BETA THALASSEMIA AND HEART DISEASE: THREE DECADES OF GRADUAL PROGRESS*,**

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NEW YORK

Transfusion therapy permitted survival of babies with thalassemia major into childhood and beyond. In the 1950's it became evident that the treatment that saved their lives as children caused their death from cardiac disease in adolescence or early adulthood.

RECOGNITION

Soon after the tenth birthday early signs of cardiac impairment presented in two forms. One was recurrent attacks of pericarditis (1), sometimes mild but on other occasions severe, with large pericardial effusion and even cardiac tamponade. Fluid from pericardiocentesis was serous and serosanguinous and sterile on bacteriologic culture. The illness resembled viral pericarditis though this etiology was not proven. It was self-limited and responded to bed rest and analgesics. Pericardiocentesis was used for tamponade. One patient with severe, recurrent effusions required pericardial resection. Though a nuisance, this illness when recognized and treated was not life-threatening as the second cardiac complication was.

The second complication began as asymptomatic cardiac enlargement early in the second decade and progressed to serious cardiac impairment, with arrhythmias and cardiac failure (Figure 1) that despite treatment, usually ended in death within one year (2, 3). The first electrocardiographic sign of cardiac hemachromatosis was atrial premature contractions followed by atrial tachyrhythmias—paroxysmal atrial tachycardia, flutter or fibrillation. Somewhat less common were ventricular premature beats, followed by high-grade ventricular ectopy and tachycardia. At the same time atrioventricular conduction time lengthened to first degree heart block and rarely, second or third degree block. Voltage consistent

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** This research was supported in part by the NIH Heart, Lung, and Blood Institute, Grant R01 HL 19898-06, by a grant from the New York State Cooley's Anemia Project, by the Children's Blood Foundation and by the Pediatric Cardiology Research Fund.

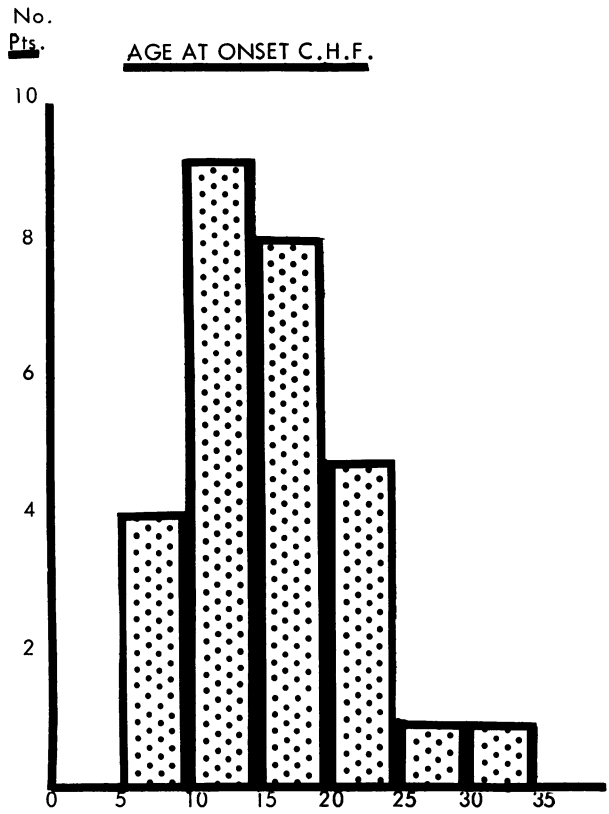

FIG. 1. Age at onset of cardiac failure in the first 28 patients. The youngest child was eight years of age; most were in the second decade.

with left ventricular hypertrophy began to decrease. T wave abnormalities unrelated to digitalis were common.

These arrhythmias usually preceded the onset of frank congestive heart failure, which was predominantly right-sided, with gross dependent edema. Despite use of antiarrhythmic agents and of digitalis and diuretics, death followed often within a few months and usually within one year of the appearance of decompensation.

The external appearance of hemosiderosis in the skin was mirrored on examination of the organs, which were heavily laden with iron and were scarred. The myocardium was rusty-brown and on microscopic examination (Figure 2), large amounts of iron deposits were evident in myocardial cells that were in various stages of necrosis. Interstitial fibrosis was widespread. Iron deposition and fibrosis were more marked in myofibrils than in the cardiac conduction system and the sinus node was spared more than the atrioventricular node (4).

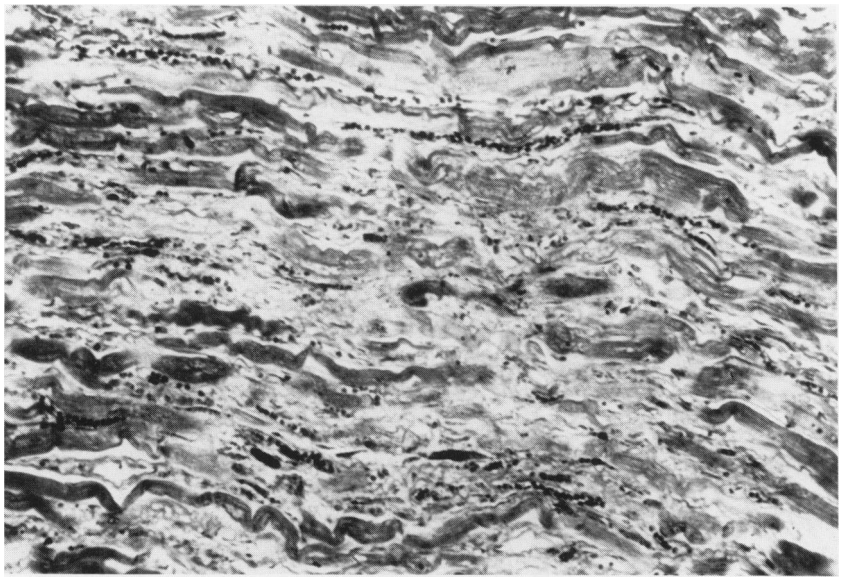

FIG. 2. Microscopic examination showed widespread deposition of iron, the darkly staining material, in myofibers in various stages of cell death. Interstitial fibrosis was marked.

During this time, the basic hematologic abnormality in this heritable disorder was characterized. In 1925 Dr. Thomas Cooley had first described the hereditary refractory anemia characterized by ineffective erythropoiesis and by hemolysis (5). It was recognized that some individuals had the trait, while others had a mild form of the disease that rarely required transfusion, but those of whom we speak had the severe form, thalassemia major. They not only acquire iron from transfusion therapy but also by excessive absorption through the gastrointestinal tract. The interval between transfusions gradually decreases as hypersplenism develops (6).

By 1980 the genetics of this heritable hemoglobinopathy came to be understood. Parents of an affected child are usually asymptomatic carriers. The hemoglobinopathy results from deficient globin-chain synthesis (7, 8). In alpha thalassemia deletions of one or more alpha chains occur. In beta thalassemia, abnormally low or absent synthesis of β-globin exists due to mutation within or next to the β-globin gene. Homozygous β-thalassemia results in the condition with the serious cardiac consequences we are concerned with. The heterozygote has thalassemia minor or minima with few if any symptoms.

MANAGEMENT

Chronic transfusion therapy with packed red blood cells was instituted on an ambulatory basis in the transfusion clinic in the 1940's by the late Dr. Carl Smith. Transfusions were given when the hemoglobin level dropped to 7.5 or 8 gm/100 ml. Patients received transfusions every two or three weeks. When transfusion interval decreased and signs of hypersplenism were evident, splenectomy was carried out (6). When the risk of sudden, overwhelming, often rapidly lethal infection post-splenectomy was recognized, chronic antibiotic prophylaxis was instituted together with prompt hospitalization and evaluation with treatment for sepsis (9). Beginning in 1976 a regimen of more frequent transfusions was instituted so that the hemoglobin level did not drop below 10.5 gm/100 ml. This resulted in a lessening of the cardiovascular adaptations to the anemia per se and to a feeling of well-being and less fatigability. However, this "hypertransfusion" regimen increased the transfusional iron load. It was hoped that this would be somewhat offset by reduced gastrointestinal absorption of iron.

From a cardiac standpoint, more sophisticated methods to detect arrhythmia on ambulatory monitoring and new antiarrhythmic agents and more potent diuretics came into use. But the outcome remained the same. The average age at death in heart failure in 1964 was 17 years and in 1976, 18 years (10, 11).

PREVENTION

The first hope for prevention came with the use of an iron-chelating agent, desferrioxamine (DFO) (12). It is administered overnight subcutaneously by a pump. Young children approached iron balance, and those in the second decade achieved iron balance when they complied with this regimen.

In 1978 we began a prospective study of this drug to answer the question whether it could prevent or retard the cardiac complications of the disease. Although 62 patients were enrolled in the study, and their cardiac profiles established in the year before chelation therapy (10, 11), only 43 complied sufficiently during the five years of chelation therapy to permit an analysis of the effects of this agent on clinical course and cardiac disease.

The 20 male and 23 female thalassemic individuals were five to 26 years old at the outset of chelation therapy. Splenectomy had been performed in 22 before the study and in 14 more during the study. They were divided according to age into four groups.

TABLE 1
Desferrioxamine Study Population

Group	Age (years)	Number
A	5–8	11
B	9–12	9
C	13–20	16
D	21–26	7

TABLE 2
Arrhythmias Prior to and on DFO

Group	No. Pts.	Prior	After 5 Yrs.
A	11	0	2
B	9	5	2
C	16	8	9
D	7	4	7

The ages of those who began as groups A and B were comparable after five years to those in groups C and D at outset.

Noninvasive cardiac studies included annual plus clinically indicated 12-lead electrocardiogram (ECG), 24-hour continuous ECG, and M-mode echocardiogram. Twenty-six patients had radionuclide cineangiography (RNCA) at rest and on symptom-limited exercise; 17 had serial RNCA studies.

Pericarditis. Before chelation 10 patients had experienced 14 episodes of pericarditis at ages 10–21 years. Two of these episodes occurred in the 12 months before chelation. On chelation, one or two episodes per year for a total of five continued to occur in patients aged 17–15 years.

Arrhythmias. The incidence and severity of arrhythmia tended to lessen in the younger subjects, A and B, as the five years on desferrioxamine continued.

Of 11 who died during the five years, 10 required therapy for high-grade ventricular ectopy. Nine developed supraventricular paroxysmal tachycardia or flutter or both.

Conduction Delay. Prolonged PR at onset of chelation was present in five patients. After five years on therapy, first degree heart block was evident in 14 patients. Of 11 patients who died during the five years, nine had developed first degree heart block, and one of them, second degree block. The youngest age group, A, did not yet show such a conduction delay.

Cardiac Function measured by M-mode echocardiography was preserved until the onset of cardiac failure. Although left atrial and left

ventricular dimensions exceeded the 95th percentile and increased during the five years of the study (from 2% to 21% of patients for left atrial and from 21% to 37% of the patients for left ventricular dimensions), left ventricular wall thickness greater than the 95th percentile decreased from 53% of the patients pre-chelation to 42% of them after five years. Mean values for ejection fraction and shortening fraction were in the normal range in all subjects before DFO but mean values were decreased at the end of five years or at death. This decrease in mean value was due to the marked reduction that occurred in the older subjects in groups C and D when cardiac failure appeared.

Radionuclide cineangiography (RNCA) at rest and on symptom-limited bicycling exercise was a more sensitive indicator of declining cardiac function than was M-mode echocardiography. Fifty studies were carried out in 30 patients. Ejection fraction was less than the lower limit of this laboratory's normal of 45% in 23 studies on 19 patients and was lower than the normal limit of 55% on exercise in 32 studies on 26 patients. When the M-mode echocardiographic measurements were abnormal, the RNCA was as well. However, of 30 in which M-mode values were normal, the RNCA detected abnormality in 19 before the M-mode did and before cardiac decompensation developed. When treated for cardiac failure, two patients on repeat study showed some improvement in ejection fraction.

Cardiac Failure and Death. Although no patient developed this complication in the first two years of the study, 14 patients went into cardiac failure in the next three years and death occurred within one to 13 months (average four months) of onset in nine of them. Four individuals survived the fifth year but then died subsequently, 17 months to 47 months after onset of failure. Their greater longevity brought the average age at death up to 23 years, in comparison to 17 or 18 years in earlier times. One patient died at age 17 years while free of arrhythmia and heart failure but while being monitored for an episode of acute chest pain and hypotension.

Thus, more intensive medical management and chelation therapy may have retarded the manifestations of cardiac hemachromatosis in these subjects with homozygous β-thalassemia begun on, and compliant with chelation therapy with desferrioxamine. However, chelation therapy in this manner when begun after the age of five years did not prevent the complications.

THE FUTURE

Is there hope for prevention? It may lie in early onset of chelation therapy when transfusions are begun. If so, perhaps a more effective chelating agent and a less cumbersome and uncomfortable means of

delivery can be devised for those subjects born with this hematological disorder.

For those yet unborn, genetic counseling with identification of couples at risk and recognition of the affected fetus may reduce the incidence of the condition (13–15). Couples at risk have usually been recognized only after birth of an affected child. However, the carrier state can be suspected by careful family history and by the smaller than normal mean corpuscular volume of red blood cells in the absence of iron-deficiency anemia and by a higher than normal level of minor adult hemoglobin (Hb A2).

Since 1975 it has been possible to diagnose hemoglobinopathies prenatally by fetoscopy or placental aspiration. Yet another new technique involves chorionic biopsy, which permits detection of the affected fetus earlier in pregnancy than with the other methods mentioned (16). Direct gene analysis of chorionic villi is made on the trophoblast biopsy.

Affected fetuses have markedly decreased ratios of Beta-1 globin synthesis and so can be distinguished from unaffected heterozygotes and from normal fetuses with a misdiagnosis rate of about 1%. In addition to fetal blood analysis, it is now also possible to perform fetal DNA analysis for direct detection of mutations. In β-thalassemia there are 24 known mutations within or flanking the β-globin gene. Twenty-two of these are produced by a single nucleotide substitution or by deletions/insertions. Restriction endonuclease mapping is done. Absence of a restriction site at the locus of a polymorphism produces a larger DNA fragment than when the restriction site is present. Boehm in 1983 reported on the results of this analysis in amniocyte DNA in 32 pregnancies with fetal risk for thalassemia and with correct prenatal diagnosis in each (15). Orkin in 1984 reported another method which involves DNA analysis by the indirect approach of linkage analysis of sequence polymorphisms in regions of DNA surrounding the mutant gene (17). These rapid developments and the early success lead to optimism for prenatal detection of fetuses at risk for thalassemia.

A select few thalassemics may also be cured of the defective β-globin mutation by receiving a bone marrow transplantation from an identical HLA-matched sibling donor. The donor may be normal or a heterozygote with HLA-D identity confirmed by mutual nonresponsiveness in mixed lymphocyte culture (MLC). Medical centers in the United States and Italy are currently investigating the preparative regimen which will effectively damage the defective stem cell population and achieve sufficient immunosuppression to allow successful allogeneic engraftment. A marrow transplant of normal histocompatible marrow if successfully engrafted should replace the host thalassemia erythroid cells and produce normal hemoglobin. Early trials to identify the optimal preparative

regimens and the ideal low-risk patients are currently being performed (18, 19). The full potential of transplantation to correct thalassemia has not yet been evaluated, but it offers another possible means of help.

CONCLUSIONS

Transfusion therapy for the chronic refractory anemia of thalassemia saves the lives of young children but leads to iron overload that damages tissues and causes the heart disease which is fatal in adolescence or early adulthood despite intensive medical management. Chelation therapy, if begun before five years of age, may retard the cardiac consequences. If a more effective and less cumbersome agent becomes available, it may even prevent them. Bone marrow transplantation from an identical unaffected HLA-matched sibling may correct the defective β-globin synthesis. Prenatal recognition of the fetus at risk for β thalassemia offers the possibility of prevention of thalassemia and its accompanying heart disease.

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DISCUSSION

Wheby (Charlottesville): Dr. Engle, that was a nice updating. I'm sorry the study turned out the way it did. Have you done any myocardial biopsies? In idiopathic hemochromatosis, we know that phlebotomy, which is much more efficient than chelation in removing iron, can remove iron from the myocardium. There have been serial biopsies done during phlebotomy therapy to show this. I don't know whether chelation can remove the excess myocardial iron. Would you comment?

Engle: I appreciate your question and I can tell you that we have not done the biopsies that you talk about. I think perhaps idiopathic hemachromatosis is a bit different from this kind of acquired hemachromatosis but I do not know the answer to your very good question about the kind of iron and the biopsies. I can assure you that from the biopsies of spleen and liver that we have done, that iron is there, that the cell damage is there, that the fibrosis is there. We've done those annually in these patients from age five on up. If that's a reflection of what's happening in the heart, the hemasiderosis and hemachromatosis are ongoing.

Schreiner (Washington): Some years ago, Dr. Engle, we described in *Lancet* an iron proximal myopathy in dialysis patients. And although a very significant percentage of chronic dialysis patients have an increased iron burden in tissues (i.e., increased ferritin), the number who actually get clinical myopathy is relatively modest. In exploring these people we found a disproportionate number of HLA antigens similar to those in families with familial hemachromotosis. So, my first question relates to the distinction between iron burden and cardiomyopathy—is there any difference between the people who actually get *myocardial* iron deposition and/or cardiomyopathy in terms of their genetic background or HLA antigens? My second comment is that we had the same feeling, that if we didn't get at them early, then the damage was already done. Of course we can't use your methods of diuretics because our patients just don't have any kidneys. So we have to remove the chelate and the iron by other methods, such as dialysis or hemoperfusion of the iron-chelate complex. It occurred to me as I was listening to you, I didn't know that your patients got in trouble so quickly after their first symptomology and I have never been asked to treat a patient with Thalassemia. I just wondered whether the people who treat this disease such as yourself have entertained the notion of trying for a very rapid massive removal of iron by giving chelate and removing it by extra-corporeal methods. And that might be a way to test the hypothesis of whether you are really too late or whether the cardiac condition is reversible if removal of iron is massive and rapid enough.

Engle; Thank you for your question. I think perhaps the difference in your patients on dialysis may be purely the load of iron. It is so great in our children who have to be transfused all the time. It is very hard to get ahead of it. It's been known that these individuals absorb excessive amounts of gastrointestinal iron. So, even if they were not

transfused, they would be getting it just from the GI tract. It was one of the ideas about hypertransfusion therapy that giving more iron by transfusion might minimize the gastrointestinal excessive absorption. But I think our heavily iron-overloaded patients don't have very much chance. Insofar as exchange transfusion and a large amount of withdrawal, I really cannot answer that question; I have had no experience with it nor do I know of any others who have.

Wallerstein (San Francisco): There is some feeling that splenectomy in Thalassemia Major aggravates the iron loading in other tissues. Have some of your patients not been splenectomized and if so have they done equally badly as the ones that have?

Engle: I think the answer is that splenectomy has not had very much effect on whether this happened to the myocardium or not. In the first groups of patients that we saw, the timing of splenectomy had not yet been worked out. Some people were saying that if you did it very early, then maybe you would help the children. And then finally the concept came to be that the spleen is better left in place until hypersplenism occurs and the interval between transfusions gets shorter and shorter, and that for the last 15 years has been the indication for splenectomy. In this group of patients, of the 43, 14 had been splenectomized prior to the prospective study and 12 more were splenectomized during that time and I really could not tell the difference in cardiac outcome, with or without spleen.

Langford (Jackson): Is Desferrioxamine reasonably precise as an iron chelator? I am thinking especially of the possibility of producing zinc and copper deficiencies.

Engle: Your question concerns the efficacy of desferrioxamine for removing iron. This was introduced by English researchers and was and I think still is the best iron chelating agent and it does primarily remove iron. In iron-balance studies which my hematologic associates in this study have carried out, the older ones do achieve or approach iron balance and the older ones do eliminate more iron while on the chelator than they get as transfused iron. So it does remove iron, but what effect it may have on magnesium and so on, I cannot tell you.

Owens (Baltimore): I rise just to point out another possibility in managing these individuals. It has to do with the use of bone marrow transplantation. The clinical techniques for accomplishing transplantation are improving all the time. There is a small but growing experience with bone marrow transplantation in Italy where the outcome is encouraging. Since there is a very good way of detecting the disease very early in life, transplantation could be performed prior to the onset of major disability. George Santos is strangely silent; I don't know whether he might have a comment to add or not.

Engle: I can tell you that I did not list that as an option for the 80's but probably I just neglected to do it because its application would be limited to HLA-compatible donors, and it is premature to report results. We have had one child who has had irradiation and bone marrow replacement. It is generating but the outcome is too soon to tell; it's just been done this last year. So this is another possible hope for those born with this condition.