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### Anaemia associated with malnutrition in the tropics

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During the past two decades workers in the tropics have become increasingly aware of the importance of anaemia among indigenous inhabitants and many believe that it is second only to malaria as a public-health problem. Certainly it is usual to find several cases of severe anaemia even in small hospitals throughout the tropics and not uncommonly half the patients in the medical wards and most of those in obstetric wards are moderately or severely anaemic. There is, of course, an enormous literature relating to the problem but most work has been concerned with a particular aspect of this group of diseases, and studies of the overall incidence of anaemia among different communities are comparatively uncommon. Napier (1940), however, drew attention to the great amount of morbidity and mortality associated with it in pregnancy in India. Dr M. K. Krishna Menon, Medical Superintendent of the Government Lying-in Hospital, Madras, in a personal communication states that at the hospital once every 6 weeks a pregnant woman dies as a direct consequence of anaemia and that one out of fifty of the patients has a haemoglobin level on admission of less than 5.6 g/100 ml. Pandit (1948) reports maternal mortality rates in Madras of 16.6 per thousand live births, in Calcutta of 24.4 and in Bombay of 13.5. Anaemia was responsible for 13.4% of the maternal deaths in Madras, 23.5% in Calcutta and 17.1% in Bombay; it was second only to puerperal sepsis in importance as a cause of maternal mortality. In the report of this investigation it is stated that 'anaemia may indirectly be responsible for a much larger proportion of maternal deaths than the above figures would indicate'. Foetal mortality among these cases

was also high, and in one large city it was 51%. Pandit (1948) also found anaemia to progress rapidly during the last 3 months of pregnancy with the result that 15% of anaemic women died undelivered. In this work it was shown that the incidence of anaemia was higher among multiparous than among primiparous women, apparently being commonest during the third pregnancy. By contrast in this country deaths from anaemia in pregnancy are of the utmost rarity.

The Indian Council of Medical Research (1953) in *A Review on Haematology* state that regarding haematological values 'the normal data of the average Indian will not be in any way different from that of average values in Western and other temperate climates'. Ramalingaswami & Venkatachalam (1950) found no appreciable difference in the mean haematological values for males in their region as compared with other parts of India. However, a survey among children from poor and lower middle-class families in the same region (Someswara Rao, Taskar & Ramanathan, 1954) showed that haematological values for these children were strikingly lower than those of British children and some other children. In the tropics the three common conditions to be considered as causes of anaemia are malaria, infection with hookworms, and malnutrition. It is, therefore, of importance to note that Someswara Rao *et al.* (1954) state that the region in which they worked is one 'which for all practical purposes is free from hookworm infestation and malaria'. Anaemias are not uncommon among adult males in India and in the tropics generally, but there is little need to state in this Society that a disease found to be specially prevalent in childhood and in pregnancy should be suspected of being of nutritional origin for at both of these times the demand for nutrients imposed by growth is maximal. The low haemoglobin values found among these Indian children and the frequency of anaemia in pregnancy suggests that nutritional factors may be important in their causation.

#### *Nutritional megaloblastic anaemia*

There are, of course, certain well-recognized forms of nutritional anaemia in the tropics, and of these that which has received greatest attention in the past is megaloblastic anaemia. There are good grounds for believing that it is in many instances nutritional in origin; more than 20 years ago Wills (1934) came to this conclusion and Taylor & Chhuttani (1945) found that in meat eaters in the Indian army anaemia was mostly normochromic and normocytic whereas in vegetarians it tended to be macrocytic. In the Caribbean region megaloblastic anaemia associated with the so-called sprue syndrome there has been found among those living on a diet considered to be low in folic acid (Lopez, Spies, Menendez & Toça, 1946), and a similar cause may be responsible for the megaloblastic anaemias so common in India and in the tropics elsewhere. These megaloblastic anaemias in the tropics are interesting but I do not believe that they are of great importance as a public-health problem. Thus in a recent tour of India made specially for the purpose of studying anaemias and during which I saw personally and examined some 200 cases in a variety of centres only six cases of megaloblastic anaemia were encountered.

From the inception of studies of this type of anaemia there have been conflicting reports regarding the therapeutic responses obtained to different substances. Thus Wills (1933) found the condition to respond to Marmite, but Mudaliar & Menon (1942) found Marmite ineffective. Wills, Clutterbuck & Evans (1937) and Napier (1938) found crude liver extracts effective in the disease but refined liver extracts ineffective or effective only in large doses, whereas Sundaram (1944) and Patel & Bhende (1949) found refined liver extract effective in small doses. Das Gupta (1950) and Das Gupta, Gangulis & Chatterjea (1946) describe anaemias which have failed to respond to folic acid but have later responded to liver extract. Das Gupta (1952) also finds vitamin B<sub>12</sub> ineffective in the majority of cases, whereas Chaudhury (1951) finds it effective, although higher doses are necessary than in pernicious anaemia. The failure of some of these megaloblastic anaemias to respond to folic acid, vitamin B<sub>12</sub> and refined liver extracts may be due to their being caused by deficiency of a secondary haematopoietic factor such as the Wills factor. It is, however, also probable that in some cases a marrow which is macronormoblastic is being confused with one which is megaloblastic and the anaemia when associated with the former fails to respond to a specific haematopoietic factor. It is possible that in some cases of this type in which the marrow is macronormoblastic, protein malnutrition may be a factor concerned in causation.

An important subvariety of nutritional megaloblastic anaemia is that complicated by haemolytic features (Fairley, Bromfield, Foy & Kondi, 1938), and it is possible that hypertrophy of the reticulo-endothelial system brought about by malaria is responsible for this haemolysis.

#### *Iron-deficiency anaemia*

Iron-deficiency anaemia is common in the tropics but is probably seldom a truly nutritional disease. In most instances it is caused by blood loss secondary to hook-worm infection. If a daily intake of 15 mg iron is considered sufficient for basic needs, including those of pregnant women and growing children, then the diets of the majority, but not all, tropical peoples are adequate in this nutrient. Thus Mitra (1953) reported that 6.5% of 843 Indian families had a daily iron intake per person of less than 15 mg. The most recently published dietary survey carried out in Bombay State (Radhakrishna Rao, 1954) shows that the iron intake in 37 out of 185 persons in the Humgaon area of that State averaged only 16.5 mg/day. In seventy-five persons it was 24.8 mg and in the remaining seventy-three persons, 33.5 mg. It is clear that those in the group having the barely adequate 16.5 mg/day are in no position to withstand even the small iron losses that might be caused by light hook-worm infection. It is possible, therefore, that some cases of iron-deficiency anaemia are truly nutritional in the sense that they are due to inadequate dietary intake of iron, but in the majority of cases dietary inadequacy has been aggravated by parasitic infection.

An interesting suggestion, recently brought forward, is that in the hot wet tropics sufficient iron may be lost in the sweat to precipitate iron deficiency (Foy, 1955). Moore (1950), however, concludes from work with radioactive iron that under con-

ditions of maximal sweating a person loses only approximately 0.5 mg iron daily. It appears highly unlikely therefore that sufficient iron is lost in this way to cause marked anaemia.

*Anaemia associated with protein malnutrition*

It is not proposed here to discuss anaemia which may occur as part of the clinical picture of specific nutritional diseases such as pellagra; these, though important when they occur, do not on the whole present a large public-health problem. On the other hand, anaemia occurring in association with protein malnutrition is important from the public-health view-point. Reference has already been made to the large numbers of patients suffering from anaemia in the tropics and of these a high proportion are suffering from some of the manifestations of protein malnutrition. My attention was first directed to this problem in 1950 when investigating the cause of anaemia in a series of pregnant women in Nigeria. These women were suffering from an obstinately refractory type of anaemia which failed to respond to liver and specific haematopoietic factors or to iron. The women in almost all instances had some hepatomegaly, and liver biopsies showed that several of them had fatty infiltration of the liver and almost all had some degree of fibrosis. Their plasma albumin was low, the mean being 3.15 g/100 ml. (range 1.9–4.1) and analyses of diets recently carried out has indicated that they were probably taking an average of 36 g protein daily (Woodruff, 1955). Treatment with a well-balanced diet supplemented with protein produced some improvement in their general condition, in the haematological findings and in the plasma-protein values. The working hypothesis reached was that protein malnutrition was playing a part in the causation of the anaemia and that when it was corrected the anaemia improved.

Studies were later extended to children with kwashiorkor and to males and non-pregnant females suffering from severe chronic protein malnutrition. Anaemia found in all these groups exhibited many points of similarity and has been reported in detail elsewhere (Woodruff, 1955). It is an anaemia which may be confused with megaloblastic nutritional anaemia, for on looking at a stained blood film the red cells are frequently seen to be of a diameter greater than normal; the red blood cell precursors in the bone marrow are also large but nuclear maturation is normal, this type of marrow appearance commonly being referred to as macronormoblastic. The volume of the erythrocytes is seldom greatly increased, for although broader they are also thinner than normal. The anemia is therefore usually normocytic or slightly macrocytic, the mean corpuscular haemoglobin concentration is within the normal range and erythropoiesis is normoblastic.

In anaemias associated with protein malnutrition the ratio of the diameter of the erythrocyte to its thickness is usually greater than normal. Larsen (1948) has reported that in patients with liver damage and anaemia the cells are almost invariably of this type.

Fatty infiltration of the liver may be found in patients suffering from anaemia and protein malnutrition, in childhood and in pregnancy. It seems then that, in pregnancy, anaemia may be associated with protein malnutrition severe enough to

cause fatty infiltration of the liver of the same type as that produced in kwashiorkor in childhood. It may be that in both pregnancy and childhood the demand for protein imposed by growth is the precipitating factor. A similar condition may less frequently also be found in non-pregnant adults suffering from chronic severe protein malnutrition, but the disease in them is not usually as acute as in childhood and pregnancy, the causative factor having usually been operative for longer. There is evidence that a similar process may commence even before birth. Silvera & Jelliffe (1952) have shown fatty infiltration and fibrosis to be present at birth in infants delivered of severely malnourished mothers. There was no cardiovascular or other known cause for this fatty infiltration and fibrosis. It seems, therefore, that liver damage may in some instances commence even in intra-uterine life, be aggravated during the post-weaning period and lead to cirrhosis at an early age. Haemolytic anaemia is recognized in association with cirrhosis even in temperate regions, having been reported by Davidson & Fullerton (1938) and by Coleman (1948). In the tropics such anaemia is correspondingly more common and may occur in association with advanced cirrhosis even in young children (Pl. 1).

Serum-albumin values in these malnourished children and adults with anaemia were lower than they were in the pregnant women, the mean value in five children studied (Woodruff, 1955) was 1.39 g/100 ml. (range 0.20-3.88); in twelve adolescents, adult males and non-pregnant females it was 1.96 g/100 ml. (range 0.62-3.34). Whipple (1948) in experiments with dogs showed that haemoglobin in its production can draw on plasma proteins, and Davies (1945) has reported marked lowering of serum-protein values during recovery from severe anaemia in man. Foy (1955) has also reported cases of anaemia in which full therapeutic responses could not be obtained until the patients had been given supplements of protein in the diet. It seems probable, therefore, that in cases in which the serum proteins are low or deranged haemoglobin synthesis may be impaired. It is difficult to ascertain the role of the liver damage so often found in such cases. It may be that it is the prime lesion in the disease and that albumin synthesis is impaired and a tendency to haemolysis produced by it; alternatively, both it and the hypoalbuminaemia could stem from dietary causes and be aggravated by the demand for protein imposed by growth or by parasites.

Evidence therefore suggests that protein malnutrition, particularly during stress periods may be associated with anaemia and liver injury, and this association of circumstances, together with interplay of zymotic factors, creates a problem probably greater in public-health importance than that posed by the megaloblastic and other nutritional anaemias.

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#### EXPLANATION OF PLATE

Typical 'hob-nail' liver from a malnourished anaemic African child who died aged 8. Histological examination revealed gross fatty change as well as fibrosis.

### The anaemias of pregnancy in Dublin

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#### *Iron deficiency anaemia in pregnancy*

Dublin, a city of over half a million, is served by three large maternity hospitals and over 80% of the pregnancies in the city are cared for by these hospitals. Each hospital has its own 'district' from which it draws most of its patients. These women usually return to the same hospital on each successive pregnancy, and each maternity centre over a chosen number of years has its own group of patients which is fairly constant. About 5000 deliveries are managed by the Rotunda Hospital each year, and about 25% of the attendance is made up of primigravidae but the remainder are multi-gravidae, almost all of which have attended the hospital on their previous pregnancies. Large families are common and the average parity of the total attendance at the hospital in 1953 was 3.8.

Though it had been realized for some time that anaemia in pregnancy was common and often severe, it was not until 1953 that actual figures of the incidence were obtained. From the beginning of 1953 the problem of anaemia has been specially investigated at the Rotunda. These investigations have been under the direction of Dr H. C. Moore, Pathologist to the Hospital. Every pregnant woman on her first