COOLEY'S ANEMIA
SEVENTH SYMPOSIUM
Cover Art: Expression of globin genes. The flow of genetic information from the DNA sequence to the final protein product involves several discrete steps. First, the coding strand is copied into RNA by a process called transcription. Processing of the RNA species includes modifications of the 5' end, referred to as capping, addition of adenosines on the 3' end, and splicing to remove intron sequences. The final mRNA species is transported to the cytoplasm where it is translated into protein. The α- and β-like chains assemble spontaneously to form hemoglobin molecules. Mutations that cause thalassemia may interfere with any one of these major processes, namely transcription, processing, transport, or translation. (From National Heart, Lung, and Blood Institute/NIH report, Cooley’s Anemia: Progress in Biology and Medicine - 1995) Spacecraft photograph Most of Africa and portions of Europe and Asia can be seen in this spectacular photograph taken from the Apollo II spacecraft during its translunar coast toward the moon. Apollo II, with Astronauts Neil A. Armstrong, Michael Collins, and Edwin E. Aldrin, Jr. aboard, was already 98,000 nautical miles from Earth when this picture was taken (courtesy of NASA).

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Survival and Disease Complications in Thalassemia Major

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ABSTRACT: We studied survival and disease complications in 1,146 patients with thalassemia major, born from January 1, 1960 to December 31, 1987. At last follow-up, in March 1997, probability of survival to age 20 years was 89% and to age 25 years was 82% for patients born in the years 1970–1974. Patients who died had a serum ferritin level, measured the year before death, significantly higher than those who survived. Diabetes was present in 5.4% of the patients; heart failure in 6.4%; arrhythmias in 5.0%, thrombosis in 1.1%, hypothyroidism in 11.6%, HIV infection in 1.8%. Hypogonadism was diagnosed in 55% of 578 patients who had reached pubertal age: 83.5% of hypogonadic females and 78.6% of males were receiving substitutive hormonal therapy. In conclusion, the survival of patients with thalassemia major is good and improving, but the prevalence of severe complications is still high.

Organ damage and early death used to be inevitable consequences of thalassemia major. The prognosis of the disease, however, has been improved by regular transfusions and iron chelation.

In the last 14 years, as a part of a cooperative study, we followed a large number of patients with thalassemia major treated at seven Italian hospitals, and we confirmed that the survival of transfusion-dependent patients has been steadily and significantly increasing. Unfortunately, the prevalence of complications due to iron overload is still high.

Address for correspondence: C. Borgna-Pignatti, Department of Clinical and Experimental Medicine, Pediatrics, University of Ferrara, Via Savonarola 9, 44100 Ferrara, Italy. Fax: 39-532-202 103; E-mail: bre@dns.unife.it
PATIENTS AND METHODS

Seven Italian teaching hospitals contributed their patients with thalassemia major to this study. Inclusion criteria required that the patients be born after January 1, 1960 and be alive at the time since when, at each center, clinical records were complete and reliable. The first data collection took place in 1983. Latest follow-up was March 1997.

The patients notified by the participating centers were 1,146 (614 males and 532 females). The distribution by calendar period of birth is shown in Figure 1.

The Kaplan-Meier method and log-rank test were used to estimate and compare survival and appearance of complications. Since, for older patients, no information could be drawn on mortality in the first decade of life, overall survival was evaluated only for patients born in or after 1970, while survival after the first decade of life was evaluated for all patients. In addition we collected, by means of specially prepared forms, data on complications potentially affecting the quality of life of the patients. Complications considered were: insulin-dependent diabetes, hypothyroidism requiring substitutive therapy, thrombosis, heart failure or arrhythmias requiring therapy, absence of signs of puberty at age 15 years for females and at age 17 for males, and HIV positivity. Mean yearly serum ferritin was available for the years 1991–1996. Since it was not normally distributed, a preliminary logarithmic transformation was required for subsequent analysis. Comparison of ferritin levels between groups was performed by Student’s t test.

RESULTS

At last follow-up, 769 patients of 1,146 were alive with thalassemia, 26 had been lost to observation, and 248 had died. One hundred and three had undergone bone marrow transplantation; 13 of them had died as a consequence of the procedure. Crude death rates ranged from 67% for patients born before 1965 to 2.5% for those born after 1979.

FIGURE 1. Distribution by cohort of birth of patients with thalassemia major who entered the study.

The serum ferritin level of the year before death was, for patients who died between 1991 and 1996, significantly higher than for patients who survived (3,314 ± 2,468 versus 2,002 ± 1,455, \( p < 0.001 \)).

When data for males and females were analyzed separately, we found that females have a significantly better survival than males, both for the whole group born between 1960–1974 \( (p = 0.0242) \) and for the older patients (1960–1969) alone \( (p = 0.039) \).

Heart disease was the most frequent cause of death, being directly responsible for the death of 71% of the patients. Infection directly caused the death of 12% of the patients. Liver disease represented the third most frequent cause of death being directly responsible for the death of 6% of them. Other causes of death are reported in TABLE 2.

The risk of developing complications was evaluated only for patients born after 1970 (718). The prevalence of heart failure at age 15 was found to have decreased from 5% in patients from the cohort 1970–1974 to 2% in patients born in 1980–1984. Corresponding values for diabetes are 2.6% and zero. On the contrary, hypothyroidism is apparently becoming more frequent, being present, at age 15 years, in 4.8% of the patients born between 1970 and 1974, but in 8% of those born between 1980 and 1984. Overall, diabetes was present in 5.4%, heart failure 6.4%, arrhythmias 5.0%, thrombosis 1.1%, hypothyroidism 11.6%, and HIV infection 1.8%. Hypogonadism was diagnosed in 55% of 578 patients who had reached pubertal age: 83.5% of hypogonadic females and 78.6% of males were receiving substitutive hormonal therapy.

DISCUSSION

In the last three decades, the treatment of thalassemia major has changed in many ways. Administration of deferoxamine by the intramuscular route became available to the majority of Italian patients in 1975, while regular subcutaneous infusion was started between 1979 and 1981. In the same years the transfusion regimen evolved from correction of symptomatic anemia to the so-called hypertransfusion or supertransfusion regimens, aimed at maintaining a minimum hemoglobin level from 9–10 g/dl to above 12 g/dl. The impression that the supertransfusion regimen had increased the iron overload and its consequences has recently induced most centers to return to hypertransfusion. In addition, the early detection of complications has been actively pursued and their aggressive treatment has become the rule. A major pivotal point in the history of thalassemia treatment has been the introduction in 1981 of bone marrow transplantation from an HLA-identical sibling.4 This progress has made information about survival and complications with conventional therapy particularly important.

Not many data have been reported so far on survival of transfusion-dependent patients with thalassemia. Economidou reported in 19825 that at age 28 only 24% of Greek patients with thalassemia major and intermedia were alive. In 1982, Modell and coworkers6 found that the probability of reaching age 25 years was 25%. There is convincing evidence from several reports that iron chelation improves organ function,7–9 and that it is capable of preventing the development of cardiac disease.10 More recently, Brittenham and coworkers observed that the risk of dying and of developing diabetes and cardiac disease were decreased by the early use of deferoxamine.11 Data from Olivieri and coworkers, who studied 97 patients born before 1976, demonstrate that after 15 years of chelation therapy, the probability of being free from cardiac disease is 91%, provided that less than one third of serum ferritin values exceeded 2,500 ng/ml.12 In our study we found that serum ferritin, and therefore, presumably, the iron burden, was higher in patients who died than in patients who survive.

### TABLE 1. Survival by Birth Cohort at Different Ages of Patients with Transfusion-Dependent Thalassemia

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>98% (96–99)</td>
<td>98% (96–99)</td>
<td>99% (95–100)</td>
</tr>
<tr>
<td>15</td>
<td>95% (92–97)</td>
<td>97% (94–98)</td>
<td>98% (93–100)</td>
</tr>
<tr>
<td>20</td>
<td>89% (85–92)</td>
<td>96% (93–98)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>82% (77–86)</td>
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</tr>
</tbody>
</table>

### TABLE 2. Causes of Death Reported in Patients with Thalassemia, Born between 1960 and 1984

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac causes</td>
<td>171</td>
<td>71%</td>
</tr>
<tr>
<td>Liver</td>
<td>15</td>
<td>6%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>6</td>
<td>3%</td>
</tr>
<tr>
<td>Infections</td>
<td>28</td>
<td>12%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>Tumors</td>
<td>7</td>
<td>3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>2%</td>
</tr>
</tbody>
</table>
We reported in 1989 the fatality rate and the causes of death in a group of patients with thalassemia major born since 1960. A remarkable improvement in life expectancy was observed when different birth cohorts were compared. This improvement was mainly due to the decrease in mortality for cardiac causes. Conversely, mortality due to causes other than heart disease had not decreased. The results have not changed at subsequent follow-ups. At the latest data collection the difference in survival between cohorts is still striking (Table 1). Moreover, the study of complications has confirmed that patients born in more recent years have a lower risk of developing heart disease, diabetes and hypogonadism, than patients born earlier. The trend is not so clear for hypothyroidism, which, in the past, was probably underdiagnosed.

With modern therapy, complications and death should be unusual in the first ten years of life. This expectation is confirmed by our data. Only four patients out of 283 from the cohort 1970–1974, and none from the subsequent cohorts, have developed heart failure in the first decade of life. However, diabetes developed in the first decade of life in two children from the cohort 1975–1979.

In conclusion, the favorable trend that we observed in the past seems to continue for patients who had the advantage of early chelation therapy. Despite the fact, however, that thalassemia is no longer a rapidly fatal disease and that the majority of the patients will reach the age of employment and of marriage, the prevalence of complications is still high. Research should therefore be aimed at containing as much as possible the complications of the disease that could make the life of these patients unsatisfactory and not productive. Less invasive methods of chelation, such as oral or intermittent chelation could also contribute to making the life of these patients easier.

REFERENCES