adjustment to secure that neither too much nor too little water is reabsorbed, and a small error by way of excess in reabsorption throughout the day will result in a real retention of water and salt in the body so long as sufficient quantities of these are taken in.

The effects of this view of functional activity may be matched in a general way with the anatomical features which the hydropigenous nephritides possess in common—namely, diffuseness of lesion and the persistence in bulk of tubular or reabsorbing tissue. Considered more in detail, it fits in very well with the three conditions showing some degree of blockage of glomerular capillaries, especially for the stage most difficult to explain—namely, where there is already oedema and water and salt retention, but sufficient excretion of urea. Here we may suppose that, owing to partial blockage of capillaries, the tufts can no longer produce a sufficient amount of filtrate by working in relays as normally, but all have to be perfused continuously, possibly with the aid of increased blood pressure. A normal total amount of filtrate with a sufficient total amount of urea is thus being produced, but it is distributed to all the tubules instead of to the smaller number, a third or a fourth, corresponding to the number of tufts normally functioning at a time. The opportunity for reabsorption is thereby increased. With a worsening lesion of the tufts this system would still carry on with a rise of blood urea, for a greater percentage of urea in the original filtrate would mean an equal total elimination from a less amount of fluid. Ultimately, however, definite urea retention would show, as it often does, in later periods of acute and subacute glomerulonephritis. This may be regarded only as a type of explanation, and is by no means necessarily the correct one: it would not apparently apply to the elucidation of conditions in nephrosis. On the other hand, in nephrosis the anatomical fact of apparent freedom of circulation seems to demand excessive reabsorption as the likeliest explanation for the oliguria, especially with urea excreted normally. The imbalance of reabsorption and filtration may well be produced on some less obvious principle.

The account which has been given in opening this discussion is doubtless open to the charge of bias in favour of a renal retention origin of renal oedema. It would, however, have been difficult in the time available to do justice to all the more important theories, and at the same time convey an idea of the need for reconsideration of certain important dicta. It is hoped that some of the arguments brought forward will be accepted as justifying the view that some reconsideration is possible. As a minor form of excuse for attacking the purely extrarenal theories, it may be urged that while these have been highly developed and made to assume great probability, they are diverse and probably cannot all be correct, while none of them produces a principle applicable to all stages of the oedema. In the end, when it is desired to remove the pathological accumulations of fluid, it is to the kidney that appeal has to be made, and if diuresis cannot be established the condition remains essentially unchanged.

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AUTOLYSED YEAST PRODUCTS IN THE TREATMENT OF ANAEMIA

BY

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The number of publications which have appeared within the past two years regarding the value of vitamin B preparations, especially those derived from yeast, in the treatment of anaemia is evidence of the interest which the problem has aroused in the minds of clinical haematologists and laboratory workers alike. In view of the scientific and practical importance of the subject, and the fact that considerable divergence of opinion exists regarding the therapeutic efficiency of such products, the time appears ripe for a review of the whole problem.

YEAST PRODUCTS IN THE ANAEMIAS

I. HYPOCHROMIC ANAEMIA

(a) The milk anaemia of rats. Parsons¹ has shown that when yeast is added to the milk diet the anaemia is cured, growth proceeds satisfactorily, and reproduction may occur. The progeny, however, develop anaemia. This can be prevented by supplying iron as well as yeast to the pregnant mother rat.

(b) Nutritional anaemia of infants. Although the hypochromic anaemia of milk-fed rats and infants appears to be similar, since iron deficiency is the essential feature, Parsons found that yeast products generally failed to influence the nutritional anaemia of infants, which, however, responded to adequate doses of iron. In a few resistant cases the supplemental effect of adding yeast or copper, or both, to the iron ration appeared to produce beneficial results.

(c) Iron-deficiency anaemias of adults. In 1931 I published the results of my investigations² into the therapeutic value of yeast preparations in the treatment of hypochromic anaemia in adults, particularly of the type associated with achlorhydria. Marmite was found to be as useless as liver extract in the treatment of hypochromic anaemia, a point on which all workers in this field agreed.

II. HYPERCHROMIC MACROCYTIC ANAEMIA

Wills³ showed that the tropical macrocytic anaemia of Indian women responded to small doses (12 to 30 grams) of autolysed yeast product (marmite), by showing a

reticulocyte crisis and a rise in the blood level as prompt and as satisfactory as that obtained by liver extract. Similar results have been reported by Vaughan and Hunter⁴ in the macrocytic anaemia which is found occasionally in coeliac disease; and by Castle and Rhoads⁵ in cases of sprue. Mudaliar and Rao,⁶ however, found in eleven cases of pernicious anaemia of pregnancy that marmite in doses of one drachm three times a day was ineffective, although only one of them failed to respond to subsequent liver treatment. Parsons¹ treated two infants suffering from a macrocytic hyperchromic anaemia with a yeast product, for one and four months respectively, with negative results.

For the purpose of the discussion which follows, Castle's⁷ hypothesis regarding the aetiology of pernicious anaemia is accepted—namely, that megaloblastic blood formation is due to a lack of some specific anti-anaemic factor which is formed by the interaction of a ferment secreted by the stomach (intrinsic factor) upon some constituent of the proteins of foodstuffs (extrinsic factor). In the above types of anaemia the gastric secretion appears to be normal, and the deficiency of the specific anti-anaemic factor is the result of a lack of extrinsic factor consequent upon dietary deficiency or imperfect assimilation from the gastro-intestinal tract. In Addisonian pernicious anaemia the essential fault lies in defective gastric secretion, while failure in absorption plays a minor part in the pathogenesis of the disease.

Contradictory results regarding the therapeutic value of yeast products have been published. Thus Goodall⁸ and Ungley⁹ report some successes when large amounts of marmite were administered daily, while Castle¹⁰ and Groen,¹¹ using smaller amounts, have only recorded failures, although the same quantity of marmite incubated with normal gastric juice was found to produce positive results. Having previously reported two successes and several failures,^{2,12} I came to the conclusion that autolysed yeast products could not be considered in their present form to be substitutes for liver extract. In addition—for reasons which need not be recapitulated here—the conclusion was reached that “it is highly improbable that vitamin B and the anti-anaemic factor are in any way related,” a view which has been substantiated by the recent work of Lucy Wills and of Groen.

Sixteen cases of pernicious anaemia treated with autolysed yeast products or alcoholic extracts made therefrom form the basis of this communication. The diagnosis was based on a full clinical and haematological examination, including red and white cell counts, haemoglobin estimation, colour index, cell volume index, iron index, estimations of cell diameter, van den Burgh reaction, and gastric analysis. Blood counts and reticulocyte counts were made every second day throughout the test periods.

To those who were present at the meeting of the Association of Physicians of Great Britain in 1933 it is clear that considerable misunderstanding exists among different workers regarding the dosage of yeast products employed. This confusion is also apparent in the literature on the subject. Thus Ungley stated that the amount of marmite administered by him daily was four ounces, while Goodall stated that the amount given to his cases was one and a half ounces. It now transpires that Ungley refers to weighed quantities (four ounces equals 120 grams), while Goodall was referring to tablespoonfuls. An average tablespoonful of marmite weighs about 50 grams. I used the term “drachm,” meaning a teaspoonful, while the “drachm” referred to by Wills¹³ in her latest communication is a weighed measure equalling 4 grams. One average teaspoonful of marmite has been found by me to weigh approximately 15 grams. Castle and Groen of Amsterdam report their dosages in grams. For purposes of comparison I have estimated all the amounts published by the different workers in terms of grams.

SURVEY OF CASES

Below are given case records showing the therapeutic effects of autolysed yeast products (marmite) and extracts made therefrom. For the final proof regarding the potency of any agent it is necessary to show in cases where no response is elicited that an effect can be produced when a known active preparation is subsequently used. A short note on each case is accordingly necessary.

Case 1.—A. G., aged 62, was admitted to hospital with a red cell count of 1,000,000 and a haemoglobin of 28 per cent. Liver extract was given for eight days; a 20 per cent. reticulocyte crisis resulted, and a gain of 1,800,000 red cells occurred in twenty-four days. After a control period of twelve days, treatment with marmite (45 grams daily) was begun, and as no change occurred in ten days the patient was given liver and liver extract, iron being added later, with the result that his blood count rose to: red cells, 5,000,000; haemoglobin, 100 per cent. The patient was still at this level one year later.

Case 2.—G. G., aged 65. Blood count on admission to hospital: red cells, 2,120,000; haemoglobin, 48 per cent.; colour index, 1.15; white cells, 3,750; reticulocytes less than 1 per cent. After three weeks' treatment with marmite (45 grams daily) the count was: red cells, 1,790,000; haemoglobin, 53 per cent.; colour index, 1.51; reticulocytes less than 1 per cent. The patient was then given a series of injections of campolon, which produced an increase of 2,500,000 red cells in three weeks.

Case 3.—W. T., aged 70. Blood count on admission to hospital: red cells, 1,840,000; haemoglobin, 43 per cent.; colour index, 1.19; white cells, 3,430; reticulocytes, 1 per cent. Fourteen days' treatment with marmite (45 to 90 grams daily) produced no change in the blood level. Accordingly, the patient received seventeen daily injections of campolon, which resulted in a reticulocyte crisis on the seventh day and a gain of 1,800,000 red cells in four weeks. The patient has been taking two pounds of liver weekly for the past nineteen months. Blood count on July 17th, 1932, was: red blood cells, 4,400,000; haemoglobin, 92 per cent.

Case 4.—W. S., aged 55. Blood count on admission to hospital: red cells, 2,210,000; haemoglobin, 66 per cent.; colour index, 1.5; reticulocytes less than 1 per cent. No response having been obtained as a result of giving large doses of marmite (120 to 180 grams daily) for fourteen days, the patient was given half a pound of liver daily. A gain of 1,000,000 red cells was observed in sixteen days. As the patient was a bad case of subacute combined degeneration, injections of liver extract were then started, and a further gain of 1,000,000 red cells occurred in nine days.

Case 5.—Miss C. S., aged 36, has been under my charge in three severe relapses. In the first one she responded to ventriculin with a 50 per cent. reticulocyte crisis, but failed to continue treatment after she left hospital, to which she returned some months later with a blood count of 700,000 red cells. She responded with a 36 per cent. reticulocyte crisis to treatment for ten days with a dogfish-liver extract made in Aberdeen, gaining 1,800,000 red cells in three weeks. When the blood count was stationary at 2,500,000 red cells large doses of marmite (180 grams daily) were given for fourteen days with no effect. On discharge, treatment with a new preparation of desiccated hog's stomach was begun, and in fourteen days she gained 750,000 red cells. She was then given “pepsac,” one tablespoonful twice daily, and as the blood level began to fall this was increased to three tablespoonfuls daily. Some of this was lost by vomiting, and the patient was readmitted to hospital on June 15th, 1933, with a red cell count of 1,400,000; haemoglobin 30 per cent. Hepatex was given intravenously and intramuscularly on alternate days, and a 25 per cent. reticulocyte crisis occurred on the eighth day, with a gain of 2,200,000 red cells in twenty-five days.

Case 6.—J. S., aged 45, was admitted to hospital with a blood count of 1,100,000 red cells, haemoglobin 30 per cent. Large doses of marmite (90 grams daily for ten days, and 180 grams daily for eight days) were administered, with no result. The patient was then treated with an autolysed yeast product, which had been activated with hog's stomach tissue. The result was negative, and Dr. Groen of Professor

Snapper's clinic, Amsterdam, also found this batch inactive, although a previous preparation, made by N. V. Organon, had been effective. The patient was next treated for ten days with 60 grams of marmite which had been incubated with gastric juice withdrawn from a case of pernicious anaemia that had recovered the power of secreting hydrochloric acid. Details of this case have already appeared separately in a previous issue of this *Journal*.¹⁴ Reticulocytes increased to approximately 10 per cent. on the fifth day, and a gain of half a million red cells was made within a week. This clearly proved that the donor of the gastric juice had recovered the power of secreting some intrinsic factor as well as hydrochloric acid. The patient was then

4,100,000 red cells, 90 per cent. haemoglobin, when the patient left hospital.

Case 8.—Mrs. I. T., aged 54, was a very bad case of subacute combined degeneration of the cord. Her blood count on admission was: red cells, 4,050,000; haemoglobin, 88 per cent.; colour index, 1.1. Treatment with marmite (90 grams daily) for thirty-three days, failed either to raise the blood level materially or to improve the neurological manifestations. Since leaving hospital she has continued marmite in smaller doses (45 grams daily), and also iron, liver, and pepsac, with little real improvement in her clinical condition.

Case 9.—Mrs. E. A., aged 47, a severe case of subacute combined degeneration, was admitted to hospital with a

given a series of injections of hepatex intravenously and intramuscularly, and a gain of 1,500,000 red cells and 20 per cent. haemoglobin occurred in fourteen days. Liver, half a pound four times weekly, and pepsac on alternate days, rapidly caused the blood level to exceed 4,000,000 red cells (see Graph).

Case 7.—G. McC., aged 61, was admitted to hospital with a blood count of: red cells, 1,890,000; haemoglobin, 50 per cent.; colour index, 1.32; white cells, 3,750; reticulocytes, less than 1 per cent. Twenty days' treatment with marmite in small doses (45 grams daily) failed to produce any alteration in the blood level. The patient was given liver extract for one week, which caused his blood count to rise to: red cells, 2,520,000; haemoglobin, 50 per cent. Treatment with marmite (90 grams daily for fourteen days) was again totally ineffective. He was subsequently treated with liver, liver extract, and iron, and the blood count rose slowly to

blood count of: red cells, 3,500,000; haemoglobin, 72 per cent.; colour index, 1.03. Treatment with 90 grams of marmite for twenty-six days failed to produce any haematological or neurological improvement. Treatment at home with campolon, liver, and iron produced a slow and poor haematological response, with no change in the neurological manifestations.

Case 10.—Miss A. D., aged 57, was transferred to my ward, having failed to improve on liver extract in another department of the hospital. A history of diarrhoea during childhood, increase of fat in the stools, and osteoporosis of the bones suggested that the macrocytic anaemia might be due to Gee's disease. Achylia gastrica was present. Blood count on admission was: red cells, 2,990,000; haemoglobin, 68 per cent.; colour index, 1.15. Treatment with marmite for seventeen days (45 grams daily for fourteen days, and 135 grams daily for three days) was ineffective, the blood

count being lower than when treatment started. Intensive treatment was then given with liver, liver extract by mouth and injection, and iron, and this resulted in a gain of 1,800,000 red cells in about six weeks. Blood count on July 17th, 1933: red cells, 4,630,000; haemoglobin, 80 per cent.

Case 11.—D. S., aged 42, was an example of very severe subacute combined degeneration of the cord. On July 6th, 1932, the patient was admitted to hospital with a blood count under 1,000,000 and slight neurological changes. Treatment for five days with a fish-liver extract made in Aberdeen was followed by a gain of 1,600,000 red cells and 40 per cent. haemoglobin in seventeen days. After leaving hospital the patient failed to carry out the treatment recommended to him, and returned in a paralysed condition six months later. The blood count was: red cells, 3,210,000; haemoglobin, 79 per cent.; colour index, 1.23. He was treated with large doses of marmite (45 grams daily for ten days, 60 grams daily for five days, and 180 grams daily for eight days), but this failed to produce any haematological or neurological improvement. Diarrhoea and vomiting started. He was then given an alcoholic fraction of marmite (referred to below) for twenty-two days, with no effect. He subsequently responded slowly to liver, liver extract, and iron, gaining 1,600,000 red cells and 25 per cent. haemoglobin in two months, with some improvement of the central nervous system manifestations.

Case 12.—N. D., aged 56, was admitted to hospital with a blood count of: red cells 1,810,000; haemoglobin 49 per cent.; colour index, 1.36; reticulocytes less than 1 per cent. He failed to react to seven days' treatment with marmite (45 to 90 grams daily), and also to a further week's treatment with fractioned marmite (referred to below). He was then treated with a preparation of marmite activated with hog's gastric tissue (made by N. V. Organon), with some slight degree of response. He was finally treated with pepsac and liver extract, on which he gained 1,500,000 red cells and 25 per cent. haemoglobin in forty days. He reported at the blood clinic on July 15th, 1933, when his blood count showed 4,220,000 red cells and 98 per cent. haemoglobin.

Case 13.—Mrs. M. S., aged 50, was admitted to hospital with a blood count of: red cells, 2,400,000; haemoglobin, 54 per cent.; white cells, 2,600; reticulocytes, 12 per cent. Patient had been taking liver for five days before admission. After a control period of fifteen days the blood count was stationary at: red cells, 1,930,000; haemoglobin, 56 per cent.; reticulocytes 1 per cent. Treatment for ten days with a 65 per cent. alcoholic extract from 100 grams of marmite daily produced no change in the blood level. Since Case 15 (see below) had responded excellently and remained well for 435 days on 45 grams of marmite daily, it was decided to test his gastric juice for intrinsic factor. Accordingly gastric lavage was carried out at night, and every morning for eight days injection of three-quarters of a milligram of histamine was given subcutaneously and the stomach contents removed. Owing to a rapid emptying rate, or to a failure in secretion, only 30 to 40 c.cm. of gastric juice were obtained daily, which had no free hydrochloric acid or pepsin. The alcoholic extract from 100 grams of marmite was mixed with the gastric juice, incubated for two hours at 37° C., and the mixture transferred into the stomach of Mrs. M. S. through a duodenal tube every morning for eight days. No change in the red cell or reticulocyte count occurred. The experiment, therefore, failed to demonstrate the presence of intrinsic factor in the gastric juice of Case 15. (Whether this failure was really due to a complete absence of intrinsic factor, or whether the small quantities of gastric juice obtained contained insufficient intrinsic factor to activate the marmite, is a problem which unfortunately cannot be answered.) Mrs. M. S. was next treated with a liver extract made by hydrolysing liver with N/50 hydrochloric acid for ten days, according to the method described by Herron and McElroy.¹⁵ The filtrate from 9 lb. of hydrolysed fish liver was given during a period of six days, with an insignificant effect, although the originators of this method claim that by its use markedly increased potency results. The patient was then given liver and liver extract, which resulted in an increase of 1,600,000 red cells and 17 per cent. haemoglobin in seventeen days* (see Graph).

Case 14.—Miss J. F., aged 60, was admitted to hospital with a blood count of: red cells, 720,000; haemoglobin, 18 per

cent. She was treated with a fish-liver extract for seven days. This resulted in a 25 per cent. reticulocyte crisis and a gain of 2,500,000 red blood cells in three weeks. After a control period in which the blood count was stationary, marmite therapy (45 to 90 grams daily) was instituted, and the patient gained 500,000 red cells and 20 per cent. haemoglobin in three weeks. The patient returned home with instructions to take marmite, and she remained well for some months. Six months later she died, the cause of death, according to a relative, being kidney disease.

Case 15.—J. C., aged 62, was admitted to hospital with a blood count of 1,000,000 red cells and 26 per cent. haemoglobin. He was placed on small doses of marmite (45 grams daily). The reticulocytes rose to 16 per cent. on the eighth day, and he gained 3,200,000 red cells and 64 per cent. haemoglobin in forty-five days. He left hospital, and for the past eighteen months has taken no liver or liver extract. Two hundred and thirty days after discharge his blood count was 3,500,000 red cells, 90 per cent. haemoglobin, and it transpired that he was taking only one and a half teaspoonfuls of marmite daily. This was increased to three teaspoonfuls daily, and 435 days after discharge (on July 12th, 1933) his blood count was 4,500,000 red cells, 98 per cent. haemoglobin. He was in perfect health, and showed no signs of subacute combined degeneration of the cord.

Case 16.—W. G., aged 51, was admitted to hospital with a blood count of: red cells, 1,760,000; haemoglobin, 48 per cent.; colour index, 1.37; white cells, 2,800; reticulocytes less than 1 per cent. He was treated with fractioned marmite (referred to below) for nineteen days, with a gain of 1,000,000 red cells. He was then unsuccessfully treated with marmite (90 grams daily) for thirteen days. A further nineteen days treatment with fractioned marmite resulted in a further gain of 1,000,000 red cells. Twenty-eight days' treatment with 35 grams of marmite daily resulted in an insignificant rise in the red cell level and a gain of 12 per cent. haemoglobin. The patient was placed on two tablespoonfuls of pepsac four times weekly and half a pound of liver on two days, but his blood count remained stationary at 4,000,000 red cells, 99 per cent. haemoglobin. He was then given two pounds of liver and two ounces of pepsac weekly, and fourteen days later (on July 17th, 1933) the blood count was: red cells, 4,560,000; haemoglobin, 100 per cent.

SUMMARY OF RESULTS

Group I.—Cases 1, 2, 3, 4, 5, 6, and 13 failed to respond to marmite or an extract made therefrom, but responded rapidly and well to the anti-anaemic factor contained in liver, liver extract, or hog's stomach tissue.

Group II.—Cases 7, 10, 11, and 12 failed to respond to marmite, but did so satisfactorily to the administration of anti-anaemic factor. The response was, however, slower, and the effective dosage required was greater than in the cases in Group I.

Group III.—Cases 8 and 9 failed to respond to marmite, either haematologically or neurologically, but other forms of treatment were also unsatisfactory.

Group IV.—Case 14 responded moderately well to marmite, while Case 15 gave an excellent response, and remained well for 435 days on a small maintenance dose. Case 16 responded to fractioned marmite (see below).

Fractioned Marmite.—Since the active principle in liver is water-soluble and precipitable in 95 per cent. alcohol, it was decided to extract marmite by the same method as was used for making liver extract. By this means marmite was concentrated to half its bulk. Cases 11 and 12 failed to respond to a daily dose of this fraction, made from 70 grams of marmite, which, however, was effective in Case 16. Case 13 was treated with the filtrate obtained from extracting marmite with 65 per cent. alcohol for twenty-four hours. The alcohol was evaporated and the patient received the filtrate from 100 grams of marmite daily for nineteen days. No improvement in the blood level resulted.

* On "Day 72" (see Graph) the actual count was: haemoglobin, 90 per cent.; red cells, 4,010,000.

Cases of Pernicious Anaemia-Treated with Yeast + Wheat Embryo (Dr. Ungley)

Case	Treatment	Duration	R.B.C.	Hb %	Reticulocytes
9. Atypical P. A. HCl present	Bemax, 160 grams	Days 1-7	1.4	38	0.6 per cent. 13.0 per cent.
		11	1.7	42	
11. P. A.	Bemax, 270 grams	1	1.02	36	Started to rise before treat- ment 11.8 per cent.
		11-20	1.4	48	
		32	?	?	
12. P. A.	Bemax, 123 grams	1-10	1.9 No change	50 No change	(1.8) 4.3 per cent. on 6th day; negli- gible rise
13. P. A.	Bemax, 240 grams	1-10	0.87 No change	18 No change	— No rise
10. Atypical P. A. HCl present	Marmite, 120 grams	1-31	1.6 2.83	43 75	3.0 per cent. 27.2 per cent. on 9th day
		84	4.43	81	
14. P. A.	Marmite, 60 grams	1-18	1.42 2.0	38 53	0.8 per cent. 13.1 per cent. on 10th day
15. P. A.	Marmite, 120 grams	1-44	1.16 2.5	30 68	1.8 per cent. 18.6 per cent. on 10th day
16. P. A.	Marmite, 120 grams	1-21	2.3 3.4	64 90	2.4 per cent. 12.0 per cent. on 9th day
17. P. A.	Marmite, 120 grams for 10 days, then 60 grams Marmite + iron further 28 days	1-10	2.69	70	Not observed
		10-25	2.89	80	
		25-63	3.27	84	
			3.41	84	
			4.53	96	
18. P. A.	Yestamin, 48 grams for 10 days. Marmite, 120 grams for 9 days	1-10	1.37	30	5.0 per cent. on 4th day
		11-19	No change	No change	No rise
19. Mrs. H. D., P. A.	Alcoholic extract of marmite from 120 grams for 42 days	1-10	1.65	45	(3.6)
		10-24	2.05	54	8.8 per cent. on 8th day
		24-42	2.45	64	
			3.58	50	
20. Mrs. H. S., P. A.	Alcoholic extract of marmite from 120 grams for 53 days	1-12	1.34	40	(3.7)
		12-22	2.26	56	27.2 per cent. on 10th day
		22-30	2.93	66	
		30-44	3.39	80	
		44-51	4.07	90	
		51-58	4.89	98	
			5.12	97	

RESULTS COMPARED WITH THOSE OF OTHER OBSERVERS

Through the kindness of Dr. Ungley⁹ I am able to show in the table an analysis of the blood examinations made by him in twelve cases of pernicious anaemia treated with various preparations rich in vitamin B' complex. The following conclusions appear to me to be justified: treatment with bemax in large quantities failed to produce any material rise in the red cell count in Cases 9, 11, 12, and 13, or in the reticulocyte percentage count of Cases 12 and 13. The reticulocyte crises which occurred in Cases 9 and 11 were subnormal in degree, and must be discarded for the present purpose—in Case 9, since hydrochloric acid was present in the gastric juice, and therefore possibly intrinsic factor, and in Case 11, because the rise began before treatment started. Marmite was used in large doses in Cases 10, 14, 15, 16, 17, and 18. The therapeutic effect was entirely negative in Case 18, but in the others a rise in the blood level occurred. For comparison it should be remembered that when adequate amounts of potent liver extract are given to a case with a blood count below 2,000,000 cells an increase of at least 2,000,000 cells should be obtained within thirty days. It will be seen from the Table that the therapeutic effects of marmite were slow and poor, and in no way comparable to this, since the increase of red cells in

Cases 14, 15, 16, and 17 was 0.5, 1.34, 1.1, and 0.72 million in 18, 44, 21, and 63 days respectively. The extent of the rise in reticulocytes was most marked in Case 10, in which free hydrochloric acid, and therefore possibly intrinsic factor, was present. In Cases 14 and 15 the reticulocyte crises were subnormal in extent and delayed in appearance. Cases 19 and 20 were treated with a 65 per cent. alcoholic extract of marmite. By this means the proteins are precipitated and the active principle can be obtained in a more concentrated and, therefore, more potable form. Case 19 showed a moderate response, while Case 20 responded excellently.

Goodall⁸ treated three cases of pernicious anaemia in the relapse stage with large doses of marmite (150 grams daily) and produced a definite rise in reticulocytes and red cells, which was, however, subnormal in quantity and delayed in time compared to what can be obtained from efficient liver therapy. Thus Case 1, despite a satisfactory reticulocyte rise, gained only 0.8 million red cells after four months' treatment; Case 2 gained 1.4 million red cells in forty-three days; and Case 3, after a satisfactory beginning in which a gain of 1.9 million red blood cells occurred in thirty days, progressed so slowly that the red cell count was only 3.7 million after 120 days' treatment. When Goodall combined intravenous liver therapy with marmite by the mouth the speed of blood regeneration was enormously increased: thus the fourth case in his series gained 3.8 million red cells in sixty days and the fifth case gained 2.5 million red cells in twenty-six days.

On the whole, Ungley and Goodall have had somewhat better results with marmite therapy than I have, although Case 15 of the present series shows, perhaps, the most dramatic effect so far published. This difference can be explained on two grounds—namely, the dose of material administered and the initial blood level at which treatment started. Castle and Groen's failures, and a few of mine as well, may be ascribed to insufficient dosage. This explanation cannot hold good for Cases 4, 5, 6, 7, 11, 12, and 13, in which doses as large as, or larger than, those used by Ungley were employed. The more likely cause of the discrepancy lies in the initial blood level at which treatment started, since it is universally recognized that small amounts of liver extract, which may cause a moderate reticulocyte rise and a small increase in the red cell count when the blood level is around 1,000,000, are totally ineffective when the blood count approaches 3,000,000. Only seven of the sixteen cases reported by me started marmite therapy with a blood count below 2,000,000, two of which approached the 1,000,000 mark. In Ungley's series of twelve cases ten started with a count below 2,000,000, seven of which approached the 1,000,000 mark. Accordingly, the chances of Ungley's cases showing some therapeutic effect from the administration of marmite were greatly increased. An examination of the case reports given above makes it certain that cases of pernicious anaemia in severe relapse may fail to respond to large doses of yeast products, and that others in the semi-remission stage, with blood counts between 2 and 3 million red cells, fail to improve, although subsequent treatment with active principle, in the form of liver, liver extract, or hog's stomach tissue, is entirely successful. Nevertheless, sufficient positive evidence has now been accumulated to establish the fact that marmite contains a small amount of an active principle which can stimulate blood formation in some cases of pernicious anaemia. Its concentration is poor, as judged by the large quantities of marmite which must be given, and in consequence its effectiveness is uncertain, and when an action is produced it is generally poor in quality and delayed in time.

DISCUSSION

NATURE OF HAEMOPOIETIC FACTOR IN MARMITE

If it is admitted that marmite has some therapeutic value in the treatment of pernicious anaemia it becomes necessary to identify the active principle. Yeast is known to be a rich source of the vitamin B complex, and it also contains iron, copper, and manganese, and the two proteins—zymocasein and cerevisine. Excluding the minerals, since they are definitely of no value in the treatment of the relapse stage of pernicious anaemia, the problem is narrowed down to vitamin B₂ and the yeast proteins or their katolytic products. It is unnecessary to recapitulate here the evidence which has accumulated during the past few years regarding the connexion which appears to exist between the active principle in liver and vitamin B₂. From his investigations into the characteristics and distribution of the extrinsic factor present in different substances, both animal and vegetable, Castle¹⁰ concluded that they correspond to those of vitamin B₂. The recently published work of Lucy Wills,¹³ however, is definitely against this hypothesis. She found the following vitamin B preparations therapeutically inactive in the tropical macrocytic anaemia of Indian women:

(a) Vitamin B₁ and B₂, made from rice polishings adsorbed on to china clay.

(b) Vitamin B₂, made from egg-white, in a concentration seven times greater than the vitamin content of 30 grams of marmite.

(c) Large doses of dried yeast or watery yeast extracts.

The cases subsequently responded adequately to 30 grams of marmite. Moreover, a case of pernicious anaemia treated with vitamin B₂ made from egg-white failed to react to the egg-white extract, either before or after incubation with 150 c.cm. of normal gastric juice, although a subsequent response was immediately obtained from liver extract.

Confirmation of these findings has been obtained by independent investigation by Dr. Groen¹¹ of Amsterdam, whose unpublished results I have the privilege to report. The results of treatment in ten cases of pernicious anaemia may be summarized as follows:

(a) Marmite (24 to 36 grams daily) was inactive, but when incubated with 150 c.cm. of gastric juice an immediate response resulted (four cases). Autoclaving did not destroy the active principle.

(b) Dried yeast in doses of 60 to 75 grams, either in the form of watery extracts or 50 per cent. alcoholic extract, was inactive even when incubated with 150 c.cm. gastric juice. The patients immediately responded to marmite and gastric juice or to liver extract (four cases).

(c) Egg-white from twelve to twenty eggs, plus 150 c.cm. gastric juice, was inactive; a satisfactory response to liver extract subsequently resulted (two cases).

Lastly, Chick and Copping¹⁴ have shown that vitamin B₂ in watery yeast extracts is rapidly destroyed or inactivated by 70 per cent. alcohol, whereas the active principle of marmite is both alcohol stable and heat stable.

For the above reasons it may safely be concluded that the haemopoietic factor in liver, liver extract, and marmite is not vitamin B₂. A personal communication from Strauss and Castle, received on July 15th, 1933, indicates that these writers have also come to the same conclusion. Since dried yeast—or watery extract of yeast—is therapeutically inactive, but autolysed yeast products are active, it follows that the active principle is manufactured during the process of autolysis, in which case it must be a protein breakdown product of the nature of a polypeptide. Further researches into its character are required before any definite conclusions regarding its composition can be arrived at. If the active principle of marmite is the same substance as the anti-anaemic factor of liver extract, we must assume, on Castle's hypothesis, that it

is produced by the action of yeast enzyme (intrinsic factor) on yeast protein (extrinsic factor) during autolysis, and the therapeutic failures, either absolute or relative, reported above, must be dependent on insufficient dosage of the active principle due to its poor concentration. If, on the other hand, the active principle is merely concentrated extrinsic factor, variation in response to treatment must depend on the absence or presence of intrinsic factor in the patient's stomach. That autolysed yeast is a rich source of intrinsic factor is certain, since its concentration in marmite is twenty times greater than in beef protein. Moreover, small quantities of marmite which are therapeutically ineffective become effective after incubation with normal gastric juice or hog's stomach mucous membrane. Again, the rapidity, as well as the degree of response, obtained in the treatment of tropical macrocytic anaemia and the macrocytic anaemia of coeliac disease is so much greater than that occurring in Addisonian pernicious anaemia, even when much larger quantities of marmite are given, as to suggest that the amount of intrinsic factor present in the stomach is the factor upon which the response depends. That the intrinsic factor may be absent at one time and present at another has been demonstrated by Castle, a fact which was also shown in the experiments performed on Case 6. A partial return of the secretion of intrinsic factor supplies the most likely explanation of the natural remission and the maintenance of a normal blood level without treatment for months or years. It is always difficult to draw conclusions regarding the effects of treatment during remissions, but Goodall was impressed with the value of marmite in maintaining this stage, and has two patients who have kept well for one and two years respectively on small doses of marmite.¹⁶ Case 15 likewise maintained a satisfactory blood level for 435 days.

Finally, the fact that the best result recorded (Case 15) was obtained by administering marmite in amounts which were only from one-quarter to a half as great as those used by Ungley, suggests that some intrinsic factor was present in the patient's gastric juice which augmented the active principle of marmite. Unfortunately the experiment performed to prove this hypothesis failed (see Case 13). These observations suggest that the factor which decides whether a response to marmite therapy will occur, and if so in what degree, depends essentially on the ability of the stomach to secrete intrinsic factor. Sufficient evidence is not at our disposal to settle the difficult problem of the nature of the haemopoietic principle in marmite. It may eventually emerge that autolysed yeast products contain not only a large amount of concentrated extrinsic factor, but also a small amount of the specific anti-anaemic factor as well.

OTHER EFFECTS PRODUCED BY AUTOLYSED YEAST
PRODUCTS

(a) *Gastro-intestinal and Metabolic.*—In small doses (one teaspoonful three times a day—45 grams) marmite is pleasant to take, and the patients often feel improved in health even when the blood cell level remains stationary. Similarly, a gain in weight may occur, with or without haematological improvement. In large dosage (two to four teaspoonfuls three times a day, 100 to 180 grams) marmite is nauseating, and in some cases it causes gastro-intestinal irritation, as evidenced by vomiting and diarrhoea. Ungley also found similar effects. Accordingly, large doses are definitely contraindicated, except when for short periods observations are required for research purposes.

(b) *Neurological.*—Since vitamin B is the anti-neuritic vitamin, hope was entertained that such vitamin-rich substances as autolysed yeast products might be of benefit in the treatment of subacute combined degeneration of the cord. No improvement, however, was found to occur,

and in one case neurological symptoms became apparent for the first time during treatment. Similar results are reported by Ungley.

(c) *Haematological*.—A tendency for the colour index to rise under marmite therapy, due to the increase of haemoglobin in relation to red cells, is seen in cases reported by Goodall, Ungley, and myself. No satisfactory explanation for this is available. As previously noted, yeast products are valueless in the treatment of iron-deficiency anaemias in human beings.

CONCLUSIONS

The therapeutic effects of yeast products in different types of anaemia are reviewed. Records of sixteen cases of Addisonian pernicious anaemia treated with autolysed yeast products or alcoholic extracts made therefrom are described and compared with the results of other workers in this field. The conclusion is reached that such products contain some haemopoietic principle, the value of which is discussed, but its concentration is small, as judged by many therapeutic failures, relative or absolute. For this reason, autolysed yeast products in their present form should not be used as substitutes for liver, liver extract, or hog's stomach tissue in the treatment of pernicious anaemia.

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SOME NEW OBSERVATIONS ON THE DIAGNOSIS AND TREATMENT OF SYPHILIS*

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Contrary to the general impression, primary syphilis can cause symptoms before it has reached the stage when secondary signs are apparent. Anaemia, pains in the joints, persistent headache, nausea, and pyrexia occur in about 50 per cent. of primary cases, and in women these indications may justify the insertion of a vaginal speculum, which is essential if a chancre on the cervix is not to be overlooked.

It is commonly held that a primary lesion of the genitalia is always accompanied by a satellite bubo, but the absence of an inguinal lymphadenitis does not enable us to dismiss the possibility of syphilis. Internal chancres

drain into the common iliac and meso-rectal lymphatics, and even an external inoculation will cause enlargement of the inguinal glands only in about 40 per cent. of cases. To dismiss a sore on the external genitalia as being non-syphilitic because it is unaccompanied by an inguinal adenitis is therefore to incur error in a possible 60 per cent. of cases. To prevent these mistakes and to secure an accurate diagnosis at the earliest moment the dark-ground microscope must be used. Incidentally, many textbooks state that the enlarged glands which occur with a syphilitic chancre are small, hard, and shotty. On the contrary, they are generally large and elastic, and have a distinctive "indiarubbery" feeling which is characteristic of syphilis.

It is generally thought that the favourite site of inoculation is on the labia, but only 39.39 per cent. occur there, while in at least 44 per cent. of cases the primary lesion is on the cervix.¹ Owing to position, the majority of cervical chancres are undiscovered, or only diagnosed when the patient has developed secondary signs and symptoms. If the incidence of syphilis is to be reduced a larger number of these cases must be diagnosed during the first stage, so that the patient can be warned against infecting her consort. *The cervical chancre, hidden and painless, is the greatest cause of the spread of syphilis. It is the commonest source of infection because its presence is unsuspected by both sexes.*

In a series of 584 cases given by the author¹ the sites of primary genital chancres in women were distributed as follows:

	Number	Percentage
Cervix	257	44.00
Labia majora	183	31.33
Labia minora	47	8.06
Fourchette	33	5.65
Urethra	19	3.26
Clitoris	16	2.74
Vagina	8	1.37
Vestibule	6	1.03
Anus	5	0.86
Bartholin's orifice	4	0.68
Perineum	2	0.34
Thigh	2	0.34
Mons veneris	1	0.17
Buttock	1	0.17

Just as the varying gonococcal cervical discharge cannot be diagnosed by its clinical appearance so may cervical chancres range from an extensive carcinomatous-like ulceration to a small shallow abrasion. Irrespective of appearance, these clinical pictures are all deadly in their infectivity. However, certain characteristics of a cervical lesion—especially the edge and the colour—should rouse suspicion and urge us to "dark-ground" its serum. The edge of a cervical chancre, even when it is implanted on a pre-existing erosion, is generally well defined and regular. If the outline is carefully examined with magnifying spectacles, the defined regularity of the chancre's margin can be readily distinguished from the irregular raggedness of a non-syphilitic erosion. The colour of the erosive chancre, which is the common type of cervical chancre (about 71 per cent.),¹ is bluish-red, and is covered with small haemorrhagic spots, or, if it is not too recent, it may be covered with a thin greyish membrane, which also has a bluish tinge. The ulcerative type, which occurs in 24 per cent. of cervical chancres,¹ may be covered with a yellowish-grey slough, which only lasts for four or five days, and after that its base is covered by bluish-grey granulations which ooze blood and serum when touched. Although cervical chancres bleed easily those on the vulva do not. The bluish tinge of most cervical chancres is similar to the bluish colour of the congested vulva or cervix of a pregnant woman, but it is confined to the area of the chancre instead of affecting the whole cervix. This purplish or bluish hue, caused by the syphilitic infiltration of lymphatics and blood stasis, is a particularly

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