Artificially Induced Thyroid Suppression in Sickle Cell Disease

By Charles W. Seward, John W. Eaton, and Hugh Chaplin, Jr.

Depression of thyroid function in patients with hemoglobin SS disease might be expected to: (1) reduce tissue oxygen consumption, (2) decrease erythrocyte 2,3-diphosphoglycerate, (3) decrease p50, (4) increase the average level of erythrocyte oxygenation, and (5) increase in vivo red cell survival with associated improvement in anemia and possibly in musculoskeletal symptoms. Accordingly, 150-200 mg of 6-n-propylthiouracil were administered three times a day for 143 days to a 21-yr-old male with hemoglobin SS disease. Thyrosuppression was indicated by typical symptoms and appropriate changes in physical and biochemical parameters. Detailed hematologic follow-up, including multiple measurements of red cell mass, 51Cr erythrocyte survival, red cell 2,3-diphosphoglycerate, and p50, showed no change. Furthermore, musculoskeletal symptoms continued in the pattern characteristic of the euthyroid state. A possible explanation for the lack of any change in clinical status may be that decreased cardiac output, with attendant prolonged circulation time and increased tissue oxygen demand per red cell per unit time, offset the absolute decrease in tissue oxygen consumption. The study provided an opportunity to make detailed clinical observations of sickle cell disease in association with thyroid suppression. The results suggest that thyrosuppression within the limits of symptomatic and physiologic tolerance has no therapeutic application in the clinical management of hemoglobin SS disease.

HOMOZYGOUS HEMOGLOBIN S DISEASE is a hematologic disorder characterized by distortion of erythrocyte shape and reduced red cell elasticity due to intracellular tactoid formation by deoxygenated hemoglobin S. These modifications of the red cell lead to hemolytic anemia, multifocal vascular occlusions, and associated inflammation and pain. One of the generally salutory physiologic adaptations to anemia is an elevation of intracellular 2,3-diphosphoglycerate (DPG) concentration, which enhances hemoglobin-oxygen dissociation. It is ironic that, in sickle cell disease, this adaptive change probably exacerbates the intravascular sickling by promoting hemoglobin deoxygenation. Measures designed to provide a controlled reduction of hemoglobin-oxygen dissociation may offer a rational therapeutic approach to hemoglobin SS disease.
Since thyroid hormone has been shown to elevate erythrocyte DPG and to increase tissue oxygen demand, we considered that suppression of thyroid hormone production could be accompanied by reduced erythrocyte DPG levels, decreased hemoglobin deoxygenation, and amelioration of the symptoms and hematologic abnormalities of sickle cell disease. We are unaware of any detailed accounts of the clinical or chemical effects of hypothyroidism in patients with hemoglobin SS disease. Accordingly, the present investigation was undertaken to document the physiologic and hematologic effects of artificially induced thyroid suppression in such a patient.

**CASE REPORT**

**Clinical Summary**

The patient was a 21-yr-old black male in whom sickle cell disease had first been diagnosed at age 22 mo. Hemoglobin electrophoresis revealed 96% S + A2 hemoglobin and 4% F hemoglobin. The patient had been followed at the St. Louis Children’s Hospital and in the Washington University Clinics throughout his life, chiefly for painful musculo-skeletal crises three to four times yearly but rarely requiring hospitalization.

Over the preceding several years, typical ulcerations had recurred over both medial malleoli, always responding to conservative local management. In 1969, he developed symptoms and findings of a right-sided cerebrovascular thrombosis that left him with mild dysarthria, general mental slowness, and minimal left-sided weakness. He had been in his usual state of health during the 6 mo prior to admission. The purpose and plan of the study were discussed in detail with the patient and his mother, and their informed written consent was obtained prior to his admission to the clinical research ward.

Physical examination revealed mental slowness, lisping speech, and mild frontal bossing. The skin was of normal texture and intact over both medial malleoli. The thyroid gland was barely palpable and of normal consistency. The pulse was 68 and regular. Cardiac examination revealed a rolling precordial lift and a grade II/VI systolic murmur in the fourth, left intercostal space. The lungs were clear. The liver and spleen were not palpable. The deep tendon reflexes were normal.

**The Investigative Plan**

Throughout the 20 wk of hospitalization the patient was allowed full ambulatory privileges and diet ad lib. Multiple baseline observations were obtained during the first 17 days of hospitalization, prior to institution of thyrosuppressive medication. Red cell mass was measured on day 2 of hospitalization, and the initial autoerythrocyte survival study was begun on that date. Complete blood counts were obtained at least twice weekly. Protein bound iodine (PBI), bilirubin, cholesterol, red cell DPG concentrations, and p50 (the partial pressure of oxygen at which 50% of the hemoglobin is oxygenated) were obtained every 1–2 wk. Serum thyroid-stimulating hormone (TSH) and tetraiodothyronine (T4) were measured at 3–4 wk intervals. Red cell mass and autoerythrocyte survival were remeasured after 6 and 12 wk of thyrosuppressive medication. The patient’s clinical status was carefully reevaluated at least weekly throughout his hospitalization.

6-n-Propylthiouracil, 150 mg three times a day orally, was begun on the 17th day of hospitalization and continued at that dosage for 74 days. Thereafter, the dose was increased to 200 mg three times a day for an additional 69 days.

**Laboratory Methods**

Complete blood counts, serum bilirubin, cholesterol, and PBI concentrations were determined by routine methods. Serum TSH levels were measured as described by Odell et al. T4 was measured according to Murphy and Jachan. Erythrocyte 2,3-DPG was determined as described by Keitt, and p50 was measured by the method of Lenfant et al.
Red cell mass and red cell survival were measured employing the patient's red cells labeled with $^{51}$Cr. Whole blood volume was calculated employing the average radioactivity in three initial samples (drawn 20, 40, and 60 min after injection of the $^{51}$Cr-labeled red cells) and the total radioactivity injected. Red cell mass and plasma volume were calculated from whole blood volume employing the average of duplicate well-oxygenated hematocrits of the three samples, suitably corrected for trapped plasma and for the body/venous hematocrit ratio.

**RESULTS**

**Clinical Status**

During the second week of the control period, a vascular ulcer developed over the left medial malleolus, enlarging by the fifth week to a maximum area of $3 \times 4$ cm. The ulcer subsequently healed, despite thyrosuppressive medication, with complete epithelialization by the 20th week of study. Throughout the entire period of thiouracil administration, the patient had transient (3-5 days) episodes of long bone pain and arthralgias, chiefly of the elbows and wrists, typical of his previous musculoskeletal symptoms and adequately relieved by average doses of propoxyphene hydrochloride.

By the eighth week of thiouracil administration (450 mg daily), mean PBI and TSH values were consistent with early thyrosuppression (Table 1). The thyroid gland was more easily palpable but not clearly enlarged, deep tendon reflexes were normal, and the patient was symptomatically unchanged. By the 12th week, definite thyroid enlargement was demonstrable, but the patient was otherwise unchanged. The dose of thiouracil was increased to 600 mg daily, and 2 wk later the thyroid gland was estimated to be two times enlarged and firm, the Achilles reflexes were “hanging,” and the patient was somewhat lethargic. After 4 wk on the increased thiouracil dosage, the thyroid gland was two to three times enlarged, the Achilles reflexes showed marked delayed return, and the skin over the forearms and shins was dry and flaky. Although the pulse remained at 60–68 beats/min, there was a prolongation of the precordial lift and some increase in intensity of the systolic murmur. The patient’s weight had increased by 1.4 kg with no evidence of dependent edema.

The patient was discharged from the clinical research unit in the 20th week to continue thiouracil, 600 mg daily, and to be followed at 2-wk intervals as an outpatient, with the anticipation of a final measurement of red cell mass and autoerythrocyte survival 1 mo later. However, 3 wk after discharge he became increasingly lethargic and anorectic, he slept for prolonged periods, had two acute episodes of vomiting, and complained of increasing neck discomfort from the thyroid enlargement. When the patient was examined in his home, the thyroid gland was three times enlarged and firm. The skin was dry and flaky overall. Lethargy was striking. The pulse was 68 with occasional irregular beats, thought to be premature ventricular contractions. Although it was uncertain as to how much of the acute symptomatology was due to thyrosuppression, thiouracil was immediately discontinued, and whole, dessicated thyroid was instituted at 30 mg daily for 10 days and increased to 60 mg daily for an additional 14 days. The lethargy and nausea cleared within 1 wk; Achilles reflexes were essentially normal within 2 wk. The goiter regressed.
two times enlarged by 1 mo and was nearly normal size by 2 mo after cessation of thiouracil administration.

**Laboratory Results**

All the results are summarized in Table 1. Mean values, and ranges where appropriate, are grouped in four time periods, the first three coinciding with the intervals initiated by $^{81}$Cr survival studies and the fourth representing the final 2 mo of observation after discontinuance of thiouracil. Individual TSH and T4 values are illustrated in Fig. 1. Despite clinical and chemical evidence of thyroid suppression, there were no significant changes in any of the routine hematologic measurements, in red cell mass or in red cell survival. The survival data are shown in detail in Fig. 2 to emphasize their uniformity and to confirm that each represented a single exponential function throughout

<table>
<thead>
<tr>
<th>Test (Normal Range)</th>
<th>Period 1 (Days 1-56)</th>
<th>Period 2 (Days 57-106)</th>
<th>Period 3 (Days 107-162)</th>
<th>Period 4 (Days 163-222)</th>
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<tbody>
<tr>
<td>PBI μg/100 ml (4–8)</td>
<td>6.2 (4)†</td>
<td>4.3 (4)</td>
<td>2.7 (6)</td>
<td>5.5 (3)</td>
</tr>
<tr>
<td>T4 μg/100 ml (5–11)</td>
<td>7.8 (2)</td>
<td>4.4 (2)</td>
<td>&lt; 2.0 (3)</td>
<td>6.8 (1)</td>
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<tr>
<td>TSH μU/ml (2–8)</td>
<td>2.8 (2)</td>
<td>14.7 (2)</td>
<td>83 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Total blood volume ml</td>
<td>4250</td>
<td>4198</td>
<td>4400</td>
<td>—</td>
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<td>Red blood cell mass ml</td>
<td>1044</td>
<td>1073</td>
<td>1002</td>
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<tr>
<td>Plasma volume ml</td>
<td>3206</td>
<td>3125</td>
<td>3498</td>
<td>—</td>
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<td>ABC survival t'/2 days</td>
<td>8.20</td>
<td>7.40</td>
<td>7.25</td>
<td>—</td>
</tr>
<tr>
<td>DPG μm/g Hb (10–16)</td>
<td>19.04 (8)</td>
<td>19.18 (6)</td>
<td>19.08 (5)</td>
<td>20.10 (2)</td>
</tr>
<tr>
<td>p50 mm Hg (25–28.5)</td>
<td>35.88 (8)</td>
<td>36.70 (6)</td>
<td>36.45 (5)</td>
<td>35.70 (1)</td>
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<tr>
<td>Hemoglobin g/100 ml (14–18)</td>
<td>34.5–37.5</td>
<td>34.3–37.9</td>
<td>34.8–36.9</td>
<td>—</td>
</tr>
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<td>Red blood cells × 10⁶/cu mm (4.2–5.4)</td>
<td>3.31 (17)</td>
<td>3.12 (19)</td>
<td>3.12 (6)</td>
<td>3.23 (3)</td>
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<tr>
<td>Reticulocytes/100 RBC (&lt; 2.0)</td>
<td>2.98–3.69</td>
<td>2.86–3.49</td>
<td>3.01–3.48</td>
<td>2.95–3.50</td>
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<td>Hematocrit % (37–47)</td>
<td>11.1–22.0</td>
<td>10.3–25.7</td>
<td>11.0–27.2</td>
<td>14.6–26.0</td>
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<td>White blood cells × 10³/cu mm (5.0–10.0)</td>
<td>17.8 (17)</td>
<td>19.7 (19)</td>
<td>19.3 (6)</td>
<td>20.3 (3)</td>
</tr>
<tr>
<td>Platelets × 10⁶/cu mm (1.50–3.50)</td>
<td>29.2 (18)</td>
<td>28.7 (19)</td>
<td>27.0 (6)</td>
<td>29.1 (3)</td>
</tr>
<tr>
<td>Cholesterol mg/100 ml (150–300)</td>
<td>15.6 (17)</td>
<td>14.7 (19)</td>
<td>14.0 (8)</td>
<td>12.9 (3)</td>
</tr>
<tr>
<td>Bilirubin mg/100 ml (&lt; 1.5)</td>
<td>11.7–25.3</td>
<td>11.2–19.4</td>
<td>10.2–17.9</td>
<td>9.4–17.3</td>
</tr>
<tr>
<td>Platelets × 10⁶/cu mm (1.50–3.50)</td>
<td>5.81 (17)</td>
<td>5.33 (19)</td>
<td>5.76 (6)</td>
<td>6.90 (3)</td>
</tr>
<tr>
<td>Cholesterol mg/100 ml (150–300)</td>
<td>4.15–8.15</td>
<td>3.10–7.10</td>
<td>4.00–7.90</td>
<td>6.70–7.15</td>
</tr>
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<td>Bilirubin mg/100 ml (&lt; 1.5)</td>
<td>161 (3)</td>
<td>154 (4)</td>
<td>175 (3)</td>
<td>144 (2)</td>
</tr>
<tr>
<td>Patient’s weight kg</td>
<td>54.0 (7)</td>
<td>55.4 (6)</td>
<td>56.9 (3)</td>
<td>—</td>
</tr>
<tr>
<td>50.5–55.0</td>
<td>54.2–56.4</td>
<td>56.8–57.0</td>
<td>—</td>
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*Mean value; number of tests in parentheses.
†Range of values for the determinations.
THYROID SUPPRESSION IN SICKLE CELL DISEASE

Fig. 1. Relation of measurements of red cell mass (RCM) and $^{51}$Cr autoerythrocyte survival (AES) to artificially induced thyrosispression. As in Table 1, four study periods are shown. The first three coincide with intervals initiated by $^{51}$Cr survival studies, the fourth represents the final 2 mo after discontinuance of thiouracil (PTU).

Fig. 2. $^{51}$Cr autoerythrocyte survivals (AES) for study periods 1–3 shown in Table 1 and Fig. 1. Note close agreement and good fit to single exponential functions throughout the disappearance of over 90% of labeled cells on each occasion.
destruction of over 90% of the labeled cells. Consistent with the lack of improvement in any hematologic parameters, there were no detectable changes in erythrocyte DPG or p50.

DISCUSSION

Patients with hemoglobin SS disease and other severe anemias exhibit a variety of homeostatic responses, including changes in red cell metabolism and an enhancement of oxygen delivery by the red cell.\textsuperscript{2,16} The majority of the decrease in hemoglobin oxygen affinity appears to be due to an accumulation of DPG within the red cell.\textsuperscript{12} Although all of the factors that influence red cell DPG concentration in vivo are not known, it is thought that DPG elevations may be caused by alkalosis,\textsuperscript{17} increased deoxygenation of the hemoglobin,\textsuperscript{18} and increased levels of thyroid hormones (triiodo- and tetraiodothyronine).\textsuperscript{3-9}

The right shift of the oxygen dissociation curve in hemoglobin SS disease has been adequately documented\textsuperscript{19-23} and is as great as, or greater than, the shift seen in other forms of anemia. Furthermore, anemias of all sorts are frequently accompanied by increases in metabolic rate, although there may not be a perceptible increase in thyroid metabolism.\textsuperscript{24} Unfortunately, any elevation of the metabolic rate in hemoglobin SS disease will increase tissue oxygen demand and therefore favor hemoglobin desaturation. In fact, since these changes in oxygen demand and delivery progressively favor hemoglobin deoxygenation as anemia becomes more severe, they could be of primary importance in the pathogenesis of certain forms of sickle cell crises.

In sickle cell disease, it would appear advantageous to inhibit the release of large amounts of oxygen from the circulating erythrocyte and, thus, reduce the amount of sickling in vivo. Several techniques for artificially reducing both the amount of hemoglobin deoxygenation and the concentration of hemoglobin that will sickle in vivo have been attempted in the past.\textsuperscript{25-30} These therapeutic measures have been either too toxic or of too limited duration to be of significant clinical value. In addition, although these techniques may reduce oxygen delivery, they have little or no effect on oxygen demand.

Since elevation of thyroid function both shifts the oxygen dissociation curve to the right and increases the basal metabolic rate,\textsuperscript{3-9} it appeared useful to examine whether artificially induced depression of thyroid metabolism in a patient with hemoglobin SS disease would have the expected salubrious effects of: (1) decreasing red cell DPG concentrations, (2) lowering p50, (3) reducing tissue oxygen consumption, and (4) increasing the average level of oxygenation of the circulating red cell. All these changes would be expected to decrease the severity of intracellular tactoid formation, to reduce the frequency of sickling in vivo, to improve erythrocyte survival, and to reduce musculoskeletal complications.

The administration of thiouracil over a period of 143 days was associated with symptoms, physical findings, and biochemical evidence of thyroid suppression in our patient with hemoglobin SS disease. However, there was no accompanying change in red cell DPG concentration, p50, or red cell survival. The absence of change in p50 or DPG concentrations is remarkable in the
light of the previously mentioned work which indicated a close relationship between these parameters and elevations of thyroid metabolism. The present results suggest that, in the special circumstance of hemoglobin SS disease, thyroid status is not a primary determinant of the oxygen-delivering capacity of the circulating red cell.

The lack of effect on most of the parameters that were measured may have resulted from a reduction in cardiac output, which has been extensively documented in hypothyroidism. A reduction in cardiac output would increase circulation time, and the red cells would have an increased time of residence in the capillaries with consequent increased opportunity for deoxygenation. This effect would offset the over-all beneficial effect of decreases in tissue oxygen demand. It has been suggested that concentration of red cell DPG (and, consequently, p50) depends in part on the average level of deoxyhemoglobin within the circulating red cell. If this is correct, then a reduction in cardiac output would explain the absence of any effect of thyrosuppression on both red cell DPG concentration and the position of the oxygen dissociation curve.

Finally, it is noteworthy that the pattern of musculoskeletal pain was unchanged and that an incidental malleolar ulcer healed at a rate similar to that observed in the patient’s euthyroid state. No serious untoward effects were observed until the end of the period of observation, when disturbing subjective symptoms appeared with cardiac arrhythmia and symptomatic goiter.

Since only a single patient was studied, the possibility remains that the effects that accompanied thyrosuppression in this instance were idiosyncratic. However, the present study favors the view that thyrosuppression, within the limits of symptomatic and physiologic tolerance, has no detectable salubrious effects and appears to have no therapeutic application in the clinical management of sickle cell disease.

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