# The adverse effect of iron repletion on the course of certain infections

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## Summary and conclusions

**The incidence of infections was studied in 137 iron-deficient Somali nomads, 67 of whom were treated with placebo and 71 with iron. Seven episodes of infection occurred in the placebo group and 36 in the group treated with iron; these 36 episodes included activation of pre-existing malaria, brucellosis, and tuberculosis. This difference suggested that host defence against these infections was better during iron deficiency than during iron repletion.**

**Iron deficiency among Somali nomads may be part of an ecological compromise, permitting optimum co-survival of host and infecting agent.**


## Introduction

As early as 1868 Armand Trousseau noted the deleterious effect of iron repletion on pulmonary tuberculosis.[1] As he predicted, his observations were neglected, and doctors have continued to believe that iron deficiency favours increased susceptibility to and severity of infection. The issue may not be important when infections can be controlled by specific chemotherapy, but in developing and primitive societies, where antibiotics are not always readily available, an adverse effect of iron repletion might lead to progressive disease and death. Evidence from in-vitro studies favours defective phagocytosis by granulocytes and reduced immunological responses of lymphocytes during iron deficiency.[2 3] Host resistance to infection, however, is the composite effect of all known factors as well as some unknown, so that the final test must be in vivo. Somali nomads have a high incidence of iron deficiency, which has been attributed not to intestinal parasites, which are rare in nomads, but to poor intake of iron in their all-milk diet.[4] During observation in the feeding camps in the Ethiopian Ogaden we were impressed with the apparent freedom from infection of iron-deficient nomads.[5] A preliminary prospective study of 90 Somali nomads entering the camp at Aware showed 26 with iron deficiency, none of whom had clinical signs of infection (table I). Since 19 of the 64 with normal iron status had evidence of infection we decided to examine the effects of iron repletion on the course of infection.

## Methods

The feeding camp at Aware was close to the Somali border, about 300 km south-east of Harar, and contained variously between 4000 and 6000 nomads. Only those nomads who were in a stable nutritional state were studied—that is, those who were neither suffering from malnutrition nor being actively refed after a recent period of malnutrition. These were important criteria, as we have already reported reactivation of certain infections, such as malaria, brucellosis, and tuberculosis, during refeeding after famine.[5] The nomad's diet during the study was the same as the initial refeeding diet and consisted of boiled whole wheat dowsed with liquid butter distributed twice daily—a radical change from their usual all-milk fare. Iron deficiency was arbitrarily defined as a haemoglobin of less than 11 g/dl, a serum iron concentration less than 4·48 μmol/l (25 μg/100 ml), a transferrin saturation of less than 15%, and a peripheral blood smear showing microcytic hypochromasia.

TABLE I—*Incidence of iron deficiency and infections in 90 adult Somali nomads entering feeding camp (pilot study)*

| | Normal Fe state | Iron deficient |
|---|---|---|
| No of nomads | 64 | 26 |
| No with: | | |
| Malaria (positive smear) | 5 | |
| Brucellosis (titre >1/320) | 3 | |
| Tuberculosis (Z-N positive) | 2 | |
| Fever of undetermined origin | 2 | |
| Pneumonia | 2 | |
| Hepatitis | 1 | |
| Eye infection | 1 | |
| Schistosoma ova in urine | 3 | |
| Total | 19 | 0 |

As they entered the study each iron-deficient nomad was weighed and carefully examined, especially for evidence of infection. Blood was drawn and immediately examined for malaria parasites in thick and thin smears stained with Giemsa, for haemoglobin concentrations, for red cell and white cell morphology, and (in some nomads) for reticulocytes. Serum was separated and frozen for later determination of serum iron concentration,[6] transferrin saturation,[7] brucella agglutination titre, and its ability to support or inhibit the growth of *Salmonella typhimurium*. The latter test consisted of suspending $10^3$ micro-organisms in 1 ml of serum, incubating the mixture at 36°C for 18 hours, and then carrying out a colony count on sheep's blood agar using a modification of the method of Klatersky *et al.*[8] Pus and discharges were examined directly with Gram and Ziehl-Neilsen stains while urine was searched for ova of schistosomes. Any nomad showing overt signs of infection was then excluded from the study.

We considered that it would be too difficult to assess changes in physical findings such as splenomegaly and hepatomegaly as an indication of change in pre-existing disease. Furthermore, such findings of unknown duration might not be due to infection, whereas their first occurrence during the short period of iron repletion strengthened the probability that infection was their cause. This approach led to the exclusion of four iron-deficient nomads from the 141 examined. One had splenomegaly, one had a positive blood smear for malaria, one had an enlarged hard liver, and one had a suppurative tenosynovitis after a thorn puncture.

Each nomad was then allocated alternately to a treatment or placebo group. Members of the treatment group were observed to swallow 900 mg of ferrous sulphate for 30 days. Since our total supply of ferrous sulphate was 7000 tablets, only 71 patients could be treated. Members of the placebo group swallowed three tablets of aluminium hydroxide daily for the same period. These were the only suitable tablets available and did not produce unusual gastrointestinal symptoms. All the subjects were observed closely over 30 days for episodes of fever above 38°C and for symptoms and signs of infection. Every nomad was seen at least twice after the first examination, once during treatment and again at the end of treatment. When infection occurred nomads were examined again and blood drawn for the detection of malaria and brucellosis and urine searched for ova of

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schistosomes. At the end of the study blood was obtained for estimation of haemoglobin, serum iron, transferrin saturation, and (in some nomads) reticulocytes, all as an index of response to treatment with iron and placebo.

## Results

Table II records the observations on entry to the study and after treatment. Both groups were comparable in age and sex and pre-treatment haemoglobin, serum iron concentration, and transferrin saturation; their iron deficiency was moderately severe. After iron treatment haemoglobin, serum iron concentration, and transferrin saturation rose significantly; but there was no significant difference between the groups in weight, which rose slightly in both groups.

Seven episodes of infection occurred in the placebo group and 36 in the treated group (table III; $P < 0.001$, Student's $t$ test). Table IV shows the clinical findings in both groups. In the placebo group there were six episodes of fever, one from malaria, four from two abscesses, and one transient and unidentified. A tropical abscess in the left glutei and an infection in the foot from a thorn accounted for the two suppurative infections. Of the 36 episodes of infection in the treated group, several of which occurred in the same patients, 13 were due to infection with *Plasmodium falciparum* and *P malariae* and five to infection with *Brucella abortus* and *melitensis*. The latter were diagnosed on the basis of symptoms together with an agglutination titre of more than 1/640. Of the patients with enlarged spleens, seven had malaria and four had brucellosis. One enlarged liver occurred with hepatitis, four with malaria, and one with brucellosis. Two cases of localised lymphadenopathy, one cervical and the other inguinal, were probably due to tuberculosis but caseation never occurred.

TABLE II—*Age, sex, and haematological observations before and after 30 days of treatment in 137 Somali nomads. Results are means ± SE*

| Group: | Before treatment | | After treatment | |
|---|---|---|---|---|
| | Placebo | Iron | Placebo | Iron |
| No of nomads | 66 | 71 | 66 | 71 |
| Mean age (and range) in years | 29·3 (11-55) | 28·7 (13-60) | | |
| Ratio of women : men | 1·6 | 1·53 | | |
| % change in weight | | | 3·6±1·4 | 3·2±0·9 |
| Mean haemoglobin (g/dl) | 8·1±0·7 | 8·3±0·6 | 8·7±0·9 | 12·3±1·1 |
| Mean serum Fe (μmol/l) | 3·4±0·57 | 3·6±0·52 | 3·9±0·70 | 13·1±0·93 |
| Mean % saturation transferrin | 7±1·4 | 7±1·8 | 8±0·7 | 31±1·4 |
| Mean % reticulocytes (n=6) | 0·6 | 0·9 | 1·2 | 5·1 |

*Conversion: SI to traditional units*—Iron: 1 μmol/l ≈ 5·6 μg/100 ml.

TABLE III—*Iron repletion and infection in iron-deficient nomads*

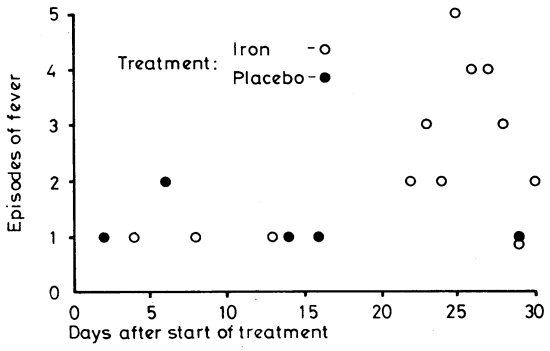
| Group: | Placebo | Iron | P value |
|---|---|---|---|
| No of nomads | 66 | 71 | |
| No of episodes of fever | 6 (9·1%) | 29 (40·8%) | <0·001 |
| No of nomads with multiple episodes | 1 | 5 | |
| No of unidentified fevers | 1 | 4 | |
| No of nomads with schistosoma ova in urine | 2 | 11 | |
| No of nomads infected | 5 (7·6%) | 27 (38%) | <0·001 |
| Total episodes of infection per group | 7 (10·6%) | 36 (50·7%) | <0·001 |

TABLE IV—*Clinical episodes during placebo and Fe treatment of iron-deficient nomads. Results are numbers of nomads*

| Group: | Placebo | Iron |
|---|---|---|
| | 66 | 71 |
| Abscess | 2 | 3 |
| Pyoderma | | 1 |
| Suppurative eye infection | | 1 |
| Jaundice | | 1 |
| Hepatomegaly | | 6 |
| Splenomegaly | | 11 |
| Lymphadenopathy | | 2 |
| Tuberculosis | | 3 |
| Malarial attacks | 1 | 13 |
| Brucellosis (symptomatic) | 0 | 5 |

Proved glandular tuberculosis occurred in two and tuberculous mastitis in one nomad. The figure shows the distribution of episodes of fever in the two groups. In the treated group these occurred from the fifth to the 30th days, but 26 of the 29 (including all frank cases of malaria and brucellosis) occurred between the 22nd and 30th days. The six episodes in the placebo group showed no unusual grouping.

Table V records the laboratory results from the two groups before and after treatment: there were 21 positive smears for malaria in the treated group, 13 of which were associated with clinical malaria and the greatest degree of parasitaemia. Two positive smears and one clinical case of malaria were found in the placebo group. Eleven nomads in the untreated group had positive titres for brucellosis of 1/80 to 1/320; all had had similar titres before treatment. Nineteen had positive titres for brucellosis after treatment; titres were more than 1/640 in 14 nomads. Discharge from the nodes and from the breast in treated patients was positive for tubercule bacilli. Schistosoma ova were more often found in the urine of treated patients. Finally *S typhimurium* never grew after incubation in iron-deficient serum but did grow after incubation in the serum of six out of eight treated patients.




Number of episodes of infection per day after treatment with placebo and iron.

TABLE V—*Iron repletion and infection; laboratory evidence of infection before and after treatment with placebo or iron*

| Group: | Placebo | | Iron | |
|---|---|---|---|---|
| | Before | After | Before | After |
| No of nomads | 66 | 66 | 71 | 71 |
| No of smears positive for malaria | 0 | 2 | 0 | 21 |
| No with parasitaemia | 0 | 4 | 0 | 11 |
| No with schistosoma ova in urine | 2 | 2 | 3 | 11 |
| No with positive Z-N titres | 0 | 0 | 0 | 3 |
| No with brucella titres: | | | | |
| >1/80 | 11 | 11 | 8 | 19 |
| >1/640 | 0 | 0 | 1 | 14 |
| No with growth of *S typhimurium* in serum* | 0 | 0 | 0 | 6 |

*Eight treated patients were tested.

## Discussion

Within the limits of this study and contrary to general belief, we have shown that iron deficiency seems to be associated with suppression of the signs of active infection, especially intracellular infections. The aluminium hydroxide tablets are unlikely to have played any part in suppressing infection in the control group, as the prevalence of infections already seemed to be reduced in untreated iron-deficient nomads entering the camp. Furthermore, correction of the deficiency by oral iron treatment seemed to be associated with a significant increase in the activity of the suppressed disease. This activity reached a peak as repletion advanced, suggesting that infection was most likely to occur near normal iron status. Since there had been no rain, no mosquitoes, and no overt attacks of malaria for over a year or access to animals and milk products for over six months, these attacks must have been related to activation of pre-existing disease. Iron deficiency probably plays a part in suppressing certain infections. This might occur because the

micro-organisms are deprived of iron either directly or indirectly through competition of unsaturated iron binding proteins of the host (although it would be difficult to explain recrudescences of malaria on this basis). Alternatively the iron might create an intracellular milieu unfavourable to rapid multiplication of the micro-organisms or host cells essential for clinical infection or suppress the inflammatory response of the host to infection. We have looked at this mostly from a negative point of view—that is, supposing that the organism is deprived of something that prevents it producing disease—but the phenomenon might equally possibly be a positive one—that is, host cells during iron deprivation may produce a chalone-like material that reduces host cellular DNA replication in an effort to conserve dwindling food reserves. Such a mechanism might also fortuitously prevent the intracellular multiplication of the infecting agent. Our studies with *Listeria monocytogenes* and *P berghei* in hypoferraemic, normoferraemic, and hyperferraemic mice[9] and those of Puschman and Ganzoni with *S typhimurium* in mice similarly treated[10] showed a substantial reduction of mortality in hypoferraemic animals. The repletion of the host with iron might therefore quickly reverse these changes, permitting unbridled division of organisms and overt clinical signs of infection.

We believe that iron deficiency in Somali nomads may be part of an ecological compromise. Animal milk, deficient in iron and often short in supply, causes chronic iron deficiency in nomads, who consume milk as their major source of energy. The iron deficiency, debilitating in some but rarely fatal, prevents the more serious consequences of potentially fatal infections with malaria, tuberculosis, and brucellosis to which the nomads are constantly exposed. A balance is struck whereby the nomads are able to co-survive with their micropredators at the price of their combined iron deficiency. We would like to end on a note of caution. It may be unwise to attempt to correct iron deficiency in the face of quiescent infection, especially in isolated societies where the natural ecological balance is often a first line of defence against severe infections.

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# How often should patients be reviewed after treatment with iodine-131 for thyrotoxicosis?

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## Summary and conclusions

**Six to 18 years after treatment with iodine-131 for thyrotoxicosis 69 euthyroid patients with raised serum thyrotrophin (TSH) concentrations (mean 25·0±SE 2·0 mU/l) and 61 with normal concentrations (mean 4·0±0·2 mU/l) were included in a prospective five-year follow-up study beginning in 1972. During this period 13 patients from the original group with raised serum TSH concentrations became hypothyroid. In contrast it was five years before hypothyroidism developed in a single patient from the group with normal serum TSH concentrations in 1972, although raised concentrations were recorded in 19 of these patients during the study.**

**Serum TSH concentrations may be used to assess how often patients need to be reviewed after iodine-131 treatment for thyrotoxicosis, thus greatly reducing the present long-term follow-up commitment in these cases.**



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## Introduction

Iodine-131 is the most widely used treatment of thyrotoxicosis in patients over 40. A major disadvantage of this treatment, however, is the increasing incidence of thyroid failure with time. Since we cannot predict either when or in whom hypothyroidism will develop such patients need to be followed up for life or until thyroxine replacement therapy is started. In the United Kingdom alone over 60 000 thyrotoxic patients have been treated with iodine-131 since the early 1950s and some 3000 new patients are added yearly. It would therefore be advantageous if follow-up of this ever-increasing number of patients could be reduced by utilising currently available tests of thyroid function. The serum thyrotrophin (TSH) concentration is a sensitive indicator of thyroid failure, and about half of all euthyroid patients treated with iodine-131 for thyrotoxicosis have raised TSH concentrations and thus impaired reserve of thyroid function.[1 2] To determine any difference in clinical course between euthyroid patients with normal TSH concentrations and those with raised values we studied two such groups prospectively over five years between 1972 and 1977.