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## SOME REMARKS ON THERAPY FOR ANEMIA\*

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I AM sincerely appreciative of the honor bestowed on me by the invitation to deliver this oration. As you are aware, my distinguished predecessors have annually instructed and entertained you with words both wise and charming. I wish, especially at this preprandial hour, that I were able to do so. Lacking such gifts, however, I have believed that in accepting this honor it would be a more suitable expression of appreciation were I to speak of matters of detail with which I have some experience than to discourse, perhaps naïvely, on a more general theme.

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The remarkable advances in the treatment of anemia of the past decade and a half, when contrasted with the yet unscalable obstacles, perhaps justify an attempt at a realistic appraisal of the possibilities and limitations of existing therapy. Today, five general methods of treatment of varying effectiveness and permanence are clearly discernible. Thus, there are substitution therapy for nutritional deficiency or for dysfunction of the endocrine system, chemotherapy, splenectomy and irradiation. Finally, on its own merits and also as a means of preparation for some other form of therapy, there is transfusion.

### SUBSTITUTION THERAPY

Starting with the pioneer clinical observations of Minot and Murphy in 1926, the effectiveness of liver and later of stomach preparations in the treatment of patients with nutritional types of macrocytic anemia has become thoroughly established. In this locality, the conditions amenable to such therapy are usually Addisonian pernicious anemia and that of pregnancy. With the further exception of certain rare cases of nutritional macro-

cytic anemia, usually due to intestinal disturbances, all types of anemia fail entirely to respond to such preparations. Valuable contributions to the practical development of the present effective therapeutic products have been made by both university and commercial research groups. Since the amount of active material remaining in the finished product depends on the efficiency of the method of manufacture, it seems unwise and uneconomical for physicians to prescribe products whose potency is defined only in terms of the amounts of tissue with which the manufacturer started his process. The obvious and satisfactory alternative definition of potency in terms of the amount of effective material in the final product is currently described in *U.S.P.* units for all antianemia remedies accepted by the *United States Pharmacopoeia* or the Council on Pharmacy and Chemistry of the American Medical Association.

Active commercial preparations of the liver for oral or parenteral use, and of the stomach or of the stomach and the liver potentiated by incubation for oral use, are available. Because in the average patient the effectiveness of a given liver preparation is from sixty to one hundred times as great when given parenterally as when taken by mouth, the former route provides a distinctly more economical manner of administration. The small volume of material to be injected (several commercial preparations contain at least 15 *U.S.P.* units per cubic centimeter) and the infrequency of injections required for maintenance (15 or 30 *U.S.P.* units at intervals of two weeks or a month) render the use of any oral preparation a doubtful policy, from the point of view of both effectiveness of treatment and convenience or expense to the patient. Few patients conscientiously persist in taking considerable amounts of medicine by mouth two or three times a day for long periods after they consider themselves perfectly well. Because a definite but unpredictable num-

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ber of patients in severe relapse fail more or less completely to respond to products administered orally in usual amounts, it is certainly unwise to initiate treatment by any other method than that of parenteral therapy, usually in terms of multiple *U.S.P.* units daily for the first few days. A similar indication is provided by patients with pronounced neural manifestations. With exceedingly rare exceptions, the present purified and concentrated preparations seem to be as effective as the older and cruder products in the treatment of pernicious anemia and its neural complications. A practical point in the early detection of the onset of remission is to determine the reticulocyte percentage on the fifth and seventh days after therapy with liver or stomach preparations has been instituted. In the response of anemic patients, the increase of the reticulocytes is so much more striking than the change in red-blood-cell or hemoglobin values in the first week that, relying only on the latter, the physician may fail to realize that the response has already begun.

Although liver extracts, especially the less highly purified products, are to some extent sources of various members of the vitamin B complex, these are apparently unessential to the remission induced by the active hematopoietic principles of liver. The treatment of pernicious anemia by vitamins is thus a waste of material. Whereas it is true that large amounts of whole or autolysed yeast may, under experimental conditions, cause detectable improvement in pernicious anemia, it is probable that these agents act only indirectly through their power to induce the formation of liver extract in the body. In actual practice, they are without significant value compared to the efficiency of active liver or stomach preparations, and their use is an additional burden on the patient and his pocketbook. Whether or not vitamin C is an effective agent in the rare macrocytic anemia of scurvy remains to be proved. Since fruit juice containing vitamin C has been shown to be capable of causing blood regeneration in such patients, it can be readily employed in any case whether its activity depends on ascorbic acid or other factors. Today, the sole essential for maintaining continued and complete remission in pernicious anemia is the exhibition of sufficient amounts of active material by a single route at regular intervals. The advances of the last fifteen years have almost deprived the adjective "pernicious" of any real meaning. Indeed, it is a puzzling question whether the diagnosis "pernicious anemia" should appear on the death certificate of a patient who by adequate treatment has been maintained through many years with a normal blood count and who has died of causes entirely unrelated to his original anemia.

The effective use of iron in the treatment of anemias now known to be hypochromic is older than the record of history. Its latest and presumably permanent reappearance on the platform of sound therapy dates from the independent observations of Barkan and Meulengracht, in 1923, in Europe. They abandoned the small amounts of iron advised by theory and used dosages comparable to those effectively employed today. It is now known that almost any sort of iron, if orally administered in a finely divided form or as a nonirritating iron salt, is effective in the treatment of hypochromic anemias in which loss of hemoglobin and consequently of iron has been brought about by bleeding, pregnancy or growth. Observation shows that ferrous compounds are in general more effective than ferric. The dosage of ferrous compounds is about 5 gr. three times a day, best given just after meals to avoid gastric irritation. Many injections of iron have been made without much effect because of the minute amount of iron in these often expensive and elegant ampules. Today, it is recognized that it is very rarely necessary to promote hemoglobin regeneration by injections of iron. If, however, because of failure of oral therapy in adequate dosage, such a procedure is required, suitable preparations—sterile solutions of ferric ammonium citrate or ferrous gluconate—are available.

The indication for the use of iron is a low hemoglobin concentration in the red blood cells or a low color index. Unfortunately, the hypochromic anemia of chronic infections and that of the so-called "Mediterranean anemia," although possessing these characteristics, do not respond to iron. Experimental animals with hypochromic anemia that have failed to respond to iron are often relieved by vitamin B<sub>6</sub>, but this is not true of patients, at least in my experience. In growing experimental animals, carefully deprived of access to copper, it has been convincingly shown that this element as well as iron is essential for relief of the anemia that develops. Some authors have reported a similar use for copper in anemic infants given small doses of iron. There is, however, no convincing evidence that patients failing to respond to usual doses of iron will respond to the addition of copper. Liver and stomach preparations are useless. Moreover, indiscriminating polypharmacy obscures the effective agent and may lead to needless and expensive types of maintenance therapy. Iron, therefore, appears to be the only agent of practical importance in the treatment of hypochromic anemia.

Patients with myxedema commonly have some degree of hypochromic and occasionally macrocytic anemia, especially if gastric anacidity is pres-

ent. Hypopituitary syndromes are also sometimes associated with anemia. Treatment in both conditions depends on suitable endocrine therapy, and may be accelerated by the use of liver extract or iron, according to the character of the anemia.

#### CHEMOTHERAPY

Chemotherapy, although primarily employed for the infection itself, is more than incidentally a means of combating hemolytic anemias, such as those due to the streptococcus or to the malaria parasite. The unrecorded experiments of Indians with Peruvian bark long antedate modern chemotherapy. The latest advance is that initiated by Domagk in 1933 by the discovery of the bacteriostatic action of a sulfonamide in experimental streptococcal infections. To discuss in detail the use of sulfonamides or quinine is obviously beyond the scope of these remarks. Chemotherapy may also be of value as an accessory in the treatment of blood dyscrasias of which an infection is an important complication. Thus, the advent of an infection of the respiratory or urinary tract may even be fatal in a patient with severe anemia otherwise easily amenable to therapy. The signs of infection, however, may be falsely simulated in a patient with a hemoglobin level of less than 25 per cent by a fever of 1 or 2°F. that may be entirely due to the anemia; even higher temperatures may result when an active hemolytic process is present entirely without infection. For the local-tissue necrosis and secondary infection encountered, usually in the oral cavity, in agranulocytosis, aplastic anemia or leukemia, especially the monocytic variety, the relatively small experience available already indicates a value for the sulfonamides. Their utility consists in holding in check the invasion of the infection until other remedies may have an opportunity to act on the underlying blood dyscrasia.

It seems clear that in general, as in the presence of primary infections associated with leukopenia, the possibility of further depression of the granulocytes is not so great a risk as the danger from the infection when uncontrolled by chemotherapy. Sulfonamides, like certain other cyclic compounds, have caused acute hemolytic anemia, leukopenia, thrombopenic purpura and aplastic anemia. Fortunately, such undesirable results occur in only a very small percentage of cases, and their manifestations can usually be prevented by early detection. Because the chance of such an occurrence is small, one should never hesitate to administer these valuable drugs when a serious infection presents a clear indication for their use. On the other hand, the widespread and indiscriminate employment of the sulfonamides for trivial infections may well produce from only a small percentage incidence a

considerable number of hematologic complications, immediate or remote.

#### SPLENECTOMY

In 1911, Micheli observed the benefit of splenectomy in a case of acquired hemolytic jaundice, and in the next two years, Eppinger and Banti independently reached the conclusion that it was a logical and successful procedure in congenital hemolytic jaundice. In this community, Dameshek has recently done a service by calling attention to various types of acquired hemolytic jaundice and by re-emphasizing the therapeutic value of splenectomy in some of them. The success of splenectomy in such anemias depends on the predominance of pathologic blood destruction in the spleen. In congenital hemolytic jaundice, the red blood cells almost invariably exhibit some increase in fragility in hypotonic saline solution, and the spleen is usually large and the pulp engorged with blood. A successful splenectomy is almost always dramatically effective in returning the patient's blood values to normal. If necessary, as a preliminary to operation, rapidly repeated transfusions should be given to bring the hemoglobin level to at least 50 per cent of normal. Although this may be difficult in the face of a crisis of rapid blood destruction, splenectomy not only promptly abolishes this phenomenon but also, by extrusion of blood from the spleen during operative manipulation, provides an autotransfusion, often immediately raising the hemoglobin level by 15 per cent or more. Consequently, splenectomy should not be unduly delayed.

In patients with acquired hemolytic jaundice, a term that includes several distinguishable acute and chronic forms of disease, a generalization concerning the effect of splenectomy is impossible. Perhaps, however, it can be stated that after certain causes of hemolytic anemia that are amenable to other forms of treatment have been excluded, splenectomy is likely to be beneficial if the fragility of the red blood cells in hypotonic saline solution is significantly increased and if the spleen is distinctly enlarged. Splenomegaly alone, however, provides no guarantee of success for splenectomy. Before the procedure is undertaken, the duration and nature of the hemolytic process should be carefully studied. Thus, in acute cases, the history may reveal exposure to hemolytic compounds, such as phenylhydrazine, sulfanilamide and arsine, or in other cases, dark urine (hemoglobinuria) after exposure to cold or after sleep. A blood culture or film may demonstrate septicemia due to bacteria or malaria parasites. Exposure to pure carbon dioxide causes anoxic microscopic sickling in sickle-cell anemia, and in paroxysmal nocturnal hemoglobinuria alone, the carbonic acid causes

hemolysis. A positive serologic test for syphilis and hemolysis on chilling (Donath-Landsteiner phenomenon) confirm the diagnosis of paroxysmal hemoglobinuria *e frigore*. Such patients are not suitable for splenectomy. In other patients, autoagglutination of the red blood cells has been remarked; Dameshek has found hemolysins in the serum independent of isohemolysins in a certain group of cases. Bone-marrow biopsy or splenic puncture may disclose other causes of acquired hemolytic anemia, such as aleukemic leukemia, Hodgkin's disease and agnogenic myeloid metaplasia. Suffice it to say that if the conditions enumerated above, which are amenable to other types of therapy, can be excluded and if severe hemolytic anemia with acholuric jaundice and manifest signs of active blood regeneration persist for some days despite frequent transfusions, splenectomy may be indicated, at least as a means of somewhat reducing excessive blood destruction and, possibly, of abolishing it.

It is to be emphasized that the expectation of success from splenectomy in so-called "acquired hemolytic jaundice" is quite different from that in the congenital condition, and as in thrombopenic purpura, although splenectomy is the only therapy likely to be effective, its success is far from certain. Likewise, splenectomy in Banti's syndrome, in which the hypochromic anemia is probably to a considerable extent due to chronic and often occult bleeding from varices, is not always of benefit. The operation is often technically difficult because of the adherence of the spleen to nearby structures, and only when the obstructing vascular lesion is confined to the splenic vein is there considerable certainty of complete relief. Unfortunately, some type of hepatic cirrhosis is most frequently responsible for "chronic congestive splenomegaly," the highly appropriate descriptive term for Banti's syndrome that was coined several years ago by a Boston physician, the late Dr. Ralph C. Larrabee.

#### IRRADIATION

Irradiation by roentgen rays or radioactive phosphorus is today considered the chief weapon in treating leukemias and related conditions. Yet, although in discussions of such treatment great attention is paid to the number and character of the leukocytes, a disabling and frequently fatality-determining feature of leukemia is the anemia that sooner or later appears. Indeed, the problem in the irradiation of leukemias is not so much how to effect a reduction in the number of white blood cells as how to increase the number of red blood cells (or platelets). Since it is usually considered unsafe to apply x-ray therapy in the presence of severe anemia, preliminary transfusions to bring

the hemoglobin to a level of at least half the normal value are indicated.

The justification for discussing the use of irradiation, a highly technical procedure requiring special apparatus and experience, is that the best results from such therapy in leukemias can be obtained only when collaboration between clinician and roentgenologist is close and intelligent. It is assumed, for purposes of discussion, that the anemia in the leukemias is due to a considerable extent to the mechanical inhibition of normal red-cell production in the marrow cavity by overcrowding with immature leukocytes. In other cases of myelophthisic disease, the bone marrow is invaded by the cells of metastatic carcinoma or is replaced by lipid-bearing cells or by fibrous or osseous tissue, as in osteosclerotic anemia. Because the cells of most metastatic carcinomas, like those of fibrous or osseous tissue, are presumably insensitive to irradiation, no improvement of the red-cell level is to be expected from irradiation in such cases. Accordingly, when there is doubt regarding the character of the disturbance in the marrow, sternal biopsy is indicated before one decides whether x-ray therapy is to be given.

Although the use of x-rays in the treatment of leukemia was introduced by Senn as early as 1903, it is even now difficult to choose the most suitable procedure and amount among the variety of methods and dosages that have been and still are employed. Experience agrees, however, that in acute leukemias the process is inherently of such a kind or its rate of progress is so rapid that irradiation is not only useless but detrimental. By contrast, in the management of chronic leukemias, especially the myelogenous, the skillful use of irradiation is frequently a means of providing a comfortable and useful existence during months or even years.

In the treatment of chronic leukemias, a trend can be observed toward the use of small amounts of irradiation applied to the body generally, in contrast to heavy local exposure of obviously enlarged organs, such as the liver and spleen. Because the abnormal cells in chronic leukemia diffusely invade the active bone marrow, this tendency seems logical. Since, however, it is never possible to gauge with accuracy the effect of a physical agent on a complex biologic system, overdosage of the entire bone marrow is most surely avoided by exposure of only a portion of it to the action of x-rays at one time. It is desirable, whenever possible, to avoid heavy local irradiation, which, despite a selective effect on immature cells, injures all cells—even those of normal tissues. I have observed enlargement of the spleen to remain substantially undiminished after relatively

large doses of x-ray therapy applied locally, only to have the organ later diminish in size, apparently as a result of repeatedly administered small amounts of general irradiation. If an interval at first of a few days and later a week or two is allowed to elapse between exposures of a quadrant of the body to no more than 75 to 100 r, a leukocyte count preceding each contemplated irradiation becomes a good measure of the effects of previous therapy and thus tends to prevent over-dosage. Finally, observation suggests that significant increase of red blood cells may not begin for some weeks after sufficient irradiation to cause marked lowering of the leukocyte count. Because it is seemingly within the somewhat narrow range of dosage between suppression of leukocyte production in the marrow and suppression of erythrocyte production that the effects of irradiation are most beneficial, it is desirable to proceed with sufficient deliberation to allow for observations on the production of both types of cells.

The use of radioactive phosphorus, logically introduced in the treatment of leukemias by Dr. John H. Lawrence, of San Francisco, is still undergoing evaluation. Nevertheless, it seems probable from the results already reported from several localities that radioactive phosphorus is not the final answer to the problem. The impression gained by one who, it should be said, has had no personal experience with the method is that it represents, like x-ray therapy, a form of irradiation theoretically more selective in its effects on leukemic cells and simple to administer. To my mind, however, it has the theoretical objection that all the hematopoietic organs are exposed simultaneously to irradiation. Nevertheless, eminently satisfactory results have been obtained with radioactive phosphorus in the treatment of chronic leukemias, especially those classified as myelogenous. It is still too early to be certain that such effects are superior to those obtained with modern x-ray treatment. In the management of acute leukemias, aleukemic leukemias and leukemias in which severe anemia persists with or without previous x-ray treatment, radioactive phosphorus appears to fail to cause benefit as consistently as any other form of irradiation does.

#### TRANSFUSION

The final therapeutic aid in the treatment of anemia is blood transfusion. Today, the use of citrated blood, possessing as it does the important advantages of comparative leisure in collection and administration and convenience in transportation or storage, is the method of election. In spite of theoretical objections, fresh citrated blood apparently possesses no practical disadvantages compared with unaltered whole blood. Increased care in the

preparation of glassware, tubing and citrate solutions has eliminated many of the febrile reactions to such transfusions. Since, with anemia, the hemoglobin content of the recipient's blood is always reduced, whole blood rather than fresh, preserved or reconstituted plasma is the medium of choice. Thus, in the treatment of anemias, the plasma serves largely as a vehicle for the conveyance of red blood cells. Were it possible at present — when war places a premium on the collection of plasma — to discover a means of preserving the discarded red blood cells intact over relatively long periods, this by-product of emergency activity would no longer largely be wasted.

In the treatment of anemia, blood transfusion plays a significant, although entirely passive, role. Since the hemoglobin concentration in the circulating blood is increased, the blood is better able to carry oxygen from the lungs to the body tissues. With one unimportant exception, there is no evidence that transfusion has a stimulating action on the bone marrow, so far as the production of red or white cells or platelets is concerned. The exception is that, as a result of the eventual destruction of the transfused red blood cells, iron and possibly other materials necessary for new red-cell production may slowly be made available. This delayed and feeble action of transfusion, demonstrable only in hypochromic anemia, can scarcely compare with the effectiveness of the oral administration of a few grams of iron. On the other hand, there is no evidence that transfusion has any depressing effect on the bone marrow unless it raises the hemoglobin above normal values. Transfusion never passively raises the recipient's leukocyte count for more than a few minutes, but may, probably by introducing platelets, cause a cessation of bleeding in thrombopenic purpura for several hours or a few days. The effect of transfusion on bleeding in hemophilia is by virtue of the introduction of a clot-accelerating agent, probably enzymic, associated with the plasma globulins.

Transfusion provides a valuable and sometimes lifesaving procedure in the treatment of anemia, for it may give time for other methods of treatment to become effective or for spontaneous improvement to occur. Thus, patients with sufficiently low hemoglobin values may die before the effect of liver extract or iron therapy takes place. The use of transfusions as a means of carrying patients through hemolytic crises or of preparing them for splenectomy or for x-ray therapy has already been mentioned. In patients with a temporary suppression of red-cell production, as in benzol poisoning, adequate hemoglobin levels may be artificially maintained until Nature initiates new blood formation in the bone marrow. Finally, in patients with aplastic anemia, or with aleukemic

leukemia, a reasonably comfortable existence may sometimes be prolonged for many months by the skillful use of transfusions alone.

For the effective employment of transfusions, two conditions must be met: blood must be readily available and of the proper type; and the technic of the transfusions must be satisfactory and their use judicious. The availability of suitable blood in urban communities is largely an economic question. In fact, the cost of repeated transfusions often becomes prohibitive for many persons able to employ private physicians. The relative difficulty of drawing blood in the past and the comparative rarity and dramatic setting of the procedure have much to do with the present high cost of a pint of blood in many localities. Rarely, today, does the professional donor from whom blood was formerly drawn by an incisional approach to his veins have this unnecessary cause to raise the value of his contribution. The solution, like that of other price situations depending on the economics of supply and demand, will probably come through extension of the organization and invention that have produced the blood bank, the volunteer-donor registry and the emergency blood-procurement service. It is logical to replace the iron lost by the donor by means of a two weeks' course of orally administered ferrous iron.

Time does not permit a discussion of the problems of blood typing except to say that mistakes can most certainly be avoided by the use of typing serums of high agglutinating titers. The relatively rare possibility of the development of anti-Rh agglutinins by the recipient during pregnancy or as a result of previous transfusions has recently been disclosed by the brilliant work of Landsteiner, Wiener, Levine and their associates. A final direct test involving incubation of the donor's cells in the recipient's serum for half an hour, with subsequent microscopic inspection, will almost certainly detect incompatibilities, although to determine their precise nature may require special methods. However, despite the use of compatible blood and of scrupulous care, some unknown quality of certain patients with anemia due to other causes than blood loss renders mild or even severe febrile reactions likely to occur.

From the recipient's point of view, the technic of transfusion includes skillful venipuncture with a short-bevel needle of small caliber that tends to minimize injury to the vein. The blood should be run in slowly, especially in severely anemic patients, to avoid a sudden increase in blood volume, which may overburden an already hard-pressed circulation. The alkalization of the recipient's urine with 12 gm. of sodium bicarbonate, given an hour or two before transfusion, prevents the precipitation of hemoglobin in the renal tubules

if, for any reason, hemoglobinuria results from the transfusion. As a "biologic test," it is desirable to inject not more than 50 cc. of blood in the first half-hour and to watch for symptoms and signs of a reaction. In the management of patients with anemia, the fact that subsequent transfusions may be required should always be borne in mind. Although cutting down on the recipient's vein and its ligation after transfusion are rarely necessary, this unfortunate practice still exists. As a result, patients whose veins have been destroyed by several previous transfusions may present a serious technical problem. Fortunately, in such cases, it is sometimes possible to use the femoral vein or, according to the recent work of Tocantins, to infuse blood directly into the marrow cavity of the sternum. Aside from its physiologic benefit to the patient, the facile performance of transfusion has a desirable psychologic effect in dispelling the dramatic or ominous connotations of the method in the mind of the layman.

If the use of transfusions is to be fully effective, the objective to be obtained should be kept clearly in mind. For example, if the hemoglobin level of a patient with pernicious anemia is considered dangerously low for the interval of a few days before parenteral liver-extract therapy becomes effective, a single transfusion often suffices. On the other hand, in a patient with a type of anemia in which improvement may be long delayed or may never occur, transfusions repeated at appropriate intervals should be given to raise the hemoglobin and to maintain it at a level compatible with moderate activity in convalescence or at light work. It is a waste of precious and potentially useful weeks or months of such a patient's life if, owing to parsimony in the number of transfusions, he is needlessly confined to bed or home.

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It is a truism that proper treatment depends on accurate diagnosis of the type of anemia. Perhaps it is not so well known that this is often impossible from the examination of the blood alone but requires, as in any other field of medicine, careful history taking and physical examination and special laboratory examinations. The final proof of the correct diagnosis of nutritional-deficiency anemias is an orderly hematopoietic response to substitution therapy at the expected time. Because certain types of anemia may masquerade as cardiac, renal, nervous or even orthopedic conditions, a correct determination of the patient's hemoglobin level should be as routine a procedure as the performance of a urinary examination. Even when one is dealing with an incurable ailment, therapy effectively directed at an associated anemia may sometimes bring reward to both patient and physician.