THE USE OF LIVER AND IRON IN THE TREATMENT OF ANEMIA

RUSSELL L. HADEN, M.D.

Anemia is a reduction in the capacity of the blood to transport oxygen. Hemoglobin is the direct carrier of oxygen; the red cell acts as a container for the hemoglobin. In every anemia there is a decrease in hemoglobin; there may or may not be a reduction in the number of erythrocytes. The red cells are always altered, however, since the amount or concentration of hemoglobin in the cell must be abnormal, even if the number of erythrocytes is unchanged.

The total mass of red cells or erythron, which is best thought of as a vessel containing hemoglobin, is always changing. The normal erythron is kept at a constant volume, is made up of a constant number of red cells, and contains a constant amount of hemoglobin. In an adult male it has a volume of 2250 cc., contains nearly 800 grams of hemoglobin, and is made up of about 25 trillion red cells. The continuous alteration in the erythron is due to the fact that a red cell lives only about one month. When a cell dies, the stroma making up the framework disintegrates and hemoglobin is set free. The hemoglobin released is not used again as such but is broken up. Iron is split off, however, and a large part becomes a part of newly-made hemoglobin. It is possible the porphyrin nucleus of the disintegrated hemoglobin may be similarly employed. The stroma is not used again. Roughly, each day a trillion cells with a volume of 100 cc. and containing 30 grams of hemoglobin are destroyed so the same number must emerge from the bone marrow to keep the cell level constant. Nearly one billion red cells must be formed every minute of every day.

To make erythrocytes, water, mineral salts, protein, fat, and carbohydrate are required since the cells contain all these elements. Such nonspecific building materials are necessary to make all cells. To make the stroma of a normal red cell, at least one specific element is necessary. This is a chemical substance, the exact composition of which is unknown, formed by the action of a specific secretion of the gastric mucosa (the intrinsic factor of Castle) on some element in the food (the extrinsic factor of Castle). This substance is contained in liver and liver substitutes. It has the property of specifically maturing the cell or supplying the finishing touches in preparation for emergence from the bone marrow. This substance has been designated the erythrocyte-maturing factor (EMF).

As stroma is formed by nonspecific components and the specific erythrocyte-maturing factor, hemoglobin is deposited in the stroma to saturate it and make one-third of the final volume. The hemoglobin is elaborated by the reticulo-endothelial cells of the bone marrow. The

porphyrin nucleus needed for building the hemoglobin molecule seems abundant. One specific element, iron, is necessary for making hemoglobin. This is often deficient because the store of iron in the body is very small. To replace the 30 grams of hemoglobin normally destroyed each day, 100 mg. of iron are required. The total amount of iron in the body is roughly 4 grams and about 3 grams of this is in hemoglobin. Only about 85 to 90 per cent of the 100 mg. of iron set free from hemoglobin broken down each day is used again, so 10 to 15 mg. must be supplied daily to replace the deficit. The diet seldom contains much iron, so if there is a deficient intake of iron-containing foods an iron deficiency develops rapidly. When external hemorrhage occurs the most important loss is in iron. With internal hemorrhage the iron is conserved. A deficient iron intake or a loss of iron quickly causes a fall in hemoglobin.

With growth the total hemoglobin of the body increases since the blood constitutes a fixed fraction (about 1/13) of the body weight. If a normal man has 800 grams of hemoglobin, a child one-half his weight has only 400 grams of hemoglobin. As the total hemoglobin increases with growth, the store of iron in the body must become greater if properly supplied by food or medication. This growth factor is important in the anemia of younger individuals.

The formation of normal red cells containing the normal amount of hemoglobin is influenced also by conditions other than an adequate supply of the specific elements, the erythrocyte-maturing factor (EMF) and iron. Both specific factors are absorbed from the gastro-intestinal tract. With various abnormalities such as achlorhydria or diarrhea, absorption may be interfered with. Likewise, general conditions such as hypometabolism, infection, toxemia as from nephritis, or poisons, as lead, may interfere with normal marrow activity and so influence the building of red cells and hemoglobin. All such possible influencing factors must be taken into consideration in the use of liver and iron in the treatment of anemia.

In clinical anemia there may be a lack of the erythrocyte-maturing factor, of iron, or of both specific elements. This may be due to a deficiency in supply, absorption, or utilization, or result from increased need from growth, pregnancy, or increased metabolism.

An iron deficiency is the most common defect because of the small reserve supply of iron, the needs for growth, the relatively small amounts of iron in food, and the frequent loss of iron by chronic long-continued hemorrhage as from hemorrhoids or menorrhagia. An iron lack is detected by a decreased amount of hemoglobin per cell or low color index. At the onset of an iron deficiency the cells may be of normal volume but without the normal complement of hemoglobin as

shown by a low color index. If an iron deficiency continues the cells become smaller, seemingly because there is no use in having stroma if there is no hemoglobin to be carried. Every iron-deficiency anemia is thus hypochromic first and later microcytic as well as hypochromic.

Young, immature cells are larger than mature erythrocytes. As the cells mature with the incorporation of the erythrocyte-maturing principle, they become smaller. If there is a deficiency of the erythrocyte-maturing factor the cells are larger and the anemia is macrocytic and usually hyperchromic.

If there is a deficiency of both iron and the erythrocyte-maturing factor, the microcytosis of the iron deficiency may be cancelled by the macrocytosis of the EMF deficiency so a normocytic anemia may be the result of the deficiency of the two elements.

Iron and liver or liver substitutes for supplying the erythrocyte-maturing factor are indicated if there is a deficiency in supply or lack of absorption. In some cases where there is deficient utilization, an added supply may enable the bone marrow to take up more of the specific factor. Thus in chronic nephritis if the percentage of utilization of iron is lowered the anemia may be influenced by giving more although the supply may be adequate for normal utilization. Little is known about the actual amount of the erythrocyte-maturing factor used. In the hemolytic anemias with rapid regeneration of erythrocytes as shown by the high reticulocyte count, it is possible that the supply of erythrocyte-maturing factor is not adequate so added liver may be indicated to supply the excessive demand even if the production in the body of the specific principle remains constant.

The following facts concerning the physiology of the red cell have been emphasized:

1. Red cells and hemoglobin are constantly being lost and replaced.

2. The rate is very rapid as shown by a normal loss and replacement of a trillion cells and 30 grams of hemoglobin each day.

3. Specific and nonspecific elements are necessary for building red cells and hemoglobin.

4. The nonspecific elements are those required for making all cells.

5. The specific principles required are: (a) the erythrocyte-maturing factor (EMF) supplied by liver and liver substitutes to make the stroma of red cells and (b) iron for the synthesis of hemoglobin.

6. The erythrocyte-maturing factor is usually supplied to meet even abnormal demands as the liver and other organs contain a large reserve supply.

7. Added amounts may be required when: (a) a normal supply is not made in the stomach as in idiopathic pernicious anemia, (b) the

bone marrow cannot utilize the principle normally, and (c) when there is an excessive long-continued demand as in chronic hemolytic anemia where the production of new cells proceeds at an abnormally rapid speed to compensate for the cells lost.

8. The reserve store of iron is very small so an iron deficiency develops quickly if iron is lost through hemorrhage, or the intake is insufficient to meet normal needs.

9. Added iron is required to supply the (a) normal increased store that comes with growth, the physiologic increased need with pregnancy and lactation, and the loss of iron with menstruation, and (b) the deficit due to an inadequate intake, increased loss through hemorrhage, pathologic increased needs as in hyperthyroidism, decreased absorption as in achlorhydria, or impaired utilization by the marrow as in myxedema.

10. The need for liver is manifested by a macrocytosis of the red cells as shown by an increased volume index.

11. The need for iron is shown by a hypochromia of the red cells indicated by a low color index. With a long-continued iron deficit, a microcytosis is present also.

How may the erythrocyte-maturing factor be supplied? Glandular organs as the liver, kidney, and stomach all contain it. Liver and gastric mucosa are highest in specific content. Yeast also contains a significant amount. Where this principle is to be supplied, the inclusion of an adequate amount of protein and some liver in the diet should be insisted on. It is difficult, however, to get enough of the specific principle unless concentrates of liver and gastric mucosa are employed. The liver concentrates are the preparations of choice since these are available for both oral and parenteral use. Preparations of the gastric mucosa can be given by mouth only.

The parenteral use of the erythrocyte-maturing principle is the most efficient. The same amount of specific principle is 30 times as active with parenteral as with oral use. The efficiency of oral administration often decreases with age and continued use. Parenteral use is also more economical than oral administration when one considers the comparative amounts of specific principle necessary to bring the blood to normal and keep it so.

The ideal way to supply the specific maturing principle is to take a complete diet adequate in protein, fruits, and vegetables which includes a liberal serving of whole liver once or twice a week and to add to this liver extract parenterally.

Today, there are many liver extracts on the market. These have been increased greatly in potency and therapeutic effect. The better extracts are now standardized on the basis of units. One unit is the amount of effective principle needed each day to keep the blood normal.

Patients with idiopathic pernicious anemia vary greatly in the amount of principle required to return the blood to normal and to keep it at a normal level. The extracts can be standardized only on patients so one cannot be sure that a unit is always the same. A potent preparation of a responsible manufacturer only should be used. Even with such a preparation the best method of administration should be determined by each clinician. The concentrated extracts usually contain 15 units of the specific principle per cubic centimeter.

The most important use of liver extract is in the treatment of idiopathic pernicious anemia. This disease is most serious as is well shown by the fact that all patients suffering from the disease died before the advent of liver therapy. If undertreated, the patient may get along very well but continue to have a persistent, mild anemia. With undertreatment, however, a subacute combined sclerosis is very apt to develop and produce permanent crippling. It is much better to overtreat than to undertreat pernicious anemia, since the cost of liver extract is small as compared with the seriousness of the disease. Many different plans of treatment have been suggested. We have found the following plan very satisfactory over a number of years. When the patient first presents himself with active pernicious anemia or when in relapse, an injection of 1 cc. of a concentrated extract containing at least 15 units per cc. is given twice a week for the remainder of a 3 month period. For the second three months an injection is given once a week, and for the next six months one every two weeks. After this period of one year, usually only one injection each month is required although calculating from the unitage this is not sufficient. We have many patients who have gone as long as five years with the blood remaining normal under this plan of treatment. If the patient does not have a cord lesion when first seen, he should never develop one if efficiently treated. If there is already a cord lesion when treatment is begun, the treatment should be even more vigorous if the neurologic symptoms are marked. This may be carried out by continuing the frequent injections for a longer period, by giving liver oftener, and by adding liver extract orally.

The best criterion of efficient and complete therapy is the maintenance of a normal volume of the red cell. A complete blood study should be done at least every three months for the remainder of the life of the patient. An increase in the mean volume of the red cell always heralds a relapse or indicates incomplete therapy.

The manner of administration of liver extract in congenital hemolytic jaundice, in pregnancy, in sprue, and other conditions in which there is decreased absorption, increased need or impaired utilization must be determined by the severity of the need and treatment given accordingly. Here there is usually a macrocytosis of the red cells just as in pernicious anemia.

The question always arises concerning the value of liver in a frank hypochromic or iron deficiency anemia. With an achlorhydria there is always a possibility that liver extract may do good. With normal gastric acidity it is very unlikely that the liver extract will influence the anemia.

A hypochromia with or without a microcytosis indicates that the stroma of the cell is not sufficiently supplied with hemoglobin. This deficiency is due to a defect in supply of iron to the bone marrow or a lack of utilization of iron in the marrow. If the hypochromia is due to defective utilization of the iron from chronic nephritis, malignancy, infection, or hypothyroidism, the anemia may be helped by giving large amounts of iron since the total amount utilized is increased although the percentage may be unchanged.

If the hypochromia is due to a deficient supply of iron by reason of deficient intake, or by reason of an increased iron loss due to hemorrhage, the effect of giving iron is usually rapid and complete if the proper preparation of iron is taken.

What preparation of iron should be employed? Iron is present in the hemoglobin molecule in the ferrous form. All the evidence indicates that iron given in the reduced state must be oxidized to the ferrous form and if given as a ferric salt must be reduced to the ferrous state. Almost any iron preparation is potent if given in large enough amounts, but smaller amounts of the ferrous salts are required than of reduced iron or ferric salts. The best preparations are ferrous carbonate, ferrous chloride, and ferrous sulphate. These are all cheap and efficient. The relative utilization of the different medicinal preparations is given as follows by Witts:

Preparation	*Effective Daily Dose Grains*	*Iron Content Mg.*	*Utilization of Iron Per Cent*
Metallic:			
Reduced iron	20-90	1200-1500	0.5-2
Ferrous:			
Ferrous chloride	4-8	100-200	12.5-25
Ferrous sulphate	9-12	180-240	14.0
Ferrous carbonate (As Blaud's pills)	45-60	300-400	8.0
Ferric:			
Ferric ammonium citrate	60-120	800-1600	1.5-3

It is evident from these data that reduced iron and ferric salts should never be given if ferrous preparations are available. Ferrous sulphate should be given in doses of 9 to 18 grains daily. Smaller amounts of

ferrous chloride are required (9 to 12 grains). The chloride is best given in a 5 per cent solution in a mixture of 3 parts water and 1 part simple syrup. I have long used a pill containing 2 4/5 gr. ferrous sulphate and 1 4/5 gr. sodium carbonate. Six tablets are given daily. Blaud pointed out over one hundred years ago that this is a most efficient preparation. In my hands it has been the most satisfactory of all preparations.

The oral preparations of iron are so efficient there seems little reason for using parenteral iron therapy. It is true that iron given parenterally is 30 times as active as when given by mouth but the margin between effective and toxic doses is small. Utilization is good by mouth and ferrous salts are very cheap.

With the administration of an active iron preparation in optimum amounts the hemoglobin will increase 1 to 2 per cent each day. If the fault is due to poor utilization, the rise is much smaller unless the cause for the poor utilization is corrected, as by giving thyroid extract in myxedema. If the cells are small to begin with, they get larger as iron is supplied to make hemoglobin. If the cause for the iron deficiency such as hemorrhoids is corrected after the hemoglobin returns to normal, iron medication does not need to be continued. In certain cases, as in idiopathic hypochromic anemia where absorption seems impaired, it is best to continue iron one week of each month. This method seems to keep the supply up to normal.

Should other metallic elements, such as copper, be given with iron? In adults, at least, there is little evidence that added copper is of value. All medicinal iron preparations contain some copper, so if any is needed this should be enough. In the same way there seems no reason for adding vitamin B to complement or supplement iron.

Should iron and liver therapy be given together? If the erythrocyte-maturing principle is needed, iron is seldom lacking. If iron is indicated, the anemia is seldom influenced by liver extract. Only rarely does an iron deficiency occur with a deficiency in the specific principle of liver. If there is an achlorhydria with the hypochromia the effect of liver may be tried. Cases of a combined deficiency, however, are rare. The important thing in every anemia is to determine the need and supply this effectively. There is no point in wasting money on liver extract if no deficiency in the specific maturing principle exists; iron should not be given if there is no lack of iron.

Summary

1. The physiology of the red cell has been reviewed and the factors influencing the supply and use of iron and the specific principle of liver emphasized.

2. The erythrocyte-maturing principle is best supplied as liver extract administered parenterally.

3. When the specific principle is needed, as in pernicious anemia, an adequate amount of a potent extract must be given.

4. Pernicious anemia should be overtreated rather than undertreated.

5. With complete therapy the macrocytosis characteristic of a deficiency in the erythrocyte-maturing factor should disappear.

6. Iron should be given in the ferrous form and in adequate dosage.

7. There is seldom an indication for parenteral iron therapy.

8. With correct therapy the hypochromia and microcytosis characteristic of an iron deficiency should disappear.

9. Both liver extract and iron are seldom needed. Liver extract should be given in a hypochromic anemia only if an achlorhydria is present.

10. Careful attention should be given to correcting factors which unfavorably influence the absorption and utilization of the specific factors.