

## CHAPTER 5

### SERUM IRON AND FACTORS AFFECTING THE SERUM IRON VALUES

It was not until 1713, that Lemery and Goeffy showed that iron was present in blood (ash). Later on in 1746, Menghini demonstrated that foods rich in iron could elevate amount of iron in the blood.<sup>51</sup> Iron is present in the blood in three forms: (1) Haemoglobin iron, (2) Non-haemoglobin iron and (3) Plasma iron.

Having been absorbed in the ferrous form, the oxygen tension of the plasma is such that the combination with globulin involves conversion to the ferric form. Thus, though the iron is well-absorbed in the ferrous form, it is transported and stored in the ferric form. Iron is stored both as ferritin and haemosiderin, the latter probably is the polymer of ferritin. When the storage capacity of the liver is exceeded, the serum iron increases and the secondary

tissue receptors such as bone marrow, spleen and kidney begin to fill with iron. Iron balance is maintained by the regulation of absorption according to the body requirements rather than by the excretion of unwanted excess. Excretion is minimum as the circulating iron is always bound to protein. Plasma is the vehicle for the transport of iron.

#### SERUM IRON

Serum iron represents the non-haemoglobin iron component of the blood. In a normal adult, it amounts to about 4 mg., that is, about 0.1 per cent of the total body iron. Like ferritin, serum iron is non-porphyrin in nature, but it differs from ferritin in the ease with which it can be reduced. Serum iron represents iron in transport to and from the bone marrow and the storage depots. It is firmly bound to a specialised transport-protein of the plasma which is  $\beta_1$  globulin ~~fraxixxxxxxx~~ known as transferrin or siderophilin. Each molecule of transferrin binds two atoms of ferric iron to form a coloured complex called Iron-transferrin. There is no exchange between serum iron and the iron of mature erythrocytes.

Transferrin is neither dialysable nor ultrafiltrable. It has a molecular weight of about 90,000. By electrophoretic techniques there are some eight different transferrins

recognised which differ in different races.<sup>130</sup> Not more than two transferrins have been found in one individual (Staveley and Douglas, 1960; Turnbull and Giblett, 1961). Heilmeyer (1961) and Heilmeyer et al. (1961) have reported a case of congenital deficiency of transferrin in a child aged 7 years with hypochromic anaemia. Both parents had greatly reduced transferrin level.

Human serum contains about 2.4 gm. of transferrin per litre, and each gram of transferrin binds 1.25 mg. of iron. Thus, in an average normal adult, 300 to 360 mcg. of iron can be bound to the transferrin present in 100 ml. of serum. This is the limit of saturation of the specific iron-binding protein and is known as Total Iron-binding capacity (T.I.B.C.) of the serum. Holmberg and Laurell (1945) concluded that the amount of iron in normal plasma by no means attains the limit of saturation of the specific iron-binding protein.<sup>43</sup>

Since the serum iron concentration in normal adult males is 118 to 142 micrograms per cent and that in adult females is 90 to 123 micrograms per cent, it is obvious that transferrin is normally only one-third saturated with iron; the unsaturated portion, that is the amount of iron which can be additionally taken up by the serum in presence of added iron, is referred to as the Unsaturated or Latent iron-binding capacity (L.I.B.C.) of the serum. It is,

therefore, clear that serum iron level plus the Latent Iron-binding capacity of serum is equivalent to total iron-binding capacity. The per cent saturation would be the ratio of serum iron to the total iron-binding ~~area~~ capacity.

When iron preparations are injected intravenously, the iron-binding capacity of the serum gets rapidly saturated; iron in excess of that which saturates transferrin causes characteristic toxic effects. Neither the serum iron level nor the total iron-binding capacity influences the rate or the amount of iron absorption by the gastro-intestinal tract.

The concentration of serum iron is unrelated to that of serum copper, despite the fact that all crucial aspects of iron metabolism (absorption by the intestinal mucosa, storage in liver as well as other depots and incorporation into haemoglobin) are intimately dependent on copper. Presumably serum iron is normally in equilibrium with iron stores and its level is determined by the balance between iron absorption and deposition, incorporation of the metal into haemoglobin, and its release therefrom. Of these multiple factors, haemoglobin synthesis is the primary factor regulating the rate of serum iron turnover. Thus, the serum iron level and the

degree of saturation are regulated, and in this regulation the liver, being the main storage organ, plays an important role.

#### NORMAL VALUES

The normal serum iron values obtained by different investigators show great variations perhaps because of the different techniques employed and different types of subjects (Indian or otherwise) selected for the purpose. Furthermore, there are multiple factors influencing the serum iron values. Hence the normal serum iron values will depend upon whether such factors are considered and possibly controlled or not. However, one author's values may be quoted here.

The normal range of serum iron is 80 to 160 mcg. per 100 ml. in males (average 125) and 60 to 135 mcg. per 100 ml. (average 90) in females.<sup>23</sup> However, a normal range as wide as 60 to 220 mcg. per 100 ml. has been found by Smith (1952).<sup>135</sup>

The normal range of total iron-binding capacity of serum is 300 to 400 mcg. per 100 ml., with about 40 per cent saturation in males and 35 per cent in females.<sup>23</sup>

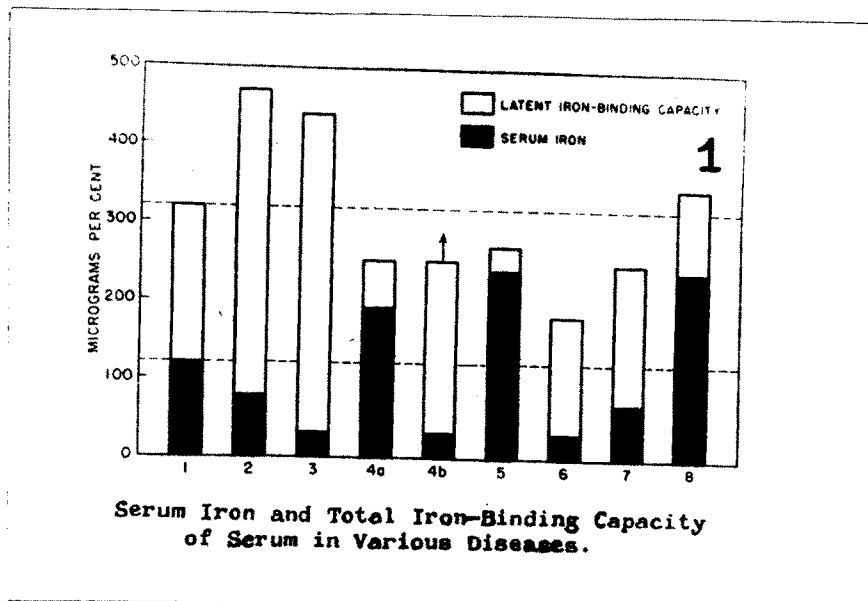
Rath and Finch (1949), using a spectrophotometric technique, and Feinstein et al. (1952), using radio-iron, made studies of iron-binding capacity of serum in man and

found, in round figures, that the normal serum iron averaged 100 mcg., the observed latent iron-binding capacity 200 mcg., and the total iron-binding capacity 300 mcg., all per 100 ml. of serum. The iron-binding protein was, therefore, approximately one-third saturated with iron.

### INTERPRETATIONS

The serum iron concentration and the total iron-binding capacity of the serum vary markedly in different physiological as well as pathological conditions, for example, the serum iron level is higher in males than in females, and higher in the morning than in the evening. The terms hypoferremia and hyperferremia are used respectively to describe low and high serum iron concentrations.

Hypoferremia characterises iron deficiency anaemia, anaemia of infection, and various infectious diseases. In cases of infection and malignancy without anaemia the serum iron values may also be low (Verloop~~et~~ et al., 1958). Hyperferremia characterises hemochromatosis, transfusion hemosiderosis, acute hepatitis and certain ~~known~~ non-hypochromic anaemias such as untreated pernicious anaemia, hemolytic anaemia and aplastic anaemia. The Iron-binding capacity of serum decreases in acute and chronic infections, pernicious anaemia, hemolytic anaemia, cirrhosis of liver, uremia and malignancy. The capacity increases in acute and chronic blood loss and in pregnancy (Photograph No.1).



The full height of each column (i.e. Serum iron plus Latent Iron-binding Capacity) represents the total iron-binding capacity.

The lower horizontal dash line represents the normal level of serum iron. The upper line represents the normal level of iron-binding capacity of human serum.

1. Normal adult
2. Late pregnancy
3. Chronic iron deficiency, polycythemia vera
- 4a. Hemolytic, pernicious, aplastic and myelophthisic anaemias
- 4b. Hemolytic and pernicious anaemias during remission
5. Hemochromatosis and transfusion hemosiderosis
6. Acute infections
7. Chronic infections, malignancy, myelomatosis, uremia, leukemias, hepatic cirrhosis, acute or subacute liver atrophy
8. Acute hepatitis (2nd to 5th week)

The level of serum iron as well as the degree of saturation of the iron binding protein are not correlated with the haemoglobin level of the blood, though iron deficiency and hypochromia are usually accompanied by decreased serum iron values and increased latent iron-binding capacity.<sup>130</sup> It is not uncommon to observe patients with iron deficiency anaemia of only moderate severity in whom serum iron level is reduced below 10 mcg. per 100 ml. and total iron-binding capacity is ~~xxx~~ raised above 600 mcg. per 100 ml.<sup>44</sup> Thus, ~~the~~ in iron deficiency anaemias the total iron-binding capacity is elevated, but the serum iron is low, giving an increased latent iron-binding capacity. Hence, in these diseases the simple measurement of serum <sup>iron</sup> and latent iron-binding capacity may be helpful in differentiating the type of anaemia. The latent iron-binding capacity is usually over 300 mcg. per cent in iron deficiency and under 150 mcg. per cent in pernicious anaemia.<sup>23</sup>

In simple iron deficiency, the serum iron level is low and total iron-binding capacity is increased. In cases of iron deficiency anaemia accompanying infection, the serum iron level is low, but at the same time there is a marked reduction in total iron-binding capacity.<sup>44</sup> In infection, malignancy and chronic hepatic or renal disease the serum iron may be normal whilst the total iron-binding capacity is decreased.<sup>26</sup>



Pronounced increase in serum iron, together with normal or reduced iron-binding capacity, have been observed in viral hepatitis in contrast to the normal values found in jaundice due to extrahepatic biliary obstruction.

#### IMPORTANCE OF SERUM IRON STUDIES

The quantity of iron present in the serum is a measure of: <sup>32,89</sup>

1. The amount of iron absorbed from the gastrointestinal tract.
2. The adequacy of the iron reserves of the body.
3. The capacity of bone marrow to utilise iron for haemoglobin synthesis.
4. The rate of haemoglobin synthesis.
5. The activity of haemolytic processes.
6. The physiological and pathological equilibrium existing between 4 and 5.

The determination of serum iron is valuable not only in the study of nutrition and blood formation but also in the routine clinical work and practice. The wide normal range is not entirely correlated with the time of the day, meals or age, and this reduces the value of serum

iron estimation in which the factors affecting the serum iron values are not given due consideration. In principle, a low level of serum iron indicates iron deficiency requiring iron therapy, and such a state may be found even with a normal haemoglobin level. It is important to consider that decreased serum iron level with increased total iron-binding capacity as well as increased latent iron-binding capacity is a better indication of iron deficiency anaemia. However, a low serum iron level may be found without iron deficiency in infection and malignancy but at the same time there is a marked reduction in total iron-binding capacity whilst the latent iron-binding capacity may or may not be reduced.

The test may also be extended to detect deficiencies of iron storage, and of perenchymal iron by determining the serum iron at intervals before and after the administration of a test dose of an iron salt. If the rise in serum iron is small the patient has sufficient stores of iron, but if the serum iron concentration rises rapidly and greatly exceeds the approximate maximum normal value of 220 mcg. per 100 ml., a state of iron deficiency requiring iron therapy is indicated. This is the oral iron absorption test.

It appears that the iron absorption into the blood stream is direct, in that a rise in iron content of the

plasma is not preceded by a rise in the ~~xx~~ iron content of the lymph of the thoracic duct. In principle, the plasma iron is low when the tissue stores are hungry for iron, as with haemorrhage or gross iron deficiency, but is high when blood formation is depressed. These principles are applied as the oral iron absorption test to determine the need for iron and to estimate the probability of a good therapeutic response.

A fall in plasma or serum iron is one of the earliest indications of the successful treatment of pernicious anaemia, and so is the rise of serum iron level in idiopathic hypochromic anaemia.<sup>89</sup>

In great majority of instances haemoglobin deficiency is a manifestation of true iron deficiency and it is customary and justifiable to prescribe iron. Occasionally, haemoglobin deficiency is present because of interference in the synthesis of the pigment. Such condition is prone to occur in chronic infection, chronic renal or hepatic disease, and active rheumatic states. In these diseases the blood picture may be indistinguishable from that of true iron deficiency, but the presence of stored iron can be demonstrated in the tissues, for example, in bone marrow. It is in such cases that alterations in the serum iron, and in the iron-binding capacity of serum may provide strong evidence of a departure from the simple iron deficiency

picture. In simple iron deficiency the serum iron is low and the iron-binding capacity is increased. In infections, malignancy and chronic hepatic or renal diseases the capacity is diminished whilst the serum iron may be normal.<sup>26</sup>

Estimation of serum iron and iron-binding capacity of serum is also helpful in differentiating the type of anaemia. In iron deficiency anaemia the serum iron is low and iron-binding capacity is usually over 300 mcg. per 100 ml. whereas in pernicious anaemia the serum iron is raised and iron-binding capacity is under 150 mcg. per 100 ml.<sup>23</sup>

These estimations afford a relatively easy laboratory test in suspected cases of haemochromatosis<sup>43</sup> in which the serum iron level is markedly increased and total iron-binding capacity is markedly diminished. So also it is true in case of acute hepatitis.

Serum iron estimation and iron-binding capacity help in differentiating jaundice due to viral hepatitis from that due to extra-hepatic biliary obstruction.

Serum iron estimation is an important investigatory tool in experimental research work, for example, in studying the mechanism of hypoferremia and also in studying the changes in serum iron in health and diseases.

Serum iron estimation serves as a useful guide during the treatment of iron toxicity. Intravenous infusion

of calcium disodium versenate (E.D.T.A.) is to be given daily until the serum iron level is normal.

Serum iron estimation is one of the methods for studying iron absorption. Serum iron estimation before and after the administration of a particular iron preparation indicates whether the iron in that form is absorbed adequately or not and hence whether the oral iron therapy is going to become successful or not. Such estimation conducted on first day of therapy will, therefore, suggest whether to continue the oral iron therapy with that particular iron preparation or to switch on to another oral iron preparation or even to parenteral iron therapy. Similarly, serum iron estimation can be adopted as one of the important investigations conducted during clinical trial of a new oral iron preparation ~~be~~ put forward in the market where it can ~~be~~ likewise provide useful information about the new drug and hence it can help in evaluating the therapeutic efficacy of the iron preparation under clinical trial.

#### METHODS FOR ESTIMATION OF IRON ABSORPTION

No field in medicine is so complex and has been so confused by contradictory results, difference of interpretations and diversity of opinion than that of iron absorption. Each discovered hypothesis, instead of simplifying the subject, brought new problems in its train.

Various methods have been adopted by different workers to study the unknown or imperfectly understood details involved in the complicated process of iron absorption. It will not be out of way, therefore, to consider here the various methods briefly, and particularly so because serum iron estimation is one of the methods under consideration. The various methods<sup>45</sup> are given below:

1. Serum Iron Method :

Serum iron absorption curves have been used to measure the iron absorption. After ingestion of inorganic iron, the plasma iron concentration increases three to four fold in about 2 - 4 hours, falling subsequently over a period of 6 - 12 hours depending upon the amount ingested.<sup>32</sup>

The interpretation of serum iron values is by no means easy, as the values depend partly upon the intestinal absorption, partly upon the rate of deposition in the tissues and partly upon the iron-binding capacity of the plasma proteins. However, a rise in serum iron can be interpreted as meaning that iron is in fact being absorbed and comparative iron curves give an idea of the relative absorption of different iron compounds.<sup>130</sup>

In iron deficient subjects the proportion of oral dose appearing in the blood is indeed a good measure of absorption. When an investigation is concerned not so much

with the actual amount of iron absorbed but with a comparison between two iron preparations, or two different experimental conditions, the two preparations or isotopes are both given by mouth and the ratio between the two values in blood gives the comparative absorption.<sup>31</sup>

Josephs considers that a good rise of serum iron level after the test dose clearly indicates good absorption, but the reverse is not necessarily true.<sup>45</sup>

## 2. Iron Balance Method :

In this method, the amount of iron ingested and the amount of iron excreted in faeces is estimated chemically. This method which was used by McCance and Widdowson many years ago, is difficult because the technique of estimation needs exceptional care and all clinical balances need great vigilance. Nevertheless, it has the advantage that the observations can be continued for as long as is necessary and can be repeated. Josephs concluded that the chemical iron-balance method, with all its difficulties, has given results that constitute the standard for judging other methods.

## 3. Isotope Balance Method :

In this method radio-active iron isotopes incorporated into iron salts or food have been utilised. This

technique is much easier but has a disadvantage that it cannot be repeated on individual patients because there is a limit to radioactive doses.

#### 4. Haemoglobin Method :

The last method to estimate iron absorption is to determine the rise in haemoglobin level in the patient's blood. It is based on the implified assumption that all absorbed iron is used only for haemoglobin formation, but it may ~~be~~ not always be correct. However, Neerhout et al. showed that in dogs 95 per cent of absorbed isotope-tagged iron is present in red cells mass fourteen days after feeding.

It is evident from the foregoing discription that serum iron estimation is comparatively less complicated method for measuring the iron absorption and hence the importance.

#### FACTORS AFFECTING THE SERUM IRON VALUES

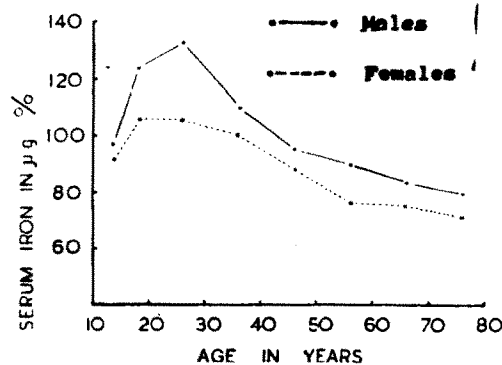
There are many physiological as well as pathological factors which influence the normal serum iron values. An accurate and adequate consideration of all these factors is extremely important for selecting the subjects for the



estimation of normal serum iron values as well as for the interpretation of serum iron levels in different diseases. Accordingly, the various factors are considered here.

### 1. Age :

The serum iron of umbilical cord blood at parturition is high (173 to 193 mcg. per cent) but in twelve hours hypoferrremia is found. Until two months of age a normal or increased serum iron level is present but after this time hypoferrremia of varying degree develops. Values in older children successively approach adults levels.<sup>136</sup> Then, there is a significant decrease in serum iron in both sexes with increasing age.<sup>99</sup> (Photograph No.2)



The Relationship of Serum Iron to the Progress of Age.

## 2. Sex :

Serum iron in males is significantly higher than in females. The cause for low serum iron in females is not known. But some workers believe that the difference in serum iron between two sexes is due to the iron loss incurred by menstruation while others believe that the difference is due to the hormonal factor.<sup>54</sup> If it be admitted that a rise in haematological values takes place in males after puberty, whereas the values remain the same in females, it would appear that the endocrinal influences may be responsible for the difference in normal serum iron values in the two sexes. It is interesting to note that the difference in serum iron is maintained at any particular age and also all throughout the life (Photograph 2).

## 3. Obesity :

There is a significant decrease in serum iron in obese individuals<sup>130</sup> (Wenzel et al., 1962).

## 4. Menstruation :

McCance in 1936 suggested that the menstrual blood loss is responsible for the lower values of normal serum iron in females.<sup>54</sup> This view was later on supported by Pirrie<sup>72</sup> ~~in~~ in 1952.

Moore, Minnich, and Welch (1939) concluded that spontaneous variations of 18-64 mcg. per cent do occur but that these changes are "oscillating in type and have no persistent directional characteristics." However, Hemmeler has defined a normal range of 80-100 mcg. per cent for menstruating women, while for non-menstruating women he has found the range to be the same as that for men, that is 100 - 130 mcg. per cent. Powell (1944) extended the analysis to determine the effect of menstruation on serum iron of normal women and classified the results into four groups corresponding to the four weeks of the menstrual cycle. The means and standard deviations of these groups were :<sup>100</sup>

TABLE NO. 2

SERUM IRON VALUES IN RELATION TO MENSTRUAL  
CYCLE OF NORMAL WOMEN

Menstrual cycle	Serum Iron values in mcg.%	
	Mean	Standard deviation
1st week (during menses)	100	27
2nd week	118	25
3rd week	124	17
4th week	131	23
2nd, 3rd and 4th weeks together	125	22

Thus, the results indicate considerable likelihood of a real periodicity in the serum iron level of normal women.

#### 5. Diurnal Variation :

It is generally recognised that plasma iron undergoes a regular diurnal variation (Hoyer, 1944; Hamilton et al., 1950; Laurell, 1953). Hyperferremia has been reported in the morning, hypoferremia occurring in the evening.<sup>54</sup> Gupta et al.<sup>54</sup> suggested that this variation is not sufficiently regular in occurrence to predict any individual's pattern.

The plasma iron is highest between 5 a.m. and 1 p.m. and lowest between 5 p.m. and 1 a.m.<sup>130</sup> There is a similar variation in plasma bilirubin suggesting that these parallel alterations are a reflection of haemoglobin breakdown and resynthesis (Laurell, 1953).

#### 6. Diet :

Highly significant difference in sub-groups based on dietary habits viz. vegetarians and non-vegetarians has been found.<sup>72</sup> Thus, the mean serum iron value has been found to be higher in vegetarians (taking lot of green vegetables) as compared to that in non-vegetarians (Johri, 1959). It is likely that this difference might be due to the fact that green vegetables and particularly the leafy

vegetables are rich sources of iron.

### 7. Drugs :

Iron preparations and drugs containing iron increase the serum iron level. Oral administration of ascorbic acid, by virtue of its reducing property, increases the iron absorption and thereby it might raise the serum iron. On the other hand, Moore, Bredman, Minnich, and Arrowsmith (1940) have reported that parenteral ~~and of~~ administration of ascorbic acid causes marked lowering of serum iron level, which points to the utilisation of iron for haemoglobin synthesis.<sup>100</sup>

Salicylate administration produces a fall in serum iron (Izak et al., 1962). The cause of the drop in serum iron values in patients receiving salicylates is not clearly understood. It is conceivable that the salicylates alter the function of the reticuloendothelial system, as a result of which circulating plasma iron is removed from the circulation and deposited in the reticuloendothelial cells.<sup>66</sup>

Liver therapy soon after its commencement in cases of pernicious anaemia reduces the serum iron level.

### 8. Body Temperature :

Reginster (1943) believed that fall in plasma iron was related to a rise in body temperature. Gupta et al.

(1959) in a study on the influence on plasma iron of rise in body temperature observed some correlation between the degree of pyrexia and the extent of hypoferremia in patients with infection, but low plasma iron was also found in a few afebrile cases. However, no hypoferremia was observed in animals subjected to physical hyperthermia. It was, therefore, concluded that the drop in plasma iron is not due to an increase in body temperature per se, but may be the result of other associated factors which lack in physical hyperthermia.<sup>53</sup> That hypoferremia is not secondary to rise in body temperature is further suggested by the fact that patients of infection without any fever also show a decrease in plasma iron.

#### 9. Infection :

Infection is one of the most important factors influencing the serum iron values. It has been observed that patients with infection and experimentally infected animals show hypoferremia and decrease in the concentration of iron-binding protein. A review of literature shows that in spite of extensive study on iron metabolism in infections, the mechanism of hypoferremia is far from clear.

In patients with infection the rise in plasma iron following the standard dose orally is very little as compared to normals. This is because of the fact that in

infections, the absorption of iron from gastro-intestinal tract is considerably diminished. If ~~xx~~ it is admitted that iron absorption is impaired in infections, it is unlikely that it is a major factor in the production of hypoferremia.

The main factor responsible for hypoferremia appears to be an increase in the rate of iron removal from the plasma. Kumar et al. (1959) found that the rate of removal of iron from plasma was twice as rapid in patients with infection as in normal subjects. The iron transferred from plasma is not excreted in the urine but is deposited at the site of ~~the~~ inflammation and more so in the liver, spleen and bone marrow.<sup>82</sup> Tissue-iron studies in experimentally infected animals have shown that the iron content of the liver, spleen and bone marrow is almost double under the influence of infection. It has been further suggested that such accumulation of iron in liver spleen and bone marrow has something to do in connection with the defence mechanism of the body (Kumar et al., 1959). However, there ~~is~~ no accepted explanation to account for the occurrence of hypoferremia in infection.

#### 10. Reticulo-Endothelial System :

It is generally believed that the functional ~~f~~ activity as also the demand for iron of the reticulo-endothelial cells is increased in infection (Vannotti and

Delachaux, 1949; Cartwright et al., 1950). Kumar et al (1959) studied the role of reticulo-endothelial system in the regulation of plasma iron and observed that the 'blockade' of R.E. system by injection of vital dye like Evans blue, results in hyperferremia.<sup>83</sup> It has been shown that 'blockade' of R.E. system by vital dyes does depress its multiple functional activities. It is, therefore, reasonable to assume that hyperferremia observed to follow the 'blockade' of R.E. system may be due to the depression of its function.

It was further observed that previous injections of Evans blue abolished the hypoferremic effect of turpentine injection, which acts by producing sterile inflammation. This means that the drop in plasma iron under the influence of turpentine is brought about by an increase in the transfer of iron from plasma to R.E. cells. Possibly a similar mechanism operates in infections. Thus, it may be concluded that since R.E. cells has a vital role to play in the defence mechanism of an organism and since iron is an important constituent of cellular enzymes, these cells are likely to require more iron for their increased function consequent to infection.

#### 11. Adrenal-Cortex :

It has been observed that hypoferremia ~~shows~~ follows a variety of divergent stimuli besides systemic invasion



by an infective agent. Thus, widely divergent stimuli such as electric shock and operative truma produce hypoferremia (Gupta et al., 1960). Baird et al. (1957) have shown that after any major surgical operation there is a conspicuous fall in the serum iron and the iron absorption curve is flat.<sup>130</sup> These return to normal within three months. Hypoferremia in patients subjected to operative trauma is also accompanied by eosinopenia, which is one of the recognised manifestations of adreno-cortical hyper activity.

Hypoferremia has also been reported to occur in patients with coronary ~~area~~ occlusion and traumatic injuries (Feldthusen and Lassen, 1954).

Adreno-cortical hyperfunction induced by injection of ACTH was followed by a significant decrease in plasma iron in rabbits.<sup>52</sup> Furthermore, accompaniment of eosinopenia with hypoferremia in patients subjected to operative stress is suggestive of an associated adreno-cortical hyper activity.

Thus, it is obvious that various divergent stimuli produce hypoferremia as a common biochemical change. These divergent stimuli manifest a common state of distress. Therefore, it is postulated that 'stress' caused by these stimuli may be concerned in some way with the production of hypoferremia. It is note-worthy in this context that

hypoferremia has been reported to occur in association with general adaptation syndrome (Selye, 1950). Whether this change is brought about by an increased activity of the ~~x~~ reticulo-endothelial system, or adrenal cortex, or through an entirely different mechanism cannot be definitely stated at present.