Case 77 (Table II)

This case is of considerable interest, since, after discharge from hospital, the patient became pregnant. She was seen regularly at intervals of one month, later fortnightly, and was kept on a daily dose of 20 to 30 grams of desiccated hog's stomach. At no time during the period of gestation did the count fall below 4,200,000 red blood cells and a haemoglobin percentage of 78. Two weeks before parturition the count was: red blood cells 4,256,000, white blood cells 5,900; haemoglobin 90 per cent.; colour index 1.05. Three weeks after parturition the red blood cells were 4,440,000, white blood cells 4,800; haemoglobin 78 per cent.; colour index 0.9. The count fourteen days later is given in the table.

The following two cases have been chosen to illustrate this group; the first was treated as an out-patient from this laboratory, the second as an in-patient.

Case 54 (Table II)

A matine engineer, aged 61, attended the out-patient department of the Manchester Royal Infirmary complaining of considerable weakness, dyspnoea on exertion, indigestion, and paraesthesiae in the hands and feet. He had been unable to work for two years. There was no sore tongue or diarrhoea, but he was very constipated. For about four months he had noticed the progressive development of a yellowish pallor over the body. He had not lost much weight, and his appetite was fairly good.

Previous Medical History.—He had been treated for pernicious anaemia six months previously, but had not continued the liver diet. Family history disclosed nothing of note.

Examination.—Pale lemon-yellow colour; conjunctivae deep yellow; considerable pyorrhoea present and teeth very septic; liver and spleen were not enlarged, and no other abnormality was found. Wassermann reaction was negative. Blood count was as follows: red blood cells 976,000, white blood cells 6,200; haemoglobin 24 per cent.; colour index 1.3; platelets very scanty; anisocytosis and poikilocytosis very marked. Fractional gastric analysis showed achylia gastrica.

Day of Treatment	Erythrocytes	Leucocytes	Percentage Haemoglobin
1	976,000	6,200	24
5	1,576,000	2,700	35
13	1,816,000	3,500	50
27	3,216,000	4,500	80
39	3,968,000	5,400	88
55	5,168,000	5,100	97
69	5,072,000	5,800	96
175	5,720,000	7,400	98

He was given a daily dose of 25 grams of an active desiccated hog's stomach preparation and attended this laboratory as an out-patient throughout the treatment. No blood transfusion was given. The very rapid and progressive response obtained with this treatment is indicated by the figures in the preceding table. He is now in perfect health and free from symptoms.

Case 62 (Table II)

A shopkeeper, aged 54, first came under observation at the Manchester Royal Infirmary on October 9th, 1928, complaining of lassitude, weakness, and an increasing pallor since March of that year. It became more noticeable in June, when shooting pains in the back and legs incapacitated him from walking. His appetite was poor, and he had had attacks of vomiting for two to three weeks. There was no history of sore tongue or diarrhoea, but the bowels were constipated. The feet swelled occasionally and the left foot felt numb. There was no marked loss of weight.

Previous Medical History.—Appendicitis at 16 years of age had been treated medically. For some years he had worked in a rubber factory and had been troubled with gastric disturbances. He stated that he had had lead poisoning several times, and neuritis during the last twelve years. He had been a shopkeeper for the last ten years. His family history disclosed that his mother died of diabetes mellitus, and that his father died, aged 78, from gangrene.

Examination.—Marked yellow pallor; teeth artificial; tongue furred and flabby; weight 9 st. 7 lb.; knee-jerks present; spleen slightly enlarged. Blood count: red blood cells 1,150,000, white blood cells 4,800; haemoglobin 25 per cent.; colour index 1.17.

The patient was treated with liver (four ounces), iron, arsenic, and salol, and improved very much, so that on his discharge from hospital on November 28th his weight was 10 st. 10 lb., and the blood count: red blood cells 4,200,000, white blood cells 6,200; haemoglobin 86 per cent.; colour index 1.02; differential count normal.

He was not seen again until July 25th, 1930, when he was readmitted to the Manchester Royal Infirmary with a recurrence of the original symptoms of lassitude, pallor, loss of appetite, and shortness of breath on exertion. This time also he complained of a constant pain in the epigastrium, loss of weight, and had had paraesthesiae in both legs for the last eighteen months. He stated that he had been taking lightly cooked liver (2 lb. per week), with iron and arsenic mixtures, but no hydrochloric acid.

Examination.—Pale lemon-yellow colour; teeth artificial; tongue clean; weight 9 st. 5 lb. Left leg was wasted to a greater extent than the right; left knee-jerks absent, and there was difficulty in walking. Wassermann reaction was negative. The blood count on July 31st showed: red blood cells 1,440,000, white blood cells 5,800; haemoglobin 50 per cent.; colour index 1.8. Fractional gastric analysis showed achylia gastrica.

He was given a daily dose of 30 grams of desiccated hog's stomach in cold milk, and hydrochloric acid (B.P., dil., 1:1000) with each meal. The improvement was extremely satisfactory, and he was discharged on August 30th with a blood count as follows: red blood cells 3,600,000, white blood cells 3,300; haemoglobin 98 per cent.; colour index 1.3. After sixteen weeks of treatment the count showed: red blood cells 6,100,000, white blood cells 7,400; haemoglobin 102 per cent.; colour index 0.8. He is in perfect health, doing his full-time work, has put on weight, and is free from all symptoms.

Group III.—Return of Symptoms after Liver Treatment

The patients in this group had been taking liver diet in some form or other. Many of them had discontinued the treatment, but others had relaxed the dose or were cooking the liver too much. Two had been taking a type of "liver extract" that I have found to be unsatisfactory.

The initial erythrocyte counts in these cases were relatively high, but the colour indices were greater than unity in all of them. Although these patients had relatively good blood counts, they complained of a very marked return of the original symptoms—for example, weakness and shortness of breath, sore tongue, gastrointestinal disturbance, paraesthesiae in fingers and toes, etc. In nearly all these cases the pepsin and hydrochloric acid mixture had been discontinued for many months.

They were given desiccated hog's stomach, 15 to 30 grams daily as above, in place of the liver diet.

Results.—The twenty-five cases in this group have been under observation on hog's stomach treatment for an

average of twenty-two weeks. All the patients are very well and obviously in much better health than before receiving this treatment, while the symptoms have entirely disappeared. A few of them were also given the hydrochloric acid mixture.

The average blood count for the whole group before treatment showed: red blood cells, 4,370,000; haemoglobin 89 per cent.; after treatment during an average of twenty-two weeks there were 5,160,000 red blood cells and a haemoglobin percentage of 95.6.

Summary of Results

The results in 52 cases of untreated pernicious anaemia and in 31 definitely relapsed cases (Groups I and II) indicate that 92.7 per cent. (77 patients) are perfectly well and free from symptoms of any kind, while 6 per cent. (five patients) are well, but are still suffering from some degree of nervous impairment, although this has much improved. Not one failed to respond to treatment satisfactorily. These figures should be compared with the corresponding figures of 50 per cent. and 15 per cent. obtained in patients treated by liver.¹⁴

From these results, obtained by the use of active preparations of hog's stomach, both fresh and desiccated, in 108 cases of pernicious anaemia, it is abundantly clear that this is the best treatment so far known for the disease. While liver diet is also an excellent method of treatment, there are many cases that do not respond to this form of therapy. On the other hand, when adequate treatment has been given with an active preparation of hog's stomach no case of true pernicious anaemia, from my own experience, has failed to respond.

The use of a mixture of hydrochloric acid and pepsin, in addition to liver diet, for the relief of certain gastrointestinal symptoms in pernicious anaemia has been discussed in an earlier paper.¹³ In the newer treatment with hog's stomach this mixture is rarely necessary, and none of the symptoms have, so far, been found to recur.

CHANGES IN THE BLOOD PICTURE

In all the cases recorded in this paper the improvement and good health have been maintained. Many patients, however, who have continued on full doses of hog's stomach after reaching normal blood counts have shown tendencies towards excessive erythrocytic reaction until the doses have been reduced. An increase to over 6 million red cells has been observed in seven cases (six in Group I, one in Group II), but three have returned to normal levels after suitable reductions in dosage. The others have only recently reached these higher values, and have not been examined since the reductions. All these cases showed a marked "lag" in haemoglobin increment over 110 per cent., so that the colour indices have fallen steadily with increasing red cell counts over 6 million. This has automatically corrected itself with the return of the erythrocyte counts to normal value.

The question then arises of the possibility of producing a polycythaemia as a result of continued large doses of hog's stomach. So far as I am aware no such cases have been recorded in which liver or liver extracts have been used, and the subsequent progress of these cases is being closely observed. The point is illustrated by the following case.

Case 26 (Table I)

A foreman lockgate-keeper, aged 49, complained of weakness and dizziness, associated with frequent nausea and headaches, for eighteen months prior to coming under my observation. He had indigestion and flatulence, and paraesthesiae in the hands and feet, but had only had a sore tongue for about two weeks. There was no history of diarrhoea, constipation, or loss of weight, but his appetite was poor. He had noticed the development of a gradually increasing yellow colour over the whole body. Apart from a slight attack of malaria twenty-five years previously, there was nothing of note in

his previous medical history. His son suffers from purpura haemorrhagica.

Examination.—A slightly built man, with very marked yellow pigmentation of the conjunctivae and sclerotics, slightly less marked over the whole body. Tongue clean, teeth artificial. Nothing else found abnormal. Wassermann reaction was negative. Fractional gastric analysis showed achylia gastrica. On March 31st, 1930, his blood count showed: red blood cells 1,700,000, white blood cells 3,600; haemoglobin 39 per cent.; colour index 1.1; very marked anisocytosis and poikilocytosis; platelets scanty; nucleated red cells, polychromasia, and megaloblasts present.

The patient was given 28 grams of desiccated hog's stomach daily, and rapidly responded to this treatment (see below), the reticulocytes rising to 37 per cent. on the nineteenth day. On May 12th his blood count showed: erythrocytes 5,912,000, white blood cells 5,100; haemoglobin 98 per cent., colour index 0.83.

The dosage was reduced to 10 grams daily of the desiccated preparation, and the patient was seen at monthly intervals. The erythrocytes steadily increased in number, but the haemoglobin did not show a correspondingly rapid rise, so that the colour index fell below unity. On October 21st the blood count was as follows: red blood cells 7,260,000, white blood cells 5,500; haemoglobin 100 per cent., colour index 0.68. There was no eosinophilia at any time. A similar observation was made in Case 3 (Table I), but on reducing the dose for this patient the erythrocytes fell, while the colour index again increased.

The patient was perfectly well, and did not complain of any ill-effects from this excessive blood reaction. All treatment, however, was discontinued, and three weeks after these notes were written the count showed: red blood cells 5,360,000, white blood cells 5,000; haemoglobin 90 per cent.; colour index 0.9.

Date	Erythrocytes	Percentage Haemoglobin	Colour Index
1930			
March 18	1,700,000	38	1.1
April 11	2,160,000	52	1.2
April 17	2,740,000	58	1.06
April 26	4,030,000	83	1.03
May 12	5,910,000	98	0.8
June 16	5,780,000	92	0.8
July 14	6,560,000	108	0.8
August 12	6,750,000	109	0.8
Sept. 9	6,590,000	96	0.69
Oct. 21	7,260,000	100	0.68
Nov. 11	5,360,000	90	0.9

Progress of Improvement in Blood Picture.

From a general survey of the results obtained in this series of cases the progress of improvement in the blood picture appears to be somewhat as follows. The erythrocyte count and the haemoglobin value increase simultaneously at the beginning until the haemoglobin is approximately 40 to 60 per cent. (or perhaps a little higher, according to the individual), when it remains roughly constant for a short time until the red cells have reached 3.5 to 4 million. The haemoglobin then continues to improve until it reaches 95 to 100 per cent., by which time the erythrocytes, if the dosage is not reduced, are approaching 5 million or a little more. Occasionally the position may be reversed, the haemoglobin improving progressively while the erythrocytes show the first "lag." In some cases this step-like progress is not shown.

From this stage only the erythrocytes increase, the haemoglobin very rarely rising above 110 per cent. Thus the colour index throughout the course of the treatment shows a general tendency to fall from above to below unity as the red cells increase—that is to say, the colour index varies inversely with the height of the erythrocyte counts. An erythrocyte count approximating to a

polycythaemia thus produces a colour index of a marked secondary type of anaemia.

This is so characteristic when it does occur that it suggests very strongly (a) the possible value of iron at this stage in conjunction with the treatment; (b) that the erythrocytes and haemoglobin may be produced by entirely different mechanisms, although to some degree interdependent, and possibly even at different sites. The importance of this consideration upon the general question of anaemia is being investigated.

The Reticulocyte Response

It is well known as a result of the work of Minot and others¹⁵ that the reticulocyte response varies inversely with the initial erythrocyte level. Confirmation has been obtained in this laboratory. With this as a basis of comparison the observations on the reticulocyte responses following this form of therapy which have been published by others fall considerably short of those obtained in my series of patients described above. Thus, where they have reported "peaks" of 15 to 20 per cent. of reticulocytes, in cases with similar initial blood pictures I have obtained 25 to 40 per cent.—more usually the latter—and in some cases even higher. I have found by experiment that the use of an inadequate dose or a less active preparation usually results in such lower reticulocyte responses, which may also be delayed in reaching their maxima for perhaps fourteen days or more.

COMPARISON OF METHODS OF TREATMENT

In a previous paper¹⁴ the results of treating pernicious anaemia with iron and arsenic in 47 cases were compared with those obtained by the liver treatment (33 cases). These figures represented the average percentage increases of erythrocytes, haemoglobin, and leucocytes respectively after a period of forty-five days' treatment in hospital in each case. For comparison, I have now added the corresponding results obtained by this newer treatment with hog's stomach, and Table III indicates the relative values of the three forms of treatment in exactly comparable cases. In order to avoid complications, the figures are compiled from the 52 cases that have had only hog's stomach treatment.

TABLE III

Treatment	No. of Cases	Average Percentage Increase in 45 Days		
		Erythrocytes	Haemoglobin	Leucocytes
Iron, arsenic, blood transfusion	47	+ 46	+49	- 8
Liver diet	33	+ 94	+77	+41
Hog's stomach	52	+157	+91	+41.5

It will be observed that the rates of improvement in the erythrocyte counts and haemoglobin values are, respectively, 1.7 and 1.2 times quicker than those obtained with the liver treatment, but 3.4 and 1.8 times respectively than the older iron-arsenic-blood-transfusion treatment.

The relative merits of these methods of treatment are extremely well illustrated by the following case.

Case 71 (Table II)

A clerk, aged 41, was admitted to the Manchester Royal Infirmary for the first time on November 4th, 1924, complaining of increasing anaemia (six weeks' duration), weakness, vomiting (several months' duration, but worse during the five weeks prior to admission), vertigo, and shortness of breath on exertion. There had been some diarrhoea, indigestion, and flatulence, but no loss of weight or sore tongue.

Previous Medical History.—Psoriasis vulgaris, eczema, erythema multiforme at various periods; "gastritis" in 1915; was "gassed," and had septicaemia during the war period. Family history disclosed that his father died of Bright's disease, and one sister died of dropsy.

Examination.—Teeth septic; no enlargement of spleen or liver; knee-jerks present; weight 10 st. 13 lb.; nothing else

of note. Wassermann reaction was negative. Blood count: red blood cells 1,336,000, white blood cells 6,800; haemoglobin 28 per cent.; colour index 1.05; platelets scanty; very marked anisocytosis and poikilocytosis; megaloblasts present.

Treatment mainly consisted of iron and arsenic preparations. He was discharged slightly improved on December 15th, and remained in a moderate state of health for twelve months, when the symptoms returned as before.

On September 15th, 1926, he was readmitted to hospital, but this time soreness of the tongue was also present, together with epistaxis and intermittent pain in the legs.

Examination.—Skin, mucous membranes, and conjunctivae a markedly yellow colour; teeth very septic, with marked pyorrhoea; liver slightly enlarged to two inches below the costal margin; knee-jerks present. Blood count: red blood cells 948,000, white blood cells 6,000; haemoglobin 20 per cent.; colour index 1.05.

He was treated with large doses of arsenic (oral and intramuscular), iron, streptococcal vaccines, salol, and artificial sunlight, and again showed some slight improvement. When discharged on January 18th, 1927, the blood picture was: red blood cells 1,440,000, white blood cells 4,800; haemoglobin 36 per cent.; colour index 1.3; platelets scanty; marked anisocytosis and poikilocytosis.

After a second relapse, he was again an in-patient from July 6th to August 24th, 1927. He complained of similar symptoms as previously, but not diarrhoea. The blood count showed: red blood cells 1,160,000, white blood cells 10,200; haemoglobin 30 per cent.; colour index 1.3; platelets scanty; anisocytosis and poikilocytosis very marked; polychromasia and punctate basophilia also present.

The previous treatment was renewed vigorously, with the addition, for the first time, of four ounces of lightly cooked "potted" liver per diem. This time he showed a much better response to treatment, probably due to the liver, and the blood count on discharge from hospital was: red blood cells 3,340,000, white blood cells 4,400; haemoglobin 70 per cent.; colour index 1.0.

He was sent home to continue this liver diet (four ounces daily), but relapsed a third time, being readmitted from January 8th, 1929, to February 16th. The symptoms were similar to those previously recorded, and he had a marked lemon-yellow colour; the tongue was pale and flabby, and the lower teeth were still very septic. Examination did not reveal any other abnormal features. Blood count: red blood cells 1,064,000, white blood cells 4,600; haemoglobin 26 per cent.; colour index 1.3.

He was again given vaccines, large doses of iron and arsenic, and four ounces of lightly cooked liver per diem until his discharge, when the blood count was: red blood cells 2,780,000; haemoglobin 58 per cent.; colour index 1.03. Four months later, on this treatment, the count was: red blood cells 3,016,000; haemoglobin 82 per cent.; colour index 1.3.

He was not seen again until December 11th, when he was admitted as an urgent case to the Manchester Royal Infirmary with the following count: red blood cells 696,000; haemoglobin 14 per cent.; colour index 1.6. He was in a very bad, semi-comatose condition, with a marked lemon-yellow colour all over the body.

A blood transfusion (one pint) of citrated blood (Group IV) was given, and the earlier treatment continued. To the daily four ounces of fresh liver was added liver extract (half an ounce of a fluid preparation); hydrochloric acid and pepsin were also given with each meal (gastric analysis showed achylia gastrica). On February 15th, 1930, he was discharged from hospital on a diet consisting of four ounces of liver, together with liver extract and hydrochloric acid. The blood count at that date was: red blood cells 3,740,000, haemoglobin 80 per cent.; colour index 1.06—the best count recorded since he came under observation.

(I am indebted to Dr. C. H. Melland for the above notes on this patient, who was under his care in the Manchester Royal Infirmary.)

The patient attended this laboratory, as an out-patient, from this time onwards, at frequent and regular intervals, but there was no improvement on the last count, even when the dose was increased to eight ounces of raw liver daily.

On July 8th the blood count was: red blood cells 3,240,000; haemoglobin 92 per cent.; colour index 1.4. In view of this

the whole of the previous treatment was discontinued, and replaced by 28 grams daily of desiccated whole hog's stomach. The blood picture showed an immediate and progressive improvement such as had never been observed before in this patient. The most recent blood count shows: red blood cells 5,430,000; haemoglobin 92 per cent. The patient himself is perfectly well, and states that he has never been so fit for over seven years. He is now working, and starting to play football.

GENERAL OBSERVATIONS

Active desiccated preparations of hog's stomach should have extremely good peptic activities. An examination of the commercial desiccated products offered by several wholesale houses in Europe and America has disclosed very widely varying peptic activities in different samples. If this pepsin content is also an approximate index, as I think it may be, of the coexisting "anti-anaemic" value of the product, then the lower and slower responses to treatment with such preparations obtained by certain other workers is explained.¹⁶

Many of the patients have been re-examined at intervals by fractional gastric analyses, but so far no alteration has been noted in the achylia gastrica.

It is important that the patient should understand that, as with liver, hog's stomach does not constitute an absolute cure for the condition. One patient, however, under observation at present is perfectly well after nearly twelve months of abstinence from all forms of treatment. As a rule, a greater or less maintenance dose must be taken at fairly regular intervals, so far as is known, for an indefinite period, and possibly for life. This involves regular blood counts for the control of the patient's condition, and it should be borne in mind that the blood picture is profoundly affected by colds and other infections: it is advisable at these times to increase the dose temporarily.

This maintenance dose may be taken in small regular daily amounts (this is usually the most satisfactory method), or, as has been well illustrated in Case 1 above, it may be administered in relatively large doses for a day or two every few weeks. A somewhat similar observation has been made by Riddle and Sturgis,¹⁷ who gave massive doses of liver extract (equivalent to 3 kg. fresh liver) to three patients. It appears, therefore, that the maintenance of good health and a normal blood condition in these cases requires the supply of a definite minimal quantity of the active principle within certain time limits, probably fourteen to twenty-eight days, the body being unable to store this necessary, as yet unknown, substance, at any rate in an available form, for more than this short period.

At the present time fresh hog's stomach is the cheapest and the most active form of treatment, while a certain desiccated preparation available is as cheap as fresh liver when taken in the average maintenance dose.

SUMMARY

1. The earlier observations upon the value of hog's stomach have been extended to 108 cases of pernicious anaemia, and the results are here discussed.

2. Treatment has been described using fresh and desiccated preparations of hog's stomach tissues. The dose and administration have been indicated.

3. After periods of observation up to eighteen months no relapses have occurred, and all the cases have done well.

4. This new form of treatment for pernicious anaemia with active preparations of hog's stomach has given highly satisfactory results—undoubtedly better than with liver, while the relative effective dose is less than the liver dose.

5. More than 92 per cent. of the patients treated with hog's stomach are perfectly well, and the majority are doing their full time work. A further 6 per cent. are

much improved, but still suffer from varying degrees of nervous impairment.

6. Hog's stomach therapy is superior to liver diet in the speed of remission of the condition, the erythrocytes and haemoglobin increasing 157 per cent. and 94 per cent. respectively, compared with 90 per cent. and 77 per cent. respectively with liver under comparable conditions.

7. Hog's stomach therapy has qualitative effects on the blood picture similar to those of liver, but the erythrocytes and haemoglobin increase in a characteristic step-like manner in many cases. The colour index varies inversely with the red cell count.

8. Eosinophilia is frequently seen, but not in every case.

9. Clinically, the immediate results are similar to those obtained with liver. They are more prompt and, ultimately, the normal health is reached more quickly; work is resumed sooner; and all the gastro-intestinal symptoms appear to be relieved. This is not always the case with liver treatment, hydrochloric acid and pepsin being frequently required in addition to relieve the indigestion, flatulence, and occasional sore tongue.

10. Achylia gastrica persists despite the treatment.

11. Hydrochloric acid and pepsin do not appear to be necessary for the relief of symptoms with this form of treatment.

12. There is a minimum dose of hog's stomach to maintain the normal health of each patient. Regular blood counts are essential for the control of this dose, owing to seasonal variations and the profound effects of even minor infections.

13. Hog's stomach in normal doses readily produces an excessive erythrocytic response, approaching polycythaemia, and several cases with counts over 6 million are now under observation.

14. Fresh hog's stomach can be taken in adequate doses for a few days every three to four weeks with a maintenance of normal health.

15. Several cases with early postero-lateral involvement of the spinal cord have shown remarkable improvement, and paraesthesiae of hands and feet (without alteration of reflexes) have been almost completely cured in nearly every case. These have always been the symptoms most resistant to treatment.

I have to thank the honorary physicians of the Manchester Royal Infirmary for kindly supplying me with the clinical material essential for this work, and also Professor H. S. Raper, F.R.S., for his continued interest. The majority of the blood counts have been done by the clinical pathologists of the Manchester Royal Infirmary, and by Dr. Agnes Bodoano in this laboratory, to all of whom I express my deep appreciation of their invaluable assistance.

Addendum.—Since this paper was written this series has been extended to 133 cases, and the periods of observation in Tables I and II can be increased by eight weeks in each case. Those cases with relatively low final blood counts have all reached normal values. There is no material alteration in the other figures requiring comment.

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