The Bone Marrow in Hyperthyroidism and Hypothyroidism

By Arnold R. Axelrod, M.D. and Lawrence Berman, M.D.

During the past half century there has been an extensive accumulation of literature dealing with the relationship between the function of the thyroid gland and the status of the blood and bone marrow. Much of it is fragmentary and contradictory. We have attempted to gather the available facts and augment these with original observations in order to provide a clearly defined point of departure for future studies.

This work is based on a review of literature and analysis of the blood and marrow findings of 26 patients with hyperthyroidism and 9 patients with myxedema. The three parts of this paper deal with: I Hematologic findings in hyperthyroidism; II Hematologic findings in hypothyroidism; III Discussion of the relationship between disturbed thyroid function and hematopoiesis. Methods are indicated in the Appendix.

I. Hematologic Findings in Hyperthyroidism

Anemia is not a frequent finding in patients with hyperthyroidism; however, when present, it may be of any type. Erythrocytosis, on the other hand, is fairly common. Some of the features of the peripheral blood changes, such as increased osmotic fragility of erythrocytes, “microcytosis” in absence of hemorrhage, and increased excretion of bile pigments, are suggestive of a hemolytic component for the anemia, which may be present in hyperthyroidism. In regard to the leukocytes, our findings corroborate those given in the literature; namely, that the total leukocyte count is elevated, normal, or only slightly depressed, with normal differential counts, neutropenia, lymphocytosis, or eosinophilia. As shown by others, our material reveals that the changes in the peripheral blood are not necessarily related to the severity or duration of hyperthyroidism.

The marrow has not been studied as thoroughly as peripheral blood. In general, it is reported that in experimental hyperthyroidism there is hyperplasia of all myeloid elements, but especially erythropoietic tissue. Bone marrow studies in patients with hyperthyroidism are of two types: those based on autopsy material and those based on material aspirated from living patients. The autopsy studies have been fragmentary, and in most instances limited to gross inspection of marrow. Aspiration biopsies have been more complete and have included analysis of qualitative changes in the various myeloid activities. The few studies of quantitative nature have been based on rather crude methods.

From the Departments of Medicine, Pathology and Anatomy, Wayne University College of Medicine, and City of Detroit Receiving Hospital, Detroit, Mich.
Autopsy material. Gross examination of marrow or inspection of sections prepared from various bones reveals extension of red marrow in long bones with or without local hyperplasia. Various authors have mentioned predominance of certain cells in sectioned postmortem material, but there is little uniformity in the patterns reported. It must be noted that although gross changes are apparent in autopsy material, sectioned material obtained after death often is unsuitable for differentiation of marrow cells because of the rapid autolysis which precludes accurate identification of many of the marrow cells.

Biopsy material. The chief advantages of aspiration biopsy of the marrow are the relative ease of identification of cells because of the avoidance of autolytic changes and the availability of sectioned material for use in estimating relative cellularity, fat content and frequency of megakaryocytes. Although it has been reported that the relative volume occupied by nucleated cells is greater than normal as determined by centrifugation of fluid aspirated marrow, data on the relative fat content of marrow in hyperthyroidism are not available. The volumetric increase of the layer of nucleated cells in centrifuged fluid marrow was considered by some authors to be evidence of marrow hyperplasia; however, the volumetric method of estimation of cell content yields a wide range of values and is not as reliable an index of cell content of marrow in any given case as is the section method.

The myeloid-erythroid ratio (ME ratio) represents the relative frequencies of myeloid leukocytes and erythroblasts in the smears of aspirated marrow specimens. Several studies include data of this type. We have also calculated ME ratios from data presented by other authors. The combined statistics from a total of 97 cases yield ME ratios ranging from less than 1:1 to 20:1. However, in 80 per cent of cases the ME ratio was within the normal range, or over 4:1. Thus, there is no great tendency for predominance of erythrocytogenesis, but on the contrary, there is a slight tendency for relative increase of leukogenesis.

Few reports mention the differential distribution of erythroblasts. Wilson stated it was normal; others noted increase of polychromatophilic forms, as well as Sampaio and Silva, noted a left shift. Megaloblasts have not been seen in hyperthyroidism except when there is coexistence of pernicious anemia. Some observers have reported normal or increased megakaryocyte counts. It has been shown, however, that estimations of megakaryocyte content of bone marrow by means of scanning smears are generally unsatisfactory.
It is odd that there are very few references to lymphocytes in the marrow in contrast to the numerous studies of these cells in the peripheral blood of patients with hyperthyroidism. A few authors mentioned an increase of lymphocytes in the marrow.82, 83, 89

Original Observations

Relative fat and cell content of marrow. As determined by centrifugation of aspirated marrow specimens, the fat volumes ranged from 0 to 4 per cent, and the nucleated cell volumes varied between 2 and 42 per cent. Because of the lack of reliability of the centrifugation method for detecting small variations in relative fat or cell content of marrow samples, we made estimates which were based on examination of sections of aspirated marrow particles, using methods described by Berman and Axelrod.13, 14

The results are illustrated in figures 1 and 2. The cell content of the samples of marrow of all patients with hyperthyroidism was the reciprocal of the fat content. In the marrow particles there were practically no parts composed of bone or tissue other than myeloid or fat components. The observations on material from hyperthyroid patients should be compared with those made on normal persons, as shown in the figures. As a group, the marrow samples from hyperthyroid patients have a greater relative cell content than is the case for normal persons. The difference is significant (table 1). A representative section of marrow aspirated from a patient with hyperthyroidism is shown in figure 3. For comparison, a section of marrow from a normal individual is shown in

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**Fig. 1.**—Relative areas occupied by fat in serial sections of aspirated sternal marrow particles from hyperthyroid, normal and hypothyroid individuals.
figure 4. The hyperplasia of the sternal marrow in the hyperthyroidism group as a whole is not a characteristic of each individual case. Some marrows in hyperthyroidism had normal cellularity. In spite of normal findings in the sternum, the marrow organ actually may be hypertrophied in hyperthyroidism because of extension of functioning marrow into the long bones. We found no relationship between the degree of cellularity of the marrow and the presence or absence of anemia. The most important fact was that hyperplasia of marrow occurred in the absence of anemia.

Myeloid-erythroid ratios. In 85 per cent of our patients the ME ratio was 2:1 or greater, the highest being 8:1. Three patients had ME ratios of 1:1. These low ratios remained unexplained, as there was no evidence of recent blood loss or erythrocytosis. One of our patients had a reversed ratio (1:2), but this could be explained on the basis of acceleration of erythropoiesis following gastrointestinal hemorrhage.

Erythrocytogenesis. Except for a slight increase of polychromatophilic forms,
there were no changes in differential counts of erythroblasts. In patients with microcytic hypochromic anemia we observed polychromatophilic cells with pyknotic nuclei and poorly hemoglobinized cytoplasm, as is characteristic of iron deficiency.87

Myeloid leukogenesis. There were no significant qualitative changes. The group of neutrophils, including metamyelocytes, band and filamented forms, were increased in number at the expense of less differentiated cells in the majority of our patients (18 of 27 marrows). This is a right shift in leukocytogenesis.

Megakaryocytogenesis. Our estimates of megakaryocyte content, based on study of serial sections of marrow tissue particles, reveal a definite increase of these cells (table 2). This can be seen in figure 3, which should be compared with figure 4 of the normal marrow section. The increased megakaryocyte content of the marrow samples from hyperthyroid patients was not related to anemia. We noted a slight tendency for increased numbers of megakaryocytes in patients with symptoms of shorter duration (less than six months), thus supporting Markoff's87 observation that increased megakaryocytogenesis is one of the earliest marrow changes in hyperthyroidism.

Fig. 3.—Section of aspirated bone marrow from a patient with hyperthyroidism. There is myeloid, erythroid and megakaryocytic hyperplasia at the expense of fat.
Lymphocytes. Fourteen of 27 marrows (52 per cent) had lymphocyte counts higher than the maximum seen in our control series of 16 normal persons. Ten patients had increased numbers of lymphocytes in sternal marrow in spite of normal numbers in the blood. Lymphocytes comprised between 30 and 40 per cent of the leukocytes of the marrow in 6 of our patients. This borders or lies within the range usually suggestive of chronic lymphatic leukemia according to some authors. Even though we never found lymphoblasts, Rieder cells or immature lymphocytes, it would be difficult from marrow examinations alone to exclude a diagnosis of chronic lymphatic leukemia in such instances since in the early stages the erythropoietic and granulopoietic systems are unaffected and the lymphocytes are predominantly fully differentiated.

Other cells. As far as could be determined by studying smears, imprints or sections of marrow particles, no qualitative or quantitative changes affected plasma cells or reticulum cells.

The available information concerning the bone marrow in hyperthyroidism can be summarized as follows:

1. There is extension of the red or functioning marrow into the shafts of long bones with diminution or absence of fat and osteoporosis.
2. Hypertrophy of the marrow organ may occur with or without anemia and with or without increased cellularity in the normal sites of hematopoiesis.

3. There is a tendency for relative myeloid leukocytic hyperplasia, as indicated by myeloid erythroid ratios.

4. The differential distribution of erythroblasts is unaltered.

5. The only common change in leukocytogenesis is a relative increase in the proportion of mature granulocytes.

6. Megakaryocytes are of normal or increased frequency. Increased megakaryocytogenesis may be the first sign of marrow hyperplasia in hyperthyroidism. The increase of megakaryocytes is independent of anemia and is not reflected by alteration of the peripheral platelet count.

7. Relative lymphocytosis is the most constant significant change in the marrow pattern in our patients with hyperthyroidism. This has not been pointed out by others. Since lymphoid aggregates are known to occur in marrow and because generalized lymphoid tissue hyperplasia is a feature of hyperthyroidism, it is possible that the increase of marrow lymphocytes originates from the marrow itself. This is also indicated by the fact that several of our patients exhibited marrow lymphocytosis without lymphocytosis in the peripheral blood.

8. There are no constant changes in plasma or reticulum cells.

The presence of cellular marrow, microcytosis of erythrocytes (spherocytosis?) even without blood loss and increased osmotic fragility of erythrocytes suggest the possibility of hemolysis in certain patients with hyperthyroidism. A similar hematologic pattern has been observed in experimental hyperthyroidism. The possibility of a hemolytic disturbance has not received much attention. Nevertheless, Heilmeyer reported increased excretion of fecal urobilinogen in patients with hyperthyroidism. De Renzi and Galeotti noted an increase of fecal bile in normal subjects after administration of thyroid extract.

II. HEMATOLOGIC FINDINGS IN HYPOTHYROIDISM

Anemia is a common but not constant finding. Maerocytic hypochromic anemia of moderate severity is the typical anemia of uncomplicated hypothyroidism. The experimental approach to the study of the marrow function in hypo-
thyroid states has been applied to the rat and rabbit. Some investigators found a decrease of marrow cellularity, but others did not find remarkable changes in the marrow.

Several postmortem studies of cretins indicated a marked increase of fatty marrow at the expense of cellular marrow, although the flat bones appeared to contain relatively more cellular marrow than other bones. Stoccada reported an abundance of lymphoid tissue and eosinophils in the marrows of cretins. Maresch mentioned fatty replacement of marrow and Custer noted hypoplasia of marrow, especially with respect to the formation of early erythroblasts. Radiologic examination of long bones of cretins showed changes said to be characteristic of aplasia of marrow.

Biopsy material from the sternum or long bones has been obtained by aspiration. Migone and Landolt found excessive fat in smears of marrow particles. Disturbances of maturation of erythropoietic and leukopoietic elements have been reported. Sampaio and Silva found a decreased incidence of mitoses.

Estimates of fat content have not been reported, but certain authors have determined the relative volume occupied by nucleated cells in specimens of
aspirated marrow fluid. This was done by centrifugation of the marrow specimens. The nucleated cell volume ranged from 1.5 to 4.5 per cent, with a mean value of 2.4 per cent. This has been regarded as evidence of hypoplasia of the marrow in patients with hypothyroidism. As we have already shown, the volumetric method yields values which are less reliable than those based on inspection of sections of marrow.

The ME ratios, or data from which they can be calculated, were given in only three papers. The ratios ranged from 1:1 to 6:1.

Fig. 6.—Section of aspirated bone marrow from a patient with hypothyroidism. The marrow is hypocellular and fatty.

Decreased erythropoiesis or marked reduction of polychromatophilic erythroblasts have been noted by many. Both increases and decreases of leukopoietic elements have been reported. Migone reported a slight increase of lymphocytes, plasma cells and histiocytes, but megakaryocytes were reported as normal, increased or decreased.

Original Observations

Relative fat and cell content. Volumetric determinations of fat in the aspirated marrow samples from our patients with hypothyroidism ranged from 0 to 20 per cent, with a mean value of 4.4 per cent. The nucleated cell volumes ranged
from 1 to 14 per cent, with a mean of 5.4 per cent, which is roughly one-third that of the mean value in patients with hyperthyroidism. For more reliable estimates of relative fat and cell contents the section method was used.\textsuperscript{13,14} The results are shown in figures 1 and 2.

Marrow from patients with hypothyroidism generally had fat contents within or above the range observed in normal individuals (figure 1). With the exception of three cases the cell content of the marrow samples was the reciprocal of the fat content. The cell contents were generally near the lower limits of

\begin{figure}
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\caption{Section of aspirated bone marrow from a patient with hypothyroidism. The marrow is extremely hypocellular. The bulk of the space is occupied by hyperemic tissue and congested sinusoids.}
\end{figure}

the normal range (figure 2). In 3 patients with hypothyroidism, in whom the cell contents were not the reciprocals of the fat contents, the bulk of the marrow area between fat spaces consisted of masses of erythrocytes in which there were occasional scattered nucleated cells and acellular material resembling fibrin (figure 5). In the 3 cases the marrow was definitely hypocellular although the fat content was within normal limits. Two other types of marrow patterns were noted in the sectioned material in our hypothyroid patients. One of the types, illustrated in figure 6, is characterized by severe hypoplasia of all elements with increase of fatty marrow. In the other type, shown in figure 7, there is hypo-
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plasia of all elements in addition to hyperemia with normal or increased amounts of fatty marrow. We were unable to find a relationship between the degrees of cellularity of the marrow sections and the severity of anemia.

Myeloid-erythroid ratios. The ME ratios were within the normal range in all but 1 patient. This patient had relative myeloid hyperplasia, for which there was no obvious explanation.

Erythropoiesis. There were no striking changes in the differential distribution of erythroblasts, although there was a slight right shift, as indicated by a relative increase of polychromatophilic forms. The patients with hypochromic anemia had poorly hemoglobinized polychromatophilic forms consistent with iron deficiency. Megaloblastic erythropoiesis was not seen.

Myeloid leukopoiesis. The only notable change was an increase in the proportion of differentiated myeloid cells at the expense of the less differentiated forms, so that in some patients polymorphonuclear neutrophils predominated. Significant maturation asynchronism was not observed.

Table 3.—Estimates of Megakaryocytes in Sections of Aspirated Marrow from Patients with Hypothyroidism and from Normal Individuals

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<th>Cells per 50 fields</th>
<th>Mean ± S. E.</th>
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<tr>
<td>Normals</td>
<td>14 to 60</td>
<td>31 ± 3.6</td>
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<tr>
<td>Hypothyroids</td>
<td>0 to 33</td>
<td>16 ± 3.5</td>
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<tr>
<td>Difference</td>
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<td>15 ± 4.8</td>
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Megakaryocytopoiesis. Adequate material for estimation of megakaryocyte content was available in 9 cases. The megakaryocytes were diminished, but morphologically normal in our group of hypothyroid patients (table 3), although the peripheral platelet counts were normal.

Other cells. There were no significant morphologic or quantitative changes in lymphocytes, plasma or reticulum cells.

The information on bone marrow in hypothyroidism may be summarized as follows:

1. There is decreased total functioning marrow in hypothyroidism.
2. Although the active marrow is hypoplastic in hypothyroidism, there may or may not be an increase of fatty marrow. Hyperemic tissue and acellular material may occupy the bulk of the space in marrows which do not have increased fat contents.
3. The myeloid erythroid ratio is usually normal. The hypoplasia affects all myeloid systems about equally.
4. The megakaryocyte content of the sectioned marrow particles is usually lowered, but this is not reflected in the peripheral platelet count.

III. Relationship Between Disturbed Thyroid Function and Hematopoiesis

An erythropoietic function of the thyroid gland is suggested by experimental work indicating increased erythropoiesis, or enhanced regeneration of erythro-
cytes after bleeding, in animals and man treated with thyroid substances. The anemia associated with myxedema has been explained as due to inhibition of maturation of erythroblasts mediated by a deficiency of thyroid hormone. According to other authors, deficiency of thyroxine itself does not cause anemia, nor is thyroxine the marrow stimulating hormone, in spite of claims that thyroid extracts can cause temporary erythrocytosis. These authors believe that a special hormone which they claim to have isolated from thyroxine, namely, the "myelotropic hormone," is the direct cause of the apparent stimulatory action of thyroxine on the marrow. Unfortunately, this work has not yet been repeated.

It is known that the anemia which follows hypophysectomy in rats can be corrected by administration of hypophyseal material apparently devoid of the gonadotropic, growth and thyrotropic hormones. Meyer et al. and Vollmer et al. have shown that although the "hematopoietic hormone" is a possibility, other hormones, including thyroxine and testosterone, are also effective in correcting the anemia which follows hypophysectomy in the rat. Vollmer et al. suggested that anoxia might release the hormone to stimulate the marrow. The studies of Meyer and co-workers support this idea, since they showed that hypophysectomized rats do not respond to low oxygen tension except when growth hormone is given.

Bomford regards the hematologic changes in hyperthyroidism and myxedema as manifestations of adaptation to increased or decreased oxygen tension. Although decrease of erythropoietic tissue may be accounted for on the basis of diminished tissue requirements for oxygen in hypothyroidism, it does not seem to us to account for the hypoplasia of the leukopoietic and megakaryocytic elements of the marrow. Conversely, the hyperplasia of these elements of the marrow in hyperthyroidism cannot be accounted for by adaptation to increased availability or utilization of oxygen. Merino and Reynafarje studied the marrows of persons subjected to the decreased oxygen tension of high altitudes. Hyperplasia was limited to the erythropoietic tissue, an observation which confirms the opinion that decreased oxygen tension is a factor which specifically and exclusively affects erythroid elements.

It seems more likely to us that the marrow changes in both hypo- and hyperthyroidism are a more direct effect of the thyroid gland dysfunction. This is supported by observations of Askanazy, Mansfeld, and Meyer et al., who noted that thyroidectomized animals failed to exhibit an erythrocytic response when subjected to lowered oxygen tension. As we have shown, the myeloid and megakaryocytic elements also suffer as a result of the thyroid deficiency. Furthermore, upon removal of the deficiency by administration of thyroid hormone, the marrow shows evidence of increased activity of all myeloid systems.

With regard to the increased lymphocyte counts observed in our hyperthyroidism bone marrow material, the role of the adrenal cortex and its effect on lymphoid tissue has to be considered. The adrenal cortical steroids oxygenated in position 11 of the steroid nucleus cause lymphopenia, eosinopenia and decrease in the size of the thymus and lymph nodes. A few investigations
have shown decreased excretion of adrenal cortical steroids in patients with hyperthyroidism. Wallach and Reinecke observed a decrease in ascorbic acid content of the adrenal cortex in experimental hyperthyroidism in rats and Le Compte noted a decrease in the width of the adrenal cortex in patients with hyperthyroidism. Warthin described hypoplasia of the adrenal glands as a feature of the "Graves constitution." These observations suggest that the generalized lymphoid tissue hyperplasia in patients with hyperthyroidism is due to decreased activity of the adrenal cortex. On the basis of evidence accumulated up to this time, it is not permissible to reach a conclusion as to whether the changes of lymphoid tissue and lymphocytosis in the bone marrow of patients with hyperthyroidism are due to direct effects of the thyroid gland, or to secondary effects of adrenal origin.

CONCLUSIONS

In hyperthyroidism, the marrow at a given site such as the sternum is hypercellular. The hyperplasia involves all myeloid systems. In addition, there is extension of the marrow organ as indicated by the increase of red marrow in the long bones. The hematologic changes seen in some patients with hyperthyroidism may be due, in part, to excessive hemolysis.

The generalized hyperplasia of lymphoid tissues of the hyperthyroid patient involves the bone marrow. Hyperthyroidism must be included among the conditions associated with lymphocytosis of the marrow.

It is of considerable interest that the increased megakaryocyte content of the marrow is not reflected by an increase or decrease of the peripheral platelet counts. This, of course, is a useful point in separating this marrow finding from that seen in hypersplenic conditions with low peripheral platelet counts, or reactive states such as that following acute blood loss, splenectomy or in some cases of malignant disease with high peripheral platelet counts.

In hypothyroidism, there is hypoplasia of all myeloid systems, as revealed by examination of a single site, such as the sternum. The hypocellularity of the marrow is not always accompanied by a reciprocal increase of fat. In some instances, the marrow space contains an excess of hyperemic or edematous nonhematopoietic tissue. The absence of significant blood changes is an indication that the total marrow organ is not seriously depleted in hypothyroidism, in spite of the hypocellular appearance in a single biopsy. Nevertheless, hypothyroidism must be included among the causes of hypocellularity of marrow and should be strongly considered in any patient having hypocellular marrow with macrocytic anemia.

APPENDIX

Marrow specimens were obtained by sternal aspiration by methods previously described. Estimations of fat, cell and megakaryocyte content of marrow specimens were based on examination of serial sections of aspirated marrow particles. The myeloid-erythroid ratios were calculated by dividing the relative frequencies of myeloid cells exclusive of lymphocytes by the relative frequencies of erythroblasts in smears of aspirated
marrow. The hematologic terminology used follows that in current use by Bell,9 Berman et al.14 and Jones.22

All studies were made shortly after admission of the patient either before treatment was started or within the first week of therapy. The serum cholesterol determinations were made according to the method of Bloor.19 Control data on blood and bone marrow were obtained from 16 healthy persons.10 11

All persons presented unequivocal symptoms and signs of hyper- or hypothyroidism, as noted by two or more examiners. In the hyperthyroid group there were 3 males and 22 females; 1 of the latter was studied twice. In the hypothyroid group there were 5 males and 4 females; 1 of the latter was studied twice.

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