Essential Nutrients *in the Management of* Hematopoietic Disorders of Human Beings: *A Résumé*

By Richard W. Vilter, M.D.*

It is probable that all nutrients are necessary for the formation of the normal erythrocyte, leukocyte, and platelet, and of the plasma in which these elements float. Most of these substances are so readily available that they are never limiting factors in blood formation. A select few are not so accessible to the bone marrow, cannot be synthesized by the body, and, when a deficiency occurs, may limit blood formation. These are the essential nutrients around which this conference has revolved. These are iron, for hemoglobin formation, and folic acid and vitamin B_{12}, for nucleic acid synthesis. It is probable that protein and particularly some of the amino acids are just as important and just as likely to be deficient when diets are inadequate or stress excessive. However, so little is known concerning the protein requirements for hematopoiesis in human beings, that no full-dress discussion of the subject was considered to be profitable. There has been clear demonstration that the protein requirements for hemoglobin formation in anemic hypoproteinemic dogs takes precedence over serum protein and tissue protein formation. In hypoproteinemic animals with normal hemoglobin levels, hemoglobin and tissue protein have equal priority. In animals, protein and tryptophane, methionine, histidine, phenylalanine, and lysine deficiencies induce an anemia which is usually microcytic and slightly hypochromic. Our group here in Cincinnati has been impressed with a form of nutritional hypoplastic anemia in exceedingly malnourished persons. We have thought that this anemia might be the result of protein malnutrition, but have not been able to demonstrate a response to casein supplements alone, although these persons will recover slowly when fed a complete diet. In kwashiorkor, a disease due primarily to protein malnutrition, no specific type of anemia has been described. Most infants with this syndrome are anemic, but the cause is usually iron deficiency, chronic infection, or parasitic infestation. Even though we have not established protein as a limiting factor in blood formation in human beings, the basic need for protein in blood regeneration is recognized and a diet rich in animal and vegetable protein should be a basic tool for the treatment of anemia. If it does nothing else, it may keep hemoglobin regeneration from stealing protein from some other part of the body.

Likewise, much time could have been spent on a discussion of the niacin, riboflavin, and vitamin B_6 requirements of laboratory animals for blood formation. These vitamins, the precursors of important oxidation, decarboxylation and transamination enzyme systems are essential parts of every growing cell; yet in human beings, deficiencies of these substances have not been shown to induce anemia. Apparently, other organs and systems are so adversely affected that death occurs before the function of the bone marrow is seriously impaired. Nevertheless, since we recognize their importance to all cellular metabolic functions, we should prescribe a diet rich in the B-complex vitamins when we treat nutritional anemia. Until a patient can take a diet rich in protein and these vitamins, we may

From the Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio.

* Associate Professor of Medicine, Director of the Laboratory of Hematology and Nutrition.

wish to supplement his intake with protein in the form of powdered milk and with a mixed-vitamin capsule. We must recognize that this prescription is merely in lieu of an adequate diet and has no specific effect on blood formation. It is supportive therapy.

Bile pigment is a very important part of the hemoglobin molecule, but there is no evidence that it ever becomes a factor limiting blood formation. Rather, as Dr. James has shown, it is important as a means of studying blood destruction and some of the steps in the synthesis of porphyrins and hemoglobin. Of all the essential nutrients, only folic acid and vitamin B_6 might be limiting factors in pigment metabolism, but, as yet, we know of no therapeutic considerations in this field.

As has been pointed out many times, iron, folic acid, and vitamin B_{12} have very specific metabolic functions. Ascorbic acid influences the metabolism of these substances, too. These functions are so specific, in fact, that accurate diagnosis of the type of anemia is essential; otherwise, nine times out of ten the therapy will fail, and the patient's money and time will be wasted. On the other hand, if diagnosis is accurate, a deficiency of one of these substances is found to exist and if the physician sets about correcting it by giving the deficient substance by a satisfactory route of administration, a brilliant therapeutic result will be obtained.

Dr. Carl Moore has shown us that the absorption of food iron is improved by vitamin C or other reducing agents. Inorganic iron as used in treatment—ferrous sulfate and ferrous gluconate, given in full doses of one or two grams daily—does not require accessory substances for satisfactory absorption or utilization. A ferrous sulfate or ferrous gluconate tablet costs a penny, and delivers to the patient just as much, if not more, iron than a complex formula containing many nutrients essential for other things but not for blood formation in the iron-deficient patient. For those persons whose irritable gastrointestinal tracts are upset by the simple iron compound—and one finds these in the carriage trade practice much more frequently than in the free or part pay clinic—one may reduce the dose or give saccharated oxide of iron by vein or mouth.

Two warnings should be given at this point:

1. Be sure you know the source of blood loss in the patient with microcytic hypochromic anemia, and deal with it as effectively as possible.

2. Don't use iron as a placebo—you may be giving it to a patient with incipient hemochromatosis.

Dr. George Cartwright has presented a beautiful physiologic study of copper in hematopoiesis and has demonstrated that this element is necessary for the absorption, utilization, and movement of iron from iron stores. He has also shown us that the anemia of copper deficiency in swine is due, at least in part, to the formation of an erythrocyte whose life span is short. There is still more to be learned concerning copper in hematopoiesis, but there is no need for this element in pill or capsule form except under the rarest of circumstances. It is difficult to find a diet containing an insufficient amount of copper; a new-born infant has large copper stores even though his blood plasma copper level is low; and inorganic iron preparations contain sufficient copper as an impurity.

The functions of cobalt in hematopoiesis are unknown, except as this element is an essential part of the vitamin B_{12} molecule. Cobalt, in large doses, 100 to 150 mg. daily as cobalt chloride, will induce polycythemia in human beings. It will force the bone marrow to make more cells even when nephritis or chronic infection are the causes of the anemia. It is doubtful whether this effect is physiological, and the benefits of such therapy are still questioned by most hematologists.

The other trace elements, zinc, molybdenum, magnesium, and manganese have not been shown to effect hematopoiesis.

Much has been learned in recent years of the metabolism and clinical interrelationships of vitamin B_{12}, folic acid, and ascorbic acid. Doctors Williams, Mueller, Will, and Schilling have covered this field in detail, and Dr. Jukes has shown how antimetabolites of some of these substances have been used successfully in hematologic research. These hematopoietic

vitamins are very specific chemical compounds with clear-cut metabolic functions. These are: the formation of the purine ring, the interconversion of pyrimidine ribosides, the formation and metabolism of certain essential amino acids, and the maintenance of reduction potentials within the cell. They will improve hematopoiesis only when a deficiency of one of them has interfered with blood formation. Vitamin B_{12}, given parenterally in doses of 10–15 μg. daily, is the therapy of choice in pernicious anemia in relapse and in nutritional macrocytic anemia. Actually, 1 μg. daily is all that is required, but we usually give ourselves a tenfold margin of safety. In larger doses, vitamin B_{12} is usually effective in sprue, but relapse may occur after several years of treatment. It may be effective also in tropical macrocytic anemia and in the anemia associated with blind intestinal pouches or fistulae. It is usually not effective in megaloblastic anemia of infancy, pernicious anemia of pregnancy, and achrestic anemia. In these three conditions, and in sprue, the drug of choice is folic acid administered orally in doses of 5 mg. three times daily. Less is required in the infant, of course. Folic acid and folinic acid are roughly equivalent in these anemias, although the synthetic folinic acid, because of its spatial configuration, is only half as potent as natural folinic acid or folic acid.

Folic acid alone is dangerous to the patient with pernicious anemia, whether it be prescribed by a physician or purchased in a mixed vitamin capsule. It allows cord damage to occur, usually without signs of anemia to give a warning. However, only one microgram of vitamin B_{12} daily is necessary to relieve the neurologic degeneration that usually occurs in patients with pernicious anemia treated with folic acid or folinic acid alone, and such small doses would probably prevent the degenerative changes.

Vitamin B_{12} combined with intrinsic factor for oral use is not equally effective in all patients with pernicious anemia; it is expensive (about 40 cents daily), and cannot yet be compared favorably with 20–30 μg. of vitamin B_{12} given parenterally every three to four weeks (about 40 cents a month) for maintenance of patients with pernicious anemia.

The use of massive doses of vitamin B_{12} in various neuritides and in tic douloureux is not yet supported by undisputed experimental data, though I strongly suspect that where there is so much smoke, there must be some fire. There is clear-cut evidence that vitamin B_{12} is involved in ribose nucleic acid metabolism of nerve cells (Nissl substance), and it may act as a protecting agent under certain circumstances.

Dr. Crafts has shown in rats that the cortical steroids, thyroxine and androgens are essential for normal hematopoiesis and affect the utilization of certain essential nutrients, particularly protein. These hormones probably govern the pace or speed of blood formation by the bone marrow. They are all interrelated, but only ACTH and the cortical steroids will stimulate the bone marrow to increased activity, whether or not there has been a deficiency of the hormone. These same statements probably apply to human beings, too.

I hope all of our guests have enjoyed this Symposium as much as I have. It has been a great pleasure to participate in it. To any investigator whose work has been neglected, I offer my apologies. We have tried to cover a large field in a very short time and, unfortunately, all important subjects could not be mentioned. However, I think this group of speakers has given a clear description of the mechanisms of blood formation known at this time. I hope everyone can see as clearly as I one great lesson for every practicing physician. Each of these nutrients will usually do only one job, and in order to discover that job, an accurate diagnosis must be made. Otherwise we waste money, time, and effort.