

Influence of Iron Nutrition on Work Capacity and Performance

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Interest in the effects of iron deficiency and anemia on physical work capacity and productivity has only recently developed (1). The key role of iron in the transport and utilization of oxygen explains the widely recognized fact that severely anemic individuals cannot carry out tasks involving muscular work. For this reason, it is amazing that individuals with 2 or 3 g/dl of hemoglobin (80–85% deficit) can continue to be physically active in regions where chronic iron deficiency is endemic. This phenomenon provides evidence for the known series of compensating mechanisms that come into play when iron deficiency develops slowly. In addition, limitations on spontaneous physical activity and overall "tiredness" are manifestations of chronic iron deficiency anemia only when the anemia is severe (hemoglobin level lower than 7 g/dl).

Iron deficiency is prevalent and particularly severe among tropical rural-poor populations that are dependent upon physically demanding tasks for survival and economic development. Such people are victims of chronic hunger, high rates of infection, and environmental deprivation that limit developmental stimuli and educational opportunities. Under these circumstances, it is difficult to isolate the effects of iron deficiency as a cause of "lack of ambition and general inactivity." In children, inadequate human milk feeding (primarily an urban phenomenon), poor weaning, generally inadequate feeding practices, and early repeated infections (including hookworm, whipworm, and malaria) are responsible for the high prevalence of anemia (2) (Table 1). These children are apathetic, listless, irritable, and have altered development and diminished growth velocity. These manifestations could easily be assigned to iron deficiency, overall malnutrition, lack of stimulation, chronic and/or repeated infections, or to several of these factors. At the same time, moderate and severe protein-energy malnutrition diminishes the severity of iron deficiency by slowing growth rates and, where loss of active tissue mass ensues, by a contraction of the total circulating hemoglobin mass (3,4).

TABLE 1. Estimated prevalence of anemia in children by geographic region (1980)^a

Region	0-4 years		5-12 years	
	Percentage	Number ^b	Percentage	Number ^b
Africa	56	48.0	49	47.3
Latin America	26	13.7	26	18.1
East Asia ^c	20	3.2	22	5.6
South Asia	56	118.7	50	139.2
World ^d	43	183.5	37	217.4
Developed regions ^e	12	10.3	7	9.1
Developing regions	51	183.2	46	208.3

^aFrom ref. 2.^bNumbers = millions.^cExcluding China.^dAccording to United Nations regions, including North America, Japan, Europe, Australia, New Zealand, and the Union of Soviet Socialist Republics.

TABLE 2. Summary of studies in children exploring the effect of anemia and iron deficiency on physical work capacity.

Population	Age (years)	Hemoglobin (g/dl)	Reference
Male/female	10-20	8.9-19.7	8
<i>Main findings:</i> Hemoglobin is directly associated with speed, strength, and sustained muscular effort; not so with the Harvard Step Test and Endurance Step Test (both near VO ₂ max).			
Male/female	10-16	10.9-16.5	6
<i>Main findings:</i> Hemoglobin correlates with VO ₂ max but not when corrected for body weight or when groups of children by sex and age are studied independently.			
Male/female	7-14	7.1-14.0	9
<i>Main findings:</i> Hemoglobin and body weight explain most variance in submaximal VO ₂ .			
Male	12-15	Mean: 14.0 SD: 1.0	10
<i>Main findings:</i> Hemoglobin highly correlated with VO ₂ max. VO ₂ max also correlated with vitamin A and vitamin B ₂ nutritional status.			
Male/female	11-14.5	9.7-15.1	11
<i>Main findings:</i> Responses to iron and vitamins C, B ₁₂ , and B ₆ were associated with decrements in submaximal VO ₂ . Changes in hemoglobin were negatively related to changes in VO ₂ in standard submaximal work.			
Male/female	4-7.5	2.9-11.5	5
<i>Main findings:</i> Five clinical cases; remarkable lack of correlation between hemoglobin and "exercise tolerance" in chronic anemia; not so in acute anemia; little improvement with transfusion.			
Male/female	Mean: 14.0 SD: 2.3	Mean: 8.0 SD: 0.6	7
<i>Main findings:</i> VO ₂ for a given work load was not affected by anemia. Heart rate was elevated and VO ₂ max reduced in anemic children even when expressed per kg of body weight or lean body mass.			

The influence of iron deficiency on spontaneous physical activity of children has not been measured; and not many studies have explored the effect of anemia or iron deficiency on physical work capacity in children. Furthermore, results from such studies are far from clear (5-11). In general, mild to moderate anemia (hemoglobin concentration as low as 9.5 g/dl) fails consistently to affect submaximal oxygen uptake in school-age children (Table 2). Similarly, hemoglobin levels as low as 10.8 g/dl do not consistently reduce maximal aerobic power in 10- to 16-year-olds (6) (Fig. 1). These findings contrast with findings in the adult population, where consistently positive linear correlations are found between hemoglobin concentration and maximal work situations (12-14). It is possible that children may be able to compensate more efficiently for iron deficiency and anemia in terms of physical work capacity, that the methodology used to detect alterations in physical work performance in children is not as well standardized and precise as in adults, or both. The need for research in this area is evident.

Given the similarities in effects of iron deficiency on hematological and endocrine alterations in both adults and children, what is known from studies in the adult might be assumed to be relevant to infants and children until bet-

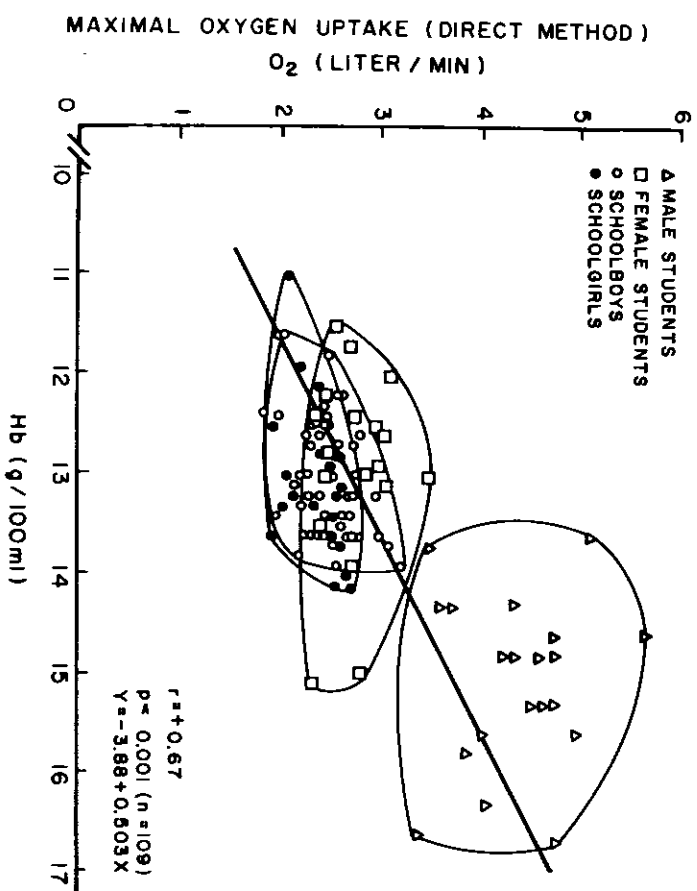


FIG. 1. Maximal aerobic capacity (VO₂max) of children relative to hemoglobin concentration. (Reproduced from ref. 6 with permission from Alonquet & Wilmsell Periodical Co., © 1971.)

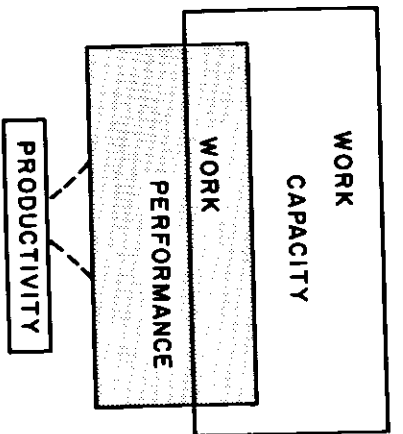


FIG. 2. Schematic model of an approach to the study of productivity.

ter definitions of specific compensatory mechanisms are developed. Similarly, the mechanisms by which iron deficiency impairs physical working capacity and performance in severely iron-deficient animal models may serve as a guide for additional research on the effects of iron deficiency on physical activity and performance in humans (adults and children).

The relationship between work capacity, work performance, and productivity is the result of complex processes (Fig. 2), with overlap between the conditions that determine each component (Figs. 3 and 4).

Briefly, the genetic makeup of the individual (host) and interaction with the environment and various agents (some nutrients) determine the growth, health, and nutritional status of the individual (Fig. 3). Human development, in turn, is determined by the final functional expression of these components at the point

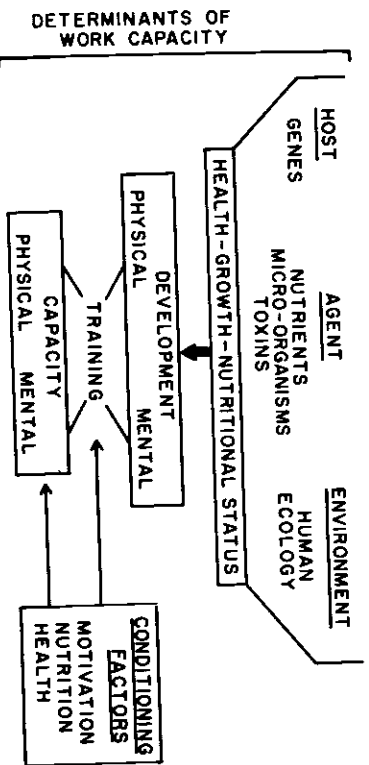


FIG. 3. Diagram of factors that affect work capacity.

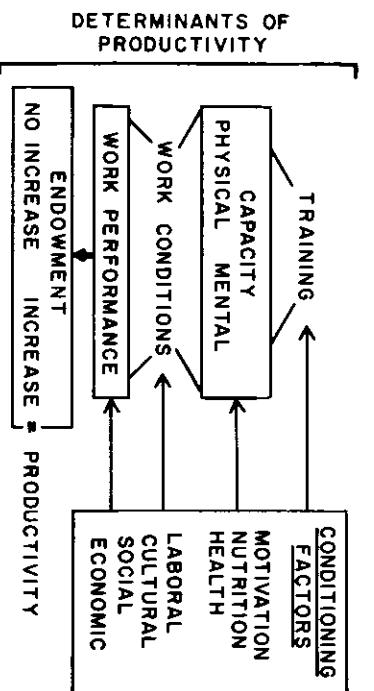


FIG. 4. Diagram of factors that affect work performance and productivity.

where they interact. The addition of a purposeful component, identified as training (including education), provides the final specific modulation to the level of general development, expressed as capacity to perform specific tasks.

Figure 4 illustrates the determinants of a specific performance of work. Here, additional and more specific training as well as the development of greater dexterity in a specific task can improve performance, building upon an already existing capacity. The conditions under which this capacity is to be exercised as productive work as well as the social and economic meaning of such work also determine performance. The final factor is the value of such performance in modification of human endowment. A positive modification may not necessarily imply an improvement in economic terms. For example, more satisfying or edifying expenditure of leisure time constitutes a positive modification of human endowment, particularly in children, and, as such, must be considered a productive human performance.

THE ROLE OF IRON IN THE DEVELOPMENT OF PHYSICAL WORK CAPACITY

Body Size and Composition, Health, and General Nutrition

Physical work capacity, expressed as work performed per unit time, is positively correlated to body size, lean body mass, and, more specifically, to the absolute amount of active tissue mass, of which functional muscle mass is the largest component (15-17). In controlled animal experiments, iron deficiency has consistently demonstrated a negative effect on growth that is reversible when the deficiency is corrected (18). A plausible explanation for this phenomenon is reduced food intake, which is exacerbated by decreased feed efficiency in deficient animals. This effect appears to occur

only when the dietary-induced deficiency is moderate to severe (19,20). In human populations in developing countries who show both inadequate growth and iron deficiency, the relative role of the iron deficit cannot be defined. However, a basis exists for implicating iron deficiency as contributing to poor growth, poor muscle mass development, poor health, and poor general nutrition in such populations.

In the same ecological setting, iron-deficient children show growth deficits relative to non-iron-deficient children (21). Iron deficiency and poor growth may be the consequence of various phenomena that coincide in these children and serve as covariates.

Several immunological defects have been documented in iron-deficient humans and animals (22-24), which in the presence of infection may have a role in the magnitude of the "disease phenomenon" of developing populations. Indirect evidence (25) suggests that repeated infection hampers growth, food intake, iron absorption, and iron metabolism (26-29). Finally, iron deficiency has been associated with aberrations in eating patterns (pica, for example) that can increase the potential for infection with all of its consequences.

Iron-deficient animals have a reduced functional muscle mass (30) and iron-deficient anemic adults have a lower body mass index than non-iron-deficient individuals (31). Unfortunately, it is impossible to determine if this last finding is due to lower adiposity or to lower lean body (and muscle) mass, or if it occurs independent of iron deficiency. However, the fact that anemic iron-deficient adults react with higher oxygen consumption to cold exposure than their normal counterparts (31) suggests an additional mechanism by which iron deficiency may burden already marginally nourished, often-infected populations.

General Development

The capacity to perform work depends not only on the physical attributes of the individual but also on his/her cognitive and emotional development (32). Hormonal derangements demonstrated in iron-deficient humans (31,33,34) and animals (35-37) can also interfere with normal development, in particular alterations in thyroxine metabolism (36,37). Several enzymatic defects in the neuroendocrine axis and in the liver are other factors by which iron deficiency may interfere at critical stages of development (38,39).

Also important to development is the diminution in spontaneous activity demonstrated by iron-deficient rats relative to iron-sufficient controls (19,40) (Fig. 5) and by human adult groups in Sri Lanka (41) (Fig. 6). Diminished physical activity may be another mechanism involved in impaired growth (42).

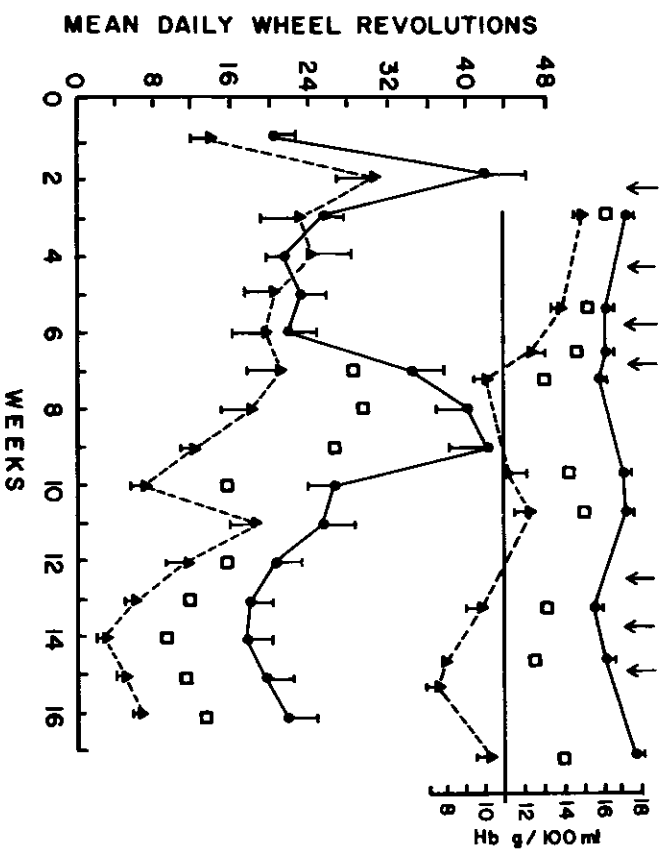
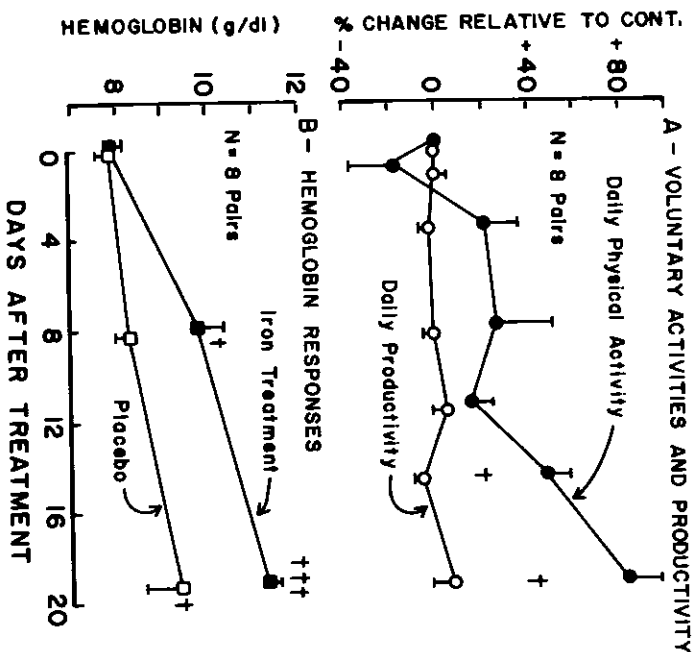


Fig. 5. Hemoglobin concentration and voluntary activity in anemic and control rats. Arrows indicate days when blood was drawn. Upper graph: mean \pm SEM of concentration in control (—) and anemic rats (- -). Lower graph: mean \pm SEM of spontaneous activity in the same rats. \square = $p < 0.05$. Taken from ref. 40.

Training

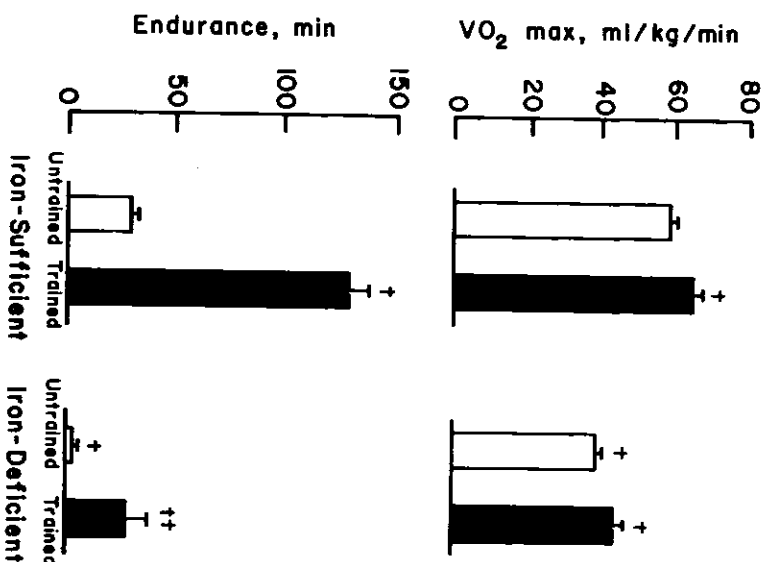
Until recently, nothing was known about the effect of iron deficiency on physical training or the converse effect of physical training on iron deficiency. Studies in growing (43-46) and in adult rats (47) have shown that physical training in iron-deficient rats is associated with a relative improvement in iron status compared to untrained, iron-deficient controls. Enhancement of iron absorption as a consequence of intense physical activity may be responsible for this improvement (47), together with mobilization of small amounts of storage iron toward the heart and other active muscles (43,44). However, very strict control of iron contamination of the training treadmill used in these studies markedly diminished differences in hemoglobin concentration and in iron-containing mitochondrial enzymes in muscle (46).

Although mild to moderate training improved endurance work significantly in both iron-deficient and iron-sufficient rats, the latter exhibited a greater response, indicating that iron deficiency limits the response to training. Maximal aerobic capacity ($\dot{V}O_{2max}$) exhibits a small, often insignifi-



cant response to mild or moderate training independent of iron status. Consistently, trained and untrained anemic rats demonstrated significantly impaired performance in both endurance and maximal work when compared to normal controls (45) (Fig. 7).

No specific studies have been carried out to explore the effect of training in iron-deficient and control human subjects. In a double-blind study in Guatemala, 44 physically active adult agricultural workers (both anemic due to iron deficiency and nonanemic) were divided into two paired groups: one received therapeutic doses of iron, and the other received an identical placebo (48). Neither the subjects performing the Harvard Step Test (HST) nor the investigators knew which subject belonged to which group. The HST was performed at baseline and at 2-, 4-, and 16-week intervals. Although the treated subjects improved in hemoglobin concentration and hematocrit and HST, the placebo group did not change, suggesting that there was no training effect in this group (48). Similarly, 10 Ceylonese anemic individuals who received placebo for 16 days and performed maximum work tests every 4 days did not exhibit any training effect (14). Two drawbacks to the inter-



pretation of these results are apparent: (a) the training was far from intensive, and (b) Guatemalan subjects were already in good physical condition from living in the mountains.

MECHANISMS INVOLVED IN THE RELATIONSHIP BETWEEN IRON NUTRITION AND PHYSICAL WORK CAPACITY

Overall Physical Work Capacity

In humans, a linear relationship exists between hemoglobin concentration and the level of maximal work capacity by the HST (13,49) (Fig. 8) or by measurement of maximal aerobic capacity (VO_2 max) (12,14,50,51). The

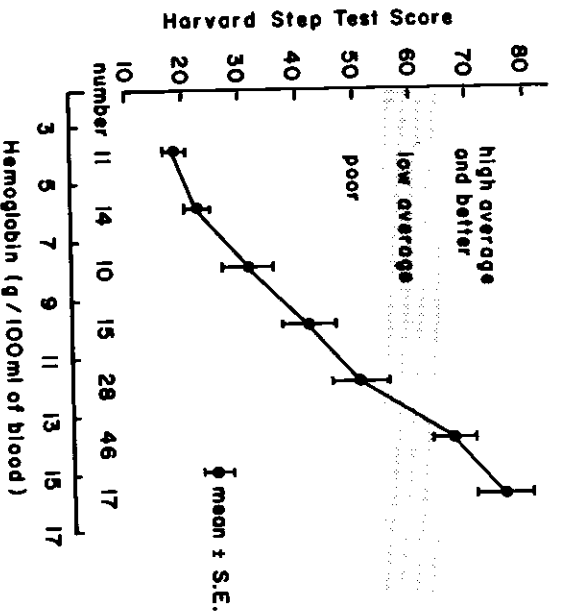


FIG. 8. Relationship between severe physical exercise performance, as measured by the Harvard Step Test score, and hemoglobin concentration in adult men. (Reproduced from ref. 13 with permission from W. B. Saunders, UK, © 1974.)

detailed studies of Gardner et al. (50) on female workers in Sri Lanka provided information on heart rate and lactic acid levels in response to standard exercise loads, all indicative of progressive limitations on heavy physical work in direct relation to the deficit in hemoglobin concentration (severity of anemia). Similar results were reported by Celis and Ekblom (52). At the same blood lactate concentration, anemic subjects were closer to their $\dot{V}O_{2max}$ than these same subjects to their respective $\dot{V}O_{2max}$ when the anemia was corrected. $\dot{V}O_{2max}$ increased parallel to hemoglobin concentration. At a lactate concentration of 4 mM, $\dot{V}O_2$ in the corrected state or before anemia was induced was higher than $\dot{V}O_{2max}$ when moderate anemia (Hgb = 11 ± 0.8 g/dl) had been induced by bleeding. These findings suggest that the reduction of $\dot{V}O_{2max}$ in anemia is more limiting than lactate accumulation.

Similar results have been obtained with rats under rigorously standardized conditions (18,40,53-55). Studies in iron-deficient rats (56,57) indicated that $\dot{V}O_{2max}$ decreased in relation to the decline in hemoglobin concentration with two different slopes. When hemoglobin levels were lower than 8 g/dl, the slope was steep, but when hemoglobin levels exceeded 9 g/dl in response to treatment, the slope was flat. The response in rats contrasts with data on humans that show no difference in slope whether hemoglobin levels decrease or whether they increase in response to iron therapy or transfusion (13,14,51).

Adaptation Mechanisms

Because oxygen delivery and utilization by active tissues are essential in order to maintain function, adaptation mechanisms compensate for the diminution in oxygen-carrying capacity induced by chronic iron deficiency anemia. Important among these mechanisms at rest and at submaximal exercise levels are well-documented elevations in cardiac output, the lowering of peripheral resistance with redirection of blood flow, and shift in the oxygen dissociation curve of hemoglobin towards maximizing oxygen delivery at low oxygen tensions (58-61). The elevation in cardiac output occurs through an increase in heart rate for a given exercise load, while oxygen extraction in the peripheral tissues also increases. Each mechanism contributes about 50% to the physiological adaptation when anemia is mild to moderate, i.e., a hemoglobin concentration > 9 g/dl (62). Among individuals with similar active tissue mass, maximal aerobic power, as defined by $\dot{V}O_{2max}$, is dependent on circulating hemoglobin levels, since cardiac output does not increase significantly above normal in anemic states. On the contrary, a mild or nonsignificant reduction in $\dot{V}O_{2max}$ of 5% to 8% with hemoglobin levels around 11 to 12 g/dl is not unusual in otherwise healthy men (51,61). $\dot{V}O_{2max}$, however, can be increased by hyperttransfusion and by an adequate exercise training regimen among healthy individuals. In the first instance, an average of 18.9 ± 6.4 (SD) ml/min/g of change in hemoglobin/liter of blood has been documented (maximum Hgb near 20 g/dl). In the second instance, $\dot{V}O_{2max}$ can be increased by 20% or more (51,58). All of these mechanisms may compensate for the modest reduction in oxygen-carrying capacity that results from chronic moderate anemia in order to maintain adequate tissue oxygenation. However, when maximal or near-maximal aerobic capability is demanded, or when hemoglobin levels are so low (< 7 g/dl) as to compromise tissue oxygenation even with minimal effort, these compensatory mechanisms fail.

Several studies (63-66) have demonstrated enzymatic and composition changes in muscle at the cellular level in iron deficiency and the response to iron therapy. Substantial evidence indicates that iron deficiency occurs in twice as many individuals as those exhibiting anemia (67), since the latter condition is a relatively late manifestation of iron deficiency.

In the mid-1970s, a series of elegant functional studies examined the role of iron deficiency at the muscle level independent of anemia. They demonstrated that muscle function in the rat was impaired by iron deficiency, even when the capacity of the blood to deliver oxygen to muscle was still adequate. This impairment was caused by a series of structural and enzymatic deficiencies that reduced the oxidative capacity of muscle primarily by means of a decreased functional mitochondrial mass. Muscle capacity was probably further impaired by a lower intramuscular oxygen diffusion capac-

ity consequent to a reduction in myoglobin. These defects resulted primarily in reduced endurance and submaximal work performance.

In growing rats, the sequence of changes in cytochrome c and transferrin saturations (Fig. 9) clearly shows a rapid decline in cytochrome c and transferrin saturation with progressive iron deficiency, followed shortly by a reduction in hemoglobin and myoglobin concentrations. All of these changes occur when liver iron reserves are exhausted (68). In iron-deficient adult rats, however, myoglobin reduction does not occur (69). Iron deficiency also produces substantial declines in the activity of key iron-sulfur proteins, mitochondrial oxidative enzymes, dehydrogenases, cytochromes, and flavoproteins involved in electron transport and oxidative phosphorylation. These changes reduce the mitochondrial capacity to produce high-energy phosphates (ATP) (30,70,71) and reduce markedly the bioenergetic function of mitochondria. Mitochondrial mass also appears to be reduced in muscle from iron-deficient rats (30). These alterations are further complicated in iron deficiency by the demonstrated decline in the α -glycerophosphate oxidase system that drives the operation of the α -glycerophosphate shuttle. This system, together with the malate-aspartate shuttle, contributes not only to

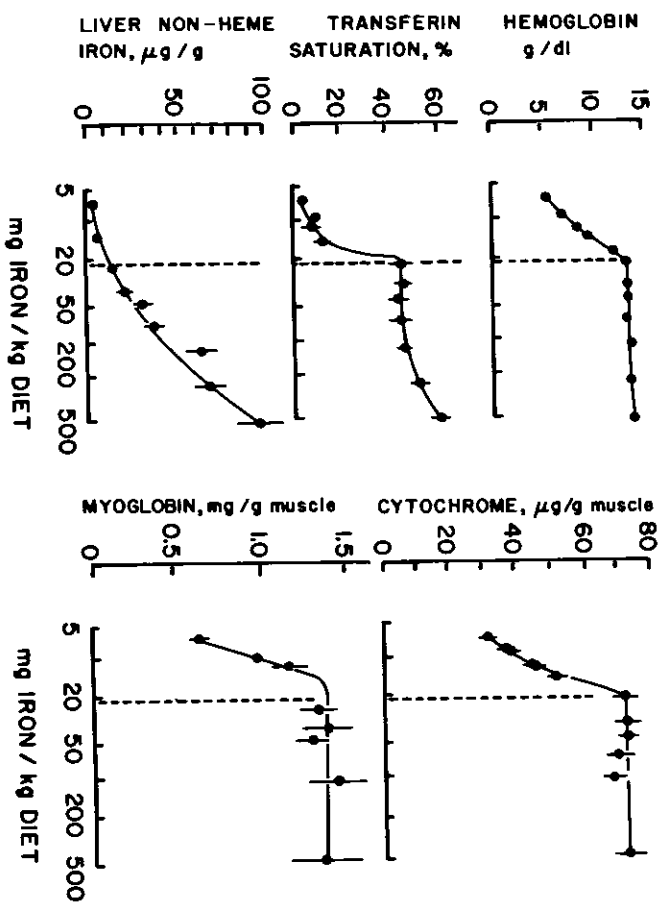


FIG. 9. Effects of various levels of dietary iron deficiency in growing rats on various iron-dependent variables in liver, blood, and muscle (mean \pm SEM). (Reproduced from ref. 68 with permission from the American Journal of Clinical Nutrition, © 1980.)

the electron influx into the mitochondria but also to the regeneration of cytoplasmic NAD^+ , essential for glycolysis (30,57,71,72). As a result of these limitations in functional mitochondrial oxidative capacity and glycolytic activity, alternative cytoplasmic NAD^+ regeneration, which is indispensable for extramitochondrial ATP production, must occur in muscle. One way to achieve such regeneration is through the increased utilization of glucose and pyruvate via lactate, resulting in increased glucose utilization, lactate turnover with greater recycling through glucose, and lactic acidosis. These phenomena have been implicated in the limitations exhibited by iron-deficient rats even when performing submaximal exercise (40,71-74). Endocrine responses to exercise (elevations in glucagon, cortisol, epinephrine, and norepinephrine) in favor of neoglucogenesis and gluconeolysis have been demonstrated in the anemic dog when compared to the nonanemic state (75). In humans, Gardner et al. (50) demonstrated a progressive lactic acidosis in direct proportion to the severity of the anemia and inversely proportional to maximal aerobic capacity in human volunteers performing maximal exercise tests.

Recently, a series of studies that measured the impact of iron deficiency on maximal or near-maximal effort and endurance capacity demonstrated the relative importance of muscle dysfunction in iron deficiency. The practical importance of these studies relates to the fact that most human physical work is submaximal (at around 40% of VO_{2max}) and demands various degrees of endurance.

These studies gave rise to the α -glycerophosphate hypothesis as the cause of impaired muscle function and lactic acidosis in iron deficiency. The independence of muscle dysfunction from anemia in iron deficiency was clearly demonstrated by Finch et al. (57), who reported that iron-deficient rats performed poorly on standardized strenuous exercise tests even when they were transfused to the same hemoglobin levels as iron-sufficient animals. They also demonstrated that when iron therapy was provided, work performance improved within 4 days, concomitant with a rise in the activity of the α -glycerophosphate oxidative system. Subsequent studies exploring endurance capacity in iron-deficient rats (30,55,56) provided evidence that muscle bioenergetic dysfunction in this animal is primarily responsible for alterations in exercise endurance, while the reduction in maximal aerobic power (VO_{2max}) is primarily the consequence of impaired oxygen delivery to muscle, resulting from reduced hemoglobin concentration. It would appear that reductions in endurance appear early in progressive iron deficiency and are more severe (76) than limitations in maximal aerobic power. The response pattern to iron repletion suggests that endurance recovers more slowly than VO_{2max} (30) (Fig. 10). Physical training appears to stimulate the activities of non-iron-dependent enzymes in the tricarboxylic acid cycle of iron-deficient rats, while it has no effect in iron-sufficient animals (77,78). This adaptation increases muscle oxida-

tive capacity, improves lactate homeostasis, and enhances the response to energy demands for endurance in the face of adequate oxygen delivery systems.

Impaired muscle function appears to be subject to iron deficiency at four different key points (Fig. 11). While all four probably are in play simultaneously, each contributes to a different degree depending upon exercise demands. Changes in general metabolic fuel utilization, favoring glucose dependence, appear to be induced by iron deficiency, with loss of metabolic efficiency as a consequence.

Few of the metabolic alterations demonstrated in the iron-deficient rat have been corroborated in the human. Although strong evidence exists for excessive lactic acidemia, as well as some indications of a beneficial effect of iron therapy beyond correction of hemoglobin, evidence for decreased endurance and rapid response to iron therapy is lacking (79,80). Moreover, studies on human skeletal muscle from severely chronic iron-deficient individuals have failed to demonstrate changes similar to those well documented in rats (81).

The role of "anemia" and of iron deficiency in the more general metabolic effects demonstrated in animals needs to be defined in humans, including the sympathetic-norepinephrine and thyroid dysfunction upon which many of the iron-energy and thermoregulation interactions are based (37,82).

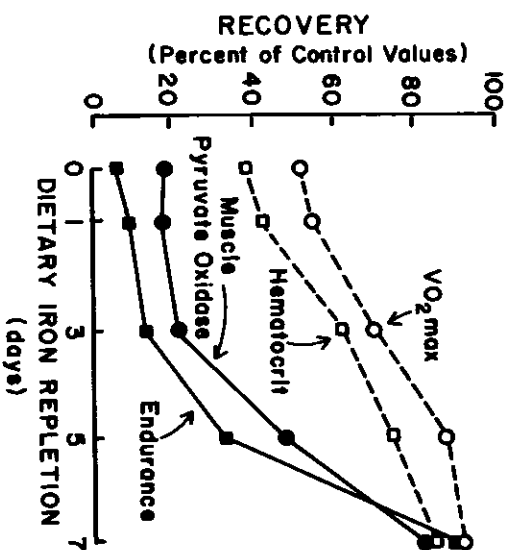


FIG. 10. Recovery of VO_{2max} , hematoctrit, endurance capacity, and muscle homogenate pyruvate-malate oxidase activity of iron-deficient rats during dietary iron repletion (mean percentage of each day's control rats). (Reproduced from ref. 30 with permission from the American Physiological Society, © 1982.)

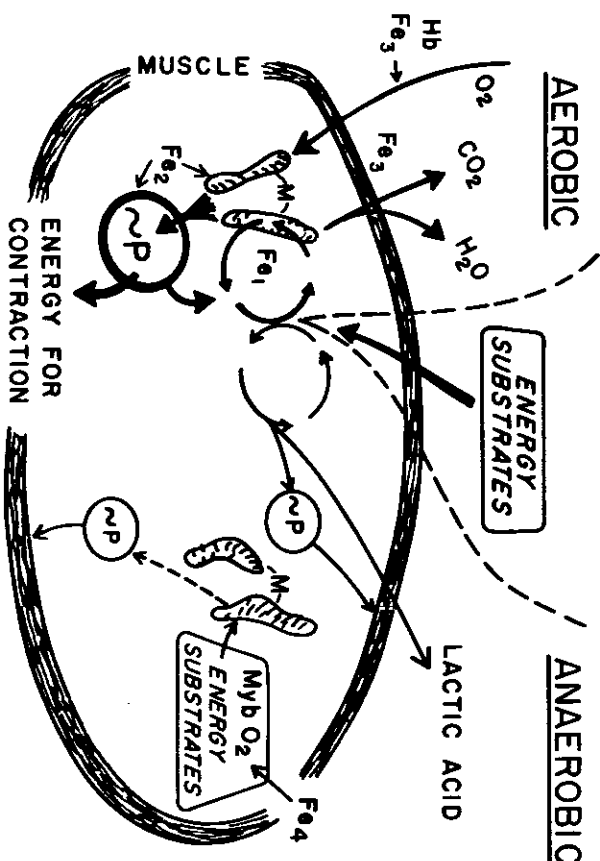


FIG. 11. Schematic representation of sites where iron deficiency induces reduction in muscle function and impairs physical work capacity. Fe₁ = phosphoglycerate shuttle; Fe₂ = oxidative phosphorylation system (muscle oxidative capacity), cytochromes, oxidases, dehydrogenases; Fe-S clusters; Fe₃ = hemoglobin O₂-CO₂ transport; Fe₄ = myoglobin O₂ content.

EFFECTS OF IRON DEFICIENCY AND ITS CORRECTION ON WORK PERFORMANCE AND PRODUCTIVITY

Given the complexity of factors that modulate work performance, most ordinary workday environments do not lend themselves to exploration of the effect of iron deficiency on work capacity and productivity. Two major studies, one in Sri Lanka (41) and the other in Indonesia (38,49,83), have demonstrated the effects of iron deficiency and its correction in work performance and productivity. Both studies included placebo controls and were as free from bias as possible. In Sri Lanka, tea pickers increased their average daily tea weight harvest by 0.3 kg in response to iron administration. The response was greater among those whose hemoglobin concentration was initially < 9 g/dl (1.9 kg/day). This effect occurred "despite the constancy of the physical and psychological environment" provided by rather rigid social concepts of work and labor conditions (41) (Fig. 12). In Indonesia, both rubber tappers (paid by the piece) and weeders (paid by the day) exhibited better work performance and productivity when their hemoglobin levels were higher than their counterparts both throughout the study and as their hematological condition and iron status improved. In the higher hemoglobin group, the measured total latex harvested was almost 16% higher and the

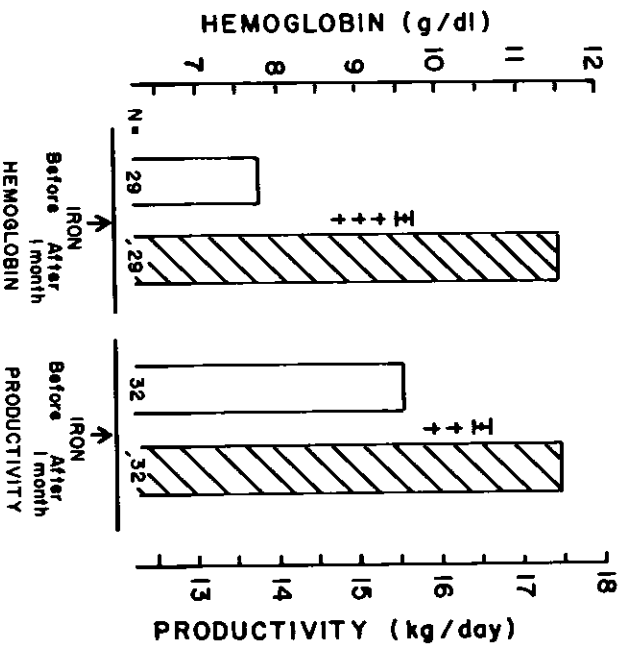


FIG. 12. Effect of oral iron treatment of anemic female tea pickers (Hgb < 9 g/dl) on hemoglobin and kg of tea plucked/day. Bars = mean \pm SEM of differences in 1 month time. $p < 0.001$; $p < 0.01$. From ref. 41.

area weeded was nearly 15% larger than the totals of their "anemic" counterparts. When the area weeded was expressed on a time basis, the workers with higher hemoglobin values performed better than those with lower hemoglobin values during the first 2 hr of work, although there was no difference in the next 3 hr of the measured work day.

In terms of cost efficiency, the results of both studies justified the economic investment needed to correct iron deficiency. For the rubber tappers, the benefit/cost ratio could be as high as 260:1. In addition, the workers without anemia remained healthier and had less absenteeism than their iron-deficient counterparts (49).

CONCLUSIONS

The maintenance of adequate iron nutrition throughout life seems to favor the achievement of an optimal physical work capacity. In addition, the treatment of iron deficiency produces significant improvements in work capacity and performance. Techniques to achieve both goals are at hand and appear to be highly cost-effective. In the human, the biochemical mechanisms operating at the cellular level in muscle still need clarification. Moreover, the

effects of iron deficiency on whole body energy substrate regulation and utilization at rest and during exercise also need to be explored in depth.

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