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Nutritional anaemias

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It was to highlight the work of Ben Platt and his influence that this Meeting was conceived and the Council of the Royal Society of Tropical Medicine and Hygiene were very pleased when the Nutrition Society expressed willingness to join in this event. His influence on thought concerning nutrition throughout the world was very great and is exemplified by the many international committees on which he sat, particularly those of the WHO, UNICEF and FAO. If it were possible to assess quantitatively influence which nutritionists have had on a world-wide basis, I am sure that Ben Platt's name would be among the select group at the top. Particularly would this be so if influence on students and young research workers could be included. I have a personal reminiscence here; almost exactly 20 years ago I discussed with him my interest in anaemia associated with kwashiorkor; his reaction was warm and immediate, he invited me to his laboratories, then at Hampstead, and I will never forget the long afternoon and evening which he gave up to discussing and demonstrating to me work on anaemia. Much which we have been able to do stems from the kindly help received at that time. Throughout these 20 years Ben Platt's interest in it has been unfailing and culminated 3 years ago in collaboration between our two Departments in a series of experiments using dogs reared in and maintained on special diets within his Department. The results of some of these experiments I propose to put before you this afternoon.

The great prevalence of anaemia in the tropics needs no emphasis; many studies

have drawn attention to it, including some of our own (Woodruff, 1959). When the several causes of anaemia other than protein malnutrition in the tropics have been excluded there remain a very considerable number of anaemias in which the cause is unexplained or only partly explained. Trowell (1937) drew attention to such anaemia in patients with kwashiorkor, and Woodruff (1951, 1955) demonstrated that anaemia of this kind, unresponsive to iron, folic acid or vitamin B_{12}, was commonly associated with evidence of protein malnutrition, and that the anaemia would steadily improve with protracted protein therapy.

The relationship between these other defects and anaemia is easier to demonstrate than is the relationship between protein malnutrition and anaemia. In some instances the ease with which the relationship is demonstrated may result from the fact that administration of only relatively small quantities of the deficient substance can result in a cure of the anaemia; in other words, deficiency of relatively small amounts of these substances may lead to the imposition of a limiting factor on haemoglobin production. This principle is seen particularly in the case of deficiency or disturbance in the metabolism of vitamin B_{12}; it is also apparent in folic acid deficiency and even in iron deficiency. Protein, however, is a major constituent of haemoglobin and when it is deficient in an animal many tissues in addition to the blood are deprived of it; when therapy with protein is instituted only a fraction of that which is administered is utilized for haemoglobin production, much is diverted to other tissues and the haematological response to treatment is rendered proportionately more difficult to determine.

If there is deficiency of protein in man there is almost invariably also deficiency of other substances such as minerals and vitamins, and multiple infections are also often present. It has been difficult therefore to unravel the effect of the many contributory factors to anaemia associated with protein malnutrition. To these difficulties has been added that caused by the expansion of the plasma volume consequent upon increase in serum albumin brought about by treatment with protein. In kwashiorkor and some other protein malnutritional states this expansion of plasma volume, leading as it does to haemodilution, masks for a considerable time any improvement in the haemoglobin concentration which has occurred. It undoubtedly has given rise to the impression that treatment with protein has no, or only a limited, beneficial effect. In drawing attention to this factor, Allen & Dean (1965) made an important contribution to understanding the anaemia associated with kwashiorkor. Wharton (1968) has found further evidence of this process of haemodilution during therapy of kwashiorkor. The difficulties involved in sorting out the relationship between protein malnutrition and anaemia in malnourished children make animal experiments, in which the number of variables can be strictly controlled, particularly valuable in this field. Platt, Heard & Stewart (1964) showed that, in pigs, protein deficiency was consistently followed by anaemia and that this anaemia was aggravated by additional carbohydrate which converted a marasmus-like state into a kwashiorkor-like state. Sood, Deo & Ramalingaswami (1965) have also shown that protein-deficient monkeys consistently develop normocytic normochromic anaemia of moderate severity and that this is associated with falls in serum-

iron binding capacity, total plasma protein and albumin and a rise in γ-globulin. Control animals in their series did not show any of these changes.

From this experimental work and from observations in man there is now good evidence of a direct relationship between protein malnutrition and anaemia. We have proceeded from this situation and asked ourselves the question how this anaemia is brought about. The two main possibilities are, first, that the erythrocytes formed during the malnutritional state might have a shorter life-span than normal and that the anaemia may therefore be haemolytic. To examine this possibility, erythrocytes of protein-malnourished and of control animals were labelled with ^{51}Cr and their life-span was determined. The second main possibility is that bone-marrow of the malnourished animals who have anaemia may not be producing red cells adequately. If this were so, then it would not be able to utilize iron for the production of new red blood cells, and iron administered intravenously to such animals would be deposited in the iron stores of the body and not reappear in the circulation as rapidly as it should in newly formed erythrocytes. The rate of appearance of iron in such erythrocytes can be measured by the use of ^{59}Fe.

Procedure and Methods

The animals were maintained in the Nutrition Unit of the Medical Research Council; they were of beagle ancestry and after weaning at between 6 and 8 weeks of age were reared on diets providing either 5, 7 or 10 net dietary protein calories % (NDpCal%) referred to respectively as 05, 07 and 010 diets. The main constituents of these diets are oats, casein, dripping and dextrin and they are balanced so that they include all necessary minerals and vitamins. Full details of them have been published by Platt & Stewart (1968). Isotopic procedures were standard and have been described by Woodruff, Shafei, Awwad, Pettitt & Abaza (1966).

Each individual experiment has been performed on litter-mate pups. In the majority of instances pups on 05 diets have been paired with equal numbers of litter-mate pups on an 010 diet.

Results

The mean haemoglobin in seven protein malnourished (05) dogs was 11·3 g/100 ml and was very significantly lower than that in the corresponding control (010) group which was 15·06 g/100 ml ($t=4{\cdot}406$, $P<0{\cdot}0025$).

The investigation of haemolysis as a possible cause of the anaemia

No statistically significant difference has been found between the life-span of the erythrocytes of the animals raised on the 010 diet and those raised on a stock diet, nor has any statistically significant difference been found between the life-span of the erythrocytes of animals on 05 and 07 diets (Table 1). Chromium studies in a pooled group of five animals on 010 diets and four on stock diets revealed a mean

Table 1. *Chromium half-times for erythrocytes of dogs given a stock diet or diets containing* 10 (010), 7 (07) or 5 (05) NDpCal%

	Chromium half-time (d)			
	Stock diet	101 diet	07 diet	05 diet
	19	22	17	18
	22	24	15	21
	28	20		16
	32	18		24
		16		
Mean	25·2	20·0	16·0	19·7

Comparison between means:

Stock against 010	$t=1{\cdot}733$ $0{\cdot}1<P<0{\cdot}2$, not significant
07 against 05	$t=1{\cdot}39$ $0{\cdot}2<P<0{\cdot}5$, not significant
Stock+010 against 07+05	$t=1{\cdot}624$ $0{\cdot}1<P<0{\cdot}2$, not significant

chromium half-time of 22·3 d, and in four on 05 and two on 07 diets, 18·5 d. There is a suggestion that the life-span of the erythrocytes is longer in the well-nourished than in the malnourished animals, but the difference between these means does not reach conventional levels of significance. Nevertheless, the observation is of interest in view of suggestions that have been made regarding haemolysis which is reduced in human patients with kwashiorkor. There is here, however, no evidence that shortening of the life-span of the erythrocytes in these animals is sufficient to be a prime cause of the anaemia in the malnourished group.

The investigation of marrow functions in malnourished and control animals

As there was no evidence that the anaemia in the malnourished group was haemolytic, attention was turned to marrow function and each pair of animals in which a chromium study had been done was subjected to a study in which ^{59}Fe bound to plasma was injected intravenously. The rate at which the marrow removed radioactive iron from the plasma was measured and these measurements were followed by others on the rate of reappearance of ^{59}Fe in the circulation as a constituent of haemoglobin in new erythrocytes.

Iron storage. Removal of radioactive iron from the plasma and storage in the marrow and elsewhere were slower in the malnourished than in the control animals, the mean plasma ^{59}Fe half-time in six well-nourished animals being 50·5 min and in seven litter-mates from the malnourished (05) group 19·4 min longer at 69·86 min. The difference between these means just fails to reach conventional levels of statistical significance ($t=1{\cdot}699$, $0{\cdot}05<P<0{\cdot}1$). It seems that the iron-storage organs, of which of course the principal is the marrow, are less active in the malnourished group.

Iron utilization for haemoglobin production. The studies of the disappearance of iron from the plasma suggested that the marrow in the malnourished animals was not fully active but, of course, the liver and other organs store iron so that proof of impaired marrow activity cannot be obtained from that type of experiment. The proportion of the injected radioactive iron appearing in red blood cells as newly-

formed haemoglobin was therefore studied in six animals on 010 diets and compared with seven of their litter-mates raised on the 05 diet. In all the 05 animals the iron reappeared more slowly in the malnourished than in the control group. To compare the graphs showing iron incorporation into erythrocytes, a single index obtainable from each has been introduced by Joske, McAlister & Prankerd (1956). The deduced value, known as the marrow index, is obtained by determining the ultimate percentage of the amount of injected iron incorporated into erythrocytes and dividing this amount by the time in days taken for half of it to appear in the erythrocytes. This has been done for a period of observation; for the well-nourished group the marrow index is 48·78 and for the malnourished group 28·37 (Table 2). The difference

Table 2. *Marrow indices for seven protein-malnourished (group 05) dogs and their well-nourished control litter-mates (group 010)*

	Marrow index	
	Group 05	Group 010
	42·73	73·83
	33·33	38·18
	28·25	33·46
	22·95	57·22
	20·84	50·00
	19·88	40·00
	30·64	
Mean	28·37	48·78

For a comparison between these means, $t=3{\cdot}12$, $P<0{\cdot}01$.

between these means is highly significant and as assessed by the t test could arise by chance only once in 100 such experiments.

This work therefore indicates that impaired marrow activity is the main factor in the production of the anaemia of protein malnutrition.

The actuating mechanism in depressing marrow activity might be an effect upon it of impaired protein metabolism and this was the view put forward by Allen & Dean (1965). It is also possible that the depression might be mediated by deficiency of, or abnormality of enzymes, all of which are, of course, proteins. A further possibility is that, in protein malnutrition, erythropoietin is depressed and results in a retardation of protein synthesis in the erythroid precursors. This view has been developed by Reismann (1964*a*,*b*) as a result of work on protein-malnourished rats but has not been upheld by McKenzie, Friedman, Katz & Lankowsky (1967).

Conclusion

Anaemia occurs as a direct result of protein malnutrition. Evidence from these experiments indicates that haemolysis is not a major factor in its causation although a statistically insignificant shortening in the life-span of erythrocytes in protein-malnourished dogs has been observed. The major aetiological factor appears to be an impairment in the ability of the malnourished animal to produce new erythrocytes, i.e. the anaemia is truly dyshaemopoietic. In reaching this conclusion we

would like to acknowledge with gratitude the help, collaboration and inspiration which we received from the late Professor Ben Platt and to pay tribute to the influence he had on knowledge of nutrition in general and of nutritional anaemias in particular.

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Host—parasite relations: nutrition and genetics in filariasis

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The term 'host—parasite relations' is misleading. Conventionally, parasites are considered as being related to hosts in the way that a pathogenic bacterium produces a disease. Parasitism, however, is more than this. It is a biological system which enables creatures to live together. The system enables each to adapt itself to some extent to the other but again this system is more than merely host and parasite. Many parasites are transmitted by vectors, sometimes by several. The parasite, the host and the vector all have their own environments, which are mostly separate, but must be shared on the instant that the parasite is transmitted. One should therefore consider host–parasite–vector–environment combinations; each of the components has evolved within the evolution of the whole combination.

Parasites are dependent for transmission on the accident of the environment and on accidents of the habits of their hosts. The accident of environment may allow a parasite to be transmitted to one host and give no opportunity of transmission to another, thus providing an example of specificity limited by environmental accident. An example is *Loa loa*, a filarial parasite living in the connective tissue of man and certain monkeys in the rain forest in West and Central Africa. It produces the transient swellings known as Calabar swellings, and an alarming incident when