Studies in Mediterranean (Cooley's) Anemia

I. Clinical and Hematologic Aspects of Splenectomy, with Special Reference to Fetal Hemoglobin Synthesis

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THE WIDESPREAD INCIDENCE of Mediterranean anemia beyond the original geographic and racial confines has resulted in a growing interest in problems of management. In locations such as the New York metropolitan area, with large concentrations of genetically susceptible persons of Italian and Greek origin,1 the establishment of clear-cut criteria for splenectomy represents a recurring challenge when frequently repeated transfusions fail to support adequate hemoglobin levels.

It is acknowledged that the primary defect in severe Mediterranean anemia is intracorpuscular and relates to an inherited, but not as yet well defined abnormality in hemoglobin synthesis and red cell formation. In the absence of specific therapeutic agents, periodic transfusions and splenectomy in selected cases constitute the basis of current treatment. The difficulties in maintaining a satisfactory hemoglobin concentration with multiple transfusions, so characteristic of the severe disease, involve a consideration of a number of interrelated factors. These include the accelerated destruction of imperfect red cells produced by the patient, the varying rates of intrinsic blood formation, and the fate of transfused red cells in the circulation.

It is the purpose of this paper to investigate two extrinsic mechanisms which contribute to the anemia and to the inadequacy of transfusions, namely, the hemolytic activity of the spleen and the suppressive effects of transfusions on endogenous erythropoiesis and hemoglobin synthesis. By analyzing critically the effects of transfusions and splenectomy we hoped to formulate more accurate criteria for these. Systematic observations were conducted on a group of patients with respect to these measures, both clinically and with the aid of a variety of laboratory procedures. The latter included determination of the survival of transfused red cells, red cell and circulating hemoglobin mass and fetal hemoglobin. The fact that fetal hemoglobin occurs in extraordinary amounts in severe Mediterranean anemia suggested its value as a biologic tag of endogenous hemoglobin synthesis.

Initial consideration will be given to the efficacy of splenectomy with respect

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to changes in transfusion requirements, to the influence of the age of the patient on the survival of transfused blood, and to the bearing of the latter factor on the optimal period for the operation. The inhibitory effects of transfusions on endogenous hematopoiesis, which are more readily investigated in the post-splenectomy period, will be dealt with separately.

There are conflicting reports on the merits of splenectomy in severe Mediterranean anemia. Baty and his co-workers,2 for instance, represent those who regard splenectomy without value in alleviating symptoms or in modifying the course of treatment, and Gross,3 in concurring in this opinion, ventures further that it may even aggravate the condition. In recent years, the experience of others4-10 has led to greater optimism. With this, however, has come the realization that splenectomy does not influence the basic hematologic disorder but does alleviate a superimposed hemolytic state. Two of the earliest reports11, 12 describe the removal of the spleen in a child of nine years hospitalized in The New York Hospital. Although originally classified as Von Jaksch anemia, the diagnosis of Cooley’s anemia was later established. This patient, operated on in 1917, survived a period of 15 years despite a minimum of transfusions. The recent studies by Lichtman and his co-workers5 represent the first attempt aimed at characterizing the hemolytic function of the spleen by determining the pre- and post-splenectomy survival of transfused normal red cells, thereby providing a basis for projecting future benefits in a particular patient. Accelerated destruction of morphologically normal red cells is defined by the term “extra-corpuscular hemolytic state.”

A group of nine patients with severe Mediterranean anemia and one with combined Mediterranean anemia–sickle cell disease, ranging in age from 4 to 18 years, was intensively studied before and after splenectomy. Brief reference to this group has been made in a previous publication,13 at an earlier period following splenectomy. Additional patients were also included for the elucidation of related features. Evaluation of these data, as in all studies on Cooley’s anemia, must be done with the realization that patients with the severe or major type of the disease manifest varying grades of clinical and hematologic disturbance. This reservation applies to patients in the present group, although the demand for transfusions was constant and urgent in each individual.

Methods

Routine blood counts were performed on venous blood containing dried oxalate mixture as the anticoagulant. Hemoglobin concentrations were determined photoelectrically according to the method of Evelyn.14 Fetal hemoglobin concentrations were determined by the alkali denaturation method of Singer et al.14 Plasma volumes were determined with Evans Blue dye (T1824) by the method of Nitshe and Cohen.15 A dye constant (K) was determined individually in the plasma of each patient every time plasma volume was measured. The exact amount of dye injected was determined by weight. Red cell and total blood volumes were calculated from plasma volume and venous hematocrit. In these calculations the venous hematocrit was multiplied by 0.95 to correct for trapped plasma,16 and by 0.91, the latter expressing the ratio of whole body hematocrit to venous hematocrit, as derived by Gibson et al.18 The formula for total blood volume was constructed according to the method of Mollison et al.19 as follows:

\[
\text{Blood Volume} = \frac{\text{Plasma Volume}}{100 - 0.91 \times (\text{venous hematocrit} \times 0.95)}
\]
Red cell volume was then obtained by the difference between plasma volume and total blood volume. Multiplication of hemoglobin concentration by total blood volume permitted calculation of total circulating hemoglobin; multiplication of the latter value by the percentage of fetal hemoglobin yielded values for total circulating fetal and adult hemoglobins.

The survival of transfused erythrocytes was studied by the Ashby technique modified by Young et al. All but one of the patients studied were in blood groups A, B, or AB and were transfused with compatible group O blood; one patient (DM) was in blood group 0, MN and was transfused with donor blood of group 0, N. In addition to the usual compatibility tests the donor blood was checked in each instance by the indirect Coombs test and by the trypsinization technique. The tagged erythrocytes were administered as packed cell transfusions containing a minimum of plasma.

**Results**

**Relationship of Splenectomy to Transfusion Requirements**

The indications for splenectomy in severe Mediterranean anemia consist of massive enlargement of the spleen producing discomfort from its mechanical presence, interference with the functioning of adjacent organs, and an increase in transfusion requirements. Operative intervention becomes urgent when there is a progressive demand for administration of blood to maintain satisfactory hemoglobin levels. While other areas of the reticuloendothelial system contribute to the shortened survival of transfused cells, primary attention is directed to the spleen as the major site of blood destruction. As a guide to management it is our experience that with few exceptions patients with the severe disease do not require transfusions until hemoglobin levels drop to 7 to 7.5 Gm. per 100 ml. blood or below, when disabling symptoms may appear. The problem is further complicated by the growing knowledge that the continued support of these declining levels carries with it the potential hazard of hemochromatosis from excessive iron deposition.

Many of the published cases of splenectomy in severe Mediterranean anemia have disclosed a reduction in transfusion requirements following operation. This improvement would be expected on the basis of removing an overactive organ exercising a disproportionate hemolytic function. The benefits of this procedure, from this standpoint, can be readily ascertained by comparing transfusion requirements before and after the operation.

In the present study, the quantitative estimate of these changes has been expressed in terms of the amount of packed red cells required each month, instead of on a daily basis of whole blood described by Lichtman and his co-workers. As shown in table 1, the period of one year preceding splenectomy served for comparison because this interval was usually marked by an increasing difficulty in maintaining adequate blood levels. Improvement will be noted in each of the 10 patients as manifested by increased hemoglobin levels despite reduced amounts of blood transfused. While the elevation in hemoglobin varied in degree, the benefits with regard to transfusion were marked in every instance. It will be observed that this tendency to maintain similar and in most cases elevated hemoglobin levels with decreased amounts of blood, extends over a considerable post-splenectomy period. Examination of these data suggests furthermore that with the exception of the three year old patient, M. G., removal of the spleen becomes
Table 1.—Results of splenectomy in 9 patients with severe Mediterranean anemia and 1 patient with combined Mediterranean–Sickle cell disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Splenectomy</th>
<th>Pre-Splenectomy (Date for 1 yr prior to surgery)</th>
<th>Post-Splenectomy (Date for entire follow-up period)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average Hb. gm. %</td>
<td>Transfusions ml. packed rbc per month</td>
<td>Follow-up months</td>
</tr>
<tr>
<td>M. C.</td>
<td>3 3/12</td>
<td>6.7</td>
<td>466</td>
</tr>
<tr>
<td>D. B.</td>
<td>5 10/12</td>
<td>7.5</td>
<td>571</td>
</tr>
<tr>
<td>J. B.</td>
<td>7 6/12</td>
<td>6.5</td>
<td>581</td>
</tr>
<tr>
<td>D. E.</td>
<td>7 9/12</td>
<td>5.7</td>
<td>798</td>
</tr>
<tr>
<td>F. G.</td>
<td>7 12/12</td>
<td>6.5</td>
<td>586</td>
</tr>
<tr>
<td>S. E.</td>
<td>11 6/12</td>
<td>8.0</td>
<td>480</td>
</tr>
<tr>
<td>J. V.</td>
<td>13 5/12</td>
<td>6.8</td>
<td>608</td>
</tr>
<tr>
<td>J. P.</td>
<td>13 8/12</td>
<td>6.7</td>
<td>736</td>
</tr>
<tr>
<td>R. P.</td>
<td>15 9/12</td>
<td>6.9</td>
<td>562</td>
</tr>
<tr>
<td>A. N.</td>
<td>17 6/12</td>
<td>7.6</td>
<td>625</td>
</tr>
</tbody>
</table>

*Cooley’s = Single
**1 Trans. for study purposes

Increasingly valuable when this is carried out in the older individual. The results in the patient R. P. are particularly noteworthy inasmuch as with the exception of a single postoperative transfusion for red cell survival studies, no further blood supplements were required. The data summarized in this table are graphically represented in figure 1, demonstrating again, the inverse relationship between hemoglobin levels and transfusion requirements before and after splenectomy. The sharp decrease in blood needs following splenectomy to maintain hemoglobin concentrations of varying grades of improvement, is conclusively demonstrated in the upper and lower sections of the figure respectively.

Figure 2 presents, in greater detail, both the markedly reduced transfusion requirements and the improved hemoglobin levels following splenectomy in four representative cases from the group shown in figure 1 and table 1. The same tendency noted previously, with regard to age, is once more apparent, namely, the higher average hemoglobins in the two older children, J. P. and R. P., and the more moderate elevations in the younger children, M. G. and J. N. Another noteworthy feature is observed in the case of M. G. in whom, following splenectomy, the effects of a single transfusion, with respect to the distinctive rise and fall of hemoglobin levels, are more predictable. The reasons for the more irregular course of the presplenectomy hemoglobin level in each case depend on the interaction of a number of forces which will be discussed later.

Survival of Transfused Normal Erythrocytes Prior to Splenectomy

The explanation of certain of the hematologic and clinical features of severe Mediterranean anemia depends on knowledge of basic mechanisms relating to the fate of erythrocytes within the circulation. Considerable data have accumu-
Fig. 1.—Hemoglobin concentrations and transfusion requirements in pre- and post-splenectomy periods. Data for figure is listed in Table 1.

Fig. 2.—Hemoglobin concentrations as related to administration of transfusions in pre- and post-splenectomy periods in 4 patients with severe Mediterranean anemia.
Survival of normal erythrocytes in 5 non-splenectomized patients of varying age with severe Mediterranean anemia. Red cell longevity was measured by Ashby technic, correlated from following the survival of the patient’s red cells when transfused into normal persons and of blood from normal donors transfused into patients with the severe disease by the Ashby method. Presumably the rates of destruction of each of these morphologically different cells are separate and distinct and are unrelated.

The shortened survival of the patient’s red cells in the circulation of the normal recipient has been uniformly demonstrated and substantiates the existence of an intracorpuscular defect in this disease. On the other hand, the same agreement does not hold with regard to the survival of normal red cells in the circulation of patients with severe Mediterranean anemia. Lichtman and his co-workers have recently described a shortened survival of transfused normal erythrocytes in the severely anemic patient, whereas a normal life span had been heretofore reported by several groups of workers. The following observations provide a plausible explanation for these discrepancies.

To test the fate of transfused blood in the patient with an intact spleen, red cell survival studies were undertaken in five patients of varying age, not included in the present group, employing the Ashby method of differential agglutination. It will be noted in figure 3 that the life span of transfused erythrocytes is normal in the one year old child while decreased in each of the four others. It may also be seen that in the one year old child the slope is linear while in the remaining four patients the survival curves appear to approach the exponential. The decreased survival curves of exponential type indicate random destruction of transfused cells regardless of their age. Finally, the data suggest that the life span of transfused erythrocytes becomes progressively shortened with advancing age of the patient. Thus it appears that a secondary hemolytic mechanism develops in patients with severe Mediterranean anemia. These findings suggest a pathogenetic basis for the observations previously recorded (table 1, figs. 1 and 2), with respect to increased transfusion requirements in the pre-splenectomy period.
Red Cell Survival Following Splenectomy

The postponement of splenectomy in the patients described in figure 3 necessitated an examination of other sources for postoperative survival studies. Three patients from the present series (J. P., R. P., and A. V., table 1) in the older age group were available in the post-splenectomy period as well as an additional patient (F. P., fig. 5), with combined Mediterranean anemia–sickle cell disease of a milder type, whose red cell survival was studied before and after splenectomy. In two of these patients, J. P. and R. P., it had been previously demonstrated (table 1, figs. 1 and 2) that, in the year prior to operation progressively frequent transfusions were needed in order to maintain an adequate hemoglobin concentration. It will be observed in figure 4, that in contrast to the shortened pre-operative survival noted previously (fig. 3), the life span of transfused cells in this group of splenectomized patients was normal. Also, in patient F. P. (fig. 5), 50 per cent of transfused cells disappeared at about 4 weeks, in the pre-splenectomy period as compared with 8 weeks in the post-splenectomy period.

The reversal to a normal red cell survival confirms the existence of a hemolytic component in this disease and provides one explanation for the beneficial effects of splenectomy. These results confirm the observations of Lichtman and his colleagues who called attention to the extracorpuscular type of hemolytic anemia.

![Graph showing red cell survival before and after splenectomy](image-url)

**Figure 4.**—Survival of normal erythrocytes in 3 patients with severe Mediterranean anemia after splenectomy.
in this disease, also noting that in the one patient in whom splenectomy was ineffective, no significant alteration in red cell survival occurred.

The Effect of Splenectomy on Total Circulating Hemoglobin Mass and on Fetal Hemoglobin Synthesis

The extent of recovery in terms of reduced transfusion requirements can be further evaluated by a comparison of the absolute amounts of circulating hemoglobin in the pre- and post-splenectomy periods. Combined blood volume and hemoglobin determinations permitted an accurate estimate of the total circulating hemoglobin mass by eliminating the influence of errors inherent in shifting blood volumes resulting from growth, transfusions and the removal of a markedly enlarged organ. The total hemoglobin mass so obtained was further separated into adult and fetal hemoglobin components, the latter by the method of alkali denaturation. Since fetal hemoglobin normally occurs in high concentrations in severe Mediterranean anemia its determination serves as a valuable index of endogenous hemoglobin production.

The serial changes before and after splenectomy, utilizing absolute values, correspond in general to those already noted in table 1, figures 1 and 2. It will be observed that in both J. P. (fig. 6) and A.D. (fig. 7), the post-splenectomy circulating hemoglobin mass equaled or surpassed the pre-splenectomy level, despite fewer transfusions. The postoperative fetal hemoglobin in these two cases ranged from 25 to 61.8 per cent and 5.5 to 23 per cent respectively, reflecting the hematologic differences known to exist in this disease.

Figure 8 demonstrates a similar pattern in patient R. P., but with more beneficial results from splenectomy than in the other patients. Following splenectomy,
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Fig. 6.—Effect of splenectomy on transfusion requirement, hemoglobin concentration, and circulating total and fetal hemoglobin masses. Patient, male, age 14 yrs.

Fig. 7.—Effect of splenectomy on transfusion requirement, hemoglobin concentration, and circulating total and fetal hemoglobin masses. Patient, male, age 17 yrs.
Fig. 8.—Effect of splenectomy on transfusion requirement, hemoglobin concentration, and circulating total and fetal hemoglobin masses. Patient, female, age 16 yrs.

with the exception of one transfusion for study purposes, the peripheral hemoglobin concentration, as well as the circulating hemoglobin mass, reached higher levels than in the pre-splenectomy period. It should be emphasized that the values in the last determinations were obtained 16 weeks after transfusion, so that the entire circulating hemoglobin mass of over 300 Gm. of hemoglobin may be properly regarded as of the patient's own manufacture. The preponderance of fetal hemoglobin (74 per cent) at this time, obviously entirely of endogenous origin, provides further proof that the patient was subsisting on her own blood. The reason for the synthesis of fetal hemoglobin in such large proportions in severe Mediterranean anemia, when transfusions are no longer required, awaits further study.

The increases in total circulating hemoglobin mass following splenectomy, with few or no transfusions in these three cases, may result from several mechanisms. While the removal of a hemolytic organ permits increased longevity of transfused normal erythrocytes it is likely that more prolonged survival of the abnormal erythrocytes elaborated by the patient results as well. Another factor to be discussed at greater length in the accompanying paper relates to the inhibitory effects of transfusions on endogenous hematopoiesis. The increased synthesis of fetal hemoglobin noted in figures 6, 7 and 8 when transfusions are reduced following splenectomy, supports this hypothesis.

That the presence or absence of an enlarged spleen does not, per se, influence the synthesis of fetal hemoglobin as observed in figure 9. The two young adults, S. M. and D. M., with severe Mediterranean anemia, whose earlier clinical and hematologic course had been previously described were able, for many years, to continue routine activity with subnormal hemoglobin levels unsupported by transfusions. Splenomegaly was marked in both patients. The presence of fetal
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Fig. 9.—Fetal hemoglobin concentrations in 2 patients with intact spleens and 2 patients post-splenectomy, all having severe Mediterranean anemia.

hemoglobin of 56.5 and 72.5 per cent respectively in these patients with intact spleens, correspond to maximal values in J. P. and R. P. of 61.8 and 74 per cent respectively, following splenectomy. These results indicate that the alkali-resistant hemoglobin can be elaborated in large amounts independent of the presence or absence of the spleen, particularly when the administration of blood is kept at a minimum.

Comment

Our observations coincide with those of Lichtman and his coworkers in demonstrating not alone the reduction in transfusion requirements following splenectomy, but also that hematologic improvement can be correlated with changes in red cell survival. While the size of the spleen and impingement on adjacent organs constitute prime indications for its removal, it is even more important to estimate its capacity for hemolyzing transfused normal blood, a function separate from hypersplenism which is directed more specifically towards red cells of endogenous origin.

Our data provide an explanation for the increased pre-operative destruction of transfused donor blood observed in each of these studies in contrast to the normal survival rates noted by others. It was shown that the age of the patient influenced the red cell survival to the extent that transfused blood was more rapidly eliminated from the circulation with advancing age. On the basis of these findings, a normal red cell life span is to be expected in an infant and a sharply decreased survival time in the older child and young adult. Exceptions have been encountered in certain infants in whom transfusion needs are already excessive when first observed. One such patient demonstrated antibodies (anti E), ap-
parently developed following several incompatible transfusions administered elsewhere. In addition several older patients have been seen, who, despite presenting the usual clinical and laboratory evidences of severe Cooley’s anemia, have apparently been able to maintain satisfactory hemoglobin levels with minimal numbers of transfusions. The factors of age and degree of severity must, therefore, be considered in evaluating red cell survival rates in severe Mediterranean anemia. The cases cited in the literature with normal red cell survivals can be explained on this basis. The patient described by Hamilton, Sheets, and DeGowin was aged 7 weeks and the two cases of Kaplan and Zuelzer were 2 and 7 years respectively. In these three, the number of transfusions were probably limited, in the first instance based on age, and in the latter two, as indicated by the normal serum iron and considerable iron-binding capacity. In our experience the severe case of Mediterranean anemia receiving only a moderate number of transfusions shows an elevated serum iron and absent iron-binding capacity. These observations emphasize the extreme variability of the disease as reflected in transfusion requirements. While the relationship of red cell survival to the age of the patient is apparent in these results, it should be emphasized that greater experience is required for corroboration. The reservation made by Eadie and Brown that there was no simple relationship between the degree of shortening of the life span and intensity of the destructive factor probably applies with equal force in severe Mediterranean anemia.

It is difficult to designate a specific anatomic lesion in the spleen to explain the extra-corpuscular defect on which the life span of transfused normal blood is based. Microscopic examination of the spleen in our cases failed to disclose any relationship between red cell survival and the extent of fibrosis, erythropoiesis, follicular changes or iron deposition. Progressive functional derangements of this organ probably result from the impact of continued blood destruction by inadequately oxygenated tissues.

Since the spleen serves as the initial reservoir for transfused red cells from which iron is degraded, it might be assumed that its removal might accentuate iron deposition in other tissues and hasten the development of hemochromatosis. Finch and his co-workers have shown, however, that over a period of time iron is redistributed to the liver and secondary sites through the serum iron compartment irrespective of the mode of administration. In addition doubt has recently been thrown on the concept that excessive iron storage alone inevitably leads to hemochromatosis in this disease. Howell and Wyatt from the examination of the tissues of a 13 year old child with Cooley’s anemia suggested that the development of parenchymal fibrosis depends on the intervention of other factors, among them continued hypoxia, rather than the exclusive accumulation of iron. Ellis, Schulman and Smith came to a similar conclusion from a study of the histologic findings in this disease, supported in part by cases included in the present series. They found that while hemosiderosis and increased fibrosis frequently coexisted, no causal relationship could be established between the two.

With the exception of the three year old patient, our results strongly suggest the greater effectiveness of splenectomy in the older patient as indicated by the more marked reduction in postoperative transfusion requirements in the latter. The optimal time for splenectomy might be anticipated in later adolescence when
cessation of growth and diminishing basal metabolic needs permit adequate function at lower hemoglobin levels. From many standpoints removal of a hyperactive spleen represents a major concern in the patient approaching adult life, but whether splenectomy should be deferred until this period whenever possible awaits more extensive experience. The excellent results in the 17 year old Thailand patient reported by Minnich and her co-workers, corresponds to 16 year old R. P. in the present series (table 1, fig. 1) who has not required supportive transfusions in the two years since the operation. In the absence of accessory spleens, the frequent failure of lasting improvement may be based on hyperactivity in other areas of the reticuloendothelial system. The two patients with combined Mediterranean anemia–sickle cell disease (A. V., table 1, and F. P., fig. 5), both older individuals, have responded unusually well, as would be expected from the milder course of this condition as compared with severe Mediterranean anemia.

The high concentration of alkali-resistant hemoglobin in severe Mediterranean anemia, representing almost the entire hemoglobin content in certain instances, awaits explanation. A congenital inability to effect the transfer from the fetal to the adult mechanism of hemoglobin synthesis and blocking of normal hemoglobin synthesis by the gene for Mediterranean anemia so that fetal hemoglobin continues to be elaborated have both been postulated. Chernoff demonstrated immunologically that the alkali-resistant hemoglobin fractions in a number of hematologic diseases including Mediterranean anemia are not specific but are identical with the fetal hemoglobin of newborn infants. From the standpoint of oxygen affinity, Allen, Wyman, and Smith could find no advantage of fetal over maternal hemoglobin and indicate that reported dissimilarities may result from environmental differences of the hemoglobin molecule. Our data corroborate those of Minnich and her colleagues in demonstrating the lack of correlation between the intensity of the anemia and the percentage of fetal hemoglobin. From the foregoing it may be concluded that the pathogenetic basis of this disease must be sought, not alone in deviations of the biosynthesis of hemoglobin, but in imperfections in the red cells which account for their continued increased destruction throughout the course of the disease regardless of splenectomy. That the presence of this disproportionate alkali-resistant component serves as a convenient tag of endogenous hemoglobin synthesis has been demonstrated in the present study and will be extended in the discussion on the inhibiting effects of transfusion.

Several collateral aspects of splenectomy in Mediterranean anemia worthy of note concern the incidence of skeletal pain, susceptibility to infection, and the occurrence of erythroblastemia. The occurrence of skeletal pain in children with Cooley's anemia is not uncommon in our experience. In several children, as exemplified by J. P. and A. D., this symptom appeared to be accentuated after splenectomy. The fact that transfusions relieve bone pain in both splenectomized and nonsplenectomized cases suggested its relationship to demands on the bone marrow for red cell formation when blood supplements are inadequate or have been interrupted over any prolonged period. The relative freedom from discomfort prior to operation in the two children, indicated that this effort had been
previously minimized by periodic transfusions with resulting depression of endogenous erythropoiesis.

While susceptibility to infection represents a serious complication of advanced Mediterranean anemia, this hazard has been largely reduced through the use of antibiotics. The sudden fatal illness of patient D. B. (table 1) and of a recent 14 year old patient not included in the present series, 16 months and 2 weeks respectively following splenectomy, both with high fever, severe prostration and coma, requires some explanation. This unexpected circumstance may have been entirely fortuitous judging from its infrequency in the large numbers of splenectomized patients on record. King and Shumacker have, however, reported five infants under the age of 6 months with congenital spheroctytic anemia, four of whom developed either meningitis or overwhelming meningococcemia within 5 weeks to 3 years after the operation with one fatality. In the other child death followed a few days after discharge with a rapidly fatal febrile illness. While Rowley demonstrated the increased antibody responses after intravenous antigen injections in the individual with an intact spleen, the splenectomized patient in our experience has been capable of combating infections successfully with the aid of current therapy. In the light of the cases cited, however, such patients should receive immediate and energetic treatment in the event of sudden serious illness. Studies are currently being carried out to determine the value of prophylactic administration of antibiotics in patients who have been treated for various hematologic disorders by splenectomy.* In addition, investigations are under way to compare the immunologic responses of splenectomized and non-splenectomized patients.

The increase of nucleated red cells in the peripheral blood following splenectomy, which characterized this disease, probably reflects the removal of an inhibiting influence from the bone marrow where these cells predominate. The interval following the operation may be prolonged several days before this feature is detected. In three patients the bone marrow revealed a sharp drop in the percentage of normoblasts for a variable period following the operation. The values for nucleated red cells, ranging from 60 to 83 per cent preoperatively, fell from 12 to 28 per cent for several weeks postoperatively. No reason could be given for the failure to maintain this decrease in the bone marrow for any appreciable period, while peripheral erythroblastemia persisted.

It is worthy of note also that clinical features, physical signs and electrocardiographic changes suggestive of acute benign pericarditis were observed in four patients following splenectomy and in one a second attack occurred within the space of a year. Pericardial effusion was noted in only one patient although a pericardial friction rub associated with severe chest pain and fever, occurred in all. Although absent in our nonsplenectomized cases, pericardial effusion has occasionally been observed in Cooley's anemia in patients with intact spleens. Whether splenectomy renders patients with this disease susceptible to pericardial involvement remains to be determined although this complication must be kept

* Terramycin and Permapen, used in these studies, were supplied through the generosity of the Charles Pfizer Co., New York.
in mind. Furthermore, the presence of hemosiderin in cardiac structures may also conceivably be involved in lowered resistance to the etiologic agent responsible for the recently reported increase in the incidence of acute benign pericarditis. A more extended analysis of this complication in splenectomized patients will be dealt with at greater length in a subsequent publication.

It must be stressed, in conclusion, that modern concepts of patient care, involving, among others, surgical technic, treatment of infection and management of cardiac dysfunction, are important factors determining benefits from splenectomy. These factors, though apart from the basic hematologic disorders, must be considered when comparing present results in Mediterranean anemia with those of earlier days, and apply to splenectomized and nonsplenectomized patients as well. None of the various methods of management, however, has altered this basic intracorporeal defect.

Conclusions

In a group of patients ranging in age from 4 to 18 years with severe Mediterranean anemia, splenectomy resulted in a striking reduction of transfusion requirements. With the aid of blood volume determinations, it was shown that the post-splenectomy circulating hemoglobin mass equaled or surpassed the pre-splenectomy level with fewer transfusions.

Greater benefits were usually observed when this procedure was carried out in the older patient. In one child of 16 years no further supplements have been required for a period of several years.

A shortened survival of transfused normal erythrocytes determined by the Ashby method was observed in patients with intact spleens. The age of the patient influences red cell survival to the extent that transfused blood is more rapidly eliminated from the circulation with advancing age. Normal life spans of transfused red cells were noted in three patients in whom the spleen had been removed.

These findings of decreased transfusion requirements had increased life span of transfused red cells in patients who had undergone splenectomy are in accord with previously published results. They suggest the existence of an extracorporeal hemolytic component in this disease and offer one explanation for the beneficial effects of splenectomy.

It remains to be determined in what manner fetal hemoglobin, which occurs in large amounts in this disease, can be integrated with the pathogenesis of severe Mediterranean anemia. The synthesis of this component is independent of the presence or absence of a hyperactive spleen, particularly when the administration of blood is kept at a minimum.

The incidence of skeletal pain, acute pericarditis, susceptibility to infection and the occurrences of erythroblastemia in the post-splenectomy period were discussed.

This favorable report does not imply indiscriminate removal of the spleen in the severe disease. Furthermore, the benefits recorded here must be tempered by the knowledge that this procedure represents a palliative measure, which does not influence the fundamental intracorporeal defect. Information is not yet available as to the complete clinical and hematologic course and the ultimate
outcome in the post-splenectomy period on the basis of the principles outlined in this paper.

**Conclusiones in Interlingua**

In un gruppo de 10 patientes de etates inter 4 e 18 annos, omnes con sever anemia mediterranee, splenectomia resultava in un frappante reduction del requerimentos transfusional. Per medio de determinationes del volumine de sanguine il eseva demonsrate que post le splenectomia—i.e. a un periodo quando le numero del transfusiones habeva essite reduce—le massa de hemoglobina circulante equalava o excedeva illo constatate ante le splenectomy.

Le effectos benefici del splenectomy eseva generalmente plus pronunciate in le patientes de etates plus avantiate. In un paciente de 16 annos nulle transfusiones additional eseva requirite durante un periodo de plure annos.

In patientes con splen intacte un reducece superviventia del transfundite normal erythrocytos eseva constatate per medio del methodo Ashby. Le etate del patiente affice le supervivencia erythrocytic in tanto que sanguine transfundite es eliminate plus rapidemente ab le circulation in proportion que le etate avantia. Del altere latere in tres patientes splenectomisate le supervivencia de erythrocytos transfundite eseva normal.

Iste constatationes—le reducece requerimentos transfusional e le augmentate supervivencia de transfundite erythrocytos in patientes splenectomisate—es de accordo con le resultatos publicate per previe autores. Illos suggere le existentia de un agente hemolytic extracorpuscular in iste morbo e assi offere un possibile explication del effectos benefici de splenectomy.

Il remane a determinar in qual maniera hemoglobina fetal, que se incontra in grande quantitates in iste morbo, es connectite con le pathogenese de sever anemia mediterranee. Le synthese de iste hemoglobina fetal non depende del presentia o absentia de un hyperactive splen, specialmente quando le transfusiones de sanguine non excede le requerimentos minimal.

Es discutite le frequentia post-splenectomy de dolores skeletal, de pericarditis acute, de susceptibilitate a infections, e del occurrentia de erythroblastemia.

Iste reporto favorabile de splenectomy in sever anemia mediterranee non implica un recommendation de ectomia in omne casos sever de iste morbo. In plus, le hic-descritbe effectos benefici non debe inducer nos a oblidare que splenectomy in sever anemia mediterranee es un operation palliative que non affice le defecto intracorpuscular fundamental. Nos nondum possede complete informaciones pro evalutar, super le base del principios hie presentate, le integre curso clinic e hematologic e le ultime resultato del periodo post-splenectomy.

**REFERENCES.**

STUDIES IN MEDITERRANEAN (COOLEY'S) ANEMIA


Studies in Mediterranean (Cooley's) Anemia: I. Clinical and Hematologic Aspects of Splenectomy, with Special Reference to Fetal Hemoglobin Synthesis

CARL H. SMITH, IRVING SCHULMAN, RICHARD E. ANDO, GERTRUDE STERN, ELEANOR FORT and JOYCE PRESTWIDGE