elucidated. It is concluded that these two sciences have, in fact, entered upon a new phase of usefulness in the study of psychiatric disorders.

My thanks are due to Professor Alfred Meyer for his continued interest in the problems of a clinician.

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The American Embassy in London has issued details of United States pre- and post-doctoral training programmes on the peaceful uses of atomic energy. The courses are open to foreign nationals and last one to two years. The subjects are industrial medicine, industrial hygiene, and radiological physics (radiation protection). Excluding travel, the cost of participation is estimated at a minimum of \$2,800 per student for each of the first two courses, and over \$4,000 for the last. At present there are no United States funds available to assist foreign students, and it is assumed that the costs will be met by the foreign government or other foreign sponsor. A memorandum giving further details of these courses may be obtained from Mr. P. J. SEARBY, Atomic Energy Office, 1, Richmond Terrace, Whitehall, London, S.W.1.

ANAEMIA OF PREGNANCY IN AFRICANS OF LAGOS

BY

C. G. BERRY, M.B., Ch.B.

Assistant Pathologist (Weir Research), St. James' Hospital,
London, S.W.12

Severe anaemia is a common complication of pregnancy in all tropical countries (Fairley *et al.*, 1938; Napier, 1940; Russell, 1941). It is one of the most important causes of maternal and infant mortality and one of the most difficult to treat. Experience in Lagos, as elsewhere, has shown that these patients respond poorly to treatment. It has been the custom to put all severely anaemic patients on treatment with iron, liver, and folic acid from the moment they are admitted to hospital rather than wait for the result of blood investigations. Even so, the majority of these patients have shown little response and pregnancy commonly terminates in abortion.

An attempt has been made to investigate these anaemias in some detail, and this paper is a review of 30 patients seen over a period of eighteen months. These were taken at random from the large number of women admitted to hospital for treatment of anaemia. None had had any form of treatment before the first blood and marrow specimens had been examined. Thirteen were subsequently treated with vitamin B₁₂, and their response is described.

Local Geography and Background of Patients

Lagos, the capital of Nigeria, is a busy town and seaport on the coast of West Africa within 10 degrees of the Equator. In this region of high forest, swamps, and lagoons the humidity is high, and although the shade temperature rarely exceeds 90° F. (32.2° C.) the climate is oppressive and encourages a state of torpor in European and African alike.

Though a Yoruba town, Africans of many other tribes are seen, and the population is continually being increased not only by Yorubas from other parts of the western region of Nigeria but also by Ibos from the east and Hausas from the north, attracted to Lagos by the prospect of higher wages. Many of these live in conditions of poor sanitation and gross overcrowding. The cost of living is high, and few Africans can afford the more expensive foodstuffs. Consequently most Southern Nigerians are vegetarian by necessity; meat is too costly to be an important part of their diet. Meals are monotonous and starchy, consisting of stews prepared from cassava, yams, rice, maize, or guinea-corn, with plenty of palm oil or groundnut oil. This may be supplemented with fruit (oranges, bananas, and plantains) and white bread made of high-extraction American flour, which is becoming increasingly popular. Eggs are too expensive and milk is unobtainable.

Apart from the high price of food, many Nigerians (not only those in the poorer sections of the community) will not "waste" money in an attempt to improve their diets, but prefer to spend it on clothing, an important mark of social distinction. The possession of a wife is another indication of prosperity. It is still the custom for the groom to pay his future father-in-law a sum of money, often very considerable, for his bride. This

being so, it is not unusual for a man to start married life in debt, and so be unable to provide for himself, or his wife, or for the family which will shortly arrive.

Procedure

All patients were seen immediately after their admission to hospital. A medical history was obtained and a physical examination made. Blood was removed for a complete cell count, including a reticulocyte count, and calculation of the standard indices. The figures quoted in this paper for the mean corpuscular volumes have all been subjected to correction for reticulocytosis (Foy *et al.*, 1950). The haemoglobin concentration was determined by conversion to alkaline haematin and comparison with Harrison and Gibson's artificial standard in an EEL photoelectric colorimeter. (The standard itself was checked against a freshly prepared solution of alkaline haemin.) The red cells were examined for the sickle-cell trait, and thick films were examined for malaria parasites.

Sternal puncture was performed, the marrow fragments being separated from the aspirated material and smears made. In 27 cases sufficient blood was obtained for the estimation of total and differential serum proteins and for direct and indirect van den Bergh tests. Specimens of stool and urine were examined for blood and parasites in 24 patients. Gastric analysis was done in only three.

Although it is desirable to do daily reticulocyte counts for as long as a week before the onset of treatment, this was not permissible in any of the patients in this series. The severity of the anaemia and the risk of abortion demanded immediate treatment. After the first dose of vitamin B₁₂ reticulocyte counts were done every alternate day, and the haemoglobin concentration and number of red cells were estimated at weekly intervals. None of the patients had any form of dietary control; meals were provided by friends and relations, who visited the hospital daily.

A complete follow-up of patients was found to be impossible. Such is the congestion at the maternity hospital that patients are discharged as soon as their haemoglobin concentration has reached a level of 50–60%, with instructions to attend the out-patient department for continued treatment; others discharged themselves against advice. Many fail to reappear after they have left the hospital. Only three of the patients in this series consented to visit the pathological laboratory for weekly blood examinations.

The criteria used in this investigation as evidence of a deficiency of haemopoietic liver principle are (a) the presence in either the marrow or peripheral blood of abnormal white cells (giant stab cells or metamyelocytes, giant multi-segmented polymorphs) and/or (b) the presence in the marrow of typical Ehrlich megaloblasts or intermediate megaloblasts (Zuelzer *et al.*, 1947; Dacie and White, 1949).

Clinical Features

Twelve of the women were primiparae. Nine were seen within the first week after delivery, and the remainder (with two exceptions) were seen during the second half of pregnancy.

Although many of the women were profoundly anaemic their symptoms were rarely sufficient to cause them grave inconvenience. Few complained of any more than increasing weakness and lethargy, dyspnoea on exertion, or dizziness and fainting. One girl presented herself at the out-patient department, having walked unaccompanied to the hospital, with a red-cell count of 915,000 per c.mm. and a haemoglobin concentration of 3.2 g.%; she would admit to no symptoms other than those of pregnancy.

Five of the patients showed poor physical development, two of whom had mild oedema which could not be attributed to either the pregnancy or renal or cardiac disease. None of the patients had soreness of the tongue or mouth, and none had skin lesions suggestive of poor nutrition. There was palpable enlargement of the liver in 13 patients and of the spleen in 18 (including all of those with large

livers). Five women were clinically jaundiced. Low-grade fever was present in 10 patients, all of whom had either a urinary or an upper respiratory tract infection.

Laboratory Findings

Haematology

The red-cell counts when first examined were below 1 million in 5 cases, 1–2 millions in 17 cases, 2–3 millions in 5 cases, and over 3 millions in 3 cases (range 0.69–3.4 millions per c.mm.). The haemoglobin concentrations varied between 2.5 and 11 g.%. The range of mean corpuscular volumes and the distribution of cases according to cell size are shown in Table I. The high incidence of macrocytic anaemias is well demonstrated, and there would seem to be a tendency towards macrocytosis even when the M.C.V. falls in the normal range of 82–95 cubic microns.

TABLE I.—Mean Corpuscular Volume (Range: 69–132 cubic microns)

	Microcytic M.C.V. Below 82	Normocytic		Macrocytic M.C.V. Over 95
		M.C.V. 82–88	M.C.V. 89–95	
No. of cases seen...	2	2	6	20
No. of cases with evidence of deficiency of haemopoietic principle	1	0	4	15

Although 13 cases were hyperchromic as shown by their colour indices and mean corpuscular haemoglobins, only five had a mean corpuscular haemoglobin concentration in the normal range of 32–38%. The majority of these patients, therefore, were iron-deficient, or were liable to become so in the event of a rapid response to treatment. The mean corpuscular haemoglobin concentrations were below 20% in 1 case, 20–25% in 2 cases, 25–32% in 22 cases, and over 32% in 5 cases (range, 18.5–35%).

The mean corpuscular diameter was measured in only seven cases, all of them macrocytic, as shown by the M.C.V. In all of these the M.C.D. was greater than 7.7 microns, the upper limit of normal (Whitby and Britton, 1953), and the range was 7.8–9.3 microns.

The leucocyte counts varied between 4,300 and 19,600 per c.mm., and were below 5,000 in 2 cases, 5,000–8,000 in 9 cases, 8,000–12,000 in 10 cases, and over 12,000 in 9 cases. In all cases neutrophil polymorphs were the predominant cells. There appears to have been no depression of the myeloid series as was described by Woodruff (1951) in his series of cases seen at Ibadan.

The sickle-cell trait was present in 4 of the 30 patients. One other (Case 5) showed marked sickling of her red cells, with large numbers of bizarre filamentous forms. She became deeply jaundiced after delivery of a live child (which died, however, within a few hours of birth), and she died without showing a response to any form of treatment. It is probable that she had sickle-cell anaemia, but this was not confirmed.

Malaria parasites were found in only one patient; another carried microfilaria of *Loa loa*.

Marrow Examinations.—In almost every patient the marrow was highly cellular, the appearance being one of hyperplasia of both red- and white-cell series with erythroblasts often predominating. The myeloid:erythroid ratios varied between 3.5:1 and 1:3.0. There appeared to be no relationship between the severity of the anaemia and the cellularity of the marrow. Seven patients had typical Ehrlich megaloblasts, six had intermediate megaloblasts, and seven others had abnormal white cells only. Thus 20 patients had evidence of a deficiency of the liver haemopoietic principle; of these, 15 had macrocytic anaemias, four were normocytic (all in the upper range of normal), and one had a microcytic anaemia. Apart from intermediate megaloblasts in her marrow this last patient (Case 13) had numerous giant stab cells and metamyelocytes and multi-segmented polycytes in both peripheral blood and marrow (Tables I and II).

TABLE II.—Distribution of Cases with Megaloblasts and Abnormal White Cells

Cell Type	M.C.V. (Cubic Microns)		
	Below 82	82-95	Over 95
Abnormal white cells only	0	1	6
Intermediate megaloblasts	1	2	3
Ehrlich megaloblasts	0	1	6

Biochemistry

Total and differential serum proteins were estimated in 27 patients, and the figures agree well with those of Woodruff (1951), using the same normal values: total serum protein, 5.6-8.5 g.%; albumin, 3.4-6.7 g.%; globulin, 1.2-2.9 g.%; albumin/globulin ratio, 4/1-1.2/1. The total protein values were within normal limits in 22 patients, although half of these were approaching the lower limit of normality. Four patients had values below normal, and one above (range, 5.2-9 g.%). The albumin was low in 16 patients (range, 1.5-4.5 g.%) and the globulin raised in 24 (range, 1.7-5.4 g.%). Only six patients had normal albumin/globulin ratios (range, 2.65/1-1/2.65). No account has been taken of the hydraemia which normally occurs during pregnancy, but this would not be sufficient to account for the degree of abnormality of these figures or for the reversal of the albumin/globulin ratios. Similar figures have been found in other Africans admitted to hospital for investigation of anaemia (males and non-pregnant females) and in those in whom marked fatty degeneration of the liver was demonstrated at necropsy. Woodruff (1951) also found that many of his patients had livers fibrosed or infiltrated with fat. Low albumin and high globulin levels have been described in patients with liver disease (Maizels, 1946), and it is thought that this may be an explanation of the abnormal protein levels in the patients of this series. It is believed that the protein-deficient diets of the local Africans are an important factor in the aetiology of this condition.

The van den Bergh test was done on specimens of blood from the same 27 patients. The bilirubin was raised above 0.8 mg. per 100 ml. (the upper limit of normal) in seven patients, the highest reading being 4 mg. per 100 ml.

Fractional Test Meal

This test was done in only three of the megaloblastic patients. Two had normal acid curves, and the third (Case 21) had a histamine-alcohol-fast achlorhydria. As this patient's condition improved, however, her free gastric acid returned and she eventually had an acid curve well within normal limits.

Stool Examinations

Specimens of stool were examined (by the routine direct wet film method and also by a simple concentration technique) from 24 patients: ova of *Ascaris lumbricoides* were present in 12, *Trichuris trichuria* in 9, and *Ancylostoma duodenale* in 11. Both free and encysted forms of *Entamoeba histolytica* were present in one patient.

Response to Treatment with Vitamin B₁₂

Thirteen patients were treated with vitamin B₁₂ and iron, nine during pregnancy and four immediately after delivery. The dosage of vitamin B₁₂ ("cytamen") used depended on the severity of the anaemia and the response following the first injection. In most cases 100 or 200 µg. was given initially, followed by 20 or 50 µg. at weekly intervals. These patients responded as follows:

Patients Treated After Delivery

Two patients did not respond to vitamin B₁₂ or to any other treatment. The first of these (Case 5) had a reticulocytosis from 3.2 to 32.3% after six days, but then became deeply jaundiced and died 13 days after the onset of treatment. As mentioned previously, sickle-cell anaemia with a haemolytic crisis was probably the true diagnosis in this case. The second (Case 19) had a very hypoplastic marrow with no evidence of active erythropoiesis, and died two weeks after admission to hospital.

Case 20 (R.B.C., 1,370,000 per c.mm.; Hb, 4.2 g.%; M.C.V., 105.4 cubic microns) had a macronormoblastic marrow with large numbers of abnormal leucocytes. She was given 200 µg. of vitamin B₁₂, followed by 50 µg. weekly. Her reticulocytes rose to a maximum of 14% on the seventh day. On the seventeenth day the red-cell count was 3,400,000 and the Hb 8.4 g.%. She was discharged one month after the onset of treatment, when the blood count was 4,000,000 and Hb 9.4 g.%.

Case 23 (R.B.C., 1,500,000; Hb, 3.6 g.%; M.C.V., 100 cubic microns) showed intermediate megaloblasts and abnormal leucocytes in her marrow. She received 200 µg. of vitamin B₁₂, followed by 20 µg. weekly, and the reticulocytes rose from 4.8 to 11.8% after seven days. After 14 days the Hb concentration had more than doubled (to 8.6 g.%) and the red-cell count had risen to 2,810,000. Seven days later she was discharged, the red-cell count then being 3,100,000 and Hb 9.5 g.%.

Although these last two patients appeared to respond well to vitamin B₁₂, the response coinciding with the beginning of treatment, it is not possible to exclude a spontaneous recovery following the termination of pregnancy.

Patients Treated During Pregnancy

Case 6 (R.B.C., 915,000; Hb, 3.2 g.%; M.C.V., 120 cubic microns) showed megaloblastic erythropoiesis and abnormal leucocytes. She was given 100 µg. of vitamin B₁₂, followed by 20 µg. weekly, and her reticulocytes rose from 1.8 to 14% in 11 days. After six days the red-cell count had risen to 1,700,000 and the Hb to 4.7 g.%. She was discharged 13 days after the commencement of treatment, when the Hb was 7.7 g.%.

Case 8 (R.B.C., 1,490,000; Hb, 5.4 g.%; M.C.V., 116 cubic microns) had macronormoblastic erythropoiesis with abnormal leucocytes. She received the same treatment as Case 6 but iron was withheld. The reticulocyte count rose from 8.4 to 14% in eight days, and five days after the first injection the red-cell count had become 2,130,000; the Hb, however, had fallen to 4.9 g.%. She was then given "ferrivenin" (5 ml. on alternate days); six days later she was discharged from hospital with a red-cell count of 2,870,000 and Hb 7.7 g.%.

Case 12 (R.B.C., 1,060,000; Hb, 3.6 g.%; M.C.V., 113 cubic microns) had megaloblastic erythropoiesis and abnormal leucocytes. She was given the same treatment as Case 6, and her reticulocytes rose from 2.4 to 16% in nine days. On the fourth day the red-cell count was 1,830,000 and the Hb 5.6 g.%. Five days later the Hb was 6 g.%, and 15 days after the beginning of treatment she was discharged with an Hb concentration of 8 g.%.

Case 18 (R.B.C., 880,000; Hb, 2.5 g.%; M.C.V., 91 cubic microns) showed megaloblastic erythropoiesis with large numbers of abnormal leucocytes. She received 200 µg. of vitamin B₁₂, and as the response appeared to be slow this was followed by another 200 µg. one week later; she had two further injections of 100 µg., each at weekly intervals. After 10 days the Hb concentration had only reached 3.8 g.%. Eight days later the red-cell count was 2,230,000 and the Hb 5.3 g.%. Twenty-four days after the onset of treatment the Hb was 7.3 g.% and the patient was discharged.

Case 21 (R.B.C., 1,270,000; Hb, 3.4 g.%; M.C.V., 101 cubic microns) had megaloblastic erythropoiesis and abnormal leucocytes. There was a histamine-alcohol-fast achlorhydria. She was treated with folic acid, to which she showed no response. (She received a total dosage of 140 mg. of folic acid, administered over seven days. At the end of this time the Hb concentration was 3.1 g.%) The folic acid was discontinued and she was given 100 µg. of vitamin B₁₂. This was repeated after one week, and subsequently she was given 50 µg. weekly. The reticulocyte count was high when she was first seen (10%). After an initial rise to 16% it slowly fell and at the end of the second week it was 1.4%. Her blood counts improved as follows: Original count: R.B.C., 1,270,000; Hb, 3.4 g.%. One week after folic acid: Hb, 3.1 g.%. Six days after vitamin B₁₂: R.B.C., 1,580,000; Hb, 5 g.%. After 10 days: R.B.C., 2,220,000; Hb, 6.3 g.%. After 21 days: R.B.C., 2,430,000; Hb, 7.5 g.%. After four weeks: R.B.C., 3,000,000; Hb, 8.8 g.%.

There was no further improvement, and she was discharged. She was delivered of a live child 11 days after the last blood count. This patient had been deeply jaundiced, with a palpable liver and spleen, when she was first examined. The jaundice slowly disappeared and the serum bilirubin was normal when she reached full term. It may be that the slow improvement was largely due to the termination of the haemolytic process. The marrow was examined again before she was discharged and was then normoblastic. Fractional test meal was repeated and showed normal gastric acid production.

Case 24 (R.B.C., 1,700,000; Hb, 4.2 g.%; M.C.V., 88 cubic microns) had intermediate megaloblasts and abnormal leucocytes in the marrow. She was given 200 µg. of vitamin B₁₂ followed by 50 µg. weekly. The reticulocytes rose from 3.4 to 18.6% after 10 days. One week after the commencement of treatment the red-cell count had risen to 2,230,000 and the Hb was 5.5 g.%. She was discharged six days later, when the red-cell count was 3,040,000 and Hb 7.1 g.%.

Case 25 (R.B.C., 1,000,000; Hb, 2.5 g.%; M.C.V., 132 cubic microns) had a hypocellular marrow with megaloblastic erythropoiesis. She was given 100 µg. of vitamin B₁₂ daily for three days, followed by 100 µg. weekly. The reticulocytes rose from 7.6 to 16.4%, but this was not followed by any improvement of the anaemia. Six days later the red-cell count had fallen to 730,000 and the Hb was 2.3 g.%. In addition to the vitamin B₁₂ she was given liver and folic acid, but there was still no response, and she aborted five days later. She continued on the same treatment and slowly recovered over a course of many weeks.

Case 29 (R.B.C., 3,400,000; Hb, 11 g.%; M.C.V., 96 cubic microns), although only mildly anaemic, was macrocytic and had intermediate megaloblasts in the marrow. Treatment brought about a reversion to normoblastic erythropoiesis, but there was little change in the blood picture. (The Hb concentration reached 11.9 g.% and then remained stationary.)

Case 30 (R.B.C., 2,200,000; Hb, 6.8 g.%; M.C.V., 100 cubic microns) showed megaloblastic erythropoiesis with abnormal leucocytes. She had one injection of 200 µg. of vitamin B₁₂. The reticulocytes were 10% on admission to hospital and remained at this level. Seven days later her Hb concentration was 8.3 g.%. Unfortunately she then left the hospital against advice before any further red-cell counts were done.

Discussion

The cases described demonstrate the high incidence of macrocytic anaemias in pregnant women admitted to hospital in Lagos. The M.C.D. was calculated (and found to be increased) in only seven cases, but it has been assumed that the high M.C.V. in other cases does in fact represent an increase in cell diameter; this assumption was substantiated by the appearance of the red cells in the stained film. Woodruff (1951) commented that this increase in cell diameter was present in many anaemias which would be classified as microcytic or normocytic if judged by the M.C.V. alone, and concluded that there must be a diminution in cell thickness in these cases. In the patients described here the increase in cell volume was not accompanied by a corresponding increase in haemoglobin content, and most of the women were hypochromic.

Also outstanding was the high proportion of patients who were shown to be deficient in the liver haemopoietic principle; their anaemias might be classified as being nutritional, although they were not necessarily macrocytic. The occurrence of megaloblastic erythropoiesis in patients with microcytic or normocytic anaemias was observed by Foy *et al.* (1952) in East African patients.

The high incidence of abnormal serum protein values agrees with the findings of Woodruff (1951). Similarly, evidence of a haemolytic process, commonly found in these patients, has been reported before (Fairley *et al.*, 1938; Foy *et al.*, 1950, 1952; Woodruff, 1951). Whether these haemolytic anaemias are secondary to hypersplenism, a sequel of liver damage, or whether they are a result of chronic malaria has still to be decided. Foy *et al.* (1952) believe that "any factor that predisposes the individual to enlargement of the spleen may lead to the development of this splenic haemolytic anaemia," and they suggest that schistosomiasis may play a part in the aetiology of this condition. In Southern Nigeria, however, schistosomiasis is not commonly seen, and malaria (which is highly endemic in this region) is probably a more important factor. Whatever the cause of this haemolytic type of anaemia in pregnant women it seems unlikely that either malaria or worm infestations do more than add to the patient's burden: they aggravate an anaemia which is already present, and which is primarily nutritional in origin, and they hinder the patient's recovery.

The precise nature of the deficiency in these cases is still a matter of some doubt. It is generally believed that the

megaloblastic pregnancy anaemias seen in temperate climates and those seen in the Tropics are not identical in aetiology. The former respond well to treatment with folic acid, and it is thought that they may be due to a state of folic acid deficiency (Thompson and Ungley, 1951), possibly a result of a temporary inability either to store or to mobilize it from the liver. Similar anaemias in the Tropics will not respond to folic acid, however, and it has been stated that their response to any form of treatment before parturition is disappointing, and that in most cases it is only possible to arrest the progress of the anaemia (Napier, 1940; Woodruff, 1951). Patel and Kocher (1950) reported five cases of megaloblastic anaemia of pregnancy in Indians, all of which were treated with vitamin B₁₂ alone (four had 40 µg. and one had 20 µg.), and all responded. No such response was observed in Woodruff's patients at Ibadan.

In the present series nine patients were treated before parturition, the doses of vitamin B₁₂ used being larger than those used by previous workers. Seven patients responded to treatment, four of them rapidly and three more slowly. In all of these the clinical improvement was striking; six were discharged with instructions to attend the out-patient department for further supervision, and the seventh felt so well one week after the first injection of vitamin B₁₂ that she discharged herself. Unfortunately, only three patients were followed up for any length of time, and they showed no further improvement after the haemoglobin concentration had reached a level of 8-9 g.%. These results appear to be very similar to those described by Das Gupta *et al.* (1953) in Indian patients with nutritional macrocytic anaemia who were treated with vitamin B₁₂. Although all of their 22 patients showed a good initial response, in only five was there complete remission. The remainder needed crude liver or folic acid to effect recovery. It seems possible that the patients described in this paper might have responded further had folic acid been given at the stage when vitamin B₁₂ ceased to be effective.

The lack of response to folic acid of pregnancy anaemias in African women does not necessarily imply that these cases differ in aetiology from those seen in temperate climates. It is obvious that there must be a multiple deficiency, and that complete recovery cannot be expected to follow the use of only one of the many haemopoietic factors. It may well be that the primary aetiology is the same in all patients, whether African or European—that is, a temporary deficiency of folic acid brought about by a metabolic upset which is precipitated by the stresses of pregnancy. In the African this upset is augmented by the presence of liver disease, while parasites in the blood or in the intestines add to the severity of the anaemia. It is possible that the African woman will not respond to folic acid, however, until the secondary deficiency of extrinsic factor has been corrected. Presumably this is brought about by vitamin B₁₂, and the lack of response beyond a certain level coincides with the depletion of the already low reserves of folic acid. The deficiency of extrinsic factor may be the result of a change in intestinal flora which is encouraged by the high-carbohydrate and low-protein diet. After parturition, though there may be a slow spontaneous recovery as folic acid again becomes available, the secondary deficiency persists, and vitamin B₁₂ given to these patients will lead to a more rapid recovery.

Summary

Severe anaemia is commonly seen in pregnant women in Lagos. It is an important cause of maternal mortality, and the risk of abortion in these cases is very great. Thirty patients have been investigated and 13 of them were treated with vitamin B₁₂. The clinical and laboratory findings are described, and the response to treatment is discussed with reference to the aetiology of the anaemia. The following conclusions have been reached.

1. Most of the anaemias are macrocytic and hypochromic, and the incidence of nutritional anaemias, diagnosed by the presence of Ehrlich or intermediate megaloblasts and/or abnormal white cells, is higher than has generally been supposed.

2. Many cases are complicated by disease of the liver and by the presence of parasites in the blood or intestines. These add to the severity of the anaemia, and they may be important as causes of hypersplenism and the resulting haemolytic type of anaemia.

3. All patients should be treated with iron, and many will respond to vitamin B₁₂ in doses of 100–200 µg. Folic acid may be necessary in addition for complete remission of the anaemia.

4. It is suggested that there is a multiple deficiency in these patients. Although in all pregnancy megaloblastic anaemias the primary defect may be the non-availability of folic acid, the local Africans have in addition a deficiency of extrinsic factor and will not respond to folic acid until this has been corrected.

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DIVERGING SEX-MORBIDITY TRENDS IN CANCER OF THE MOUTH

A HOSPITAL MORBIDITY STUDY

BY

MARION H. RUSSELL, A.I.S.

Statistician, Christie Hospital and Holt Radium Institute,
Manchester

A salient feature of the total incidence of cancer is its apparent uniformity after cognizance has been taken of such influences as improved diagnostic facilities and the ageing population. Despite this overall consistency, gradual changes do occur in morbidity and mortality patterns for specific anatomical sites. An obvious and widely publicized example is the continuing increase in cancer of the lung.

Another progressive trend which has engendered comment is the apparent decrease in cancer of the mouth suggested by a falling standardized mortality rate for both sexes beginning in the later part of the decade 1930–9 (Registrar-General, 1947). That the observed decrease was not entirely attributable to a higher success rate in treatment was confirmed by hospital statistics (Paterson, Tod, and Russell, 1946, 1950). The inference from mortality statistics is that the decrease applies to both sexes (Registrar-General, 1953; Minister of Health, 1954).

The object of this survey is to show that in the North-west of England, over an interval of a decade, there is evidence of a marked decrease in the incidence of cancer of the mouth in men only, a trend which is not apparently common to the adjacent anterior and posterior sites of lip and pharynx. In women, on the contrary, there is evidence of an increase in the morbidity rate, and it seems feasible that the falling mortality rate may be accounted for by their better response to treatment (Russell, 1954).

Basis of the Survey

The data used are culled from the individual statistical abstracts of cases of previously untreated or "new" cancer of the mouth registered at the Christie Hospital and Holt Radium Institute and its peripheral clinics in the North-west of England during the periods 1935–9 and 1945–9. After the inception of the National Health Service in July, 1948, and the establishment of regional hospital board areas, three clinics were ceded to the Liverpool Region. For the purpose of ensuring comparability, therefore, all registrations of patients from the affected territory have been excluded from both series.

The map printed overleaf shows the Manchester R.H.B. area and the location of the peripheral clinics held regularly by consultants from the Christie Hospital and Holt Radium

TABLE I.—Populations in Surveyed Parts of Manchester R.H.B. Area

Local Authority	Mid-Year Estimates	
	1937	1947
County boroughs	1,816,220	1,747,970
Municipal boroughs and urban districts	1,523,088	1,592,319
Rural districts	257,856	271,878
Total	3,597,164	3,612,167

Institute. Some of these clinics were established over twenty years ago and had steadily expanded as their advantages became obvious. Detailed investigation of registrations in each separate clinic area indicates that it is valid to use for comparison in the two five-year periods registrations from all the remaining area with the exception of the shaded part of East Lancashire, which was not served by the Christie Hospital and Holt Radium Institute in 1935–9, although it was subsequently. The analyses in both periods relate, therefore, to patients residing in the area left unshaded on the map.

The whole R.H.B. territory is nearly 3,000 square miles in extent, and the population is approximately 4½ million (47% men, 53% women). South Lancashire is the most heavily industrialized community in the world; consequently the average density of the population in the R.H.B. area is 2.6 persons per acre, compared with 1.2 for England and Wales. Although the area is only one-twentieth the size of England and Wales, it contains one-tenth of the population. Immigration of other races has been of too recent development to have any influence on the investigation.

Table I gives the population in 1937 and 1947—the mid-year of the periods 1935–9 and 1945–9—for the unshaded part of the map according to the type of local authority. These figures have been compiled from the mid-year estimates of the Registrar-General (1938 and 1949) for individual county and municipal boroughs, urban and rural districts.

Criteria of Classification

In the analyses individual cases have been classified according to the site in which the primary lesion was believed to originate. They are shown in three main groups: (a) tongue; (b) main oral cavity—that is, the anterior part, comprising the upper and lower alveoli, cheek, hard palate, and floor; and (c) faucial region (or posterior oral cavity),