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PANELS IN THERAPY

XII. Hypoplastic-Aplastic Anemia

Panel

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Moderator

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THE PROBLEM of hypoplastic and aplastic anemia seems to be an ever recurrent one in hematologic practice. Whatever the cause of the greatly reduced bone marrow activity—whether due to aromatic solvents, paint removers, certain drugs, or undue exposure to ionizing radiation—the situation is indeed a very grave one. The outlook probably depends in large measure upon the degree of bone marrow hypoplasia, reflected more or less imperfectly in the blood picture. Pancytopenia, often of severe degree, is invariably present, and the greater the reduction in the cellular elements of the blood—red cells, leukocytes, and platelets—the more serious is the prognosis. However, so many variables are present in this non-malignant disease that one must in any event proceed to treat, and to treat vigorously. It may be possible in some cases to maintain the patient on continued transfusions alone, and when the patient is replete with borrowed blood, he usually looks very well. In fact, the striking feature of the patient with hypoplastic anemia is his fundamentally healthy status; he does not have a proliferative process like leukemia or a malignant lesion like lymphosarcoma invading the marrow. A certain degree of hope may be said to exist even in the blackest of situations and thus therapy with all available methods must be carried out until it has been conclusively shown that nothing further can be accomplished. Variations in therapeutic methods for aplastic anemia having been noted in different clinics throughout the world, a panel of experts was asked their opinion on the following question:

A man aged 35 has pancytopenia of marked degree with very low platelets, and the marrow examination indicates marked hypocellularity with only occasional megakaryocytes being found. There is no evidence of leukemic infiltration. Although the patient has taken various sedative and antibiotic medications in the past five years, there is no

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clear-cut history of drug or chemical poisoning. What would your therapeutic regimen be in this case? Specifically, would you advise splenectomy?

DR. CROSBY:

The problem is an all-too-familiar one. We see two or three such patients each year. Following a period of observation, never less than three months long, splenectomy was carried out in most of them and in several instances the patients appeared to have been benefited. Where improvement occurred the transfusion requirement was reduced or eliminated or the platelet count was increased slightly but significantly: from 5,000 per cu. mm. it went to 25,000, and a dangerous situation became not quite so dangerous. We have recommended splenectomy in such cases not in hope of a cure, but because the operative risk, in the competent hands of our surgical "spleen team", is low and any possibility of improving this dismal hematologic situation seemed worthwhile. The patients were prepared at the time of surgery by transfusions of strictly fresh, whole blood drawn into plastic bags and transfused immediately. (The cross match was completed before the blood was drawn.) In two instances the surgical incision was made before transfusion was begun, and it was interesting to see a wet, oozing operative field become dry as the viable platelets were given. We have not used platelet transfusions for such patients except for surgery and would not recommend that they be used otherwise. Steroids appear to have been unbeneficial. At the time of admission to Walter Reed, most of the patients had been given trials of steroid therapy, some of them intense and prolonged. None was benefited. When leukopenia is severe in hypoplastic diseases of the bone marrow, the use of steroids is probably useless and may be dangerous.

DR. FEINSTEIN:

Experience in our hematologic clinic gives us a basis for the consideration that the essential therapy of aplastic and hypoplastic anemias is the utilization of repeated small transfusions of fresh erythrocytic mass (packed red cells). In the complex therapy of this disease in the clinic we utilize likewise the various B complex vitamins: folic acid, nicotinic acid, B_1, B_2, B_6 and B_{12}.

Hormonotherapy in the form of adrenocorticotrophic hormone or cortisone is given only to such patients who have the illness without hemorrhagic manifestations. There is a crystallizing impression that these hormonogenic substances are capable of increasing the loss of blood in patients with aplastic and hypoplastic anemias. There is a favorable indication of coping with hemorrhages by the use of vitamin P in connection with large doses of ascorbic acid.

Regarding splenectomy, we do not advise its application in cases of aplastic and hypoplastic anemia. Our observations do not support any positive results in cases where the spleen had been removed.

DR. HEILMEYER:

The therapy for the case in question demands consideration of the nature of pancytopenia as this term covers only a syndrome and does not represent a pathogenetic disease state. Particularly as to the question of splenectomy, this can only be answered if further examinations are made.

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Pancytopenias may originate from an allergy against certain therapeutic agents. If there is no evidence for this assumption in the case at hand, then the possibility that autoantibodies have been produced against all three types of cells should be considered. During the past year alone we were able to observe three cases, all of them showing production of autoantibodies against all three cell systems. Among them was one patient who had never previously received transfusions. If, by application of highly specialized methods, the examination reveals the existence of autoantibodies, therapy with adrenal steroids or ACTH should be tried first. In our cases the indication for splenectomy depends largely on the red cell survival time study. If this time is distinctly shortened, splenectomy often shows good results. Splenectomy may show favorable effects in a triple way:

1) The production of autoantibodies may be reduced or even totally stopped.

2) The bone-marrow may be improved, this being determined by examining this function by means of irritants.

3) The shortened survival of erythrocytes can be prolonged by splenectomy.

If splenectomy appears to be impossible, therapy should be symptomatic with the use of blood transfusions, adrenal hormones and liver extracts.

PROF. KAWAKITA:

In my opinion, this patient is suffering from primary aregenerative anemia with pancytopenia. Although there is no clear-cut history of drug or chemical poisoning, the matter of pancytopenia or secondary aregenerative anemia due to chemical agents cannot be completely ruled out.

Suggested therapeutic regimen:

1) Repeated blood transfusions. The anemia will improve with this treatment; however, there will be little if any increase of reticulocytes and platelets. If transfusions are discontinued, the patient will ordinarily become anemic again and further transfusions will be required. One has little hope of permanent recovery from anemia or of the return to normal of leukocyte and platelet counts, even if repeated transfusions are administered, and in any event, the transfusions should not be used indiscriminately, since hemorrhagic diathesis and liver damage may develop and may prove fatal.

2) Medication and other medical treatments.

Heretofore, aregenerative anemia has been treated in various ways without much result. Some results appear to have been obtained by the administration of following agents: Folic acid, vitamin B_{12}, ACTH, cortisone, powdered hog stomach, feeding of raw marrow from cattle or fowl, injecting into the bone marrow of the patient the marrow from a normal individual, transplantation of rabbit bone marrow, x-ray therapy, and the injection of Parotin (a hormone of the salivary gland).

Here are some of our experiences: (1) In one case temporary improvement of anemia with marked reticulocytosis occurred following administration of powdered hog stomach by mouth. (2) Parenteral folic acid injection was effective in two cases, namely, one with secondary aregenerative anemia due to Thioacetasone and the other, a splenectomized case. (3) Injection of vitamine B_{12} caused a slight temporary improvement of anemia in one case and a reticulocyte increase without recovery of anemia in another case. (4) Following injection of

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cortisone the erythroblasts of the bone marrow increased with slight or no improvement of anemia in two cases. In one case there was a temporary increase of reticulocytes in the peripheral blood and an increase of the erythroblasts in the bone marrow with slight improvement of anemia.

(3) Splenectomy. If no permanent improvement is obtained by the methods mentioned above, I would advise splenectomy. Since 1939, 19 patients with primary aregenerative anemia have undergone splenectomy in our clinic. Of the 19 cases, thirteen showed good results, two died at the end of five months without showing any improvement; one patient died immediately after the operation and one patient died three days after the operation from pneumonia. Of the 13 patients with good results: eight were almost completely cured, three showed a lesser degree of recovery, and two only slight improvement. The first two splenectomized patients are still living and lead normal lives, 17 years after operation.

When anemia, leukopenia and thrombocytopenia are slight, the prognosis after splenectomy is good; if the pancytopenia is marked, the prognosis following splenectomy is poor. But sometimes it is difficult to predict the results of operation from the blood and bone marrow findings.

After splenectomy, several months to a year are required before the anemia corrects itself. After operation, the leukocytes usually increase—approaching the normal count. The neutrophilic leukocytes increase both relatively and absolutely. The diameter of the lymphocytes before splenectomy is smaller than normal; but after splenectomy it increases gradually to normal. The phagocytic activity for granules of India ink and the motility of neutrophils improve remarkably following splenectomy but are not restored to normal. The platelets lag behind red blood cells and increase more slowly.

Following splenectomy, the bone marrow may gradually approach normality. The nucleated cells in the sternal marrow increase in the cases of aplastic type with fatty marrow or decrease in the case of hyperplastic bone marrow. Maturation arrest of erythroblasts and leukocytes decrease. The changes in the cells of the megakaryocytic series are most noticeable: the number of cells increase and particularly the platelet-forming function of the cells improve.

Therefore, judging from my experiences as related above, I wish to recommend that blood transfusions and other medications be given to this patient; and if the results are not satisfactory, splenectomy should be performed. If the response is not very satisfactory we advise steroid hormones or folic acid medication. If anemia increases, one should continue with blood transfusions—amount and frequency of which must be gauged by the condition of the patient. Then permanent cure may be expected.

DR. WHITBY†

There is not, so far as I know, any specific therapeutic regimen for a case of this type who will need to be sustained with appropriate transfusions of blood, preferably direct, but failing this, as fresh as possible, in a siliconized apparatus. In my view, there is little doubt that a direct transfusion provides factors, at

† This note was written by Sir Lionel Whitby about one month prior to his untimely death on November 24, 1956. With Dr. Whitby's passing, we lose a valued contributor and friend. An obituary will appear in an early issue.—W. D.

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present inestimable, which occasionally assist a hypoplastic marrow to regain some functional capacity. Blood which is directly transfused has also the advantage of maximum survival. In principle, one may say that an attitude of despair should never be adopted in these cases since some, even after years of transfusion life, have eventually recovered. These, presumably, can be assumed to be those in which toxic damage has not been complete and irreversible.

I would not advise splenectomy in the face of the hypocellular marrow unless the spleen were enlarged or unequivocal antibodies could be found. This view is based on the parallel with hemolytic anemia, where antibodies are far more easily demonstrated, and, where a hypercellular marrow is evidence of a vigorous reaction to the hemolytic process. When the marrow is hypoplastic, antibodies are rarely found in hemolytic anemia, and in such cases the results of splenectomy are disappointing. It may, however, be argued that splenectomy if not beneficial, will at least do no harm, and I would accept this argument in cases in which it is socially advisable to do something active; appreciating, however, that the prospects of benefit were infinitesimal.

Evidence of sensitization to the sedation taken (or antibiotics) should be sought, and if found, then administration *should* be prohibited.

Moderator's Comment

This panel, comprising individuals from various parts of the world with presumably varying forms of therapy, is unanimous in asserting that therapy should be carried out, however little the prospective value of treatment might be. Some panelists rely on transfusions alone; others are more or less enthusiastic about splenectomy. Sir Lionel Whitby voiced what is probably the most important point of all: "Never give up!"—at least, *almost* never. These people are non-neoplastic, and thus even if the bone marrow has been excessively destroyed, there is a sporting chance for recovery.

Transfusions, preferably of fresh blood, and preferably from plastic bags or siliconized bottles, should be given, and continued to be given, but not to completely normal values of hemoglobin and red blood cells; 8–9 Gm. of hemoglobin in a chronically anemic person are enough for a reasonably active life. There is of course always the danger of transfusion reactions and of the deposition of iron in the tissues, but they must be continued. The Russians are convinced of the value of small units of "red cell mass" (packed red cells) but the special virtue of such packages is open to some question. Fresh blood may have a special virtue, as Sir Lionel suggests. Siliconized bottles and plastic bags are preferable for the collection and administration of fresh blood, since red cells and particularly platelets are well preserved in these receptacles.

But transfusions are not enough. They may in fact at times be worse than useless, since too many may cause the marrow to "lay down," i.e., reduce marrow activity. Steroids are very helpful. Whether or not they have a myelostimulatory effect is open to question. However, some cases appear to be "steroid dependent," i.e., develop a striking remission with steroid and relapse without steroid. These cases are certainly unusual, but they nevertheless do occur. The steroids are always helpful in reducing the bleeding tendency—probably through a "nonspecific" mechanism. In the occasional presence of a hemolytic mechanism,

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especially of an immunologic type, the value of the steroids is preeminent. Despite their obvious disadvantages (Cushing syndrome, diabetes, electrolyte disturbances, tendency to infection, etc.), they should be given a fair trial.

As for splenectomy, our experience with this procedure has in general been unsatisfactory. In the presence of a markedly hypocellular marrow, splenectomy has been useless. However, when the marrow has at least a fair number of islands of nucleated red cells and *some* megakaryocytes, splenectomy may result in a sustained though slight rise in platelets and perhaps eventually in a gradual increase in red cells. We have seen this happen on several occasions. The very slow increase in red cells might indicate that the improvement in blood levels was perhaps spontaneous and without relationship to the splenectomy. Nevertheless, despite the real doubts about this operative procedure it seems advisable to do it, at least in the relatively young, and unless the marrow appears almost completely aplastic.

One should remember that there are almost always three elements in the hypoplastic condition: the anemia, the leukopenia (granulocytopenia), and the thrombocytopenia. Severe granulocytopenia may lead to recurrent infections, thus requiring antibiotic therapy; severe thrombocytopenia, the use of fresh blood collected in siliconized or plastic receptacles; severe anemia, the use of transfusions. Although granulocytopenia and thrombocytopenia are often serious problems, particularly the latter, anemia is by all odds the most important, because life is possible without platelets or granulocytes, but not without red cells. Fortunately, of the three elements of the pancytopenic state, anemia is usually the first to recover; thrombocytopenia, the last.

Curiously enough, the panel, except for the Japanese member, comes up with nothing unorthodox. Thus there is no mention of the use of possible marrow stimulants (erythropoietic hormone, male sex hormone, etc.). To be sure, there is an unfortunate lack of myelostimulatory materials from our present therapeutic armamentarium. It is also an unfortunate fact that all the liver extract, iron, B complex vitamins, folic acid, B_{12} so readily available do not make a particle of difference on the hypoplastic state, unless the unlikely possibility of an associated deficiency state is present. As work with the erythropoietic hormone continues, one may hope that eventually stimulatory factors will become available.

As for the question of actual transplantation of human normal marrow into the marrow-depleted patient, this is at present fraught with all kinds of difficulties, chief amongst which is the matter of isoimmunization. One can look forward, however, to the development of methods for marrow preservation and for conquering antigenicity. It seems inevitable that such methods will be found, thus allowing the ultimate conquest of what is now a frequently hopeless situation.—*W. D.*

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