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THE EFFECT OF CHANGES IN NUTRITION ON THE HOST-PARASITE RELATIONSHIP

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Anaemia and parasitism in man

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Introduction

This paper reviews in general the problem of parasitism and anaemia in people living in the tropics. Wherever poverty is common, malnourished subjects are likely to be encountered frequently and anaemia is a usual clinical finding. Wherever insect vectors are prevalent and sanitation is defective, parasitic infection is common and, in many instances, anaemia is a complication. Infection by parasites being common, and anaemia being common, it is to be expected that both should often be discovered in the same patient, and interest is aroused in the problem of cause and effect.

Much investigation has been reported concerning the place of parasitic infections in causing anaemia. There is little opportunity in tropical conditions, however, to investigate how far anaemia, or malnutrition in general, predisposes to infection by parasites. This is an aspect of the subject in which there is scope for experimental study in animals, whose environment can be carefully controlled.

Types of anaemia

Myelophthisic anaemias. First we may consider those patients in whom some change occurs in the bone marrow, preventing the production of healthy blood cells. In visceral leishmaniasis (kala-azar), trypanosomiasis, and possibly toxoplasmosis multiplication of infected reticulo-endothelial cells in the marrow may reduce the volume of blood-forming tissue and cause orthochromic normocytic anaemia of varying degree. However, especially in kala-azar, the possibility must be remembered of secondary hypersplenism causing the anaemia. Depression of marrow function due to toxæmia in the more severe protozoal infections must also be recollected and it may be that aplastic anaemia, an uncommon complication of falciparum malaria, is due to this cause.

Haemorrhagic anaemias. Secondly, anaemia may be due to blood loss, and, with parasitic infections, it is usually chronic blood loss which produces hypochromic, microcytic anaemia. Acute blood loss due to parasites must be uncommon, though I have seen a boy in East Africa suffering from severe anaemia due to blood loss caused by a leech attached on the posterior pharyngeal wall.

Amoebic dysentery continuing unchecked over a long period may result in sufficient blood loss to cause anaemia. Schistosomiasis is a widespread, chronic disease in which repeated small losses of blood occur from the bladder or the bowel. Gerritsen, Walker, de Meillon & Yeo (1953) investigated eight adult, male Bantu patients suffering from severe urinary schistosomiasis with persistent haematuria. They found the daily blood loss to range from 1.3 ml to 6.1 ml, representing daily losses of iron ranging from 0.57 mg to 2.1 mg. Obviously the daily intake of iron by such subjects must be known if one is to assess the likelihood of anaemia resulting. The problem of determining the effects of infection with schistosomes is arousing great interest at the present time, and Walker & de Lacy (1962) have recently reported the anomalous results they have found among Bantu children infected with schistosomiasis, some of whom show greater mean heights and weights than their uninfected fellows.

Investigations of infection by the whipworm (*Trichuris trichiura*) might shed some interesting light on the host-parasite relationship. It is a very widespread infection, apparently of no consequence to the health of most of the hosts. Yet, rarely in children in some parts of the world, of which the Mississippi delta area is one, intense infections are found with numerous worms seen attached to the mucosa of the lower bowel, prolapse of the rectum, and the passage of blood and mucus from the bowel with coincident anaemia (Jung & Beaver, 1951). What factors of environment, diet, race or habit, climate, soil, or the association of other parasites produce this rare, but quite serious condition?

Infection with hookworms is probably the most widespread parasitic cause of blood loss in tropical areas. It will be discussed below.

Haemolytic anaemias. Thirdly, haemolysis may occur. The most serious parasitic cause of haemolysis in the tropics is malaria, especially *Plasmodium falciparum* infection. The repeated maturing of schizonts with consequent rupture of the erythrocytes containing them results in anaemia. McGregor & Smith (1952) reported the results of a survey in an area of hyperendemic malaria in the Gambia, West Africa. They found *P. falciparum* to be present in 54.7% of the blood films examined, and *Plasmodium malariae* was present in 8.5%. The incidence of malarial infection reached a peak in children of 2-5 years of age, and decreased gradually in later childhood and adolescence. Using Dare's haemoglobinometer McGregor & Smith surveyed the levels of haemoglobin and found that the lowest were in the age groups from 2 to 5 years, the period when parasite density was at its greatest.

Blackwater fever is a serious episode of intravascular haemolysis occurring in a patient infected with *P. falciparum* and irregularly dosed with varying amounts of quinine as prophylaxis or treatment. Fortunately, with the newer antimalarials this complication is becoming rarer. Its exact cause is not known. Parasitized cells are

destroyed, as also are some of the non-parasitized cells, yet there is no evidence of circulating haemolysins, nor any evidence of a special haemolytic strain of the parasite. The present theory is that some process of autosensitization of erythrocytes takes place related to *P. falciparum* infection and to quinine. Then some added stress factor such as chill or injury precipitates haemolysis. It is possible for half the circulating erythrocytes to be lost in 24 h in this condition. The theory of autosensitization received support by the demonstration by my former colleague Dr J. C. L. Adams (Linley-Adams, 1953) that cortisone will control the haemolysis. Trowell & Vaizey (1956) have confirmed the value of steroids in blackwater fever.

Dyshaemopoietic anaemias. Fourthly, the dyshaemopoietic anaemias are those in which adequate supplies of the necessary substances for the production of healthy erythrocytes are not available in the bone marrow. The list of identified substances is already long, but among the most important nutriments required are iron, vitamin B₁₂ (cyanocobalamin), folic acid, and protein. The influence of parasitic infections on the ingestion, digestion, absorption, and utilization of these and other haemato-poietic substances has been the subject of extensive research.

Intestinal parasites may cause diminished appetite with consequent reduction of intake of nutriments. Or the parasites may compete with the host for available material. Probably the best example of the latter situation is infection by the fish tapeworm, *Diphyllobothrium latum*, which uses cyanocobalamin (cf. Nyberg, 1963). Or defective digestion may occur as the result of inhibition of normal enzyme action by material produced by the parasites. Finally, absorption may be interfered with, either owing to the bulk of the parasites limiting the absorptive area of the intestinal villi, or owing to irritation of the bowel, increased peristalsis and intestinal hurry, and so cause malabsorption of the products of digestion.

An example of some of these consequences of parasites in the intestinal canal is recorded by Venkatachalam & Patwardhan (1953). A careful investigation was made of the nitrogen intake and excretion by the alimentary tract in nine children infected with roundworms (*Ascaris lumbricoides*) and was repeated after anthelmintic treatment. The mean faecal nitrogen output of the nine children before deworming was 1.315 g/24 h, and after deworming 0.755 g/24 h. These workers showed that, though a certain amount of nitrogen is lost in roundworm eggs, it is a very small amount compared with the considerable difference in nitrogen loss before and after removing the worms. They believe that heavy roundworm infection in children may result in decreased digestion of protein, possibly owing to anti-enzymes produced by the worms. They refer to other parallel studies, and, in particular, to those of Stewart (1932-3) and Shearer & Stewart (1932-3) who found defective utilization of dietary protein in sheep heavily infested with nematodes. Trowell (1949) has drawn attention to the part played by parasitic infection in the development of protein-calorie malnutrition.

Anaemia and parasitism in practice

Though for purposes of classification it is useful to divide the anaemias in this way, in practice it is nearly always an oversimplification to do so. For example, certain

parasitic infections may produce anaemia in several ways at the same time. Thus malaria causes fever with consequent anorexia and sometimes recurrent vomiting which must lead to impaired dietary intake. But it will also cause haemolysis, and, in severe infection, it may depress marrow function.

Again, in practice we usually find more than one cause operating to produce anaemia in the same patient. In many instances we suspect that the diet is defective, and several kinds of parasites may be present at the same time. (Platt (1957) refers to work done in his unit by Barakat (1948) who showed that lysine deficiency in the diet of rats interfered with their ability to develop resistance to a nematode parasite *Nippostrongylus muris*. He refers also to work by Seddik (1950) who found that only animals completely deprived of lysine succumbed to infections with rat hookworm whereas normally fed animals survived.) Moreover, we usually do not know for how long these various factors have operated, so that different degrees of depletion of iron stores in the body will be found. Frequently liver damage is also present, and changes in the plasma proteins are found which may have a bearing on the rate at which the patients, freed from parasites, recover from anaemia.

Finally in this connexion allowance must be made for the development of immunity, about which a little is known in relation to protozoal infections, but very little in relation to metazoan infections. The pattern of malarial incidence in areas where the disease is endemic illustrates this. It is believed that the newborn infant acquires some passive immunity from the mother but it is soon lost. However, there is some evidence that the presence of foetal haemoglobin inhibits the development of malaria in infants. These points were brought out in an investigation by Gilles (1957) of 300 breast-fed Gambian infants all under 6 months of age. During the peak period of malarial transmission he found that the mean parasite rate, mainly due to *P. falciparum*, increased from 10% in the first 2 months of life, to 42% in the 3rd and 4th months, and to 53% in the 5th and 6th months. In twenty-five infants whose foetal haemoglobin was measured there was an apparent relationship between decreases in content of this haemoglobin in the children's blood and increase of malarial infection. It is well recognized that the dangerous time of life in such endemic malarial areas is that before active immunity has been acquired. Bruce-Chwatt (1958) states 'The period of transition between passively inherited and actively acquired immunity to malaria constitutes for the child in endemic areas the most dangerous phase in the development of its host-parasite relationship. In these areas malaria can be incriminated as a direct cause of about 12% of all deaths of African children up to 3 years of age. During this period of changing host-parasite relationship holoendemic malaria affects the growth and development of African children. The nutritional handicap caused by any febrile disease with symptoms of vomiting and anorexia is in this case increased by the direct effect of the parasite load on the developing organism'.

McGregor, Gilles, Walters, Davies & Pearson (1956) compared the clinical state of children in the Gambia, some of whom were protected against malaria from birth by weekly dosing with chloroquin, with that of others not so protected. They found that the slight lag in general health suffered by the unprotected was made up after

2 years of age. It is however, during this period when active immunity is being acquired that deaths directly caused by malaria are numerous.

Hookworms and anaemia. The literature on the subject of anaemia in patients infected with hookworms is very extensive. Foy & Kondi (1960) list references to investigators who have found little correlation between hookworm infection and anaemia and others who have found a close correlation. They point out, however, that most of these studies have been based on the use of counts of hookworm eggs in faeces as a means of assessing worm load, and this method is not very reliable. Both Roche (1956) himself and with his colleagues (Roche, Perez-Gimenez, Layrisse & Prisco, 1957) reported blood losses in hookworm infection, using ^{51}Cr -labelled red cells. Tasker (1961) used a similar method, and counted the hookworms passed after vermifuge treatment with tetrachlorethylene. He found that the daily blood loss increased from about 2 ml with light infections of the order of twenty hookworms to 90 ml with heavy infections of 1500 or more worms. The blood loss per worm decreased as the number of worms increased. His patients were all anaemic but he calculated that with normal haemoglobin levels iron losses would range between 1 and 40 mg/day. Foy & Kondi (1960) found in fifteen patients infected with both *Necator americanus* and *Ancylostoma duodenale* that the daily average iron loss was 6.5 mg, but iron losses must be high early after infection when the haemoglobin level is still high, and so the iron stores of the body are soon depleted. Even allowing for a greater absorption of dietary iron than normal in these anaemic subjects, and allowing for some absorption of iron from blood released from hookworms in the intestine, the average diet of the tropics yielding 30–50 mg iron daily (Indian Council of Medical Research, 1951; Aykroyd, Patwardhan & Ranganathan, 1951; Walker, 1956) may not meet the needs of the patient. Progressive anaemia is likely in heavily infected patients. In addition, however, merely to reduce the hookworm load by vermifuges may not result in reticulocytosis and blood regeneration. The depleted iron stores must be made good for recovery to take place. Stott (1961) reporting on the causation of iron-deficiency anaemia which he found to be widespread in Mauritius stated that of 284 anaemia patients 250 (88%) were infected with hookworms, and in 92 of them in whom the hookworm load was measured it averaged 84 worms, with a maximum of 944.

The causation and treatment of anaemia in some Gambian patients

As an example of the complexities revealed in trying to determine the cause of anaemia in patients in the tropics, I would like to refer to an investigation I made in the Gambia during two visits to the Medical Research Council Laboratories, Fajara, from December 1955 to March 1956 and from May to September 1958. My thanks are due to the Director of Medical Services, the Gambia, for permission to use clinics and to bring patients to the research centre, to Dr McGregor, director of the Medical Research Council Laboratories, and to the medical and nursing staff there. I have to acknowledge the help in planning the investigation given by Professor Woodruff.

I will not include details of the way in which patients were found through village clinics, and at the hospital in Bathurst, or of the standard haematological methods which were used in investigating them. The groups of anaemic subjects are listed below, with the possible parasitic causative factors for anaemia which were found.

Microcytic anaemia (mean corpuscular volume less than $78 \mu^3$). There were fourteen patients, nine males and five females, whose blood picture was:

	Mean value	Standard deviation	Range
Haemoglobin (g/100 ml)	6.81	1.57	3.6- 8.8
Erythrocytes ($10^{-6}/\text{mm}^3$)	3.23	1.03	1.2- 4.7
Mean corpuscular volume (μ^3)	68.8	5.89	57.9-77.8
Mean corpuscular haemoglobin concentration (%)	32.5	6.28	24.4-45.0
Reticulocytes as percentage of erythrocytes	1.99	1.45	0.4 - 5.4

Of parasitic diseases found, one male had active urinary schistosomiasis and one woman had active Bancroftian filariasis. In two patients only, malarial parasites were found: one woman had scanty *P. falciparum* gametocytes in her blood; one child aged about 4 years had a mixed *P. falciparum* and *P. malariae* infection. Thirteen of these fourteen patients had hookworm eggs in their stools. In seven patients in whom hookworms were counted after a vermifuge the average number of worms was 219, with a range from 1 to 787 worms.

Normocytic anaemia (mean corpuscular volume $78-94 \mu^3$). There were eleven patients, four males and seven females whose blood picture was:

	Mean value	SD	Range
Haemoglobin (g/100 ml)	7.8	1.28	5.2- 9.5
Erythrocytes ($10^{-6}/\text{mm}^3$)	3.05	0.34	1.9- 4.1
MCV (μ^3)	84.5	4.24	81.2-93.1
MCHC (%)	30.5	2.31	25.0-34.1
Reticulocytes as percentage of erythrocytes	2.94	1.92	0.5- 5.7

Of parasitic diseases found among these patients, one pregnant woman had in her blood *Trypanosoma gambiense*, *P. falciparum* trophozoites, and *Acanthocheilonema perstans* embryos. One woman had typical toxoplasmic choroido-retinitis with a positive dye test in her blood serum. As well as the woman mentioned, two children had malarial infections. Ten of these eleven patients had hookworm ova in their faeces. Only three patients had the worm loads counted and the average number of worms was forty-one.

Macrocytic anaemia (mean corpuscular volume $95 \mu^3$ or more). There were six patients, two males and four females, in this category and the blood picture was as follows:

	Mean value	SD	Range
Haemoglobin (g/100 ml)	6.95	1.87	3.7- 9.5
Erythrocytes ($10^{-6}/\text{mm}^3$)	2.08	0.6	1.3- 3.0
MCV (μ^3)	106.9	8.85	95.6-121.4
MCHC (%)	31.5	1.9	28.8- 34.1
Reticulocytes as percentage of erythrocytes	1.42	1.06	0.4- 3.0

One child showed scanty malarial trophozoites in the blood. All these patients had hookworm ova in their stools. The worm load was counted in two patients and was found to be 45 worms in one, and 210 worms in the other.

Thus in these thirty-one anaemic patients (fifteen males and sixteen females) the parasites found were *P. falciparum*, *P. malariae*, *Trypanosoma gambiense*, *A. perstans*, *Schistosoma haematobium* and hookworms; there was also evidence of definite infection with *Toxoplasma gondii* and *Wuchereria bancrofti*. There were other causes of blood loss which I have not mentioned since they are irrelevant to the subject of this paper.

Treatment was given to all those infected with malaria and hookworms, and maintenance on a prophylactic dose of pyrimethamine (Daraprim) continued while the patients were under observation. An average period of 2 weeks was allowed to elapse after such treatments in order to observe any improvement in the anaemia. No definite reticulocytosis or any consistent change in the blood picture was observed. The patients were now treated in groups: in general those with microcytic anaemia were given iron (ferrous sulphate) by mouth, most often 1.2 g (six tablets) daily; those with macrocytic anaemia were usually given supplementary protein (Casilan), 4 oz daily. Some patients were treated with both iron and protein together. The results were that when iron was given a reticulocytosis was to be expected in 7-10 days and a rapid improvement in the blood picture. When the patients with microcytic anaemia were contrasted with those having macrocytic anaemia it was noticed that the mean serum albumin levels in the blood were 2.66 g/100 ml and 2.25 g/100 ml respectively. The administration of protein resulted in improvement in the blood in that macrocytosis disappeared, though no reticulocyte response occurred. Possibly those given protein supplement enjoyed improvement in appetite, for their general condition appeared to improve and their body-weight to increase.

Conclusion

Parasitic infections are widespread in the tropics and may produce anaemia in various ways. Probably the most important parasitic cause of blood loss is hookworm infection, but the result depends upon the dietary intake of iron as well as upon the load of worms. When intake of iron is marginal, severe hookworm anaemia is likely and, because iron stores are depleted, removal of the worms alone is unlikely to cure the patient. Malaria may cause haemolysis. Other parasites may utilize or limit the digestion and absorption of nutriment required by the host and so lead to anaemia and malnutrition. In the human being infected with parasites multiple factors are usually involved in the causation of anaemia.

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***Diphyllobothrium latum* and human nutrition, with particular reference to vitamin B₁₂ deficiency**

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The effect of intestinal helminths on their hosts has been widely studied, and the importance of relating these effects to the nutrition of the host is evident. As regards *Diphyllobothrium latum*, the only relatively well-known aspect of its nutritional influence is the vitamin B₁₂ deficiency it causes in its host. Therefore, I shall expand mostly on this theme. During recent years the possibility of disturbances in the utilization of other vitamins has also been subjected to preliminary investigations. Further, knowledge has accumulated regarding the symptomatology of fish-tapeworm infection, which may also have nutritional implications.

Vitamin B₁₂ deficiency and fish-tapeworm infection

The views of our group regarding what happens in an intestine containing *D. latum* are diagrammatically represented in Fig. 1. Normally, a considerable proportion of the vitamin B₁₂ ingested in the food is absorbed. In the presence of worm infection there is competition between the parasite and the host for the vitamin B₁₂ available. In this situation the worm almost always utilizes most of the vitamin, leaving inadequate amounts to be absorbed by the host. The consequence is a gradually developing vitamin B₁₂ depletion with a vitamin B₁₂ deficiency state as the final result. This state manifests itself as the well-known disease called pernicious anaemia. The investigations that have led to this conclusion have been extensively