Brief Report

The Di Guglielmo Syndrome: Studies in Hemoglobin Synthesis

By THOMAS F. NECHELES AND WILLIAM DAMESHEK

THE DI GUGLIELMO SYNDROME is characterized, among other features, by generalized hyperplasia of the bone marrow, often associated with bizarre proliferation of the erythroblastic elements. The morphology of the marrow may range from an almost pure red cell proliferation (“erythremic myelosis”) to an almost completely leukemic state in the terminal phases of the disease. The persistent refractory anemia, which is in marked contrast to the erythroblastic cellularity of the marrow, is probably due to ineffective erythropoiesis. An increase in red cell and tissue iron (iron loading) and, occasionally, an unstable hemoglobin have been found. Previous studies by Steiner et al. demonstrated abnormalities in some of the enzymes important in the biosynthesis of heme. Investigations into the synthesis of globin and its correlation with the clinical course have not, however, been previously reported. These are the subject of the present report.

MATERIALS AND METHODS

Routine hematologic and ferrokinetic studies were performed using standard technics. The morphology of the bone marrow fulfilled the criteria for the Di Guglielmo syndrome as described by Di Guglielmo and extended by Dameshek et al. Of the five cases studied, Cases 1 and 2 were acute (i.e., survived for less than 6 months after initial diagnosis), whereas the other three (Cases 3-5) exhibited a more chronic course (from 1 to over 6 years survival). All patients showed evidence of ineffective erythropoiesis. Cases 2 and 4 showed intraerythrocytic hemoglobin precipitates (“Hb H” bodies) such as previously described by Beaven et al.

In vitro studies of globin synthesis were carried out on bone marrow cell suspensions as previously described for thalassemia. The synthesis of heme was followed by measuring the incorporation of glycine-2-C

From the Blood Research Laboratory, New England Medical Center Hospitals, and the Department of Medicine, Tufts University School of Medicine, Boston, Mass. These studies were aided with funds from the U.S. Public Health Service (Grant No. CA 04168-07 from the National Cancer Institute) and carried out while the senior author served as a U.S. Public Health Service Trainee under Graduate Training Grant No. T1 5210-05.

First submitted May 18, 1966; accepted for publication Nov. 8, 1966.

THOMAS F. NECHELES, M.D., PH.D.: Established Investigator, American Heart Association; Assistant Hematologist, Boston Floating Hospital, New England Medical Center Hospitals; Instructor in Medicine, Tufts University School of Medicine, Boston, Mass.

WILLIAM DAMESHEK, M.D.: Formerly Consultant in Hematology, New England Medical Center Hospitals, and Professor of Medicine, Tufts University School of Medicine, Boston, Mass., presently, Attending Hematologist, The Mt. Sinai Hospital, and Professor of Medicine, The Mt. Sinai School of Medicine, New York, N. Y.

BLOOD, Vol. 29, No. 4, Part I (April), 1967
in Table 1 on the distribution of nucleated red cells in the incubation suspensions as well as on the rate of glycine-2-C\textsuperscript{14} incorporation into heme and globin. Heme synthesis was significantly depressed ($p < 0.01$) in the four patients in which it was measured. Globin synthesis, in contrast, was significantly reduced in only those two patients (Cases 1 and 2) who survived for less than 6 months. No consistent abnormalities were noted in chromosomal karyotypes performed by technics previously reported from this laboratory.\textsuperscript{8}

**Discussion**

The frequent presence of abnormalities in iron metabolism as well as the occasional finding of Hb H-like precipitates in the erythrocytes\textsuperscript{4} and the presence of increased quantities of fetal hemoglobin\textsuperscript{5} suggest that hemoglobin synthesis may be defective in the Di Guglielmo syndrome. Steiner et al.\textsuperscript{1} demonstrated defects in the activities of some of the enzymes of the heme biosynthesis pathway. The present studies confirm the presence of defects in heme synthesis and, in addition, demonstrate the presence of a defect in globin synthesis in some, but not all, patients. Interestingly enough, those patients showing a defect in globin synthesis exhibited an acute clinical course. The variability in the rate of globin synthesis in the Di Guglielmo syndrome is in marked contrast with the uniform inhibition of globin synthesis found under similar conditions in thalassemia.\textsuperscript{6}

It is probable that neither the changes in hemoglobin synthesis nor the chromosomal abnormalities previously reported\textsuperscript{8-10} represent the primary defect in this syndrome; both could conceivably be reflections of a more basic underlying disturbance in proliferation and maturation. The variability of the biochemical, cytochemical and clinical manifestations of this syndrome all suggest that it may consist of a group of related diseases all secondary to various acquired and probably neoplastic disturbances in proliferation and differentiation within the erythroid series.

**Summary**

The in vitro synthesis of heme and globin has been studied in bone marrow cell suspensions obtained from five patients with Di Guglielmo syndrome. In all, a defect of heme synthesis was demonstrated, but globin synthesis was greatly reduced in only two of the five; in these two, the clinical course was a rapid one.

**Summario in Interlingua**

Le synthese in vitro de heme e de globina esseva studiate in suspensiones de cellulas de medulla ossee obtenite ab 5 patientes con syndrome de Di Guglielmo. In omnes, un defecto del synthese de heme esseva demonstrate, sed le synthese de globina esseva reducite marcatemente in solo 2 del 5 casos. In iste 2, le curso clinic esseva rapide.

**Acknowledgments**

The authors wish to thank Dr. W. J. Mitus for his constructive criticism and to acknowledge the skilled assistance of Heidi J. Meyer.
Table 1.—Hemoglobin Synthesis in Bone Marrow Cell Suspensions

<table>
<thead>
<tr>
<th>Patient</th>
<th>Reticulocytes × 10⁶</th>
<th>Total Normoblasts × 10⁶</th>
<th>Per Cent Total Normoblasts</th>
<th>mM Glycine-C¹⁴ Incorporated /Normoblast ×10⁻¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Basophilic</td>
<td>Heme</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Polychromatophilic</td>
<td>Globin</td>
</tr>
<tr>
<td>Normals (5)</td>
<td>0.21</td>
<td>17.0</td>
<td>9.3</td>
<td>5.29 ± 0.71</td>
</tr>
<tr>
<td>AIHA* (1)</td>
<td>1.20</td>
<td>137.0</td>
<td>31.2</td>
<td>5.91</td>
</tr>
<tr>
<td>Patient 1</td>
<td>0.17</td>
<td>23.3</td>
<td>28.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Patient 2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.01</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.19</td>
<td>25.2</td>
<td>9.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.11</td>
<td>16.9</td>
<td>23.7</td>
<td>0.87</td>
</tr>
<tr>
<td>Patient 5</td>
<td>0.18</td>
<td>73.7</td>
<td>6.3</td>
<td>—</td>
</tr>
</tbody>
</table>

*Autoimmune hemolytic anemia.
REFERENCES


THOMAS F. NECHELES and WILLIAM DAMESHEK