inventory, depressed adjective check list) were used to evaluate depression. In general patients in all groups improved during the trials and patients in the exercise groups did either better than those receiving no treatment,[14 15] or as well as those receiving different forms of psychotherapy.[16 17] There has been no trial of using exercise treatment either alone or in conjunction with antidepressant drugs or electroconvulsive treatment in more severely depressed patients.

Exercise may also sometimes be bad for mental health. Patients have been identified ("obligatory runners") in whom strenuous physical exercising is a means of losing weight, and it has been argued that excessive exercising may be an "analogue of anorexia nervosa."[18-21] The term "exercise dependence" has been proposed to describe the psychopathology of this group of patients. They show many psychological symptoms common to other dependence states including a withdrawal syndrome characterised by dysphoria on stopping the exercise schedule.[22]

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Regular Review

Iron and infection

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Because iron is needed in essential biochemical reactions and in oxygen transport living organisms have developed efficient mechanisms for its acquisition, transport, and storage. In man, transferrin and lactoferrin are responsible for binding ferric iron and transporting it in plasma and secretions, whereas non-functional iron is stored in the cells as ferric oxohydroxy crystals within ferritin molecules.[1] To compete with these powerful iron conserving systems microorganisms have developed their own chelating compounds, the siderophores, which enable them to make iron soluble and assimilate it from their environment.[2 3] This function is closely related to their virulence.

Hypoferraemia is one of the most constant features of infectious disease, and since iron deprivation in bacterial cultures is regularly associated with inhibition of growth it has been suggested that hypoferraemia may be an important host defence mechanism. The term "nutritional immunity" was coined by Kochan in 1973 to underline the importance of iron deprivation in limiting the growth of invading organisms.[4] The relation between infection and iron availability has now been studied intensively,[5-14] and, although some evidence favours the nutritional immunity hypothesis, few clinical data support the importance of iron deficiency or overload in determining the severity or prevalence of infectious disease in man.

Plans for adding iron to diets in many developing countries are currently being formulated for nutritional reasons, but because recent studies have again highlighted the potential deleterious effects of iron supplementation[14 15] we have examined the possibility that such policies may result in an increased risk of infection. In particular we have reviewed the clinical evidence that suggests that iron state is associated with the incidence and severity of microbial infection.

Chronic iron overload

If iron is an important limiting factor in infection—as proposed by the "nutritional immunity" theory—then chronic iron overload should lead to a severe impairment of protection against infection. Transferrin saturation in primary and secondary haemochromatosis is high. In some patients transferrin is completely saturated and some of the

iron in the plasma appears as low molecular weight iron loosely bound to albumin.[15-20] Such iron complexes should be readily available to invading bacteria.

Death in idiopathic haemochromatosis is mainly caused by cardiac and hepatic failure, hepatoma, and diabetes,[21] but about 12% of patients die with pneumonia. Yet in patients with established cirrhosis or diabetes such a complication cannot be attributed to iron alone. Weinberg quotes five papers to illustrate the increased susceptibility to infection of patients with idiopathic haemochromatosis.[5] Three describe unusual infections—for example, with *Pasteurella pseudotuberculosis* or *Yersinia enterocolitica*—in patients with advanced cirrhosis, some of whom also had haemochromatosis.[22-24] These reports underline the difficulty in distinguishing between the effects of chronic liver disease and those of iron overload on host defence mechanisms. The other two papers quoted by Weinberg describe irreversible shock in idiopathic haemochromatosis and Bantu siderosis,[25 26] an obscure complication of haemochromatosis that is characterised by unexplained severe abdominal pain and occasionally by extremely high serum iron concentrations. Irreversible shock in haemochromatosis has not been clearly linked to infection as in most patients blood cultures remained sterile; it has been assumed that the sudden release of ferritin or of tissue iron was instrumental in producing irreversible shock.

Sickle cell anaemia is associated with a high incidence of infectious complications. The bacterial infections are most commonly pneumococcal infections, salmonella osteomyelitis, and pneumonia. These complications are most common in the first decade of life,[27] when iron overload is not well established. The infections are rare later on despite the progressive accumulation of excess iron, which is a convincing argument against iron excess being important in the infectious complications of sickle cell anaemia. Vaso-occlusive episodes cause functional hyposplenism to develop in these children at an early age, but the immunological response of these patients to antigenic challenge is normal.[28]

Homozygous β thalassaemia and thalassaemia intermedia are associated with severe iron overload caused by transfusional siderosis and increased iron absorption. If untreated, iron accumulation results in symptomatic haemochromatosis and death in the teens or twenties. Severe bacterial infections are an important cause of morbidity and mortality in thalassaemia major[29]: among 58 thalassaemic patients in the United States Smith *et al* reported 12 episodes of serious infection and six fatal infections.[30] Similarly in Britain Modell and Berdoukas reported 48 episodes of serious infections among 129 patients with thalassaemia major and intermedia.[31] The incidence of pneumonia was one for every 54 patient years, and for other serious infections it was one for every 63 years. Severe infection was believed to be the primary cause of death in 10 of 55 patients who died with thalassaemia major.

Splenectomy appears to be a major risk factor in causing increased susceptibility to infection in thalassaemia.[32] All six fatal infections in the report of Smith *et al* occurred among the 35 patients who had had their spleens removed; there were none among the 23 patients who still had their spleens. Similarly in the British series all but two of the fatal infections, 13 of the 14 episodes of severe pneumonia, and all cases of other severe bacterial infections occurred in patients without spleens.[31] The increased risk of infection associated with splenectomy in thalassaemia is probably explained by the reduced primary and secondary immune response to antigens given intravenously and to reduced clearance of blood borne bacteria.[33] Another important risk factor for infection is severe anaemia. In the British series the incidence of pneumonia in patients with haemoglobin concentrations below 99 g/l was one for every 36 patient years against one for every 282 patient years in patients with haemoglobin concentrations ranging from 100 to 140 g/l. Wasi *et al* reported a relative reduction in serum IgM concentrations in children with thalassaemia[34] but others found normal or increased immunoglobulin and C3 concentrations in patients with and without spleens.[35-37]

Iron overload has also been proposed as an important cause of infection in thalassaemia. Caroline *et al* have shown that the serum of thalassaemic patients without spleens supported the in vitro growth of *Candida albicans* much better than control serum,[38] which is a function of transferrin saturation. Although transferrin saturation is high in thalassaemic patients dependent on transfusions we could find no clinical evidence that iron is important in the infectious complications of thalassaemia: *Candida albicans* has not been described as the cause of fatal infection in any of the cases listed above; transfusional iron overload increases with age, whereas the incidence and severity of infections in thalassaemia are not age related[31]: and, finally, of the 10 patients with fatal infections in the British series four received regular desferrioxamine treatment for three to six years, and in three others the estimated total intravenous iron load was less than 5 g. Indeed, with the effective control of iron overload infections may become the most important cause of death in thalassaemia.[31]

Thus clinical iron overload is not associated with an impressive increase in the incidence or severity of bacterial infections. It does, however, matter in anaemic thalassaemic patients or those without spleens, in patients with a functional splenectomy because of sickle cell disease, and in causing an increased risk of infection with *Yersinia enterocolitica*, a normally non-virulent pathogen which is unable to produce its own siderophore and which may thrive in iron excess.[39] There is no information on the susceptibility of patients with primary or secondary haemochromatosis of malaria, although such information would be interesting because malaria appears to be one of the main problems associated with iron treatment.

Chronic iron deficiency

Surprisingly, few studies have described the susceptibility of iron deficient patients to infection. It is also uncertain whether a clear distinction between true iron deficiency and the hypoferraemia of inflammation has been made in such studies that are available. One infection associated with iron deficiency is candidiasis. Higgs and Wells studied 31 patients with chronic mucocutaneous candidiasis and found iron deficiency in 23. Iron treatment resulted in clinical improvement in most.[40]

One of the most misquoted studies dealing with the relation between iron deficiency and infection is that of Masawe *et al*.[41] These authors studied 110 anaemic patients admitted to a hospital in Tanzania with a mean haemoglobin concentration of 58 g/l; it is not clear how many had been treated with iron before admission. Eighteen of the patients had malaria, and 33 had bacterial infections, including 12 with tuberculosis. The prevalence of malaria was 24% in the

iron deficient group compared with 5% in those with other anaemias. Conversely, the prevalence of bacterial infections was 7% in iron deficient patients compared with 65% in others. Unfortunately, patients with refractory anaemia and megaloblastic anaemia are not good controls for patients with iron deficiency anaemia. This study, which is often quoted to show a reduced prevalence of infection in patients with iron deficiency, actually shows an increased prevalence of malaria in iron deficiency.

The effect of iron treatment on infection

Several studies have examined the effect of iron treatment on infection. Most have used parenteral iron, usually iron dextran. A few used oral iron, either in small doses for long term dietary supplementation or in short term pharmacological doses.

Parenteral iron

Between 1970 and 1972 some Polynesian infants were given prophylactic intramuscular iron dextran soon after birth.[42,43] During this period the incidence of neonatal infection (mostly with *Escherichia coli*) increased to 22 for every 1000 but dropped to 1·8 for every 1000 when the supplementation was stopped in 1973. Most of the infectious episodes occurred within four to 10 days of injection, and there was no evidence of focal infection at sites of injection. There are several flaws in this study, casting doubt on the authors' conclusion that iron treatment caused the Gram negative neonatal infections. Incidence rates of neonatal infection before 1970 are not provided, and as the entire population had been treated no controls are available. Finally, it is not clear whether iron itself or the parenteral iron dextran preparation might have been responsible for the effects.

In contrast to this study, no increase in susceptibility to infection has been observed in a study of premature infants in the United States receiving prophylactic iron dextran injections.[44] Moreover, early iron treatment in a group of premature infants in Finland halved infections during the first 6 months of life compared with untreated controls.[45] These contrasting findings may result from differences in exposure to pathogens. Indeed, most of the reports that support an increased risk of infection after iron treatment are from developing or tropical countries. The original report on Polynesian infants has been supported by another uncontrolled retrospective study from New Zealand.[46]

Recently a more extensive and carefully designed prospective, double blind, randomised longitudinal study has been performed among infants in Papua New Guinea in a population where malaria is endemic.[47,48] A total of 486 newborn infants were randomised to receive either 150 mg elemental iron (intramuscular iron dextran) or placebo at 2 months. After 12 months' follow up death rates were similar in the two groups, the primary cause of death being lower respiratory infection related to measles or pertussis. In the group treated with iron dextran there was an increase in measles associated admissions, otitis media, severe lower respiratory infections, malarial parasite and spleen rates, and malaria associated hospital admissions. After six months 18·5% of the treated group and 11·3% of controls were positive for malaria, and after 12 months 33% of the treated group and 20% of the controls were positive—that is, there was about a 50% increase in the iron treated group. There was no significant difference, however, in the density of parasitaemia in the positive blood samples.

Exacerbation of infection after parenteral iron in adults has been reported in uncontrolled studies. Byles and D'sa treated 917 pregnant women in Tanzania with total dose intravenous iron dextran infusions.[49] Both generalised febrile reactions and local reactions to iron dextran such as thrombophlebitis were reduced by antimalarial treatment. The incidence of postinfusion malaria was 2·8%, whereas the incidence of generalised reactions was 7·4%. This study is often quoted to show that iron treatment causes a flare up of malaria, but without untreated controls the proportion of patients who might have developed parasitaemia without iron is unknown.[49] Exacerbation of pyuria has been reported in patients with chronic pyelonephritis treated by intramuscular injections of iron sorbitol.[50,51] In contrast to iron dextran, iron in the sorbitol citrate complex (Jectofer) is loosely bound and saturates serum transferrin rapidly—and about a third of the injected dose is excreted in the urine. The renal complications of Jectofer may be related to this massive urinary excretion of iron; its urinary excretion is a major disadvantage clinically, and its use in iron deficiency has been largely abandoned.

Oral iron

Several large studies in children have shown either a reduction or no change in the rate of respiratory or gastrointestinal infections after iron supplementation. In an early study Mackay showed a halving in respiratory or gastrointestinal infections in those given iron supplements compared with children not given supplements.[52] A serious limitation of this study was the absence of simultaneous controls: the comparison was between successive years of treated and untreated populations. In another study a large group of children were randomised to receive milk formulas, either fortified or not fortified with iron.[53] The apparent effects of iron fortification were shown by the prevalence of anaemia being reduced from 76% in those not given supplements to 9% in those given them. There were significantly fewer respiratory infections in those given supplements, but this study has been criticised for the loose criteria for defining infection and for dependence on recall of illness after interviewing parents. The same criticism applies to another study in which infants were randomised to receive iron supplementation or no supplementation and in which no difference was found between the two groups.[54]

In contrast to long term studies of iron supplementation, short term iron treatment in pharmacological doses is associated with serious adverse effects in malnourished African children. A direct correlation between serum transferrin concentrations and survival in kwashiorkor was described by McFarlane *et al*,[55] and in a group of 40 children treated with a high protein diet, antimalarials, vitamins, and iron survival was correlated with the concentrations of various serum proteins. Overwhelming infection was the most important cause of death. After two weeks of treatment the serum transferrin concentrations in children who survived was 1·3 g/l as against 0·3 g/l in those who did not. The authors concluded that the combination of low iron binding capacity and iron treatment may have provided free iron for bacterial consumption and so contributed to

uncontrolled infection and death. All children who died had low serum albumin concentrations, indicating protein starvation as well as infection. The most likely explanation for the findings of McFarlane *et al* would be a more severe inhibition of transferrin synthesis and increased transferrin catabolism in those patients destined to die. Thus, although serum transferrin concentrations might be a useful indicator of prognosis in kwashiorkor, the conclusion that it may contribute to death cannot be justified.

The studies of the Murrays are widely quoted as evidence of a protective effect of iron deficiency in infection.[56 57] They are based on observations in nomads treated in central African relief camps. The first deals with 72 adult patients admitted for causes other than malaria and 109 of their relatives. They all received an energy rich diet supplemented by vitamins but not by iron. Refeeding was followed by a considerable increase in transferrin saturation, which peaked after two days. Attacks of malaria occurred in 23 patients and 51 relatives within five days, and the percentage of red blood cells containing parasites increased from 2% on arrival to 15%. This course of events was interpreted by the authors as evidence for iron induced proliferation of the malarial parasite. Equally possible, however, correcting protein-energy malnutrition (which inhibits malarial parasite growth in experimental animals[58] rather than correcting iron deficiency caused the malarial relapse in these undernourished patients.

The second study of the Murrays was a prospective, randomised trial conducted in 137 adult Somali nomads with iron deficiency anaemia.[57] In this study only patients with a stable and presumably normal nutritional state were included. They were randomised to receive daily either 900 mg of oral ferrous sulphate for one month or three tablets of aluminium hydroxide placebo. Iron treatment increased serum iron and haemoglobin concentrations. There were three episodes of infection in the control group and 36 in patients receiving iron. The most dramatic differences were in episodes of malaria (13 versus 1), brucellosis (5 versus 1), and tuberculosis (3 versus 0). In contrast to the Murrays' previous study, when the peak incidence of malaria was after five days, most of the infections in this study occurred between 22 and 30 days after treatment. This difference in the timing of infection reinforces the impression that malarial relapse in the first study was caused by correcting other nutritional deficiencies and not specifically by giving iron. Although it has been criticised for the short follow up and the lack of double blind design, the second study of the Murrays is the most convincing evidence that iron treatment increases the incidence of infectious disease.

Suppression of pathogens by desferrioxamine

If pathogens depend on iron for their unimpeded growth it might be possible to interfere specifically with their proliferation by using selective iron binding agents such as desferrioxamine. One pathogen that has shown remarkable sensitivity to desferrioxamine is *Plasmodium falciparum*. When grown in vitro in human red blood cells *P falciparum* is inhibited by as little as 15 μmol/l of desferrioxamine and almost totally suppressed at 30 μmol/l, a concentration that is easily achieved in patients.[59 60] We do not know how desferrioxamine affects malaria in man, but interesting observations have been made with *Plasmodium vinckei* in mice. Desferrioxamine (0·3 mg/g injected 8 hourly) prevents death and suppresses parasite growth provided treatment is given from the first day of infection.[61] Pretreatment for 14 days and stopping desferrioxamine one day before infection were totally ineffective. Similarly, stopping desferrioxamine after seven days of infection resulted in an immediate flare up. Unfortunately no direct measurements of serum iron or tissue iron concentrations have been made.

Nevertheless, some assumptions based on these observations may be made on the mechanism of parasite inhibition. The early inhibitory effect of desferrioxamine shows that it cannot work by depleting iron stores or producing iron deficient erythrocytes. Similarly the immediate loss of inhibitory effect on stopping prolonged treatment cannot be explained by replenishment of iron stores or resumption of normal erythropoiesis—as neither would have happened so quickly. The most likely explanation is a direct interaction with a labile iron pool available for immediate use by the parasite. Such an assumption is in line with the exquisite sensitivity of plasmodium to in vitro inhibition by desferrioxamine. These considerations justify a prospective controlled trial to evaluate the effect of desferrioxamine on severe cerebral malaria (in which mortality is still high)[62] or in drug resistant malaria.

Comment

Although the weight of experimental studies overwhelmingly favours iron being critically important in determining the rate of bacterial growth, there is little clinical evidence to show that iron is important in host resistance in man. Idiopathic and transfusional haemosiderosis are not associated with an important risk of bacterial infection, despite low molecular weight iron being in the plasma of many of these patients in a form readily available for microbial use. The severe infections occasionally associated with idiopathic haemochromatosis are probably manifestations of end stage cirrhosis. In secondary haemochromatosis infections are encountered only in association with splenectomy or functional asplenia. Nor is there much support for iron deficiency protecting against infection: studies have not shown any advantage of the iron deficient state; and in some studies infectious complications were actually rarer in the normal population than in the iron deficient population. This is particularly true of chronic mucocutaneous candidiasis, which seems to be more common in iron deficient than in normal subjects.

The hypoferraemia of inflammation is not identical to iron deficiency, which unfortunately has been disregarded by many writers. Serum iron, storage iron, and functional iron in enzymes and oxygen transport systems may all be depleted in severe iron deficiency. Hence the beneficial effects of iron deficiency in limiting bacterial growth may be offset by its interference with other host defence mechanisms. In contrast, the hypoferraemia of inflammation does not represent genuine iron deficiency but rather a redistribution of iron in which hypoferraemia prevails in the face of normal or increased iron stores. Thus it may have all the advantages of reduced iron supply to pathogens without adverse effects on host resistance. The critical question therefore is not whether iron deficiency is associated with fewer infectious complications but whether correcting the hypoferraemia of inflammation may deleteriously affect existing infection. This has not been directly studied.

It is in this context that the reports from tropical or

developing countries on the increased incidence or severity of infectious disease after iron treatment should be viewed. Some reports are anecdotal observations, but others are careful prospective, randomised clinical trials. These studies show that in populations with a high prevalence of endemic infectious disease iron treatment is followed by a higher incidence of infectious complications or by a flare up of existing low grade disease. Most important—both in terms of the size of populations at risk and the dramatic response to iron treatment—is malaria. The interrelationship between iron treatment and malaria appears to be genuine, but more information based on carefully designed prospective studies, such as those reported by Oppenheimer,[47 48] is needed. This is illustrated by a recent preliminary report of randomised iron supplementation in prepubescent school children in Papua New Guinea, which failed to show any adverse effect on malaria.[63 64]

We alluded at the beginning to the paucity of clinical evidence supporting the nutritional immunity hypothesis. Most investigators in this subject were trained in microbiology, and the scepticism of doctors is understandable in view of the sweeping generalisations made by some of the most enthusiastic proponents of the hypothesis. The availability of iron may in some circumstances, however, have an important influence on the clinical expression of infectious diseases. Since serious consideration is being given to fortifying diets with iron there is an urgent need for further clinical studies on this important problem.

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