PANELS IN THERAPY

XIII. Hypoplastic Anemia of Childhood

Panel

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Moderator

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Hypoplastic anemia in the young child, occurring without any indication of chemical exposure, and associated with a striking reduction in the red cell precursors of the marrow, has become better known in the past several years, particularly as the result of the investigations of Carl Smith, Conrad Gasser and others. Gasser has stressed the occurrence of arrested red cell development in the acute infections of childhood, whereas Smith has described "pure red cell" anemia occurring as a chronic, perhaps congenital condition. Adults, too, have "pure red cell" or "aregenerative" anemia, and this may be associated with such conditions as hemolytic anemia, hypersplenism, thymoma, or as a completely "idiopathic" condition. Because the childhood condition was first described and is better known, it was decided to ask a panel of pediatric hematologists their thoughts on the treatment of this disorder by means of the question which follows:

A child of three is found to have a normochromic, normocytic anemia with the following hematologic values:

Hemoglobin	**10.0 Gm.**
RBC	**3.0 M**
Hematocrit	**30%**
Reticulocytes	**1.0%**

A bone marrow aspiration reveals a normally cellular marrow with normal groups of granulocytes and megakaryocytes but with greatly reduced normoblasts. The picture remains relatively static for several months but eventually the anemia becomes more marked. What would your therapeutic program be in this case?

DR. ZUELZER:

It is difficult to formulate a therapeutic program on the basis of the information given. Before one begins to talk about a therapeutic program, it is axiomatic that the etiology and pathogenesis of the normocytic anemia be elucidated.

In broad general terms the possibilities one would think of in this situation are: (1) chronic infection; (2) renal disease and chronic renal insufficiency; (3) malignancy, not necessarily involving the hemopoietic apparatus; (4) specific hematologic diseases—(a) one or the other unusual pattern of leukemia; (b) aplastic

anemia; (c) congenital hypoplastic anemia, either of the Fanconi type or a so-called pure red cell aplasia.

A great deal would depend on the assumption that the aregenerative erythroid picture persists. It is possible that the initial findings simply represent an acute aplastic state and that later erythroid hyperplasia and reticulocytosis might be found so that a basically hemolytic process is by no means excluded. The therapeutic program would naturally depend upon the demonstration of one or the other of these various possibilities.

DR. SMITH:

Before proceeding with a program of treatment, I would like to make a few remarks regarding the type of anemia in this child. While pure red-cell or chronic aregenerative anemia appears to be the most likely diagnosis, a definition of this entity is pertinent because of the increasing number of case reports of this disease appearing in the literature. Pure red-cell anemia represents a chronic and, in infants and children, usually a congenital aregenerative anemia in which bone marrow failure is confined to erythropoiesis without simultaneous depression of granulocytes, platelets or their precursors.

In order to evaluate therapy more precisely and to project the type of response, the extent of erythroid depression must also be ascertained. Because of the relative rarity of this condition, a questionnaire was sent several years ago to hematologists in and out of the United States to obtain specific information concerning several phases of this relatively uncommon condition. The object was to determine the hematologic criteria of this disease in use in various clinics, the time of onset, therapy, especially with regard to splenectomy, and the outcome. From the replies, it was apparent that there was no unanimity as to the degree of erythroid hypoplasia which this anemia involved. No clear separation was being made between conditions in which the bone marrow was practically depleted of normoblasts (less than 2 per cent) and those in which these elements were reduced but still present in moderate number. The myeloid-erythroid ratios varied from moderately to markedly elevated values. The problem of precise designation is exemplified by the report of Cathie who described 5 children with congenital hypoplastic anemia under the heading of "erythrogenesis imperfecta" in which several bone marrow examinations showed a variation between erythroid hypoplasia and hyperplasia.

Reported cases suggest that a more favorable response to selected therapeutic agents such as ACTH and the steroids could be expected in cases with moderate numbers of normoblasts in the bone marrow than in those patients whose bone marrow was practically depleted of normoblasts. A more benign group also included those in whom the severe anemia was not present from birth but appeared in later childhood, adolescence or adult life. In these patients splenectomy might be more effective. In instances in which a bone marrow toxin such as infection, drug, or chemical could etiologically be established recovery might be looked for following its elimination. Another important factor in evaluating therapy is the possibility of spontaneous remission, as occurred in 3 of 12 cases in Diamond's group. Remission can occur at any period from early childhood to adolescence with stabilization at a lower hemoglobin level.

It is obvious that more extensive information is needed to assess specific therapy in an anemia whose clinical and hematologic criteria are subject to variable interpretation. This is especially pertinent in a condition of such prolonged duration and whose ultimate prognosis is so uncertain.

The condition in this patient is to be classified as a progressive anemia based on a selective depression of erythroid elements in the bone marrow. Major therapy consists of ACTH and steroids, transfusions and splenectomy introduced in the following order:

ACTH and Steroids. Cortisone, hydrocortisone or prednisone are given primary consideration since they represent the most potent form of therapy. They are prescribed in a daily dosage of 100 mg., 80 mg. and 40 mg. respectively given in divided doses every 6 hours. With optimal dosages, evidences of the ability of the bone marrow to produce red cells should be manifest within 3 to 4 weeks. The dosage of each of these drugs is arbitrary. If and when the patient responds, the dosage should be reduced to the minimum which maintains a remission so as to avoid side effects. With erythroid hyperplasia, reticulocytosis, increased hemoglobin and red cell levels, smaller amounts of the steroids should be tried such as 25 mg. of cortisone, 20 mg. of hydrocortisone, or 10 mg. of prednisone daily. Any evidence of infection should prompt the administration of a suitable antibiotic. Despite the persistently low hemoglobin levels these patients are not unduly susceptible to infection. If no response is obtained with the steroids in the prescribed period, ACTH by intramuscular or subcutaneous injection should be substituted, either as the gel in daily dosage of 40 mg. or 10 mg. of the liquid preparation at 6 hourly intervals. Here too, the response varies with each patient so that no fixed amount can always be prescribed. With a favorable response, reducing, and stopping the drug entirely should be attempted periodically to determine the capacity of the patient to establish spontaneous erythropoietic function.

Transfusions. Although physiologic needs for the growing child implies a need for maintaining optimum hemoglobin levels, this objective cannot be achieved without the danger of "iron overload" or hemosiderosis. The hemoglobin value at which a transfusion is indicated cannot be arbitrarily fixed but varies with the associated signs and symptoms of the individual patient. As a guide to management we have found that with few exceptions patients with illness in the category of chronic anemia do not require transfusions until hemoglobin levels decrease to 7 to 7.5 Gm./100 ml. at which point clinical symptoms usually appear. It is apparent that hemosiderosis is to be expected from repeated transfusions over long periods of time. Another limitation of frequently repeated transfusions is its depressant effects upon endogenous erythropoiesis and hemoglobin synthesis.

Splenectomy. This procedure which is frequently recommended only as a last resort in pure red-cell anemia has nevertheless proven effective on occasion in both reducing the number of transfusions and in restoring erythropoiesis. When transfusions are required at increasingly frequent intervals to maintain a physiologically sufficient although reduced hemoglobin level, the development of an extracorpuscular hemolytic component presumably located in the spleen may be postulated. In one of our patients with pure red-cell anemia, marked enlarge-

ment of the spleen was present. This finding is contrary to an accepted criterion of the aplastic-hypoplastic group of anemias—namely the failure to palpate the spleen. In this instance, however, removal of the spleen resulted in extending the interval between transfusions although depression of erythropoiesis persisted. Undoubtedly in cases without enlargement, splenectomy is justified where a hemolytic factor for donor blood is demonstrated by technics revealing a shortened survival of transfused normal erythrocytes. The presence of such a hemolytic factor would be clinically suspected where regularly spaced intervals for transfusions are suddenly shortened.

For patients in whom no hemolytic component is apparent splenectomy is based on the principle that an abnormally functioning spleen may depress the erythropoietic function of bone marrow. This procedure is recommended when ACTH, the steroids and other therapeutic agents alone or in combination have received extensive trial without success. There is less reluctance to remove the spleen when the bone marrow is not entirely devoid of erythroid elements in any stage of development. In any event the procedure may be justified on the basis of a splenic humoral factor which inhibits maturation of precursors either visualized or potentially present in unidentified primordial cells such as hematogones. The fear that removal of the spleen deprives the patient of needed resources of erythropoietic tissue is not justified by experience in this disease. Although the majority of cases are not improved by splenectomy, the condition is not aggravated. Occasionally splenectomy alone has a beneficial effect in restoring erythropoiesis. In other cases, cortisone and other therapeutic agents have proven more effective after splenectomy.

In 3 patients under current observation from 9 to 10 years of age with classical pure red-cell anemia dating from early infancy, ACTH and steroids have been ineffective in restoring erythropoiesis. The spleen was removed in two of the children without influencing erythropoiesis.

The hazard of serious and at times overwhelming and fatal infection, most frequently with the pneumococcus, in infants and children splenectomized for this and other anemias necessitates an alertness to this possibility for at least two years following the procedure.

These three agents constitute the mainstay of the therapeutic program in current use. Their skillful application has resulted either in dramatic responses or they have been useful in tiding the patient over until the time of a spontaneous and much hoped for remission. Severe infections and particularly heart failure to which many patients succumbed in the past are better managed today with modern therapy. For these reasons the extremely guarded prognosis heretofore given for this anemia may be relaxed in future cases particularly with the introduction of ACTH and the steroids.

These agents by no means exhaust the entire therapeutic armamentarium of the disease. Worthy of note is the use of cobalt and members of the vitamin B complex. The administration of iron is potentially harmful because of its increased absorption from the gastro-intestinal canal in refractory anemias supplementing the already excessive iron stores within the tissues from transfusions.

The use of cobalt has had its many advocates with sporadic favorable reports in this and other chronic anemias in children. Its possible side effects such as

anorexia, nausea and thyroid enlargement in children preclude its widespread use except under controlled conditions.

Each of the following vitamin B factors in suggested dosage has been given to patients in this and other members of the hypoplastic-aplastic group of anemias: B_{12}, 1,000 micrograms intramuscularly three times weekly, riboflavin 10 mg. three times daily, nicotinic acid 25 mg. daily and folic acid 5 mg. three times daily. While many of these substances are known to function in specific phases of erythropoiesis, their value in this anemia is still debatable. Occasionally they appear to stimulate red cell formation, particularly after splenectomy.

Perhaps a more rational therapeutic approach would result from further exploration of preliminary observations suggesting that pure red-cell anemia represents an inborn error of tryptophan metabolism.

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DR. STURGEON:

This child would be classified in our Clinic as one having a pure red cell anemia associated with bone marrow erythrogenic hypoplasia. The probable etiologic diagnosis, in the absence of any other positive clinical or laboratory findings, would be "congenital" or "acquired idiopathic" hypoplastic anemia. Irrespective of which of the latter two categories this patient was placed in, our therapeutic approach would be the same. First, as was followed in this particular case, we would observe the patient for several months in anticipation of a spontaneous remission or the development of some underlying condition such as a slowly progressive neoplastic process, a myeloproliferative disease or an aplastic anemia.

After the period of observation, a course of steroid therapy would be tried. Prednisone, 1–2 mg., or, Cortisone, 2–4 mg. per kilogram of body weight, divided into three doses per day would be prescribed. In the absence of a response, the course of therapy would be continued for 6–12 weeks. In the event a response was obtained, the dose would be gradually discontinued over a 1–3 months period. If during this time, or shortly thereafter, a relapse occurred, the therapy would be re-instituted or the dose increased slightly until a minimal dose was found that would maintain the remission. In one case this proved to be 2.5 mg. of Cortisone per day. The ultimate criterion for a complete remission would be maintenance of the patient's hemoglobin concentration above 11 grams for a

minimum of 3 months. The reticulocyte count and the percentage of normoblasts in the bone marrow would also be used in the evaluation of therapy. Assuming there was no response to steroid therapy, or at best only a transitory one, the drug would be discontinued. A second 1–6 months period of observation would then be followed. Supportive treatment with transfusions of packed red cells would be given whenever the hemoglobin concentration decreased to approximately 6 grams.

Splenectomy would be performed next. The same observations as those suggested above would be made to evaluate any response. Again, assuming there was no improvement, another 1–6 months period of observation would ensue. If at the end of this period a spontaneous remission had not occurred (the odds for which are as great as they are for inducing a remission), cobalt therapy would be attempted.

In this Clinic, cobalt chloride has been administered orally in doses approximating 1 mg. per lb. per day, in a single dose, and continued for as long as three months. We have also employed a special injectable cobalt amino-acid complex given in small (in the vicinity of 1 mg./day) doses. The methods of observation have been essentially the same as those suggested above in evaluating responses to steroids. Assuming this also failed, as is most likely, consideration would then be given to other possibilities. These have not been used routinely; such measures as diathermy to the marrow cavity (as suggested to us by Doctor Nelson of Minnesota) and the administration of plasma thought to contain increased amounts of the erythropoietic factor have been tried.

From our experience, the probability of success, with the use of the therapeutic procedures suggested, is poor. During the past 10 years, of the 14 patients under observation in this Clinic who have had anemia characterized at the onset by bone marrow erythrogenic hypoplasia, 9 are classified as having congenital hypoplastic anemia. At present, although all of these patients are alive, only one is in remission; this is maintained on a daily oral dose of 2.5 mg. of Cortisone. Steroids proved unsuccessful in the other 4 cases in which they were tried. In one of these a minor transitory effect was obtained. Splenectomy has been performed four times without success. Cobalt has been used in 6 of these cases. Only a partial temporary remission of approximately 5 months duration occurred in one patient treated with the injectable cobalt preparation. Spontaneous remission has not occurred in any of our cases despite the fact that 3 of the patients are more than sixteen years old.

Five other cases classified as acquired or atypical congenital erythrogenic hypoplastic anemia have been observed. After several years of observation spontaneous remission occurred in one case and has persisted 8 years. Splenectomy was followed by remission in another case; in four instances it was unsuccessful. Steroids were of no help in the 3 cases given this form of therapy. Two of this latter group of five patients have expired, one ultimately showing signs of an atypical leukemia; the other aplastic anemia.

Moderator's Comment

There can be no question that as much information as possible is advisable in the consideration of any anemic state, particularly when a condition, such as

lack of regeneration of nucleated red cells, occurs under a variety of circumstances (infections, hemolysis, chemical exposure, congenitally, perhaps on the basis of iso-sensitization in utero, etc.). In a chronic condition in childhood, the likelihood of infection, increased hemolysis, chemical exposure and the like would be very small, and chronic "aregenerative" or "pure red cell" anemia would be most likely. The question was slanted in that direction.

It is obvious from Dr. Smith's and Dr. Sturgeon's answers that treatment of the latter condition is far from satisfactory, and as in the adult cases of hypoplastic anemia discussed in a previous issue, one has little to offer other than ACTH and the corticosteroids and splenectomy, with transfusions as indicated, and various trial measures that might be at hand. How to make the red cell precursors grow is the outstanding problem here, and perhaps this depends, as Dr. Smith indicates in his last statement, upon further knowledge of the enzymes, aminoacids and humoral factors concerned in erythropoiesis. In any event, the statements of the panelists represent a fair indication of the unsatisfactory state of our therapy of the present day; it is hoped that within the next decade, the picture will be radically improved.—*W. D.*