# THE BEHAVIOUR OF THE IRONS AND COPPER OF THE BLOOD DURING REGENERATION FOLLOWING ANAEMIA.

By

TOM McEWAN.

# INTRODUCTION.

When this paper was commenced in 1938 very much less was known about the non-haemoglobin iron of the blood than is the case now, as a great deal of work has been carried out in this direction during the war years and many points have been clarified. The object of the work was an attempt to determine the relationship, if any, between the haemoglobin and non-haemoglobin iron of the blood throughout the process of regeneration following anaemia. The writer feels that his results compare favourably with those in more recent papers and that the work would have been of definite value, and original, had it been published on its completion and without the delay resultant from his war service. As it is, the method of approach to the subject is different in the main from other work previously published, although undertaken at a date later than this paper. The discussion which follows has required much modification from its original form due to the findings published during the intervening years.

## Discussion.

It is now well accepted that the blood contains iron in two forms, a haemoglobin and a non-haemoglobin form. Of the former, only a brief note is required as its physiological function, chemical nature and the methods of its estimation are universally known.

### Haemoglobin Iron.

Haemoglobin iron is normally present in amounts of 14 to 14.5 gms. per 100 ccs. of blood. Iron is a constituent of the haemoglobin molecule which has been calculated by Morrison and Hisey (1935) to have a molecular weight of approximately 66,000 and Bernhart and Skeggs (1943) have found that the iron content of crystalline human haemoglobin, dried at 105°, is 0.340 per cent. The correct maintenance of haemoglobin at its normal level depends mainly upon the amount and availability of its iron constituent in the diet, and on the absorption of this from the gastro-intestinal tract.

Iron may be made available to the organism through the presence of either organic or inorganic iron in the diet. Elvehjem (1932) has shown that organic iron is less readily absorbed than the inorganic form as the former has first to be converted in the intestines into an ionisable state and/

and Moore (1944) has also shown that organically combined iron is poorly assimilated by the body.

Inorganic iron may occur in either the Ferrous or Ferric state. Using radioactive iron Moore et Al; (1944) show that, in humans, the ferrous irons are the more readily absorbed whilst, in dogs, both forms of valancy may be absorbed equally well. In severe microcytic hypochromic anaemias absorption of the bivalent form of iron was in a ratio of 2 - 15 times as much as that of the trivalent iron. Their explanation of these findings is that either,

a. Only the bivalent form of iron is absorbed by the body and the trivalent form does not undergo complete reduction in the intestines into the bivalent state, or

b. Both forms of valancy are absorbed but to an unequal degree, or,

c. Ferric iron may be made less available by forming complex insoluble compounds within the gastro-intestinal tract.

They explain the absorption of both types of iron by dogs by suggesting that they (a) either reduce ferric iron more completely than do humans, or, (b) are able to absorb both forms of iron in equal degrees.

Witts,/

Witts, (1936) has shown that absorption occurs mainly from the duodenum, but also from the stomach and, in some circumstances, from the small intestine. Fuhr and Steenbock, (1943) demonstrated that excessive calcium in the diet inhibits the absorption of iron and may result in the production of a mild anaemia. They also showed that neither a high nor a low Ca:P ratio in the diet affected iron absorption provided that there was a sufficiency of iron in the diet. Moore, (1939), proves that the presence in the duodenum of reducing agents, such as ascorbic acid, facilitate iron absorption and suggests as a result of their work that - Ingested iron is subjected to the influence of the gastric acidity which ionises and dissolves irons not already in solution, or ionised, and also delays the formation of insoluble compounds which may occur above a pH 5. In the duodenum, iron is subjected to the alkaline contents containing certain reducing substances which cause the reduction of the trivalent ferric iron into the ferrous state before it can change into non-ionisable salts. After absorption the iron passes into the blood stream and not into the intestinal lymph vessels. Balfour and Hahn, (1942) using radioactive iron have studied the absorption of iron and from their results, believe that when the body stores of iron are depleted iron will be absorbed from the gastrointestinal tract/

tract in relative abundance. Low haemoglobin levels in themselves are not enough to stimulate absorption if the body reserves in the liver, spleen and marrow are adequate. They moreover suggest that the mucosa of the gastro-intestinal tract has the power to accept, or refuse, iron present in the gastric contents. They have shown that in pregnancy women absorb 2 to 10 times the normal absorption of radioactive iron, whereas in Pernicious Anaemia, and states in which the body iron stores are replete, little absorption, even less than normal occurs.

Non-haemoglobin Iron of the Serum.

For some considerable time it has been recognised that small amounts of iron are present in the serum, or plasma, after the removal of the blood corpuscles, but was present in such small amounts that its investigation was difficult.

At first it was suggested that any iron present was the result of haemolysis occuring upon venipuncture, or upon trauma caused by centrifuging the specimen. This supposition has since been proved erroneous as the following evidence indicates.

Fowweather (1934) has shown the presence of iron in the serum after withdrawing whole blood in an oiled syringe and immediately centrifuging this in a paraffined tube. This technique resulted in a plasma which contained

no/

no coagulent and which was sensitive to an extremely sensitive Benzedine reaction; a reaction which would have been present in the presence of one part in a million of haemoglobin. In 1927, Henriques and Roche, and again in 1934, Marlow and Taylor, by examining the serum specimens spectroscopically showed that, although a minute quantity of the iron present might be attributed to the presence of haemoglobin, by far the greater part was of non-haemoglobinous origin. It was concluded that any iron estimated, resulting from haemolysis, was negligible unless there was visible lysis and that no one would use such a specimen when estimating iron. To quote from Moore et al; (1937) -

"It is therefore possible to ;-

(a) Prepare serum, or plasma, which for all practical purposes is free from haemoglobin.

(b) Quantitate small amounts of contaminating haemoglobin in the serum.

(c) Precipitate any contained haemoglobin along with the serum proteins with trichloracetic acid" .

This latter statement is especially applicable to this paper as Tompsett's modification of the trichloracetic acid method of obtaining a protein free filtrate is used. Fowweather, (1934) and Tompsett, (1934) both note that/

that minute quantities of true non-haemoglobin iron are carried down in the precipitate when using trichloracetic acid and the readings are thus a little lower than might be the case when using other methods. This very slight disadvantage is offset by the knowledge that the iron estimated is truly of non-haemoglobinous origin and presumably, if at all, there will be a small standard error which will not alter the perspective of the investigation in toto. Using the more modern method of radioactive investigation Hahn, (1939), has proved that a non-haemoglobin iron is present in the plasma.

Many writers have noted the presence of this iron in the blood and for convenience it shall be called "Serum or Plasma Iron" throughout this paper in place of its long title of " The Non-haemoglobin Iron of the Serum or Plasma". Fowweather (1934), Aberhaldane and Moller (1928), Moore, Arrowsmith, Quilligan and Read (1937) have all shown that the difference between the non-haemoglobin iron content of the serum and that of the plasma is so minute as to be a negligible factor and thus the terms 'serum' and 'plasma' may be regarded, for all practical purposes, as interchangable.

The nature of the serum iron has not yet been determined with exactitude. Starkenstein, (1933) believed/

believed it to be an organic form and was combined to the serum globulin and in a trivalent state. Barkan, (1936) showed that it was non-dialysable unless acidified and hence that it was not in an ionised state. This change of the serum iron into an ultrafiltrable state, after incubation with dilute HCL at 37° C, became known as the "Barkan phenomenon" . This was explained by Tompsett, (1940) who showed that plasma iron, in vitro, was in a ferric valancy, when obtained under conditions which did not prevent the reoxygenation of haemoglobin, but when the plasma was acidified and allowed to stand the iron became reduced to the ferrous state and thus ultrafiltrable. He is careful to state this does not indicate that this is the permanent state of the plasma iron, in vivo. It seems essential that at some stage the plasma iron becomes, at least in part, changed into the ferrous state for otherwise it is difficult to visualise how the plasma iron can be regarded as transport iron unless ultrafiltrable.

The significance of its presence in the serum suggests that it is an essential phase of iron metabolism and Dominici, (1929) put forward the suggestion that it was iron in the process of transportation in the bloodstream. Moore et al; (1937), (a) and (b) ) have demonstrated that/

that this is so and that plasma iron is of metabolic importance in the role of iron transportation in the mammalian organism. Hahn et Al; (1939) using radioactive iron confirm these findings and show that the transference of radioactive iron from the plasma to the red corpuscles occurs within a few hours of intestinal ingestion of this iron. How the conversion of this 'transport iron' into haemoglobin occurs is yet incompletely understood.

The average amount of plasma iron is between 0.05 to 0.18 mgm. (50 - 180 microgrammes) per 100 ccs. of plasma. Locke, Main and Rosbach, (1932) in a study of twenty-eight normal cases give the average normal figures as, for men 100 + or - 15 microgrammes per 100 ccs, and for women as 77 + or - 15 microgrammes per 100 ccs of serum. In this present series of cases the serum iron of twenty normal males, Naval officers, and ratings, was estimated giving an average result of 124 microgrammes per 100 ccs of serum. The complete table of these results is appended below, Table 1, and the results are compared with those of four other workers, Table 2.

| Normal Cases - Serum Iron Results. | | | | |
|---|---|---|---|---|
| Case | R.B.C. | Hb% | C.V. | S.Fe. |
| 1. | 5.58 | 91 | 40.5 | 90.0 |
| 2. | 4.76 | 93 | 39.6 | 150.0 |
| 3. | 4.69 | 94 | 43.2 | 130.0 |
| 4. | 5.62 | 109 | 45.0 | 170.0 |
| 5. | 4.71 | 91 | 37.8 | 120.0 |
| 6. | 4.85 | 98 | 41.5 | 89.0 |
| 7. | 5.10 | 100 | 44.0 | 80.0 |
| 8. | 5.05 | 94 | 40.5 | 130.0 |
| 9. | 4.89 | 98 | 37.5 | 170.0 |
| 10. | 5.26 | 98 | 40.0 | 120.0 |
| 11. | 4.73 | 94 | 38.0 | 140.0 |
| 12. | 5.35 | 97 | 42.0 | 140.0 |
| 13. | 4.46 | 96 | 40.0 | 100.0 |
| 14. | 4.95 | 96 | 39.0 | 126.0 |
| 15. | 4.71 | 91 | 38.0 | 155.0 |
| 16. | 4.75 | 102 | 41.5 | 160.0 |
| 17. | 4.67 | 90 | 40.0 | 100.0 |
| 18. | 4.72 | 94 | 41.0 | 108.0 |
| 19. | 5.30 | 94 | 38.0 | 99.0 |
| 20. | 4.39 | 91 | 37.0 | 107.0 |

Mean = 124.2 Mean error of Mean = 6.1
Standard Deviation = 27.6

TABLE 1.

The normal results obtained in the present investigation are higher than quoted by Locke et al; (1932) but compare favourably with those noted in Table 2. The writer thus considers that the method of estimating iron used in the paper, may be considered satisfactory.

TABLE 2.

| Authors. | Cases. | Mean + or - mean. error of mean | Standard Deviation. |
|---|---|---|---|
| Heilmeyer and Plotner 1937 | 25 | 126.2 + or -4.3 | 21.4 |
| Moore et Al; 1937 | 15 | 121.5 + or -6.7 | 25.8 |
| Vahlquist 1941 | 50 | 142.0 + or -6.1 | 43.0 |
| Powell 1944 | 35 | 143.0 + or -4.1 | 24.0 |
| Present Investigation | 20 | 124.2 + or -6.1 | 27.6 |

Variations in the individual serum iron levels are found to occur. Hemmeler, (1944) has shown that diurnal variations in the average figures are noted in the individual case; the figure tends to be high in the morning, decreases during the day and rises again during the night. In women, Powell, (1944) points out that a menstrual periodicity in the serum iron levels is found, there being a depressed phase during the first week of menstruation.

Many methods of serum iron estimation have been devised, several since this work was completed. New methods, using radioactive irons are now in vogue, and the use of the photoelectric colorimeter has greatly facilitated estimation. At the outset of this investigation the methods of Kennedy, (1927) - McIntosh,(1933) - Fowweather, (1934) - Tompsett,(1934) - Bing and Hanzal,(1935) - and Moore, Doan and Arrowsmith, (1937) were studied. The method devised by Tompsett, a modification of the trichloracetic acid method, was decided upon and used in this investigation. It will be described in detail later. It is believed that, whilst outmoded, the method gives results which can still be compared satisfactorily with more recent estimations.

Non-haemoglobin Iron of the Whole Blood.

Several writers have devised methods of estimating a non-haemoglobin iron of the whole blood which is present in amounts ten to sixteen times as much as that found in the serum. McIntosh, (1933) and Tompsett, (1934) have both estimated such an iron and the results of the two investigations closely approximated each other, giving values of 0.8 to 1.6 milligrammes of iron per 100 ccs. of whole blood. Barkan, (1927) has been an assiduous worker in this field and has investigated an iron for which he/

he coined the phrase "Leicht abspaltbare bluteisen". This term he used to designate an iron which is 'set free' from its lightly bound state in the erythrocytes and plasma upon the addition of an acid to a specimen of blood. He has shown in his experiments that different types, and concentrations, of acid 'set free' different quantities of iron from the same specimen of whole blood: Sulphuric and nitric acids, for instance, split off more iron than does hydrochloric acid, and the amount split off is furthermore affected by the length of time the blood is exposed to the action of the acid and the temperature at which the mixture is maintained. It appears that Tompsett's explanation with regard to the Barkan phenomenon in the serum holds equally well here.

The whole blood iron of this series of cases was estimated by Tompsett's Method, (1934) and an attempt was made to standardise any error which might appear. The blood was thus exposed in each case to acid 'digestion' for five minutes only, prior to filtration, and this latter process was completed in each case within twenty minutes.

In each case a standard time was thus set for the process of digestion and presumably a representative equal amount of iron was 'split off' in each case. What type of iron this is, and what significance it may have, still requires answering. Since the paper was completed it has

been/

been decided to ignore this aspect of the investigation as the results obtained shed no light upon an extremely confused aspect of blood biochemistry.

## THE BLOOD COPPER.

It has been estimated that 100 - 150 mg of copper are present in the adult body (Harrow, 1940) and that to maintain the copper level a daily intake of 2 - 4.8 mg is required (Chou, 1935; Summerson, 1940). Sachs, Levine and Fabian (1935) have found that a level of 132 - 141 micrograms % of copper is present in the average normal blood. The former figure they obtained using the iron precipitation method of estimating copper (Sachs, 1935); the latter figure resulted from using McFarlane's method (1932) but they believe this method is the less reliable and gives higher results than should be the case. In women, an average blood level of 131 micrograms % was determined by Sachs' method. The blood copper level had been found to be increased in pregnancy, in infectious diseases and in anaemic infants (Gorter, 1931 and 1933; Sachs, Levine and Fabian, 1935). In 1930, McGowan pointed out that copper takes the place of iron in the blood pigments of certain invertebrates, in the haemocyanin of their corpuscles, but Schultze (1941) has shown that copper is not a part of the haemoglobin molecule and is evenly distributed between the cells and the plasma.

## Copper in the Anaemias.

What firstly attracted the research worker's attention to copper and its relationship to the anaemias is uncertain, but McHargue (1925) demonstrated the presence of copper in the livers of calves and young rats. He found that it was stored in this organ in quantities greatly in excess of that present in the respective adult animal and he considered these stores of copper to be analagous to the iron stores in the livers of newborn mammals and humans. Lindow, Elvejhem and Peterson (1929) found that heifers milk has a low copper, as well as a low iron, content and suggest a relationship to the storage of these essential salts within the young body and this low milk content.

Hart, Steenbock, Elvejhem, Waddell and Herwin (1925, 1927, 1928, 1929) proved in the milk deficiency anaemias of rats and rabbits that -

(a) Iron alone was insufficient to produce satisfactory haemoglobin regeneration.

(b) Pure ferrous sulphate did not improve the anaemia to any extent, whereas an impure salt did so rapidly.

(c) Iron-free chlorophyll, added to the iron therapy, resulted in increased haemoglobin formation. This has also been shown by Minot (1932).

As a result of their experiments Hart et al; (sup) came to the conclusion that both traces of iron and copper/

copper were essential for the cure of this milk anaemia.

Schultze, Elvejhem and Hart (1936 a & b) showed that when anaemic pigs had a bodily store of copper they responded well to iron therapy alone but, when these stores of copper were depleted, pure iron was ineffective in curing the anaemia and copper required to be added to the therapy. When the nutritional anaemia was due to a deficiency of both iron and copper the blood copper fell to a low level and they suggest that continued haematopoiesis cannot occur in pigs unless the blood copper level remains above a minimum of 20 micrograms %. Elvejhem and Sherman (1932) found, when iron had been given to anaemic rats without producing a haemoglobin response and its administration discontinued, that there was an immediate response in haemoglobin regeneration to the exhibition of copper alone; this they attributed to its effect in aiding the utilisation of previously stored iron. Hill (1930) by a different approach to the subject also showed this to be the case. Neal, Becker and Shealey (1931) pointed out that ferrous ammonium citrate does not cure a deficiency anaemia occurring in suckling calves but that it does so when given in conjunction with a copper salt.

Titus, Cave and Hughes (1928, 1929) produced evidence which showed manganese to be almost as effective as copper as an adjuvant to iron therapy and suggested there was a group of substances which had similar effects and could be/

be called 'trace elements'; however, Krauss (1931) and Keil and Nelson (1931) after testing various such 'trace elements' came to the conclusion that copper was the only one which was of physiological significance.

In humans, Morrison and Nash (1930), and Cunningham (1931), showed that copper storage occurs in the foetus during intrauterine life. Sachs et al; (1935) found that there was a cupraemia in pregnant women of 195 micrograms %, compared with a normal blood copper level of 131 micrograms %, and that the blood iron content was lowered. In infants the reverse was found; the blood copper in the umbilical vein was at an average low level of 82 micrograms % whilst the blood iron was high. This evidence, taken in conjunction with the storage of copper in the foetus (Cunningham, 1931) suggests that - Copper is mobilised during pregnancy in the maternal blood stream but is stored in the liver, and possibly in the spleen, of the foetus and does not appear in the foetal blood. Chou and Adolph (1935) estimated that less copper is present in the livers of anaemic infants than in those of normal infants and it appears possible that, either the copper stores have been used in combating the anaemia, or it could be postulated that the defective stores of copper have contributed, in part, to the production of the anaemia.

Josephs (1931), Lewis (1931) and Goldstein (1935), in studies of anaemic infants, all found a more rapid response/

response to combined therapy with iron and copper than to iron alone, and Hutchison (1937) showed that pure inorganic iron was incapable of curing the nutritional anaemia of infants. Fowler and Barer (1940) found, in mild hypochromic anaemias of adults, that the addition of copper sulphate to an inorganic iron salt did not increase haemoglobin regeneration but no note was made whether the iron they used was chemically pure or not. MacKay (1933), in her work upon anaemic infants, concluded that copper deficiency might occur in isolated cases of nutritional anaemia but not in the great majority; she was able to cure most upon iron alone but the iron preparation she used was not chemically pure and she suggested that the poor results obtained with some iron therapy might be due to the iron used being chemically pure. Sheldon and Ramage (1932) have shown that the distribution of copper in iron preparations is inconstant and in some preparations may be quite high.

## MODE OF ACTION OF COPPER.

Copper metabolism and function are not yet understood although several functions have been claimed for the salts of the metal. Smith (1944) found there was an increase in the erythrocytes, in association with the haemoglobin rise after/

after copper therapy, and suggested that copper should be considered a 'stroma substance'; Muntwyler and Hanzal (1933) found a similar response whilst Schultze (1936) states that it is not possible to assign a specific function to copper on erythropoiesis. Hutchison (1938), Elvejhem (1932) and Schultze (1936) consider it has a catalytic effect and converts stored iron into a 'transport form' with its resultant mobilisation and subsequent conversion into haemoglobin. Keil and Nelson (1934 a ) believe that copper may play some part in the absorption of iron from the intestine although the majority of investigators insist that this does not occur and that copper acts upon the iron already present in the body.

Schultze (1939, 1941) has proved, in the iron deficiency anaemia of rats, that the cytochrome oxidase activity is increased when copper is given and that the cytochrome c oxidase activity is low in copper deficient rats but is restored to normal, or above this, on adding copper to the diet. Voegtlin (1931) has shown that the oxidation of crystalline glutathione is increased by copper therapy and he suggests a possible physiological relationship between the two substances; Weissberger (1944) has pointed out that glycolysis may be activated by copper. These findings suggests that copper is connected with the enzyme system of the body.

For practical purposes what is known of the mode of action of copper may be summarised by quoting from a/

a conference on the Therapy of Blood Diseases when Catell (1940) concluded, "Copper has been shown to play an important part in haemoglobin formation. All that is known regarding its mode of action is that in some way it facilitates the conversion of stored iron into haemoglobin. Although it is reasonable to assume that it has a similar function in heamotopoiesis in human beings, it has been impossible to demonstrate this, except possibly in the nutritional anaemias of infancy ..... In adults, it is questionable whether any benefit is derived from the addition of copper to iron therapy".

The foregoing evidence proves the value of copper in the nutritional anaemia. In this present investigation, whilst not nutritional anaemias, it was determined to observe the progress of the blood copper levels during regeneration and to attempt an assessment of the value of copper therapy in these cases.

THE BLOOD VITAMIN 'C'

There is no recognised "normal" blood vitamin 'C' level and the figures obtained by various investigators vary considerably; it is generally accepted, however, that a level of 0.8 to 1.0 mg per 100 cc. is adequate (Roe, Keuther and Zimler, 1947; Farmer and Abt, 1935). Moore et al; (1939) claimed/

claimed that vitamin 'C' increases the absorption of ferric iron from the intestine by causing its reduction into the ferrous state and Powell (1944) has upheld the claim that it helps to increase the haemoglobin level. On the other hand, no connection betwen a low plasma vitamin 'C' level and anaemia was noted by Croft and Snorf (1939). Moore, Bredman, Minnich and Arrowsmith (1940) reported that vitamin 'C' caused a lowering of the serum iron level and suggested that this indicated the utilisation of serum iron to form haemoglobin. The effect of vitamin 'C' on the progress of anaemias is confused and it is only known with certainty that it is essential in the anaemias secondary to Scurvy, or a sub-scurvy state.

In a few cases in this series the blood Vit. 'C' levels were observed and will be discussed later.

## AIMS.

The primary purpose of the investigation was a study of the haemoglobin and non-haemoglobin iron of the serum throughout the period of regeneration subsequent to blood loss. It was thought that it might be possible to shed some light on the following:

1. How did the two irons behave throughout the blood regeneration?
2. Was there any relationship between the two types of iron.

3./

3. If such was noted, did it act as a constant variant?

4. What effect did therapeutic administration of iron have upon the two types?

5. Did Copper added to the therapy have any effect?

6. If so, could anything be said about its mode of action?

## INVESTIGATIONS.

In each case the state of the blood was determined at intervals during regeneration from anaemia. It is unfortunate that, at the time, it was difficult to obtain true cases of nutritional anaemia which would have been ideal for the investigation. Few, however, were seen and, when they did occur, were rarely sufficiently severe to warrant hospital care. It was decided that it was not feasible to treat these patients, nor to investigate them, as out-patients since there is little doubt that the treatments would not be adhered to and the results would be rendered worthless. Cases of nutritional anaemia in infants were available from time to time but it was considered too difficult to obtain the necessary amount of blood required for the investigations.

It was thus decided to fall back on the cases of hypochromic anaemia which were most frequently seen in a medical ward - these were the cases of anaemia secondary to/

to haemorrhage, generally from a peptic ulcer. When obtained early these showed a marked hypochromia though some of them did not run a straight course due to further slight undetectible haemorrhages which are apt to occur.

Every care was taken to notice any such relapse and allow for it, and after reviewing a few cases it appeared that unless such a relapse was serious and easily detectible no appreciable difference was noted in either the haemoglobin or corpuscular levels. Nor was it noticed that the underlying lesion in the gastro-intestinal tract had any definite effect upon iron absorption - as instanced by haemoglobin regeneration.

In all cases under observation, other than the four suffering from a megaloblastic hyperchromic anaemia, the blood loss had been marked. In many instances the patients were very ill on admission to the wards, and for the purposes of this paper quite unsuitable, as haemorrhage was still continuing. Investigation began when the condition of the patient showed, by a steadying of the pulse, examination of the contents of the stomach and intestines, and a cessation in the downward fall of the R.B.C.'s and Haemoglobin that the bleeding had stopped. In order that the effects of therapy might be assessed the basic level of each case was taken as the first blood count/

count done after haemorrhage had ceased and before therapy began. After these primary examinations, succeeding ones were carried out at intervals until completion of the case. Iron therapy was started after the first blood examination generally, and any addition to, or alteration in, the therapy was always begun immediately after a specimen had been obtained. To maintain as much uniformity as possible, the blood specimens, were withdrawn at periods midway between the times of therapy - for instance, where a case was receiving iron in one of its forms at 6 a.m. and at noon, specimens were obtained on each occasion between 9 and 9.30 a.m. In no case was there a predetermined time limit for the length of observation: the cessation of this depended upon the progress of each individual case. Certain cases returned at intervals to have blood examinations done as outpatients.

## HAEMATOLOGICAL INVESTIGATIONS.

The investigation of the blood can be divided into two distinct groups, firstly, a very complete laboratory examination was carried out, and secondly, the blood was tested in the bio-chemical laboratory to determine the non-haemoglobin iron of the blood.

## Clinical Laboratory Investigation.

### Arterial Blood.

Arterial blood was utilised in the following investigations and was obtained as follows:-

After cleaning the patient's thumb with spirit and allowing it to dry, an incision was made with the sharp point of a cleaned Hagedorn needle. The capillary blood so released was utilised for:-

1. Red and White Cell Count:

Throughout the series of cases under examination, the same respective red and white cell pipettes were used; likewise the same counting chamber. The diluting fluids were standardised and filtered prior to use. When it was found that the white cell count was normal, the examination was not done each time, but only at intervals to ascertain that no abnormality was developing. As the investigation was primarily that of the red cells, it was considered unnecessary to count the white corpuscles each time.

2. Haemoglobin Estimation:

This was carried out, the same haemoglobinometer and graduated pipette being used each time. The water used for diluting the blood-acid mixture was glass-distilled. The haemoglobinometer was a Sahli-Wert model, standardised [illegible]ter, and readings were taken both in percentage

Haldane and in grams of haemoglobin per 100 c.c. of blood. Using the usual routine for such investigations, after addition of Acid Hydrochloric Dil: the blood was left for a period of twenty minutes, before the water was added and the colour judged. A reading of 15 gms. per 100 ccs. was found to be equivalent to 100% on the Haldane scale.

3. Blood Films:

Films were made by the cover-slip method and were stained with freshly filtered Leishmann's stain. The films were examined, and the progress of the regeneration checked in this manner.

Venous Blood.

Immediately upon the collection of the above capillary blood specimens a venipuncture was performed. A sterile syringe, which had been washed through in sterile normal saline, was used to withdraw twenty-one cubic centimetres of blood: twenty cubic centimetres of this were at once transferred to a dry test tube containing forty milligrammes of Potassium Oxalate with which the blood was thoroughly mixed. This prevented coagulation and only caused a very slight shrinkage of the corpuscles. This oxalated blood was used to find the Corpuscular Volume, the non-haemoglobin irons, and in the later cases the blood vitamin 'C' content. The one cubic centimetre of unoxalated blood was used to determine the corpuscular fragility.

4. Corpuscular Fragility:

At the first investigation the blood fragility was determined. If it happened to be normal this was not repeated as the one normal result was sufficient to show that the patient was not suffering from a haemopoietic disease in which this factor was increased.

5. Corpuscular Volume:

This is the volume of packed corpuscles per hundred cubic centimetres of whole blood and gives the ratio of cells to serum. When the oxalated blood had been thoroughly mixed to ensure even distribution of the corpuscles, some was removed by micro-pipette, and was transferred to a Wintrobe tube which was filled up to the mark 100. This tube was then "spun" at 2,500 revolutions per minute for one hour, at which time the centrifuge was stopped and the level of the packed corpuscles noted. This gave the corpuscular volume as a percentage of the whole blood, but in order to allow for the slight shrinkage of the cells which resulted from the addition of the Potassium Oxalate the result had to be multiplied by 0.9 to obtain the true answer.

The Mean Corpuscular Volume, Volume Index, Mean Corpuscular Haemoglobin, Mean Corpuscular Haemoglobin Concentration, and Saturation Index were calculated from the above data.

## NON-HAEMOGLOBIN IRON.

### Method of Tompsett, (1934).

6. Whole Blood Iron.

4 c.cs. of oxalated blood were placed in a dry test tube; to this were added 4 c.cs. of glass distilled water and 8 drops of 90 % Thiolacetic acid and the whole thoroughly mixed: 4 c.cs. of 20% Trichloracetic acid was further added and the whole mixed once more. This mixture was filtered through a No. 42 Whatman Filter paper and the protein free filtrate collected in a dry clean test-tube. In this filtrate all non-haemoglobin iron of the whole blood was present, except for a minute quantity which may have been carried down in the protein precipitate. 5 c.cs. of this protein free filtrate were then taken; 2 drops of thiolacetic acid and 1 c.c. of ammonia (Sp. Gr. 0.88) were added, and when mixed, this was compared against a standard in a colorimeter.

The standard was made as follows:-
4 c.cs. of glass-distilled water, 1 c.c. of Iron Alum Standard Solution (containing 0.0117 mg. of Fe per litre) and 2 drops of thiolacetic acid were taken; the whole was mixed and 1 c.c. of Ammonia (0.88 sp. gr.) was added.

Standard/

Standard and unknown were compared in the colorimeter after setting the standard at 20. The reading was then taken and the iron present calculated as follows:-

$$\frac{14.04}{R} = \text{Mgm.\% Fe, where R = Unknown reading.}$$

7. Serum Iron:

5 c.cs. of serum, and an equal volume of trichloracetic acid, with 2 drops of thiolacetic acid were mixed and then centrifuged. 5 c.cs. of the supernant fluid, containing the soluble non-haemoglobin iron of the serum was then pipetted off. To these 5 c.cs. were added 2 drops of thiolacetic acid and 1 cc. of Ammonia (sp. gr. 0.88) and this was compared with a set of standards, freshly made up, as the amounts of iron were too low to allow the use of a colorimeter.

The set of standards were prepared as follows and were placed in test tubes of uniform thickness and diameter:-

| Tube: | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Fe Alum Standard: | 0.1cc | 0.2cc. | 0.3cc. | 0.4cc. | 0.5cc. | etc. |
| Water | 5.ccs. | 5.ccs. | 5.ccs. | 5.ccs. | 5.ccs. | " |
| Thiolacetic Acid. | 2 drops | 2 drops | 2 drops | 2 drops | 2 drops | " |
| Nh4OH. | 1cc. | 1 cc. | 1 cc. | 1 cc. | 1 cc. | " |
| Total Fe Content. | 0.00117 | 0.00234 | 0.00351 | 0.00468 | 0.00585 | mgm. |

Ten such standards were made and the unknown was compared, in a similar test-tube, and matched to the nearest standard or to the nearest two standards when it would have a value in between these two standards.

Now Filtrate ÷ 2 = Plasma (volumetrically)

Should only 4.5 c.cs. be available for the purpose estimation the calculation was performed as follows when the unknown was matched between tubes 4 and 5.

4.5 c.cs. of filtrate = 2.25 c.cs. of serum.

Thus 0.00526 mgm. Fe = Serum Fe in 2.25 c.cs. of serum.

$$= \frac{526}{100,000} \times \frac{100}{1} \times \frac{4}{9} = \frac{2104}{9,000} = 0.23 \text{ mgm Fe /100 cs. serum.}$$

8. Whole Blood Copper.

The estimation of the blood copper was carried out and was used mainly as a check upon the therapeutic administration of copper, and the behavior of the blood copper level during the course of regeneration is discussed later. The estimation was performed by colorimetric method as follows:-

One part of blood was mixed with three parts of water and one part of 20% trichloracetic acid. After thorough mixing the solution was centrifuged and then filtered. 25 ccs. of the filtrate were taken and added to 1 cc. each of Sodium pyrophosphate, Concentrated Ammonia, and/

and Sodium diethyldithiocarbamate and to 5 ccs. of Amyl Alcohol. The mixture was shaken vigorously, centrifuged and the amyl alcohol layer separated off. This was then compared in the colorimeter with the standard.

The standard solution was one which contained 0.01 milligrammes of copper.

The average level of blood copper found in normal individuals is taken to be 132 microgrammes per 100 ccs. of whole blood.

9. Vitmain "C" of the Blood.

The Vitamin "C" of the blood, carried out as a check on therapeutic measures, was not estimated until the last few cases, as it was only then that a reliable method of doing this was devised; a method upon which some reliance could be placed. This was as follows:-

5 c.cs. of oxalated blood were centrifuged after 4 drops of a 4% solution of Sodium Cyanide had been added to it. 2 c.cs. of the serum thus obtained were mixed with 8 c.cs. of a 3% solution of freshly prepared Metaphosphoric acid, which caused a precipitation of the protein. This mixture was then centrifuged and 5 c.cs. of/

of the supernant fluid pipetted off; representing 1 c.c. of the deproteinised serum. This was titrated, by micro-pipette, against 2.6 Dichloro-phenolindophenol and the answer expressed in milligramms of Ascorbic Acid per hundred cubic centimetres of blood.

10. Test Meals.

A test meal was carried out in each case, the main purpose being to ascertain the presence of HCL which is so essential for iron absorption. This was found to be present in all cases of hypochromic anaemia reported.

## DIETS.

All cases, except the megaloblastic anaemias, which were on standard Hospital meals, were put upon a modified Sippy diet. As the iron content of Benger's Food, Horlick's Milk, Cow's Milk and Orange juice, which constitute this diet in the main, is respectively 0.08, 0.08, 0.07 and 0.06 milligrammes of iron per ounce, the patients were on a very low iron diet which would not increase the iron intake to any noticable degree.

## THERAPY.

Cases were started upon iron immediately it was considered that haemorrhage had ceased. They were given half of the normal dose for two days, and then put upon full dosage. The iron used in each case was pure copper-free Ferri et Ammon. Citrate 30 grs. doses t.i.d., Copper Sulphate was added to the therapy at varying intervals, in doses grs. 1/30th., t.i.d. In three cases Ferrous Sulphate in 5 gr. doses t.i.d. was used.

The cases of magoloblast anaemia were treated with iron and copper as well as with Campolon (Bayer) or Reticulogen (Lily). All dates of commencement and types of therapy are noted in the graphs, and tables.

## CASES.

Twenty four cases in all were examined, made up of four pernicious anaemias and twenty hypochromic anaemias resulting one from haemoptysis and nineteen from haematemesis. Of these, only 13 cases of haematemesis and the four pernicious anaemias are brought forward for review. Of the other seven cases one or two ommissions resulted in lack of continuity of the results in three cases; fresh haemorrhage occurred in four cases which was so severe that the treatment had to be recommenced from the beginning.

The succeeding pages are comprised as follows:-

(1) A Description of the Results.

(2) A Comment on the Results

(3) The Summary.

As reference to the various graphs is desirable whilst the following pages are studied, it has been considered expedient to have all the tabulated and graphed data collected together in a seperate appendix. In this manner any graph, mentioned in the text, may be referred to with ease.

The data for each case included in the appendix consists of:-

(1) A brief history of the case.

(2) The laboratory data in tabulated form.

(3) A brief description of the graphed data.

(4) The graphed data.

## RESULTS.

The series of cases herewith investigated fall naturally into two groups. Group 1 consists of thirteen cases of post-haemorrhagic hypochromic anaemia, and Group 2 of four cases of pernicious anaemia - these being cases Nos. 4, 5, 13, and 14. After examining the results of the investigation, Group 1 was found to fall into a further two groups, depending upon whether the cases had been treated with Fe et Ammon. Cit., or with Ferrous Sulphate. The group treated with the ferric salt was the larger, being composed of nine cases and will be called group 1a. Cases Nos. 7 and 11, from this group, are of insufficient duration, or completeness, to warrant a detailed study and thus seven cases of this group are left for discussion. The ferrous salt treated cases are the remaining four cases, Nos. 3, 15, 20 and 22, and will be discussed together as group 1b.

### THE HYPOCHROMIC ANAEMIAS. (Group 1.)

Examination of the graphed data of the eleven cases of hyprochromic anaemia, contained in groups 1a and 1b, reveals the initial serum iron levels to be at the low limits of normal (80 - 100 micrograms %) in three cases, whilst in the other eight the level is well below this, being/

being 60 micrograms % or lower. These findings compare with those of Locke, Main and Rosbach (1932) and Moore et al: (1937 b) who have shown a lowered iron level in the anemias secondary to haemorrhage; they are not however as low as the average of 47 micrograms % found by Powell (1944) in her series of hypochromic anaemias.

Group 1a showed only a slight response to the therapeutic administration of Fe et Ammon. Cit.; one case (No 10) alone showing a rise to 160 micrograms % within fourteen days whilst the majority only reached a level between 80 - 130 micrograms %. In each case the serum iron remained relatively low until copper had been added to the therapy when a rapid upward rise was noted. This rise continued until the serum iron reached a peak from which it more gradually descended towards normal. The height of the rise varied in each case; in one it was only 150 micrograms %, whilst in two others it reached 600 and 450 micrograms respectively. The majority reached a level around 200 micrograms %.

In group 1b there was an immediate response to the administration of the ferrous salt and a rapid upward rise in the serum iron to between 230 - 450 micrograms % in a similar period of fourteen days. The lowest and highest peaks reached during the administration of iron were 230 and 520 micrograms respectively, but within a short space of/

of time they subsided slowly towards normal. The addition of copper to this group of cases had no effect in raising the serum iron except in one case (No. 20) in which the ferrous sulphate was stopped on the seventh day and replaced by Fe et Ammon. Cit., after which the serum iron level still rose for a further three weeks.

The Blood Copper level in each case in group 1 began well above normal, most commencing between 330 and 380 micrograms %, and then the level slowly dropped towards normal. Few cases fell below the 180 micrograms % level which suggests that there were relatively adequate body stores of copper available and these were withdrawn from the storage areas into the blood stream. Despite this, on the addition of copper to the therapy, an upward rise to around the 280 mark resulted within a short space of time and it is suggested that the highest point reached be termed the "absorption peak" as it appears to represent the blood level reached through the absorption of copper from the intestine. This was succeeded by a gradual downward fall once more. The rise following the exhibition of copper shows that absorption of copper does occur even although, as has been suggested, there are relatively adequate initial body stores of the substance and the fall which succeeds the "absorption peak" may indicate that copper is present in the blood

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in sufficient concentration and any excess is being deposited in the body stores.

The demonstration of a high initial blood copper level in these cases agrees with the findings of Sachs, Levine and Fabian (1935) who noticed levels of 220 to 136 micrograms % in both hypochromic and pernicious anaemias. Locke, Main and Rosbach (1932) found high copper levels in several cases of anaemia, whilst Sheldon and Ramage (1931) found spectroscopic evidence which indicated that the greatest increase in the blood copper occurred following haemorrhage. This latter finding may explain why the average initial copper level in this series of post-haemorrhagic anaemias is so much higher than in Sachs' series (sup).

It is interesting to note that in almost every case in group 1a the serum iron and blood copper ratios were in inverse proportion during the first part of observation and until copper was added to the intake. After this both rose until the copper had either reached its "absorption peak", or had risen above 200 micrograms %. when the serum iron began to fall towards normal and was followed in a similar manner by the copper within a short space of time.

In group 1b the blood copper and serum iron curves were inverse almost throughout. The copper showed a steady fall/

fall from the start whilst the iron rose and then, when copper therapy began, the blood copper started to rise and the serum iron showed an immediate fall towards normal. In cases Nos. 15 and 22, as a serum iron level of 120 micrograms was reached the iron curve steadied around this level. This steadying of the iron curve was associated with the copper reaching its "absorption peak" and falling downwards again. It is thus seen in this group that iron and copper behave in a reciprocal relationship until copper has reached its absorption peak and, as has been suggested above, begins to leave the blood for the body storage depots. An inverse relationship between these two substances had been suggested, but not proved, by Sachs et al; (1935).

In all hypochromic cases under review the haemoglobin curve showed a slight fall until iron therapy was commenced and then it showed a slow upward movement. The initial rise amongst the group 1a cases was less than that seen in the group 1b cases and due presumably to the more rapid absorption of the ferrous form of iron. Both groups showed a flattening of the haemoglobin regeneration curve after the primary rise and then an increased upward trend with the addition of copper to the dietary intake and the associated rise in the blood copper. In a few cases the most acute upward rise was noted when the copper "absorption peak" had been reached and the copper curve was falling; as

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has already been pointed out, this is related to a fall in the serum iron levels. In case No.20 a slight fall in the haemoglobin resulted on the 26th day, following a haemorrhage, but was not associated with a fall in the serum iron.

The vitamin 'C' content of the serum was estimated in three cases of hypochromic anaemia. In case No. 18 (group 1a) the serum vitamin 'C' began at a low level of 0.6 mg. per 100 cc. and slowly fell until the vitamin was added to the diet when it rose to 1.9 mg. % within twenty-one days and then fell slowly towards normal. No alteration was noticed between the curves of the serum iron and haemoglobin of this case and those cases not treated with vitamin 'C'. Two cases (No. 20 & 22) in group 1b were given vitamin 'C' in the diet; the serum vitamin 'C' commenced at low levels of 0.7 and 0.4 mg. % respectively and remained around this level until the vitamin was added to the intake when they rose quickly to 2.3 and 1.2 mg. % respectively, only to subside again. The behaviour of the serum iron and haemoglobin curves in these two vitamin 'C' treated cases did not differ in any appreciable manner from those of the other two cases of group 1b which had no vitamin therapy. This neither confirms Powell's observation (1944) that vitamin 'C' enhances haemoglobin formation nor that of Moore et al; (1940) who reported a lowering of the serum iron after vitamin 'C' administration, but

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as this present evidence is based upon only three cases it may be considered insufficient. Both vitamin 'C' treated and untreated cases showed a fall in the serum iron level in group 1 and it is hoped to show subsequently that this is due to the presence of a high blood copper. If this is the case it would mask the effect of vitmain 'C', as both were added to the therapy within a short period of each other and it suggests, presuming Moore's conclusion (sup). to be correct, that both copper and vitamin 'C' have a similar effect upon the serum iron.

There was no uniformity in the response of the red blood corpuscles to the various therapeutic agents in any of the hypochromic cases and the increase in erythrocytes attributed to copper therapy by Smith (1944) was not noted in this investigation.

## THE PERNICIOUS ANAEMIAS. (Group 2.)

Four cases of pernicious anaemia compose this group. The serum iron level began well above normal in every case, the initial ranges varying between 620 and 250 micrograms %, and this was followed by a slow fall towards levels between 100 and 130 micrograms %. Two cases (Nos. 4 and 14) were given combined iron and copper therapy but no upward rise in the serum iron was noted. Cases Nos. 5 and 13 were given iron alone, to which copper was added at a later date, and in each a slight rise in the serum iron occurred after the latter had been given. The serum iron and blood copper in these two cases were below normal before this rise resulted. Moore et al; (1937 b) and Powell (1944) have found similar high initial serum irons in pernicious anaemia, whilst Locke et Al; (1932) found the serum iron rose in cases of pernicious anaemia after liver therapy had begun. This latter finding has not been substantiated in this paper, but the reverse appears to be the case and has already been pointed out by Moore et Al; (1937). The serum iron level was noted to fall in all cases after liver therapy started and this was associated with a rise in the haemoglobin. The serum iron never fell below a level of 100 micrograms % in any of the pernicious anaemias. The high initial iron levels found/

found in pernicious anaemia may be explained as follows - there is no iron deficiency in the body in pernicious anaemia and the body stores are being added to continuously by the iron resulting from the breakdown of the red blood cells which is always proceeding. Very little utilisation of the stored iron occurs in this disorder due to the diminished red cell formation. It is possible to visualise, under such conditions, that the body storage depots become saturated and an overflow occurs into the peripheral blood stream with a resulting high serum iron. When red cell regeneration results from the administration of liver extract the serum iron falls due to its conversion into haemoglobin, and at the same time stored iron is also being converted into transport iron and then being as rapidly converted into haemoglobin. A fall in the serum and stored iron thus results, depending upon the amount of haemoglobin required, and as a result when iron is added to the intake at a later date a little of it is absorbed. This at first results in a slight rise in the serum iron, followed by a fall as this excess iron is deposited in the partially depleted body stores. The fact that the serum iron did not fall below 100 micrograms % in any of the cases shows that the body stores were not completely depleted - otherwise a lower level would have been expected.

The blood copper levels of this group varied considerably. In case No. 5 it commenced at 330 micrograms/

micrograms % and fell slowly to 50 micrograms %, only to rise sharply after the addition of copper therapy; it followed a similar course to that found in the hypochromic anaemias. Two cases (Nos. 4 and 14) also revealed a raised initial level although they were lower than those found in the hypochromic anaemias. Case No.4 began at 190 micrograms %, fell at once to 120 micrograms %, only to rise more slowly to 180 micrograms % after the addition of iron and copper. Case No. 14 started at a level of 195 micrograms % and remained at this level until the 37th day when it rose to 260 micrograms %, eight days after iron and copper therapy began. Case No. 13 had a commencing level of 70 micrograms % and did not become raised above 90 micrograms % until the forty-fourth day when it rose to 180 micrograms %, some six days after copper was added to the diet. The most marked rise in the blood copper level following copper therapy, was seen in case No. 13 which had a low blood copper prior to copper therapy - presumably indicating a low body store of copper - and in this case there was a secondary rise in the serum iron as the blood copper approached its "absorption peak".

With the rise in the blood copper, subsequent to copper therapy, all cases showed a continued, or accentuated, downward fall in the serum iron levels.

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An inverse relationship was not definitely discernible between the serum iron and copper curves, although such almost occurred in case No. 13; a relationship, however, was present and will be discussed later. The initial blood copper levels were higher than normal in three cases, although they could not compare with the height seen in the hypochromic group. In one the level was well below normal. These findings are presumably comparable with those of Sachs et Al; (1935), who found high initial levels in pernicious anaemias.

The haemoglobin curves in all cases were almost in inverse relationship to the serum iron curves; regeneration being most rapid when the serum iron fell rapidly and slowing up as the serum iron fall steadied. This occurred in less marked degree in the hypochromic group of cases and was briefly mentioned above. In case No. 13, which showed a consistently low blood copper, the haemoglobin rose only to 9.7 g % until copper therapy began when it rose to 12.5 g %. In cases Nos. 4 and 5 the haemoglobin increase was seen to slow up when the blood copper fell below 150 micrograms %, despite moderately high serum iron levels. All cases in this series showed a disappointing haemoglobin response to treatment and only reached levels of 12 - 12.5 g % when dismissed/

dismissed from hospital. None reported back for observation, as was requested, and it is felt that a more complete picture would have resulted had they done so.

The blood vitamin 'C' level was low in all cases investigated and rose with the therapeutic administration of the vitamin. It has not been possible to determine any relationship between vitamin 'C' and the other data plotted in this group.

## COMMENT.

The present investigation has confirmed the findings of several workers and these have been mentioned already when the graphed results were described. To recapitulate briefly, it has been ascertained that:-

(1) The initial serum iron levels are low in hypochromic, and high in pernicious anaemias.

(2) The initial blood copper levels are high in both types.

(3) In hypochromic anaemias treated with an easily assimilable iron salt there is an initial rise in the serum iron and a fall in the blood copper.

(4) In hypochromic anaemia therapeutic administration of copper enhances haemoglobin formation.

(5) No definite increase in erythropoiesis can be attributed to copper therapy.

(6) No rise in the haemoglobin, or decrease in the serum iron level, was found after the exhibition of Vitamin 'C'.

(7) In pernicious anaemia, the serum iron level falls after the administration of liver extract.

The results of this investigation suggest that copper has two important functions and it is presumed that the/

the following is the proceedure during haemoglobin regeneration resulting from iron and copper therapy. When copper and a ferrous salt are given the iron is absorbed without the aid of, but along with, the copper. When copper and a ferric salt are administered, iron is absorbed with the copper and as a result of the catalytic effect exerted by it. In both cases, when sufficient copper has been absorbed and a 'critical level' reached in the blood, the catalytic function of copper results in any excess serum iron being converted into haemoglobin. The evidence in favour of this dual role of copper may be considered as follows.

The role of copper in haemoglobin regeneration.

It has been claimed that copper is responsible for the mobilisation of stored iron into the serum (Elvejhem, 1932; Hutchison, 1938; Schultze, 1936), but the results of the present investigation do not bear this out. Examination of pernicious anaemia cases has revealed that both the initial serum iron and blood copper levels are high, and it might be supposed that the serum iron is high because of this 'mobilising function' which is attributed to copper. In the hypochromic group of cases, however, which were secondary to haemorrhage and where it seems reasonable to assume/

assume that the body iron stores were not deficient in stored iron, the initial serum iron levels were low and remained so for many days even in the presence of raised blood copper levels. If copper possessed the function of mobilising stored iron a high iron level might be expected in the presence of this excess blood copper. It may be suggested that mobilisation was proceeding but the iron, mobilised from the body stores, was being so rapidly converted into haemoglobin that no appreciable elevation in the serum iron might be noted; this postulates a rapid rise in the haemoglobin and no such rise has been found. Therefore, in the absence of evidence of a mobilisation function of copper, it is considered that the initial high serum iron level in pernicious anaemia is due to the body stores being so saturated with iron that there is a resulting overflow of this into the serum which the body does not utilise in the absence of the liver factor.

If copper does not mobilise iron from the body stores what is the significance of a high blood level in both pernicious and hypochromic anaemias? In pernicious anaemia an inverse relationship is noted between the serum iron and the haemoglobin curves, whilst there is a definite relationship between the serum iron and the blood copper levels. A more complex relationship is discernible between all three curves in hypochromic anaemias. The less complicated picture

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in pernicious anaemia is explained by the fact that absorption of iron from the intestine does not occur in the initial stages as the storage depots are well saturated with iron.

In the pernicious anaemia cases of group 2. an initial fall in the serum iron, and a proportionate rise in the haemoglobin, occurs upon the injection of liver extract. This suggests that there is a conversion of serum iron into the haemoglobin which is required for the new and increased number of red blood corpuscles resulting from the 'liver stimulated' erythropoiesis. As the rate of fall of the serum iron decreases there is a corresponding slowing in haemoglobin regeneration indicating, presumably, that less serum iron is being converted into haemoglobin. Again, when the serum iron has fallen below its average normal level, haemoglobin formation slows markedly indicating, this time, that there is little serum iron available for conversion into the organic form. It thus appears that the amount of serum iron available is one of the factors upon which haemoglobin formation depends, whilst the rate of regeneration is proportionate to the rapidity with which the serum iron level falls. Examination of the serum iron and blood copper curves suggests that this rate of subsidence in the serum iron may be related to the blood copper level. It is noticed that, while the blood copper is above a level

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of 150 - 200 micrograms %, there is a rapid fall in the serum iron which slows appreciably if the blood copper falls below this level, which, it is suggested, might be termed the 'critical level' of copper during recovery from anaemia. Once copper is added to the therapy, in cases showing this feature, and the blood copper rises above this 'critcal level', an increased rate of fall in the serum iron occurs again.

The picture presented by the hypochromic cases is different but this appears only to be due to the low initial serum iron; haemoglobin regeneration being slow whilst the serum iron remains below its average normal level, even in the presence of a raised copper level. In the ferrous treated cases (group 1b), after iron is absorbed from the intestine, the serum iron level rises rapidly to its 'peak level' and the picture from then on is comparable with that seen in pernicious anaemia. With a blood copper above the 'critical' level, there is a rapid fall in the serum iron from its 'peak; the higher the blood copper rises, the greater the accentuation of the serum iron fall. As the serum iron 'peak' in all but case No. 20, which will be discussed later, coincides with the start of copper therapy and a resulting rise in the blood copper, this fall is marked and continuous. Rises in the haemoglobin, proportionate to the falls in the serum iron, occur in this hypochromic group as in the pernicious anaemia/

anaemia group. Similar features are discernible in group 1a but are less obvious and are complicated by factors in absorption which will be discussed later.

The above evidence suggests that two factors are essential for continued haemoglobin regeneration, namely, a serum iron and a blood copper level which remain at, or above, their respective normal levels. It is felt moreover, that evidence is presented of the direct conversion of serum iron into haemoglobin and that copper plays an essential part in assisting this to occur. It is not possible, however, to clarify its mode of action in this respect and one can only fall back upon the previous suggestions that it has a catalytic function (Moore, 1944).

The serum iron level has been shown to be of importance in haemoglobin formation and it is known that its level depends upon a balance between, on the one side, the iron abstracted from the body stores, that absorbed from the intestine and, in lesser degree, that which results from red cell catabolism and on the other side, iron deposited from the serum into the body depots and that converted into haemoglobin. In non-nutritional hypochromic anaemia, where the necessity for haemoglobin formation is paramount, an increased demand for serum iron results

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and is met primarily by the abstraction of iron from the body stores. Later, when available supplies of iron are present in the intestine, the serum iron level will depend mainly upon the absorption of this iron which will have to serve two purposes - that of forming haemoglobin and, that of restocking the depleted iron stores of the body.

The role of copper in the absorption of iron.

It is believed that this investigation clarifies certain features in the absorption of iron in hypochromic anaemias. In the following assessment of the intestinal absorption of iron it should be remembered that, as free hydrochloric acid is present in the gastric contents of all the cases under review, one factor is excluded which might have resulted in individual variations in the results.

The serum iron levels are initially low in all the cases of hypochromic anaemia, but after the start of iron therapy a totally different picture is noted in the serum iron behaviour between the cases treated with a ferrous salt and those treated with a ferric salt. In the ferrous treated group an immediate rapid rise in the serum iron occurs,/

occurs, and continues until a 'peak level' is reached; this finding is only further proof of the ready absorption of ferrous salts (Moore et Al; 1944). In the ferric treated group the serum iron level shows a slow and slight response to iron therapy, suggesting that only a partial reduction of salt occurs in the intestine and poor absorption results. It has been shown that absorption of the ferric salt is enhanced by the presence of a reducing agent in the intestine (Powell, 1944; Moore, 1939), and it is noteworthy that an increased absorption, as indicated by an immeidate rise in the serum iron, occurred on the addition of copper to the diet in every case. Evidence has been presented above to show that this rise is not due to the mobilisation of iron stores and hence must be due to the increased absorption of iron.

It would thus appear that copper aids in the absorption of the ferric form of iron from the intestine; a function which had previously been suggested by Keil and Nelson (1934) but which has been disputed by other investigators who have studied this subject. The mode of action cannot be ascertained from the work in the present paper but it is suggested that, whilst copper is not in itself likely to effect the reduction of ferric iron, it may act as a catalytic agent which either renders ferric iron

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more susceptible to reduction, or may convert some substance present in the intestine into a reducing agent which will act upon the iron.

In case No. 20 ferrous iron was given for seven days and then followed by ferric iron and copper. Little difference is noted between the rate of serum iron increase during the two stages of therapy and this shows that the absorption of the ferric iron - copper combination closely approximates that of the ferrous iron. Once the blood copper has passed the 'critical level', which shows slight variation between 150 - 200 micrograms % in individual cases, the serum iron drops and haemoglobin regeneration increases. In this case copper may be seen to exert its double role - that of a catalyst enabling the absorption of ferric iron from the intestine and that of a catalyst either aiding, or causing, the conversion of serum iron into haemoglobin.

## S U M M A R Y.

1. The literature pertaining to iron and copper metabolism has been reviewed.

2. It appears necessary that the serum iron and blood copper remain at, or above, their respective average normal levels for continued haemoglobin regeneration.

3. The present investigation suggests that copper has no effect upon the mobilisation of the stored iron in the body, but assists haemoglobin regeneration by aiding (a) the absorption of ferric iron from the intestine and (b) the conversion of serum iron into haemoglobin.

4. It is suggested that copper acts in the above two instances in the role of a catalyst.

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# A P P E N D I X.

## Results of Blood Examinations.

The results are appended in the following pages and consist of :-

1. A brief history of each case.
2. A table of the results of the investigation.
3. A graph of some of the results.
4. An attempted interpretation of the graphs along the lines of the "aims" as laid down at the outset of the investigation.

## Abbreviations.

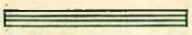
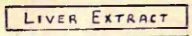
The following abbreviations are used in the tabulation of the results, or the graphs, of the blood examinations in each case.

| | | |
|---|---|---|
| R.B.C. | = | Red Blood Corpuscles (in millions) |
| Hb % | = | Haemoglobin percentage (Haldane) |
| C.I. | = | Colour Index |
| Hb gms. | = | Haemoglobin in grammes per 100 ccs. |
| C.V. | = | Corpuscular Volume |
| M.C.V. | = | Mean Corpuscular Volume. |
| V.I. | = | Volume Index. |
| M.C.H.C. | = | Mean Corpuscular Haemoglobin Concentration. |
| S.I. | = | Saturation Index. |
| W.B. Fe. | = | Whole Blood Iron. |
| S. Fe. | = | Serum Iron. |
| W.B. Cu. | = | Whole Blood Copper. |
| M.C.H. | = | Mean Corpuscular Haemoglobin. |
| mcgs. | = | Microgrammes per 100 ccs. Blood or serum. |
| Vit 'C' | = | Vitamin C in milligrammes per 100 ccs. blood. |

In The Graphs:

| | | |
|---|---|---|
| R.B.C. | = |  |
| Hb gms. & % | = |  |
| C.V. | = |  |
| S.Fe. | = |  |
| W.B. Cu. | = |  |
| Vit 'C' | = |  |

Duration of Therapy.

| | | |
|---|---|---|
| Iron Therapy | = |  |
| Iron + Cu " | = |  |
| Vit 'C' " | = |  |
| Liver " | = |   |
| Combined " | = |  |

group 1a.

Hypochromic Cases treated with Fe et Ammon.

Cit. and Copper. Comprising cases

numbered.

1, 2, 6, 7, 8, 9, 10, 11, 18.

## CASE NO.1.

## HISTORY.

### Hypochromic Anaemia (Seq. to Acute Peptic Ulcer.)

This patient, a female, age 53 years, was admitted to Hospital after an acute attack of abdominal cramp accompanied by a considerable haematemesis. She had no history of previous gastric trouble. Two further haematemeses occurred after admission, but by the 4th day her stools were only faintly positive to chemical tests, and the blood investigation was commenced. General systemic examination revealed no abnormality but X-ray reported "a query acute peptic ulcer". Her degree of anaemia was only moderate and she made an uncomplicated recovery and was discharged from Hospital in forty four days.

CASE NO. 1. FEMALE. Age. 53 yrs. 27.10.38 - 15.12.38.

| DAYS | 1st | 10th | 14th | 19th | 25th | 32nd | 37th | 42nd | 48th |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 27.10 | 7.11 | 11.11 | 16.11 | 22.11 | 29.11 | 4.12 | 9.12 | 15.12 |
| R.B.C.(Mils) | 3.67 | 4.37 | 4.30 | 5.04 | 5.00 | 4.78 | 4.90 | 4.80 | 5.30 |
| Hb% | 73 | 68 | 72 | 74 | 80 | 81 | 86 | 90 | 96 |
| Hbgms. | 10.95 | 10.2 | 10.8 | 11.1 | 12 | 12.15 | 12.9 | 13.5 | 14.4 |
| C.V. | 32.5 | 30.8 | 30.8 | 38.7 | 41.8 | 44.7 | 42.0 | 43.0 | 45.0 |
| M.C.V. | 88.56 | 70.48 | 71.63 | 76.79 | 83.60 | 93.51 | 85.71 | 89.58 | 84.91 |
| V.I. | 1.03 | 0.82 | 0.83 | 0.89 | 0.97 | 1.09 | 1.0 | 1.04 | 0.99 |
| M.C.H. | 29.84 | 23.34 | 25.12 | 22.02 | 24.0 | 25.42 | 26.33 | 28.13 | 27.17 |
| M.C.H.C. | 33.69 | 33.12 | 35.06 | 28.68 | 28.71 | 27.18 | 30.71 | 31.40 | 32.0 |
| S.I. | 0.99 | 0.97 | 1.03 | 0.84 | 0.84 | 0.80 | 0.90 | 0.92 | 0.94 |
| W.B.Fe. | 1.59 | 1.08 | 1.07 | 0.76 | 0.45 | 0.94 | 0.99 | 1.56 | 0.83 |
| S.Fe. | 0.09 | 0.08 | 0.08 | 0.14 | 0.15 | 0.13 | 0.11 | 0.10 | 0.10 |
| W.B.Cu. | 0.27 | 0.26 | 0.25 | 0.22 | 0.17 | 0.29 | 0.28 | 0.25 | 0.25 |

Fe et Ammon.Cit grs 30 t.i.d. from 28.10.38

+ Cu Sulph. gr 1/30 t.i.d. from 16.11.38.

## CASE NO.1.

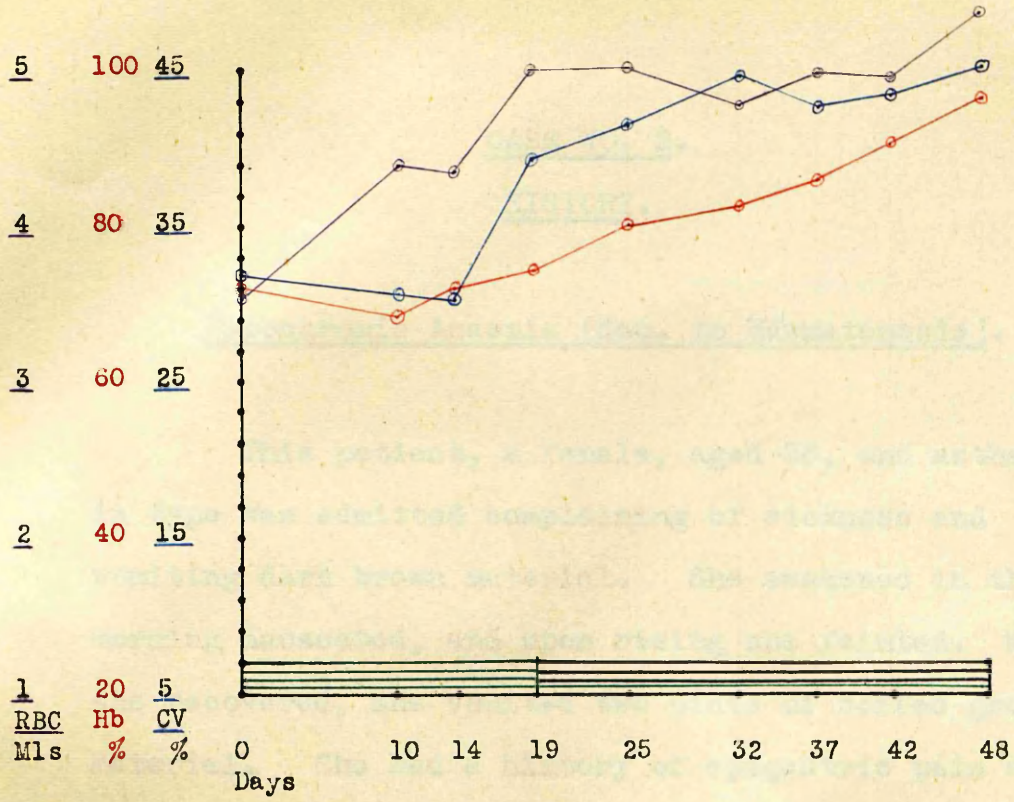
### Interpretation of Graphed Data.

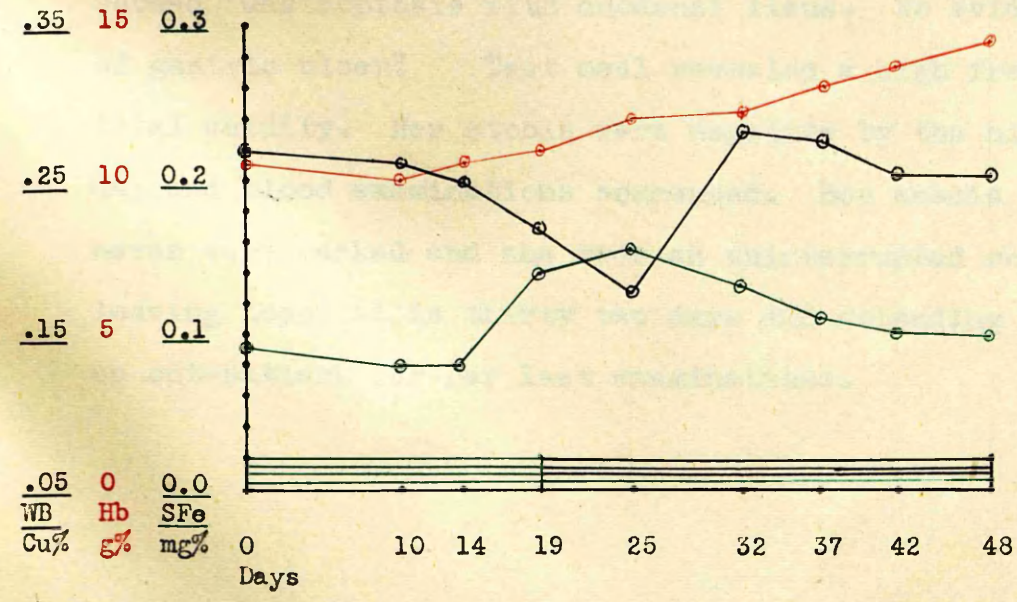
1. The Serum Fe was noted to begin low and then a rise was seen. This rise was proportionately greater than that seen in the Hb. Fe, and it fell again after the 25th day.

2. Hb. iron rose slowly to begin with, but, after the serum Fe had reached its height it rose a little more rapidly and another increase was noted after the blood Cu had reached its peak.

3. The Blood Cu level began high at 270 mcgs and fell steadily towards the normal 150 mcgs level but, with the administration of therapeutic copper, it rose to a level higher than its original one and then more slowly began to subside. The most rapid increase in haemoglobin occurred after the blood copper had reached its height: The serum Fe also achieved its height after copper therapy had commenced.

4. No definite relationship in the two iron curves was noted until the latter half of the therapy when "mirror" images were noted.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 10 14 19 25 32 37 42 48
Days


.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 10 14 19 25 32 37 42 48
Days

CASE No. 1.

## CASE NO. 2.

## HISTORY.

### Hypochromic Anaemia (Seq. to Haematemesis).

This patient, a female, aged 25, and asthenic in type was admitted complaining of sickness and vomiting dark brown material. She awakened in the morning nauseated, and upon rising she fainted. When she recovered, she vomited two pints of coffee ground material. She had a history of epigastric pain of two years duration and had kept upon a low diet. General examination revealed no abnormality. X-ray showed "Gastroptosis with duodenal ileus. No evidence of gastric ulcer". Test meal revealed a high free and total acidity. Her stools were negative by the ninth day and blood examinations commenced. Her anemia was never very marked and she made an uninterrupted recovery leaving hospital in thirty two days and attending as an out-patient for her last examinations.

CASE NO. 2. FEMALE. Age 25 yrs. 4.11.38 - 12.12.38.

| DAYS | 1st | 5th | 9th | 14th | 18th | 22nd | 28th | 33rd | 39th |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 4.11 | 8.11 | 12.11 | 17.11 | 21.11 | 25.11 | 1.12 | 6.12 | 12.12 |
| R.B.C.(Mils) | 3.58 | 3.80 | 4.00 | 3.95 | 4.18 | 4.51 | 4.48 | 4.70 | 5.12 |
| Hb% | 68 | 63 | 67 | 64 | 79 | 75 | 78 | 84 | 93 |
| Hbgms. | 10.2 | 9.45 | 10.0 | 9.6 | 11.85 | 11.25 | 11.7 | 12.6 | 13.95 |
| C.V. | 29.8 | 26.0 | 25.5 | 28.3 | 32.6 | 34.0 | 37.0 | 42.0 | 44.0 |
| M.C.V. | 83.24 | 68.42 | 63.75 | 71.64 | 77.99 | 75.39 | 82.59 | 89.37 | 85.93 |
| V.I. | 0.97 | 0.80 | 0.74 | 0.83 | 0.91 | 0.88 | 0.96 | 1.04 | 1.0 |
| M.C.H. | 28.49 | 24.89 | 25.0 | 24.30 | 28.35 | 24.94 | 26.12 | 26.81 | 27.25 |
| M.C.H.C. | 34.23 | 36.35 | 39.22 | 33.92 | 36.35 | 33.10 | 31.62 | 30.0 | 31.70 |
| S.I. | 1.0 | 1.07 | 1.15 | 1.0 | 1.07 | 0.97 | 0.93 | 0.88 | 0.93 |
| W.B.Fe. | 1.33 | 1.24 | 1.48 | 0.70 | 0.40 | 0.54 | 1.04 | 1.46 | 1.29 |
| S.Fe. | 0.08 | 0.06 | 0.08 | 0.14 | 0.10 | 0.12 | 0.22 | 0.20 | 0.18 |
| W.B.Cu. | 0.30 | 0.29 | 0.19 | 0.19 | 0.17 | 0.21 | 0.28 | 0.30 | 0.26 |

↑ Fe et Ammon. Cit. grs 30 t.i.d. from 9.11.38

† ↑ Cu Sulph. gr 1/30 t.i.d. from 20.11.38

## CASE NO. 2.

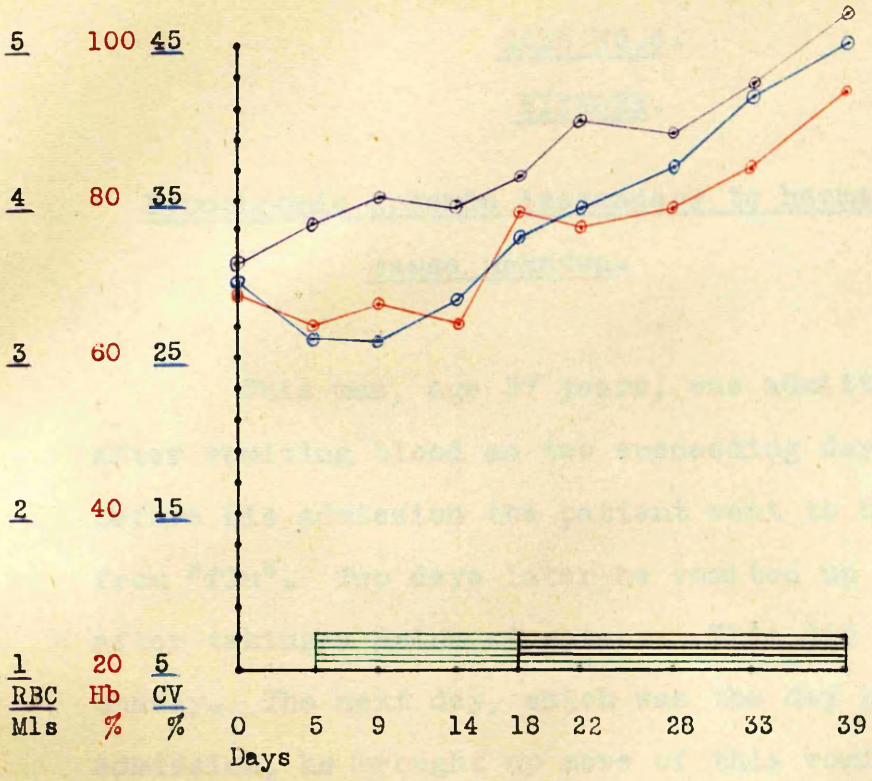
### Interpretation of Graphed Data.

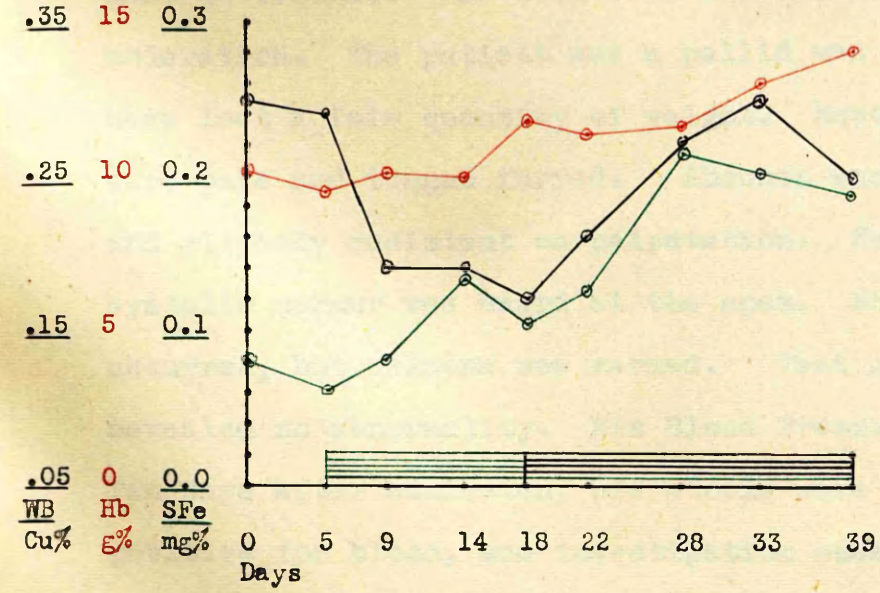
1. The serum Fe began at a low level of 80 mcgs and fell to 60 mcgs before iron therapy began. It then rose slowly until Copper was added therapeutically when it rose more rapidly to reach 200 mcgs, after which it slowly subsided.

2. Hb. iron rose only slowly to begin with, but after the serum Fe had reached its height, it rose a little more rapidly, and another increase was noted after the blood Cu had reached its peak.

3. Blood Cu commenced high at 300 mcgs and fell sharply to a level of 190 mcgs. After copper therapy started it rose for two weeks to 300 mcgs and then began to fall. The most marked rise in haemoglobin occurred after the Cu had risen to above 250 mcgs. The most rapid increase in serum Fe occurred after the start of Cu therapy.

4. No definite relationship was noted, although the two iron graphs appeared to be almost complementary, or "mirror" images, in the latter half and after copper therapy began. After each noticeable rise in serum Fe there was a rapid increase in the Hb., whereas, after any sharp Hb. rise there was a fall in the serum Fe.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 5 9 14 18 22 28 33 39
Days


.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 5 9 14 18 22 28 33 39
Days

CASE No. 2.

## CASE NO.6.

## HISTORY.

Hypochromic Anaemia (secondary to haematemesis - cause unknown.

This man, age 37 years, was admitted to Hospital after vomiting blood on two succeeding days. Four days before his admission the patient went to bed suffering from "flu". Two days later he vomited up some material after taking a drink of water. This did not worry him unduly. The next day, which was the day prior to his admission, he brought up more of this vomitus and after doing so fainted. There was no history of previous gastric trouble. He took both alcohol and tobacco in moderation. The patient was a pallid man and appeared to have lost a fair quantity of weight. Mucous membranes were pale and tongue furred. Abdomen was rather full and slightly resistant on palpatation. Heart: A blowing systolic murmur was heard at the apex. No further vomiting occurred, but melaena was marked. Test meal and X-ray revealed no abnormality. His Blood Pressure was 120/70. Ten days after admission, his stools were only faintly positive for blood, and investigation commenced. He made an uninterrupted recovery and was discharged from Hospital forty four days after admission.

CASE NO. 6. MALE. Age 57 yrs. 4.1.39 - 27.2.39.

| DAYS | 1st | 7th | 13th | 20th | 34th | 41st | 48th | 55th |
|---|---|---|---|---|---|---|---|---|
| DATE. | 4.1 | 10.1 | 16.1 | 23.1 | 6.2 | 13.2 | 20.2 | 27.2 |
| R.B.C.(Mils) | 3.20 | 3.87 | 3.72 | 4.26 | 4.47 | 4.59 | 4.80 | 5.20 |
| Hb % | 59 | 52 | 57 | 72 | 83 | 85 | 92 | 96 |
| Hbgms | 8.85 | 7.80 | 8.55 | 10.8 | 12.45 | 12.75 | 13.8 | 14.4 |
| C.V. | 26 | 29 | 32 | 39 | 40 | 44 | 44 | 42 |
| M.C.V. | 81.25 | 74.94 | 86.02 | 91.55 | 89.48 | 95.86 | 91.67 | 80.77 |
| V.I. | 0.94 | 0.87 | 1.00 | 1.06 | 1.04 | 1.11 | 1.07 | 0.94 |
| M.C.H. | 27.66 | 20.16 | 22.98 | 25.35 | 27.85 | 27.78 | 28.75 | 27.69 |
| M.C.H.C. | 34.04 | 26.9 | 26.72 | 27.69 | 31.13 | 28.98 | 31.36 | 34.29 |
| S.I. | 1.0 | 0.79 | 0.79 | 0.81 | 0.92 | 0.85 | 0.92 | 1.0 |
| W.B.Fe | 0.74 | 0.69 | 0.78 | 0.82 | 1.22 | 0.86 | 0.74 | 0.80 |
| S.Fe | 0.06 | 0.06 | 0.08 | 0.12 | 0.10 | 0.10 | 0.18 | 0.16 |
| W.B.Cu | 0.33 | 0.28 | 0.22 | 0.21 | 0.20 | 0.28 | 0.28 | 0.24 |

↑ Fe et Ammon. Cit. grs 30 t.i.d. from 13.1.39

‡ Cu Sulph grs 1/30 t.i.d. from 25.1.39

## CASE NO. 6.

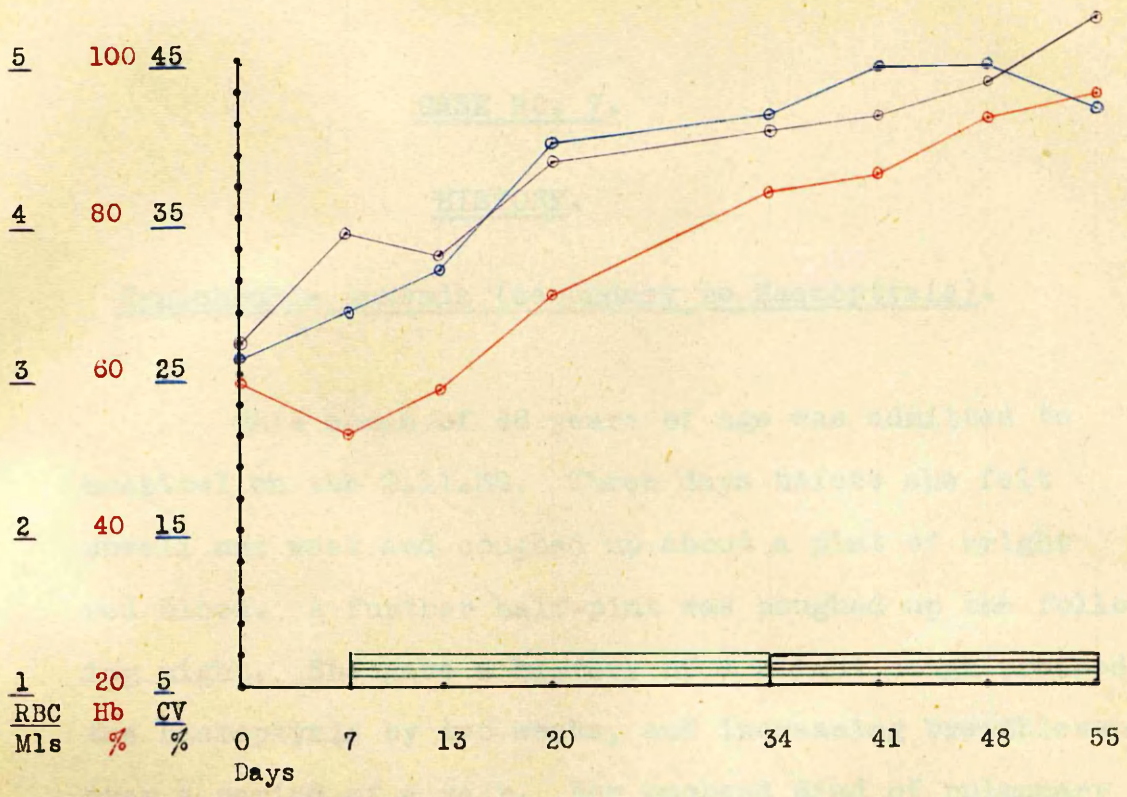
### Interpretation of Graphed Data.

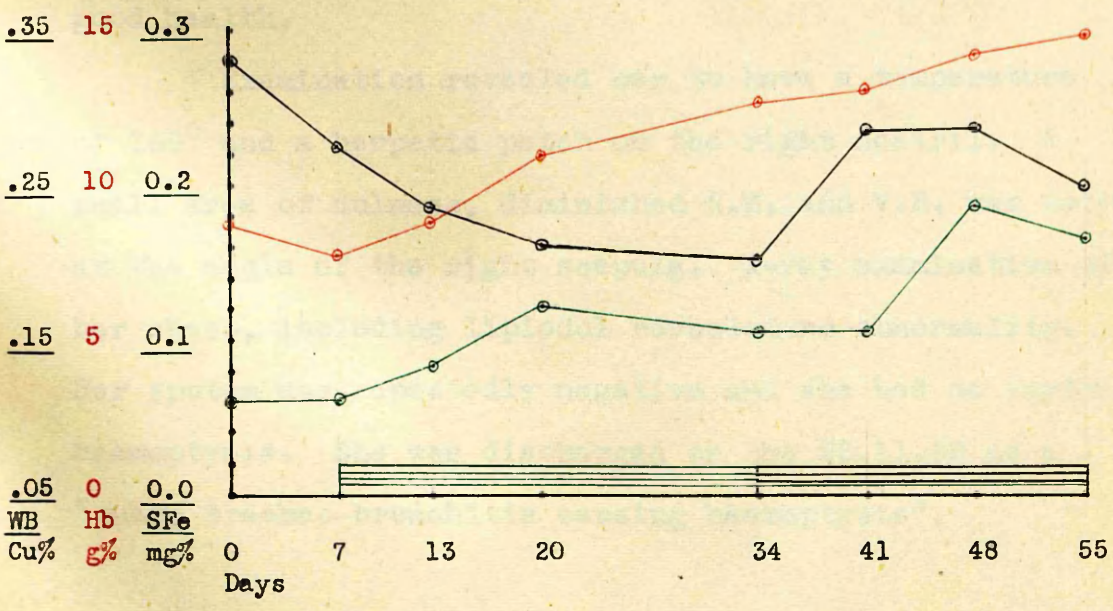
1. Serum Fe, which was low to begin with, rose after the start of iron therapy but, after reaching 120 mcgs, remained between this and 100 mcgs until copper was given in addition. It then rose quickly to 180 mcgs and more slowly subsided towards normal. Its peak was reached after the blood Cu had reached its highest point.

2. The Hb, curve showed a slow steady rise after iron therapy was started and following an initial slight fall. The rate of regeneration then slowed until copper was given with the iron, when it rose again after the blood Cu and serum Fe had reached their peaks.

3. The blood Cu began high at 330 mcgs. and fell steadily during the exhibition of iron to 200 mcgs. but the week after copper therapy began, it rose rapidly to 280 mcgs. It was after this rapid rise in the copper level that the serum iron rose to its greatest height.

4. No relationship was noted between the two iron curves.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 7 13 20 34 41 48 55
Days


.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 7 13 20 34 41 48 55
Days

CASE No. 6.

## CASE NO. 7.

### HISTORY.

Hypochromic Anaemia (secondary to Haemoptysis).

This woman of 48 years of age was admitted to hospital on the 2.11.38. Three days before she felt unwell and weak and coughed up about a pint of bright red blood. A further half-pint was coughed up the following night. She gave a history of a slight cough preceeding the haemoptysis by two weeks, and increasing breathlessness over a period of a year. Her husband died of pulmonary tuberculosis twenty years ago and she had a son who was in good health.

Examination revealed her to have a temperature of 100° and a herpetic patch on the right nostril. A small area of dulness, diminished R.M. and V.R. was noted at the angle of the right scapula. X-ray examination of her chest, including lipiodol revealed no abnormality. Her sputum was repeatedly negative and she had no further haemoptysis. She was discharged on the 23.11.38 as a "query tracheo-bronchitis causing haemoptysis".

CASE NO. 7. FEMALE. Age 48 yrs. 5.11.38 - 19.11.38.

| DAYS | 1st | 5th | 11th | 15th |
|---|---|---|---|---|
| DATE. | 5.11 | 9.11 | 15.11 | 19.11 |
| R.B.C.(Mils) | 3.51 | 3.99 | 3.73 | 4.21 |
| Hb % | 51 | 52 | 50 | 55 |
| Hb gms | 7.65 | 7.80 | 7.50 | 8.25 |
| C.V. | 26.5 | 27 | 27 | 35 |
| M.C.V. | 75.50 | 67.67 | 72.39 | 83.14 |
| V.I. | 0.88 | 0.79 | 0.84 | 0.97 |
| M.C.H. | 21.79 | 19.55 | 20.11 | 19.60 |
| M.C.H.C. | 28.87 | 28.89 | 27.78 | 23.57 |
| S.I. | 0.85 | 0.85 | 0.82 | 0.69 |
| W.B.Fe | 0.96 | 1.16 | 0.33 | 0.66 |
| S.Fe | 0.04 | 0.08 | 0.16 | 0.10 |
| W.B.Cu | 0.30 | 0.24 | 0.20 | 0.20 |

↑ Fe et Ammon Cit grs 30 t.i.d. from 10.11.38

↑ + Cu Sulph gr 1/30 t.i.d. from 14.11.38.

## CASE NO. 7.

### Interpretation of Graphed Data.

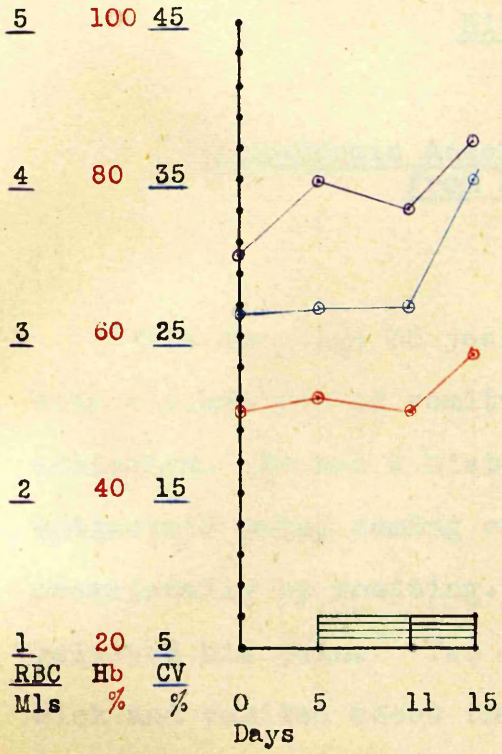
1. Serum Fe began low and rose rapidly to 160 mcgs and this curve was in inverse relationship to that of the blood Cu.

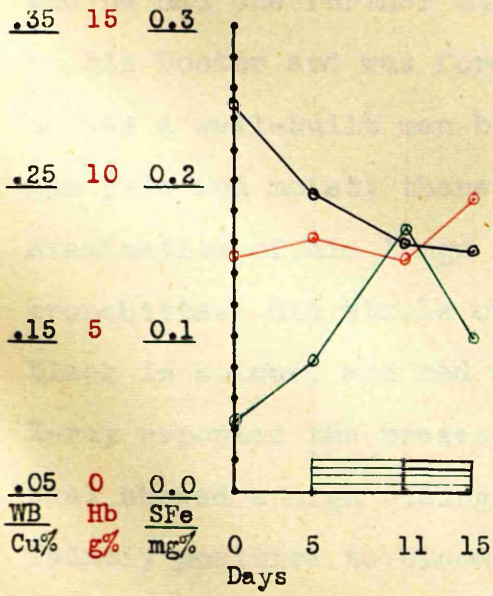
2. Hb. iron remained more or less steady until four days after copper therapy began when it started to rise.

3. The blood Cu level was high at the outset and steadily fell, slowing up after copper therapy was started.

4. The two iron curves are almost "mirror" curves.

5. This case is of such short duration that no valuable data can be obtained from it.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 5 11 15
Days


.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 5 11 15
Days

CASE No. 7.

CASE NO. 8.

HISTORY.

Hypochromic Anaemia (secondary to Haematemesis from Duodenal Ulcer.)

This man, age 35 years, was admitted to Hospital with a complaint of vomiting blood for two days prior to admission. He had a history of two years post prandial epigastric pain, coming on about two hours p.c. and relieved occasionally by vomiting. Alkaline mixture generally relieved his pain. Two days before admission he felt sick and vomited about three quarters of a pint of brown bitter material. He went to work but felt weak and faint. When at stool he noticed there was blood in his motions and he had one further attack of vomiting. He reported to his Doctor and was forwarded to Hospital. On examination he was a well-built man but was extremely pallid. Skin was pale and moist; there was no abdominal tenderness. Examination of his lungs revealed him to have a purulent bronchitis. His stools on examination were fluid and black in colour, and had a strong positive benzidene reaction. X-ray reported the presence of a Duodenal Ulcer, and a test meal showed a high rising curve. His stools, were only faintly positive to blood on the sixth day, and general blood investigation commenced. He improved rapidly and was discharged from Hospital forty four days after admission, with a normal blood count.

CASE NO. 8. MALE. Age 35 yrs. 4.1.39 - 27.2.39.

| DAYS | 1st | 7th | 20th | 34th | 41st | 45th | 55th |
|---|---|---|---|---|---|---|---|
| DATE. | 4.1 | 10.1 | 23.1 | 6.2 | 13.2 | 17.2 | 27.2 |
| R.B.C.(Mils) | 2.00 | 3.20 | 4.14 | 4.33 | 5.43 | 5.30 | 5.50 |
| Hb % | 33 | 41 | 63 | 72 | 77 | 86 | 92 |
| Hbgms | 4.95 | 6.15 | 9.45 | 10.8 | 11.55 | 12.9 | 13.8 |
| C.V. | 19 | 20 | 31 | 38 | 45 | 44 | 45 |
| M.C.V. | 95.00 | 62.50 | 74.88 | 87.76 | 82.87 | 83.02 | 81.82 |
| V.I. | 1.10 | 0.73 | 0.87 | 1.02 | 0.96 | 0.97 | 0.95 |
| M.C.H. | 24.75 | 19.22 | 22.83 | 24.94 | 21.27 | 24.34 | 25.09 |
| M.C.H.C. | 26.05 | 30.75 | 30.48 | 28.42 | 25.67 | 29.32 | 30.67 |
| S.I. | 0.77 | 0.90 | 0.90 | 0.84 | 0.76 | 0.86 | 0.90 |
| W.B.Fe | 0.58 | 0.45 | 0.56 | 0.67 | 0.70 | 0.94 | 0.80 |
| S.Fe | 0.06 | 0.08 | 0.12 | 0.12 | 0.46 | 0.38 | 0.20 |
| W.B.Cu | 0.37 | 0.30 | 0.20 | 0.19 | 0.18 | 0.28 | 0.34 |

↑ Fe et Ammon.Cit. grs 30 t.i.d. from 10.1.39

↑ + Cu Sulph. gr 1/30 t.i.d. from 25.1.39

## CASE NO. 8.

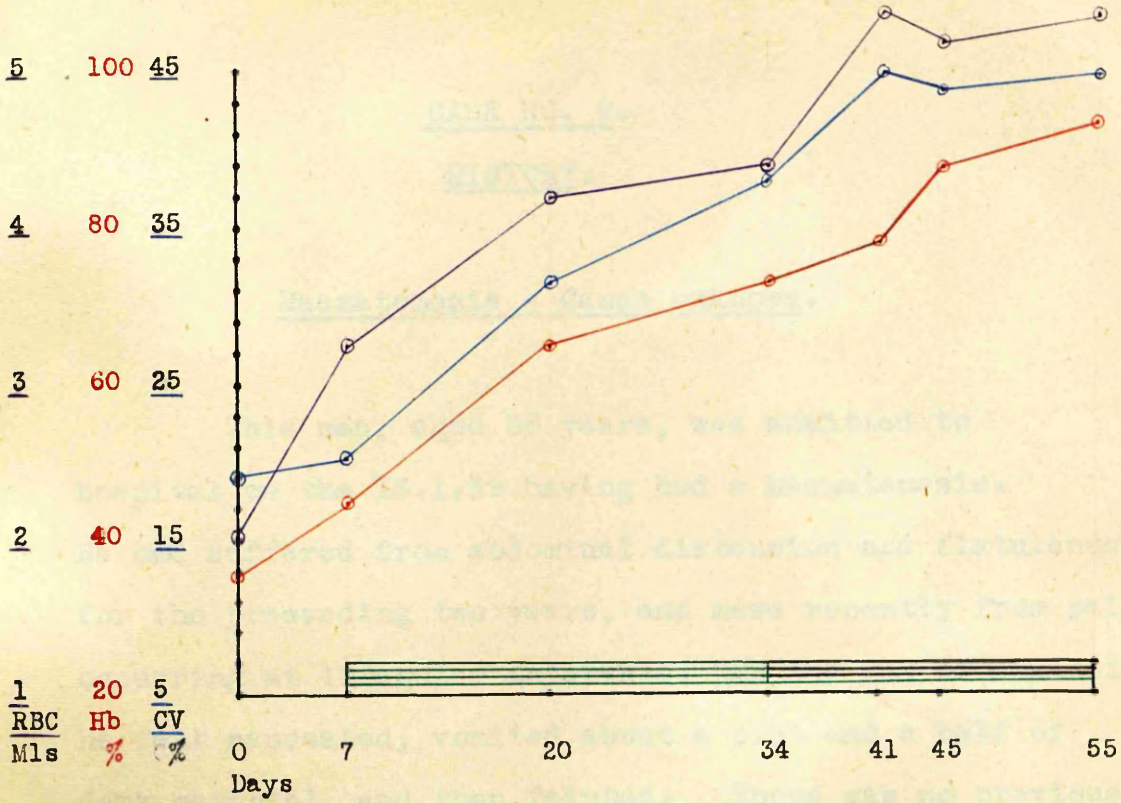
### Interpretation of Graphed Data.

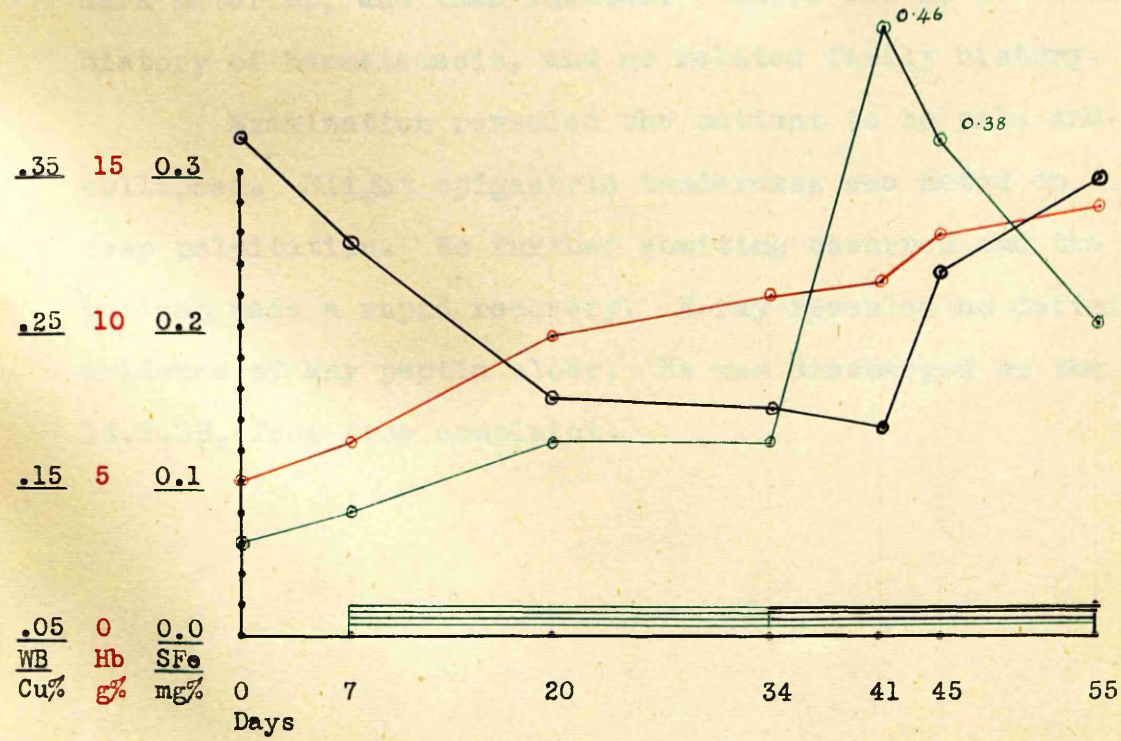
1. Serum Fe began low and showed a slow steady rise from 60 - 120 mcgs during iron therapy. On the addition of copper therapy it rose very rapidly to 460 mcgs and then fell back more slowly to 200 mcgs.

2. The Hb. iron rose steadily with iron therapy but after the addition of copper, and after the serum Fe had reached its peak, an increased rate in Hb. regeneration was noted.

3. Blood Cu commenced at a high level and fell towards normal, only to rise sharply and continuously after copper therapy began. Hb. rise appeared accelerated as the blood Cu rose.

4. No definite relationship was noted in the two iron curves.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 7 20 34 41 45 55
Days


0·46
0·38
.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 7 20 34 41 45 55
Days

CASE No. 8.

## CASE NO. 9.

## HISTORY.

Haematemesis - Cause unknown.

This man, aged 38 years, was admitted to hospital on the 16.1.39 having had a haematemesis. He had suffered from abdominal distension and flatulence for the preceeding two years, and more recently from pain occurring at irregular intervals. On the day of admission he felt nauseated, vomited about a pint and a half of dark material, and then fainted. There was no previous history of haematemesis, and no related family history.

Examination revealed the patient to be pale and collapsed. Slight epigastric tenderness was noted on deep palpitation. No further vomiting occurred and the patient made a rapid recovery. X-ray revealed no definite evidence of any peptic ulcer. He was discharged on the 14.2.39, free from complaint.

CASE NO. 9. MALE. Age 38 yrs. 24.1.39 - 20.3.39.

| DAYS | 1st | 14th | 21st | 28th | 56th |
|---|---|---|---|---|---|
| DATE. | 24.1 | 6.2 | 13.2 | 20.2 | 20.3 |
| R.B.C.(Mils) | 3.54 | 4.33 | 4.34 | 4.90 | 4.80 |
| Hb % | 65 | 72 | 76 | 91 | 92 |
| Hb gms | 9.75 | 10.8 | 11.4 | 13.65 | 13.8 |
| C.V. | 35 | 36 | 38 | 41 | 42 |
| M.C.V. | 98.87 | 83.14 | 87.56 | 83.67 | 87.50 |
| V.I. | 1.15 | 0.97 | 1.02 | 0.97 | 1.02 |
| M.C.H. | 27.54 | 24.94 | 26.27 | 27.86 | 28.75 |
| M.C.H.C. | 27.86 | 30.0 | 30.0 | 33.29 | 32.86 |
| S.I. | 0.82 | 0.88 | 0.88 | 0.98 | 0.97 |
| W.B.Fe | 0.59 | 1.27 | 0.82 | 1.40 | 0.84 |
| S.Fe | 0.06 | 0.10 | 0.26 | 0.60 | 0.14 |

Fe et Ammon Cit grs 30 t.i.d. from 27.1.39

+ Cu Sulph gr 1/30 from 12.2.39.

## CASE NO .9.

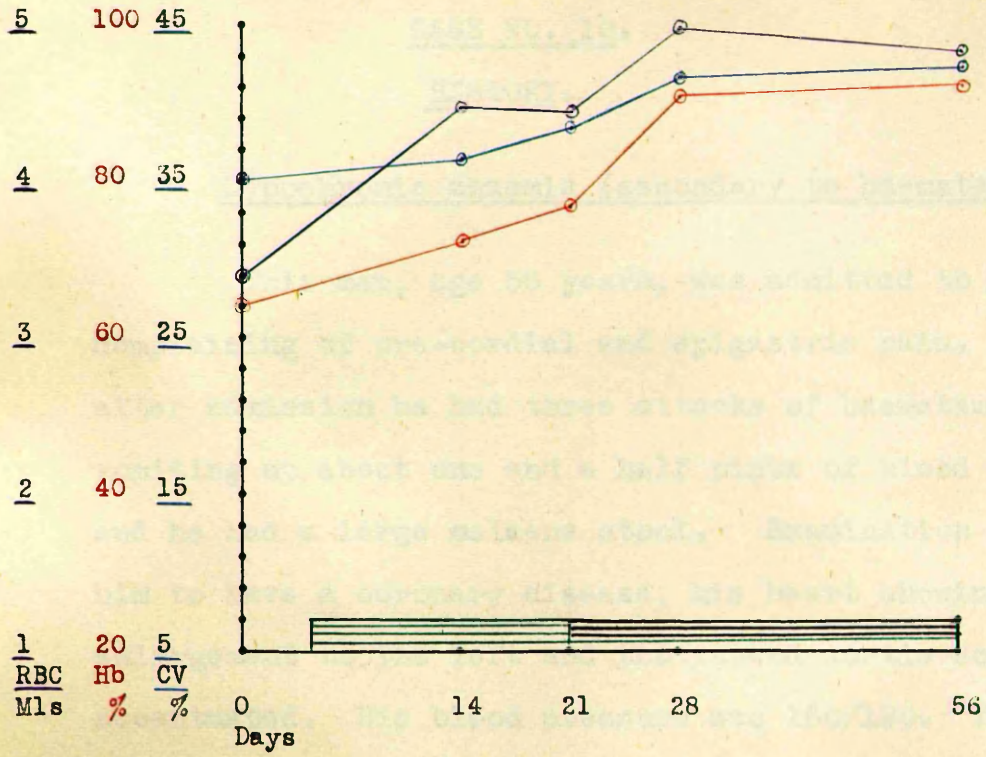
### Interpretation of Graphed Data.

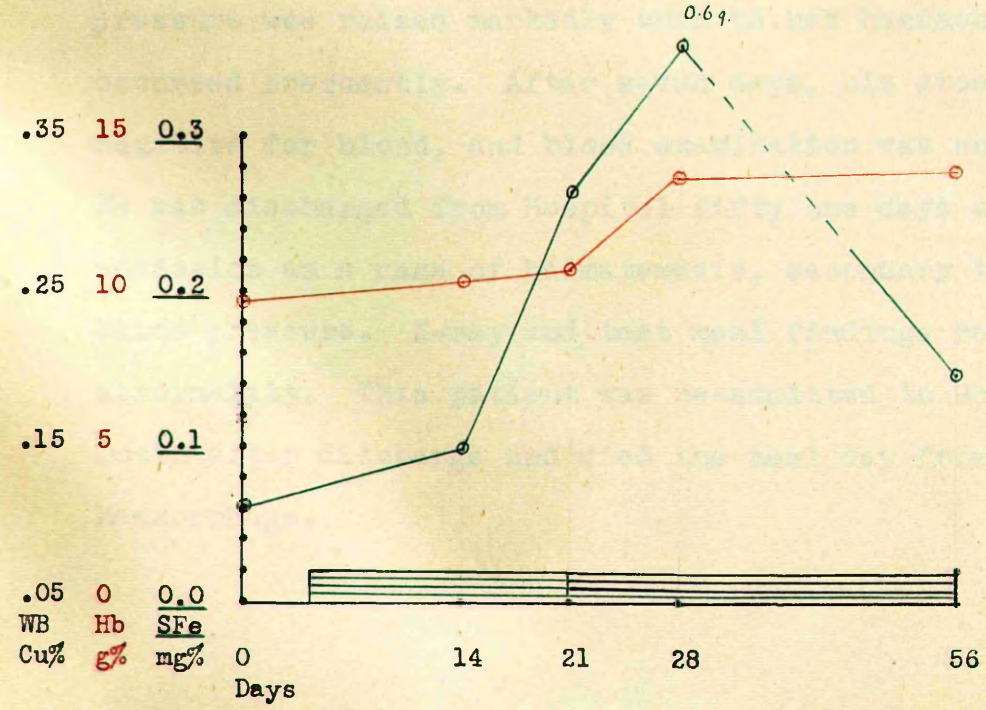
1. The serum Fe began at a level of 60 mcgs but rose with the start of iron therapy and a very rapid rise to 600 mcgs occurred after the addition of copper to the iron. A slow fall back towards normal after the peak level had been reached succeeded this.

2. The Hb. iron began low and showed a continuous slight rise with iron therapy. An accelerated rise in Hb. regeneration occurred after the serum Fe reached 240 mcgs, only to slow up again as the Hb. approached normal.

3. No blood Cu estimation was undertaken in this case.

4. No definite relationship between the two blood irons was detected.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 14 21 28 56
Days


0.6 g.
.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 14 21 28 56
Days

CASE No. 9.

## CASE NO. 10.

## HISTORY.

Hypochromic anaemia (secondary to haematemesis).

This man, age 55 years, was admitted to Hospital complaining of pre-cordial and epigastric pain. The day after admission he had three attacks of haematemesis, vomiting up about one and a half pints of blood in all, and he had a large melaena stool. Examination revealed him to have a coronary disease, his heart showing slight enlargement to the left and the second aortic sound being accentuated. His blood pressure was 160/120. This blood pressure was raised markedly when he had headaches which occurred frequently. After seven days, his stools were negative for blood, and blood examination was commenced. He was discharged from Hospital fifty one days after admission as a case of haematemesis, secondary to high blood pressure. X-ray and test meal findings revealed no abnormality. This patient was re-admitted to Hospital one month after discharge and died the next day from cerebral haemorrhage.

CASE NO. 10. MALE. Age 55 yrs. 5.11.38 - 21.12.38.

| DAYS | 1st | 5th | 10th | 14th | 19th | 25th | 33rd | 41st | 47th |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 5.11 | 9.11 | 14.11 | 18.11 | 23.11 | 29.11 | 7.12 | 15.12 | 21.12 |
| R.B.C.(Mils) | 4.00 | 3.69 | 3.50 | 4.18 | 4.14 | 4.40 | 4.20 | 4.80 | 5.20 |
| Hb % | 62 | 57 | 61 | 64 | 74 | 74 | 76 | 84 | 96 |
| Hbgms | 9.3 | 8.55 | 9.15 | 9.60 | 11.1 | 11.1 | 11.4 | 12.6 | 14.4 |
| C.V. | 21.5 | 24.0 | 28.0 | 32.6 | 36.1 | 38.0 | 42.0 | 43.0 | 46.0 |
| M.C.V. | 53.75 | 65.04 | 80.0 | 77.99 | 87.20 | 86.36 | 100.0 | 89.58 | 88.46 |
| V.I. | 0.63 | 0.76 | 0.93 | 0.91 | 1.01 | 1.00 | 1.16 | 1.04 | 1.03 |
| M.C.H. | 23.25 | 23.17 | 26.14 | 22.97 | 26.81 | 25.23 | 27.14 | 26.25 | 27.69 |
| M.C.H.C. | 43.26 | 35.63 | 32.68 | 29.45 | 30.75 | 29.21 | 27.14 | 29.30 | 31.30 |
| S.I. | 1.27 | 1.05 | 0.96 | 0.87 | 0.90 | 0.86 | 0.80 | 0.86 | 0.92 |
| W.B.Fe | 0.90 | 1.16 | 1.10 | 0.41 | 0.39 | 0.64 | 0.80 | 0.74 | 0.88 |
| S.Fe | 0.06 | 0.08 | 0.12 | 0.16 | 0.16 | 0.18 | 0.19 | 0.20 | 0.14 |
| W.B.Cu | 0.38 | 0.21 | 0.18 | 0.19 | 0.18 | 0.25 | 0.28 | 0.26 | 0.25 |

Fe et Ammon. Cit. grs 30 t.i.d. from 9.11.38

+ Cu Sulph. gr 1/30 t.i.d. fr. 23.11.38

## CASE NO. 10.

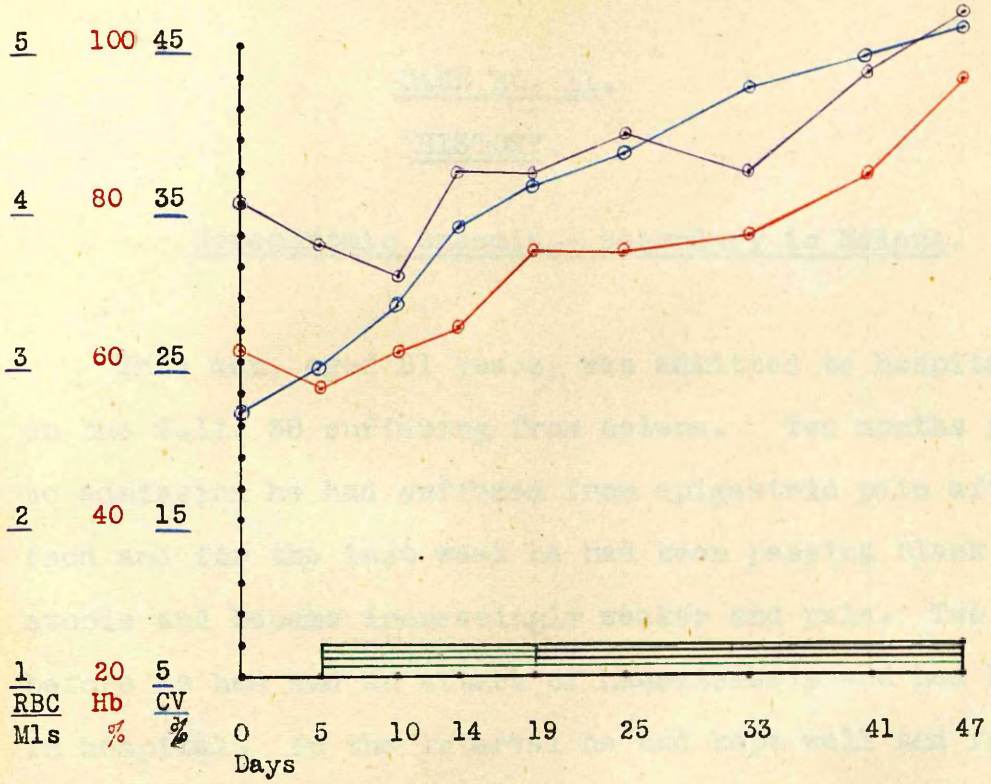
### Interpretation of Graphed Data.

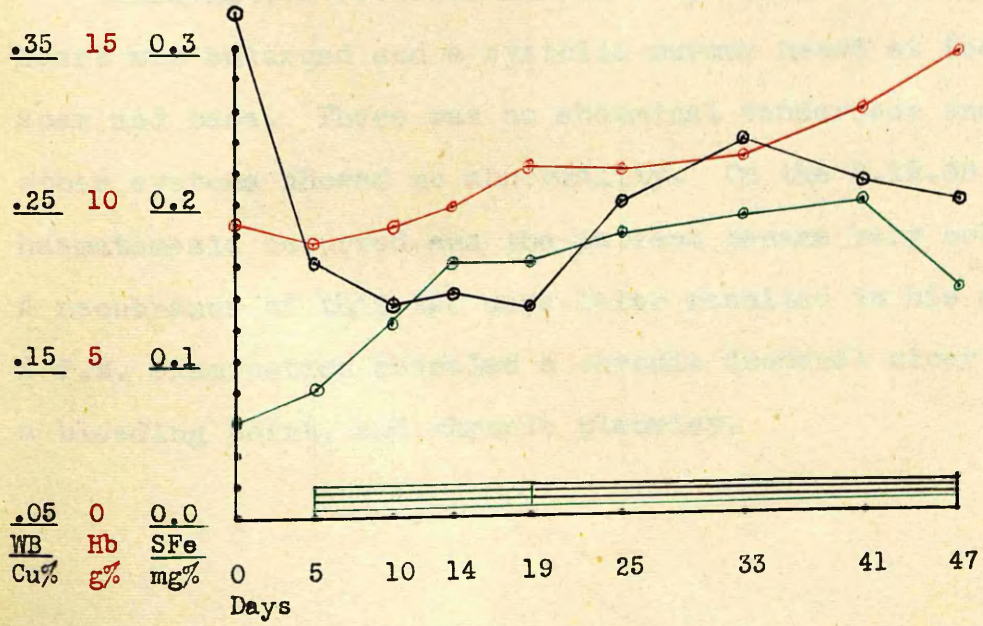
1. Serum Fe began at a low level and began to rise fairly rapidly to 160 mcgs, after which it slowed up despite the addition of copper to the intake. It rose, however, to a height of 200 mcgs: This occurred after the blood Cu had reached its peak of 290 mcgs, and then the serum Fe fell slowly towards normal.

2. Hb. iron started low, and after an initial fall, rose quickly when iron was given. When copper was added to the therapy the curve flattened out, only to show a sharp upward rise after the blood copper had reached its peak.

3. The blood Cu started high and rapidly fell towards normal. With the onset of copper therapy it rose rapidly to reach its peak at 290 mcgs within two weeks, after which it fell back slowly to its normal level.

4. The serum and Hb. irons tend to reveal an inverse relationship to each other, but this is not constant.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 5 10 14 19 25 33 41 47
Days


.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 5 10 14 19 25 33 41 47
Days

CASE No. 10.

CASE NO. 11.

HISTORY.

Hypochromic Anaemia - secondary to Melena.

This man, aged 61 years, was admitted to hospital on the 2.11. 38 suffering from melena. Two months prior to admission he had suffered from epigastric pain after food and for the last week he had been passing black stools and became increasingly weaker and pale. Two years before he had had an attack of haematemesis and had been in hospital. In the interval he had kept well and free from pain until its recurrence two months ago.

Examination revealed him to be pale and thin. The heart was enlarged and a systolic murmur heard at the apex and base. There was no abdominal tenderness and the other systems showed no abnormality. On the 8.12.38 a haematemesis occurred and the patient became very collapsed. A recurrence of this two days later resulted in his decease. A P.M. examination revealed a chronic duodenal ulcer with a bleeding point, and chronic pleurisy.

CASE NO. 11. MALE. Age 61 yrs. 15.11.38 - 7.12.38

| DAYS | 1st | 7th | 12th | 17th | 23rd |
|---|---|---|---|---|---|
| DATE. | 15.11 | 21.11 | 26.11 | 1.12 | 7.12 |
| R.B.C.(Mils) | 1.77 | 2.00 | 2.54 | 2.67 | 1.50 |
| Hb % | 28 | 32 | 38 | 50 | 37 |
| Hb gms | 4.2 | 4.8 | 5.7 | 7.5 | 5.55 |
| C.V. | 13.4 | 15.0 | 19.4 | 25.0 | 17.0 |
| M.C.V. | 75.71 | 75.0 | 76.38 | 93.63 | 113.33 |
| V.I. | 0.88 | 0.87 | 0.89 | 1.09 | 1.32 |
| M.C.H. | 23.73 | 24.0 | 22.44 | 28.09 | 37.0 |
| M.C.H.C. | 31.34 | 32.00 | 29.39 | 30.0 | 32.65 |
| S.I. | 0.92 | 0.94 | 0.86 | 0.88 | 0.96 |
| W.B.Fe | 0.33 | 0.54 | 0.24 | 1.00 | 0.64 |
| S.Fe | 0.10 | 0.10 | 0.16 | 0.22 | 0.12 |
| W.B.Cu | 0.40 | 0.39 | 0.26 | 0.24 | 0.23 |

10.12.38 Haematemesis and died

Melaena

Fe et Ammon.Cit. grs 30 t.i.d. from 16.11.38

+ Cu Sulph gr 1/30 t.i.d fr. 2.12.38.

## CASE NO. 11.

### Interpretation of Graphed Data.

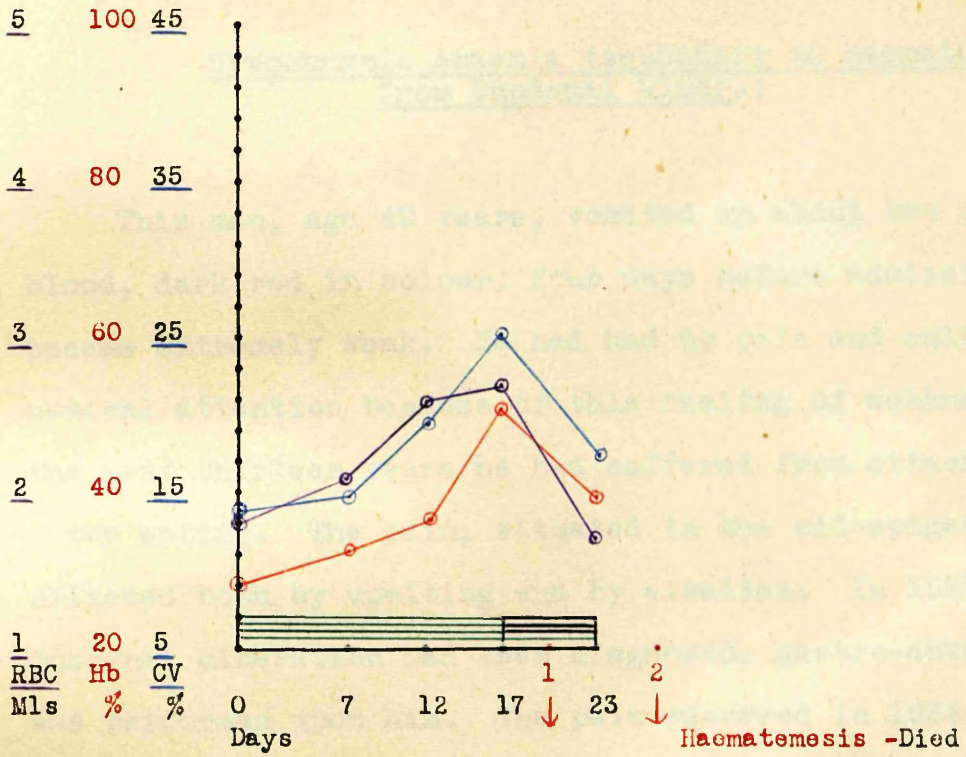
1. Serum Fe rose rapidly from a low level after the beginning of iron therapy. A few days after the addition of copper a haematemesis occurred with a fall in the serum Fe and a fatal haematemesis took place a few days later.

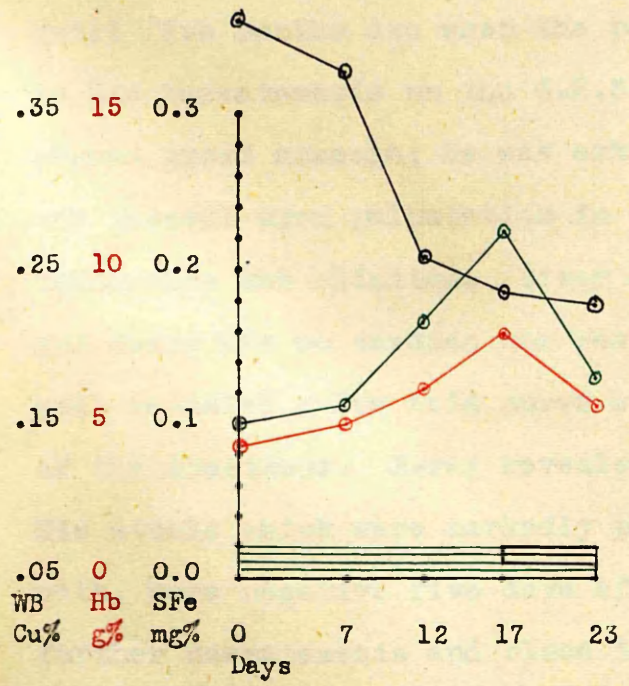
2. The Hb. curve followed a parallel course to the serum Fe.

3. The blood Cu fell rapidly from its high level towards normal and death occurred before any upward trend was noted.

4. The two iron curves ran a parallel course.

5. This case is of short duration, complicated by two haematemesis, and is not worth inclusion in the series.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 7 12 17 23
Days
1
2
Haematemesis -Died


.35 15 0.3
.25 10 0.2
.15 5 0.1
.05 0 0.0
WB Hb SFe
Cu% g% mg%
0 7 12 17 23
Days

CASE No. 11.

CASE NO. 18.

HISTORY.

Hypochromic Anaemia (secondary to haematemesis from Duodenal Ulcer.)

This man, age 42 years, vomited up about two pints of blood, dark red in colour, four days before admission. He became extremely weak. He had had no pain and only requested medical attention because of this feeling of weakness. For the past thirteen years he had suffered from attacks of pain after eating. The pain, situated in the mid-epigastrium, was relieved both by vomiting and by alkalies. In 1927, after duodenal ulceration had been diagnosed, gastro-enterostomy was performed upon him. The pain recurred in 1934 when another operation was performed but no ulcer found. He had been well until five months ago when the pain recurred; this culminated in his haematemesis on the 6.2.39. The patient was thin and showed gross anaemia; he was extremely weak. Slight resistance was present upon palpatation in the mid-epigastrium but no tenderness was elicited. Liver and spleen were not palpable and there was no cardiac nor respiratory abnormality. Test meal revealed a low acid curve and no blood was present in any of the specimens. X-ray revealed "Ulceration of the duodenum". His stools which were markedly positive for blood to commence with, were negative five days after admission. He had no further haematemesis and blood investigations and treatment were carried out from then onwards. He made a rapid and uneventful recovery, responding extremely well to all therapy.

CASE NO. 18. MALE. Age 42 yrs. 13.2.39 - 30.3.39.

| DAYS | 1st | 8th | 18th | 25th | 30th | 36th | 41st | 46th |
|---|---|---|---|---|---|---|---|---|
| DATE. | 13.2 | 20.2 | 2.3 | 9.3 | 14.3 | 20.3 | 25.3 | 30.3 |
| R.B.C.(Mils) | 2.21 | 2.85 | 3.61 | 3.59 | 4.20 | 5.00 | 5.10 | 5.06 |
| Hb % | 35 | 40 | 55 | 59 | 62 | 74 | 85 | 92 |
| Hb gms | 5.25 | 6.00 | 8.25 | 8.85 | 9.30 | 11.1 | 12.75 | 13.8 |
| C.V. | 16 | 21 | 27 | 40 | 45 | 43 | 43 | 44 |
| M.C.V. | 72.40 | 73.68 | 74.79 | 111.42 | 107.14 | 86.0 | 84.31 | 86.96 |
| V.I. | 0.84 | 0.86 | 0.87 | 1.29 | 1.25 | 1.0 | 0.98 | 1.01 |
| M.C.H. | 23.76 | 21.05 | 22.85 | 24.65 | 22.14 | 22.2 | 25.0 | 27.27 |
| M.C.H.C. | 32.81 | 28.57 | 30.56 | 22.13 | 20.67 | 25.81 | 29.65 | 31.36 |
| S.I. | 0.97 | 0.84 | 0.90 | 0.65 | 0.61 | 0.76 | 0.87 | 0.92 |
| W.B.Fe | 1.46 | 1.40 | 1.28 | 1.12 | 0.79 | 0.84 | 0.86 | 0.92 |
| S.Fe | 0.04 | 0.06 | 0.09 | 0.09 | 0.18 | 0.21 | 0.17 | 0.14 |
| W.B.Cu | 0.36 | 0.26 | 0.19 | 0.20 | 0.22 | 0.28 | 0.24 | 0.20 |
| S.Vit C | 0.62 | 0.56 | 0.46 | 1.30 | 1.90 | 1.56 | 1.64 | 1.20 |

Fe et Ammon Cit grs 30 t.i.d. from 13.2.39

Vit C mgm 300/day from 1.3.39 - 22.3.39

+ Cu Sulph gr 1/30 t.i.d. from 4.3.39

## CASE NO. 18.

### Interpretation of the Graphed Data.

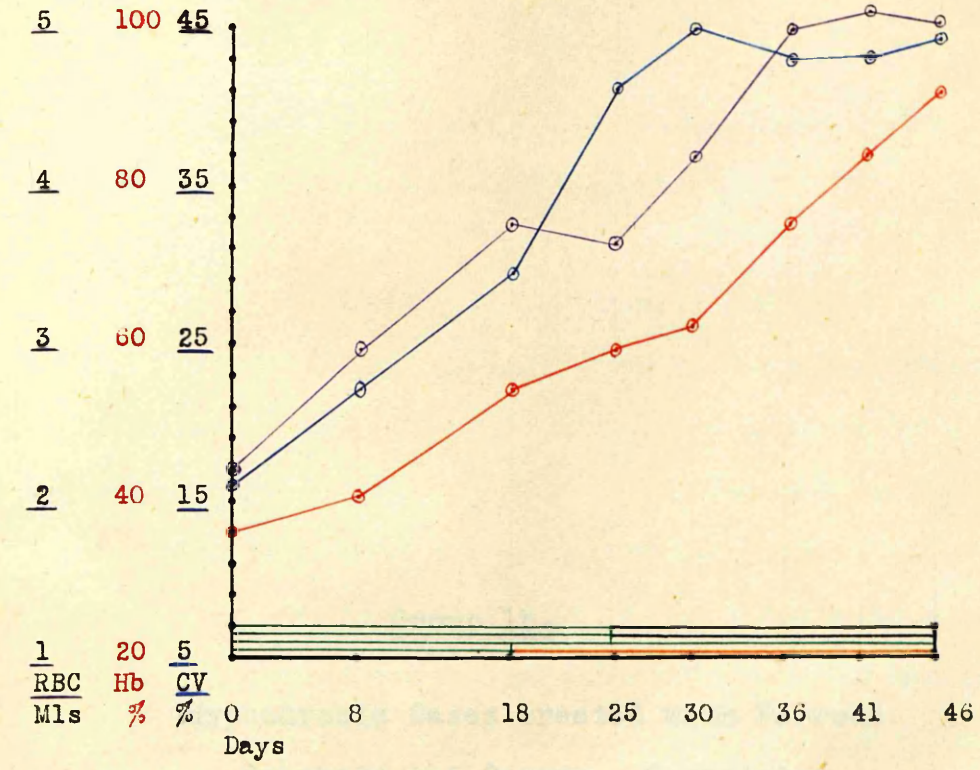
1. Serum Fe level began at 40 mcgs and rose slowly throughout iron therapy to 90 mcgs, only to rise rapidly to 210 mcgs once copper was added to the drug intake. It then more slowly subsided towards normal.

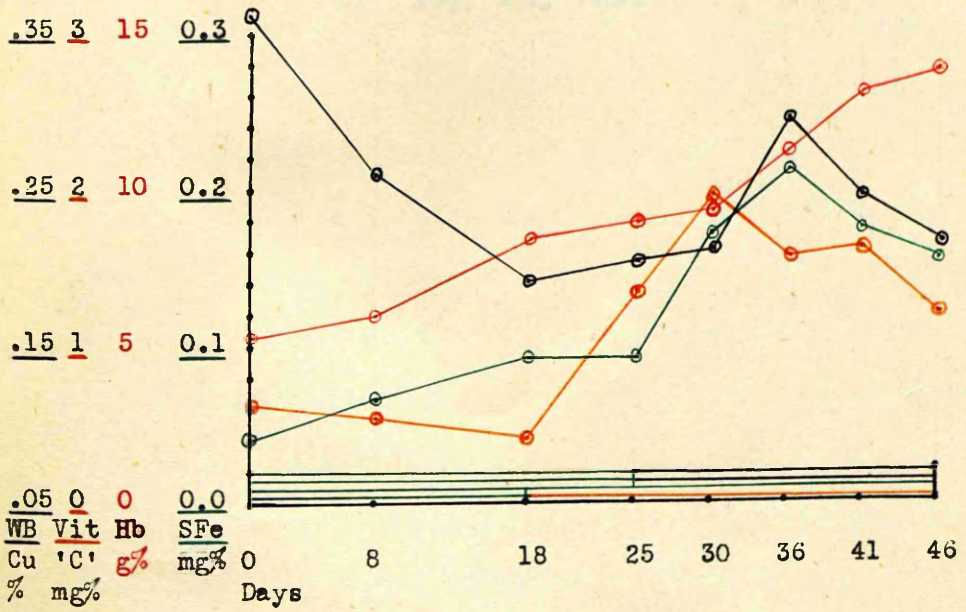
2. The Hb. iron began low and rose steadily, but moderately slowly, during iron therapy. It showed an increased upward rise after the addition of copper and after the blood Cu and serum Fe had begun to rise rapidly.

3. The blood Cu began at 360 mcgs and fell steadily towards 200 mcgs, when it rose again to 290 mcgs after the addition of copper to the intake.

4. The serum and Hb curves tend towards "mirror" images, especially in the latter half of thereapy.

5. The Blood Vit 'C' level was very low at the beginning of therapy and remained so until the vitamin was added to the diet when it rose quickly to 190 mgm per 100 ccs. The rise in blood Cu began with the rise in Vit 'C' level but it was only slight until copper was added to the diet a week later. No marked rise in the Hb. was noted in association with the beginning of Vit 'C' intake.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 8 18 25 30 36 41 46
Days


.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg%
% mg%
0 8 18 25 30 36 41 46
Days

CASE No. 18.

## Group 1b.

Hypochromic Cases treated with Ferrous Sulphate and Copper. Comprising cases numbered.

3, 15, 20, 22.

CASE NO. 3.

HISTORY.

Hypochromic Anaemia (secondary to haematemesis from Duodenal Ulcer.)

This female, age 38 years, was admitted to Hospital the day after she had had three attacks of haematemesis, vomiting on each occasion about one pint of brownish material. She had had epigastric pain occurring one to two hours after food for the seven months preceding this. The pain became most acute on the day prior to the haematemesis. Examination revealed her to be markedly anaemic and she had fairly marked epigastric tenderness. Her heart and lungs revealed no abnormality, although she had been twice investigated for pulmonary tuberculosis. A test meal three weeks after admission revealed a normal acid curve. X-ray showed "Duodenal defect present, probably due to ulcer". Seven days after admission her stools were negative for chemical blood tests, and her blood examination was commenced. Her anaemia was fairly marked and a further slight haemorrhage was detected by chemical test which occurred on the eighth day after investigation had started. This reduced her total Red Cell Count and Haemoglobin slightly. After this, she progressed most favourably and was discharged from Hospital markedly improved, thirty eight days after admission. She reported back as an out-patient for further examinations.

CASE NO. 3. FEMALE. Age 38 yrs. 22.11.38 - 14.1.39.

| DAYS | 1st | 7th | 12th | 18th | 24th | 37th | 43rd | 47th | 54th |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 22.11 | 28.11 | 3.12 | 9.12 | 15.12 | 28.12 | 3.1 | 7.1 | 14.1 |
| R.B.C.(Mils) | 2.70 | 3.30 | 2.63 | 3.56 | 4.20 | 4.32 | 4.38 | 4.48 | 4.40 |
| Hb% | 43 | 47 | 43 | 55 | 70 | 80 | 82 | 82 | 90 |
| Hbgms. | 6.45 | 7.05 | 6.45 | 8.25 | 10.5 | 12.0 | 12.3 | 12.3 | 13.5 |
| C.V. | 16.2 | 20 | 16.0 | 30 | 33 | 38.5 | 40.0 | 42.0 | 42.0 |
| M.C.V. | 60.0 | 60.60 | 60.83 | 84.27 | 78.57 | 89.12 | 91.32 | 93.75 | 95.45 |
| V.I. | 0.70 | 0.70 | 0.71 | 0.98 | 0.91 | 1.04 | 1.06 | 1.09 | 1.11 |
| M.C.H. | 23.89 | 21.36 | 24.52 | 23.17 | 25.0 | 27.78 | 28.08 | 27.46 | 30.68 |
| M.C.H.C. | 39.81 | 35.25 | 40.31 | 27.5 | 31.82 | 31.17 | 30.75 | 29.29 | 32.14 |
| S.I. | 1.17 | 1.04 | 1.19 | 0.81 | 0.94 | 0.92 | 0.90 | 0.86 | 0.95 |
| W.B.Fe | 0.38 | 0.53 | 0.70 | 0.88 | 0.93 | 0.80 | 0.70 | 0.70 | 0.62 |
| S.Fe | 0.06 | 0.08 | 0.42 | 0.52 | 0.46 | 0.45 | 0.38 | 0.34 | 0.20 |
| W.B.Cu | 0.32 | 0.30 | 0.29 | 0.26 | 0.23 | 0.25 | 0.28 | 0.31 | 0.29 |

Slight Haematemesis.

Fe Sulph. grs 5 t.i.d. from 29.11.38

+ Cu gr 1/30 t.i.d. from 4.12.38.

## CASE NO.3.

### Interpretation of Graphed Data.

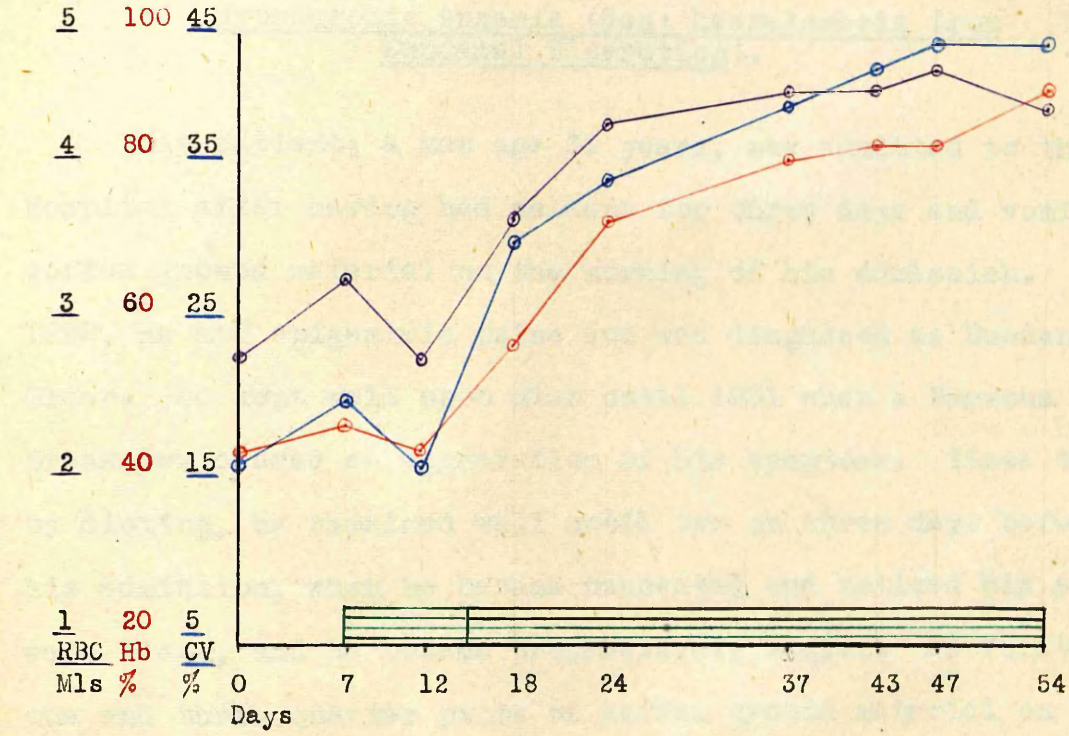
1. Serum Fe began at a low level and rose rapidly after the beginning of iron therapy to 520 mcgs. The addition of copper to the therapy made little difference although the serum Fe maintained a high level above 300 mcgs % for four weeks.

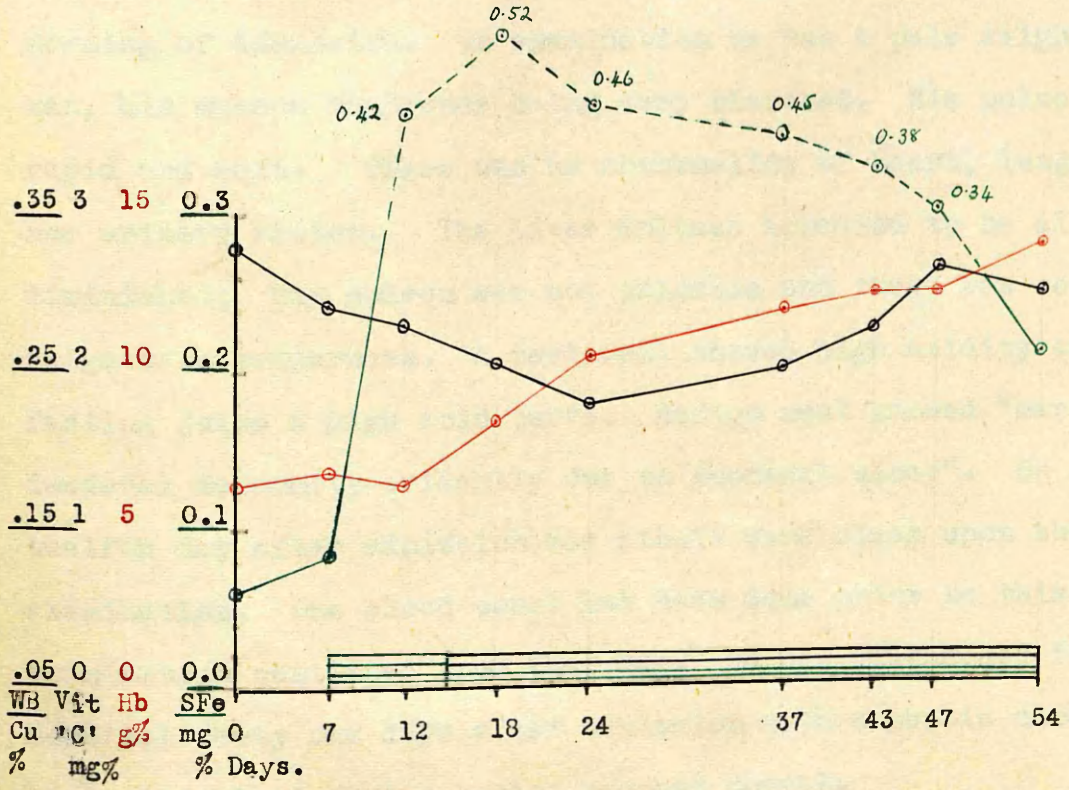
2. Hb. iron began low, but after the rapid rise in the serum Fe so did there occur a marked increase in Hb. regeneration which continued, even after the serum Fe began to fall. A slight haematemesis on the 8th day resulted in a slight fall in the Hb. level but did not appear to affect the serum Fe level.

3. The blood Cu commenced high at 320 mcgs and fell slowly to 230 mcgs until two weeks after copper therapy had started; it then rose more slowly to reach 310 mcgs. It was never at a low level in this case but again it is noticed that, towards the end of therapy, the most rapid Hb. rise occurs after the blood Cu had reached its peak. Serum Fe levels do not appear to be related to the rises in the blood Cu curve, but in this case the copper level is high above normal at all times.

4. No definite relationship in the two iron curves was noted apart from the more rapid Hb. regeneration when the serum Fe was either rising sharply or at its height.

5. The iron given in this case was Ferrous Sulphate.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 7 12 18 24 37 43 47 54
Days


0·52
0·46
0·42
0·45
0·38
0·34
.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu C g% mg
% mg%
0 7 12 18 24 37 43 47 54
% Days.

CASE No.3.

CASE NO. 15.

HISTORY.

Hypochromic Anaemia (Seq: haematemesis from Duodenal Ulceration).

This patient, a man age 39 years, was admitted to the Hospital after having had melaena for three days and vomiting coffee ground material on the morning of his admission. In 1922, he had epigastric pains and was diagnosed as Duodenal Ulcer. He kept well upon diet until 1931 when a Nervous Breakdown caused an aggravation of his symptoms. Since then, by dieting, he remained well until two or three days before his admission, when he became nauseated and noticed his stools were black, and he became progressively weaker. He vomited one and three quarter pints of coffee ground material on the morning of admission. On examination he was a pale slight man, his mucous membranes being very blanched. His pulse was rapid and soft. There was no abnormality of heart, lungs, nor urinary system. The liver dulness appeared to be slightly diminished; his spleen was not palpable and there was no epigastric tenderness. A test meal showed high acidity and fasting juice a high acid curve. Barium meal showed "marked duodenal deformity evidently due to duodenal ulcer". On the twelfth day after admission his stools were clear upon chemical examination. One blood count had been done prior to this and examination continued from that day. He was discharged from Hospital forty one days after admission upon a peptic ulcer diet, his blood almost having reached normal.

CASE NO. 15. MALE. Age 39 yrs. 17.6.38 - 23.7.38.

| DAYS | 1st | 5th | 8th | 12th | 18th | 24th | 30th | 37th |
|---|---|---|---|---|---|---|---|---|
| DATE. | 17.6 | 21.6 | 24.6 | 28.6 | 4.7 | 10.7 | 16.7 | 23.7 |
| R.B.C.(Mils) | 2.30 | 3.18 | 3.00 | 3.23 | 3.39 | 4.62 | 4.80 | 5.04 |
| Hb % | 45 | 60 | 62 | 66 | 85 | 86 | 90 | 94 |
| Hb gms | 6.75 | 9.00 | 9.6 | 10.2 | 12.75 | 12.9 | 13.5 | 14.1 |
| C.V. | 25.5 | 29 | 28 | 32.5 | 38 | 44 | 42 | 43 |
| M.C.V. | 110.87 | 91.19 | 93.33 | 100.62 | 112.09 | 95.24 | 87.50 | 85.32 |
| V.I. | 1.29 | 1.06 | 1.09 | 1.17 | 1.30 | 1.11 | 1.02 | 0.99 |
| M.C.H. | 29.35 | 28.3 | 32.0 | 31.58 | 37.61 | 27.92 | 28.13 | 27.98 |
| M.C.H.C. | 26.47 | 31.03 | 34.29 | 31.38 | 33.55 | 29.32 | 32.14 | 32.79 |
| S.I. | 0.78 | 0.91 | 1.01 | 0.92 | 0.99 | 0.86 | 0.95 | 0.96 |
| W.B.Fe | 0.60 | 0.56 | 1.28 | 1.00 | 1.63 | 1.42 | 1.44 | 1.38 |
| S.Fe | 0.10 | 0.20 | 0.27 | 0.24 | 0.20 | 0.14 | 0.12 | 0.12 |
| W.B.Cu | 0.32 | 0.26 | 0.21 | 0.29 | 0.31 | 0.27 | 0.27 | 0.25 |

FeSO4 grs. 5 t.i.d. from 19.6 38

+ Cu Sulph. gr 1/30 t.i.d. from 24.6.38

Campolon 2 ccs on 4.7.38.

## CASE NO. 15.

### Interpretation of Graphed Data.

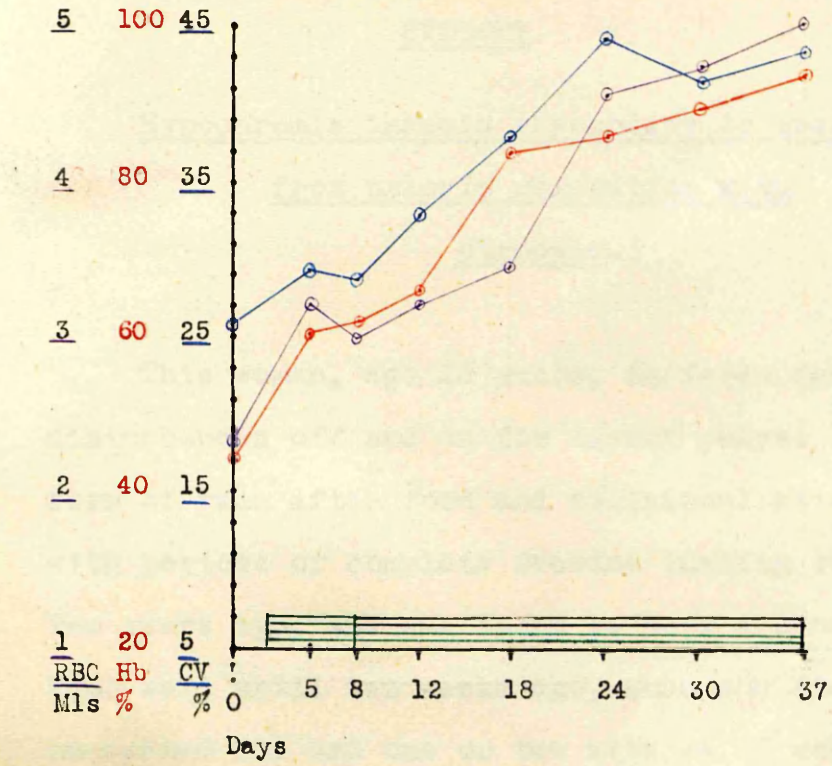
1. Serum Fe began at 100 mcgs and rose rapidly to 270 mcgs in eight days. It fell slowly to normal after this, and the addition of copper to the therapy did not affect the course of the curve.

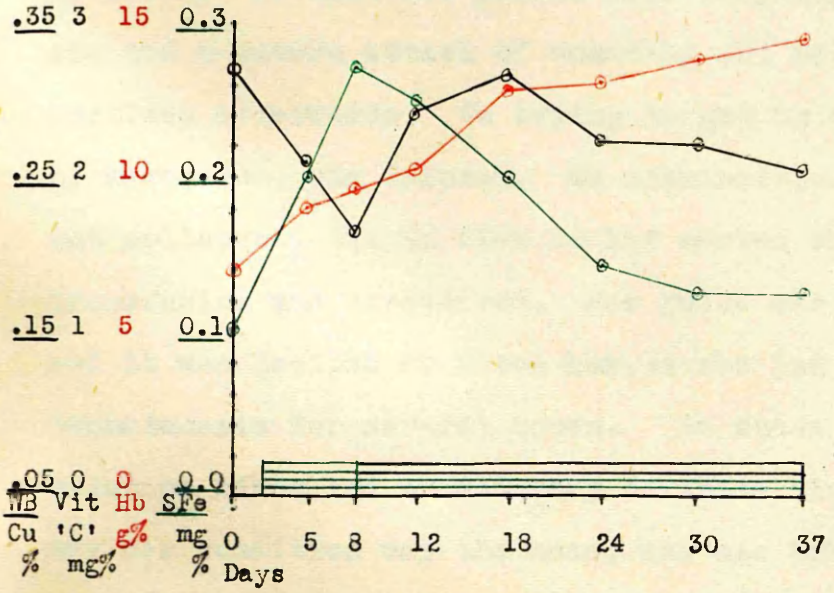
2. Hb. iron revealed a rise from the beginning of iron therapy. This curve flattened out before copper therapy began only to rise again after its addition to the iron. This increased rise also coincided with the blood Cu reaching its highest point.

3. The Blood Cu level began high at 320 mcgs and fell rapidly until the copper therapy began when it again rose rapidly.

4. No definite relationship was noted in the two iron curves.

5. The iron given in this case was Ferrous Sulphate.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 5 8 12 18 24 30 37
Days


.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg
% mg% %
0 5 8 12 18 24 30 37
Days

CASE No. 15.

CASE NO. 20.

HISTORY.

Hypochromic Anaemia (secondary to haematemesis from pyloric ulceration with stenosis.)

This woman, age 52 years, suffered from gastric disturbances off and on for twenty years. This took the form of pain after food and occasional attacks of vomiting, with periods of complete freedom lasting two or three years. Two years ago, she was found to have a Duodenal Ulcer. She kept well until two weeks ago, when she started to be nauseated and had one or two attacks of vomiting. There had been pain but it was not related to food. Two days before admission she noticed that some vomitus was black in colour and that her faeces were very dark. Next day she had a severe attack of vomiting and felt weak and restless afterwards. On trying to get up on the morning of admission, she fainted. On examination, patient was not collapsed, but in view of her marked anaemia, blood transfusion was considered. Her pulse was relatively good and it was decided to watch her, as she had had no haematemesis for several hours. An enema wash-out was returned black and showed very definite blood. The next day her condition was the same, she was taking sips of food without any vomiting and was feeling remarkably/

HISTORY of CASE NO. 20. Contd.

remarkably well. By the ninth day she had gradually recovered although she was still extremely anaemic, and her stools were negative for blood. Iron treatment and investigation was started from this point. She responded only slowly to treatment and had a further slight haemorrhage on the day after treatment had started. From this time she made rapid progress and was dischraged from Hospital sixty-eight days after admission. She reported back as an outpatient.

CASE NO. 20. Female. Age 52 yrs. 16.12.38 - 27.2.39

| DAYS | 1st | 7th | 21st | 26th | 40th | 54th | 61st | 68th | 74th |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 16.12 | 22.12 | 5.1 | 10.1 | 24.1 | 7.2 | 14.2 | 21.2 | 27.2 |
| R.B.C.(Mils) | 1.86 | 2.50 | 3.72 | 2.63 | 3.20 | 4.60 | 5.12 | 5.04 | 5.20 |
| Hb % | 33 | 40 | 42 | 35 | 40 | 52 | 60 | 78 | 90 |
| Hb gms | 4.95 | 6.00 | 6.30 | 5.25 | 6.00 | 7.80 | 9.00 | 11.7 | 13.5 |
| C.V. | 16 | 18 | 23 | 25 | 36 | 42 | 45 | 44 | 43 |
| M.C.V. | 86.02 | 72.0 | 61.83 | 95.06 | 112.50 | 91.30 | 87.89 | 87.30 | 82.69 |
| V.I. | 1.00 | 0.84 | 0.72 | 1.10 | 1.31 | 1.06 | 1.02 | 1.02 | 0.96 |
| M.C.H. | 26.61 | 24.0 | 16.93 | 19.96 | 18.75 | 16.96 | 17.58 | 23.21 | 25.96 |
| M.C.H.C. | 30.94 | 33.34 | 27.39 | 21.0 | 16.67 | 18.57 | 20.0 | 26.59 | 31.40 |
| S.I. | 0.91 | 0.98 | 0.81 | 0.62 | 0.49 | 0.55 | 0.59 | 0.78 | 0.92 |
| W.B.Fe | 0.86 | 0.47 | 0.70 | 0.86 | 0.78 | 0.61 | 0.64 | 0.72 | 0.62 |
| S.Fe | 0.05 | 0.16 | 0.23 | 0.26 | 0.30 | 0.20 | 0.16 | 0.06 | 0.08 |
| W.B.Cu | 0.36 | 0.26 | 0.21 | 0.22 | 0.24 | 0.29 | 0.28 | 0.14 | 0.19 |
| S.Vit C | 0.66 | 0.72 | 0.54 | 0.59 | 1.67 | 2.14 | 2.08 | 2.59 | 1.68 |

Fe Sulph. grs 5 t.i.d. from 16.12.38 - 21.12.38.

Fe et Ammon Cit grs 30 t.i.d. from 21.12.38

+ Cu Sulph grs 1/30 t.i.d. from 5.1.39

+ Vit C mgm 300/day from 10.1.39

Slight Haemorrhage.

## CASE NO. 20.

### Interpretation of Graphed Data.

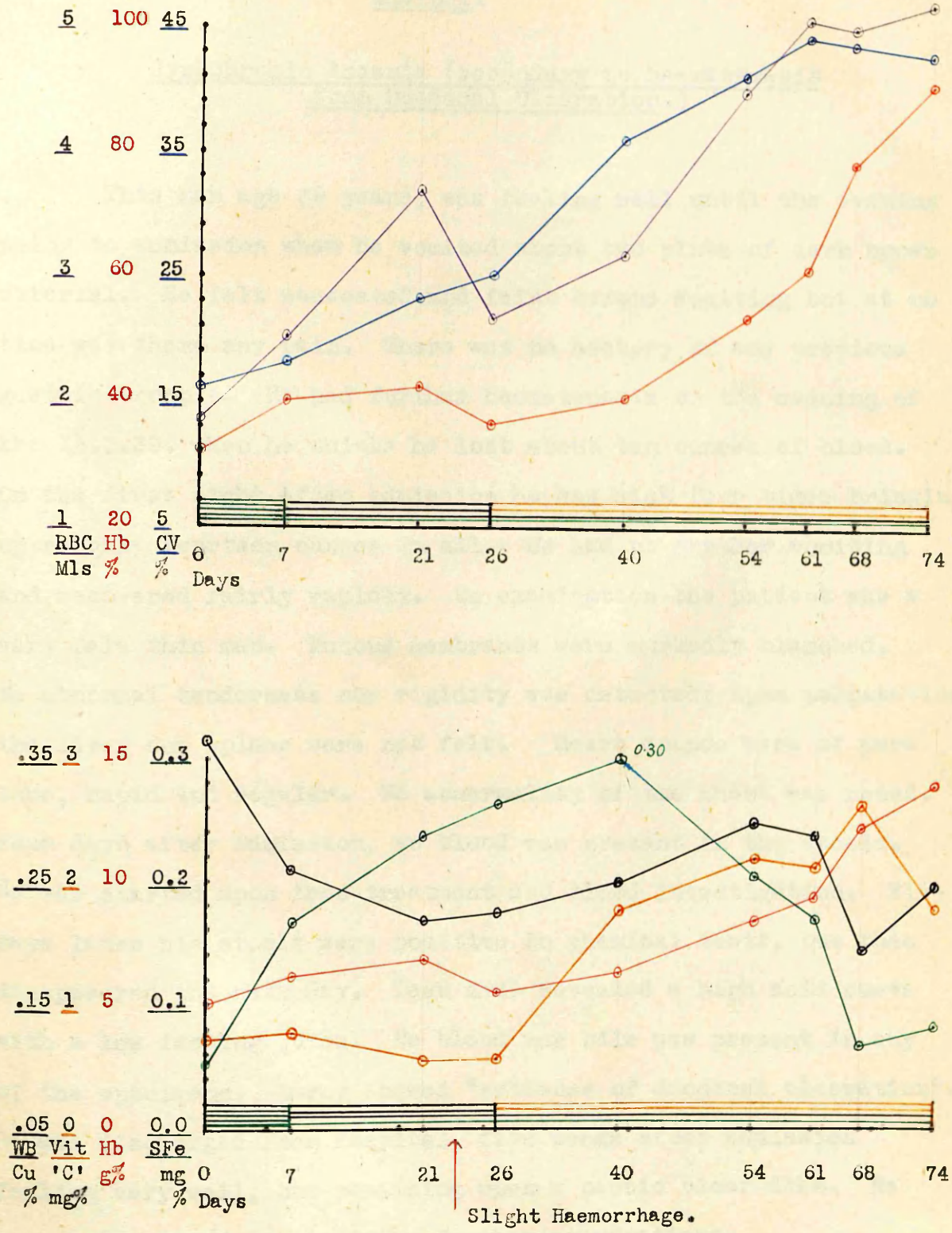
1. Serum Fe curve commenced at a low level of 50 mcgs and rose quickly to 230 mcgs with iron therapy. It rose still higher to 300 mcgs with copper therapy, and then started to fall towards normal.

2. Hb. iron began at a low level at 4.95 gms% and despite iron therapy only increased slightly to 6.3 gms. when a slight haemorrhage occurred and it fell back to 5.25 gms. Thereafter, it rose rapidly and this rise coincided with the peak in the serum Fe being reached. A still more rapid rise occurred after the blood Cu had reached its peak.

3. The blood Cu was high at 360 mcgs at the start and it fell towards normal only to rise again to 290 mcgs after copper therapy began. As it reached its peak the Hb. iron showed an increased rate of regeneration.

4. No definite relationship was noted in the serum Fe and Hb. iron curves except in the latter half of the course when an inverse trend was noted.

5. Blood Vit 'C' began low, to rise after Vit 'C' therapy started and this coincided with the rise in the blood Cu and the improved increase in Hb. rise.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 7 21 26 40 54 61 68 74
Days
.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg
% mg% %
0.30
0 7 21 26 40 54 61 68 74
Days
Slight Haemorrhage.

CASE. No 20

## CASE NO. 22.

## HISTORY.

### Hypochromic Anaemia (secondary to haematemesis from Duodenal Ulceration.)

This man age 39 years, was feeling well until the evening prior to admission when he vomited about two pints of dark brown material. He felt nauseated and faint before vomiting but at no time was there any pain. There was no history of any previous gastric trouble. He had further haematemesis on the evening of the 12.3.39. when he thinks he lost about ten ounces of blood. On the first night after admission he was sick four times bringing up roughly fourteen ounces in all. He had no further vomiting and recovered fairly rapidly. On examination the patient was a very pale thin man. Mucous membranes were markedly blanched. No abnormal tenderness nor rigidity was detected; upon palpatation the liver and spleen were not felt. Heart sounds were of pure tone, rapid and regular. No abnormality of the chest was noted. Four days after admission, no blood was present in the stools. He was started upon iron treatment and blood investigation. Five days later his stools were positive to chemical tests, but this disappeared the next day. Test meal revealed a high acid curve with a low fasting juice. No blood nor bile was present in any of the specimens. X-ray showed "evidence of duodenal ulceration". He was discharged from Hospital, five weeks after admission feeling very well, but remaining upon a peptic ulcer diet. He reported as an Outpatient for further examinations.

CASE NO. 22. MALE Age 39 yrs. 16.3.39 - 2.5.39.

| DAYS | 1st | 7th | 14th | 20th | 28th | 35th | 38th | 42nd | 49th |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 16.3 | 22.3 | 28.3 | 3.4 | 11.4 | 18.4 | 21.4 | 25.4 | 2.5 |
| R.B.C.(Mils) | 2.86 | 3.01 | 3.63 | 4.28 | 4.36 | 4.38 | 5.03 | 4.94 | 5.06 |
| Hb % | 50 | 61 | 68 | 77 | 82 | 82 | 86 | 92 | 96 |
| Hb gms | 7.5 | 9.15 | 10.2 | 11.55 | 12.3 | 12.3 | 12.9 | 13.8 | 14.4 |
| C.V. | 35 | 32 | 39 | 38 | 46 | 45 | 51 | 46 | 44 |
| M.C.V. | 122.38 | 106.31 | 107.44 | 88.78 | 105.50 | 102.74 | 101.39 | 93.12 | 86.96 |
| V.I. | 1.42 | 1.24 | 1.25 | 1.03 | 1.23 | 1.19 | 1.18 | 1.08 | 1.01 |
| M.C.H. | 26.22 | 30.4 | 28.10 | 27.0 | 28.21 | 28.08 | 25.65 | 27.94 | 28.46 |
| M.C.H.C. | 21.43 | 28.59 | 26.15 | 30.39 | 26.74 | 27.33 | 25.29 | 30.0 | 32.73 |
| S.I. | 0.63 | 0.84 | 0.77 | 0.89 | 0.79 | 0.80 | 0.74 | 0.88 | 0.96 |
| W.B.Fe | 0.62 | 0.60 | 0.72 | 0.71 | 0.60 | 0.46 | 0.78 | 0.79 | 0.86 |
| S.Fe | 0.06 | 0.09 | 0.14 | 0.16 | 0.24 | 0.20 | 0.12 | 0.12 | 0.10 |
| W.B.Cu | 0.29 | 0.22 | 0.22 | 0.21 | 0.20 | 0.28 | 0.28 | 0.26 | 0.21 |
| S. Vit C. | 0.39 | 0.71 | 0.53 | 0.60 | 0.59 | 0.69 | 0.73 | 1.20 | 1.00 |

↑ Fe Sulph grs 5 t.i.d. from 21.3.39

↑ Cu Sulph grs 1/30 from 15.4.39

↑ Vit C mgm 300/day fr 20.4.39

CASE NO. 22.

Interpretation of Graphed Data.

1. Serum Fe level was found to be low at the onset of the investigation and with the start of iron therapy it rose quickly to reach a peak of 230 mcgs on the 28th day, then it began to fall towards normal. No rise was noted after the addition of copper to the iron.

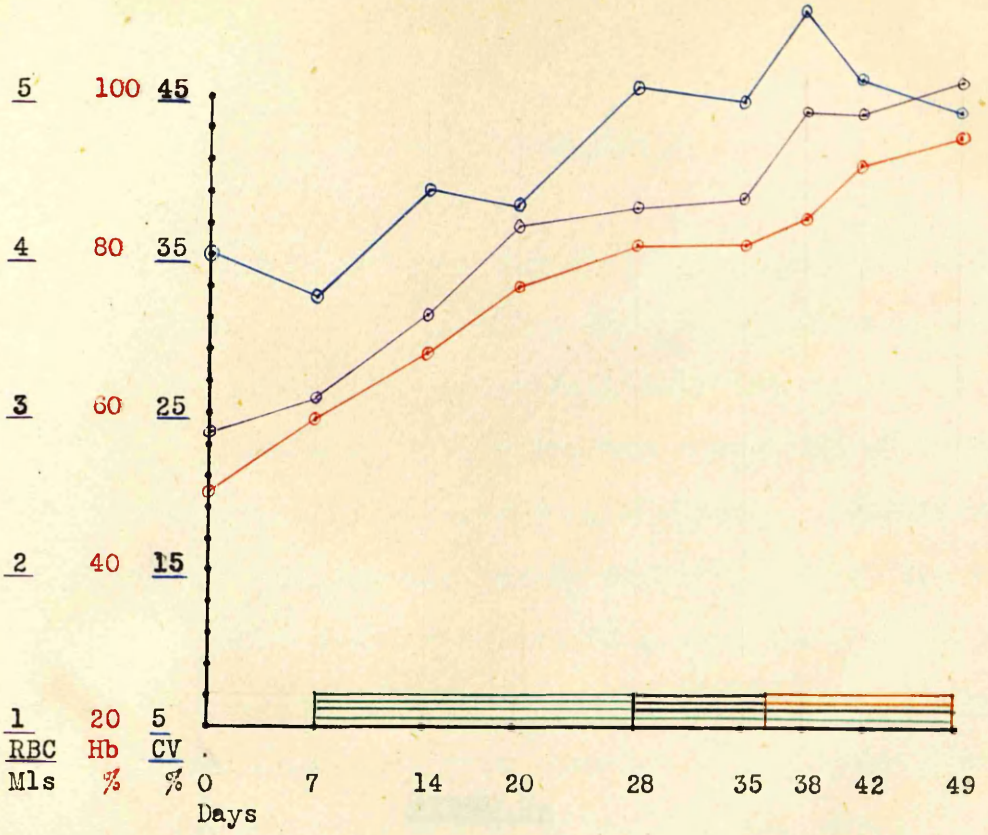
2. The Hb. iron began low, to slowly and steadily rise throughout iron intake. The addition of copper did not appear to increase the rate of regeneration until the copper had reached its peak, when a slightly increased rate in rise was noted.

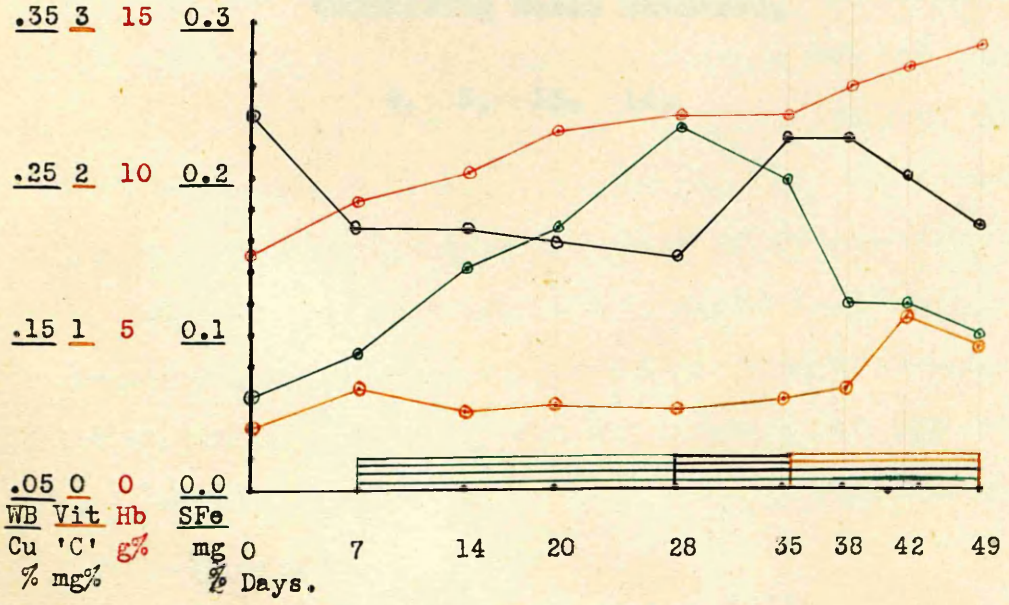
3. Blood Cu started at a level of 290 mcgs and fell steadily downwards till the 28th day when copper therapy began. It then rose quickly to 290 mcgs again, which level it maintained for a short time before it fell more slowly. The rate of Hb. regeneration increased slightly after the blood Cu had reached its peak.

4. No relationship was noted between the Hb. and serum irons.

5. The blood Vit 'C' was low throughout but showed a slight rise to 120 mgm after Vit 'C' therapy began. It did not appear related in any way to either the Hb. or Serum Fe curves.

6. The iron given in this case was Ferrous Sulphate.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 7 14 20 28 35 38 42 49
Days


.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg
% mg% %
0 7 14 20 28 35 38 42 49
Days.

CASE No. 22.

## Group 2.

Pernicious Anaemia

cases.

Comprising Cases numbered.

4, 5, 13, 14.

## CASE NO. 4.

## HISTORY.

### Pernicious Anaemia.

This patient, a woman age 50 years, commenced treatment for pernicious anaemia in 1936, two years before her admission to Hospital. She kept relatively well but had a few relapses. Some months before admission she had a sore throat and since then had suffered from increasing weakness. Within the last two weeks, her ankles had become swollen towards the evening and for the last week there had been some swelling of her eyelids most noticeable in the morning. Some numbness of both feet and hands had been present for the past three months; she had no soreness of her tongue. She was taking extract "Hepastab" Liquid at irregular intervals. She was pale, with a lemon tinted skin and xanthochromic sclerotics. She looked well nourished. The tongue was pale, smooth, and non-tender. Spleen was slightly enlarged but not tender. Liver N.A.D. Heart was enlarged slightly towards the left, sounds were of pure tone, soft and regular, but no murmurs were detected. Other systems reveal no abnormality, and although the patient complained of early symptoms of cord involvement, no signs were present on careful examination. Patient was treated with iron and later copper and campolon, she made a good recovery and was dis charged from Hospital forty-four days after admission.

CASE NO. 4.* FEMALE Age 50 yrs. 28.12.38 - 7.2.39.

| DAYS | 1st | 9th | 16th | 22nd | 28th | 42nd |
|---|---|---|---|---|---|---|
| DATE. | 28.12 | 5.1 | 12.1 | 18.1 | 24.1 | 7.2 |
| R.B.C.(Mils) | 1.66 | 2.83 | 3.20 | 3.68 | 4.05 | 4.30 |
| Hb % | 43 | 68 | 67 | 72 | 74 | 81 |
| Hb gms | 6.45 | 10.2 | 10.05 | 10.8 | 11.1 | 12.15 |
| C.V. | 19 | 29 | 30 | 32 | 38 | 40 |
| M.C.V. | 114.46 | 102.47 | 93.75 | 86.96 | 93.83 | 93.02 |
| V.I. | 1.33 | 1.19 | 1.09 | 1.01 | 1.09 | 1.08 |
| M.C.H | 38.86 | 36.04 | 31.41 | 29.35 | 27.41 | 28.26 |
| M.C.H.C. | 33.95 | 35.17 | 33.5 | 33.75 | 29.21 | 30.38 |
| S.I. | 1.0 | 1.03 | 0.99 | 0.99 | 0.86 | 0.89 |
| W.B.Fe | 0.70 | 0.44 | 0.56 | 0.66 | 0.88 | 0.64 |
| S.Fe | 0.31 | 0.23 | 0.21 | 0.21 | 0.10 | 0.10 |
| W.B.Cu | 0.18 | 0.12 | 0.12 | 0.15 | 0.18 | 0.18 |
| S. Vit C | - | - | 0.67 | 0.74 | 0.52 | 1.20 |

Campolon 2ccs daily for five days, then every third day fr. 28.12. 38

Fe et Ammon Cit grs 30 + Cu Sulph gr 1/30 t.i.d. fr 5.1.39

Vit C mgm 300 daily fr. 24.1.39

## CASE NO. 4.

### Interpretation of Graphed Data.

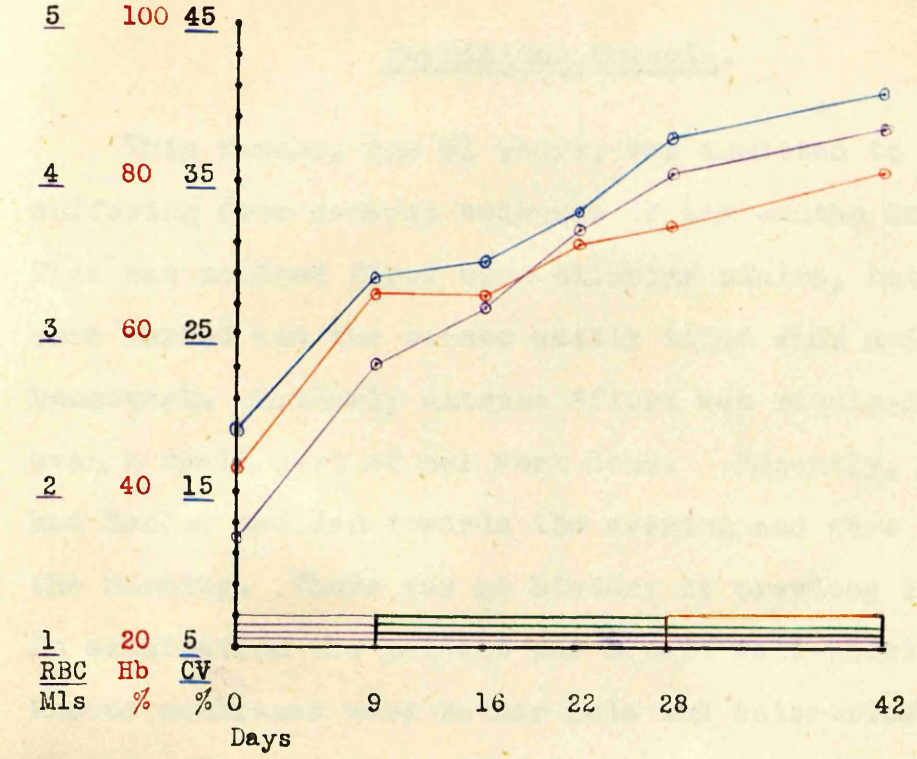
1. The serum Fe began high at 300 mcgs and fell steadily, during both liver extract and iron and copper therapy, to 100 mcgs at which level it remained.

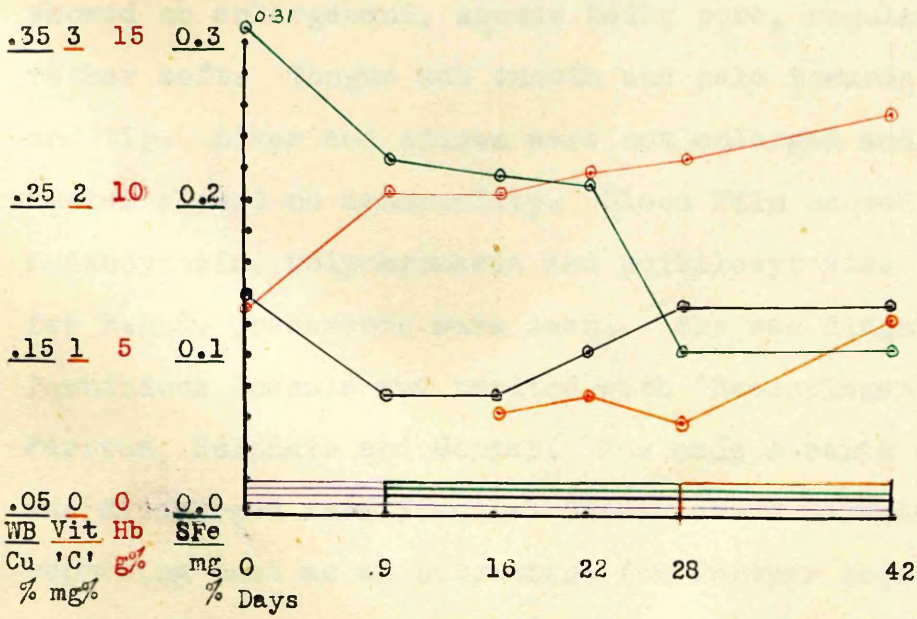
2. Hb. iron increased rapidly with the onset of treatment but a slightly increased rate of regeneration was noticed after the blood Cu had reached its height.

3. The blood Cu started slightly above normal and then fell towards the normal line. After the addition of iron and copper therapy it again rose.

4. The two iron curves appeared to be in an inverse ratio.

5. The blood Vit 'C' started at a low level and then rose after the addition of the vitamin to the therapy. No relationship between this and the iron and copper curves was noted.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 9 16 22 28 42
Days


0·31
.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg
% mg% %
0 9 16 22 28 42
Days

CASE No. 4.

## CASE NO. 5.

## HISTORY.

### Pernicious Anaemia.

This female, age 51 years, was admitted to Hospital suffering from general weakness of six months duration. This was noticed first upon climbing stairs, but became more marked and she became easily tired when doing her housework. Latterly extreme effort was required to get even a small part of her work done. Recently, her ankles had become swollen towards the evening and were better in the morning. There was no history of previous ill health. On examination the patient was a pale well-nourished woman. Mucous membranes were rather pale and sclerotics yellow tinged; skin was lemon tinted. There was no cynanosis. Odoema was present in the ankles but nowhere else. Heart showed no enlargement, sounds being pure, regular and rather soft. Tongue was smooth and pale towards the edges and tip. Liver and spleen were not enlarged and respiratory system showed no abnormality. Blood Film showed marked anisocytosis, polychromasia and poikilocytosis. Only a few R.B.C. precursors were seen. She was diagnosed as Pernicious Anaemia and treated with "Reticulogen", Campolon, Ferrous Sulphate and Copper. She made a rapid recovery and was discharged from Hospital twenty seven days later, reporting back as an outpatient for further injections and examinations.

CASE NO. 5.* FEMALE Age 51 yrs. 8.12.38 - 25.1.39

| DAYS | 1st | 8th | 13th | 19th | 24th | 30th | 36th | 49th |
|---|---|---|---|---|---|---|---|---|
| DATE. | 8.12 | 15.12 | 20.12 | 26.12 | 31.12 | 6.1 | 12.1 | 25.1 |
| R.B.C.(MIls) | 1.14 | 1.67 | 2.75 | 2.82 | 3.87 | 3.68 | 4.20 | 4.52 |
| Hb % | 36 | 44 | 51 | 64 | 73 | 77 | 79 | 80 |
| Hb gms | 5.4 | 6.6 | 7.65 | 9.6 | 10.95 | 11.55 | 11.85 | 12 |
| C.V. | 14 | 21 | 26 | 29 | 31 | 34 | 34 | 36 |
| M.C.V. | 122.81 | 125.75 | 94.54 | 102.84 | 80.1 | 92.39 | 80.95 | 79.65 |
| V.I. | 1.43 | 1.46 | 1.10 | 1.20 | 0.93 | 1.07 | 0.94 | 0.93 |
| M.C.H. | 47.37 | 39.52 | 27.82 | 34.04 | 28.29 | 31.39 | 28.21 | 26.55 |
| M.C.H.C. | 38.57 | 31.43 | 29.42 | 33.10 | 35.32 | 33.97 | 34.85 | 33.33 |
| S.I. | 1.13 | 0.92 | 0.87 | 0.97 | 1.04 | 1.0 | 1.03 | 0.98 |
| W.B.Fe | 0.70 | 0.74 | 0.70 | 0.74 | 0.78 | 0.70 | 0.79 | 0.93 |
| S.Fe | 0.26 | 0.22 | 0.12 | 0.10 | 0.10 | 0.13 | 0.12 | 0.10 |
| W.B.Cu | 0.33 | 0.26 | 0.20 | 0.18 | 0.10 | 0.16 | 0.21 | 0.26 |

↑ Reticulogen .5cc daily till 10.12, then every two days for 3 doses.

↑↑ Campolon 2cc every three days, from 19.12.38.

↑ Fe Sulph grs 5 t.i.d. from 16.12.38

↑ + Cu Sulph gr 1/30 from 2.1.39

## CASE NO. 5.

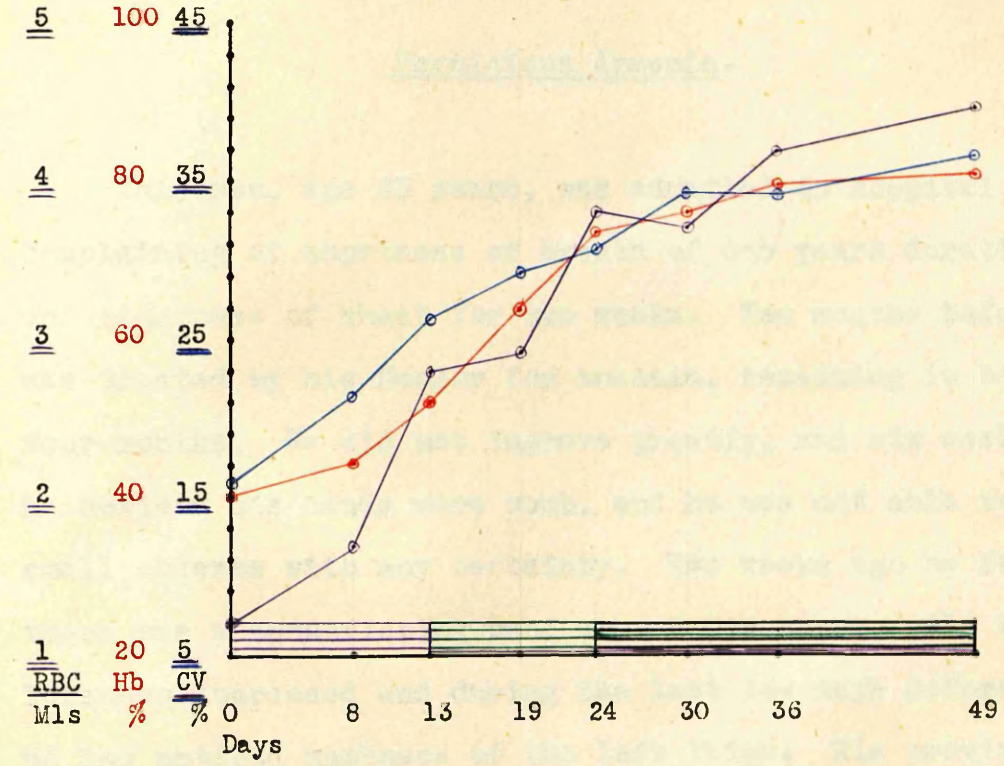
### Interpretation of Graphed Data.

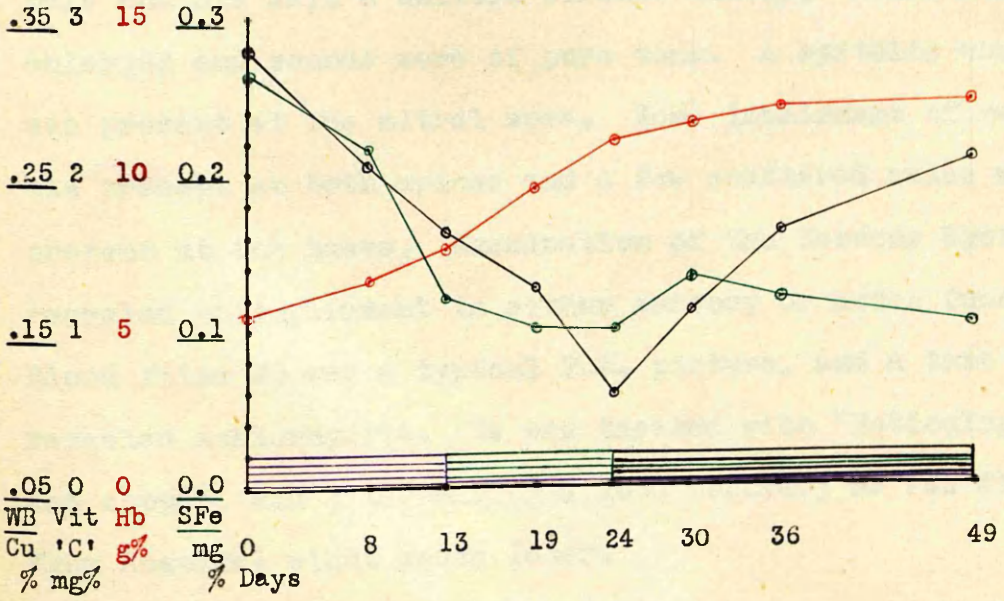
1. The serum Fe began high at 260 mcgs and fell slowly and steadily to 100 mcgs. It then showed a slight rise after the addition of copper to the therapy.

2. The Hb. iron showed a steady upward rise from the start of therapy, and no increase was noticed after the addition of either iron, or copper, to the therapy.

3. The blood Cu began high at 330 mcgs and fell steadily to 50 mcgs. At this point copper was added to the therapy and the blood Cu rose sharply again to 260 mcgs.

4. The serum and Hb. irons are almost in direct inverse ratio.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 8 13 19 24 30 36 49
Days


.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg
% mg% %
0 8 13 19 24 30 36 49
Days

CASE No. 5.

CASE NO. 13.

HISTORY.

Pernicious Anaemia.

This man, age 65 years, was admitted to Hospital complaining of shortness of breath of one years duration, and tightness of chest for two weeks. Ten months before he was treated by his Doctor for aneamia, remaining in bed for four months. He did not improve greatly, and six weeks ago he noticed his hands were numb, and he was not able to grasp small objects with any certainty. Two weeks ago he felt that there was a constricting band around his chest. His breathlessness increased and during the last few days before admission he had noticed numbness of the left thigh. His previous health had been good and there was no relative family history. Patient was a well-nourished man; his mucous membranes were pale and his skin a uniform biscuit colour. Heart was not enlarged and sounds were of pure tone. A systolic murmur was present at the mitral area. Some impairment of resonance was present at both apices and a few scattered rales were present at the bases. Examination of the Nervous System revealed no impairment in either sensory or motor functions. Blood films showed a typical P.A. picture, and a test meal revealed achlorhydria. He was treated with "Reticulogen" iron and copper, and after making a good recovery he was discharged from Hospital eight weeks later.

CASE NO. 13. * MALE. Age 65 yrs. 13.2.39 - 14.4.39.

| DAYS | 1st | 8th | 15th | 23rd | 30th | 38th | 44th | 50th | 61st |
|---|---|---|---|---|---|---|---|---|---|
| DATE. | 13.2 | 20.2 | 27.2 | 7.3 | 14.3 | 22.3 | 28.3 | 3.4 | 14.4 |
| R.B.C.(Mils) | 1.20 | 2.00 | 2.90 | 4.00 | 3.83 | 4.10 | 4.52 | 4.37 | 5.10 |
| Hb % | 30 | 40 | 53 | 65 | 65 | 65 | 74 | 72 | 84 |
| Hb gms | 4.5 | 6.0 | 7.95 | 9.75 | 9.75 | 9.75 | 10.8 | 10.5 | 12.6 |
| C.V. | 14 | 20 | 31 | 36 | 37.5 | 42 | 44 | 40 | 44 |
| M.C.V. | 116.67 | 100.0 | 106.90 | 90.0 | 97.91 | 102.44 | 97.34 | 91.53 | 86.27 |
| V.I. | 1.36 | 1.16 | 1.24 | 1.05 | 1.14 | 1.19 | 1.13 | 1.06 | 1.00 |
| M.C.H. | 37.5 | 30.0 | 27.41 | 24.38 | 25.46 | 23.78 | 23.89 | 24.03 | 24.71 |
| M.C.H.C. | 32.14 | 30.0 | 25.65 | 27.08 | 26.0 | 23.21 | 24.55 | 26.25 | 28.64 |
| S.I. | 0.95 | 0.88 | 0.75 | 0.80 | 0.76 | 0.68 | 0.72 | 0.77 | 0.84 |
| W.B.Fe | 0.57 | 0.68 | 0.60 | 0.68 | 0.70 | 0.75 | 0.65 | 0.70 | 0.67 |
| S.Fe | 0.20 | 0.21 | 0.20 | 0.20 | 0.18 | 0.18 | 0.12 | 0.12 | 0.18 |
| W.B.Cu | 0.07 | 0.08 | 0.08 | 0.09 | 0.09 | 0.08 | 0.16 | 0.17 | 0.28 |
| S. Vit C | 0.54 | 0.50 | 0.66 | 0.92 | 2.60 | 1.65 | 0.68 | 0.82 | 0.94 |

↑ Reticulogen 0.5cc daily for three days and then once weekly.

↑ Vit C 300 mgm/day from 1.3.39

↑ Fe Sulph grs 3 t.i.d. from 9.3.39

↑ ‡ Cu Sulph gr 1/30 t.i.d. fr. 22.3.39

## CASE NO. 13.

### Interpretation of Graphed Data.

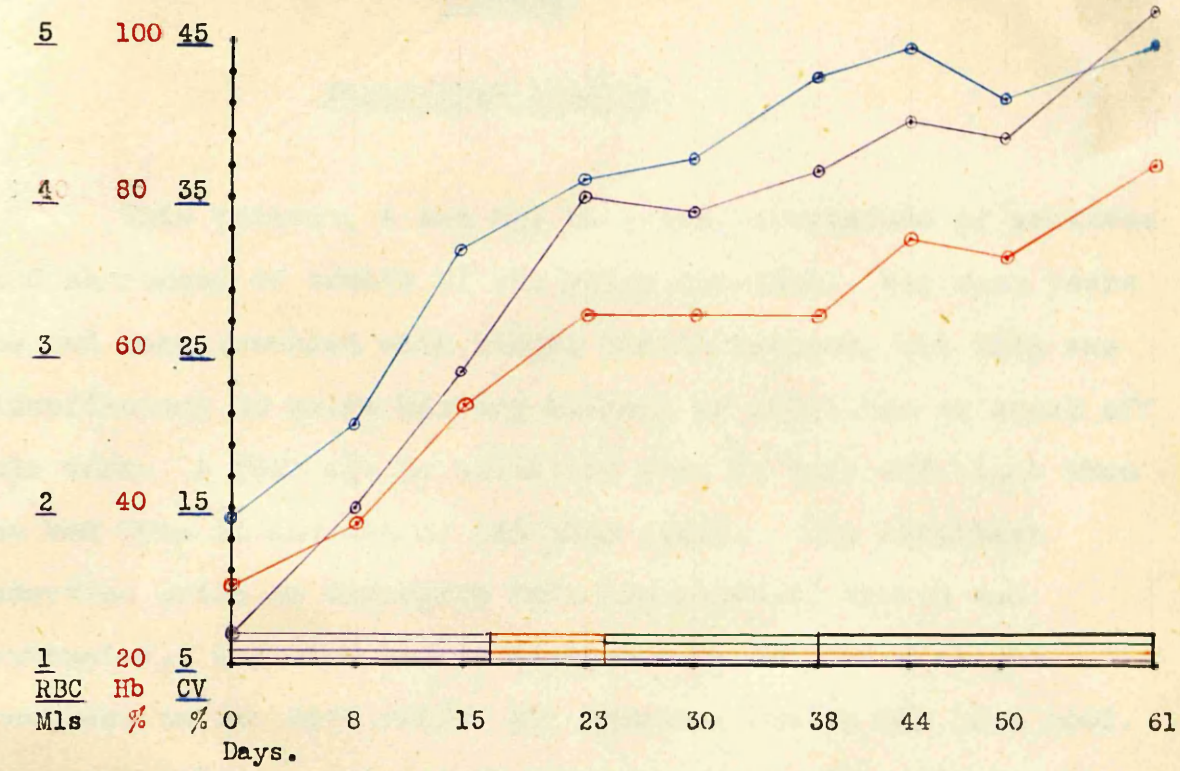
1. The Serum Fe began high at 200 mcgs and remained close to this level until copper therapy was started, when it fell sharply only to rise again almost at once as the blood Cu rose up to its peak.

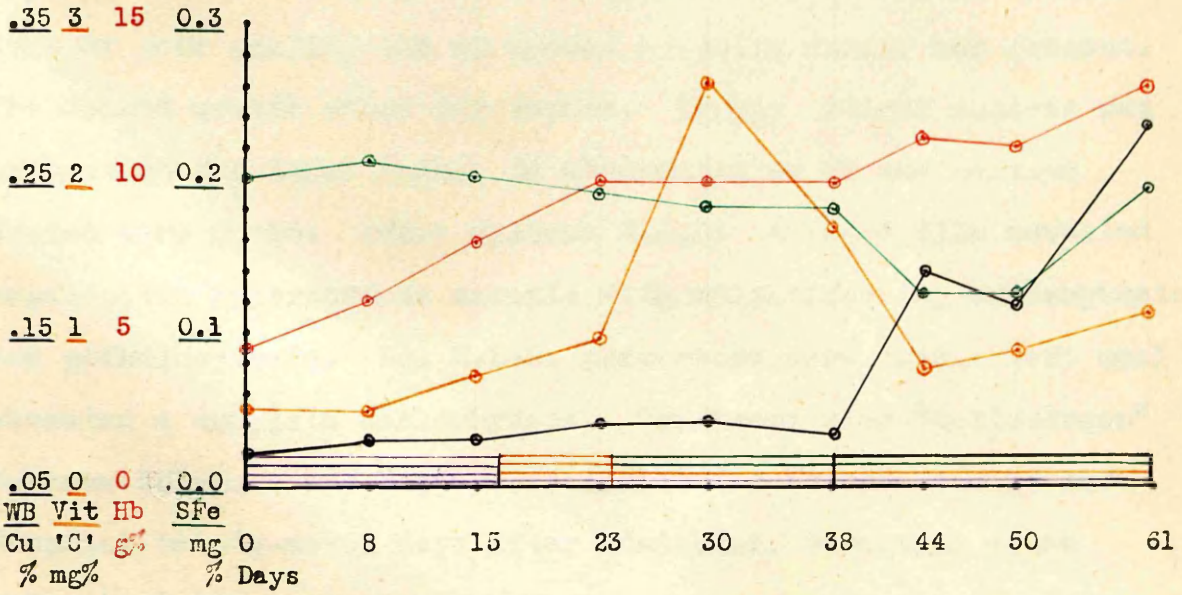
2. The blood Hb. rose slowly and steadily from the start, until the 23rd day when it slowed up for a couple of weeks to remain at the same level. With the beginning of copper therapy it began to rise again.

3. The blood Cu began low and remained so until copper was added the diet when there was a rapid upward rise.

4. The two iron curves are almost in inverse ratio except in the last week when they both show an upward rise.

5. The blood Vit 'C' started low and then rose quickly after the addition of the vitamin to the diet, but after three weeks it began to fall again. It does not appear to be related to either the iron or copper curves.


5 100 45
4 80 35
3 60 25
2 40 15
1 20 5
RBC Hb CV
Mls % %
0 8 15 23 30 38 44 50 61
Days.


.35 3 15 0.3
.25 2 10 0.2
.15 1 5 0.1
.05 0 0 0.0
WB Vit Hb SFe
Cu 'C' g% mg
% mg% % Days
0 8 15 23 30 38 44 50 61

CASE No. 13.

## CASE NO. 14.

## HISTORY.

### Pernicious Anaemia.

This patient, a man age 66 years, complained of weakness and shortness of breath of one years duration. For many years he had been troubled with slight breathlessness, but this was insufficient to cause him any anxiety or cause him to knock off his work. A year ago he collapsed when at work and since then he had been in and out of bed many times. The slightest exertion prior to admission left him short of breath and exhausted. One week before admission he noticed a slight numbness in the left foot. His previous health had been good. On examination he was a well-nourished man. His skin was lemon tinted and the mucous membranes and lips were pale; tongue was smooth. Heart was slightly enlarged towards the left; sounds were of poor quality and an apical systolic murmur was present. The second aortic sound was impure. Lungs: Slight dulness was present at the lower lobe. No abnormalities of the nervous system were noted. Other systems N.A.D. A blood film revealed megalocytic hyperchromic anaemia with polychromasia, aniscoytosis and poikilocytosis. No. R.B.C. precursors were seen. Test meal revealed a complete achlorhydria. Treatment with "Reticulogen" Ferrous Sulphate and Copper was instituted at once and he left Hospital twenty-seven days after admission, reporting as an outpatient for control.

CASE NO. 14. * MALE. Age 66 yrs. 16.2.39 - 29.3.39.

| DAYS | 1st | 8th | 15th | 22nd | 29th | 37th | 42nd |
|---|---|---|---|---|---|---|---|
| DATE. | 16.2 | 23.2 | 2.3 | 9.3 | 16.3 | 24.3 | 29.3 |
| R.B.C.(Mils) | 2.26 | 3.23 | 3.45 | 4.18 | 4.38 | 4.96 | 4.40 |
| Hb % | 51 | 65 | 66 | 78 | 82 | 81 | 88 |
| Hb gms | 7.65 | 8.4 | 8.55 | 11.7 | 12.3 | 12.15 | 13.2 |
| C.V. | 22 | 28 | 30 | 40.5 | 44 | 44 | 42 |
| M.C.V. | 97.34 | 86.69 | 86.96 | 96.89 | 100.46 | 88.71 | 95.45 |
| V.I. | 1.13 | 1.01 | 1.01 | 1.13 | 1.17 | 1.03 | 1.11 |
| M.C.H. | 33.85 | 26.0 | 24.78 | 27.99 | 28.08 | 24.50 | 30.0 |
| M.C.H.C. | 34.77 | 30.0 | 28.5 | 28.89 | 27.95 | 27.61 | 31.43 |
| S.I. | 1.02 | 0.88 | 0.84 | 0.85 | 0.82 | 0.81 | 0.92 |
| W.B.Fe | 1.00 | 0.70 | 0.66 | 0.64 | 0.88 | 0.86 | 0.94 |
| S.Fe | 0.62 | 0.40 | 0.22 | 0.12 | 0.11 | 0.11 | 0.10 |
| W.B.Cu | 0.20 | 0.19 | 0.20 | 0.20 | 0.21 | 0.26 | 0.26 |
| S. Vit C | 0.55 | 0.35 | 0.70 | 1.2 | 1.97 | 2.13 | 2.10 |

Hepastab 2ccs daily for three days, then Reticulogen 0.5 ccs every five days for three doses.

Vit C mgm 300/day from 5.3.39.

Fe Sulph grs 3 t.i.d. + Cu Sulph gr 1/30 from 9.3.39.

## CASE NO. 14.

### Interpretation of Graphed Data.

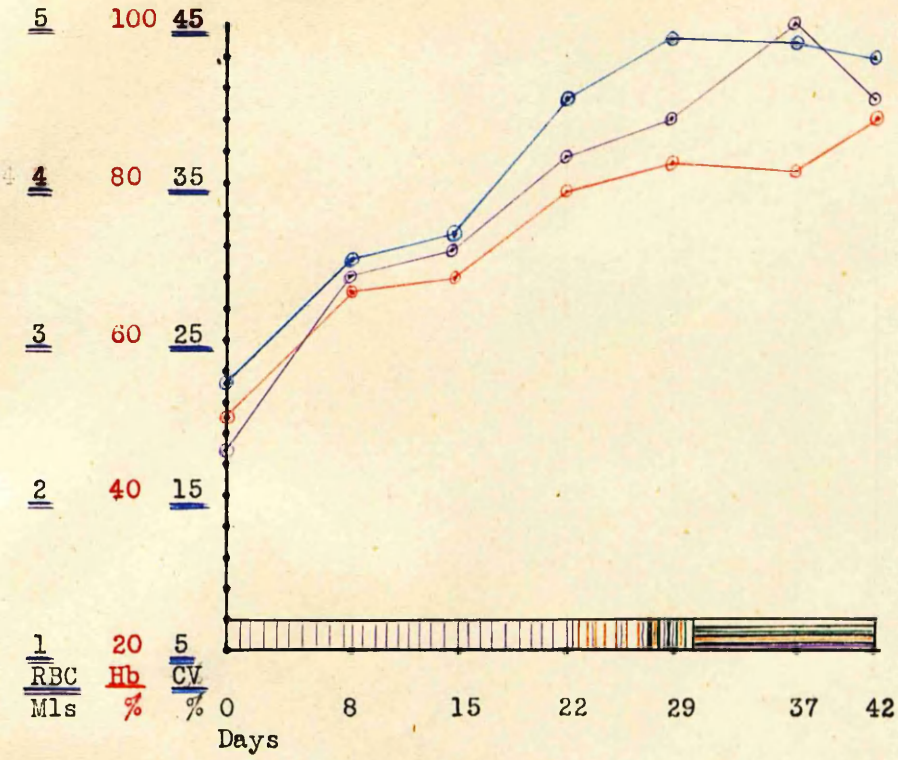
1. The Serum Fe began very high at 620 mcgs and fell rapidly to 120 mcgs, at which level it remained steady.

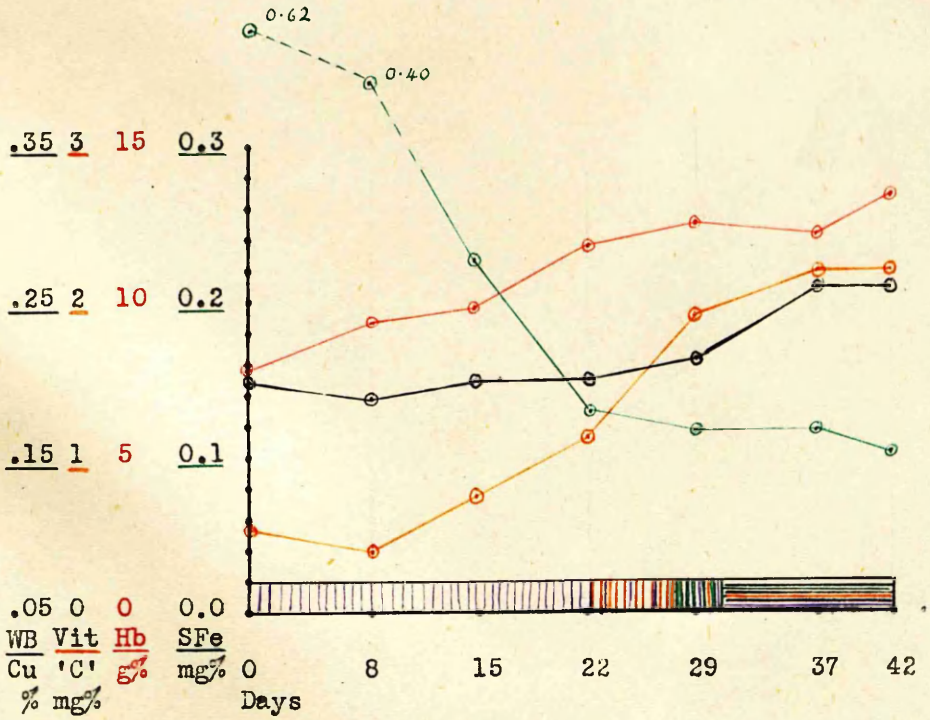
2. The Hb. iron started low and rose steadily, showing a slight increased rise after the addition of copper therapy.

3. The blood Cu began at 195 mcgs and remained at this level until after copper therapy had begun when it rose up to 260 mcgs. It was after it had reached its height that the haemoglobin showed an increased rate of increase.

4. The two iron curves appeared to be in inverse ratio.

5. The Vitamin 'C' began low and rose steadily throughout therapy to reveal an increased upward rise after Vit 'C' had been added to the diet.


5
4
3
2
1
RBC
Mls
100
80
60
40
20
Hb
%
45
35
25
15
5
CV
%
0
8
15
22
29
37
42
Days


0·62
0·40
.35
.25
.15
.05
WB
Cu
%
3
2
1
0
Vit
'C'
mg%
15
10
5
0
Hb
g%
0.3
0.2
0.1
0.0
SFe
mg%
0
8
15
22
29
37
42
Days

CASE No. 14.