Case 17.—Female, 38 years. Abscess and sinuses of abdominal wall for 12 months. 600 units during 7 weeks, with sulphapyridine powder during part of time, almost ended profuse suppuration, closed sinuses and gape of wound, and improved general condition. (Mr. I. Price.)

Case 18.—Female, adult. Large breast abscess with much swelling of surrounding breast; incised and one pint of pus removed. 200 units of penicillium filtrate instilled twice a day during five days reduced discharge to a little sero-pus and brought surrounding tissues to normal. (Dr. G. M. Palser.)

Case 19.—Female, 65 years. Cellulitis and suppuration in resutured abdominal operation wound. Local treatment by sulphacetamide (albucid) and by eusol produced very slow progress during two months; 150 units during 5 days ended suppuration, reduced sinuses and gape of wound, and produced healing edge all round. (Mr. W. T. Kenny.)

Case 20.—Female, 17 years. Two abscesses in right breast. The larger, after incision, treated with 300 units during 3 weeks, healed well in spite of a near-by pocket requiring another incision. This illustrated need for close contact of penicillin with the suppurating lesion, and the result was considered only moderately successful. (Dr. G. M. Palser.)

Case 21.—Male, adult. Osteomyelitis of tibia greatly improved in healthy granulation by 170 units; unopened abscess produced septicaemia, successfully treated by sulphathiazole. Rapid healing of sinuses and abscess then resumed. Septicaemia recurred. Systemic administration of penicillin needed. (Mr. E. T. Bailey.)

Case 22.—Female, 40 years. Acute breast abscess. After incision, 200 units in 9 days, followed by healing not more rapid than normal. (Dr. G. M. Palser.)

Case 23.—Female, 10 months. Subacute suppurative cellulitis of temporal region and brain abscess (probably due to *B. necrophorus*). Profuse suppuration in muscles of temporal and pterygoid regions subsided to oedema after 80 units during one week, but pus had rapidly decreased previously without penicillin. Necrosis of mastoid cells found at operation, and child died same day. At necropsy a well-encapsulated abscess in temporal lobe of brain without apparent connexion with surface; no suppuration in tissues outside skull. Effect of filtrate doubtful. (Mr. McCrea.)

Case 24.—Male, elderly. Chronic osteomyelitis and sinus of thigh. Very little improvement with 280 units of filtrate in a week followed by 250 units of calcium salt, although *Staph. aureus* isolated was quite sensitive to penicillin. (Mr. E. T. Bailey.)

Comment

It is considered that in the first 19 of these patients the filtrate has been successful, sometimes to a quite unexpected degree; in the other 5 success was partial, doubtful, or absent. It is claimed, however, that this series shows that the effects expected of penicillin can be obtained by the unconcentrated filtrate when it can be applied locally to tissues infected with bacteria sensitive to it.

Since the filtrate can be readily produced and assayed in a bacteriological laboratory which has a well-trained staff, it can be used for local application to acute and chronic abscesses, sinuses, and ulcers as a substitute for the partially purified substance until the latter is available. Since the filtrate retains its potency at 4° C. for at least a week, it is possible to provide a steady supply by the production of one or two batches weekly.

A specimen was dried in several portions on April 25, 1944, in Major J. E. McCartney's laboratory by Mr. A. G. Rayner by the method which he recently described (A. G. Rayner, 1943), and when the dried substance is dissolved in sterile water some portions have retained full potency for 8 days, but others are found to have lost it entirely immediately after drying. This irregularity is being investigated.

It has been found in this series, as it has been by other observers, that, in the course of treatment of external lesions by penicillin, *B. pyocyaneus* becomes prominent and may hinder healing after the penicillin-sensitive bacteria have been reduced or banished. I have confirmed, by sensitivity tests similar to those used for assay of penicillin, that *B. pyocyaneus* (4 strains) is quite sensitive to saturated solutions (4%) of boric acid; and Dr. G. M. Palser has found in three patients that the boric acid solution reduced the suppuration due to *B. pyocyaneus* and permitted continuation of healing, although the organism recurred when boric acid was stopped before healing was complete. This seems worth further trial.

Summary

Crude penicillium filtrate containing 4 to 10 units of penicillin per c.cm. may be used successfully for treating many acute and chronic inflammations by local application, in place of the partially purified calcium salt of penicillin: the filtrate can be dependably produced and assayed in a bacteriological laboratory in useful quantities.

I wish to express thanks to the surgeons for their co-operation, to Drs. A. Martin and C. H. Carrington and others of Imperial Chemical (Pharmaceuticals) Ltd., for imparting much of their experience; to Dr. J. H. Waelsch and Mr. E. Martin for helpful suggestions; and especially to Mr. R. M. Sandercott for his enthusiasm in developing and carrying out the technical work.

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AUTOLYSED YEAST IN THE TREATMENT OF NUTRITIONAL MACROCYTIC ANAEMIA

BY

G. R. SIPPE, M.B., B.S.

(From the Bacteriological Laboratory, Reduit, Mauritius)

Nutritional macrocytic anaemia has been reported from India, China, Africa, and Macedonia, and there is strong evidence that it is a deficiency disease due to the absence of one or more essential vitamin-like factors in the diet. It will therefore tend to occur in communities where, for economic or other reasons, foodstuffs containing adequate supplies of these factors do not normally form part of the diet. Thus in the poverty-stricken areas of Macedonia, Fairley *et al.* (1938) found the condition to be common among refugee peasants, and Wills (1934) stated that it was especially rife in Southern India, where rice is the staple food. In Mauritius it is particularly common among those members of the community who, for religious reasons, do not include beef flesh in their diet. The condition is found in both sexes, and is most prevalent during the second and third decades. It is especially apt to appear during the latter half of pregnancy, and it is probable that in cases of malarial splenomegaly the disease is aggravated by excessive destruction of normal and abnormal erythrocytes by the hypertrophied reticulo-endothelial system (Fairley *et al.*, 1938; Hughes and Shrivastava, 1931).

Although it is agreed that nutritional macrocytic anaemia is a deficiency disease, the part played by the factor or factors whose absence is responsible for the condition is obscure. Autolysed yeast (marmite) (Wills, 1934) and crude liver extracts both produce a maximal reticulocyte response, and Wills found that the factor or factors were water-soluble, heat-stable in an acid medium, and partially resistant to autoclaving in an alkaline medium; and Formijne (1940) has shown that potent substances can be obtained by extraction of beef flesh with 70 to 80% alcohol, but that the potency is lost in concentrations of 90% alcohol.

Wills *et al.* (1937), in the course of experiments on rhesus monkeys suffering from an artificially induced anaemia which was considered to be the counterpart of nutritional macrocytic anaemia in man, found anahaemin to be ineffective. This was surprising in view of its efficacy in cases of Addison's pernicious anaemia. Trials with anahaemin in nutritional macrocytic anaemia in man have given variable results. Wills and Evans (1938) considered it to be ineffective, and Napier *et al.* (1938) stated that some cases responded well while others failed to show any response. Fairley (1940) found very large doses to be effective in an Indian suffering from the condition.

Wills *et al.* (1937), in further experiments with campolon, which was fractionated into soluble and insoluble portions by saturation with ammonium sulphate, found that the insoluble

portion (containing the major part of the anahaemin) was very potent in cases of pernicious anaemia and inactive in monkey anaemia, and that the soluble portion was active in both conditions. It is suggested that the potency of the soluble fraction may be due to some of the anahaemin in the crude extract not being precipitated, or to a new substance not precipitated by the ammonium sulphate.

It is possible that there are two essential factors in the diet (Wills *et al.*, 1937): one which reacts with the intrinsic factor to form the liver principle, and the other—also found in the crude liver extract and not precipitated by saturation with ammonium sulphate—which is necessary for the activity of the pure liver extracts. Probably the commonest source of these factors in the average diet is beef flesh, and it has been shown that autolysed yeast (marmite) is extremely potent in the condition under discussion. Watery yeast extract and dried yeast powder (Wills, 1934) are inactive.

In treating nutritional macrocytic anaemia, the reasons for the non-consumption of foodstuffs containing adequate quantities of the necessary factors—namely, economic hardship and racial and religious prejudice—must be closely borne in mind, and it must be remembered that the condition will relapse unless means are adopted for the continuous supply of the essential foodstuffs. Autolysed yeast would appear to be the ideal substance, as not only is it rich in the necessary factors and acceptable to all communities, but, on account of its cheapness, can readily be made available to all sections of the public. Autolysed yeast is also rich in certain members of the vitamin B complex, and in Mauritius has proved valuable in the treatment of pellagrous dermatitis and angular stomatitis and glossitis (Dr. André), two conditions which by virtue of the poor diet tend to occur in regions where nutritional macrocytic anaemia is found.

A number of cases of nutritional macrocytic anaemia have been treated with yeast obtained locally as a waste product in the manufacture of alcohol by fermentation of molasses. The yeast mixture is obtained from the bottom of the vat after fermentation has ceased and the top fluid has been run off. Normally this sediment is discharged on to the fields, where on account of its nitrogen content it has some value as a fertilizer. The sediment (yeast mixture) has the consistency of thin gruel and is brownish in colour. The taste is not pleasant, but when given with water and a little sugar the mixture is more palatable.

At present work is proceeding in an attempt to render the mixture more agreeable to the taste and to obtain it in a more concentrated form, since patients very occasionally are unable to take it on account of the vomiting and diarrhoea it may produce. This intestinal upset is probably due to the taste and acidity of the mixture, which has to be taken in comparatively large amounts, and to the insoluble material present in the residue. It is hoped that preliminary washing associated with some form of evaporation in pans, similar to that employed in the preparation of salt, may prove satisfactory.

Before use it is advisable to pass the mixture through a coarse filter, such as cheese-cloth or a fine screen. Afterwards it is sterilized at 70° C. for one hour, which not only kills any pathogenic organisms that may be present but also the yeast cells themselves, and autolysis is thus hastened. It is probable that liberation of the potent factor or factors occurs only after autolysis has taken place. In these experiments amounts of yeast sufficient for two to three weeks' treatment were prepared at one time and administration was started immediately after sterilization. No work has yet been done to ascertain whether prolonged keeping will increase the potency of the preparation. The quantity of the mixture necessary to produce a satisfactory blood response has been found to be from 3 to 6 oz. a day. In pregnancy, especially during the latter half, the bone marrow may fail to react even with very large doses, and this unsatisfactory feature has been noted by Davidson *et al.* (1942). It may be due partly to increased demands by the foetus for the liver principle and a temporary inhibition of the bone marrow during pregnancy, and partly to the absence of some essential factor in the diet.

Samples of yeast mixture from two separate distilleries (Nos. 1 and 2) were analysed, with the following results:

TABLE I.—Average Composition of Yeast Liquor

Liquor No.	Solids	Protein	Yeast (approx.)	Calcium	Phosphorus Pentoxide	Iron	Calcium Sulphate	Ash	Density
1	26.6	2.0	4.0	4.5	0.16	0.024	9.2	16.5	1150
2	15.6	4.0	8.0	0.6	0.23	0.040	—	3.0	1060

TABLE II.—Average Composition of Solids from Yeast Mixture

Liquor No. (% Solids)	Protein	Yeast (approx.)	Calcium	Phosphorus Pentoxide	Iron	Calcium Sulphate	Ash
1 (26.6)	6.74	13	18.4	0.65	0.09	32.0	57.20
2 (15.6)	27.38	54	3.9	1.50	0.27	—	19.25

In distillery No. 1 the molasses used for fermentation were obtained from a sugar factory producing white (bleached) sugar, and in No. 2 the molasses were from a factory producing raw (unbleached) sugar. The large amounts of inert calcium sulphate present in the sample from distillery No. 1 result from the bleaching process, and therefore are not found in the sample from the second distillery. In the experiments to date the yeast has been obtained solely from distillery No. 1, but it is proposed in future to use the mixture from distilleries of the second type in view of the much larger quantities of yeast present in the sediment.

The following are details of cases treated with this yeast sediment. Owing to the isolation of the laboratory from the hospitals, a full blood examination was not always possible, nor was a daily reticulocyte count practicable. All cases showed definite hyperchromia and marked macrocytosis and anisocytosis. In Cases 1, 3, 5, and 6 gastric analysis was carried out after the yeast treatment; in Case 4 it was done before treatment. Free acid was found in all. Patient No. 2 was unable to swallow the tube even after treatment had finished.

Case 1.—A male Moslem aged 43 had been for four months complaining of weakness, dyspnoea, and palpitations. When seen he was weak, and pallor of the tongue and conjunctiva was extreme. The spleen was not palpable. The blood findings were: R.B.C., 760,000 per c.mm.; Hb, 2.94 g. % (Sahli); W.B.C., 4,500 per c.mm.; mean corpuscular haemoglobin, 38.7 $\gamma\gamma$. A few trichuris eggs only were found in the stools, and the urine was normal. Yeast, 6 oz. a day, was ordered, but by mistake the patient actually took 8 oz. a day. After two weeks he began to improve rapidly, and eight weeks after starting treatment the blood findings were: R.B.C., 4,050,000 per c.mm.; Hb, 11.9 g. % (Sahli); W.B.C., 7,200 per c.mm.; M.C.H. 29.7 $\gamma\gamma$.

Case 2.—A male Hindoo aged 21 had complained of weakness, palpitations, and dyspnoea on exertion for the last three years. He was pale and weak when seen. The blood findings were: R.B.C., 720,000 per c.mm.; Hb, 4.34 g. % (Sahli); W.B.C., 6,150 per c.mm.; M.C.H., 60.0 $\gamma\gamma$; packed cells, 12.95%; mean corpuscular volume, 179.8 c. μ . No malaria parasites were found. The stool examination showed no ova or protozoa; the Kahn reaction was positive (+ +); van den Bergh, 1.75 mg. bilirubin per 100 c.cm. Yeast mixture, 3 oz. a day, was ordered. Six weeks after starting treatment 20 gr. of totaquina was given daily for four days. Two weeks later he complained of burning of the mouth, and some glossitis and angular stomatitis occurred. This disappeared in about 16 days without local treatment. Two weeks before treatment ceased the dose of yeast was increased to 6 oz. a day, and the blood findings after 16 weeks' treatment were: R.B.C., 4,860,000 per c.mm.; Hb, 15.4 g. % (Sahli); W.B.C., 7,700 per c.mm.; M.C.H., 31.4 $\gamma\gamma$. The patient is now back at work and in excellent health.

Case 3.—A female Hindoo aged 24 had been sick for three months with vomiting, palpitations, and weakness. When seen, pallor was extreme and the blood findings were: R.B.C., 640,000 per c.mm.; Hb, 2.66 g. % (Sahli); W.B.C., 7,500 per c.mm.; packed cells, 8.9%; M.C.H., 41.5 $\gamma\gamma$; M.C.V., 139.0 c. μ ; van den Bergh, 1.5 mg. bilirubin per 100 c.cm. No malaria parasites were found. The stools showed no ova or protozoa. The Kahn reaction was negative. The patient was four months pregnant, and the spleen was not palpable. Treatment with yeast, 6 oz. a day, was begun, and was supplemented ten weeks later with ferri et ammon. cit. gr. 90 daily as there was a lag in the haemoglobin percentage. Four weeks later the yeast was increased to 9 oz. daily, and the following week a stillborn infant was delivered. Improvement was rapid for the first eight weeks, after which the stress of the six-months pregnancy was

manifest, and the count remained more or less constant at this level until after confinement. When she was last seen her condition was excellent. The blood findings were: R.B.C., 3,990,000 per c.mm.; Hb, 12.04 g.% (Sahli); W.B.C., 8,650 per c.mm.; M.C.H., 30.2 $\gamma\gamma$.

Case 4.—A male creole aged 22 had been sick for nine months with weakness, dyspnoea on exertion, and bleeding from the gums. When seen, pallor was marked, and there was some periodontal ulceration and sponginess of the gums, with secondary infection of the left wisdom tooth and oedema of the left cheek. The blood findings were: R.B.C., 1,890,000 per c.mm.; Hb, 8.26 g.% (Sahli); W.B.C., 5,600 per c.mm.; packed cells 27.4%; M.C.H., 43.7 $\gamma\gamma$; M.C.V., 144.9 μ ; bleeding time, 4 min.; coagulation time, 6 min. Subtertian and benign tertian malaria parasites were found. Van den Bergh: 0.6 mg. bilirubin per 100 c.cm. Stools: ankylostome ova +; urine: pus cells ++. Spleen just palpable. Treatment with yeast 3 oz. daily was begun, with quinine gr. 15 intramuscularly for four days. No treatment for hookworm was given. The patient was unusually co-operative, and in eight weeks was back at work, the R.B.C. count being 4,350,000 per c.mm., the Hb 13.44 g.% (Sahli), and the M.C.H. 30.9 $\gamma\gamma$.

Case 5.—A female Hindoo aged 38, 7-para, had complained of extreme weakness and troublesome diarrhoea since her confinement five weeks previously. Pallor and weakness were marked, and the blood findings were: R.B.C., 620,000 per c.mm.; Hb, 3.22 g.% (Sahli); M.C.H., 51.9 $\gamma\gamma$. No malaria parasites were found. Stool examination showed neutral fat and fatty acids ++; no ova or protozoa were present. The spleen was palpable on inspiration. Clinically the case did not resemble sprue, and a diagnosis of nutritional macrocytic anaemia was made. Yeast, 6 oz. a day, was given. Mist. bismuth. sed. 1/2 oz. four-hourly was prescribed for the diarrhoea, which cleared up within 48 hours and did not trouble the patient again except during several nights one week later. This again responded to the bismuth mixture. Two weeks after starting treatment mild glossitis and angular stomatitis similar to Case 2 were noted. This disappeared as the clinical condition improved. The patient was not seen again until approximately five months later, during which time the yeast had been taken irregularly. She was, however, very well. The R.B.C. count was 3,620,000 per c.mm.; the Hb 12.3 g.% (Sahli), and the M.C.H. 34.2 $\gamma\gamma$.

Case 6.—A male Hindoo aged 26 had been ill for five months with weakness, palpitations, and dyspnoea. Pallor of the mucous membranes was marked, and the blood findings were: R.B.C., 1,320,000 per c.mm.; Hb, 6.30 g.% (Sahli); M.C.H., 47.7 $\gamma\gamma$. No malaria parasites were found. He was given yeast, 2 oz. four times a day, and improvement was rapid and continuous. In seven weeks the R.B.C. count was 4,100,000 per c.mm., the Hb 13.8 g.% (Sahli), and the M.C.H. 33.8 $\gamma\gamma$. He is now well and has resumed work.

Conclusions

Sediment obtained from distilling-vats after fermentation has ceased is potent in the treatment of tropical macrocytic anaemia. This potency is due to the presence of autolysed yeast, which has been shown to contain the factor or factors necessary for the normal maturation of red cells and in whose absence an anaemia of the macrocytic type develops. Certain members of the vitamin B complex are also present in the yeast sediment, which has been used successfully to treat angular stomatitis and glossitis and pellagrous dermatitis.

It is preferable to obtain yeast sediment from factories producing unbleached sugar, as the yeast content is higher and calcium sulphate is absent. The latter may produce diarrhoea, possibly on account of its bulk. The yeast sediment used is obtained as a waste product and hence it is cheap. It is also acceptable to religious sects that will not eat beef flesh.

Concentration of the yeast extract and distribution from hospitals, estates, child welfare centres, and schools might be undertaken with valuable results in a country where tropical macrocytic anaemia is common, such as it is in Mauritius.

I am indebted to Mrs. D. Collins, M.Sc., for the analysis of yeast samples; to superintendents of the various district hospitals for permission to treat cases; and to the manager of Medine estate for supplies of yeast. I should like also to thank Dr. d'Arifat, Ag. Director, M. and H. Dept., for permission to publish this paper.

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FAMINE OEDEMA IN PRISONERS OF WAR

BY

DOUGLAS S. STEVENSON, M.B.E., F.R.F.P.S.

Brigadier, A.M.S.

Oedema or dropsy occurring under conditions of starvation or of semi-starvation has been recognized since the earliest days, in particular being associated with war, and records of it occur in literature of the ancient world. In more modern times Napoleon's army is stated to have suffered in this way in its retreat from Moscow in 1812, and there have been such records from time to time under famine conditions in Ireland, India, China, the Siege of Paris, and Central Europe from 1914 onwards during the 1914-18 war; and in these histories the clinical picture has been fully described and many theories of causation advanced (*Official History of the War*, 1914-18). These theories are all, of course, from the days when accurate biochemistry was unknown and the vitamins equally so, although it was appreciated that the empiric use of certain foods—e.g., citrus juice—did help to cure conditions such as scurvy. A frequent comment in some records is that no evidence of scurvy appeared and that people died of dropsy alone—a clinical finding worth remembering, as scurvy was greatly feared in times of want. Another observation is that in the civil population dropsy affected the adult males rather than the women and children, and it is generally agreed that when famine conditions were ameliorated most of the surviving sufferers were restored to normal health. The mortality figures vary greatly, in some cases being 50%; but seldom is there any clear reasoning as to the cause of the dropsy—simply that it was due to insufficient food.

Aetiological Factors

What are the possible and what the probable causes of such oedema or dropsy? First, avitaminosis beriberi—the wet type of beriberi with its leg weakness, unsteadiness of gait, dyspepsia, anaesthesiae, and paresthesiae—must be considered. Secondly, nephritis. Richard Bright's (Boyd, 1938) description in 1827 of oedema and albuminuria as the main clinical features and the naked-eye observations of the diseased kidneys is historic. The war nephritis described in detail in the *Official History of the War* (1914-18), and considered to be no different from the acute nephritis of civil life has also to be borne in mind, noting that dyspnoea was often the presenting symptom, oedema was of short duration, and acute uraemia was frequent. Thirdly, we have food deficiency: famine oedema, the German *Oedemkrankheit* or *Kriegsödem*, the French *Oedème de la famine ou de la guerre*—oedema associated with famine and commonly with war, so frequently partners. These are the most likely causes of oedema occurring in comparatively large numbers of persons and under the circumstances to be stated.

Cases from German Prison Camps

Recent examination of some repatriated prisoners of war, captured in May-June, 1940, in France, reveals that these men developed, in one case at four months, in an average at eleven months, and in one case at as long as fifteen months after capture—i.e., in 1941, and while in Germany—oedema of legs, face, and genitals, preceded by malaise, dyspnoea, and severe headache. Their condition otherwise at that time is not known to us, nor have we any record of the results of the examination of their urine. They were stated to be suffering from nephritis. After capture in 1940 the men were marched considerable distances on an extremely poor diet and in battle dress, some without overcoats, eventually reaching prison camps in different parts of Germany, where they were put to work, still on a diet very low in quality and quantity. This diet is described by each of them separately as consisting daily of one-fifth of a loaf of black bread, a pint of thin soup with some cabbage in it, and a few half-rotten potatoes. On occasion a portion