REVIEW OF LITERATURE

Children represent the richest resource of any country. They need an environment which prepares them for optimal growth and development and to understand and meet their own needs as well as those of the community (Bouhaire and Nader, 1977).

School age children constitute an age group that upto now does not seem to have aroused any real interest among specialists in health statistics (Jeanneret and Raymond, 1976). The children have a variety of nagging health problems, which though do not incapacitate them very much physically, certainly are bound to hamper their scholastic performance and learning capacity at school (Sundaram et al, 1978).

Although, it is generally accepted that anemia is quite prevalent among infants and preschool children, particularly in the lower socio-economic group, Singla et al (1980) have reported the magnitude of this problem in older children and adolescents as becoming apparent only in the recent years.

Since the major objectives of the present study were to evaluate the hematological and functional responses of school girls (8-15 years of age) to iron supplements, the review will survey the literature with reference to the functional impairments in iron deficiency anemia and will also discuss some of the approaches to improve the
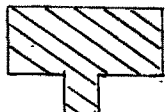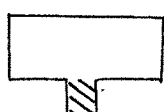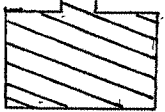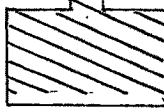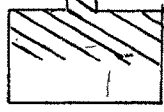
	NORMAL	IRON DEPLETION	IRON DEFICIENT ERYTHROPOIESIS	IRON DEFICIENCY ANEMIA
Iron Stores →				
Erythron iron →				
RE Marrow Fe (0-6)	$2-3^+$	$0-1^+$	0	0
Transferrin IBC (mcg/dl)	330 ± 30	360	390	410
Plasma Ferritin (mcg/l)	100 ± 60	20	10	<10
Iron absorption	normal	↑	↑	↑
Plasma Iron (mcg/dl)	115 ± 50	115	<60	<40
Transferrin Saturation (%)	35 ± 15	30	<15	<10
Sideroblasts (%)	40-60	40-60	<10	<10
RBC Protoporphy-rin (mcg/dl RBC)	30	30	100	200
Erythrocytes	Normal	Normal	Normal	Microcytic and Hypochromic

Fig 1.   The sequence of changes induced by a gradual depletion of the iron content of the body.

Taken from : Bothwell et al, 1979

functional aberrations in the population under study. The review has
thus been organised under the following sections :

1. Definition of anemia and criteria for assessment.

2. Diagnostic parameters for iron deficiency (and anemia).

3. Prevalence of anemia in school children.

4. Deleterious effects of anemia.

5. Behavioral consequences of iron deficiency anemia.

6. Impact of iron deficiency on Physical Work Capacity.

7. Iron deficiency and growth.

8. Prevention of iron deficiency anemia.

1.   Definition of anemia and criteria for assessment

Anemia is the end result of severe deficiency of iron and other
nutrients. It has been defined as "a condition in which the hemoglobin
concentration is below the level that is normal, for a given individual,
due to the deficiency of one or more of the nutrients required for
hemopoiesis and, conversely, a condition in which the hemoglobin
concentration can be raised by increasing the amount of nutrient(s) absorbed"
(Baker and DeMaeyer, 1970).

Iron deficiency results in a reduction in the total body iron
content. It may range in severity from reduced body iron stores without
any restriction of erythropoiesis to severe anemia with multiple deficien-
cies of tissue iron enzymes. There are three identifiable stages of iron
deficiency. Figure 1 gives the sequential changes in the development
of Fe deficiency.

The first, iron depletion, refers to a simple decrease in iron stores without any effect on essential body iron. The shrinking of stores is accompanied by a parallel fall in the concentration of ferritin circulating in the plasma. In the second, iron deficient erythropoiesis, there is a curtailment in iron supply to erythroid marrow. Serum iron and, to some extent total iron binding capacity estimations indicate the adequacy of marrow iron supply. As the serum iron (SI) decreases and total iron binding capacity (TIBC) increases with Fe deficiency, the most useful index is the transferrin saturation (TS) which is the ratio of SI to the TIBC, multiplied by 100 to express it as a percentage. When the TS level falls below 15%, the hemoglobin production in the developing red cells is curtailed. Another measure used to detect this stage is the erythrocyte protoporphyrin (EP). When iron supply to the developing red cell becomes restricted, the EP in the circulating red cells usually rises in advance of a discernable fall in the hemoglobin (Hb). While Hb concentration may fall slightly, at this stage it is still within the normal range, although there is an increase in the microcytic cells (England et al, 1976).

The third and final stage of iron lack is iron deficiency anemia. At this stage, there is a sufficient fall in Hb to be recognised as anemia. Most of the circulating red cells are replaced by the microcytic hypochromic population. This stage of iron deficiency is also characterised by depletion of a number of functional iron containing compounds in the extra erythroid tissues. These include myoglobin, cytochromes and

Fig 2. Stages of Iron deficiency and Criteria for assessment of each stage.

	Normal	Stores	Supply	Anemia
Iron Stores (mg)				

Iron Stores scale: + 600, O, - 600

	Normal	Stores	Supply	Anemia
SERUM FERRITIN (mcg/l) (SF)	60	< 12	< 12	< 12
TRANSFERRIN SATURATION (TS)(%)	35	35	< 16	< 16
ERYTHROCYTE PROTOPORPHYRIN (EP) (mcg/dl RBC)	30	30	> 70	> 70
HEMOGLOBIN (Hb) (g/dl)	> 12	> 12	> 12	< 12
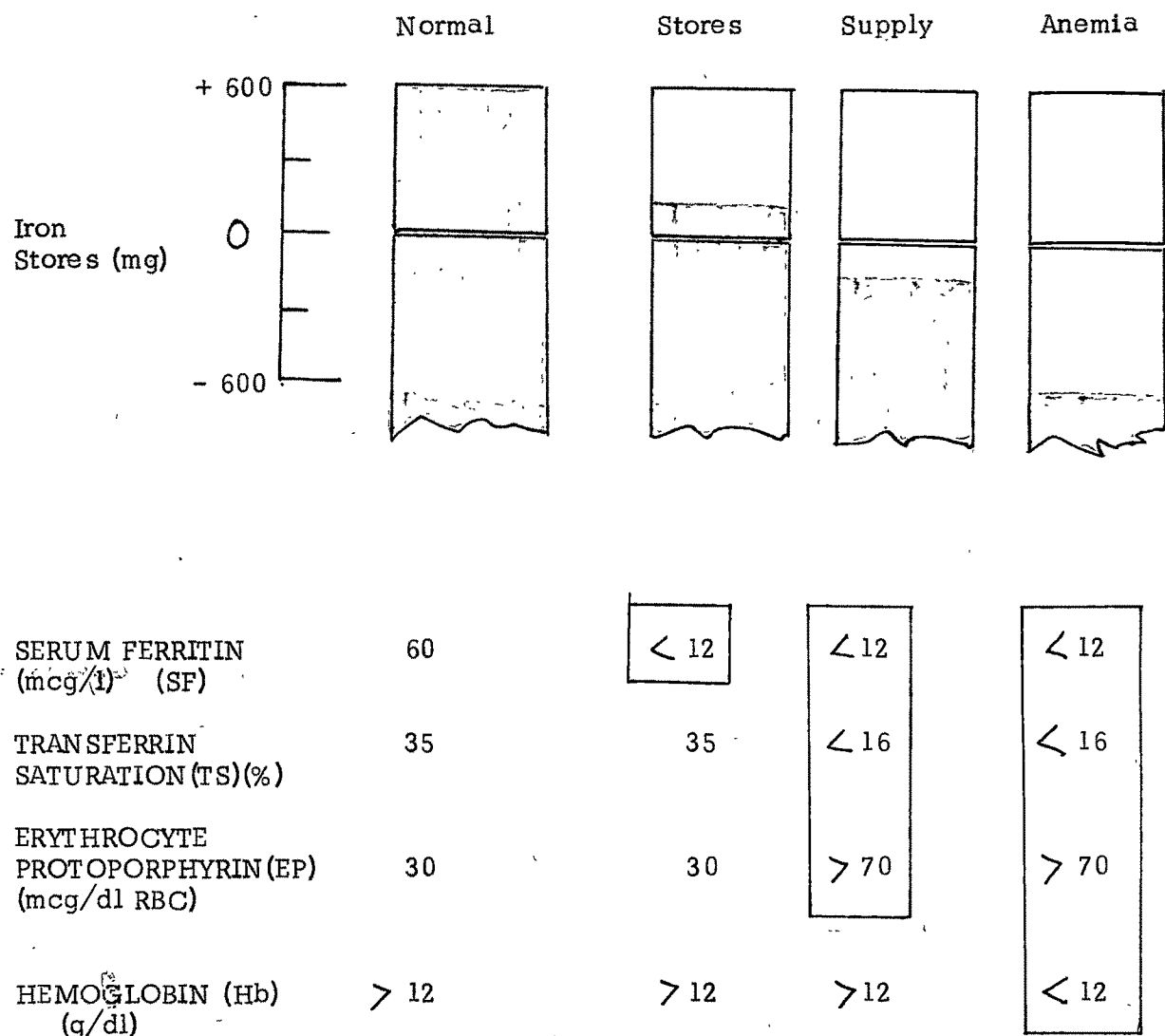
Taken from : Cook and Finch, 1979

a variety of other iron containing enzymes. Criteria for assessment of each stage are as in Figure 2.

2.   Diagnostic parameters for iron deficiency (and anemia)

The fact that a restricted supply of iron for erythropoiesis is responsible for the anemia can be readily established. The most helpful indicators of iron supply are the plasma iron concentration and the transferrin saturation (Bainton and Finch, 1964). While the erythrocyte protoporphyrin concentration is a more stable indicator of the balance between marrow iron requirement and available supply (Jacobs and Finch, 1971), it is also abnormal in lead poisoning and in certain rare abnormalities of porphyrin synthesis. A useful estimate of the quantity of iron stored in the tissues, and potentially available for the synthesis of hemoglobin is provided by plasma ferritin concentration; but the relationship is distorted by inflamation or liver disease (Lipschitz et al, 1974; Jacobs and Worwood, 1975).

A number of studies have provided information on analytical and biological variations for hemoglobin (Hb), hemotocrit (Hct), red cell morphology (RCM), Serum iron (SI), Total Iron Binding capacity (TIBC), Serum ferrin (SF) and Erythrocyte protoporphyrin (EP). Dallman(1984) in an attempt to summarise these, conveniently grouped the laboratory tests used in the diagnosis of Fe deficiency (and anemia) into the screening and confirmatory tests. The initial screening tests were Hb concentration and Hct. However, he pointed out that the measurement of Hct was not as reliable a means of diagnosing anemia as was the Hb concentration; also supported by Graitcer et al, (1981).

Table 1.   Comparison of laboratory parameters of iron status.

Parameter	Advantages	Disadvantages
HEMOGLOBIN/ HEMATOCRIT	- defines major liability - small volume - simple to perform	- detects only severe deficiency - low sensitivity* - low specificity*
ERYTHROCYTE PROTOPORPHYRIN	- small volume - simple to perform - physiologically stable	- instrumentation costly - complex standardisation - affected by lead poisoning
TRANSFERRIN SATURATION	- relatively specific - well established - detects excess iron	- requires venous blood - difficult to perform (contamination) - wide diurnal variation
SERUM FERRITIN	- highly specific - quantitative measure of store - small volume	- complex methodology - affected by inflammation - evolving technology

*Sensitivity is the percentage of iron deficient individuals identified by a given laboratory test whereas Specificity is the percentage of normal individuals wrongly identified as iron deficient by the same test. The ideal laboratory measurement has a sensitivity of 100% and a specificity of 0%. (taken from Cook, 1984).

Among the tests termed confirmatory tests for

Fe deficiency were SI, and TIBC, SF and EP. All these tests indicated errors due to biological variations. However, the biological variations in SF were greater than those for TIBC but substantially below those for SI; although, the diurnal variations in Fe can be minimised by sampling in the morning or early afternoon (values can normally fall to very low levels at night). Thus, the TS, a ratio of SI and TIBC expressed as a percentage can be a useful measure if these estimations are carefully controlled.

The SF and EP will probably replace the SI and TIBC eventually, but since the latter are now an established part of automated serum chemistry profile, this is likely to occur very slowly (Cook, 1982).

Table 1 summarises the advantages and disadvantages of various laboratory parameters of iron status. Some of these parameters require large volumes of blood while others require the use of sophisticated equipment, which is not feasible for field studies. Thus, community anemia surveys may often be best based on widespread Hb estimations and thin blood film (Jelliffe, 1966), in addition to TS determination.

3. Prevalence of anemia in school children

Amongst the earliest prevalence studies, Natvig et al (1966) reported that 9 to 31% of 10-13 year old children studied in different areas of Norway had Hb values less than 12.5 g/dl. The report also

indicated that the mean Hb values for boys were slightly higher than those for girls of the same age group. In their following study (Natvig et al , 1967), they indicated an absence of sex difference for Hb values prior to 15 years of age. Values increased in both sexes from 7 to 15 years of age, thereafter, the increase was rapid in boys upto the age of 20 years. These findings corroborate with those of Haghshenass et al (1972) for a similar Iranian population.

Surya Prakash (1973) in a study on 1093 school children, 5-13 years of age in Achampet, Andhra Pradesh, found the mean Hb levels ranging between 10.8 to 12.6 g/dl; the values for girls between 11 to 13 years of age being comparatively lower.

Singla et al (1981) also reported significantly lower Hb values for 9 to 12 year old girls (12.1 g/dl) as compared to boys (12.6 g/dl) of the same age group; the sex difference further increased in the 13 to 16 year age group (13.3 vs 12.7 g/dl). Singla et al (1980) had earlier demonstrated a similar sex difference in 13-15 year old school children on packed cell volume values in response to hematinic supplementation.

An alarmingly high prevalence figure of 90% based on the WHO criterion for anemia in the 5-13 year old school girls in Baroda city has been reported by Gopaldas et al (1983).

However, most studies do not give an agewise or sexwise classification for Hb values, hence, it is difficult to give a conclusive prevalence of anemia for girls as against that for boys.

Khanduja and Agarwal (1969) compared the hematological values of school children from different socio-economic groups. The results indicated that anemia (Hb $\angle$ 10.9 g/dl) was most prevalent (23%) in the children from the low socio-economic (LSE) group as compared to the high (HSE) and middle (MSE) socio-economic group (4% and 12% respectively). Also, it was observed that in the HSE, 20% subjects had Hb 14 g/dl in contrast to MSE and LSE with only about 13% and 4% respectively,

Aung Than Batu et al (1972) studied iron deficiency in the rural Burmese population. The study population included 182 school children, of both sexes, 5 to 14 years old, from a Rangoon school. Hb, SI and TIBC were determined for all subjects. The results of the study indicated that 3% school children had definite iron deficiency anemia (Hb $\angle$ 11 g/dl and SI $\angle$ 50 mcg/dl) and 17% had latent Fe deficiency (Hb $\angle$ 11 g/dl and SI $\angle$ 50 mcg/dl) indicative of high vulnerability to anemia.

Santhakrishnan et al (1974) in a school health service program in Madras city observed that 46% of the 500, 5-15 year old children of both sexes had Hb $\angle$ 12 g/dl. Mild anemia (Hb $\angle$ 10 g/dl) was encountered in 29% cases.

Patodi et al (1977) classified 26% children as anemic
(Hb $\angle$ 12 g/dl). The study was conducted on 5-14 year old children
in the city of Indore in Madhya Pradesh.

Among the urban children of Hyderabad in the age range of
5 to 12 years, 57% were reportedly anemic, with Hb less than 12 g/dl
(Narasinga Rao, 1978).

Hussein et al (1981) studied 186 school children of both
sexes between the ages of 6 to 13 years in a country school in
Kafr-Hafna region of Egypt. Normal Hb values of greater than 12 g/dl
was found in only 19% of the children studied.

The limitation in using Hb or Hct level alone as a single
criterion of iron deficiency is now well recognised. The major difficulty
arises from the fact that there is a marked overlap in these levels
between normal and anemic individuals. This limitation was first
recognised by Garby et al (1969) who administered oral iron (60 mg
elemental Fe as Fe^{2+} fumarate per day for 3 months) to adult women
and defined those subjects as anemic who showed a significant
increase in Hct. They observed that with a single criterion (Hb or
Hct) roughly 20% of the normal women were incorrectly classified as
anemic and an equal number had been incorrectly classified as normal.

Thus, many investigators attempted to base prevalence of
anemia in the school age population on the response to hematinic
supplementation.

Bradfield et al (1968) in a classical supplementation trial studied 156 school children (boys and girls) between 7 to 13 years of age in the Amazon Basin in Iquitos, Loreto in Peru. The subjects were screened for Hb using the oxyhemoglobin method. The results of the study indicated that 34% of the children had initial Hb levels below 10 g/dl. The benefit of iron supplementation at 5 mg elemental Fe as $FeSO_4$ for 10 weeks was greatest in this group; with little rise in Hb concentration of subjects having initial Hb values between 10 to 12 g/dl and; no response to Fe supplementation in those subjects with initial Hb values greater than 12 g/dl.

Khanduja and Agarwal (1970) intervened 7 - 15 yr old school children from the high, middle and low socio-economic classes with 200 mg $FeSO_4$ and multi-vitamins for 40 days. A significant rise in the Hb levels of only the low socio-economic group children indicated that they were anemic.

Singla et al (1980) studied apparently healthy school children between 5 to 15 yrs of age from urban and rural areas of Varanasi. The prevalence figures of iron deficiency anemia were based on the impact on PCV on supplementation with 82.5 mg Fe as Fe^{2+} fumarate, 3 mg folic acid, 5 mcg cyanocobalamine and 50 mg ascorbic acid for 10 weeks. The results indicated that 34% urban and 69% rural school children displayed a significant response in the PCV on supplementation, indicating they were anemic.

Prevalence of anemia was estimated in Eskimo children 2 yrs to 17 yrs of age based on the response to hematinic supplementation (Margolis et al, 1981). Results of a six month long intervention with 3 mg elemental Fe/kg body weight/day in the form of $FeSO_4$, demonstrated ' a response' in 43% subjects with a rise in Hb $>$ 1 g/dl; 'intermediate response' in 26% subjects with a rise in Hb between 0.5 - 1.0 g/dl and 'no response' in 31% with a rise in Hb $<$ 0.5 g/dl.

The above cited literature clearly indicates that :

1. Iron deficiency anemia is highly prevalent amongst school children, the world ever.

2. Prevalence of anemia among school age children is high in India and Baroda is no exception.

3. There is a high prevalence of anemia in school girls above 11 years of age, as compared to boys of the same age group.

4. Deleterious effects of anemia

Over the last decade several manifestations of iron deficiency have been recognised that are clinically and economically meaningful, particularly in view of the continuing high prevalence of this disorder.

The clinical manifestations of iron deficiency may be quite subtle, as is borne out by the observation that most individuals with mild iron deficiency anemia have no complaints that are dramatic enough to make them seek medical attention. Even in severe anemia, fatigue

and shortness of breath may escape notice if the development of iron

deficiency is very gradual or if the patient leads a relatively sedentary

existence (Dallman, 1982).

In the evaluation of iron deficiency, there has always been

an emphasis on anemia. This is not surprising, since hemoglobin

accounts for over two-thirds of the iron in the body (Bothwell et al,

1979) and since it is easy to estimate its concentration in the blood.

It therefore became natural to think of the manifestations of iron

deficiency primarily in terms of decreased concentration of Hb.

Recently, however, it has been possible to delineate some of the

effects of Fe deficiency on cells other than the erythrocytes and on

tissue other than the blood.

The major deleterious effects associated with anemia are

alterations/abnormalities in behavior, work performance, immune

system and to a lesser degree with growth, anorexia and pica

(Oski, 1979).

5.   Behavioral consequences of iron deficiency

The belief in the behavioral impact of iron deficiency with

and without anemia, which prevails today, is largely an outgrowth

of a long history of clinical observations in both adults and

children (Leibel, 1977).

The hypothesis that iron deficiency may alter behavior has taken on increased credibility by virtue of the observations of Symes et al (1969) that iron deficient rats have reduced hepatic and brain monoamine oxidase (MAO) activity. A decrease in MAO activity was significant within 9 days of institution of an iron-deficient diet and MAO activity returned to control values within 3 days of iron administration. Similarly, Youdim et al (1975) found that platelet MAO activity was decreased in iron deficient adults and returned to normal in subjects in whom the serum iron values returned to normal. Considering the function of various mono-amines in brain neuro-transmission and the affective and behavioral changes associated with the administration of MAO blocking agents, it seems possible that at least a portion of the behavioral aberrations commonly attributed to iron deficiency may be caused by impaired MAO function and associated excesses of Central Nervous System (CNS) catechols. A recent study on MAO, in 13 specific human brain areas obtained from subjects who committed suicide has shown significant lowering of activity in depressed patients when compared to controls (Gottfries et al, 1974).

MAO is a flavoprotein located in the outer membrane of the mitochondria and is presumed, though not proven, to contain iron. The enzyme is believed to affect the concentration of neural mediators in the brain by regulating their rate of degradation.

TYROSINE

DOPA

DOPAMINE

NOREPINEPHRINE

MAO   MAO   COMT

ALDEHYDE
REDUCTASE   NORMETANEPHRINE

DIHYDROXY   ALDEHYDE
PHENETHYLENE   DEHYDROGENASE   MAO
GLYCOL
(DHPG)

                      DIHYDROXY MANDELIC
                      ACID

                                                       ALDEHYDE
· COMT   COMT   DEHYDROGENASE

3-METHOXY-4-HYDROXY   VANILLYL MANDELIC ACID
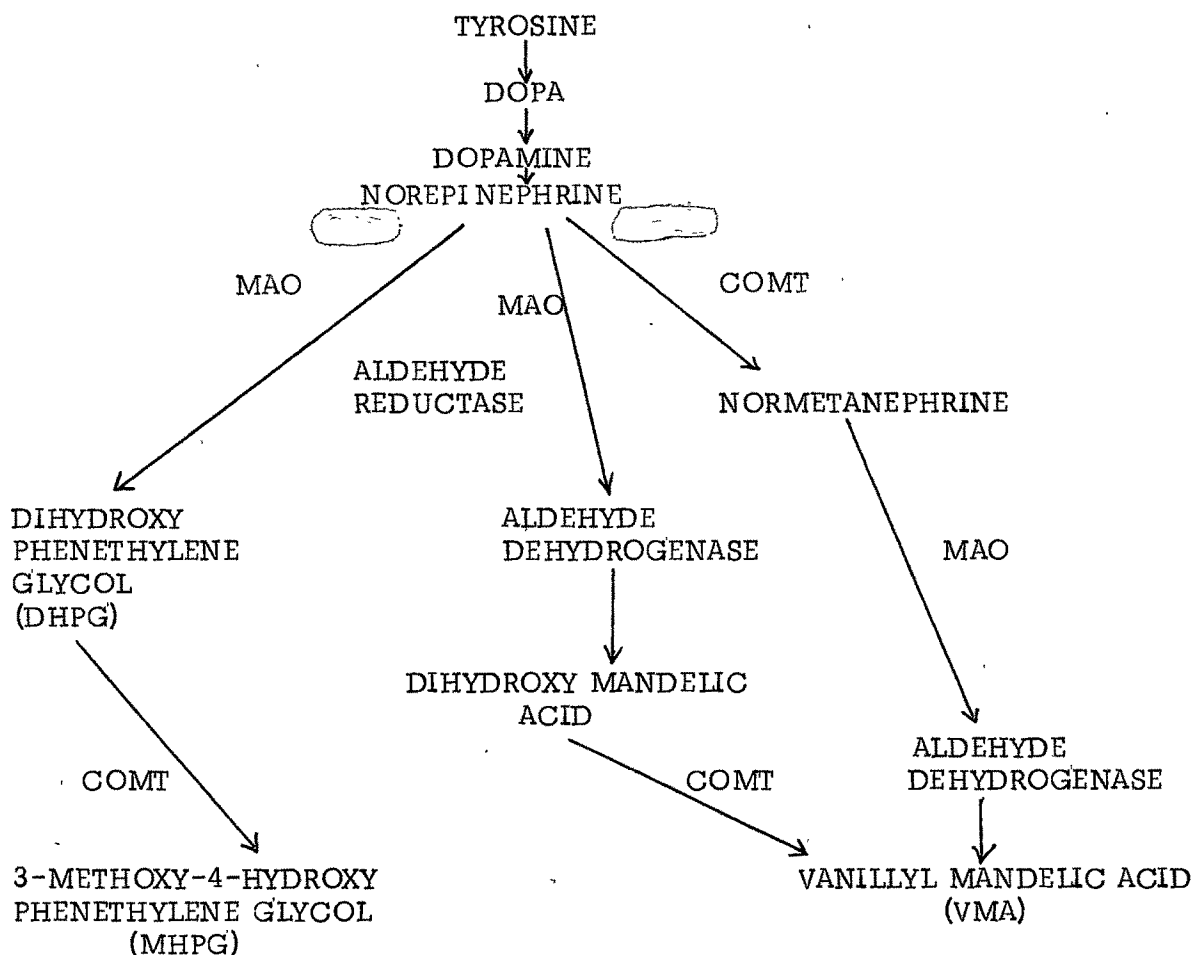PHENETHYLENE GLYCOL   (VMA)
(MHPG)

Fig. 3 : Catabolic pathway of the neurotransmitter norepinephrine

Taken : Hattox SE. In Iron Deficiency : Brain biochemistry and behavior.
from   Pollitt and Leibel, 1982.

An ⓒinitial amino acid precursor, tyrosine, is converted by tyrosine

hydroxylase and dihydroxyphenylalanine (DOPA) decarboxylase to neuro-

modulator dopamine, which is further converted by dopamine B hydroxylase

to a second neurotransmittor, norepinephrine (NE). NE is degraded by a

variety of enzymes, MAO, catechol-o-methyltransferase (COMT) to acid

and neutral end products, such as Vanillylmandelic acid (VMA), dihydroxy-

phenethylene glycol (DHPG) and 3 methoxy-4 hydroxy phenethylene

glycol   (MHPG).

MAO is an important enzyme in the catabolism of norepinephrine (NE) and NE is thought to influence behavior in man. Voorhess and Coworkers (1975) investigated the excretion of this and other catecholamines among 10 iron deficient infants (10 months to 2-1/2 years) and one child, a 13 year old boy. Hb values ranged between 4.0 to 10.2 g/dl, most had microcytosis and all had low transferrin saturation. A 24 hour urine collection was obtained before treatment and a second was obtained 3 to 6 days after intramuscular imferon treatment in 7 patients and 2 weeks after treatment in another. Nine of the 11 iron deficient children initially had urinary NE levels that were more than two standard deviations above the mean for healthy children. Shortly after treatment, values had fallen significantly and were all within or very close to the reference range. In the Voorhess study, the proposed hypothesis was that urinary NE was elevated primarily due to decreased degradation of NE by MAO; findings of this study supported the hypothesis.

There is extensive evidence that a number of monoamines e.g. norepinephrine, dopamine, 5 hydroxytryptamine are among the most important synaptic transmitters within the CNS (Cooper et al, 1974). Various affective and gross neurologic disturbances have been attributed to alterations (usually decreases) in brain levels of these compounds (Sourkes, 1976).

The catabolic pathway of the neurotransmitter norepinephrine is given in Fig. 3.

However, Mackler et al (1978) performed studies to determine the effects of iron deficiency on brain metabolism in rats. Concentrations of cytochrome pigments, oxidative phosphorylation and catalase and monoamine oxidase activities in brain tissue were unaffected by iron deficiency. Although, activities of aldehyde oxidase, a key enzyme in the pathway of serotonin degradation, were significantly reduced, and concentrations of serotonin and 5 hydroxy indole compounds were elevated in the brain tissue of the iron deficient animals. These abnormalities were reversed one week after treatment of iron-deficient animals with iron dextran; leading to the speculation that iron deficiency might result in the reduction of important iron containing enzymes in the brain tissue and alter brain metabolism. Serotonin level elevation can produce decreased attentiveness, thus providing an alternative hypothesis to link iron deficiency with behavior.

It has now been suggested that the behavior patterns of iron deficient children are related to alterations of catecholamine metabolic pathway secondary to the dependence of MAO activity on adequate iron stores.

Deficits in the ability to transfer a learned association between visual and auditory stimuli have been observed in the animals by Massaro and Widmayer (1981). Results of this study indicated that some aspects of association learning are adversely affected by concurrent iron-deficiency anemia. However, no differences were observed in visual discrimination performance of the anemic animals when compared with their well nourished counterparts.

Studies on intellectual function of iron-deficient children have purported to demonstrate varying effects of anemia on one or more cognitive processes. Behavioral abnormalities in iron deficient children are related perhaps to the changes in the concentration of chemical mediators in the brain (Pollitt and Leibel, 1976).

Sulzer et al (1973) studied over 230 male and female 4 to 5 year old black children enrolled in a Head Start program in New Orleans. Of this group, 11.7% had Hb values below 10.5 g/dl. Two batteries of psychological tests were used. The first included a global, allegedly culture free IQ test, a vocabulary test and measures of moral development and grouping behavior. The other battery comprised reaction time, attentive recall and cranking tasks. When compared with the control subjects, the performance of anemic subjects (Hb $\underline{/}$ 10 g/dl) was significantly poorer on the vocabulary tests and showed similar, but not significant, trends on all other measures. The score differentials between groups became more statistically evident when the cut off point in the Hb values was 10.5 g/dl which increased the sample of anemic subjects. Compared with the control group the anemic subjects had significantly lower scores on the IQ measure, the vocabulary test and latency and associative measures.

Cantwell (1974) administered iron dextran to 29 full term neonates and followed another 32 as controls, 6 to 18 months of age from a comparable socio-economic group. All non-treated children had Hb of 6.1 to 9.5 g/dl, whereas all those who received iron dextran had Hb of 11.5 to 12.9 g/dl,

during the same period. When examined neurologically at 6 to 7 years of age, those who had been anemic showed higher prevalence of 'soft' neurologic signs such as, clumsiness in balancing on one foot, tandem walking and repititive hand or foot movements. In addition they had lower IQs (92 vs 98 in non-anemics) and were more inattentive and hyperactive.

Marked decrease in attentiveness, narrow attention span and perceptual restriction has also been reported by Howell (1971) among 3 to 5 year old iron deficient (Hb $\angle$ 10 g/dl) children.

In an attempt to examine the relationship between iron deficiency and behaviour, Oski and Honig (1978) performed a study that demonstrated that iron deficient infants when treated with iron showed a significant (P $\angle$ 0.01) increase in their scores on the Bayley Scales of Infant Development (BSID) with 5 to 7 days of therapy. In this study, 24 infants (ranging in age from 9 to 26 months) were assigned to the treatment and control groups. All infants were iron deficient and anemic by the following criteria :

Hb $\angle$ 10 g/dl; MCV $\angle$ 73 μ^3; serum iron $\leq$ 50 mcg/dl and serum transferrin saturation $\leq$ 12%. BSID were administered before treatment with placebo or intramuscular iron dextran complex (imferon) at a dose calculated to raise the Hb level to 12 g/dl and to provide extra iron to replenish body iron stores. This test was readministered in five to eight days. Following iron therapy, the experimental group demonstrated a significant increase (P $\angle$ 0.01) in their mean Mental Development Index (MDI) score.

The control group did not attain significant increase in their mean score. The mean scores in the Physical Development Index (PDI) also rose in the experimental group following iron therapy but was non-significant. An inverse relationship (r = -0.72; p $<$ 0.01) between the magnitude of increase in the MDI scores and the initial Hb level was observed in the iron treated group. No such relationship was evident in the control group. It was concluded from this study that treatment of iron deficiency in young children produces a quantifiable improvement in measures of developmental and behavioral performance within a week. The infants appear to be more alert and responsive and display improved gross and fine motor coordination which is in consistence with the findings of Sulzer et al (1973) and of Howell (1971).

Lozoff and associates (1982) overcame the basic methodological flaw of Sulzer et al (1973) and Oski and Honig (1978) wherein no comparison was made between the performance of infants with iron deficiency anemia and normal babies. The study was conducted to assess the effect of short term oral iron treatment on developmental test performance in a double blind randomised design. The final study group consisted of 68, 6 to 24 month age subjects; 28 iron deficient (mean Hb 9.5 g/dl); all were iron deficient by the criterion of at least 2 of 3 measures of iron status indicating iron deficiency. Of these 28, fifteen were iron and 13 placebo treated; forty non-anemic controls (Hb $>$ 12 g/dl) of which nineteen were iron and 21 placebo treated. Both anemic and

non-anemic infants were randomly assigned to oral iron (5 mg Fe/kg body weight as Fe^{2+} ascorbate, twice daily for an average of one week) and placebo groups. BSID were administered before and after treatment. There were significant pre-treatment developmental test score deficits in anemic subjects. After one week of oral iron therapy, deficits in MDI and PDI persisted in the anemic infants, although all groups improved in MDI scores. Iron treated anemic infants did not increase their scores (+7.1) significantly more than either placebo treated anemics (+5.5) or the non-anemic groups (iron-treated +5.5; placebo treated +5.1). The absence of significant interactions on MDI suggests that, although there was an overall increase in scores in all groups, this increase did not vary as a function of group membership (anemic versus non-anemic) or treatment (oral iron versus placebo). Absence of impact of oral iron on the MDI and PDI scores of these subjects could be attributed either to one or more of the following : the route of administration of iron (oral), because Oski and Honig (1978) have demonstrated a beneficial effect on a similar population on short term dosing intramuscularly. Secondly, Oski and Honig calculated a dose sufficient to raise Hb beyond 12 g/dl whereas Lozoff's study did not take final Hb values into consideration and no such comparison was made. Thirdly, the defects associated with iron deficiency anemia might not be readily reversible and retesting after seven days of treatment may be too rapid to report a change in the MDI or PDI scores, indicating the need for long term oral iron treatment to assess an impact on cognitive function.

Similar results have been reported by Johnson and McGowan (1983) who examined 31 anemic and 31 non-anemic one year olds as they interacted with their mothers for behavior such as hyperactivity or apathy, impaired attention and low responsiveness which have been associated with anemia. The results of their study indicated no difference between the two groups even when the polar ends of Hb $\angle$ 8 g/dl and Hb $>$ 12 g/dl were compared. Also, no difference between anemic and non-anemic babies on Bayley Psychomotor Development Index, the MDI or on any of the Infant Behavior Record Scores was observed. The authors however, could not explain or account for the difference between the results of their study and those of Sulzer et al, 1973 and Oski and Honig, 1978.

In yet another study, Pollitt et al (1983) found reversible alternations in cognitive function in mildly iron deficient 3 to 6 year old children in Cambridge, Massachusettes. A battery of behavioral tests was administered to 15 iron-deficient and 15 matched controls, before and after the former group changed from an iron deficient to a normal iron status level. The subjects were treated with 4-5 mg Fe/kg body weight/ day for 4 to 6 months; a dose calculated such as to rectify completely any systemic iron deficiency. The battery of tests included 3 discrimination-learning tasks. In the first part of each task, a child had to learn to choose between two visual stimuli, one of which was designated as correct. In the second and more difficult part, the child had to learn to reverse the response, and choose the previously incorrect but now correct stimulus. In the first evaluation, in comparison to the controls,

the anemic children took more trials to reach a learning criterion in the

first part of the three discrimination learning tasks; in the remaining task,

the experimental children performed better than the controls.

A salient finding at the first evaluation was that the between

group differences occurred in the first and not in the more difficult part

(reversal) of the discrimination-learning task. This response pattern

indicated that when the experimental children were challenged by the

more demanding tasks in the battery of tests, the cognitive alterations

found in the simple discrimination-learning tasks were not observed.

This pattern of response strongly suggested that the locus of the cognitive

disturbances in the experimental children was most likely at the level

of reception of information, that is, in attentional process. The differences

between the two groups (experimental and control) were eliminated on iron

therapy. The results of this study are in line with those obtained by

Oski and Honig (1978).

Deinard et al (1981) in an attempt to determine if iron deficiency in

the absence of anemia could also produce alterations in behavior

studied 212 infants (101 boys and 111 girls) between 11 to 13 months of age.

The children were divided into three groups, based on hematologic status :

Group I consisted of 34 children who had serum ferritin (SF) concentration

$\angle$ 9 ng/ml; Group II consisted of 21 children with SF between 10 to 19 ng/ml;

and Group III consisted of 157 children with SF $\geqslant$ 20 ng/ml. No child in

any of these groups was anemic (Hct $\angle$ 34%). These three groups

represented the severely, mildly iron depleted and iron replete subjects

respectively. Three measures for behavior and cognitive development

were used : habituation measure, BSID and Uzgiris and Hunt Ordinal

Scales (I, II and V) of Psychological Development (U/HSPD). The

habituation measure was used as an index for attention. BSID is one

of the most carefully standardised of all infant scales; is of adequate

reliability and one of the most comprehensive measures available for

the study of infant development from ages 2 months to 2-1/2 years.

The areas covered by this test are : social orientation, cooperativeness,

fearfulness, tension, general emotional tone, object orientation, goal

directedness, attention span, endurance activity - reactivity

coordination for age and others. The U/HSPD test is designed to

measure cognitive development of young children and is based on Piaget's

notion that development proceeds in an invariant sequence for all

children.

The findings of this study indicated no differences among the

three groups of non-anemic children (iron replete, mildly depleted,

severely iron depleted) on the motor or mental scales of BSID, on the

three scales of U/HSPD or on the habituation measure. On the infant

behavior record, an isolated observation was that the group which was

most iron depleted and thus most likely to be irritable did not appear

to be so, neither did the children in that group show a lack of interest

in their surroundings or appear to be listless.

The authors concluded that the subjects classified non-anemic

may not have been so, as Hct is an insensitive measure to detect anemia.

The insensitivity of Hct as a measure to detect anemia has also been

reported by Graitcer et al (1981) and by Dallman (1984). Another possible explanation to the findings of the study was that may be a relationship with the degree or duration of iron depletion. Since iron deficiency preceeds the development of anemia, the anemic infant is probably depleted to a greater extent and for a longer duration than the non-anemic infant.

Seshadri et al (1982) studied the behavioral responses of young anemic Indian children to iron folic acid supplements in two separate studies using the Indian adaptation (Bhatt, 1973) of the Wescheler's Intelligence Scale for Children (WISC). The first an exploratory study, had 94 children of both sexes in the age group of 5-8 years from a low socio-economic group. The children were stratified by age and randomly assigned to the control (no supplement) or the experimental (20 mg Fe and 0.1 mg folic acid/day for 60 days) groups. The supplemented children showed a significant (p $<$ 0.001) increase in Hb while the control showed no change. Also, the verbal and performance IQ's of supplemented children improved significantly (p $<$ 0.001) while no change was observed in the control group. On the basis of the preliminary study, a second study was planned. Fourteen pairs of subjects, 5-6 years of age were matched initially for Hb, erythrocyte morphology, weight for age, Draw-a-man (DAM) IQ score as well as mother's education and per capita income. In this study (i) psychological testing was conducted by a trained investigator, (ii) control children were given sugar placebos and (iii) the children in the control and experimental group were initially matched. On supplementation with 40 mg Fe and 0.2 mg folic acid daily, for 60 days, a highly

significant (p $\angle$ 0.001) improvement in blood Hb and significant (p $\angle$ 0.01) improvement in verbal and performance IQ of the experimental versus the control group was observed. Improvement in the verbal IQ of the experimental group was attributed to an improvement in the information, similarities vocabulary, arithmetic and digit span subjects of WISC and that in the performance IQ was due to an improvement in picture arrangement, coding and mazes. The results suggested that an improved performance IQ may be due to improved psycho-motor function.

A spin-off result of the first study was that in the 5-8 year age subjects, when they were classified as anemic and non-anemic by WHO (1975) criterion, only anemic 7-8 year old children showed a greater improvement in the test scores on supplementation than the non-anemic children of the same age. No such trend was observed in the younger age group. This indicated the need to study intensively the impact of iron supplementation in older children (8+ years) on cognitive behavior.

The adult human brain contains about 60 mg non-heme iron, which is about 20 per cent of the content of an iron replete liver. The amount of iron in the brain is well in excess of that which can be accounted for by known enzymes and co-factors. A fraction of it is apparently ferritin, a storage form of iron. Almost all areas of the brain show an increase in iron concentration with age, the maximal increments generally occurring in the first ten to twenty years of life (Hallgren and Sourander, 1958).

However, studies on the behavioral impact of iron deficiency anemia are mostly on infants and pre-schoolers. There is a great paucity of literature concerning the school age (5-15 years) population.

The studies reported for this population which constitutes the school age children are as follows :

Iron deficiency and scholastic achievement in young adolescents was investigated in Philadelphia by Webb and Oski (1973a). Subjects were 12 to 14 year old male and female junior high school students in an economically deprived mostly black community. Following a hematological survey on 1,807 children, 92 subjects were considered anemic (Hb ranging from 10.1 to 11.5 g/dl). All anemics had hypochromic, microcytic red cell index. The control group of 101 subjects with Hb values ranging from 14 to 14.9 g/dl were also tested. A measure of scholastic performance was obtained from the composite score of the IOWA test of Basic Skills (ITBS) Levels A - F/Form 3. The composite score represents performance across 11 sub-tests which include vocabulary, reading comprehension, spelling capitalization, punctuation and usage, knowledge and use of reference materials, arithmetic concepts and problem solving. The scores of anemic subjects were significantly (p $\angle$ 0.025) lower than those of non-anemic subjects. Further, the older anemic male subjects displayed a progressive departure in performance from non-anemic control subjects. This apparent discrepancy between males and females, has been attributed to the fact that there was insufficient

information to interpret sex difference in the decline by scores as a function of age.

In another study by the same authors (1973 b) an attempt was made to document the effects of iron deficiency on cerebral function. Students 12 to 14 years of age, were compared in their scores of the ITBS, teacher ratings of personality disturbances employing the Peterson-Quay Behavioral Problem Checklist, and their performance on a standard visual after-image task. The composite score of IOWA test was found to be significantly lower among 92 anemic than the 101, age and sex matched controls. Teacher evaluations revealed that anemic students displayed significantly more conduct problems such as distractability, over-activity, disruptiveness and negativism than did the non-anemic students. The anemic group demonstrated significantly longer latency (4.08 sec) than did the non-anemics (1.81 sec) in reporting visualization of an after-image. These findings suggested that iron deficiency does alter cerebral metabolism by producing disturbances in perception and attentiveness which ultimately result in impaired scholastic performance.

However, both these studies are associated with a major methodologic flaw, that the two groups (anemic and non-anemic) came from different ethnic backgrounds and no attempt was made to match the environment, the role of which in cognitive behavior cannot be ruled out. Also, in this study no attempt was made to study the changes in the scores of the subjects on various tests as a result of iron therapy.

A controlled study communicated thus far on the relationship between iron deficiency anemia and cognitive function in school children and impact of iron therapy on cognitive function has been that by Gopaldas et al (1985a)

Gopaldas et al (1985a) reported a greater beneficial effect of iron supplementation at 40 mg Fe/day than the 30 mg Fe/day dose, as $FeSO_4$ for 60 days at a stretch on selected tests of cognitive function compared to the placebo control group receiving sugar tablets for the same period. The cognitive function tests used were Visual Recall, Digit Span, Mazes and Clerical task. The study was conducted on underprivileged school boys, 8-15 years of age with a mean Hb of 10.77 g/dl; the three groups of subjects were matched initially for age, Hb levels and individual cognitive function test scores. This study also indicated that the benefit of Fe supplementation was greater in the anemic (Hb $\leq$ 10.5 g/dl) subjects than in the non-anemics (Hb $\geq$ 11.5 g/dl), in tests for attention, memory, perception and visual motor coordination as tested by the Visual Recall and Mazes tests.

A clinical trial of iron therapy on psychomotor function in anemic women (20 years and over) by Elwood and Hughes (1970) showed that anemia had a non-significant effect on psychological test performance. In this study, 47 women with Hb values below 10.5 g/dl were randomly divided into two treatment groups for an 8 week period;

one group receiving a placebo while the other group received 150 mg

elemental Fe as ferrous carbonate daily. The performance tests

were chosen to cover a range of psychomotor functions, from an

almost pure test of intellectual function to a simple test of manual

dexterity. The tests used were mainly for concentration, arithmetic

reasoning and short term memory (serial sevens); vigilance, degree

of dexterity and concentration (E test); attention, concentration and

agility in motor function (Maze test); susceptibility to fatigue (card

sorter) and a simple test of manual dexterity (Peg board). Results

of the study showed non-significant differences in any of the tests

before and after treatment. The only trend found among the results

was the improved performance observed among those women with

the largest rise in Hb levels. However, in this study no attempt

was made to examine the iron status or changes in the iron status on

supplementation.

On the basis of the studies reviewed above, it is apparent

that the prevention of iron deficiency anemia is a desirable objective.

Iron deficiency could impair the development of the Central Nervous

System and/or cause behavioral changes affecting the scholastic

performance in children.

6.   Impact of iron deficiency on Physical Work Capacity

Work capacity under maximal work load has been shown to

be related to hemoglobin concentration and to decrease even in mildly

anemic subjects. Although most jobs do not involve near maximal work

loads, there is increasing evidence that milder degrees of anemia
may also effect work output in everyday tasks (INACG, 1977).

The individual's physical performance is determined by
several factors (Astrand and Rodahl, 1970) :

Energy liberation -
        aerobic processes
        anaerobic processes

Neuro-muscular function -
        muscle strength
        technique (coordination)

Psychological factors -
        motivation.

Depending upon the nature of the activity, and the duration
and intensity of work the relative importance of these factors may
vary. However, during prolonged severe exercise or during ordinary
daily activities, aerobic processes play the most important role. The
capacity to perform heavy-muscular work depends upon the individual's
ability to transport oxygen from the lungs to the active tissue.

Normally, 97 per cent of the oxygen transported is carried
in chemical combination with hemoglobin in the red cells with 1 g Hb
able to transport 1.37 ml of oxygen (Vellar and Hermansen, 1971).
Thus a change in the Hb concentration would change the oxygen
carrying capacity of the blood.

Oxygen needs of an organ or tissue depend, among other factors, on its size and on its metabolic rate at rest and at various levels of activity. Total body oxygen needs are the summation of all the individual requirements of tissues and organs, and vary as a consequence of functional changes which occur in everyday life. Physical activity is the most important factor in determining the total oxygen requirements. This is because it induces significant increments in the metabolic rate of skeletal muscle and to a lesser degree on myocardium (Viteri and Torun, 1974).

Muscle tissue contains all the myoglobin and also accounts for more than half the mitochondrial cytochromes in the body. The oxygen that is utilized by muscle is stored by myoglobin and partially converted to cellular energy in the form of high energy phosphate compounds by the mitochondrial cytochromes.

Anemia not only decreases the oxygen-carrying capacity of the blood, but ordinarily decreases blood viscosity as well (Varat et al, 1972). The cardiac output response to exercise is typically greater than normal in anemia. The response to exercise is a more sensitive indicator of altered hemodynamics in anemia than is the level of resting cardiac output, since this exaggerated response is frequently found in patients with Hb levels of 10 g/dl and normal resting cardiac outputs.

As stated earlier, the major physiologic consequence of anemia is a reduced oxygen-carrying capacity of the blood. The resultant tissue hypoxia evokes several compensatory mechanisms. One such mechanism is peripheral vascular dilation, which is associated with increased blood flow to the periphery. Another mechanism is increased tissue extraction of oxygen from the blood. This is accomplished, by a shift to the right of the oxyhemoglobin dissociation curve, which allows more oxygen to be unloaded from the erythrocyte at any given blood oxygen-tension (Rodman, 1960). Recently, this phenomenon has been shown to be related to increased concentration of organic phosphates, especially, 2, 3 diphosphoglycerate, within the red blood cells (Benesch and Benesch, 1967). However, in the anemics, the most important mechanism in maintaining an adequate oxygen supply to the tissues is an increase in cardiac output.

Iron deficiency and worker productivity

Much of the research work on anemia and Physical Work Capacity (PWC) carried out in the recent years has concerned the adult human and the initial work was supported by the World Bank, which was mainly interested in the affect of anemia on worker productivity.

The first of these studies was carried out by Karyadi and Basta (1973) on male road construction workers in Java. A total of 571 workers were selected, of which 41% were anemic on the basis of

the WHO norms of Hb $\angle$ 13 g/dl. The Harvard Step Test (HST) was used to measure physical endurance in 537 workers, as 3 refused to participate and 18 had to be excluded due to medical reasons. The results of the study indicated that when the cut-off point for anemia was taken as 11 g/dl for Hb, there was a significant difference in HST scores between those classified as anemics and non-anemics. However, taking 13 g/dl as the cut-off point for anemia, no differences were observed between the anemics and the non anemics. The results further indicated, a significant correlation at 10% level between Hb and HST scores.

Basta et al (1974) studied the work capacity of about 600 tappers and weeders in a rubber plantation in Java, where payments were made on the basis of the daily job performance.

Two types of work were measured and a three day average was taken for each worker. The first was collection of wet latex daily and the second was clearing of weeds from parallel rows of trees. The results indicated a positive relationship between the monthly income and Hb status; a positive correlation between the work output and Hb status was also obtained. The anemic (Hb $\angle$ 12 g/dl) tappers collected 19% less wet latex than non-anemics and as far as weeders were concerned the anemics cleared an area about 20% less than the non-anemic workers.

In yet another study, Basta et al (1979) studied the latex tappers and weeders in Indonesia. Out of 302 male workers, 16 to 40 yrs of age studied 41 per cent were anemic using Hb less than 13 g/dl cut-off point. A significant correlation between Hb concentration and HST performance of tappers and weeders were obtained. The rubber tappers were paid according to their work output and their income correlated with their Hb status.

On treatment of these subjects with 100 mg elemental Fe as $FeSO_4$ for 60 days and improvement in the Hb status of the anemic subjects was observed. The performance of these subjects on HST and work output also improved significantly, matching that of the non-anemics. This indicated that anemia even at the high cut-off point of 13 g/dl affected workers ability to perform the test of physical endurance.

Spurr et al (1977) in a study on 46, 18 to 36 years of age male sugarcane cutters of Columbia, showed that productivity was related to body size and to the physical condition as measured by VO_2 max. (maximal oxygen uptake).

Gardner et al (1975) studied the cardiorespiratory, hematological and physical performance responses of 29 iron deficient adult subjects; 13 men and 16 women with Hb ranging from 4.0 to 12.0 g/dl. The performance testing consisted of muscular strength

measurement while standing, for right and left hand grip and shoulder girdle adduction using hand grip dynamometer or cable tensiometer and a 5 min, 40 cm step test (18 steps/min for men and 12 steps/min for women). Significant improvement in the Hb levels of the iron treated group (intramuscular dose of iron dextran such as to replete iron stores for 80 days) was observed with the placebo control showing virtually no change.

The exercise (step test) heart rate showed a comparable reduction on iron treatment. The peak heart rate (HR) in response to exercise test decreased from 155 to 113 beats/min for the men and from 152 to 123 beats/min for women while no significant change was observed for either sexes in the placebo control group.

Significantly higher blood lactate values in the placebo than in the iron treated group both at rest (1.18 vs 0.64 mmoles/litre) and one minute after exercise (5.3 vs 2.68 mmoles/litre) were observed. No changes were observed following iron therapy in hand grip or shoulder adductor strength. It was thus concluded that, performance requiring high oxygen delivery is significantly affected by Hb levels.

Gardner et al (1977) studied the interrelationship of PWC and selected physiological parameters related to work

performance in subjects with a wide range of Hb engaged in their daily work tasks. The subjects were 75 female tea estate workers in Sri Lanka, 25-62 years of age, with Hb ranging from 6.1 to 15.9 g/dl. The standard multistage treadmill test in which subjects walked for 3 min up a 10% gradient at 1.59km/hr followed by an increased speed of 3.18 and 5.77km/hr for 3 min each at the same gradient. The gradients were increased to 14% and 18% only if the subject could attempt the further exercise.

Venous blood samples for Hb, SI, TIBC, P_{50} (partial pressure of oxygen when Hb is 50% saturated with oxygen), 2,3 diphosphoglycerate (2,3 DPG) and lactate determinations were collected before and after the exercise. HR was monitored continuously during the exercise and for 3 min during recovery. The subjects were divided into 7 categories with 1g/dl increments in Hb from 6.0 to 13.0 g/dl and those with Hb > 13g/dl.

The results indicated that the HR, both pre and post exercise was significantly higher in the 6.0 to 6.9 Hb/dl category than in the 13 Hb/dl category; the pre exercise blood lactate levels for all groups were similar, however, on exercise the lactate elevation in the group with lowest Hb was greatest and vice versa. The Hb and post exercise lactate levels highly correlated (r = -0.59) at post

exercise. Similar correlation coefficients were also obtained between Hb and 2,3 DPG (r= -0.52) and P_{50}(r =-0.45). Thus, the post exercise lactate concentration appeared to be directly related to the degree of anemia, and indicated the relative contribution of anaerobic metabolism to the overall metabolic stress of the exercise task.

From the study, the precise level of Hb at which a decrement in work tolerance could be exepcted was propounded as 11.0 to 11.9 g/dl. At this level, subjects showed approximately 20% decrease in their work tolerance when compared to subjects with Hb > 13 g/dl based on the HR response to work or actual work performance and was consistent with the 20% lower productivity of anemic Indonesian Workers reported by Basta and Churchill (1973).

The observations of Davies et al (1973) on African Industrial workers were in support of these studies. They detected a decrease in the aerobic work capacity when the Hb was lower than 12g/dl. At 8 to 10 g/dl it was reduced to about one-quarter and below 8g/dl by about one-third.

The inverse relationship between Hb concentration and 2,3 DPG and the P_{50} values has also been reported by Charlton et al (1977).

Edgerton et al (1981) studied selected parameters of work tolerance in 31 Sri Lankan Adults (27-55 yrs of age). The Hb concentration ranged from 2.5 to 14.0 g/dl. The mean maximal work load tolerated on a multistage treadmill increased within 24 hrs after transfusion of 570 ml of whole blood in seven subjects; post exercise blood lactate was markedly reduced. The work tolerance of these subjects was same as in other subjects with equivalent Hb levels. Results indicated that the decrement in work performance in iron-deficient and anemic subjects was a reflection of the level of anemia rather than other Hb related biochemical changes that would accompany prolonged iron deficiency anemia.

Ohira et al (1981) studied the relative importance of Hb and non-Hb iron for PWC in 45 adult male and female subjects, with a range of Hb and SI levels. Maximal work capacity, HR and blood lactate were measured before and one week after treatment with imferon. Results indicated that subjects with low Hb-high SI worked longer than those with low Hb- low SI values. A significant inverse correlation between SI and post exercise lactate levels (r= - o.41) was obtained. Although, no Hb response was obtained within one week of iron therapy, the initial low serum iron groups had significantly lower HR at a given work load relative to subjects with high iron but with similar Hb levels.

The authors concluded that, although the primary factor which affects the PWC of iron-deficient anemic subjects seems to be the Hb level, there also seems to be significant non-Hb related effect of iron treatment as well.

The effect of iron deficiency and anemia on physical fitness of 62 agricultural laborers, 16-41 yrs old, residing in the lowlands of Guatemala was investigated by Cifuentes and Viteri (1972). Iron deficiency anemia occurred in 69%, with Hb values ranging from 3.5 to 16.5 g/dl and PCV from 14 to 46. The subjects were divided into the Fe treated ($FeSO_4$, 120 mg/day) and the placebo treated groups. Hematological condition and HST were evaluated after 15,30,60 120 and 180 days of the study. A significant improvement in PCV was observed within 2 months in the iron treated group, while no change was observed in the placebo group. A significant improvement in the HST score at 15,30,60 days were obtained in the iron treated group remaining stable thereafter. The placebo group did not change throughout the study period.

Rahamathullah (1983) studied 228 women, 25 to 44 yrs of age in a tea plantation in Southern India and was able to establish that a minimal dose of 65 mg elemental iron/day for 100 days could definitely improve the tea plucking performance and number of work days among women labor.

The worker productivity and activity patterns of 199 female tea estate workers, 20-60 yrs in Sri Lanka were studied by Edgerton et al (1979), before and after treatment with iron or placebo. A significant increase in productivity in association with iron treatment, particularly among those subjects whose initial concentration of Hb was between 6 and 9g/dl was observed. The effect of iron therapy on voluntary activity was also estimated, using a small movement-sensitive recording device that was strapped to the subject body. The women who received iron treatment were found to be about 60% more active within 3 weeks than the subjects who received placebos. The results were interpreted as providing tangible evidence that tiredness and weakness could be attributed to iron deficiency.

Ohira et al (1979) demonstrated a beneficial effect of infusion of iron dextran in 6 adult men and 14 women who were anemic, on measures of work capacity within 4 days of therapy. A lower HR at a given exercise intensity in the Fe treated than the control group was observed.

Improvement in physical performance of adult males in Thailand has been demostrated by Garby and Areekul (1974), associated with a rise in PCV as a consequence of iron therapy.

Effect of iron supplementation on PWC in the elderly (58-71

yr old), apparently healthy men and women was studied by Ericsson

(1970a). The iron treated subjects received 60 mg elemental Fe as Fe^{2+}

fumarate, twice daily, between meals and the controls received placebo

tablets. The duration of the treatment was 3 months. The increase in

PWC (measured by the electrically braked bicycle ergometer) was about

4% higher in men and about 12% higher in women in the iron supplemented

group as compared to the placebo (control) group. Although, no signi-

ficant difference in the measures of PWC was indicated between the Fe

treated and placebo group, in all measures of PWC the increase was

greater in the iron group than in the placebo group. A significant

decrease only for TIBC in the iron treated group was observed and none

for SI or Hb. The authors concluded that in apparently healthy people

the increase in PWC during moderate exercise is related to the

availability of iron from the stores.

Ericsson (1970b) in another study could observe only a weak

correlation between the measures of PWC and Hb status in the elderly.

The conclusion drawn upon was that, at higher ages, the ability of

the vascular system to increase its volume (total hemoglobin) in

connection with the physical training decreases, and that the increase

in PWC is rendered possible by an increase in the arterio-venous

oxygen difference.

Animal Studies

Glover and Jacobs (1972) monitored the rat movements to measure the total daily activity and the diurnal rhythm in normal and iron deficient rats. A considerable reduction in the total number of movements in both the mildly and severely iron-deficient rats was observed. On iron therapy a significant change in the activity of the normal rats was observed; in the severely anemic a pronounced increase in activity after iron was given but a decline towards the previous level in 2 days after iron therapy was withheld; in the mildly anemic rats iron administration was continued and a smaller but sustained increase in activity resulted. A noticeable alteration in the diurnal rhythm in the mildly anemics was obtained only after 7-8 days of iron therapy.

In a study on white rats who were made anemic Edgerton et al (1972) conducted exhaustive endurance or spring run tests on a motor-driven treadmill. The results indicated a direct relationship between Hb and PCV on the endurance.

The anemic subjects ran for a significantly shorter time than their controls upon repletion to the normal iron levels, the difference in activity between the two groups was eliminated.

Koziol et al (1982) studied the compensatory mechanisms of iron deficiency anemia and some common indicators of work performance, which were : running time - till exhaustion, post

exercise venous blood lactate , 2 , 3 diphosphoglycerate and the HR
in response to exercise . The adult male rats who were mildly
anemic (Hb $\angle$ 8 g/dl) and severely anemic (Hb $\angle$ 4 g/dl) were compared
with the non-anemic controls .

The results indicated a significantly lower exhaustive run
time in the moderate and severely iron deficient rats; the post exercise
lactate was significantly increased in response to a submaximal work
load in the moderately and severely anemic rats , this was 102% and
130% greater than their controls respectively . The lower lactate -
concentration observed after exercise in the control rats despite work
loads of a higher intensity and longer duration was in consistence with
the results of Edgerton et al (1979) and Gardner et al (1977) on adult
human subjects .

Cardio vascular effects of anemia

Anemia not only decreases the oxygen carrying capacity of
the blood , but ordinarily decreases blood viscosity as well .

When anemia is moderate , the important compensatory
mechanisms are a rise in red-cell DPG due to the increased proportion
of deoxyhemoglobin, with a resultant fall in Hb affinity for oxygen ,
and also the redistribution of blood flow (Finch and Lenfant, 1972) .
The decreased viscosity facilitates the increase in cardiac output
with exercise; however, the augmented respiratory and cardiac

requirements of the anemic patient are then reflected in symptoms

of dyspnea and palpitation (Sproule et al, 1960).

In anemia the increased cardiac output principally reflects

a larger cardiac stroke volume, since tachycardia is frequently

not found and there is an increased HR. Normal human subjects,

during exercise, show an increase in cardiac output of 550 to 800

ml per 100 ml increase in oxygen consumption per minute (Donald

et al, 1955). In patients with chronic anemia the increase of

cardiac output with exercise is often from 1000 to 1500 ml or greater,

per 100 ml increase in oxygen consumption per minute (Sproule et al,

1960).

An increase in HR in response to exercise has been

demonstrated by various investigators (Astrand et al, 1958;

Wyndham et al, 1958; Sproule et al, 1960; Roy et al, 1963;

Areskog et al, 1969; Davies et al, 1973).

Astrand et al (1958) reported that the HR of 9, 56-68 year

old male subjects increased to a maximum of 163 beats/min and

the post exercise blood lactate values reached 35 mg/dl in response

to an exercise on the bicycle ergometer. Similar increase in HR,

cardiac output and blood lactate values on prolonged exercise have

also been reported by Saltin and Stenberg (1964).

Subjects with sub-normal cardiac output have reportedly

marked tendency to greater excess of lactate concentration and
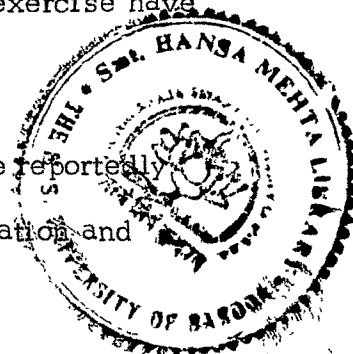
lactate/pyruvate ratios at low work levels than normal subjects (Thomas et al, 1964).

Davies et al (1973) studied the effect of iron deficiency anemia on the maximum aerobic power and responses to exercise in African males, 17-40 yrs of age. The study indicated that for a given O_2 intake the severely anemic (Hb 6.7 g/dl) subjects exercise with a higher heart rate than controls (Hb 14.5 g/dl); this was also true of the moderately anemic (Hb 9.2 g/dl) but the magnitude of response was reduced. The higher HR found in the anemics was accompanied by an elevated cardiac output.

However, Vellar and Hermansen (1971) could not demonstrate any relationship between Hb and maximal oxygen uptake, expressed as ml/kg x min in school children undertaking an uphill (3°) running test at a speed which would exhaust them within 4-6 min. Furthermore, no significant relationship between Hct, MCHC, SI, TIBC and transferrin saturation, and maximal O_2 uptake expressed as litre/min as well as ml/kg x min was observed. It must be emphasised here that the Hb of the study population ranged from 11 to 16 g/dl which may be the reason for lack of relationship.

Many authors have suggested that Fe-deficiency anemia may be wholly compensated for by one or several factors affecting the cardio-respiratory system : a shift to the right of the O_2- dissociation curve (Rodman et al, 1960), a decrease in venous saturation and

vascular resistance (Stead and Warren, 1947) and a reduction in blood viscosity (Richardson and Guyton, 1959). These changes may be associated with a reduced diffusion capacity (Guleria et al, 1971 and Cotes et al, 1972), hypoxemia and increase in alveolar-arterial O_2 gradient (Housley, 1967).

Studies on children

Physical work capacity of 243 Californian school children of both sexes, ranging in age from 6 to 14 yrs was determined by Adams et al (1961a). Work capacity was tested using the bicycle ergometer. The results correlated well with the surface area, height, weight, age and the total vital capacity.

In a similar study by the same investigators (Adams et al, 1961b) on Swedish city and country school children, ages 10, 11 and 12 years, the PWC was also found to increase with age, height, weight, surface area, heart volume and the degree of physical training.

The association of mild anemia with work capacity was studied by Ekblom et al (1972). The response to exercise was tested in seven male physical education students before and after removal of 800 ml of blood or 1200 ml over an 8 day period. A brief, intense run on a treadmill in which the maximal running time averaged 5.8 min before venesection was conducted. Two

days after blood loss, the maximal running time with the same exercise had reduced by 30%; in addition the maximal oxygen uptakes during the exercise decreased by 13% in those who had lost 800 ml and by 18% in those who had lost 1200 ml of blood. The results indicated that loss of a relatively small percentage of total body Hb, per se, was associated with a corresponding impairment in performance of a brief but intense exercise task.

Bar-Or et al (1971) however, demonstrated that for a given VO_2 level (maximum oxygen uptake) the girls had higher cardiac output, higher HR and a lower arterio-venous O_2 difference than boys 10 - 13 yrs old. However, no explanation for the sex difference could be given by the authors.

Macek and Vavra (1971) studied the exercise response in children (6-14 yrs old) at various levels of sub-maximal work. The study sample constituted of 47 boys and 52 girls from a school in Prague. The work load consisted of riding the bicycle ergometer on 3 successive days for 5 min each. The first day load was 1 W/kg body wt, the 2nd day 2 W/kg body wt and 3rd day 2.5 W/kg. body wt. The results of the study indicated that the increased energy demands for work were met by increased oxygen uptake. No difference between boys and girls was obtained in the net oxygen uptake per kg body weight. The assessment of the anaerobic participation in the energy release at work was done from blood lactic acid levels.

Significant difference between boys and girls at higher work loads was obtained. Blood lactate, in girls, seemed to have a close direct correlation with body weight.

In our own department the effect of hematinic supplementation on PWC has been studied in preschoolers (Seshadri and Malhotra, 1984) and in school children (Gopaldas et al, 1985b), using simple tests of running and jumping and only jumping in the respective studies.

Seshadri and Malhotra (1984) studied 14 pairs of anemic (Hb 8 to 10.5 g/dl) boys, in the age range of 5 to 5-1/2 yrs. The subjects were pair matched for Hb, Ht, Wt and socio-economic status. Two simple tests, running and jumping, were conducted, before and after intervention with 40 mg elemental Fe as $FeSO_4$ and 0.2 mg folic acid daily for two months to the experimental and sugar tablets to the controls for the same period of time. A significant increase in Hb levels only in the Fe treated group, which averaged 2.4 g/dl was observed. A concomitant increase in running time and total number of jumps made by the subjects was observed in the Fe treated group. This indicated a certain benefit of Fe supplementation on physical endurance of the study population.

Gopaldas et al (1985b)however, conducted a more controlled study on underprivileged school boys 8-15 years of age. The study was conducted on three groups of 16 subjects each, matched initially for age,

Hb, body surface area, blood lactic acid and pulse rate values; the effect of supplementation at 30 mg and 40 mg Fe as $FeSO_4$ for 60 days on PWC was studied and compared to a group receiving sugar tablets (controls). The HST was modified to suit the needs of the study group and was the instrument used to test PWC. Pulse rate and blood lactic acid measurements were made prior to and in response to iron therapy, both before and after the exercise. Results indicated a significant improvement in blood lactate values for both dosages in relation to the baseline and placebo control values. However, the impact of supplementation on PWC in the anemics (Hb $\leq$ 10.5 g/dl) was much more pronounced, for both pulse rate and blood lactate values, than that of the non-anemics (Hb $\geq$ 11.5 g/dl).

Also, the benefit of the larger dose was much greater and was
thus recommended for large scale programs where the anemics cannot be separated out from the non-anemics.

Thus, to conclude, the literature, available suggests that iron deficiency of a degree insufficient to produce anemia may be responsible for fatigue, malaise and poor work output because of tissue changes (Beutler et al, 1960; Dallman et al, 1978). There is however, no doubt that a variety of functional iron-containing tissue compounds are depleted in iron deficiency anemia (Jacobs, 1969). These include heme compounds such as myoglobin, the cytochromes, catalase and peroxidase, and the metalloflavoprotein enzymes, where the iron is not in the form of heme,

such as NADH, succinic, xanthine and α - glycerophosphate

dehydrogenases (Dallman et al, 1978). The reduction in the iron

containing mitochondrial enzyme, α -glycerophosphate dehydrogenase

impairs glycolysis and leads to the over production of lactic acid,

which at high levels impairs work capacity (Finch et al, 1977 and

1979). This is in support with Astrand who, as early as 1956,

put forward the measure of blood lactic acid as a valuable

parameter for the assessment of the degree of exhaustion and was

further used as a measure for the study of PWC.

7. Iron deficiency and growth

Studies on the effect of anemia on growth are relatively

few and mostly related to animals.

Dallman (1969) reported that severe iron deficiency

interfered with growth in the rats. The study was conducted on

nursing rats with limited access to exogenous iron, whose mothers

had been depleted of iron by giving chelating agents. These rats

were characterized by anemia, reduced liver iron stores and severe

growth retardation. However, it was not clear whether the reduced

growth was a direct result of iron deficiency or an associated

reduced food intake due to anorexia.

Ohira and Gill (1983) studied the effects of iron deficiency

on growth in mice. Iron deficient mice had significantly lower body

weights than controls. The study suggested that iron deficiency

may affect protein synthesis consequently leading to growth retardation.

Bowering and Norton (1981) could not demonstrate any growth retardation in moderately anemic versus adequately nourished male rats. However, for both sexes, severely iron deficient rats had an 18% growth retardation. Growth retardation was measured by weight gain in these rats.

The effects of iron deficiency and iron supplementation on growth have not been substantiated in human subjects (Oppenheimer and Hendrickse, 1983). However, various attempts to study the association between prevalence of anemia and poor growth status have been made (Garn and Smith, 1973; Margo et al, 1977).

Extensive data on Hb status and anthropometric measurements from the Ten State Nutrition Survey on 15000 children of both sexes, was analysed by Garn and Smith (1973). They reported that children with low Hb levels (less than 15th percentile for age and race) were smaller and leaner than children with normal Hb levels (greater than 85th percentile for age, sex and race), who were taller and fatter. A difference of 3 cm in height, similar to the 3 kg difference in weight was observed between the two categories. These differences further increased as the age advanced.

Rao et al (1980) reported that severe anemia was found to be more prevalent in preschool children having weight-for-age less than 60% of the standard, height and mid arm circumference less than 80% of the standard. Among various indices, weight-for-age and weight-for-height were found to differentiate between the anemics and non-anemics.

In one of the earliest studies, Judisch et al (1966) studied the effect of iron deficiency on growth patterns. Data on 156 children on whom growth records from birth to 3 years was available and also who were diagnosed anemic at 3 years of age was analysed. Subjects with a hypochromic microcytic red cell morphology, low SI and TS levels or good hematological response to iron therapy were classified as anemic. The past records were analysed for age, Hb, weight, race, birth weight and other predisposing factors such as maternal anemia and parity. The subjects were treated with 6 mg elemental Fe/kg body wt/day for 2 months. Pre and post intervention weights (when Hb was raised to 11 g/dl or above) were compared in 88 out of 156 subjects. The study revealed that there was a preponderance of children in lower weight percentile ranges to be diagnosed anemic. The weight percentile ranges skewed negatively initially, but on institution of iron therapy a normal curve was obtained reflecting a marked weight gain in under-weight subjects. The study contradicted the fallacy of the fat iron deficient child and reported that anemic children were underweight rather than overweight and correction of anemia led to an increase in weight gain. However, whether the poor weight gain prior to iron supple-mentation was a direct result of anemia or was secondary to anorexia from iron deficiency could not be elucidated in this study.

An impact of iron supplementation (20 mg elemental Fe as Fe^{2+} fumarate) for 8 months on growth (weight and height gain) was

also reported by Mahloudji et al (1975). Seventy five children, 6-12

years of age in a village near Shiraz in Iran constituted the study

sample.

Contrary to these findings, Margo et al (1970) failed to show

any association between hemoglobin (iron status) and weight for age in

children under five years of age. Although, the study sample consti-

tuted of 344 children, 1-16 yrs of age, the relationship was reported

only for children below 5 yrs.

A lack of association between Hb and growth status for Indian

preschoolers was reported by Vishweshwara Rao (1970). The report

indicated that the percent prevalence of mild and moderate anemia was

not necessarily related to growth status. Very low Hb levels and a

higher incidence of severe degree of anemia was observed in severely

malnourished children.

Findings of Desai et al (1984) were in accordance with the

above mentioned studies, wherein the Hb levels were normal

(Hb $>$ 12 g/dl) but a deficit in weight (85% of NCHS standard) and

in height (95% of NCHS standard)was observed in migrant adolescent

boys in Southern Brazil compared to their well nourished controls who

had similar Hb levels but were between 100-117 percent of NCHS

standard for weight and height.

Contradictory observations on the impact of Fe supplementa-

tion on growth have also been reported from our own laboratory.

Bhatia (1984) reported a significant improvement in weight and height in both iron treated (40 mg elemental Fe as $FeSO_4$/day) and placebo treated, preschool children, 3-5 yrs of age. The weight gain of the anemic (Hb $\angle$ 10 g/dl) iron treated children was greater than their placebo counterparts. The non-anemics (Hb > 11 g/dl) control and Fe treated children showed a similar degree of weight gain. The findings revealed that growth retardation was a feature of anemia.

Tarvady (1982), however, working in a similar population could not demonstrate any relationship between Hb status and growth indices (weight for age and height for age) in preschoolers, on iron supplementation (40 mg elemental Fe as $FeSO_4$/day) as against the placebo control group. The supplementation period in this study was only 45 days as against 6 months in Bhatia's study.

In yet another study from our own laboratory, Kanani (1984) demonstrated a significantly higher weight increment on Fe supplementation at a dose of 20 mg Fe/day for 60 days in each school term over one school year as compared to the placebo control group in 10-15 year old boys. However, in the same study, no significant improvement in height or weight of the iron treated girl subjects (5-9 years or 10-15 years) could be observed, compared to the placebo control group.

Thus, it appears that the growth promoting effect of iron supplementation is as yet unclear and that the few studies in this area have not given consistent results.

8. Prevention of iron deficiency anemia

Iron deficiency can be prevented either by identifying the vulnerable groups of the population and providing them with iron supplements or by fortifying the diet with iron so that iron nutrition of the whole population is improved. When there is a high prevalence of iron deficiency anemia in a population, supplementation is needed to treat the most severely affected individuals. This is the only way to improve iron nutrition within a reasonable time period (INACG, 1977).

The numerous pharmaceutical preparations of iron in the market often differ widely in their elemental iron content, the iron compounds employed, their pharmaceutical properties (such as their disintegration and dissolution rate in the intestine) and their cost. All readily soluble ferrous iron compounds suitable for oral administration are, in general, equally well absorbed and produce similar type of side effects with similar frequency (see Materials and Methods chapter). Oral administration of ferrous sulfate, one of the cheapest available compounds, is the treatment of choice for almost all cases of iron deficiency (INACG, 1977).

Iron can also be administered by injection. The use of such preparations avoids the problem of poor patient compliance and the rare instance of malabsorption, but is no more effective

in correcting anemia than oral therapy, and is more expensive and less safe (INACG, 1981).

Medications for young children are generally given in liquid form; administering the medication on the back of the tongue to prevent staining of teeth (INACG, 1979).

Cope et al (1956) compared the methods of treatment of iron (35 mg allowing for 35% absorption rate for oral iron) by three ways - oral, intramuscularly and intravenously. They observed that the mean Hb rise per day by all three methods was the same and was more than that could be expected with the dosage given. Hence, it was concluded that the treatment with oral iron is satisfactory.

The rate of iron absorption is dependent on the severity of the anemia. Ten days after starting the treatment of a group of subjects with iron deficiency anemia, about 20% of 100 mg ferrous iron deficiency anemia, about 20% of 100 mg ferrous iron which was administered 3 times a day as $FeSO_4$ was being absorbed (Norby and Solvell, 1974). The mean Hb concentration at this stage was 9.5 g/dl. After 30 days when the Hb concentration had risen to over 12 g/dl, the absorption rate had fallen to 11%. Another important variable is whether the iron preparation is taken in fasting state or after meals. Absorption of a 30 mg dose taken when the stomach is empty was 40% greater than that when it was taken after meals (Brise, 1962).

WHO (1975) has informally agreed to use a dose of 3 mg iron as ferrous ascorbate per kg body weight per day as a standard reference dose. With not much difference in the absorption rates of various ferrous salts, a similar dose could be recommended when ferrous sulfate is used.

Magnussen et al (1981) studied the iron absorption in relation to iron status from 3 mg dose as $FeSO_4$ in 250 male subjects. The results suggested that absorption was 20% in subjects with iron stores of magnitude of 500 mg; 40% in subjects who were borderline iron deficient - having minimal iron stores and no anemia; and about 70 to 80% in subjects having an iron deficient erythropoiesis.

There is an erroneous impression that the dosage for iron therapy must always be large. However, a clear distinction should be made between the prevention and the treatment of iron deficiency. The dosage will vary accordingly; the latter calls for a large dosage for a short duration to eleviate anemia rapidly.

The only advantage of a fairly large dose is, that it would help build stores quickly and also replenish and make iron available for various functional processes where it is required as an enzyme or a cofactor.

To conclude

The review of literature discussed in the preceeding text clearly indicates a high prevalence of iron deficiency anemia in school children, especially girls.

Iron deficient individuals are typically characterised as being irritable and apathetic. It is not unreasonable to suppose that in young children such characteristics might adversely affect the amount of stimulation they receive, with the result that their mental development could be impaired. Iron deficiency may also have effects on neurologic and intellectual function. Preliminary reports suggest that iron deficiency affects attention span, alertness and learning in both young children and adolescents, even when the degree of anemia is not severe. An enzyme apparently sensitive to the state of body iron stores is mitochondrial monoamine oxidase (MAO). Behavioral abberations commonly attributed to iron deficiency may be caused by impaired MAO function and associated excessess of CNS catechols. MAO is an important enzyme in the catabolism of norepinephrine (NE); an elevation in the urinary NE concentration could be attributed to iron deficiency. Also, because NE is thought to influence behavior in man.

The capacity to perform heavy muscular work depends upon the individual's ability to transport oxygen from the lungs to the active tissues, an activity performed in combination with Hb. Thus, a reduction in Hb levels as in anemia, impairs work capacity, and the feeling of fatigue arises. The major physiological consequence of anemia is the reduced oxygen carrying capacity of the blood. Increased cardiac output, heart rate, increased tissue O_2 extraction from the blood are some of the compensatory mechanisms evoked. The phenomenon of increased tissue oxygen extraction from the blood has been

shown to be related to increased concentration of 2,3 DPG within the red blood cell.

Increase in worker productivity in daily work output or an increase in the ability to perform an exercise for a longer duration on iron therapy indicate that these alterations are due to anemia and are reversible.

Iron deficiency anemia has been suggested to alter growth and affect appetite. However, from the reports available it is obvious that much more research needs to be done in these areas to be able to draw a definite conclusion - whether or not iron deficiency alters growth and affects appetite.

Thus, in order to improve the iron and growth status of under-privileged school girls, as well as certain key areas of function such as cognitive function and physical work capacity, it may be necessary to offer them prophylactic Fe supplementation during their school years.

This formed the basis of the present study.