Hookworm infections and human iron metabolism

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SUMMARY

Ancylostoma duodenale and Necator americanus are extremely common species of soil-transmitted helminth which flourish where poverty and malnutrition prevail. Hookworms contribute significantly to iron-deficiency anaemia, which remains one of the world's major nutritional problems, through the feeding activities of intestinal stages leading to chronic blood loss into the gut. In this article, a mathematical model is proposed to explain how human iron metabolism may respond to hookworm infection of varying intensity. The model draws attention to the importance of the regulation of stored iron levels in the process. The results from the model are presented for the effects of hookworm infection on the iron metabolism of a healthy adult male. Calculations are also presented in which the effects of hookworms on the iron metabolism of a non-pregnant woman are compared with those of a pregnant woman. Use of the model may help develop a better understanding of the pathology of hookworm disease.

Key words: Hookworm disease, iron-deficiency anaemia, pregnancy, mathematical model.

INTRODUCTION

Of the 13 species of hookworm that have been found in association with humans (Coombs & Crompton, 1991), Ancylostoma duodenale and Necator americanus are the two of major public health significance. About 900 million people are estimated to be infected with A. duodenale and N. americanus both of which are prevalent throughout tropical and subtropical countries (Pawlowski, Schad & Scott, 1991). The infections flourish when soil becomes contaminated with human faeces carrying hookworm eggs. Probably most of the infections are due to N. americanus which is mainly tropical in its distribution, but Ancylostoma duodenale is also probably more widely distributed than is usually thought to be the case (Schad, pers. comm.). Mixed infections are frequently encountered, e.g. in China (Sen-Hai & Wei-Xia, 1990). The more precise distributions of both species depend mainly on temperature, humidity, soil type and altitude. Generally, rural communities are most heavily infected by hookworms, presumably because of the constant and close contact of the people with soil. It should not be forgotten that the same communities and individuals that experience hookworm infections will also be plagued with Ascaris lumbricoides and Trichuris trichuria. Despite the fact that hookworms, roundworms and whipworms persist wherever poverty, poor health awareness and inadequate sanitation are found, there are grounds to hope that optimism that fresh strategies for the control of soil-transmitted helminth infections may help to relieve and reduce morbidity if they can be incorporated in a sustainable manner into the various patterns of primary health care which are beginning to emerge in developing countries (WHO, 1987; Savioli, Bundy & Tomkins, 1992).

An Italian physician called Dubini provided the first detailed description of hookworms in 1838 after carrying out an autopsy on a woman who had died in Milan. Later he attributed the death of other patients to these worms which he called Aphylostoma duodenale. Little attention was paid to hookworm infections, however, until an epidemic of anaemia occurred in 1880 amongst labourers digging the Saint Gotthard tunnel in Switzerland (Hegner et al., 1938). By 1903, the British Home Secretary had requested J. B. Haldane to report to both the House of Lords and the House of Commons on 'Ankylostomiasis in Westphalian Collieries' (Haldane, 1903). At that time, infections of A. duodenale were endemic in mining communities across Europe and the infection spread as poorly paid and unemployed miners emigrated to seek work. There was equal concern in the USA and in October 1909 John D. Rockefeller dedicated enormous resources to hookworm research and control programmes in recognition of their importance as agents of human disease and their impact on socio-economic development. This event led first to the establishment of the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease followed shortly afterwards with the Rockefeller Foundation (Ettling, 1990).

Much of Haldane's recommendation for tackling the hookworm problem is still relevant. He wrote 'I should like to point out the desirability of obtaining further information as to the pathology of the disease itself, the mode of infection, the conditions under which the larvae develop, the best disinfectants and the simplest methods of diagnosis: also as to the best
forms of sanitary receptacles for use underground; and finally as to the organization of satisfactory means for the examination of suspected cases of infection with the worm'. Following the intellectual energy generated by the Rockefeller Foundation, much has been discovered about the biology of hookworms, about transmission and epidemiology and about appropriate measures for prevention and control (see Schad & Warren, 1990). Although it is not disputed that chronic blood loss into the small intestine caused by the feeding activities of hookworms is a major factor in the aetiology of iron-deficiency anaemia worldwide, there remains much to be understood about the pathology of the disease. Here we present a mathematical framework for investigating how hookworm infection might disturb human iron status and for explaining how iron metabolism may respond and adapt to this destabilizing influence.

**LIFE HISTORY OF HOOKWORMS**

Hookworms are dioecious and have a direct life cycle (Fig. 1), a remarkably high specificity for the human host with transmission and the establishment of the infection usually being dependent on the successful penetration of the skin of a susceptible host by an infective third-stage larva (Table 1). Fuller details of the life history characteristics of *A. duodenale* and *N. americanus* have been described by Hoagland & Schad (1978) who concluded that *A. duodenale* is more of an opportunistic species than *N. americanus*. That *A. duodenale* has more flexibility in its life history is seen by its ability to infect humans by the oral and transplacental as well as the percutaneous route (Sen-Hai & Wei-Xia, 1990; Schad, 1991) and by its property of arrested development as a parasitic larval stage (Schad *et al.* 1973).

**EPIDEMIOLOGY OF HOOKWORM INFECTIONS**

Cases of hookworm infection are usually identified indirectly by the detection of eggs during the microscopic examination of stool samples (WHO 1992). This procedure does not readily distinguish between the species; if specific identity is required, fresh stools should be cultured by the Harada Mori method to enable larval morphology to be checked or adult worms should be examined following expulsion chemotherapy (Pawlowski *et al.* 1991). The results of numerous cross-sectional surveys of communities where hookworm infections are endemic have revealed a typical pattern. The prevalence of infection rises steadily from infancy and tends to level off or slow down in rate of increase in later childhood (Fig. 2). The prevalence then usually remains stable during adulthood.

Information about the intensity of hookworm infections, defined as the mean number of worms per infected host, is of greater importance and usefulness than estimates of prevalence. The transmission of the infections, the factors that influence their population regulation and the impact of their morbidities are dependent on worm burdens (Anderson, 1986). In practice, intensity usually has to be measured indirectly by counting eggs in stool samples and making the assumption that the number of eggs increases in relation to the number of sexually mature female worms present in the host. According to Bundy (1990), a typical age-intensity pattern for hookworm infection has still to be identified. Intensity is often observed to rise relatively slowly during childhood with the higher intensities often being observed in adults (Fig. 3).
Hookworm infections

The relationship between hookworm prevalence (%) and host age. (Reproduced from Schad et al. (1983) based on data obtained from a survey conducted in West Bengal, India.)

The observed frequency distributions of numbers of hookworms per infected host is known to be overdispersed or aggregated (Anderson, 1982). In a typical community, most infected hosts will harbour relatively few worms each while most of the worms will be found in a few of the hosts (Fig. 4). Schad & Anderson (1985) reanalysed intensity data, based on egg counts from subjects in West Bengal, and obtained statistical evidence for the existence of predisposition to intensity of hookworm infection. A statistically significant correlation was found between the number of hookworm eggs passed by individuals both before and 630 days after anthelmintic treatment. Schad & Anderson (1985) reanalysed intensity data, based on egg counts from subjects in West Bengal, and obtained statistical evidence for the existence of predisposition to intensity of hookworm infection. A statistically significant correlation was found between the number of hookworm eggs passed by individuals both before and 630 days after anthelmintic treatment. The occurrence of predisposition to infection intensity with soil-transmitted helminthiases and schistosomes is widely accepted (Keymer & Pagel, 1990), but how it arises is less well understood. Perhaps predisposition is not yet the ideal word to use to describe the phenomenon because it implies a host genetic basis while the explanation may equally well involve behavioural and ecological factors. Cases of iron-deficiency anaemia due to hookworm infection will be most likely to be found in the cohort of people who occasionally or persistently harbour heavy worm burdens.

HUMAN IRON STATUS AND ANAEMIA

The development of a mathematical model for investigating the responses of human iron metabolism to chronic blood loss depends on knowledge of three categories of factors – namely iron requirements, iron losses and iron ingestion and absorption – which interact to define the body's iron status (WHO, 1975; Jacobs & Worwood, 1982; Crompton & Stephenson, 1990). A scheme depicting, in a far from dynamic manner, some features of human iron metabolism is shown in Fig. 5. There is no overall agreement about either the amount or distribution of iron in the human body. Pawlowski et al. (1991) take 50 mg and 38 mg as reflecting the amounts of iron per kg body weight in an average adult man and woman, respectively, living in a developing country. Of particular interest are the values used by Pawlowski et al. (1991) for total stored iron (ferritin and haemosiderin) in the body; 13 mg/kg body weight for a man and 5 mg/kg body weight for a woman. While the close control of iron absorption may be central to the maintenance of the body's iron balance (Jacobs & Worwood, 1982), control of stored iron levels appears to be the key to understanding how the body adapts to the presence...
Dietary intake depends on energy intake; menstruating women need 28 mg or 14 mg if <10% or >25% energy derived from animal food. Haem iron (animal food) is 11-4 mg/100 g raw liver, 0.5 mg/100 g rice. Non-haem iron (vegetable food) is 0.5 mg/100 g rice.

Sociocultural factors, e.g., food fads, religious beliefs, traditions influence dietary intake.

Haem iron (animal food) is found in liver and other organs, e.g., 11.4 mg/100 g raw liver. Non-haem iron (vegetable food) is found in rice, e.g., 0.5 mg/100 g.

Absorption:
- About 5-10% of dietary intake is absorbed.
- Mucosal factors: Iron absorption is mainly in the duodenum and upper jejunum.
- Impaired in conditions like tropical sprue, coeliac disease, protein-losing enteropathy.
- Luminal factors: Enhancers include animal protein (cysteine), haem iron, ascorbic acid, citric acid, lactic acid, human milk, and gastric acid. Inhibitors include bran, tea (tannates), egg proteins, calcium, phosphates, and pica (clay).

Iron absorption increases as body iron decreases.

Up to 42% reabsorption of blood iron from the gut during hookworm infection.

BIOAVAILABILITY

Body iron distribution:
- Haem iron:
  - Haemoglobin (red blood cells): 2,600 mg
  - Myoglobin (muscle): 400 mg
  - Cytochromes (mitochondria): 17 mg
  - Cytochromes (microsomes): 3 mg
  - Catalase (RBCs and liver): 5 mg
  - Ferritin and haemosiderin (liver): 410 mg
  - Kidney: 48 mg
  - Muscle: 11 mg
  - Bone marrow: 300 mg
  - Brain: 60 mg
- Non-haem iron (stored):
  - Liver: 3,033 mg
  - Kidney: 1,159 mg
  - Haemosiderin: 420 mg
- Total iron: 4,592 mg

Physiological losses:
- 0.7 mg daily during menstruation
- 300 mg during birth
- 0.5-1.0 mg daily during lactation
- 0.4 mg daily in men and women (excluding menstruation)

Pathological losses:
- Infections (e.g., malaria)
- Endogenous gut haemorrhages
- Haemorrhoids
- Hookworm infections

Physiological requirements and losses:
- 2 x 10^11 red blood cells enter circulation daily.
- 300 mg transferred to foetus, mainly during last trimester.
- Up to 500 mg for increase in RBC mass during pregnancy.

As little as 0.7 mg of iron is needed for the circulating number of red blood cells to meet the oxygen needs of the body (Weatherall & Wazi, 1984). The maintenance of a sufficient population of circulating red blood cells probably has an extremely high priority in the hierarchy of iron metabolism and, since blood haemoglobin concentration, is a relatively easy measurement to make, the effect that a hookworm infection might be having on other features of its host's iron metabolism may easily pass undetected. Measurements of plasma ferritin concentration, transferrin saturation, and erythrocyte protoporphyrin could reveal deteriorating iron status.

Table 2. Features of the composition of human blood (reproduced from Crompton & Stephenson, 1990)

<table>
<thead>
<tr>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood volume 60–80 ml/kg body weight for adult men and women; red-cell volume 30 ml/kg and 25 ml/kg for men and women respectively, plasma volume 40–50 ml/kg.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cells (45%)</th>
<th>Haemoglobin^a (g/dl)</th>
<th>Red cell count^b (x 10^12/l)</th>
<th>Mean cell haemoglobin concentration</th>
<th>White cell count^b (mean ± 2SD; x 10^7/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6 months – 6 years</td>
<td>11</td>
<td>3.6–5.0 (1 yr)</td>
<td>28–33 (1 yr)</td>
<td>12 ± 6 (1 yr)</td>
</tr>
<tr>
<td>Children 6 years – 14 years</td>
<td>12</td>
<td>4.2–5.2</td>
<td>30–33</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Adult males</td>
<td>13</td>
<td>4.5–6.5</td>
<td>30–35</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>Adult females, non-pregnant</td>
<td>12</td>
<td>3.9–5.6</td>
<td>30–35</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>Adult females, pregnant</td>
<td>11</td>
<td>3.9–5.6</td>
<td>30–35</td>
<td>7 ± 3</td>
</tr>
</tbody>
</table>

| Plasma (55%) | Water (91.5%); Salts, hormones, enzymes (1.5%); Proteins (7%); Albumin (55%); Globulin (38%); Fibrinogen (7%) |

^a Dacie & Lewis (1984); note that age, physiological state, health and other factors affect the blood composition; ^b Lewis (1982); ^c WHO (1972); values below these are suggestive of anaemia.

Fig. 5. Some features of human iron metabolism of a healthy 70 kg male. (Reproduced from Crompton & Stephenson, 1990.)
before the blood haemoglobin concentration had fallen below the value judged to be normal (Table 2). Mansour, Francis & Farid (1985) investigated the iron metabolism of 103 male patients, aged from 19–48 years and known to be infected with Schistosoma mansoni. On the basis of blood haemoglobin concentrations, 52 were judged to be anaemic. Of the remaining 51 patients, with normal blood haemoglobin concentrations, 42 had plasma ferritin concentrations and 16 had transferrin saturation values below those judged to be normal. The usefulness of the mathematical model described below is to make more tractable aspects of the pathology of the human–hookworm interaction which are not easily observed.

HOOKWORM FEEDING ACTIVITY AND HUMAN BLOOD LOSS

The intestinal stage of a hookworm feeds by biting into the mucosa, puncturing capillaries in the villi and pumping blood through its gut. Presumably, the hookworm then obtains its nutrients by absorbing molecules from the human plasma in its gut lumen across its own intestinal epithelium. Experimental studies of hookworm feeding have been made by Wang et al. (1983) on infections of A. caninum in dogs. Wang et al. (1983) concluded that a single female A. caninum pumped about 0.043±0.04 ml dog blood per day and that a further 0.046±0.019 ml of blood was lost into the host’s intestine from the lacerations left when the worm moved to bite a fresh portion of mucosa. The production of an anticoagulant substance by A. caninum from dogs and by A. duodenale will facilitate this effect (Hotez & Cerami, 1983). Wang et al. (1983) found that an individual male A. caninum deprived the host of considerably less blood than a female. This result is to be expected because male worms are smaller than females which must also undergo considerable synthetic activity for egg production (see Table 1). All the estimates made to date indicate that A. duodenale is responsible for relatively more blood loss than N. americanus, the difference being due to the sizes of the worms (Table 1).

The results of studies on the blood lost into the gut during hookworm infections in humans have been reviewed by Crompton & Stephenson (1990). A widely used technique for measuring intestinal blood loss has been to obtain erythrocytes from a subject, label them in vitro with either 51Cr or 59Fe, return them to the subject’s blood circulation and subsequently measure the amount of radioactive isotope in the subject’s stools. The technique assumes that the radioactive isotopes remain fixed in the membranes of the original sample of erythrocytes. A reassuring result from such measurements has been the observation that the amount of radioactivity detected in the stools increases as the worm burden increases.

![Fig. 6. The relationship between declining blood haemoglobin concentration and increasing hookworm intensity, expressed as egg-count classes, obtained from a study of 1141 residents of South Georgia, USA. FSB indicates that the egg counts have been corrected to a formed-stool basis. (Reproduced from Hill & Andrews (1942).)](image-url)

(Tasker, 1961; Martinez-Torres et al. 1967). In a study of 54 patients infected with N. americanus and given erythrocytes labelled with 51Cr, Martinez-Torres et al. (1967) concluded that, on average, a single N. americanus caused a mean (±SD) blood loss of 0.031±0.015 ml per day. An example of the relationship between the intensity of hookworms and human blood haemoglobin concentration is shown in Fig. 6. The interpretation of the relationship is that the greater blood loss caused by the greater number of hookworms leads to the onset and persistence of anaemia. This relationship has also been observed in communities in India, Kenya, Thailand and Venezuela (see Crompton & Stephenson, 1990).

From estimates of the daily egg production of female hookworms (Table 1) and measurements of the different amounts of stool produced per day by individuals of different age, sex and size, Pawlowski et al. (1991) consider that a count of roughly 1000 A. duodenale eggs (epg) and 1000 N. americanus eggs (epg) are indicative of infections of roughly 11 and 32 worms, respectively. Given estimates of blood loss due to individual hookworms of the two species, burdens of 25 A. duodenale and 110 N. americanus would each be expected to cause a blood loss of about 5 ml into the gut lumen daily (Pawlowski et al. 1991).

Simple calculations serve to highlight the apparent pathogenicity of hookworm feeding activity and the complexity of the host’s adaptive response. Consider the case of an adult woman weighing 50 kg and carrying an infection of about 250 N. americanus. The daily blood loss into the gut would be about 10 ml containing about 3.7 mg of iron. If the woman’s average daily iron loss of about 1.5 mg were balanced by a daily iron absorption from the diet of...
about 1.5 mg and if her iron stores were about 200 mg, the iron stores would last for about 54 days. Such circumstances clearly do not prevail; given the vast numbers of people infected with hookworms and the relatively low estimated mortality rate of about 60000 per year (Pawlowski et al. 1991), the body's iron metabolism must adapt to the intestinal iron losses induced by hookworms. It is the purpose of the model described and tested below to suggest how these adaptations may occur.

A PROVISIONAL MODEL FOR HOOKWORM ANAEMIA

The first purpose of this model is to provide some qualitative understanding of why simple calculations of the kind outlined in the previous section are wrong. In other words, what is it that prevents the loss of iron brought about by the hookworms from killing the host within a few months? A second purpose is to show up places where more information needs to be obtained if better models are to be produced. Better models will be needed if the aetiology of hookworm-induced anaemia is to be better understood.

The main relationships between stored iron, red-cell iron, iron intake and iron loss are shown in Fig. 7. The system as described has two principal regulatory mechanisms. The stored iron directly regulates iron absorption in the gut, and the iron content of the blood indirectly, while the blood oxygen tension regulates the production of red cells. The schematic relationships shown in Fig. 7 may be cast into mathematical form as follows:

\[
\frac{dr}{dt} = f(r, s) - (\omega + B) r \\
\frac{ds}{dt} = -K[f(r, s) - \omega a] + A(s)[F + KBr] - P,
\]

where:

- \( f(r, s) \) describes the rate of production of red cells per litre of blood as a function of the red cell density \( r \) and the stored iron level \( s \);
- \( \omega \) is the normal metabolic death rate of red cells, per day;
- \( B \) is the fractional blood loss per day through bleeding;
- \( F \) is the iron ingested per day (all forms assumed equivalent);
- \( a \) is the fraction of the red-cell iron that is recovered and recycled in normal metabolic processes;
- \( A(s) \) is fraction of the iron entering the digestive tract that is actually absorbed;
- \( P \) is the amount of stored iron lost per day for reasons other than bleeding into the gut;
- \( K \) is the conversion factor from red cell density to total blood iron.

In writing down these equations many assumptions and simplifications have been made. Some of these, in descending order of seriousness are: (1) The use of the function \( f(r, s) \) to model red cell production implies instantaneous response to changes in \( r \) and \( s \) and the absence of any memory in the system. For these reasons it is unlikely that the model will give a correct description of the time-course of events; here, however, we are only interested in the steady-state. (2) The assumption of a linear density-dependent red cell death rate \( \omega r \) is problematic. (3) It is generally not true that all forms of dietary iron are equivalent. (4) Red cell density and blood iron concentration are not, in fact, proportional to one another. When iron stores are low red cells are produced which contain less than the normal amount of iron. We regard this as one of the less serious shortcomings of the model, however, because it can be put right simply by reinterpretting \( r \) as blood iron concentration, in peculiar units, instead of red cell density.

The general form of the iron absorption function was deduced from Lynch (1984) to be:

\[
A(s) = 1.02 - 0.62 \log(ks).
\]

The factor \( k \approx 45/\tau_0 \), where \( \tau_0 \) is the steady state stored iron level in a healthy, non-bleeding, individual of the appropriate size and sex.

The red cell production function is assumed to be given by:

\[
f(r, s) = x \cdot (r_0 - r) h(s),
\]

where \( x \) is a constant, \( h \) is a sigmoid function of \( s \), and \( r_0 \) is a reference level. For \( s \) sufficiently large \( h(s) \approx 1 \) and \( f \) becomes independent of \( s \). Under these conditions we can use equation (1) with \( B = 0 \) (no bleeding) to get estimates of the two parameters \( x \) and \( r_0 \). The steady state is given by:

\[
f = \frac{sx_0}{x + \omega}.
\]

If the red cell density is disturbed by a given amount (the result, say, of a blood donation) the perturbation decays back to the steady-state exponentially with a time constant of \( 1/(x + \omega) \). Blood donors require about 10 days to recover their red cell density so:

\[x + \omega \approx 0.1\]

Since \( \omega \approx 0.01 \), corresponding to a red cell lifetime of \( \approx 100 \) days, we readily find that \( x \approx 0.09 \) and that:

\[r_0 = 1.1f\]

The ability to pin down the parameters by such means was one of the main reasons for adopting the chosen form for \( f(r, s) \).

Equations (1) and (2) can be solved numerically without great difficulty and we present results of some calculations in Figs 8 and 9. In Fig. 8, we plot...
Hookworm infections

Oxygen tension  
<table>
<thead>
<tr>
<th>Red cell production</th>
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<tbody>
<tr>
<td>Red cells</td>
</tr>
<tr>
<td>Metabolic loss</td>
</tr>
<tr>
<td>Loss</td>
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<tr>
<td>Intake</td>
</tr>
<tr>
<td>Food</td>
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Fig. 7. A flow diagram illustrating relationships between the main elements of human iron metabolism. The 'taps' are points of control or regulation.

Fig. 8. Results from trials of the model to explore the relationship between red cell density, stored iron and hookworm intensity in a 70 kg man (see text). —○—, when stored iron is very tightly regulated; —△—, less tightly regulated; —□—, based on data from Lynch (1984).

Three sets of curves are shown, corresponding to the use of three different versions of the iron absorption function \(A(s)\), equation 3). In the first case, equation 3 was used unmodified while in the other two cases variants were used in which the change in \(A(s)\), for a given change in \(s\) was larger thus giving the model tighter regulation of the stored iron. In Fig. 9 we show similar results for two 50 kg women, one pregnant, the other non-pregnant. The first thing to notice about these figures is that for each value of hookworm intensity there is actually a steady-state. In other words, there is no runaway depletion of stored iron. The steady-state value may well be incompatible with good health, or even life, but the stored iron never vanishes completely. In this respect, at least, the present model is superior to the simple calculations of the previous section. The difference lies mainly in the feedback mechanism whereby stored-iron depletion leads to increased iron uptake from the gut and the recovery of much of the iron lost through bleeding into the gut. The same mechanism is responsible for the flattening-out of the stored-iron curves at high hookworm intensity.

It might be possible to test this point experimentally: if the iron recovery mechanism is as important as these calculations represent, it is to be expected that one should find relatively less iron in the stools of very heavily infected hosts than in those of hosts with lighter infections.

In each of the figures, the red cell density curve has a shape very similar to the data in Fig. 6. One needs to be careful, however. We have the steady-state red cell density and total stored iron against bleeding (converted to hookworm intensity) for a 70 kg man whose daily iron intake is 10 mg and whose physiological iron loss is about 1 mg/day.
used a logarithmic scale of hookworm intensity, corresponding to the (approximately) logarithmic scale of egg counts in Fig. 6, and all slowly decreasing monotonic functions take on a similar appearance plotted in this way. Nevertheless, we find in each case that up to a burden of 100–200 worms there is rather little effect on blood iron, whereas there is a much larger effect on the stored iron. At worm burdens of about 500 there is a very large reduction in blood iron. For the stored iron, on the other hand, there are no data to compare the calculations with. Generally our model seems to underestimate the iron stores in uninfected subjects. This is not too serious a flaw because the steady-state iron level is quite sensitive to some of the grosser assumptions of the model and we would expect improvement to follow refinement of the model without having to invoke new mechanisms.

Although it cannot be seen in the figures, the rate at which the steady-state is approached in the present model is quite unrealistic, as we noted earlier, and to fix this will require major changes in the dynamics of the model.

To sum up: (1) The model gives a reasonable account of the way blood iron changes with hookworm burden; (2) It shows qualitatively how it is possible to avoid the ‘no iron left after 60 days’ dilemma; (3) It is probably not yet nearly good enough to give a quantitative guide to stored-iron status as a function of egg counts. To improve the model we primarily need better information than apparently exists on the iron uptake regulation mechanism described above and modifications to the red cell production term which will have the effect of converting the simple differential equation for \( r \) into an integro-differential equation.

REFERENCES


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