The Role of Splenectomy in the Management of Thalassemia

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The extraordinary progress made in recent years in characterizing the congenital hemolytic disorders has clarified many of the clinical, hereditary and hematologic phenomena associated with Cooley's anemia. Treatment has not, however, kept pace with these advances. The urgency for corrective measures stems from the increased recognition of the disease in areas of the world beyond those originally designated and from the growth of populations with susceptible individuals.

Available evidence indicates that this disease represents a genetically determined hemolytic anemia resulting from an intracorpuscular defect and that it also involves abnormalities in hemoglobin synthesis and red cell formation for which there is as yet no specific therapy. It has been demonstrated in homozygous Cooley's anemia that the problem of establishing a level of equilibrium between destruction and production of erythrocytes compatible with normal activity is greatly exaggerated by the inability of erythropoiesis to compensate for the accelerated rate of red cell destruction, and that this inadequacy is greater than in other hemolytic anemias. Transfusions are therefore required to support the adequate hemoglobin levels which red cell production fails to achieve. The need for continuous transfusions, however, entails problems of blood procurement, reactions and excessive iron deposition. When the blood requirement to maintain hemoglobin levels compatible with normal activity and freedom from symptoms becomes excessive, splenectomy must be considered. Additional indications are massive enlargement of the spleen producing discomfort from its mechanical presence and interference with the functioning of adjacent organs.

From the large number of children with severe (homozygous) Cooley's anemia who have attended our clinic in the past 26 years, sufficient data are available in 58 to warrant review. Half of these patients have been splenectomized. This paper is particularly concerned with data obtained from the splenectomized patients over a postoperative period of 5 months to 9 years.
for whom presplenectomy data were also obtained. Postsplenectomy observations are summarized in other patients as long as 20 years following the operation. Many of these patients have been the subject of a previous report, so that the present data embrace the accumulated experience of this group at a later period, and of four additional patients in whom splenectomy has been performed since the earlier report. This presentation will deal specifically with the following topics: further delineation of the extracorpuscular hemolytic defect, the effect of splenectomy on the basic disease, the need for transfusions in the postsplenectomy period, growth and developmental patterns, cardiac complications and the abnormal response to intercurrent infection.

**Patient Material and Methods**

An evaluation of the effects of splenectomy must take into account the variability of the basic disease. Patients with the homozygous disease in whom both parents are heterozygous for thalassemia fall into two classifications: the intermediate if they function effectively without transfusions, and the severe if multiple supplements of blood are required to maintain hemoglobin levels commensurate with normal activity. In contrast to the severely affected patients, those in the intermediate group maintained concentrations of hemoglobin ranging from 7.4 to 9.9 Gm./100 ml. This separation, therefore, can usually be made clinically.

It is important also that the hemoglobin level for which blood is given be taken into consideration. The administration of blood for minimal levels of 6.5 to 8 Gm./100 ml of hemoglobin, as practiced in our clinic, will lead to lower over-all requirements than if blood is given routinely to maintain higher levels.

The close observation of 49 of the 58 children with homozygous Cooley's anemia (table 1) was facilitated by the establishment of a special out-patient clinic where transfusions of blood were provided on a routine basis. The nine remaining patients and many of the current group had previously been admitted to the hospital only when transfusions were urgent and hence were not maintained at prescribed hemoglobin levels.

**Results**

**Pre- and Postsplenectomy Survival of Donor Erythrocytes**

In our earlier study the fate of normal transfused blood was determined in patients with an intact spleen employing the Ashby method of differential agglutination. It appeared in this study that the life span of transfused erythrocytes decreased with advancing age.

The use of radioactive chromium as a tag for erythrocytes has facilitated the determination of the life span of normal donor red cells in the patient’s circulation. Studies in normal subjects show that after the injection of red cells tagged with Cr\(^{51}\) half the isotope disappears from the circulation in 26 days. The upper limit of the half period has been given as 32 days and in one study as high as 40 days. In the present investigation 26 to 32 days were taken as the average range of the half-life of chromium tagged cells.

More extended observations employing chromium-tagged cells (fig. 1) demonstrate that there are many exceptions to the inverse relationship between age of the patient and the survival of normal donor cells noted in the earlier group. Two of the younger children, A. Y. and V. P. (cases 3 and 4) show a shorter survival of donor cells than do the older patients A. C. and
Table 1.—Severe Cooley's Anemia

<table>
<thead>
<tr>
<th>Total no. of patients:</th>
<th>58</th>
<th>44</th>
<th>14</th>
</tr>
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<tbody>
<tr>
<td>Splenectomized:</td>
<td>29</td>
<td>16</td>
<td>13</td>
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Fig. 1.—Cooley's anemia. Cr\textsuperscript{51} RBC survival studies (donor cells) on non-splenectomized patients. Note the shortened survival of normal donor red cells. There is no uniform relationship between the age of the patient and life-span of the red cells, although the longest red cell survival occurred in J. V., 1½ years old, and the shortest in M. M., 18 years old.

F. P. (cases 7 and 8). On the other hand, in J. V., 1½ years of age (case 9), the youngest of the group, survival of donor cells approximated the normal, whereas the shortest survival occurred in M. M. (case 1), the oldest patient in this group. The extracorpuscular hemolytic defect may therefore be present early in life and on the other hand may not be manifest in marked degree until adolescence—in any case it is an acquired defect. The number of transfusions could thus appear to be only a possible factor responsible for its causation. With the development of the complication of a markedly shortened survival time of normal donor cells, splenectomy, in our experience, eventually becomes mandatory, as occurred in patients 1 to 6.

Moderate leukopenia and, to a lesser extent, thrombocytopenia, observed
in a fair number of our cases prior to splenectomy, may be attributed either to a hyperactive spleen or to suppression by multiple transfusion.

It will be noted in the postsplenectomy period (fig. 2) that except for patient J. F. (case 1) with a red cell survival of 25 days the chromium half-life in the others ranged from 34 to 43 days. The fact that most of these values are above the upper limit of normal suggests either that 26 to 32 days given as the range of normal is lower than more extensive data would warrant, or that in Cooley’s anemia, as perhaps in other refractory anemias, survival of donor red cells is prolonged following splenectomy. Of great importance is the observation that regardless of the length of the postsplenectomy period (3 months to 20 years; fig. 2) the life span of transfused normal donor cells remained normal. This reversal to normal survival rates in this group of patients confirms the evidence for an extracorpuscular hemolytic mechanism in this disease and provides one explanation for the beneficial effects of splenectomy.

Pre- and Postsplenectomy Transfusion Requirements

In these patients as in those previously reported the progressive development of accelerated transfusion requirements to maintain an adequate hemoglobin level necessitates consideration of splenectomy. While efforts are made in the immediate presplenectomy period to vary the number and size of the transfusion so as to defer splenectomy, the blood requirement nevertheless
becomes so extreme that the decision for the operation is usually forced. The increasing need for transfusions before splenectomy and the sharp reduction after this procedure is obvious in this group of patients.

The striking diminution in the number of transfusions following splenectomy is the result of several factors, one of which is the longer survival of transfused erythrocytes, as mentioned above. In addition it has been demonstrated that transfusions possess a suppressive effect on endogenous erythropoiesis and hemoglobin synthesis. This inhibiting effect is clearly demonstrated in the decreased synthesis of fetal hemoglobin which normally exists in substantial amounts in severe Cooley's anemia. When transfusions are reduced following splenectomy this function is restored and hemoglobin synthesis proceeds maximally in accordance with the capacity of the patient. Greater amounts of both fetal and adult types of hemoglobin result.

It is possible that in later adolescence cessation of growth and diminishing metabolic needs permit adequate functioning at lower hemoglobin levels. By removing hemolytic and inhibitory factors achieved by splenectomy, subsistence on blood of endogenous origin becomes a possibility in older patients except when infection or trauma supervenes. In that event blood supplementation will be necessary. It is to be expected, therefore, that the results of eliminating the extracorpuscular hemolytic mechanism should be manifested in an increased life span of normal donor cells, resulting in decreased transfusion requirements and therefore, greater erythropoiesis. Patient V. P. (fig. 3) is cited as an example. After an initial period in the first months of life of intermittent transfusions, blood requirements increased so markedly as to necessitate splenectomy. The increase in half-life of donor blood from 14 to 34 days is reflected in a lessened need for blood supplements. Comparing the amounts of packed red cells expressed in three month periods from the onset of the disease until splenectomy with the three years following the operation, it is apparent that less blood was required to maintain at least as good and at times improved hemoglobin levels.

Another feature worthy of note in this patient is the gain in weight concurrent with splenectomy which is undoubtedly related to the sense of well being with removal of an organ of inordinate size.

A quantitative estimate of the average monthly transfusion requirements in terms of milliliters of packed cells was made in 13 children for one year preceding splenectomy and for the subsequent postoperative period (fig. 4). The preoperative period of one year was chosen as a basis for comparison because it was associated with a progressive demand for the administration of blood. T. P. is still in the first year of observation and R. P. received a single transfusion for study purposes in the first postoperative year and 10 transfusions in the 67 months that followed. Transfusion requirements were especially compiled in the first postsplenectomy year to determine whether the need for blood in this period bore any relationship to subsequent supplements. It is sometimes assumed that lesser amounts of blood are needed immediately following splenectomy than in the following years. It will be observed, that the blood requirements in the first postoperative year are only slightly less and gradually parallel those of the later years. But in each
instance improvement was noted with respect to reduced blood requirements to maintain preoperative hemoglobin levels.

**Effect of Splenectomy on the Basic Disease**

The subsequent course of these patients indicates that the results of splenectomy must be regarded as “fringe” benefits, for the fundamental intracorpuscular defect of the disease presumably remains unaltered. One of the principal yardsticks by which the severity of Cooley’s anemia is evaluated is the level at which the individual patient establishes hematopoietic equilibrium. The measurement of blood destruction and compensatory production of red blood cells and total hemoglobin has been facilitated by reinjecting the patient’s own chromium-labeled red cells in his own circulation, thus permitting the measurement of the longevity of red cells in their natural environment. The calculations of the rates of both destruction and production involve a consideration of the mean cell life, which in turn is derived from the chromium half-life of the patient’s own cells.3

Only a limited number of patients lend themselves to a study of the life span of their red cells in their own circulation because of the need for multiple transfusions in most patients with severe Cooley’s anemia. Any sample of the blood of such patients after reinjection of their own chromium-tagged cells would necessarily contain two populations of red cells, their own
Fig. 4.—Hemoglobin concentrations and average monthly transfusion requirements in terms of milliliters of packed red cells in the pre- and postsplenectomy periods. Note that reduced blood supplements were needed to maintain preoperative hemoglobin levels. They were no different in the first postoperative year (dotted column) from later years (open column).

and the donor’s. A group of 10 patients with homozygous Cooley’s anemia at equilibrium were available in whom data could be obtained of the survival of their own chromium tagged cells within their circulation (fig. 5). Two had been splenectomized.

It will be observed that the half-life of chromium-tagged red cells ranged from 6.5 to 19.5 days as compared with the normal survival of 26 to 32 days. From the data assembled in this figure the two splenectomized patients A. D. and R. P. reveal a chromium half-life of their own cells that falls within the range of the severely affected and intermediate group. Therefore, the red cell survival in these two patients showed no improvement over patients with intact spleens, suggesting that the basic intracorpuscular defect was probably unaltered. It is obvious that to study any possible small effects of splenectomy upon the survival of the patient’s own erythrocytes a larger group must be investigated pre- and postsplenectomy.

The Factors of Growth and Development

While both transfusions and splenectomy add to the patient’s well being and prompt gain in weight, eventually growth in height and sexual development are retarded and these abnormalities remain unaltered (figs. 6 and 7). The children with Cooley’s anemia are of average height and weight at birth. They grow normally until about the age of 8 to 10 years, at which time their growth rate undergoes a marked retardation, so that they attain a
Fig. 5.—Cr\textsuperscript{51} RBC survival studies of homozygous Cooley’s anemia (patient’s cells in patient’s circulation). The severely affected and intermediate (homozygous) patients as well as the two who were splenectomized reveal equal intracorpuscular defects, as indicated by the shortened survival of their own red cells. Note also the large amounts of fetal hemoglobin and the lack of correlation with severity of the disease.

very short final height. Secondary sexual characteristics develop later than in the normal population, if at all. Normal menses are rare and in our series cease several months to several years after the onset. Whether this interference with maturation is related to chronic anemia, liver dysfunction, gonadal atrophy or to large amounts of iron seen in the pituitary, thyroid and adrenal is not clear.\textsuperscript{13}

Cardiac Complications

In common with idiopathic hemochromatosis, cardiac failure is a frequent complication\textsuperscript{10-13} and of unknown cause. Of the 10 patients so affected all but one had been subjected to splenectomy. The ages at the time of the inception of heart failure ranged from 12 to 27 years with five patients 20 years and above. While infection terminated the lives of many children with severe Cooley’s anemia in the years before antibiotics were available, they now succumb to heart failure. Long-term transfusions prolong their lives but are nevertheless responsible in part for increased tissue iron. Whether in-
fluenced by heavy deposition of iron in the myocardium or otherwise, irreversible congestive heart failure inevitably overtakes these patients. Splenectomy merely represents a remedial measure for a specific complication of Cooley's anemia. It does not appear to alter significantly the pattern of the basic disease process and does not retard the occurrence of cardiac failure.

The duration of life from the onset of cardiac symptoms ranged from four months to one year. The electrocardiograms revealed auricular premature beats initially followed by runs of paroxysmal auricular tachycardia, flutter, auricular fibrillation, ventricular premature contractions\(^\text{14}\) and in one of our cases, episodes of ventricular fibrillation.

**Pericarditis**

One of the unusual features in this series was the occurrence of 11 attacks of acute pericarditis in eight patients with severe Cooley's anemia of whom seven had undergone splenectomy. The clinical signs, symptoms and electrocardiographic findings corresponded to the adult disease which has been variously designated as benign, nonspecific or idiopathic. In a disease as complex as Cooley's anemia a variety of mechanisms may be involved in the etiology so that acute benign pericarditis represents solely a clinical designation. Sporadic attempts to establish a viral etiology in our patients have been unsuccessful. All of our cases were truly benign, self-limited and ended in complete recovery, although one child had one and another two recurrences. In only two instances was there x-ray evidence of a moderate pericardial effusion, and this also cleared spontaneously. The physical basis for the peculiar susceptibility of the pericardium is unknown. Because pericarditis occurred almost entirely in splenectomized patients, it seems likely that removal of the spleen constitutes a major incident which promotes increased susceptibility to this type of infection. Antibiotics have thus far proven valueless, and treatment consists of symptomatic relief.

**Infection**

Increasing numbers of case reports\(^\text{15-17}\) have further documented those previously reported\(^\text{18}\) dealing with postsplenectomy susceptibility to infection in children. Two additional cases of overwhelming and fatal infection in patients with Cooley's anemia have been encountered. One child 5 years of age had a splenectomy one year previously and died within 48 hours with pneumococcus sepsis. The other child 10 years of age had a splenectomy four years previously and succumbed with *E. coli* sepsis within a period of nine hours. Two children without Cooley's anemia have also recently been observed in whom serious but nonfatal postsplenectomy infections occurred. These patients had acquired hemolytic anemia and hereditary spherocytosis. Pneumococcic meningitis occurred in the former and acute adrenal insufficiency with hyperpyrexia in the latter, one year and seven years, respectively, following splenectomy. Since in the majority of cases the interval between splenectomy and infection has been two years or less, it has been our practice to place splenectomized patients on antibiotic therapy for a minimal period of two years.
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SPLENECTOMY AND THALASSEMIA MANAGEMENT

COMMENTS

While there is abundant evidence that splenectomy in severe Cooley's anemia eliminates a hemolytic component which shortens the survival of normal donor cells, the gross destruction of the patient's defective red cells probably remains unaltered. The intensity of the destruction of the patient's own cells may have been minimally reduced in the two splenectomized patients (A. D. and R. P., fig. 5), but no absolute statement can be made until more extended studies are carried out in the same patients in pre- and postsplenectomy periods.

The collective data of the present study indicate that the effect of splenectomy is to re-establish the preoperative status with regard to red cell destruction and production now no longer influenced by a superimposed hemolytic component. Still prevailing in the splenectomized patient is the difficulty in establishing adequate hemoglobin levels because of the inability of erythropoiesis to compensate for the accelerated rate of red cell destruction. This shortcoming is greater in Cooley's anemia than in any other congenital hemolytic anemia and accounts for the need of transfusion therapy in the majority of these patients.

A critical problem in Cooley's anemia is the proper selection of patients for splenectomy. In the severely affected individual the need for splenectomy is clearly indicated when transfusion requirements are persistently increased, by massive splenomegaly, and by deterioration of the clinical condition.

It is difficult at times to differentiate between the acquisition of an extracorporeal hemolytic defect concurrent with a shortened survival of the donor red cells or an exaggerated hypoplastic period due to a failure of production and frequently related to a minor infection. In such cases, auxiliary laboratory tests are useful. Measurements with the use of radioactive chromium provides an insight into the rate at which transfused blood is being destroyed. In the patient with a markedly and persistently increased transfusion requirement, criteria for splenectomy are so obvious that these measurements are unnecessary.

Additional benefits from splenectomy accruing to the splenectomized patient may stem from the greater ability of their naturally thin red cells to deliver oxygen to the tissues than cells of greater thickness. Whether the red cells of patients with Cooley's anemia already reduced in thickness are further thinned by splenectomy awaits study. The ability of anemic patients with Cooley's anemia to be physically active in spite of low hemoglobin levels may perhaps be explained on this basis.

The greater effectiveness of splenectomy in the older child is reflected in the substantially reduced postoperative transfusion requirements inherent in this age period. The function of age may be explained on the basis of a genetically milder disease permitting postponement of splenectomy until puberty. Also, with the slowing of growth and diminished basal metabolic needs in adolescence erythropoietic equilibrium can be established at levels compatible with well being and without supplementation by transfusions. Despite the preference to delay splenectomy until adolescence, it is fre-
quentely necessary to remove the spleen in the younger patient for the reasons already stated.

The data compiled in this and other papers throw no light on the possible modification of the normal immunologic and cytopoietic functions of the spleen in Cooley’s anemia. Reports of the increased susceptibility to infection in children following splenectomy in this disease indicate that the immunologic defenses residing in this organ against invading organisms are unimpaired. In the course of an investigation now in progress concerned with the causation of postsplenectomy infections, phagocytic activity has been found normal regardless of the presence of the spleen. It should again be emphasized that in comparison with the increasing numbers of splenectomies in Cooley’s anemia and in other dyscrasias in children the incidence of severe and overwhelming infections is relatively small. Nevertheless, close supervision for several years postoperatively is essential so that appropriate treatment may be immediately instituted in the event of an infection.

Transfusions which are required to support adequate hemoglobin levels produce simultaneously an increased iron deposition. Iron accumulates in the tissues and, except for the normal excretion of approximately 1 mg. daily, cannot leave the body except by bleeding. Under such conditions, hemosiderin deposits in normal storage depots increase greatly, and in addition accessory sites assume the function of iron storage. Another source of tissue iron, particularly noticeable in patients receiving minimal transfusions, is the increased absorption from the diet by the gastrointestinal tract and from iron medicaments. As in other organs, iron is stored in the cardiac muscle as ferritin. The conversion of siderotic to fibrotic areas characterizing hemochromatosis occurs most commonly in the liver and pancreas. This anatomic change probably depends on other factors in addition to the continued presence of excessive iron in tissues. Chronic anemia and hypoxia, common concomitants of Cooley’s anemia,22 may represent some of the factors involved in the production of hemochromatosis. Removal of the spleen does not retard the inevitable progression to irreversible heart disease usually occurring in the young adult.

The failure to mature normally and menstruate deprives the female patient with Cooley’s anemia of the opportunity to unload iron; thus both females and males with this disorder become susceptible to hemochromatosis. In contrast, idiopathic hemochromatosis occurs predominantly in males since the female has already achieved sexual maturity at an age when the first symptoms of this disease are likely to appear and is thus capable of losing substantial amounts of iron through pregnancy, lactation and menstruation.13

Mobilization of iron stores in idiopathic hemochromatosis has been successfully achieved by repeated phlebotomies.13,23 In Cooley’s anemia the need for maintaining adequate hemoglobin levels precludes the use of this measure. The intravenous injection of chelating agents increases the urinary excretion of iron but is impractical in treatment of conditions in which massive iron overload exists.24,25 Until specific treatment becomes available, the most serious problem confronting the patient with Cooley’s anemia is the prevention and control of heart failure. In an era when other ef-
effective therapeutic measures are at hand the most important need at present is the discovery of a means to rid the heart of excessive iron.

**Summary**

A group of 58 children with severe Cooley's anemia, half of them splenectomized, were reviewed from several of the more important clinical and hematologic aspects.

Splenectomy eliminates the extracorporeal mechanism responsible for the accelerated destruction of normal donor red cells in the patient's circulation. This represents a lasting improvement and accounts for an increased longevity of normal blood supplements and a striking reduction of transfusion requirements. Less blood was required to maintain at least as good, and at times improved, hemoglobin levels. Estimates of duration of survival of the patient's own erythrocytes suggest that the basic hemolytic defect is not altered significantly by this operative procedure.

While transfusions and splenectomy promote the patient's well being, growth in height and sexual development are retarded. Secondary sexual characteristics develop, if at all, later than in normal individuals and normal menses are rare.

Cardiac failure occurred in 10 patients; all but one had been subjected to splenectomy. This group was characterized by cardiac enlargement, multiple arrhythmias and death with refractory heart failure, usually in the second decade of life.

Cardiac complications are likely to be related to the heavy deposition of iron in the myocardium, and are comparable in this respect to a similar incidence in idiopathic hemochromatosis. One of the most serious problems in the management of Cooley's anemia is the prevention and control of congestive heart failure. This will depend on the discovery of an effective method by which the heart can be made to unload its iron deposits.

The increased susceptibility to infection following splenectomy in patients with severe Cooley's anemia indicates that the normal immunologic responses inherent in the spleen remain intact despite the stress of a continuous hemolytic process.

**Summario in Interlingua**

Esseva passate in revista, ab plures del plus importante punctos de vista clinic e hematologic, le casos de 58 patientes pediatric con grados sever de anemia de Cooley. Un medietate del patientes habeva essite splenectomisate.

Splenectomia elimina le mechanismo extracorpuscular que es responsabile pro le accelerate destruction de normal erythrocytos transfusionate in le circulation del patiente. Isto representa un permanente melioration e explica le prolongate longevitate de normal supplementos sanguinee e un frappante reduction del requirimentos transfusional. Minus sanguine esseva requirite pro mantener le mesme e a vices meliorate nivello de hemoglobina. Estimaciones del superviventia del erythrocytos del paciente mesme suggere que le basic defecto hemolytic non es alterate significativemente per le mentionate intervention chirurgic.
Durante que transfusiones e splenectomia promove le ben-esser del patiente, su crescentia in altor e su disveloppamento sexual es retardate. Le caracteristicas secundari del sexo se disveloppa, si del toto, plus tarde que in individuos normal. Le occurrentia de menses normal es rar.

Disfallimento cardiac occurreva in 10 del patientes. Omne istes, con un exception, habeva essite subjicite a spenectomia. Iste grupo esseva caracterisate per allargamento cardiac, arrhythmias multiple, e morte con disfallimento refractori del corde, usualmente durante le secunde decennio del vita.

Le complicationes cardiac es probablemente relationate al massive deposition de ferro in le myocardio e es simile in iste respecto a un comparabile incidentia de complicationes cardiac in hemochromatosis idiopathic. Un del plus serie problemas in le tractamento de anemia de Cooley es le prevention de congestive disfallimento cardiac. Su resolution va depender del discoperta de un efficace methodo per que le corde pote esser inducite a discargar su depositos de ferro.

Le augmentate susceptibilitate de contraher infectiones in patientes subjicite a splenectomia in le tractamento de sever anemia de Cooley indica que le normal responsas immunologic inherente in le splen remane intacte in especto del stress de un continue processo hemolytic.

**REFERENCES**

The Role of Splenectomy in the Management of Thalassemia

CARL H. SMITH, MARION E. ERLANDSON, GERTRUDE STERN and IRVING SCHULMAN