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Parasitism and Anemia[1]

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ANEMIA CONSTITUTES a worldwide problem and at present is a major tropical disease. Severe iron-deficiency anemia is reported from India, Africa, and South America. Though the etiology of these anemias may be manifold, it has become obvious that chronic blood loss caused by certain parasitic and helminthic infections plays an important role in their causation.

Hookworm disease is widespread and found in many tropical and semitropical countries. The infection involves over 450 million people. In Egypt up to 29% of patients admitted to the Endemic Disease Hospitals are found infected with *Ancylostoma duodenale,* and hookworm infection is the main cause of severe iron-deficiency anemia in farmers.

Over 100 million people are infected with schistosomiasis, and with the introduction of new irrigation schemes in many of the developing countries this number may be increasing. Schistosomiasis is found throughout Africa, the Middle East, South America, the West Indies, and the Far East. Over 70% of Egyptian farmers are infected with schistosomiasis and Ata (1) reviewing the etiology of anemia in Egypt reports that the most common anemia found in Egyptian patients is that which accompanies schistosomiasis whereas the severest is that which accompanies ancylostomiasis.

Recently, much progress has been made in measuring quantitatively the relationship between intensity of parasitic infection, anemia, and blood loss, and the major part of this discussion will therefore be directed towards defining the role played by the common helminthic infections in causing blood loss and iron-deficiency anemia.

The helminths associated with iron-deficiency anemia are those causing chronic blood loss either from the gastrointestinal tract or urinary system. These include hookworm infection (*Necator americanus* and *Ancylostoma duodenale*), whipworm infection (*Trichuris trichiura*), and schistosomiasis (*Schistosoma mansoni, S. haematobium,* and *S. japonicum*).

HOOKWORM

Perroncito (33), in 1880, first noted a relationship between hookworm infection and anemia, and Darling et al. (8) in 1920 emphasized the direct relationship between the intensity of hookworm infection and anemia. Reports from Brazil (38), China (40), Mexico (6), India (22), United States (3), Mauritius (41), Egypt (13), and Venezuela (27) confirmed that with increasing loads of hookworm infection there occurred a concomitant decrease in hemoglobin concentration.

With the introduction of the chromium 51-red blood cell-tagging technique (9) for the measurement of intestinal blood loss, a quantitative relationship between the intensity of hookworm infection (measured by counting all worms passed after vermifuging), actual blood loss, and degree of anemia (measured by hemoglobin concentration per 100 ml of blood) was finally established. Studies with radioisotope techniques have shown that patients

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TABLE 1

Intestinal blood and iron losses in patients with hookworm infection

Authors	Number of patients studied	Hg, g/100 ml	Blood loss, ml/day	Iron loss, mg/day	Blood loss, ml/worm per day		Number of worms harbored	Geographical area
					duodenale	*nector*		
Roche et al. (36)	21	2.0–18.1	2.0–251.0	1.2–29.0	0.2	0.03	67–3,534	Venezuela
Foy and Kondi (17)	15	1.6–9.2	0–88.0	0–14.0	0.12	0.03	7–2,522	East Africa
Tasker (43)	29	3.0–10.0	2.0–90.0			0.04–0.1	20–1,500	Malaya
Gilles et al. (20)	8		34.0–147.0			0.04–0.07	821–2,900	Nigeria
Farid et al. (14)	12	2.8–11.2	13.6–45.0	3.6–9.9	0.16–0.34		65–167	Egypt
Farid et al. (10)	12	3.2–12.5	2.3–120.0	0.31–13.0	0.11–0.29		6–419	Egypt
Mahmood (29)	20		0.3–21.0			0.005–0.13	6–976	England
Mahmood (29)	12		0.2–38.0		0.20–0.34			England

with heavy hookworm infection can lose up to 250 ml, or a quarter of a liter of blood daily, and up to 29 mg of iron in the gastrointestinal tract (Table 1).

N. americanus. Roche et al. (36) reported a blood loss of 0.03 ml/day for each *Necator americanus* worm, Tasker (43) reported a blood loss of 0.04–0.1 ml/worm per day, Gilles et al. (20) approximately 0.05 ml/day, and Mahmood (29) 0.005–0.13 ml/worm per day.

A. duodenale. Until recently reports on direct measurement of blood loss in *A. duodenale* infection with ^{51}Cr were few and variable. Mahmood (29) reported losses varying from 0.20 to 0.34 ml/worm per day and Farid et al. (14) reported in one series the mean loss per *A. duodenale* per day to be 0.26 ± 0.045 ml and, in a second series (10), 0.20 ± 0.055 ml. Clearly, *A. duodenale* causes greater blood loss than *N. americanus,* which explains the iron-deficiency anemia found in patients with comparatively light *A. duodenale* infection.

Severe hookworm infection and anemia are often associated with edema and hypoalbuminemia and recently it has been shown that intestinal protein loss in patients with severe hookworm infection may lower the total serum proteins, particularly, the serum albumin. Gilles et al. (20) measured the loss of albumin in the gut in three patients using ^{131}I-tagged albumin and an oral ion-exchange resin. They reported a daily loss of albumin in the gut ranging from 2.0 to 4.2 g. Blackman et al. (5) succeeded in showing a correlation between hookworm load and plasma albumin loss in the gastrointestinal tract and reported the loss of albumin to be roughly equal to 0.1 g/100 *Necator americanus* worms, which is equivalent to a loss of 3 ml plasma/100 worms. This small loss may, in subjects on inadequate protein intake, be sufficient to lead to hypoalbuminemia.

A malabsorption syndrome closely resembling tropical sprue has been described to occur with a number of helminthic infections (32). Layrisse et al. (26) and Sheehy et al. (37), though unable to demonstrate any malabsorption of vitamin B_{12} in patients with heavy hookworm infection, were able to show impaired folic acid absorption. Layrisse et al. (26) and Foy (16) reported low levels of serum vitamin B_{12} and folic acid in patients with heavy hookworm infection. Whether these low levels were due to dietary deficiency, malabsorption, or loss, is not clear. Woodruff (45) makes a point of noting that, although loss of iron may be the dominant feature in hookworm anemia,

this information is only of recent origin and precise information of the loss of other blood constituents including B_{12} and folic acid has not yet been properly evaluated.

Trichuris trichiura

Jung (21) and Biagi (4) reported a microcytic, hypochromic anemia in *Trichuris trichiura* infection. Woodruff (45) did not think *Trichuris trichiura* caused significant blood loss and reported no radioactivity in fecal samples in patients with light infection. Layrisse et al. (24), however, measured the blood loss using ^{51}Cr-tagged red cells in heavily infected children and reported a blood loss ranging from 0.8 to 8.6 ml/day and concluded that infections of over 800 parasites can induce anemia in children.

Schistosomiasis

S. mansoni: Foy and Nelson (18) reported that the anemia in the early stage of schistosomiasis is probably due to blood loss. Walker et al. (44) reported that *S. mansoni* infection did not significantly lead to blood loss or to iron-deficiency anemia in South Africa. Taha et al. (42), from Egypt, reported anemia in patients with bilharzial colonic and rectal polyps but did not measure the gastrointestinal blood loss. Using ^{51}Cr-tagged red blood cells, Farid et al. (10) for the first time reported blood loss in two patients with bilharzial colonic and rectal polyps, and later confirmed these studies in another 10 patients (11) (Table II). They emphasized that, though the mean daily blood loss of 12.5 ml and iron loss of 3.3 mg may not be high and may not lead to overt anemia, it certainly can lead to depletion of the body iron stores. These authors stressed the importance of the fact that other helminthic infections besides hookworm may in certain geographical areas lead to chronic intestinal blood loss.

TABLE II

Intestinal blood loss in *S. mansoni* infection, ^{51}Cr

	ml/day
Farid et al. (11)	2.3–25.9

Urinary blood loss in *S. haematobium* infection, ^{59}Fe

	ml/day
Gerritsen et al. (19)	1.3–6.1 (using chemical methods)
Mahmood (29)	0.44–6.0
Farid et al. (12)	2.6–126.0

S. haematobium: Gerritsen et al. (19), using chemical analysis, measured the urinary blood loss in eight African patients suffering from advanced chronic *S. haematobium* infection. They calculated the urinary blood loss as ranging from 1.3 to 6.1 ml/day. Mahmood (29) used in vivo ^{59}Fe-labeled red blood cells to measure the urinary blood loss in eight patients infected with *S. haematobium* and reported a loss ranging from 0.44 to 6.0 ml/day. Farid et al. (12), using the same method, measured the urinary blood loss in nine patients with *S. haematobium* infection and severe hematuria and reported it as ranging from 2.6 to 126 ml/day with a mean daily iron loss ranging from 0.6 to 37.3 mg. They noted that though the urinary blood loss in *S. haematobium* infection can be severe it usually lasts only for short periods and is not a constant steady loss as in hookworm infection. Other workers from Egypt (1) have repeatedly noted that the severest iron-deficiency anemia occurred in farmers with obvious hematuria caused by *S. haematobium* and combined *S. mansoni* and *A. duodenale* infections.

In concluding this discussion it is important to remember that human parasites may cause anemia by different mechanisms than simply direct blood loss. Work

by Farid et al. (15), Knight et al. (23), Richmond et al. (35) Marsden et al. (30), and Pryor (34) has shown the definite presence of anemia secondary to hypersplenism and hypervolemia in patients with chronic splenomegaly due to schistosomiasis, visceral leishmaniasis, and malaria. The hemolytic anemia in severe falciparum or vivax malaria and blackwater fever has been well described (2, 7, 28) as has the B_{12} megaloblastic anemia reported in *Diphyllobothrium latum* infection (31). As mentioned earlier a malabsorption syndrome resembling tropical sprue and accompanied by anemia has recently been shown to occur in patients with hookworm infection and also in patients with heavy *Strongyloides stercoralis* (45) and *Giardia lamblia* infections (32).

SUMMARY

The main parasites causing blood loss in man and leading to direct iron-deficiency anemia are the common worm infections. These include hookworm infection (*Necator americanus* and *Ancylostoma duodenale*); whipworm infection (*Trichuris trichiura*); and schistosomiasis (*Schistosoma mansoni, S. haematobium,* and *S. japonicum*).

Radioisotope studies with chromium 51-tagged red blood cells have shown that patients with heavy hookworm infection can lose up to 250 ml, or a quarter of a liter of blood, daily, and up to 29 mg of iron in the gastrointestinal tract, thus leading to direct iron-deficiency anemia.

Workers from South America and East Africa have shown that each *Necator americanus* worm can cause a daily blood loss of 0.03 ml, which means that patients infected with approximately 1,000 worms can lose up to 30 ml of blood daily. More recent work from London and Egypt has shown that the Old World hookworm, *Ancylostoma duodenale,* can cause a daily blood loss of 0.2 ml, approximately 10 times more than the American hookworm, *Necator americanus.*

Layrisse and his colleagues (24–27), using ^{51}Cr-tagged red cells, measured the blood loss caused by *T. trichiura* in heavily infected children and showed that the daily blood loss can reach up to 8.6 ml. These workers concluded that infection of over 800 parasites can lead to anemia.

Using ^{51}Cr-isotopes, Farid (10–15) and his colleagues measured the blood loss in patients with chronic *Schistosoma mansoni* polyp formation of the colon and showed that these patients can lose up to 12.5 ml of blood daily. Using ^{59}Fe-isotopes, these workers also measured the blood loss in the urine in patients infected with *Schistosoma haematobium* and demonstrated that these patients can lose up to 120 ml of blood daily. Blood loss in schistosomiasis, however, is intermittent and not constant and though it may be severe for a few days it usually ceases for prolonged periods.

It has been shown by ^{51}Cr and body surface counting of radioactivity that the large spleen in chronic schistosomiasis, leishmaniasis, and malaria, can destroy the red blood cells and lead to anemia secondary to hypersplenism.

Recent work has also shown that a malabsorption syndrome leading to poor absorption of essential nutrients may occur in patients heavily infected with hookworms, *Strongyloides stercoralis* and *Giardia lamblia.*

Destruction of red blood cells leading to a hemolytic anemia has been shown to occur in malaria, and vitamin B_{12} megaloblastic anemia has been demonstrated to occur in patients infected with the intestinal fish worm, *Diphyllobothrium latum.*

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