pregnant, and complained of breathlessness on exertion, such as walking upstairs, during the previous four weeks. She had unmistakable mitral stenosis, with a few extrasystoles, but no fibrillation—the pulse 120 and of indifferent volume and tension—no oedema, and no liver enlargement. She responded satisfactorily to treatment, which included complete rest, light diet, aperients, 10 minim doses of tinct. digitalis, sometimes combined with 5 grains of sodium bromide, and was allowed, after six weeks in hospital, to return home with strict injunctions as to rest and suitable regimen.

She returned to hospital in her thirty-fourth week. The general condition was fair—pulse 94, no auricular fibrillation; but there was some oedema of the legs, and she also complained of a recurrence of the breathlessness on even slight exertion. Under similar treatment, including 10 minims of tinct. digitalis every six hours, the oedema cleared up in a few days and, all things considered, her condition once more became satisfactory.

Although there was no indication for it from the pelvic side, I decided to induce labour mainly for two reasons: to take advantage of a favourable phase, and to avoid the possibility of a prolonged strenuous labour. Watson's medical method failing, as it so often does, bougies were introduced under general anaesthesia. The reaction was very unfavourable, and in the course of twenty-four to thirty-six hours most of the signs and symptoms of cardiac distress appeared —pulse 120, fibrillation, precordial pain, oedema, cyanosis, dyspnoea. But labour pains came on and were accelerated by small doses of pituitrin. Large doses of digitalis again controlled the pulse, reducing it to 80 a minute. The head being now well into the pelvis, forceps delivery under anaesthesia was effected, and was followed by a rather prolonged third stage, but with no undue haemorrhage. The 5 lb. infant survived, and the mother achieved a remarkable rally in three days, with a pulse of 92 and a sense of comparative well-being. A relapse followed, and again a still more marked recovery, only to be followed by a further relapse on all points, to which, on the eighth day, she succumbed.

The problem is, would this patient have had a better chance of pulling through if I had decided to allow her to go to term? In such a case it is, at best, a question of chances either way, but my impression is that the question should be answered in the affirmative.

TUMOURS COMPLICATING PREGNANCY

My final problem case is concerned with tumour conditions complicating pregnancy.

A farmer's wife, accustomed to the strenuous duties of her outdoor occupation, and pregnant for the first time at the age of 40, was sent to me by a country practitioner with the statement that the pregnancy was advanced to about the sixth month, and appeared to be complicated by a multinodulated fibroid condition of the uterus; that the patient and her husband were very anxious to have a living child; and that, if deemed to be indicated, they would agree to the performance of Caesarean section at term.

I concurred in the tentative diagnosis. There had been no menorrhagia before the onset of pregnancy, but that is not uncommon where the multinodular variety of fibroid is predominant. The abdomen was very large, and occupied by many irregularly shaped lumps. The patient had habitually enjoyed good health. Her main trouble had always been constipation, the bowels being copiously evacuated at weekly or longer intervals.

I agreed also to the line of treatment suggested, particularly as per vaginam one or two of the nodules could be felt in the pelvic cavity with the cervix partly raised above them, a condition which could effectively block the transit of the foetus. I explained, however, that it was possible that as the pregnancy advanced to the later months the enlarging uterus might pull these nodules upward out of the pelvis, even to the extent of rendering a Caesarean operation unnecessary. I had no further opportunity of checking the diagnosis because, although the patient promised to come later for another examination, she did not do so, and the next I heard of the case was over the telephone after midnight from the doctor, to the effect that labour was well on its course and that, moreover, the patient was already on her way by transport to the nursing home. I arrived at the home just in time to supervise the completion of a normal breech delivery. As was to be expected the abdominal masses were post-natally much less in evidence.

The puerperium was normal, excepting that when on the third day the action of the bowels had, in addition to aperients, to be solicited by enemata, the nurse reported that the copious result per anum was supplemented by some faecal matter coming per vaginam. Much concerned, I made a most careful examination, and could find no trace of vaginal fistula communicating with the bowel. With that temptation to complacency to which clinicians sometimes yield, I expressed the view that the nurse must have been mistaken. She, being a competent and well-trained person, said no more, but no doubt held to her opinion, although the phenomenon did not again occur.

Some months later the patient came to see me complaining that the abdominal lumps were causing her much discomfort, and that she wanted them removed. Examination showed that though altered in shape and dimensions they were still present, and in due course I performed a laparotomy, and the nature of the problem was revealed. An enormous megacolon extended almost from flank to flank and from the pelvis to well above the level of the umbilicus. A well-involuted uterus with appendages complete was *in situ*, and most of the small intestines were packed away towards the left hypochondrium. The "tumours" were partly consolidated scybala and stercoliths—one of the latter was so large and hard that I deemed it proper to remove it by excision through the colonic wall—an analogue of Caesarean section to save the poor lady the pangs of its delivery *per vias naturales*.

A very interesting case; and though it may only be in the form of a postscript to its record, I think it is due to that nurse to say that her observation was surely correct, because the patient on further inquiry recalled that one of her early childish troubles was that fluid faecal matter in small quantities occasionally came per vaginam. A rare complication of this variety of megacolon is the persistence of a communication between the bowel and the cervical canal. The conditions obtaining in the early days of the puerperium would tend to increase its patency, and so permit of the passage of some of the fluid or semifluid contents of the bowel into the genital passage. The anatomical position of the opening would account for its non-discovery by ordinary vaginal examination.

TREATMENT OF "PERNICIOUS ANAEMIA OF PREGNANCY" AND "TROPICAL ANAEMIA"

WITH SPECIAL REFERENCE TO YEAST EXTRACT AS A CURATIVE AGENT*

BY

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The anaemias mentioned in the heading of this paper might well be described under the common title of tropical macrocytic anaemia; as, except for the accident of pregnancy, they are indistinguishable from one another, but can be separated from the numerous other anaemias occurring in the Tropics by the large size of the red cells, and by the presence, at some stage of the disease, of megaloblasts. In fact, these anaemias have the blood picture of Addison's or true pernicious anaemia, but differ from this condition in that the typical blood

* A full report of this work, and of the experimental work done in connexion with it, will appear in the *Indian Journal of Medical Research*.

picture is not associated with the other symptom-complexes which are so constant a feature of pernicious anaemia.[1] It is suggested, therefore, that in future these two anaemias be described together as tropical macrocytic anaemia.

TROPICAL MACROCYTIC ANAEMIA

This anaemia occurs in India as a distinct disease, frequently associated with pregnancy, and complicating, or complicated by, malaria, hookworm disease, and sprue. In an earlier paper[1] I dealt only with the idiopathic form, but further experience has led to the inclusion of the other types, as they all respond to the same treatment. They must, however, be distinguished from the severe small-celled secondary anaemias which frequently occur in the above-mentioned conditions, but which do not respond to the same treatment as the macrocytic type. The treatment of macrocytic anaemia is of considerable interest, and throws some light on the etiology of the condition. It is generally recognized that iron and arsenic, in whatever form they are given, are valueless—Chart VI shows the result of such treatment ; there is no increase in the haemoglobin or in the red cell count. This is the common experience of all workers in India who recognize this form of anaemia; they also find that other lines of treatment, successful in secondary anaemias, are equally useless.

LIVER TREATMENT

The discovery of the efficacy of liver in the treatment of pernicious anaemia suggested a new line of treatment, which has proved very successful for macrocytic anaemia. The pregnant cases respond more slowly than the others, but apart from this the results in the two conditions are identical. As in true pernicious anaemia, the presence of severe sepsis inhibits the stimulating effect of liver. After considerable experience in treating pregnant cases, I am of the opinion that, where the condition is severe, with a haemoglobin value under 20 per cent., it is essential to give large doses of liver extract (up to as much as the equivalent of 600 grams of fresh liver daily) if a rapid response is to be obtained ; the need of this is urgent, as such patients are likely to go into premature labour and die of heart failure. The first five days of treatment, during which a response cannot be hoped for, are thus always a time of great anxiety, and the death rate is likely to remain high until the women learn to report in the earlier stages of the disease. Even without the added strain of labour, many patients are admitted only to die of heart failure in the first twenty-four to forty-eight hours ; the immediate prognosis in cases with difficult breathing is very bad. Once delivery is over and the next two days are safely passed, the majority of patients will go into a natural remission without any treatment, so that in such cases it is very difficult to gauge the efficacy of any cure. Once a good response has been obtained, the dose of liver extract can be reduced, and, later, replaced by liver meat if the patient will take it.

As stated above, the reaction to liver extract seems exactly the same as in true pernicious anaemia, but the conditions in women's hospitals are such that it is generally impossible to follow the cases through as in other countries. Indian women of the hospital class are uneducated, very frightened, and suspicious. Few remain long enough for a cure, and many leave in a pitiful condition. The demands of their homes are very pressing, and neither they nor their relatives realize the importance of treatment ; if a woman can crawl she must attend to her home duties. Hence the records are frequently incomplete ; but in such cases as have been followed up, a typical reticulocyte response, of the same order as in pernicious anaemia, is obtained, and the same rapid return to a normal blood count and picture occurs.

VITAMIN TREATMENT

The results of liver therapy, though not easily brought into accordance with the previously expressed suggestion that a deficiency of vitamins A and C is causally related to the anaemia,[1] support the view that this is essentially a deficiency disease. However, it was decided to give a trial treatment with a concentrate of vitamin A (generously provided by Messrs. Lever Brothers), associated with a diet rich in vitamin C. At the same time experiments with monkeys were arranged along the same dietetic lines.

The treatment of patients with vitamins A and C proved a complete failure, and the animal experiments showed that a deficiency of these two vitamins was not concerned in the production of such macrocytic anaemias. The latter experiments did, however, strongly suggest that some deficiency in the vitamin B complex was significant as a causative factor, and that vitamin B had curative properties. Experiments with patients were therefore begun, and marmite, a form of yeast extract, was selected as the most suitable preparation. The extract was supplied in bulk by the Marmite Food Extract Company, and a sample was very kindly tested by Dr. Harriette Chick of the Lister Institute. She reported it to be rich in both the antineuritic vitamin B_1 and the antidermatitis vitamin B_2, and comparable with yeast itself ; a dose of 0.2 gram (dry weight 0.139 gram) was found to be sufficient for a rat's daily ration. The extract was given to the patients in drachm (1 drachm = 4 grams) doses, two, three, or even four times a day, the larger doses being used for pregnant women. It was found to cause nausea in a few of the very severe cases. This was overcome by giving it iced, and with the addition of crushed peppercorns ; it was always taken cold, as the patients preferred it so. In the report given below it will be seen that the marmite was as active as liver extract in causing regeneration of red blood cells.

Before the case histories are given, it must be noted that only female patients were treated, as the author was working in women's hospitals ; but similar anaemias occur in men, and this treatment is now being tried out on them also. The following histories cannot be taken at their face value, as the women do not give reliable information. A history of fever may mean nothing, as patients will assure you that they have fever when their temperature is consistently normal or subnormal. The mean red cell count for my series of healthy women of the hospital class in Bombay is 4.06 millions and the haemoglobin 69 per cent. (100 per cent. = 13.8 grams) ; these values indicate the degree of recovery which can be expected.

CASES TREATED WITH LIVER EXTRACT

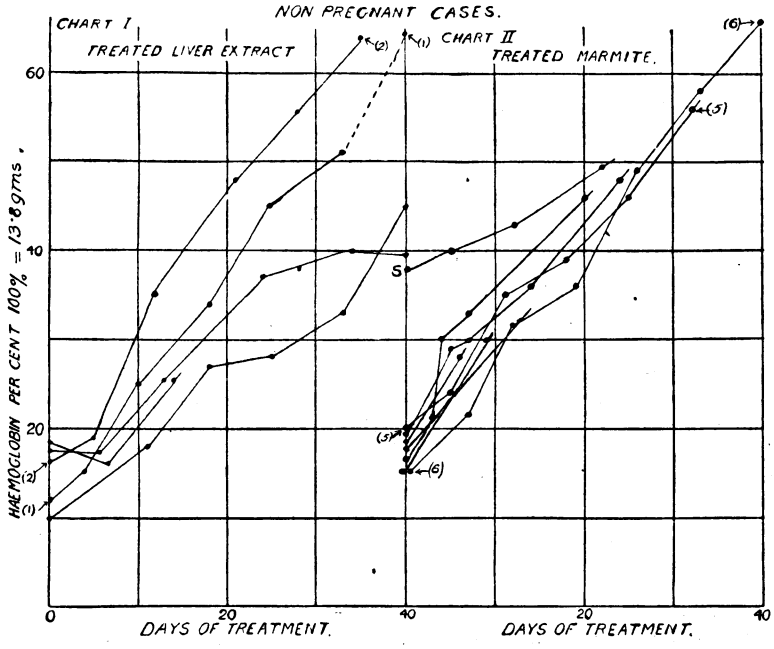
CASE I

Married woman, aged 27, 3-para, Hindu, strict vegetarian. Patient was confined five months ago ; for fifteen days before delivery she had fever and swelling of the extremities ; she improved for two months, but since then has had fever, increasing weakness, pallor, and oedema of the limbs. On admission she was semi-conscious, with a temperature swinging between 99° and 102° F. The extremities were oedematous ; there was no diarrhoea ; the urine contained a faint trace of albumin ; the Wassermann reaction was negative ; no ova were seen in the stools ; and later, a test meal showed the presence of free hydrochloric acid.

The blood count showed: red blood cells 450,000 per c.mm., haemoglobin 12 per cent., white blood cells 900 per c.mm. ; there was anisocytosis, with very large cells, and some poikilocytosis ; megaloblasts were present. A reticulocyte count gave a percentage of under 1.

Treatment consisted of digitalis for the first week only, and liver extract (hepatopson) in doses equivalent to 250 grams of fresh liver daily. Clinical improvement was obvious in five days, and thereafter the patient made an uninterrupted recovery. Daily reticulocyte counts were not made, the

maximum response observed being 12 per cent. on the eleventh day. A blood count, after thirty-three days' treatment, showed: red blood cells 3,020,000 per c.mm., haemoglobin 55 per cent., and white blood cells 9,100 per c.mm., and the blood picture was normal; twenty-nine days later the red blood cells were 3,700,000 per c.mm. (Chart I, (1)).



CASE II

Married woman, aged 27, 1-para, Hindu, vegetarian. The patient was delivered five years ago; since then not pregnant. For four months she has suffered from fever associated with vomiting and oedema. On admission the patient was extremely ill, with a temperature of from 100° to 103° F. for the first six days; she also had a sore mouth, severe vomiting, a feeble rapid pulse, and a dilated heart, and she was very restless. The urine contained no albumin; there was very slight oedema. Later examination gave a negative Kahn reaction; ova were absent from the stools, and there was free acid in the gastric contents. A blood count taken on admission showed: red blood cells 820,000 per c.mm., haemoglobin 17 per cent., and white blood cells 5,000 per c.mm.; there was anisocytosis, poikilocytosis, and some polychromatophilia. Megaloblasts were present; very few reticulocytes were seen in the whole slide.

Treatment consisted of liver extract (hepatopson), equivalent to 250 grams of fresh liver daily, and later of Lilly's extract, equivalent to 300 grams fresh liver daily. Stimulants and glucose per rectum were given for the first few days. The temperature fell after six days, the vomiting ceased, and thereafter the patient made a rapid and uninterrupted recovery. After thirty-five days' treatment the blood count was: red blood cells 3,520,000 per c.mm., haemoglobin 64 per cent., and white blood cells 8,600 per c.mm.; the blood picture was normal. Daily reticulocyte counts were not done; and the maximum response observed was 8 per cent. on the twelfth day (Chart I, (2)).

The above two cases are typical of a series of non-pregnant cases treated with liver extract; further examples are shown on the same chart.

CASE III

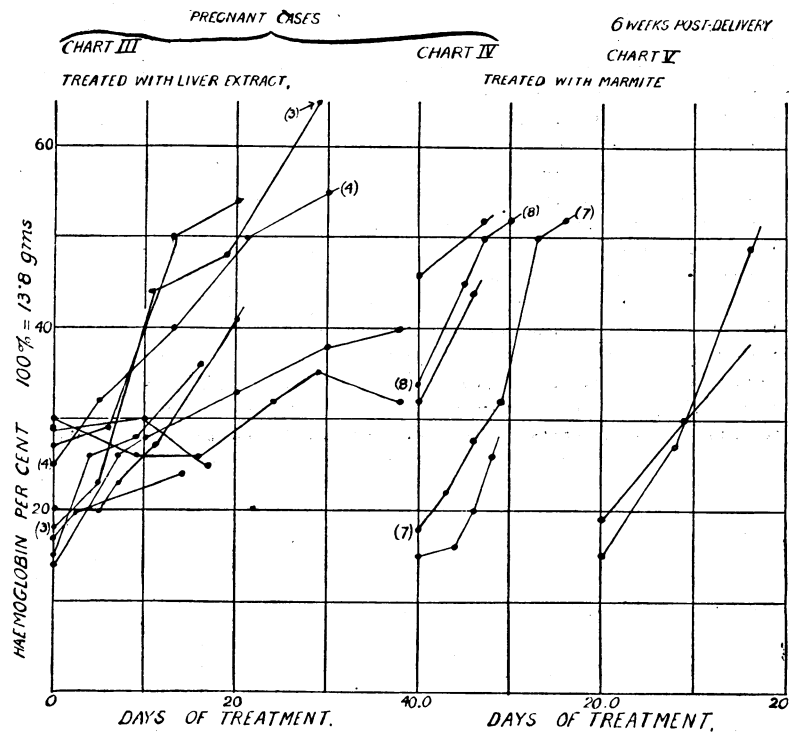
Married woman, aged 21, primipara, six and a half months pregnant, Christian, and meat-eater. Patient gave a history of recurrent attacks of fever, probably malaria, since childhood; otherwise healthy, except for severe vomiting in the early months of pregnancy. For the last month there had been increasing weakness and fever. On admission she had severe anaemia, associated with great weakness, breathlessness, and moderate oedema of the extremities. She was very constipated; temperature was 99° F. The spleen was enlarged and hard. The urine contained no albumin; the Wassermann reaction was negative, and a few hookworm ova were found in the stools. The blood count showed: red blood cells 998,000 per c.mm., haemoglobin 18 per cent., white blood cells 11,200 per c.mm.; there was marked anisocytosis, a few megaloblasts, and a very few reticulocytes.

The treatment consisted of liver extract B.D.H. fluid extract) in doses equivalent to 700 grams daily, for nine days, and after that of half a pound of liver meat daily. Digitalis, 5 minims three times daily, was taken for the first few days. The result was an uninterrupted recovery. Thymol for hookworm was given after the red cell count had passed 2 millions. The maximum reticulocyte response was 39 per cent. on the ninth day. The final blood count on the thirty-third day of treatment showed: red blood cells 3,680,000 per c.mm., haemoglobin 66 per cent., and white blood cells 7,800 per c.mm. The blood picture was normal (Chart III, (3)).

CASE IV

Married woman, aged 28, 5-para, eight months pregnant, Hindu, vegetarian. The patient gave a history of one month's fever, weakness, and sore mouth. She was admitted with severe anaemia, great weakness, slight oedema, and a temperature of 100° F. The urine showed a trace of albumin. The Kahn reaction was negative. No ova were found in the stools. The test meal was negative for free acid, but the neutral chlorides were high. A blood count showed: red blood cells 1,080,000 per c.mm., haemoglobin 25 per cent., white blood cells 8,200 per c.mm., and the usual blood picture.

The treatment was carried out with liver extract alone (B.D.H. fluid extract) in doses equivalent to 250 grams daily. The temperature fell after fourteen days; the patient improved steadily, and was delivered at term of a healthy child. The maximum reticulocyte count observed was 12 per cent. on the fifteenth day, but the count was not taken daily. The final



blood count before delivery, after thirty-three days' treatment, showed: red blood cells 3,250,000 per c.mm., haemoglobin 55 per cent., and white blood cells 6.500 per c.mm. The blood picture was normal. After delivery, on the fifty-second day of treatment, the red cells had risen to 3,420,000 and the haemoglobin to 60 per cent. (Chart III, (4)).

Cases III and IV are typical of those complicated by pregnancy which responded well to treatment ; but, as Chart III shows, there were others in which recovery was slower. At the time when the majority of patients were treated, the dose of liver extract given (for various reasons, partly that of expense) did not exceed the equivalent of half a pound of fresh liver daily. In my opinion this is not enough to produce a prompt rise in the count in all cases ; and it is probable that many of them would have done better on the larger doses now used. It is also possible that minor degrees of sepsis or other complications which inhibit the response to liver were missed.

CASES TREATED WITH MARMITE

The number of cases of tropical macrocytic anaemia treated with marmite was not large, in all twenty-two, many of which could be followed up only for a short time. The results of the treatment were, however, so striking that I feel justified in reporting them—more especially as I am leaving India, and shall not be able to continue the work. Further, it is hoped that other workers will be encouraged to give the treatment a trial.

This series consisted of eight non-pregnant women, seven pregnant, two puerperal, and five who were delivered during treatment. The non-pregnant patients, with the exception of one who had a severe *B. coli* cystitis, with much pus in the urine and acute bronchitis as well (Chart II, s), were uncomplicated by sepsis ; all responded rapidly and well to treatment (Chart II). The clinical improvement was as marked as the changes in the blood. Two cases are reported in detail below.

The seven uncomplicated cases, treated ante-natally, were unfortunately followed up only for a short time, the longest period being eighteen days ; but the improvement in four of them with severe anaemia was amazing ; clinical improvement (less oedema, easier breathing, return of appetite) was apparent on the third day, and improvement in the blood on the fourth day (Chart IV). Two of these are reported in detail below. Two others, both with red cell counts under a million, died undelivered on the second and fourth day of treatment. One died suddenly and unexpectedly, after showing signs of improvement ; but the other, a patient with general anasarca and vomiting, had little prospect of recovery from the beginning, as she could not sleep for breathlessness or retain any nourishment.

The two puerperal patients, delivered six and eight weeks before admission, had been going downhill ever since. Both were admitted with red cell counts below a million and haemoglobin values below 20 per cent. ; and both had severe diarrhoea. The one had a temperature swinging between 100° and 105°, for which no cause could be found other than the anaemia and associated diarrhoea. On marmite alone (one drachm four times daily) this patient made an uninterrupted and rapid recovery, showing a reticulocyte count of 39 per cent. on the eighth day of treatment. The other patient had a *B. coli* cystitis and recovered more slowly, the maximum reticulocyte response being only 15 per cent. on the eighth day of treatment—an example of the inhibiting effect of any septic focus.

The five cases delivered during treatment were less suitable for a trial of a new remedy ; and, with the exception of one, they were all complicated and responded slowly. In spite of this, four showed a typical reticulocyte reaction.

CASE V

Married woman, aged 25, 2-para, non-pregnant, Brahmin, strict vegetarian. The patient gave a history of two or three months' intermittent fever and increasing weakness. On admission her temperature was 99.8° F., and pulse rate 124 ; she was very anaemic, breathless, and had slight oedema of the face and extremities. The heart was dilated ; there was a systolic murmur. The mouth was clean. The liver was enlarged to one fingerbreadth below the costal margin, and was tender. The temperature persisted for the first twelve days of treatment. The urine contained a trace of albumin, which cleared later ; no ova were found in the stools, and the Wassermann reaction was negative. There was no free acid in the gastric juice, but so much bile that the test was useless. A blood count showed: red blood cells 917,000 per c.mm., haemoglobin 20 per cent., white blood cells 5,100 per c.mm. ; and there was marked anisocytosis with large cells ; only a few reticulocytes were seen. The patient was very ill, and the condition of her heart caused much anxiety.

The treatment consisted of marmite, one drachm twice daily, for the first twenty days, and then three times a day to help the appetite. Stimulants, digitalis, and camphor were given when necessary during the first four days. After this the patient improved remarkably, but the temperature did not fall to normal till the twelfth day, after which she made an uninterrupted recovery. The maximum reticulocyte count was 18 per cent. on the twelfth day. The final blood count, on the thirty-third day of treatment, showed: red blood cells 3,333,000 per c.mm., haemoglobin 56 per cent., and white blood cells 4,700 per c.mm. The blood picture was normal (Chart II, (5)).

CASE VI

Widow, aged 25, nullipara, non-pregnant. Brahmin, strict vegetarian. Patient stated that she had been healthy till four months before, when she had an attack of fever lasting fifteen days, followed by intermittent fever. She had complained of pain and distension for the last month, and vomiting for the last eight days. On admission the temperature was normal and the pulse rate 120. She was very ill, with extreme anaemia, oedema of the face and extremities, and a rapid and feeble heart beat. She was constipated, the tongue was coated, and she vomited several times. The liver was enlarged four fingerbreadths below the costal margin, and was tender. The spleen was not palpable. The urine contained a trace of albumin, which cleared later ; no ova were seen in the stools, and the Wassermann reaction was negative. In a single test meal there was no free acid in the gastric contents. The blood count showed: red blood cells 812,000 per c.mm., haemoglobin 15 per cent., and white blood cells 5,600 per c.mm. ; anisocytosis and poikilocytosis were present, megaloblasts were seen, and there were 0.3 per cent. reticulocytes.

One drachm of marmite was given twice daily, and stimulants and digitalis for the first week. The temperature remained normal after the first two days, but the rapid pulse and abdominal pain remained for some little time. On the eighteenth day of treatment, after the blood had shown a good response, both red cells and haemoglobin having doubled their original value, the patient had a rigor and rise of temperature, and malignant malaria parasites were found in the blood film. Whether this attack was a relapse or was due to an infection in the ward it was impossible to say, but after two injections of 5 grains of quinine the patient had no further attacks while in hospital, and made a good recovery. The maximum reticulocyte count was 35 per cent. on the sixth day of treatment. The liver remained enlarged. A final blood count on the fortieth day of treatment showed: red blood cells 3,544,000 per c.mm., haemoglobin 66 per cent., and white blood cells 5,200, and the blood picture was normal (Chart II, (6)).

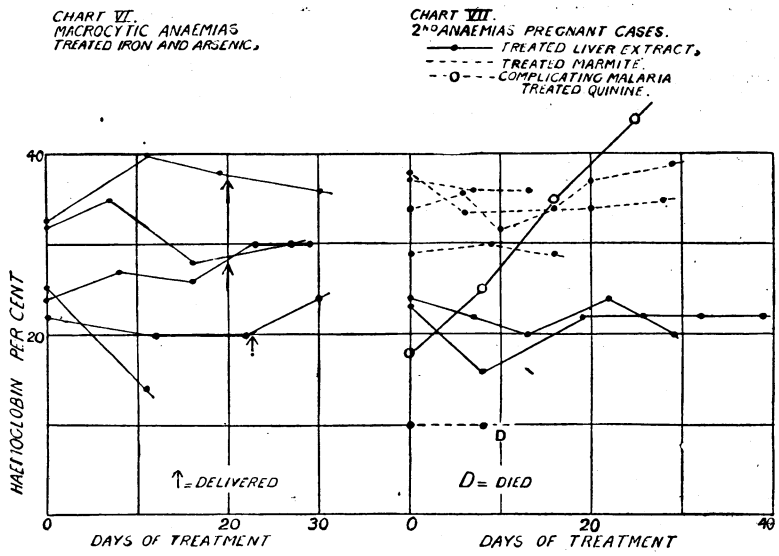
The two cases reported below represent two types complicated by pregnancy, the one typical of Bombay, with severe anaemia but only the moderate oedema associated with many severe anaemias, and the other of a type seen more frequently in Madras, with generalized anasarca as well as extreme anaemia. The latter variety is very

grave, and, admitted as they are in the last stages of the disease, the cases have a high mortality rate ; the prognosis is particularly bad when a certain type of forced breathing is present.

CASE VII

Married woman, aged 20, first pregnancy, Hindu, but not a vegetarian. Patient gave a history of an attack of fever a year ago. She was six months pregnant, and had had diarrhoea for a short time. She was admitted with severe anaemia, marked breathlessness, oedema of the face and extremities, a rapid pulse, heart sounds poor with systolic murmur, dirty tongue, pyorrhoea, and severe diarrhoea, but no temperature. The spleen was enlarged ; the urine contained no albumin ; whip-worm ova were found in the stool. A blood count showed: red blood cells 990,000 per c.mm., haemoglobin 18 per cent., and white blood cells 8,200 per c.mm. Anisocytosis was marked, with very large cells ; megaloblasts were present ; very few reticulocytes were seen.

Digitalis, 10 minims thrice daily, was given for the first ten days, and, on admission, three powders, consisting of bismuth subnitrate 30 grains, salol 20 grains, and Dover's powder 15 grains. Marmite was given in doses of one drachm four times a day. For the first two days the patient was in a critical state, which was soon succeeded by a rapid and striking improvement. The diarrhoea stopped after five days, and the oedema cleared rapidly. The reticuloctye response was 56 per cent. on the fifth day. On the thirteenth day of treatment the blood count showed: red blood cells, 2,490,000 per c.mm., haemoglobin 50 per cent., and white blood cells 6,900 per c.mm.—an amazing response for a pregnant case. By the sixteenth day the haemoglobin was 55 per cent., and the patient feeling "perfectly well." (Chart IV, (7)).



CASE VIII

Married woman, aged 20, first pregnancy, sixth month, Hindu, but not a vegetarian. Patient was a coolie woman, and the only history she gave was of feeling ill and weak for seven days. On admission the most striking feature, other than the anaemia, was the generalized oedema ; the whole body was swollen, and the labia stretched till they looked like tissue paper ; there was free fluid in the abdomen, and moist sounds all over the chest. The patient was very breathless ; the pulse rate was 64, and missing beats. There was marked pyorrhoea. The urine contained no albumin. Roundworm ova were found in the stool. The blood count was: red blood cells 1,300,000 per c.mm., haemoglobin 34 per cent., and white blood cells 8,100 per c.mm. Anisocytosis was marked, the cells being very large. A reticulocyte count gave a figure of 6 per cent.

The treatment consisted of marmite, one drachm four times a day, and nothing else. After two days of this the oedema was strikingly less ; by the seventh day there was only a slight puffiness of the feet, and by the tenth day there was none. There was a reticulocyte response of 41 per cent. on the sixth day. On the tenth day the blood count showed: red blood cells 2,560,000 per c.mm., haemoglobin 52 per cent., and white blood cells 6,600 per c.mm. The cells were still large, and 5 per cent. of the reds were reticulocytes. Probably part of the initial rise in the blood count was due to the rapid decrease in oedema ; but after all signs of this had cleared, the haemoglobin rose in two days from 45 to 50 per cent. (Chart IV, (8)).

DISCUSSION

The results recorded above suggest that in marmite we have a curative agent as potent as liver extract for the treatment of tropical macrocytic anaemia. The response of this disease to treatment with marmite is in all ways comparable with that produced by suitable doses of liver extract in the same condition or in true pernicious anaemia. Both extracts are active in this condition, even when it is complicated by malaria or hookworm, and without the treatment of the associated disease. This is in marked contrast with their complete inactivity in the secondary small-celled anaemia that so frequently complicates these infections (Chart VII). The fact that the two extracts are active in macrocytic anaemia raises the question of their etiological significance. The condition, both in its clinical manifestations and in its distribution, resembles a deficiency disease. The frequency and severity in pregnancy, the marked improvement that follows delivery (as in the case of deficiency osteomalacia), together with the frequent association of the disease with others that already lay a strain on the haematopoietic system, all suggest that some deficiency is the underlying cause. The geographical distribution is also suggestive, the regions chiefly affected being India, the Malay States, China, and the West Coast of Africa ; the possibility of a infective agent cannot, however, be ignored.

If one considers the two extracts, the question of the nature of any common constituent factor at once arises. The work of Cohen,[2] Castle,[3] and their co-workers suggests that in liver extract it is a protein breakdown product that is active, and that in true pernicious anaemia it is some defect in the gastric function which leads to a failure of absorption of this product. In the tropical anaemia there is apparently no failure in gastric function.[1] It is possible, however, that the Indian diets, which are so markedly deficient in protein, especially animal protein,[4] may be deficient in this essential product or its precursor, and that the protein of yeast, known to be of good biological value, or its breakdown products, in the marmite supplies this want. The fact that the condition is so frequent among the better-to-do classes and among Mohammedans,[5] who are meat-eaters, would suggest that a protein deficiency is not the underlying defect.

Marmite is, however, known to be a rich source of the B vitamins, and so is fresh liver meat ; commercial liver extract is also a very potent source of vitamin B_2, but it contains very much less of vitamin B_1. For a rat the minimum doses of liver extract for the two vitamins stand in the relation of even less than 1 to 10 (Chick, verbal communication) ; liver extract cannot therefore be called a rich source of vitamin B_1. The cases of anaemia seen in Bombay have no symptoms suggesting any marked deficiency of B vitamins, and beri-beri is practically unknown in the town. In Madras beri-beri occurs in all the rice-eating districts of the south and east coast, and endemic dropsy is also found in certain districts.

The frequent association of extreme oedema with the severe anaemia, and the fact that both respond so readily to treatment with marmite, are undoubtedly important. The question must, however, remain unsettled until further work can decide the common factor in the two extracts which is active. At present it is only possible to state that in marmite, and probably in other yeast extracts, there appears to be a curative agent for this dread disease which equals liver extract in potency, and has the advantage in India of being comparatively cheap and of vegetable origin.

In conclusion, it is a pleasure to acknowledge the help given by the staffs of the Cama and Albless Hospital, Bombay, and the Caste and Goosha Hospital, the Government Maternity Hospital, the Raja Sir Ramaswami Mudeliar Lying-in Hospital, and the Christina Rainy Hospital, Madras, who allowed me all facilities and showed the greatest interest in the work. The work was carried on as part of the Maternal Mortality Inquiry of the Indian Research Fund Association, which defrayed the expenses.

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THE DIAGNOSIS OF URAEMIA

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There is perhaps no condition in medicine which so frequently gives rise to difficulties and mistakes in diagnosis as that known as uraemia. This is partly due to loose definition and partly also to the fact that the manifestations included under the term, even when it is used in its strictest sense, are so varied as to simulate from time to time many other diseases. During the past twelve months, for example, cases have been seen in which, on clinical grounds, the following diagnoses were made: encephalitis lethargica, cerebral tumour, Addison's disease, pernicious anaemia, septicaemia, and leukaemia. A subsequent estimation of the blood urea, however, showed the true nature of the condition, which was confirmed at necropsy.

Now although many cases of chronic renal disease give no definite history of onset, and remain undetected for many years, all those mentioned above had had at least slight albuminuria; and uraemia, if considered at all, had been excluded on account of the absence of certain signs and symptoms generally considered necessary for this diagnosis. The absence, for example, of such symptoms as a high blood pressure, a hypertrophied heart, retinitis, foul tongue, the comparative youth of the patient, or even the small amount of albumin in the urine, had been regarded as making a diagnosis of uraemia due to chronic nephritis unlikely to be correct. The object of this paper is to point out the advantages of using the term uraemia in a more restricted sense than is usual; to emphasize certain clinical features which are of importance in the diagnosis, and which experience has shown are not sufficiently appreciated; and to bring forward a method of determining the blood urea which can be readily applied by anyone without laboratory experience or facilities.

DEFINITION OF URAEMIA

Strictly, the term uraemia should be applied only to those signs and symptoms which arise from, or at least are invariably associated with, defective elimination on the part of the kidneys; whether this be due to primary disease of these organs, a disturbance of their function secondary to disease elsewhere in the body, or to mechanical obstruction to the flow of urine—in fact, to those symptoms arising from an insufficient depuration of the blood by the kidneys. The word urinaemia is sometimes used to describe the results of mechanical obstruction to the urinary flow, but as the symptoms of this condition are identical with those of true uraemia as defined above it will not be employed here. It is true that none of the actual products of urinary retention has been proved to be the cause of the symptoms, but it is equally true that the accumulation of some or all of them in the blood generally leads to a definite train of symptoms to which alone the term uraemia is strictly applicable. Uraemia, therefore, can and does occur quite apart from Bright's disease. The term as commonly used includes many symptoms of this latter disease which are not always or necessarily associated with renal failure, as shown by nitrogen or dye retention or by diminished concentrating power of the kidneys. Particularly is this the case with regard to the symptoms of high blood pressure and cardio-vascular disease. These are often erroneously included under the term uraemia; but, as pointed out by Strauss, Ascoli, Widal, Volhard, Fishberg, and others, it is of great practical importance to differentiate clearly between those symptoms of pseudo-uraemia and those of true uraemia. As defined above, uraemia is seen in its most typical form in cases with mechanical obstruction to the flow of urine and in cases of chronic nephritis in the young; for although uraemia, as shown by nitrogen retention, etc., is frequently present in older subjects, death in these cases more often results from accompanying cardio-vascular disease.

SIGNS AND SYMPTOMS OF URAEMIA

The chief signs and symptoms of uraemia may be conveniently considered under the headings of the main systems of the body involved. The onset is usually insidious, but may be comparatively rapid, especially in acute nephritis, mechanical obstruction of the urinary tract, and in cases of chronic nephritis complicated by intercurrent infection, by bilious attacks, and following general anaesthesia. The initial symptoms vary, but physical and mental exhaustion, anorexia, vomiting, dyspnoea on exertion without signs of cardiac failure, marked anaemia, and progressive loss of weight are all common.

Nervous System

Mental apathy and drowsiness, quite apart from coma, are frequently present, and may be the only prominent symptoms for many weeks. They may be so marked as to lead to a diagnosis of encephalitis lethargica. If, in addition, there is some choking of the discs with a normal or only slightly raised blood pressure, as sometimes happens, cerebral tumour may be diagnosed. In some cases, on the other hand, there is intense mental activity, worry, and inability to concentrate, sometimes accompanied by a vague but insuperable feeling of alarm. Insomnia may be intractable, despite marked physical weakness and sense of exhaustion. Muscular weakness is often extreme. In one case seen recently it was the first symptom noted, and it increased in intensity for nine months before any other symptoms occurred, when anorexia was complained of. The blood urea was then 220 mg. per 100 c.cm. If at the same time the blood pressure is low or not much raised Addison's disease may be simulated. Most