

EDITORIAL

Aplastic Anemia

APLASTIC ANEMIA has been applied to more diverse clinical pictures than has any other hematologic term. It has been used to describe pancytopenia of varying degrees of severity with hypocellular, hypercellular, or truly aplastic marrows. In a given patient, the cellularity may vary—hypercellular foci admixed with areas of true aplasia. The degree of peripheral cytopenia may be variable and more prominent for one cell type than another. Clearly, these differences affect prognosis, in the untreated patient as well as in patients who may be considered for treatment. In some patients, the etiologic factors responsible for aplasia or hypoplasia cannot be identified. In others, it may occur in association with or as a complication of drug therapy or after exposure to irradiation. Infection may be associated with bone marrow failure, but usually this is transient. A more lasting degree of hypoplasia, however, has been associated with viral infections, particularly hepatitis. Aplastic anemia may be seen in association with genetic defects, e.g., Fanconi's anemia, in which case the aplasia is usually thought to be genetic in origin.

The relationship of hypoplastic (or aplastic) anemia to leukemia and paroxysmal nocturnal hemoglobinuria (PNH) is of interest and was the subject of an editorial by Dameshek¹ a number of years ago. Noting that some patients exposed to chemical agents, chloramphenicol in particular, developed hypoplastic anemia, either in association with or followed by PNH, and that others with hypoplastic anemia might eventually develop leukemia, he suggested that these might be differing manifestations of the same fundamental insult to the bone marrow and thus favored "lumping" rather than "splitting" these disease categories. Clearly, peripheral cytopenias may be an initial manifestation of leukemia and, when initially seen, the bone marrow may appear hypoplastic or aplastic, or there may be sufficient cellular abnormalities to term it preleukemic. PNH, however, may be seen in diseases other than hypoplastic anemia. Hansen and Killmann² have reported a high incidence of PNH in myelofibrosis with myeloid metaplasia, and we have seen several instances in our clinic. One might suggest, therefore, that PNH, rather than reflecting a specific disease entity, be considered as symptomatic of stem cell injury, and since abnormalities of platelets³ as well as red cells have been described, presumably the pluripotent stem cell is affected.

Pathophysiologically, aplasia can be viewed as the result of either of two fundamental bone marrow abnormalities, an abnormality of the pluripotent hemopoietic stem cell or a defect arising from the stromal cells and leading to an altered microenvironment. There is overwhelming evidence from transplantation studies that hemopoietic stem cells can rapidly reverse aplasia resulting from irradiation or cytotoxic drugs. Transplantation can also correct hemopoietic function in animals, such as the *W/W^v* mouse, with a genetic defect of the pluripotent stem cell. Defects involving the more

differentiated committed stem cell will lead to selective defects in that hemopoietic cell line, such as the erythroid aplasia seen in the Blackfan-Diamond syndrome.

Less generally appreciated is the influence of environment on bone marrow function. Bond and Brecher⁴ used a deuteron beam to produce a pencil-thin aplasia in the bone marrow of mice. Although active hemopoiesis was present outside of the irradiated boundaries, hemopoiesis did not recur within the exposed area. Flidner et al.⁵ emphasized the importance of structure and stromal injury in the postirradiation syndrome, particularly after high doses of irradiation. Knospe et al.,⁶ Crosby,⁷ and others have observed that, after local doses of irradiation in excess of 4000 R, there was the usual prompt initial aplasia resulting from damage to differentiated elements and the stem cell. This was followed by recovery, presumably effected by migration of normal stem cells from nonirradiated areas. However, after 2–4 wk, aplasia in the irradiated area recurred. This was thought to be secondary to the death of the more slowly proliferating stromal cells. This delayed manifestation of irradiation injury resulted in critical changes in the microenvironment, so that hemopoiesis could no longer be supported even though normal pluripotent stem cells were present. The implantation of normal stromal elements, however, reversed the aplasia. The genetically anemic *S1/S1^d* mouse has a defect in microenvironment. Transplantation of normal pluripotent stem cells will not correct this anemia but implantation of normal stroma will. The studies of Patt and Maloney⁸ on changes following the mechanical disruption of marrow support this thesis and provide further evidence for the importance of the microenvironment in determining marrow function. The studies of Trentin⁹ indicate that the environmental characteristics for erythroid and granulocyte proliferation may differ. Thus, one may postulate that selective (e.g., erythroid aplasia, neutropenia) as well as total aplasia may result from environmental changes, and from cellular or humoral defects. Selective aplasias (e.g., erythroid) may result from a failure to produce a normal regulator (e.g., erythropoietin) or the production of an inhibitor or antibody to a normal regulator. However, a general bone marrow failure, such as is seen in aplastic anemia, as a result of an altered humoral or hormonal regulator has not been documented.

In considering various therapeutic strategies in aplastic and hypoplastic anemias, the above considerations are most relevant. The variety of therapeutic approaches that have been used provide ample testimony that none is completely satisfactory. Recently, a number of clinics have reported their experience with the most widely used current therapy, the anabolic-androgenic steroids. At first glance, these reports appear to be a study in contrast, for the results have been quite different in various clinics. On further analysis, however, these differences appear to rest in the selection of patients rather than in the response to the drug. Sanchez-Medal et al.¹⁰ reported the most favorable results, 50% survival, but, if one considers only those patients with initial neutrophil counts of less than 500, the number of therapeutic responses achieved was not too dissimilar from that observed in the recent studies of

Davis and Rubin¹¹ or Li et al.¹² The major effect of the anabolic-androgenic steroids appears to be erythropoietic and several weeks or months are required before this effect becomes manifest. When neutropenia (and perhaps monocytopenia) is severe enough to permit life-threatening infection, insufficient time may be available to permit an adequate therapeutic trial with androgens. Indeed, in the Davis-Rubin series, 14 of 25 patients had died by 2 mo, primarily in consequence of infection.

Although it is clear that androgenic steroids will affect erythropoiesis, the exact mechanism of action has not been resolved. Experimentally, androgens have been shown to increase erythropoietin production, but patients with aplastic or hypoplastic anemia have markedly increased levels of erythropoietin. A further increase in erythropoietin production, thus, seems an unlikely explanation for the response to androgens. Increased sensitivity of the committed stem cell to erythropoietin, as well as, perhaps, an effect on heme synthesis may be involved. The effect of androgens on myelopoiesis and megakaryocytopoiesis is not firmly established. Thus one might anticipate that the most favorable response to androgenic steroids would be seen in those patients with mild neutropenia (WBC >500) and thrombocytopenia (platelets >30,000–40,000) but with significant anemia. In such patients, adequate time for therapeutic trial of androgens without the threat of serious infection or hemorrhage would be available, and it might be anticipated that androgens would improve erythropoiesis to such an extent that the major cause of morbidity, anemia, would be reversed. There is, of course, a problem with any drug requiring prolonged administration before the achievement of a therapeutic response, i.e., separating spontaneous remission from drug effect. This is particularly true in the milder hypoplasias and cytopenias where infection or hemorrhage do not pose a threat to survival. We have seen two such patients who had required frequent transfusions enter spontaneous remission several months after discontinuing long-term androgen therapy. Surely, relapse following discontinuation of the drug would resolve the issue in some patients, but is this maneuver warranted? If there is no relapse after withdrawal, can we say that the drug did not play a role in recovery?

Since the major causes of death from aplastic anemia are infection associated with profound neutropenia and, to a lesser extent, hemorrhage in those patients with severe thrombocytopenia, and further, since there is a high mortality within the first 2 mo before a response to androgens would be anticipated, it is clear that other therapeutic approaches must be sought. Transfusion with granulocytes and platelets, when available, might provide a temporary solution, but the logistics are formidable. Bone marrow transplantation is perhaps a more promising avenue for exploration. The presumption in this approach would be that the fundamental defect rests with the pluripotent stem cell, rather than the stroma or microenvironment. Transplantation of normal pluripotent stem cells should result theoretically in a cure if the soil is appropriate but would be doomed to failure if it is not. Unfortunately, there is no way at present to separate these two defects.

Assessment of potential for myeloid growth using in vitro or in vivo systems might provide some insight, but these techniques have yet to be proven in the present context. A decade ago, there were a number of efforts to treat aplastic anemia with bone marrow transplantation. These met with limited success largely due to immunologic problems. As a result, this type of treatment fell into disrepute. The development of improved techniques for tissue typing, the possibility of separating immunocompetent from pluripotent cells by physical means, and better understanding of pretreatment of patients with chemotherapy or irradiation hold promise that some of the problems encountered in earlier therapeutic efforts may be circumvented. In fact, Thomas et al.¹³ have reported successful bone marrow transplants in patients with aplastic anemia. In light of these considerations, wider exploration of transplantation in patients with aplastic anemia seems appropriate. This, however, must be reserved for those patients with profound pancytopenia and truly aplastic marrows. It should only be done by experienced transplant teams. The infrequency of the disease entity will preclude rapid accumulation of experience, but, perhaps, if a number of centers explore this approach, an answer as to its feasibility and practicality will be forthcoming in the not too distant future. In such studies, criteria for selection of patients will be critical. Data on the extent of bone marrow aplasia using scanning techniques; the potential of hemopoietic cell growth using tissue culture techniques; the levels of regulatory hormones and inhibitors; labeling studies of the bone marrow both before and after transplantation; as well as studies of the abnormalities of differentiated cells, e.g., PNH, should be a part of such an effort, for this may lead to better definition of a heterogeneous group of disorders.

I should like to reopen the question raised by the late Dr. Dameshek, who advocated lumping together the various types of aplastic anemia, rather than splitting them. Surely the answer, in significant measure, rests in an individual's philosophy. A strong case, however, can be made for splitting. The selection of patients for and the evaluation of the effectiveness of a therapeutic regimen seems better served by strict categorization, rather than grouping patients with mild peripheral cytopenias together with those having severe aplasia. Classification of aplasia according to etiology, when known or suspected, should also be considered. One need only look at the discordance today in describing the effectiveness of anabolic-androgenic steroids for the treatment of "aplastic anemia" to recognize that categorization is necessary. From a conceptual and experimental standpoint, would it not be better to view decreased hemopoiesis as resulting from one of several mechanisms—abnormalities of the committed or the pluripotent stem cells, changes in the stroma and microenvironment, failure of regulatory mechanisms, or the presence of inhibitors or antibodies to a specific regulator—rather than to group all under one umbrella? "End line" abnormalities, such as PNH, should be regarded as clues that there is an abnormal clone of cells, rather than as a specific disease itself. Today it may seem that such dis-

tinctions can be made only retrospectively, but as data, such as outlined above, are collected and efforts are made to separate on a physiologic basis those who respond to a therapeutic maneuver, e.g., transplantation, from those who do not, prospective evaluation of patients may become possible. If this is not to be done the approach to aplastic anemia in all probability will remain limited, empiric, and perhaps, in large measure, inconclusive.

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REFERENCES

1. Dameshek, W.: What do aplastic anemia, paroxysmal nocturnal hemoglobinuria (PNH) and hypoplastic anemia have in common? *Blood* 30:251, 1967.
2. Hansen, N. E., and Killmann, S. A.: Paroxysmal nocturnal hemoglobinuria in myelofibrosis. *Blood* 36:428, 1970.
3. Aster, R. A.: A platelet membrane defect in paroxysmal nocturnal hemoglobinuria. *J. Clin. Invest.* 47:2a, 1968.
4. Bond, V. P., and Brecher, G.: Personal communication.
5. Flidner, T. M., Sandkuhler, S., and Stodtmeister, R.: Research on the architecture of the vascular bed of the bone marrow of rats. *Z. Zellforsch.* 45:328, 1956.
6. Knospe, W. H., Blom, J., and Crosby, W. H.: Regeneration of locally irradiated bone marrow. *Blood* 26:398, 1966.
7. Crosby, W. H.: Experience with injured and implanted bone marrow; relation of function to structure. *In* Stohlman, F., J. (Ed.): *Hemopoietic Cellular Proliferation*, New York, Grune & Stratton, 1970, p. 87.
8. Patt, H. A., and Maloney, M. A.: Reconstitution of bone marrow in a depleted medullary cavity. *In* Stohlman, F., Jr. (Ed.): *Hemopoietic Cellular Proliferation*, New York, Grune & Stratton, 1970, p. 56.
9. Trentin, J. J.: Influence of hemopoietic organ stroma on stem cell differentiation. *In* Gordon, A. S. (Ed.): *Regulation of Hematopoiesis*, New York, Appleton-Century-Crofts, 1970, p. 159.
10. Sanchez-Medal, L., Gomez-Leal, A., Duarte, L., and Guadalupe Rico, M.: Anabolic-androgenic steroids in the treatment of aplastic anemia. *Blood* 34:283, 1969.
11. Davis, S., and Ruben, A. D.: Treatment and prognosis in aplastic anemia. *Lancet* 1:871, 1972.
12. Li, F. P., Alter, B. P., and Nathan, D. G.: The mortality of acquired aplastic anemia in children. *Blood* 40:000, 1972.
13. Thomas, E. D., et al.: Aplastic anemia treated by bone marrow transplantation. *Lancet* 1:284, 1972.



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1972 40: 282-286

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