STUDIES ON THE PATHOGENESIS OF THE ANEMIA OF HYPOTHYROIDISM

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ABSTRACT

The blood of 11 adult hypothyroid patients was labeled with radioactive chromium^{51}. The affinity of the erythrocytes for radiochromium *in vitro* was 54.5 per cent on the average, and the apparent half-life of Cr^{51}-labeled erythrocytes *in vivo* was 13.8 days—results distinctly different from the normal values of 80 per cent and 24 days previously established in our laboratory. The frequency of anemia in hypothyroidism may be due to the shortened life span of the erythrocytes.

THE influence of the endocrine glands on the formed elements of the blood has recently received extensive study. Axelrod and Berman (1) reviewed all published data on the relationship between thyroid function and hematopoiesis available by 1951. Much of the literature was found to be fragmentary and contradictory. The information, derived from morphologic studies of the peripheral blood and bone marrow of hypothyroid experimental animals as well as human beings, can be summarized as follows:

1. Anemia is a common finding in hypothyroidism. It is of the simple macrocytic type in uncomplicated cases, but can be hypochromic if achylia gastrica is also present and leads to iron deficiency. True Addisonian pernicious anemia may be superimposed, if the anti-pernicious anemia factor becomes deficient because of lack of intrinsic factor. There are no significant changes in the leukocytes and platelets.

2. Hypoplasia of the bone marrow is present in hypothyroid states, and affects almost equally all the myeloid elements. A normal ratio between red and white cells is thus preserved. The total quantity of active marrow, however, cannot be seriously depleted; otherwise there would be a significant depression of all cellular elements in the peripheral blood.

The anemia of uncomplicated hypothyroidism obviously is not due to bone marrow hypoplasia alone. Neither is it due to blood loss. The life span of the red cell, therefore, could be a factor contributing to the anemia. Our present report deals with a study of red-cell turnover in 11 cases of adult myxedema, using chromium^{51}.

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METHODS

For many years the normal life span of human red cells was believed to be approximately 120 days, as determined by Ashby's biologic method of differential agglutination counting of transfused blood (2). The advent of radioisotopes permitted *in vitro* labeling of red cells (3). A practical method for studying the life span of erythrocytes was found when Cr^{51} proved to be a label which, for all practical purposes, remained within the red cells until their disappearance from the circulation. The disappearance of re-injected labeled cells was determined by simply measuring the decrease in radioactivity of the peripheral blood (4–6). Erythrocyte survival determinations were then performed and compared simultaneously in some cases with those performed by Ashby's method (7). The results corroborated the fact that 120 days was the average for the life of a normal human red cell. More important, perhaps, was the finding that the rate of loss and the total decline of Cr^{51} activity were reproducible in healthy subjects. This reproducibility firmly established radiochromium survival time as an index of the life span of erythrocytes (8, 9).

We studied the correlation between red-cell affinity for Cr^{51} (*in vitro*) and the rate of disappearance from the peripheral circulation *in vivo*. This survival curve is plotted as remaining blood radioactivity against time. Two aspects of the graph thus obtained have been closely analyzed: 1) the time it takes for the initial radioactivity to decrease by 50 per cent, called the apparent Cr^{51} half-life (T), and 2) the rate of change in blood radioactivity during the first day of study. The latter is represented by the tangent to the initial slope of the curve. This is obtained by joining the plotted points for the initial radioactivity (P_0) and the radioactivity present after twenty-four hours (P_1). The projection of this tangent will intersect the time axis at a point (V) which we consider to reflect the viability of the red cells under the conditions of survival for the first day of study. This viability value (V), expressed in terms of days, is readily determined without need of graphic plotting. The mathematical formula is:

$$V = \frac{P_0}{P_0 - P_1} \quad \text{or} \quad \frac{100}{100\% - P_1}$$

The red cells of 9 normal individuals had a mean *in vitro* Cr^{51} uptake (U) of 80 per cent; their average apparent Cr^{51} half-life (T) was 24 days; and the viability value (V) approximated 10 days. These criteria serve as reference standards in our present work.

CLINICAL DATA

Eleven adult patients exhibiting definite clinical and laboratory evidence of hypothyroidism were studied. Eight of them had spontaneous primary myxedema; 2 had postoperative myxedema, and 1 had secondary

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hypothyroidism. There were 9 females and 2 males; only 4 were considered of pure white racial origin.

All had normal total blood volume. The red cell masses varied with the degree of anemia present. Six patients had peripheral red blood cell counts below 4 million per cu. mm. and hemoglobin levels below 12 Gm. per 100 ml. All but 2 had hematocrit readings below 40. The lowest values recorded were 2,900,000 red blood cells per cu. mm., 8.7 Gm. of hemoglobin per 100 ml., and a hematocrit reading of 28. The erythrocyte color index averaged 0.85. Except for moderate hypochromia in 2 patients who had intestinal uncinariasis (hookworm), the mean cell volume, hemoglobin content, and hemoglobin concentration values revealed no gross abnormalities. Reticulocyte counts averaged 0.85 per cent. Red cell fragility was normal. No developing antibodies were elicited by the Coomb's technique. The electrophoretic pattern for hemoglobin was not abnormal. Serum bilirubin and total protein levels were normal. Paper electrophoretic partition of the latter, however, revealed a frequent increase in the gamma globulin fraction at the expense of the albumin component, thus reducing the A/G ratio in such cases to around 1.2. Only 1 of the patients with hookworm infestation had a low serum iron level of 42 mg. per 100 ml. Serum copper values were normal. The blood level of total cholesterol averaged 295 mg. per 100 ml., with a maximum of 415 mg. and a minimum of 179 mg. in the case of secondary myxedema. Blood phospholipid, sodium and potassium concentrations were normal. No patient passed blood in the stools or urine. The 24-hour urinary excretion of 17-ketosteroids averaged 6.6 mg. for females and 6.1 mg. for males.

As shown in Table 1, the mean red cell uptake (U) of Cr^{51} *in vitro* was 54.5 per cent on the average (maximum 64 per cent and minimum 46 per cent) and the mean apparent Cr^{51} half-life (T) *in vivo* was 13.8 days (maximum 19 days, and minimum 6 days in the case of secondary myxedema). Viability values (V) below 10 days were found in all cases.

Five euthyroid subjects received the Cr^{51}-labeled blood from 5 of the hypothyroid patients. The apparent half-life of the labeled cells in such normal environment was 12.8 days, and the viability was less than 10 days.

The Cr^{51} uptake *in vitro* was rechecked in 2 patients with hypothyroidism as soon as they became clinically euthyroid during treatment with oral 3,5,3′-triiodothyronine. Values of 78 per cent and 64 per cent were obtained. Simultaneous peripheral red cell counts and hemoglobin levels were also closer to normal values.

DISCUSSION

These findings reveal the fact that the life of the red cell in hypothyroidism is shortened. This cellular characteristic seems to be constant in patients with deficient thyroid function. The duration of survival is uninflu-

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TABLE 1. AVERAGE UPTAKE OF Cr^{51} BY RED CELLS *in vitro* AND APPARENT HALF-LIFE OF Cr^{51}-LABELED RED CELLS *in vivo* COMPARED IN EUTHYROID AND HYPOTHYROID SUBJECTS

Subjects	No. of cases	*In vitro* uptake (U) of Cr^{51}	*In vivo* half-life (T) of Cr^{51}-RBC	Viability (V)
Euthyroid	9	80.0%	24.0 days	>10 days
Hypothyroid	11	54.5%	13.8 days	<10 days
Euthyroid recipients of Cr^{51}-labeled blood from hypothyroid patients	5	—	12.8 days	<10 days
Hypothyroid patients treated with triiodothyronine	1	78.0%	—	—
	1	—	—	—

enced by a normal endocrine environment, as shown by the results of turnover studies on Cr^{51}-labeled blood from hypothyroid patients transferred into normal recipients. Apparently an inborn corpuscular defect is involved. It is a reversible trait that may be corrected by administration of active thyroid hormone, such as 3,5,3′-triiodothyronine. The corrective action appears to be mediated through the bone marrow.

An erythropoietic function of the thyroid gland, exerting its effects by way of the bone marrow, has been suggested for many years by experimental and clinical work (10–12). Deficiency of this erythropoietic function would explain the anemia of myxedema. The nature of the deficiency could be decreased cellular production (13) and/or arrest of erythroblast maturation (14). Either of these conditions would result in fewer red cells reaching the circulation. Since these red cells last a shorter time in hypothyroidism, the frequency of anemia is understandable.

If we assume that the thyroid gland has a hematopoietic function, then we can speculate whether the effects are those of response by a target tissue to a direct stimulus, or whether they are indirect manifestations of an adaptation to variable blood oxygen tension. Decreased body tissue requirements for oxygen in hypothyroidism can conceivably lead to a decrease in erythropoietic tissue in the bone marrow, but it could hardly explain a hypoplasia of the leukopoietic or megakariocytic series. The bone marrow of human beings subjected to the low oxygen tension of high altitudes exhibits a compensatory hyperplasia limited exclusively to the erythropoietic tissue (15). A direct effect of the thyroid on the marrow seems more plausible. In thyroidectomized animals there is no erythrocytic re-

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sponse to lowered blood oxygen tension (16). All myeloid elements of the human marrow show increased activity during stimulation with thyroid hormone. The remarkable change to normal values for erythrocytic Cr^{51} uptake in 2 of our treated cases of hypothyroidism indicates a reversal to normal life span of the red cell under the influence of thyroid hormone therapy.

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