Among the physio-therapeutical methods, the simplest consists in the application of warm foot-baths, or radiant heat, but the best is diathermy (A. Wilson Gill, L. Newell Moss), which must always be applied. I have not seen any special results from x-ray applications, nor from galvanic foot-baths. Massage is strictly contraindicated, as also is any undue strain (exercise), because these can only accentuate the spasmodic condition. Balneotherapy is very important, and it is to the action on the vasomotor centres that must be attributed, in great part at least, the effects of Royat. Artificial carbon dioxide baths are not effective.

Among surgical methods Leriche's operation—arterial perisymphathectomy—which also enhances vaso-dilatation, has given some good results, but must be applied only in the last resort. Before its application a careful oscillographic exploration must be made, so as to determine that the artery is not completely obliterated, and also for the localization of the obliteration. Gangrene may be the result if these precautions are not taken.

If to all these methods is added the scrupulous care of small wounds and excoriations of the lower limbs, a very effective treatment can be instituted in a disease which is relatively frequent, is met with in all countries and in all

rates, and has not, thanks to the possibility of an early recognition, the dark prognosis which was often attached to it.

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PERNICIOUS ANAEMIA.

PRELIMINARY REPORT ON THE RESULTS OBTAINED BY
TREATMENT WITH CERTAIN PREPARATIONS
OF STOMACH.*

BY

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THE unfailing regularity with which gastric achylia is encountered in pernicious anaemia has often been pointed out. Almost invariably the gastric secretion is deficient in hydrochloric acid and pepsin, even after the use of powerful gastric stimulants; in some hundred cases which I have examined only three exceptions were found.¹ That this achylia is of some significance has been pointed out by Castle,² who fed patients suffering from Addisonian anaemia with beef that had been predigested in a normal stomach, or with normal gastric juice *in vitro*, and obtained reticulocyte responses and increased erythrocyte counts comparable with those ordinarily seen after small doses of liver. He failed to obtain any improvement using beef (a) alone, (b) predigested with hydrochloric acid and commercial pepsin, or (c) incubated with 150 grams of mucous membrane of hog's stomach. The negative result in the latter case is somewhat surprising in view of the results described below.

These observations and the success of the liver therapy have suggested the hypothesis that pernicious anaemia might be a deficiency disease in which the gastric juice was unable to elaborate some necessary principle (normally formed in a healthy individual) from the proteins of the food. This substance is present in liver and kidney, as was originally shown by Murphy and Minot, and, in consequence, these organs can be readily administered in the treatment of the disease. Attempts to identify the active principle with certain vitamins and investigations upon the effects of various foodstuffs have been made by Elders,³ and Koessler, Maurer, and Loughlin⁴ among others.

The experiments described below were based upon a somewhat different view—namely, the possibility of pernicious anaemia being a type of deficiency disease, in which some factor of paramount importance was absent from the gastric juice. Despite some of the negative results obtained by Castle, it did not seem improbable that the stomach itself might be a potent source of the anti-

anaemic substance, and the complete lack of gastric enzymes suggested the importance of investigating this possibility more closely.

Action of Normal Gastric Juice.

It was decided in the first place to try the effect of normal gastric juice. This was obtained, as required, either with or without the use of histamine, and administered in a daily dose of 150 to 200 c.cm., given during meals to ensure its action upon the protein foodstuffs. Each individual sample of gastric juice was examined carefully beforehand for the presence of free hydrochloric acid and normal peptic activity to ensure that an active and fresh preparation was being used. All samples containing bile, or less than 0.036 per cent. free hydrochloric acid, were discarded.

The following case illustrates the type of response obtained in this group.

CASE I.

A male cotton operative, aged 59, was admitted to hospital complaining of weakness in the legs and lack of energy, so that he was unable to carry on his work. Apart from bacterial food poisoning in 1906, he had enjoyed perfect health until March, 1929, when he had an attack of influenza lasting for four weeks. Since that time he had had slight paraesthesias, more pronounced in the cold weather. These became gradually worse, so that, having ceased work, he had difficulty in using his limbs accurately. He had lost 14 lb. in weight in six months. His appetite was good and there was no history of indigestion, diarrhoea, nausea, vomiting, or marked flatulence. He had soreness of the tongue and gums in cold weather. More recently, he had had some slight pains in the lower abdomen, lasting for a few minutes only; his bowels were constipated.

The previous medical history contained nothing of note. As regards the family history, one sister had died at the age of 30 from an "anaemic wasting disease."

Examination.—The patient's teeth were artificial; there was nothing abnormal in the cardio-vascular, respiratory, alimentary, or genito-urinary systems. The knee-jerks and abdominal reflexes were exaggerated; no muscular wasting was present, but there was marked weakness in the limbs and some difficulty in walking. The blood Wassermann test was negative. A cytological examination showed: red blood cells 3,850,000 per c.mm., white blood cells 4,800; haemoglobin 100 per cent.; colour index 1.4; platelets normal; slight anisocytosis and poikilocytosis; no nucleated red cells or abnormal staining detected. Repeated fractional gastric analyses revealed complete achylia.

The case was diagnosed as one of early pernicious anaemia with subacute combined degeneration of the cord and achlorhydria syndrome.

Treatment.—No liver had been taken prior to admission, when he was given hydrochloric acid and commercial pepsin. After seven days this was discontinued and replaced by 150 to 200 c.cm. of normal fresh gastric juice once daily, taken with the midday meal. During the first week, while on acid and pepsin therapy, the patient's condition became worse. The reticulocyte count remained at the normal low level, while the red blood cells diminished by nearly 300,000; anisocytosis and poikilocytosis became

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marked, and the platelets were reduced in numbers considerably. The introduction of normal gastric juice, however, gave a remarkable response. Within three or four days the reticulocytes showed an increase (Chart 1) somewhat greater than that obtained with liver in similar cases. (It should be noted that Minot, Murphy, and Stetson⁵ have

CHART 1.

was obviously much better and felt stronger, so that he was able to walk and use his hands and arms almost as normally. He had now improved so considerably that he asked to be discharged from hospital, and liver extract was substituted in place of the normal gastric juice for several days, the reticulocyte percentage falling immediately without any secondary rise, a significant point in the diagnosis and treatment of this condition. He was discharged on a liver diet.

Uncooked Fresh Hog's Stomach.

Freshly obtained hogs' stomachs were employed in the next group of cases. In order to differentiate, if possible, between the value of the mucous membrane and the muscular layer of the stomach, these were separated. This was readily accomplished by stripping and slight dissection. In this manner the two portions were obtained free from each other, weighed, minced, and fed to patients suffering from pernicious anaemia. One stomach daily was thus sufficient for the treatment of two patients. It was found subsequently that the two portions were equally potent, even when kept in a refrigerator for several days—an important practical point in treatment extending over periods of weeks or months.

It may be pointed out that the separation of the two portions of the fresh stomach as received each day successfully disposes of the argument that the potency of the stomach muscle, at any rate, is due to the action of pepsin present in the stomach post mortem.

The minced daily doses were readily administered to the patients in the usual ways as employed with fresh liver therapy, no cooking or heating being permitted (compare Wilkinson and Brockbank, loc. cit.). No hydrochloric acid or other drugs were administered during the periods of observation. The following cases illustrate the typical results obtained.

CASE II.

A woman, aged 41, who was engaged in housework, had complained of lassitude and loss of energy since 1922. She improved for a time, and then attacks of nausea, persistent vomiting, and some diarrhoea began, lasting for periods of about a week. This continued, with some intervals of freedom, from 1925 until the spring of 1929, when an appendicectomy was performed. From this time onwards she became progressively weaker and more anaemic. She had neither nausea nor diarrhoea until the day of admission to hospital, but gave a history of occasional indigestion, soreness of the tongue, and slight oedema of the ankles. There was no definite flatulence or loss of weight.

The previous medical history contained a reference to an attack of bacterial food poisoning in 1914. As regards the family history, the father died of phthisis, and the mother has a weak chest.

Examination.—The teeth were carious; the tongue was pale, but there was no marked glossitis; the skin had a pale yellowish tinge. The spleen was slightly enlarged; there was a systolic bruit over the pulmonary area, but nothing else of note was observed. A blood count showed: red blood cells 660,000 per c.mm., white blood cells 3,200; haemoglobin 17 per cent.; colour index 1.3; platelets scanty; anisocytosis and poikilocytosis marked; nucleated red cells, polychromasia, punctate basophilia, and megaloblasts all present. Fractional gastric analysis showed achylia gastrica.

This patient had not had any liver therapy prior to admission. A blood transfusion (Group IV, 350 c.cm. whole blood by the direct method) was given, followed by a daily dose of 250 grams

of freshly prepared raw mucous membrane of hog's stomach. The patient was troubled from the day of admission with severe diarrhoea, which commenced before the raw stomach therapy had been inaugurated, persisted for four or five days, and responded to large doses of hydrochloric acid.

The reticulocytes began to show a rapid response, increasing in numbers. Simultaneously, the subjective and objective conditions of the patient improved progressively and rapidly. Further supplies of desiccated mucous membrane being now available (see below), 100 grams daily was substituted for the raw preparation (Chart 2). It will be observed that after the first peak had been reached the percentage of reticulocytes fell to below 5 per cent. and then gave a secondary rise in the course of some five days to 10.6 per cent. The significance of this is not quite clear, and, so far in my series, this is the only example. The erythrocytes showed a steadily increasing count, rising from 660,000 per c.mm. before transfusion to 1,028,000 two days later, and 3,910,000 after fifty days.

CHART 2.

CASE III.

A male clerk, aged 56, complained of weakness, lack of energy, pallor, and tingling and numbness in the fingers and toes, so that he was unable to follow his employment. The onset had been insidious, but had become more pronounced during the three months prior to admission to hospital. With the onset of constipation and the passage of frequent small motions he had noticed a change of colour of his skin, and developed a very marked heaviness about the eyes. There was no history of flatulence, indigestion, diarrhoea, or soreness of the tongue. Thirty-four years previously he had had jaundice, which lasted for six to seven weeks; he was in hospital twenty years later on account of abdominal pain; no operation was performed.

The family history showed that several members of the family had had jaundice; a cousin died of gastric cancer; his mother was troubled with indigestion for years.

Examination.—The teeth were artificial; the skin a lemon-yellow colour; there was impairment of muscular power in the upper and lower limbs, and evidence of chronic bronchitis; nothing else of note. A 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; platelets scanty; anisocytosis and poikilocytosis marked; nucleated red cells, polychromasia, and megaloblasts present. Fractional gastric analyses on several occasions showed complete achylia.

Prior to admission this patient had taken small doses of cooked liver at irregular intervals. As in the previous case, he was given a diet containing 250 grams of fresh raw mucous membrane daily. Again the improvement in the patient's general condition was profound, so that he was able to attend the laboratory without assistance in less than a week.

Table (abridged) showing Improvement in the Blood Count.

Day of Treatment.	Red Blood Cells.	White Blood Cells.	Haemoglobin.
First day	1,910,000	7,600	Per cent. 50
Twenty-first day	2,820,000	6,400	60
Thirty-sixth day	3,740,000	14,100	74
Fifty-fourth day	4,390,000	13,300	72
Sixty-eighth day	4,570,000	11,100	74
Seventy-eighth day	5,072,000	8,300	84

The blood picture showed similar improvement (see table), to such an extent that, having continued the dietary after discharge from hospital, his erythrocyte count had increased from 1,910,000 to 5,072,000 per c.mm. in nine weeks from the commencement of fresh stomach therapy. He is now very well indeed, having returned to work with an almost normal blood picture within two and a half months from the original diagnosis of the condition. This compares very favourably indeed with the results obtained on a liver diet.

CASE IV.

A foreman gasworker, aged 36, was admitted to hospital complaining of progressive loss of energy, dyspnoea, and general weakness for three months prior to admission, becoming very marked during the latter portion of this time, when a yellowish pallor was also observed. In January, 1929, he had been operated

upon in another part of the country for appendicitis, since when he had had occasional slight discomfort after food and exertion. There was no history of soreness of the tongue, nausea, vomiting, flatulence, diarrhoea, or loss of weight. Slight paraesthesiae were present in the toes. There was nothing of note in previous medical and family histories.

Examination.—A slight yellowish pallor of the skin was noticed; nothing else abnormal was found. A blood count showed: red blood cells 3,180,000 per c.mm., white blood cells 5,200; haemoglobin 66 per cent.; colour index 1.04; platelets scanty; anisocytosis and poikilocytosis marked; no nucleated red cells; no abnormal staining. Fractional gastric analyses on four separate occasions showed achylia.

CHART 3.

compare Minot, Murphy, and Lawson⁶).

Here again, as in Case i, the prompt response was quite equal to that obtainable with liver therapy in cases showing an initial red cell count greater than three million (loc. cit.). No further response was obtainable with a liver diet subsequently. The patient showed a very marked improvement in his condition, and his paraesthesiae disappeared entirely on the raw stomach diet.

This case is included here in order to illustrate the type of response that is usually observed in cases with an initial high red blood cell count. It is typical for both stomach and liver therapy.

Desiccated Preparations of Hogs' Stomachs.

The obvious difficulties attending the supply and use of fresh raw hog's stomach after the patients have left hospital suggested the substitution of the corresponding dried preparations. Whilst these experiments were in progress Sturgis, Isaacs, and Sharp⁷ reported the treatment with desiccated whole stomach of three cases, which showed very similar results to my own.

I employed dried mucous membrane and dried muscular layer of hogs' stomachs in cases as described below. The preparations were obtained by desiccation at 40° C. *in vacuo*, with the addition of lactose to facilitate manipulation. Thus obtained, both portions of the stomach were in the form of light powders, which were readily administered in the following ways: (a) suspended in water or milk; (b) in lukewarm soup, etc.; (c) mixed with other previously cooked foods, particularly potted meat, in which guise the patient was unable to detect its presence; and (d) in the form of tablets to be swallowed with water or other fluid at intervals during the day. Later preparations were flavoured with chocolate and made a very palatable drink with milk. As employed at the present time these two preparations are:

Preparation A.—The usual dose of 100 grams contains 66 grams of desiccated mucous membrane of the hog's stomach, equivalent to about 280 grams of fresh mucous membrane. The remainder consists of chocolate and lactose.

Preparation B.—The usual doses employed were 150 grams, and later 100 grams. The former dose contains 100 grams of desiccated stomach muscle (equivalent to 300 grams of the fresh product), the remainder consisting of added chocolate and lactose.

The bulk of both these preparations can be considerably reduced by omitting the chocolate and lactose, but this is of little advantage in practice.

The following cases are typical examples from my series.

CASE V.

The illness in this patient—a woman teacher, aged 47—commenced in May, 1926, with soreness of the tongue and mouth, which continued with remissions for fourteen months. From this time onwards she was troubled with weakness and lack of

energy to such an extent that most of her week-ends were spent in bed, although she managed to remain at her work. In April, 1929, she had an attack of jaundice which lasted for five weeks, although the yellowish colour had never been completely lost. She had had tinglings and numbness in the hands and feet for several years, together with some indigestion and flatulence, and in the summer of 1929 complained of pain in the chest and both iliac fossae. The bowels had been constipated, and vomiting had occurred at irregular intervals after food. She had suffered from cystitis and pyelitis in 1927. There was nothing of note in the family history.

Examination.—Her tongue was clean, no evidence of glossitis; teeth good; skin lemon yellow colour; nothing else found abnormal.

CHART 4.

Van den Bergh reaction: delayed direct. Radiological examinations of alimentary tract and gall-bladder were negative. A blood count showed: red blood cells 1,890,000 per c.mm., white blood cells 5,300; haemoglobin 55 per cent.; colour index 1.45; platelets very scanty; anisocytosis and poikilocytosis very marked; no nucleated red cells. Fractional gastric analyses showed complete achylia.

This patient was sent into hospital as a case of cholelithiasis, but the diagnosis was obviously one of pernicious anaemia. She had not had any liver therapy.

For the first ten days she was given hydrochloric acid and pepsin with each meal without response. This was then amplified by the addition of 110 grams of desiccated mucous membrane (preparation A) of hog's stomach daily, but was later reduced to 100 grams daily. Chart 4 shows the almost immediate response in the reticulocyte percentage, and the progressive rise in the erythrocyte count. There was no secondary rise in the curve after it had fallen to normal (less than 1 per cent.), where it remained subsequently. The clinical condition began to show an extremely rapid rate of improvement, the paraesthesiae and icteric colour having completely disappeared within a week after the commencement of the treatment.

After thirty-five days the patient had shown an increase from 1,890,000 to 4,136,000 erythrocytes per cubic millimetre, and was discharged from hospital.

CASE VI.

An engineer's fitter, aged 45, complained of excessive tiredness after work or exercise, together with a feeling of "being run down" during the six weeks prior to admission to hospital.

Since that time he had become progressively worse, and had noticed that he was getting paler in colour and very anaemic. There was dyspnoea on slight exertion, and a history of swelling of the feet and ankles, and much indigestion. There had not been any cough, pain, loss of weight, nausea, vomiting, diarrhoea, or paraesthesia. His bowels were regular. His previous medical and family histories contained nothing of note.

CHART 5.

Examination.—He had pale yellow sclerotics, with faint yellow colour in the skin; teeth artificial; tongue clean, dry; no oedema; liver enlarged; spleen just palpable; nothing else abnormal. The blood Wassermann test was negative. Radiological examination of the alimentary tract was negative. A blood count showed: red blood cells 1,224,000 per c.mm., white blood cells 6,100; haemoglobin 45 per cent.; colour index 1.8; platelets very scanty; anisocytosis and poikilocytosis very marked; nucleated red cells, megaloblasts, polychromasia, and punctate basophilia all present. Fractional gastric analyses showed complete achylia.

The patient was treated with desiccated stomach muscle (preparation B), initially 150 grams daily, with a rapid response in both erythrocyte and reticulocyte counts. The reticulocytes (Chart 5) rapidly rose to 28.3 per cent., but had not reached a normal level again until the twenty-eighth day after commencement of the treatment, when the dosage was reduced to 100 grams daily. The red blood cells rose steadily and progressively until their count was 4,008,000 per c.mm. on the thirty-seventh day, when the patient was discharged from hospital.

Summary.

The present communication is a summary of the results obtained in a preliminary series of nine cases of pernicious anaemia. These were divided into three groups, which were treated respectively with (a) normal gastric juice, (b) raw fresh mucous membrane or muscular layer of hogs' stomachs, and (c) desiccated preparations from these two portions of the stomach of the hog.

The results were controlled by daily reticulocyte counts, frequent regular full blood examinations, and the clinical conditions of the patients, both before and after discharge from hospital.

Cases of pernicious anaemia in various stages of the disease have been examined, and the final results obtained in all cases are at least equal to, whilst the immediate clinical results appear to be distinctly better than, those obtained in corresponding cases on a fresh liver diet.

Representative cases from each group under observation have been described to illustrate points brought out in the present communication.

It is not proposed to discuss here the theoretical considerations raised until the series has been extended more fully. Briefly, however, the results are these:

1. Normal gastric juice (150–200 c.cm. daily with meals) has given a definite improvement in the clinical condition, blood picture, and reticulocyte response slightly better than is observed with a fresh liver diet under similar conditions. This tends to support some of the observations made by Castle.

2. Hydrochloric acid and commercial pepsin alone have no effect in the improvement of the haematological condition of pernicious anaemia, nor are they essential for successful treatment with stomach of the hog.

3. The mucous membrane and the muscular layer of the stomach of the hog are both active in the treatment of pernicious anaemia. The results so far obtained show that this diet, weight for weight, is at least equal to or better than a liver diet.

4. Similarly, desiccated preparations of these two separated portions of hog's stomach are potent in the successful treatment of the disease. This form is convenient and easy to administer.

5. Clinically there is little difference in the potencies of all the preparations of hog's stomach described above, whilst fresh stomachs, both whole and dissected, have been kept for several days at a low temperature without noticeable loss in activity.

6. Compared to liver, the results appear to be slightly better, and the improvement in the condition of the patients in my short preliminary series has certainly been more rapid with hog's stomach therapy. Glossitis and paraesthesiae, in particular, have been found to respond more readily.

7. Since both the peptic-enzyme-containing (mucous membrane) and the non-peptic-enzyme-containing (muscle) portions of the stomach of the hog are active, they may be placed in the same category as liver and kidney as very potent sources of the active haematopoietic substance.

8. Eosinophilia occurs with this form of therapy as with liver.

It is proposed to give fuller details at a later date of these investigations, together with certain other work now in progress, when the series will have been much extended.

I have again to thank the honorary physicians of the Manchester Royal Infirmary for kindly allowing me to use their patients in this investigation, Professor H. S. Raper, F.R.S., for his unflinching interest and help, and Drs. Agnes Bodoano and Bessie Cadness for their careful determinations of the reticulocyte and blood counts. I gratefully acknowledge, also, the invaluable assistance rendered by Messrs. Benger's Food, Ltd., of Manchester, and Dr. Bullock, who kindly went to considerable trouble to prepare for me the desiccated preparations from the fresh hogs' stomachs.

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THE INJECTION CURE OF HYDROCELE.

BY

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It must be presumed that the old procedure of injection for the cure of hydrocele of the tunica vaginalis was unsatisfactory, either because of the uncertainty of its results or on account of its painful character, and it fell into disuse. The substitution of operative measures, while satisfactory in their respective technique and results, was a somewhat severe procedure for old patients. The use of general anaesthesia, the stay in bed for some ten days or longer, and the difficulty in finding hospital accommodation for such cases, made the need for a simpler procedure desirable.

The risk of general anaesthesia might be obviated by the substitution of local, which was entirely satisfactory, but the period of convalescence was not abolished. An extended use of quinine and urethane for the injection of varicose veins suggested that one had a solution which might serve an equally useful purpose to damage the endothelium of the tunica, and that with a minimum of pain and reaction.

The method was first tried in June, 1928, at the Royal Victoria Infirmary, on a patient aged 54, who had had a right hydrocele for two years, during which time it had been tapped ten times. It regularly filled up in two months. A small area of the front of the scrotum was infiltrated with novocain, and the tunica tapped by the ordinary hydrocele trocar. As far as possible the tunica was emptied and 2 c.cm. of quinine and urethane introduced through a spinal anaesthetic needle passed through the cannula. The needle was withdrawn, and later the cannula, care being taken to avoid any contact between the solution and the other tissues. By gentle massage the solution was distributed over the whole surface of the tunica. Fluid gradually re-accumulated and was aspirated seven days later, and was found to be slightly turbid. No pain, discomfort, oedema, or fever was manifested, and the patient was then discharged. At the present time, eighteen months later, there has been no return of the fluid.

Shortly after, a second case, a patient aged 72, in whom the hydrocele had been present for some years and who had been tapped several months before, presented himself with the tunica again very tense and about the size of a coco-nut. A similar procedure was carried out, except that the hydrocele was aspirated through a spinal anaesthetic needle and injected through the needle without withdrawal—that is, by means of a single puncture. No pain was experienced. Fluid again accumulated and was aspirated a week later, it being slightly turbid as in the first case. At the present time there has been no return of the fluid; the testicle is slightly thickened, but a suspensory bandage previously worn has been discarded.

The first patient was admitted to hospital as a precaution, but all others have been dealt with as out-patients, and the treatment in no way interfered with their ordinary duties.

Since then three further patients have been treated, over a year ago, with correspondingly satisfactory results; although tapping was practised after operation in these cases, further experience may prove that this is unnecessary, the fluid being gradually absorbed.

It appears that we have now a satisfactory injection treatment for hydrocele, which is painless and, like the similar method in use for varicose veins, can be carried out without invalidity.