THE EFFECT OF ENDOCRINOPATHIES ON THE BLOOD

By William H. Daughaday, M.D., Robert H. Williams, M.D., and Geneva A. Daland, B.S.

With the rapid increase of knowledge of the many functions and interrelations of the endocrine glands, it is natural that their influences on the formed elements of the blood have received extensive study. The essential problem has been to determine just how much the elements of the blood are under direct endocrine regulation and how much they are affected by general metabolic alterations produced by hormones. Attempts to isolate a specific hemopoietic hormone or hormones have not been successful. Extracts of the anterior pituitary gland have been said to aid in the regulation of erythrocyte production and certain steroids of the adrenal cortex are known to affect lymphoid tissue. In this paper we propose to review some of the clinical and experimental evidence pertaining to this subject and to present some of our observations in an attempt to evaluate the importance of hormones in the regulation of blood production.

I. Gonads

A sex difference in the number of red blood cells and the concentration of hemoglobin has been well established for human adults. Exact figures vary but all authors agree that the values for the male are significantly higher than for the female. One authority states that the red blood cell count averages 4.8 million in females and 5.4 million in males. The concentration of hemoglobin shows a corresponding difference. This difference cannot be ascribed to blood loss in menstruation because a wide variety of mammals and even birds appear to have a well substantiated sex difference.

A mild anemia occurs after castration in the male hamster, rabbit, rat and chicken. The anemia is usually slightly hypochromic and microcytic. The administration of androgens, in general, has proved effective in restoring the red blood cell counts to normal or above normal. McCullagh and Jones have found a slight to moderate reduction in erythrocytes and hemoglobin in eunuchoid men. They showed that treatment with testosterone caused a rise in the red blood cell counts and hemoglobin; with cessation of therapy there was a reversal of these changes. An increase in the basal metabolic rate seemed to parallel the improvement in the blood picture. From these data they concluded that the sex difference in basal metabolic rate and in erythrocytes might be a related phenomenon.

Ovariectomy of rats causes a rise in the red blood cell count and hemoglobin to nearly the levels maintained by castrated males. The administration of estradiol to these animals yields values comparable to those of normal female animals. The chicken seems to respond somewhat differently in that the red blood cell count of...
ovariectomized hens is not significantly different from that in the hen. A depression or erythropoiesis follows large doses of estrogens in several species. A moderate to severe anemia has been produced in dogs with both natural and synthetic estrogens. The depression is not limited to the red cell series but a severe and sometimes fatal granulocytopenia or thrombocytopenia will occur on continued treatment. Monkeys seem to be much more tolerant of similar doses and show only a slight anemia. Hematologic complications of estrogen therapy in humans seems to be rare.

There is not universal agreement as to sex differences in the number of platelets. A slightly lower average platelet count has been reported for women by Pohle. In normal women it was found that a gradual decrease in platelets occurred during the fourteen days prior to menstruation which was followed by a rapid return to normal or increase after the onset of menstruation. Purpura hemorrhagica is found more frequently in females and cases of thrombocytopenic purpura have been described in which the purpuric episodes recurred only at the time of menstruation. These observations suggest that platelets are influenced by certain female sex hormones or perhaps by the menstrual toxin described by Smith and Smith.

2. Thyroid

Considerable clinical and experimental evidence indicates that the thyroid hormone has a definite influence on hematopoiesis. An anemia occurs with regularity in many laboratory animals following complete thyroidectomy. The changes which occur in the rat and rabbit have received the most thorough study. The characteristic picture is a moderate anemia which is normochromic and slightly macrocytic. Gastric acidity in the rabbit is unchanged and megaloblasts do not occur in the bone marrow. A diminished ability to regenerate red cells and hemoglobin following a standardized hemorrhage has been demonstrated in thyroidectomized rats. The defect was corrected by thyroxine, cobalt and testosterone, suggesting that the disturbance in blood regeneration is nonspecific.

Anemia is frequently observed in patients with myxedema. Emery attributed the first definite description of this feature of hypothyroidism to Charcot in 1881. This was seven years after Gull's original paper describing the disease. The report of the London Clinical Society on myxedema in 1888 added that "allied with the fall in body temperature are changes in the blood. There is not only anemia due to loss of corpuscles, but the relative proportions of these constituents are also altered." Following these early observations, many other authors have confirmed and extended knowledge of this anemia. The importance of the recognition of this cause of anemia was emphasized in 1921 by Dr. Minot in a clinic at which he presented "two curable cases of anemia." The changes in the blood were summarized and the beneficial effects of treatment were described. In commenting on the etiology of the anemia he said: "The anemia in this case was apparently dependent upon a decreased formation of blood. This decreased activity of the marrow is

* One patient has been found to have repeated attacks of agranulocytic angina manifested on the first day of the menstrual cycle.
entirely consistent with the diminished activity of the other functions of the body.

Stern and Altschule have described the blood changes in human beings under conditions which approach in simplicity the animal experiments referred to above. Their patients were subjected to total thyroidectomy for the relief of angina pectoris or congestive heart failure. An anemia of some degree was common and the onset of anemia seemed to coincide with the drop in the basal metabolic rate. There was a slight increase in mean cell volume and in color index. Some decrease in white blood cell counts occurred, but the differential counts remained unchanged.

Anemia in spontaneous myxedema has been found by Bomford to be of three types. A slightly macrocytic variety of moderate severity commonly occurs. Similar to the anemia following thyroidectomy, it is characterized by a slight macrocytosis and increase in color index. It differs from pernicious anemia in that there is little poikilocytosis or anisocytosis of the erythrocytes and the bone marrow is hypoactive. Gastric function may or may not be normal. No reticulocyte response follows treatment with liver or iron, but the anemia slowly disappears on prolonged treatment with desiccated thyroid.

Some cases of myxedema may be associated with a hypochromic anemia of varying degree. Splenomegaly, a smooth tongue and changes in the nails are sometimes observed. The blood smear resembles iron-lack anemia with the exception that the cells tend to be larger. Achlorhydria is common but not invariable. A reticulocyte response to iron occurs, but complete recovery depends on both iron and thyroid.

Quite rarely Addisonian macrocytic anemia may be a complication of hypothyroidism. In such patients the signs and symptoms of pernicious anemia and combined system disease may be superimposed on the features of myxedema. The blood resembles pernicious anemia except that the color index may be even higher and the cells larger. Maximum improvement depends upon combined liver and thyroid treatment.

Bomford has concluded that the simple macrocytic type is the result of a decrease in size of the erythron as a physiologic compensation for the diminished need of the tissues for oxygen. The bone marrow undergoes hypoplasia, with shrinkage of its total volume. A marked reticulocytosis following treatment is not to be expected as compared to the anemias due to a maturation arrest. The slow return of the peripheral blood to normal values was explained by the gradual resumption of activity and cellularity in the bone marrow. The other two types of anemia are due to deficiencies of iron and liver extract factor apparently dependent on defective gastrointestinal function.

The simple slightly macrocytic anemia of myxedema occasionally is mistaken for pernicious anemia. However, little variation in size and shape of the red cells occurs in myxedema and the multilobed polymorphonuclear leukocytes and bone marrow changes associated with pernicious anemia are absent. The finding of normal gastric juice occurs in about one half of the cases of myxedema. The basal metabolic rate is of considerable aid in diagnosis because it is usually elevated in pernicious anemia. A yellow color of the skin may be common to both diseases, but
this pigment is bilirubin in pernicious anemia and excess carotene in myxedema. The most important differential point, however, is the presence or absence of an adequate reticulocyte response to liver extract therapy.

The frequency of anemia in spontaneous myxedema has been reported by Lerman and Means. Sixty per cent of 52 patients with myxedema had red blood cell counts of less than four million and 52 per cent had hemoglobin concentrations which were less than 70 per cent. Achlorhydria occurred in 53 per cent and was more frequently associated with anemia than was normal gastric acidity. These authors ascribed considerable etiologic importance to these changes in gastric secretion. The coexistence of myxedema and pernicious anemia seems to be more common than could be accounted for on the basis of probability. Means, Lerman and Castle have described 5 such cases responding to liver extract.

Testosterone has been used in the treatment of anemia in myxedema by Glass. He reported the case of a 71 year old man with the classic features of myxedema. The red blood cell count was 2.8 with a color index of 1.1. Liver and iron had been given in adequate doses without increasing the number of erythrocytes. Four months of therapy with desiccated thyroid failed to correct the anemia. On the addition of testosterone and methyl testosterone to the therapeutic regime, the erythropoietic response was prompt and blood counts returned to normal in the course of a few months. An adequate hematologic response to desiccated thyroid might have eventually occurred in this patient, but the stimulating effect of testosterone on erythropoiesis cited above and the observed low excretion of 17-ketosteroids in myxedema provide a rational basis for such therapy. We have employed the combination of testosterone and desiccated thyroid in myxedema with apparent acceleration of blood regeneration, as illustrated by the following case.

Normocytic, slightly hypochromic anemia associated with myxedema with restoration of normal blood values after treatment with desiccated thyroid, testosterone propionate and ferrous sulfate.

Case 1. M. V., a housewife, aged 47, of Irish parentage entered the Boston City Hospital in May 1945 complaining of weakness which appeared at the birth of her last child five years previously. The baby had been born at full term and the delivery was uncomplicated. Lactation was normal and menstrual periods returned at normal intervals following the cessation of lactation. She did note, however, increased fatigue and weakness. Somnolence and lethargy became troublesome. For one year she had noticed thinning of her hair and dryness of her skin. Bowel movements had continued to be regular. There had been no shortness of breath, numbness or tingling of the extremities, and no soreness of the tongue.

On physical examination the patient was a pale, somewhat poorly developed middle-aged female in no distress. The skin was cool and dry and the fingernails were brittle and spoon-shaped. The hair on the scalp was thin and dry and the axillary and pubic hair was sparse. The tongue was large but possessed normal papillae. The blood pressure was 101 mm. of Hg systolic and 75 diastolic and the pulse was 94. The heart and lungs were not abnormal. The liver and spleen could not be palpated. No abnormal neurologic signs were noted.

Laboratory examinations showed the following: Repeated urinalysis demonstrated only a small amount of albumin on occasions without other abnormality. The serum cholesterol was found to be 104 mg. per 100 cc. The prothrombin concentration was 90 per cent of normal. Carotenoids were demonstrated in the serum by a presumptive test. The basal metabolic rate was -36 per cent. An insulin tolerance test using 1.5 units of insulin, intravenously, did not reveal sensitivity or hypoglycemic unresponsiveness. A "water" test and a sodium deprivation test were normal, suggesting normal adrenal function. The sella turcica was normal by x-ray.

Examination of the blood showed a red cell count of 2.98 million, and the hemoglobin concentration
The white blood cell count was 7,200 and the differential count showed the following: polymorphonuclear neutrophils 64 per cent, band forms 6 per cent, eosinophils 1.5 per cent, basophils 0.5 per cent, small lymphocytes 15 per cent, large lymphocytes 3.5 per cent, monocytes 7.5 per cent and myelocytes 1.0 per cent. The platelets appeared normal.

The patient was given a diet of about 3,500 calories supplemented with vitamins in the form of "Vegex", 90 cc. per day, 1.5 mg. of thiamin, 50 mg. of ascorbic acid and 50 mg. of nicotinic acid a day. Desiccated thyroid was begun soon after entry in a dose of 32 mg. and was later increased to 96 mg. Ferrous sulfate was administered in a daily dose of 0.9 Gm. for a week. Two cc. of purified liver extract (Lilly) containing 30 USP units was given in a single dose by intramuscular injection. Five cc. of crude liver extract (Wilson) was administered intramuscularly daily for five days. No significant increase in reticulocytes was observed following any of the above therapies. The time relations of the various medications and the hematologic response are shown in figure 1.

At the time of the patient's discharge from the hospital, the red blood cell count was 2.9 million and the hemoglobin concentration was 56 per cent. She had noted improvement in strength and general well-being. The basal metabolic rate had risen to 18 per cent. She was followed at intervals in the outpatient clinic. From September 13 to October 27, 1945 she received a total of about 1,400 mg. of methyl testosterone in daily doses of 10-50 mg., without improvement in her blood. In November 1945 she was re-admitted for more intensive treatment. At this time it was noted that axillary hair was not present and that the spoon-shaped deformity of the nails was absent. The possibility of gastrointestinal bleeding as a cause for her refractory anemia was investigated. Repeated stool examinations were negative for occult blood. The basal metabolic rate was plus 10 per cent. In addition to desiccated thyroid, testosterone

* One hundred per cent hemoglobin is equivalent to 15.6 Gm. per 100 cc. for all determinations from this laboratory.
propionate was administered three times a week in a dose of 25 mg. by intramuscular injection. Ferrous sulfate, 0.75 Gm. per day, was given for the last two weeks of her hospital stay. A progressive improvement of red blood cell count from 3.9 to 4.7 million occurred and the hemoglobin concentration increased from 65 per cent to 75 per cent. The same therapy was continued after discharge from the hospital and examination of the blood on January 28, 1944 showed normal values.

Comment: This woman noted the onset of symptoms of hypometabolism following delivery. However, there was no abnormal bleeding or shock and the history of normal lactation and the reappearance of regular menstrual cycles indicates that if postpartum necrosis of the pituitary was the cause of her hypothyroidism, there was no panhypopituitarism. However, the laboratory data are consistent with primary thyroid myxedema. She presented a moderately severe normocytic, hypochromic anemia which did not respond to therapy with vitamins, liver extract and iron. The hemoglobin had risen slightly after five months of treatment with desiccated thyroid. The addition of testosterone propionate by intramuscular injection seemed to accelerate blood regeneration. The combination of iron, testosterone propionate and thyroid proved effective in restoring the blood to normal.

The changes in the blood in hyperthyroidism have received much study. The early clinicians believed that anemia was an important feature of the disease and in particular emphasized the association of hyperthyroidism with so-called "chloretosis." With improvement in methods for counting red blood cells and estimating hemoglobin and the systematic application of these methods to large groups of patients, it became apparent that some of the features of thyrotoxicosis which had suggested anemia had been misinterpreted. In the first comprehensive study of the blood in this disease by Kocher, the red blood cell count was generally normal and sometimes even above the levels then accepted as normal. Subsequent work by many authors has sustained this finding.

Changes which occur in the white cells have given rise to a great deal of study and speculation. After examining the blood of 106 patients with thyrotoxicosis, Kocher described in 1908 what he believed to be the pathognomonic blood picture in this disease. He emphasized the following features: a tendency toward leukopenia with a reduction mainly of polymorphonuclear neutrophils; both a relative and absolute increase in lymphocytes; a moderate increase in eosinophilic leukocytes. The changes in the white blood cells were claimed to be a reliable index of prognosis and the return to normal was believed to be a valuable indication of successful treatment.

Most subsequent investigators have been unable to confirm the significance of many of the features of the "Kocher blood picture." Leukopenia was found to be usually slight and frequently absent. In general most of the reports have confirmed the tendency toward lymphocytosis, but the diagnostic usefulness of this change was lost when many other causes of lymphocytosis were recognized.

Recently Bistrom has carefully reinvestigated this problem. He made a comparative study of the morphology of the peripheral blood and bone marrow in patients with nontoxic goiters, toxic goiters and in control subjects admitted to the hospital for minor surgical procedures. The peripheral blood and bone marrow of patients with nontoxic goiters did not differ significantly from the control group.
In the group with thyrotoxicosis there were 33 patients. A moderate reduction in red cells and hemoglobin occurred in 10. The white blood cell counts were low or normal and a relative granulocytopenia and lymphocytosis were found on smear. The lymphocytic infiltration of the thyroid gland which was examined after surgical extirpation was correlated with the degree of lymphocytosis. Only minor changes suggesting greater immaturity of the predominant cells were found in aspirations of sternal marrow.

Treatment with iodine was followed by a return toward a more normal differential white blood cell count, but the three groups responded to an operation with about the same changes in the blood. The author concluded that the changes occurring in thyrotoxicosis were slight and inconstant and could not be of aid in diagnosis or in estimating prognosis. Other recent reports agree with this thesis.33,34

Probably associated with the lymphocytosis which may occur in thyrotoxicosis is the hyperplasia of lymphoid organs which occasionally is present. A generalized enlargement of the lymph nodes and spleen and a persistence of the thymus have been described.

The changes which occur in lymphocytes and lymphoid tissues have received many interpretations. It has been attributed to a constitutional abnormality not directly due to the thyroid.35 A direct stimulating effect of the thyroid hormone on lymphoid tissue has been suggested.36 Menkin37 believed that the relative lymphocytosis in cases of exophthalmic goiter was due to sympathetic stimulation of lymphoid structures, particularly the spleen.

All authors do not agree that the lymphocytes are significantly increased. Hertz and Lerman,38 using supravital staining technics, concluded that the most marked and characteristic finding in the blood of patients with exophthalmic goiter was a relative and absolute monocytosis. The lymphocytes were found to be normal in absolute numbers. The discrepancy of their observations as compared with the findings of others was attributed to the greater accuracy of the staining technic that they used.

In recent years the influence of adrenal hormones on lymphocytes and lymphoid tissue has been emphasized (vide infra). It is now evident that certain adrenal steroids oxygenated on the eleventh carbon atom cause a decrease in the number of circulating lymphocytes and a decrease in size of the thymus and lymph nodes. Selye39 has described an apparent antagonism between the thyroid hormone and adrenal hormones in controlling the size of the thymus. No significant decrease in the weight of the thymus of rats occurred after thyroidectomy, suggesting that this hormone is not requisite for the persistence of the thymus. However the induction of stress in such rats by means of formaldehyde injections was followed by a severe and often fatal ‘alarm’ reaction. The involution of lymphatic organs and thymus was much more marked than in intact animals. It appears, therefore, that animals which have been thyroidectomized are greatly sensitized to the action of adrenal hormones.

From these observations it would seem reasonable to suppose that the lymphocytosis and persistence of thymus which has been described in thyrotoxicosis
might be the expression of a relative deficiency of adrenal steroids. Some evidence that such a deficiency exists has been obtained in this laboratory. Despite the severe stress imposed on patients with thyrotoxicosis, the excretion of "cortin" as measured by a chemical method is frequently markedly subnormal. This observation has been interpreted tentatively as indicative of increased breakdown of hormone, although more studies are necessary to establish this as a fact.

3. The Adrenal Cortex

Great advances have been made in the understanding of the physiology and chemistry of the adrenal cortex. The adrenal secretes several substances which have unrelated and even antagonistic actions. One of the most interesting phases of adrenal physiology has been the demonstration of the influence of the adrenal on lymphocytes and the release of antibodies.

In all laboratory animals adrenalectomy results in death after a short period if replacement of salt and/or hormones is not provided. Adrenalectomized rats show an increase in polymorphonuclear leukocytes and lymphocytes about twenty-four hours before death. An increase in the weight of the thymus and systemic lymph nodes has been reported in adrenalectomized rats maintained in good condition by means of the addition of sodium chloride to their drinking water. In cats surviving a relatively long time after operation there is a decrease in polymorphonuclear cells and an increase in lymphocytes. Increases which have been reported in the red blood cell count and hemoglobin concentration are indications of the disturbed electrolyte and fluid metabolism which causes marked hemoconcentration. If adrenalectomized cats and dogs are maintained in fair general condition by several different methods of treatment, the peripheral blood is essentially normal.

Adrenal insufficiency in human beings produces changes similar to those in experimental animals. During an adrenal crisis there is usually a slight increase in red blood cell count and hemoglobin and a relative lymphocytosis. Restoration of normal blood volume by the use of desoxycorticosterone and saline solution frequently reveals a mild underlying anemia. A relative lymphocytosis may persist even after treatment.

Polycythemia has been a frequent, but not a constant, finding in Cushing's syndrome. Approximately one-half of the well authenticated cases have shown an elevation of the red blood cell count. Gunther has collected data on 7 patients with hyperadrenalcorticism with red counts in excess of six million. The abnormality is usually mild and associated mainly with rapid progress of the disease. In itself it does not seem to produce the complications which are observed in polycythemia vera. Many patients with Cushing's syndrome are suspected of having polycythemia in whom subsequent blood counts fail to confirm the clinical impression. A plethoric appearance of the cheeks is common and is due to atrophy and stretching of the skin which permits the transmission of the color of the underlying venous plexuses. Combined with the marked deposition of fat about the face and neck, the red cheeks constitute the pathognomonic facies described by Cushing.
White and Dougherty\textsuperscript{2-5} have studied the effects of adrenotrophic hormone and adrenal cortical steroids on red cells and hemoglobin. A single injection of either substance will cause a transitory increase in the red blood cell count, followed by a decrease to lower than pretreatment levels. The continued injection of adrenotrophic hormone resulted in a significant increase in red blood cell count and hemoglobin. The authors concluded that "it is possible that repeated hormone injection eventually leads to a stimulated production of red cells in an effort to compensate for the diminution of erythrocyte count produced by a single dose of hormone."

In a number of experimental conditions the size of the thymus varies inversely with the activity of the adrenal cortex. This has been most clearly demonstrated in the response of an animal to stress. Selye\textsuperscript{39} has introduced the concept of the 'alarm' reaction as a phase in the general adaptation of the body to harmful stimuli. An increase in the size and activity of the adrenal cortex is a fundamental element in this process. "One of the most striking and constant changes is the involution of the lymphatic organs. The loss of weight is most marked and rapid in the thymus... Here the characteristic cells of the parenchyma, the thymocytes, actually disintegrate and twenty-four hours after the onset of a severe alarm reaction only the debris of their chromatin is left lying partly free in the reticulum, partly in phagocytes which are engaged in removing it... The lymph nodes also show signs of involution but without any noticeable hyperplasia of the reticulum. The involution in them usually begins in the germ centers which may disappear almost completely." That the involution of the thymus is secondary to the adrenal cortical activity seems probable because no change occurs in adrenalectomized animals. The injection of certain adrenal steroids into intact animals or adrenalectomized animals, and the injection of adrenocorticotropic hormone into intact or hypophysectomized, but not adrenalectomized, animals, will reproduce similar changes in lymphoid tissue and thymus.\textsuperscript{52,53}

Dougherty and White\textsuperscript{2,54} have confirmed and extended these observations by reporting a remarkable decrease in the circulating lymphocytes after the injection of adrenocorticotropic hormone or cortical steroids into the mouse, rat, rabbit and dog. This phenomenon has been termed "lympholysis." Lympholysis in the mouse is particularly striking. Within an hour after the injection of adrenocorticotropic hormone there occurs a definite fall in the circulating lymphocytes which reaches a maximum in six to nine hours. Recovery to normal takes place within twenty-four hours. Probably considerable variation in sensitivity of lymphocytes to lysis exists because in our laboratory\textsuperscript{48} rats of the Sprague-Dawley strain have shown little lymphopenia after injection of aqueous adrenal cortical extract.

Minor changes in chemical structure have been shown to modify the action of various adrenal steroids on lymphocytes. 11-Desoxycorticosterone has been demonstrated to be without effect.\textsuperscript{2} On the other hand Compound E (11-dehydro-17 hydroxy corticosterone) and other active steroids with an oxygen on the eleventh carbon atom possess this property.

The destruction of lymphoid tissue is believed to be the source of the increase in
serum beta and gamma globulins which follows injections of active hormones of the adrenal cortex. Direct analysis of lysed lymphoid tissue washed free of all blood serum has demonstrated proteins which are indistinguishable from serum beta and gamma globulins. In immunized animals the lymphocyte contains antibodies which are liberated into the bloodstream by the process of lympholysis. Dougherty and White believed that the above mechanism is the explanation for the anamnestic reaction which occurs in acute infection.

The effect of adrenal steroids on the lymphocytes of human beings has not been reported in any detail. Dougherty and White reported observations on several patients with lymphocytic leukemia and also in control subjects. A suggestive drop in the lymphocytes was observed in some of the patients. Forsham et al observed the effects induced by synthetic 11-dehydrocorticosterone acetate on the lymphocytes. In thirteen experiments on patients with Addison's disease 20-60 mg of the compound were given as a daily dose. No significant decrease in the lymphocytes was found. It was noted, however, that there was an increase in urinary uric acid excretion in comparison to creatinine. These data seem to suggest that a tissue rich in nucleoproteins was being broken down and it is therefore possible that there was significant "lympholysis" which was not manifest in the circulating blood. Perera et al have used the same compound and found an inconsistent decrease in the lymphocytes following administration to human beings. Recently Thorn's collaborators have presented interesting observations on the effect of adrenocorticotropic hormone on the blood picture of man. In normal subjects four hours after the administration of 25 mg of adrenocorticotropic hormone by intramuscular injection there was a 90 per cent increase in the absolute number of polymorphonuclear neutrophils, a 40 per cent decrease in lymphocytes and a 78 per cent decrease in eosinophils. Similar changes did not occur in patients with Addison's disease. However the administration of 20 mg of 17-hydroxycorticosterone to such patients caused an increase of 129 per cent in the absolute number of polymorphonuclear neutrophils, a decrease of 53 per cent in the lymphocytes and a decrease of 76 per cent in the eosinophils.

In our experience little change in the relative or absolute number of lymphocytes follows the administration of adrenal cortical extract in doses of from 10 to 50 cc to patients with adrenal insufficiency. Figure 2 shows the results which we have obtained on treating a patient with hypopituitarism for nine days. Both adrenal cortical extract (Upjohn) and lipoadrenal cortical extract (Upjohn) were given in doses which are in excess of those required to maintain patients with Addison's disease.

Because of the apparent failure of moderate doses of adrenal cortical extract to alter the blood picture, larger doses were administered. A patient with hypopituitarism secondary to a chromophobe adenoma was selected. Immunization against heat-killed typhoid bacilli was achieved by three injections of 0.1 cc of a standard vaccine. It is interesting that despite the small size of the immunizing
dose the patient noted marked local and systemic symptoms following each injection and that there was a satisfactory rise in antibody titer. Forty cc. of adrenal cortical extract was given in two equal doses by intramuscular injection. Figure 3 shows the changes which occurred in the lymphocyte count, the anti-typhoid agglutination titer and the titer of anti-B isoagglutinin (the patient was blood group A). A brisk fall in the number of lymphocytes was noted after six hours with a return to normal after twenty-four hours. A rise in the antityphoid agglutination titer was noted at six hours; there was a decline by twenty-four hours and a return to the former titer by six days. No significant change occurred in the anti-B isoagglutinin titer.

The experiment was repeated after the injection of 50 mg. of testosterone propionate daily for three days and 25 mg. for four days. Following this treatment the antityphoid titer seemed to decline. The changes which followed injection of adrenal cortical extract were similar to those observed in this patient prior to testosterone therapy.

We have concluded from these limited observations that the lowering of the lymphocyte counts with a rise in immune bodies, which has been observed in laboratory animals, can be reproduced in human beings, but that relatively large doses of adrenal cortical extract are required.

**EFFECT OF ADRENAL STEROIDS ON RELATIVE DIFFERENTIAL COUNT**

![Graph showing changes in differential white blood cell counts in a patient with Simmonds' disease after the administration of adrenal cortical extracts](image-url)
PATIENT: G.M.

DX
HYPOPITUITARISM

ETIOLOGY:
CHROMOPHOSE ADENOMA

Other mechanisms of regulation of lymphocytes than pituitary-adrenal control must exist. This is evident from the study of adrenalectomized rats maintained on salt. Crafts\(^7\) found that such animals maintained a normal white count and differential count. De La Balze, Reifenstein and Albright\(^9\) reviewed their extensive experience with adrenal disorders in man and could not establish a significant increase in the absolute number of lymphocytes in patients with Addison’s disease, although the relative number of lymphocytes was increased.

**EFFECT OF ADRENAL CORTICAL EXTRACT ON LYMPHOCYTES AND ANTIBODIES**

![Graph showing the effect of adrenal cortical extract on lymphocytes and antibodies.](image)

**Fig. 3. Note the lymphopenia and increase in the titer of antityphoid agglutination following the administration of adrenal cortical extract.**

4. **The Pituitary Gland**

Discussion of the possible mechanisms by which this gland alters hematopoiesis has been reserved until last. It is well known that the anterior lobe of the pituitary gland controls the activity of the other endocrine glands and it could thereby aid in the regulation of formed elements in the blood. It is, therefore, evident that the anemia which is often observed following destruction of the anterior pituitary is a complicated phenomenon.

An anemia following hypophysectomy was first noted by Aschner\(^8\) in dogs in 1912. Later it was determined that rabbits\(^8\) and rats\(^8\) respond to the operation in
a similar manner. Destruction of the pituitary in man frequently results in a moderate anemia.

The decrease in the red blood cell count and hemoglobin which occurs in the hypophysectomized rat, has received the most intensive study. In 1935 Stewart, Greep and Meyer\textsuperscript{64} noted that hypophysectomized rats were anemic and that there was a decrease in the number of reticulocytes. A rise in reticulocytes occurred in normal rats exposed to reduced oxygen tension, but not in hypophysectomized ones. Increases in the red blood cell count and hemoglobin of the hypophysectomized rats occurred only if the stimulus of low oxygen tension was applied soon after operation. The reticulocyte response following substitution therapy parenterally has proved an unreliable criterion because reticulocytosis has been produced by many hormonal and nonhormonal agents.\textsuperscript{65} In general, reticulocytosis has been unaccompanied by improvement in red blood cell count and hemoglobin concentration. The conclusion was reached that the alterations in the blood following hypophysectomy were due to general disturbances in metabolism rather than the absence of a specific hematopoietic hormone.

On the other hand, the existence of a specific pituitary hormone which stimulates blood formation has been postulated by Moehlig and Bates.\textsuperscript{66} The polycythemia of Cushing's disease was attributed to an excessive production of this factor.

On the basis of the response of hypophysectomized rats to oral administration of preparations of anterior pituitary, Flaks, Himmel and Zlotnik\textsuperscript{67} postulated the existence of an erythrogenic hormone. They claimed that the anemia of hypophysectomized rats was repaired and that polycythemia was produced by their hormone preparation in intact animals. It is difficult to accept this claim because of the impotency of known pituitary hormones when administered orally.

Beneficial effects on the anemia of hypophysectomized rats have followed treatment with several hormones, pituitary as well as non-pituitary. Vollmer and Gordon\textsuperscript{68} and Vollmer, Gordon and Charipper\textsuperscript{69} found that testosterone propionate increased the red blood cell count of hypophysectomized male and female rats. Estradiol, on the other hand, seemed to intensify the anemia. Pregnant mare's serum raised the red blood cell count of hypophysectomized male rats, but lowered the counts in hypophysectomized female rats. Thyroxine plus testosterone was moderately effective. Prolactin seemed to be inactive. Desoxycorticosterone produced no definite effect on the bone marrow.

Various types of replacement therapy have been investigated by Crafts.\textsuperscript{70,71} In hypophysectomized female rats the anemia was found to be microcytic and hypochromic and accompanied by hypoplastic changes in the bone marrow. Iron or iron plus copper delayed slightly the onset of anemia. Injection of 0.01 mg. of thyroxine daily maintained a normal erythrocyte count, but did not prevent a decrease in hemoglobin concentration. Histologic examination revealed greater cellularity of the bone marrow and decreased infiltration by fat cells. This was interpreted as an indication of increased activity. The combination of thyroxine, iron and copper maintained a normal red cell count and seemed to increase the amount of hemoglobin. Hypophysectomized adult male rats developed a severe microcytic, hypochromic anemia with hypoplastic changes in the bone marrow. Testosterone
therapy prevented the decrease in the red blood cell count and restored the bone marrow to normal cellularity. Microcytosis and hypochromia were only partially corrected. Because the anemia following castration was much less marked than that following hypophysectomy, the author believed that the anemia in the latter condition was not a manifestation of decreased androgens, although androgens proved partially effective in preventing the experimentally induced anemia.

An anemia following destruction of the anterior lobe of the pituitary in man has been long recognized as a significant feature of the clinical syndrome called Simmonds' disease. Silver reviewed the literature in 1933 and observed that anemia is a constant finding. The hemoglobin averages 50 per cent, with a color index which is usually less than one. Leukopenia is common and an eosinophilia reaching 22 per cent may occur.

Snapper, Groen, Hunter and Witts described 6 cases which they believed presented evidences of pituitary or gonadal deficiency plus an anemia. Case 2 of their series was a woman with pituitary necrosis following hemorrhage and shock at the time of delivery. A macrocytic anemia of 3.2 million red blood cells was present. Case 3 was a patient with hypopituitarism secondary to a chromophobe adenoma. There was a moderately severe macrocytic anemia, accompanied by gastric achylia and evidence of combined system disease. In the other cases hypogonadism was probably primary. The importance of achlorhydria and defective absorption was stressed as the immediate cause of anemia leading to deficiency of either iron or the hemopoietic principle of liver extract. Witts later described two additional cases which he considered to be examples of hypopituitarism and which were associated with a macrocytic anemia responding to liver. He concluded: "The association of pernicious anemia with hyperthyroidism, with pregnancy and with pituitary disease, suggests that there is a hormonal element or mechanism which can lead to the degeneration of the cells which secrete intrinsic factor....We may consider the association of pernicious anemia with hypopituitarism as another example of the precocious senile changes to which the patient with pituitary disease is liable."

The effect of testosterone propionate on the anemia of hypopituitarism has been the subject of a recent report. Two cases of hypopituitarism with anemia are described that responded to the combined administration of testosterone and liver. In one patient at least it is evident that no response occurred with liver extract alone. It was suggested that testosterone enabled the bone marrow to utilize the hematinic principle, which it previously had been unable to do.

Escamilla et al. have reviewed 101 cases of Simmonds' disease, verified by post-mortem examination. Among this group the hemoglobin ranged from 102 per cent to 40 per cent, with an average of 65 per cent. Red blood cell counts ranged from 5.6 to 2.0, averaging 3.7 million. Eosinophilia was commonly observed, with 6.3 per cent as the average figure.

Sheehan has emphasized the importance of serious hemorrhage and shock at the time of delivery as an etiologic factor producing necrosis of the anterior lobe of the pituitary. The lesion is a thrombotic infarction of variable extent, which later may reduce the anterior lobe to a nubbin of fibrous tissue. This group of cases is
particularly valuable for an understanding of the anemia in Simmonds’ disease because the time of onset can be fixed with some certainty and it occurs in young adult females who may live with hypopituitarism for many years. Quite frequently the blood deficit of the precipitating hemorrhage is incompletely restored. However, for the first five years it is not uncommon for these patients to maintain relatively normal red blood cell counts, but with a rather low hemoglobin concentration. During the second five year period there is a definite tendency for the red blood cell count to decrease to between 3 and 4 million, with some increase in the color index. The blood frequently remains at this level indefinitely. Occasionally there is a further decrease in the red blood cell count to a level of from 2 to 3 million with a color index of 0.95 to 1.25. These cases showing a severe anemia and a tendency toward macrocytosis seem to occur in patients with more profound evidences of deficient thyroid function and may be indistinguishable clinically from thyroid myxedema. Leukocytes usually number between 4 to 6 thousand, although leukopenia is common. The smear characteristically shows a relative lymphocytosis with a moderate eosinophilia in about two thirds of the cases.

The results of therapy on the blood in hypopituitarism have received scant attention in the literature. The use of anterior pituitary hormones is the rational approach to the problem, but has not proved successful. Extracts of the pituitary of high potency and purity have not been available. Because of their protein nature, pituitary extracts rapidly lose their effectiveness because of the development of antihormones. Also allergic manifestations, such as urticaria and local pain are common. Because of these disadvantages it has been more practical to use the hormones of the atrophic “end-organ” glands. The combination of desiccated thyroid, desoxycorticosterone acetate and testosterone has provided a reasonably satisfactory method of treatment.

In this clinic the above therapy has been used with various modifications in the treatment of Simmonds’ disease. Marked relief from many of the disabling symptoms of this disease has been obtained, but improvement in the blood findings has been inconstant. The following case (case 2) is reported in detail because this patient had been under observation for a period of nine years and during this period adequate trial with many therapeutic agents failed to correct an anemia. Case 3 is reported to show that improvement in the blood may follow hormone treatment without the addition of liver or iron. Hematologic data on 22 patients with hypopituitarism observed during the past six years are presented in table 1.

Pituitary fibrosis of unknown etiology associated with a moderately severe normocytic and normochromic anemia which failed to respond to liver, iron and hormone therapy.

Case 2. F. S. (Details of this case have been reported elsewhere.): A white housewife of American parentage, aged 38, entered the Boston City Hospital October 18, 1934 complaining of weakness and vomiting. Following an attack of influenza two years prior to entry, she had been told that she had anemia and low blood pressure. Recovery from this illness was protracted and incomplete and she continued to suffer from asthemia, fatigability, drowsiness and anorexia. A local physician prescribed ground raw liver which she took for a period of about six months without improvement in any of her complaints. She sought hospital care after two weeks of nausea and vomiting. Her past history revealed that she had given birth to a normal child about ten years previous to entry. A hysterectomy was performed some time after delivery for pelvic peritonitis. Unfortunately details of the delivery and operation are not available.
On physical examination she appeared to be an underdeveloped and poorly nourished woman. The skin was pale, smooth and had a yellowish, waxy texture. The tongue had normal papillae. The blood pressure was 92 mm. of Hg systolic and 68 diastolic. A mass interpreted as the liver edge was felt on deep inspiration at the right costal margin. The spleen could not be felt and there was no lymphadenopathy. The only abnormal neurologic finding was a questionably positive Babinski sign bilaterally.

Laboratory examinations showed the following: The concentration of hemoglobin was 63 per cent and there were 3,35 million red blood cells. The white blood cell count was 4,800 with 66 per cent polymorphonuclear neutrophils and 33 per cent lymphocytes. The hematocrit was 31.2 per cent. Urinalysis was not abnormal. The Kahn test was at first reported as doubtful, but subsequent tests were nega-
ENCRINOPATHIES AND BLOOD

No occult blood was present in the stools. Free acid was not present in the gastric juice even after the administration of histamine.

The icteric index was 6 units. The serum cholesterol was 137 mg per

TABLE I, PART II. PITUITARY FIBROSIS OF UNKNOWN CAUSE

<table>
<thead>
<tr>
<th>Case</th>
<th>Duration of Disease, Years</th>
<th>Date</th>
<th>% Hb Absorbed</th>
<th>% Erythrocytes</th>
<th>M.C.V. in um.</th>
<th>M.C.H. in micrograms</th>
<th>M.C.H. Conc. %</th>
<th>Leukocytes X19/mm</th>
<th>Total, Granulocytes</th>
<th>Eosinophils, %</th>
<th>Lymphocytes, %</th>
<th>Monocytes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. S.</td>
<td>1</td>
<td>1/22/35</td>
<td>70</td>
<td>3.9</td>
<td>82</td>
<td>8</td>
<td>34</td>
<td>7.8</td>
<td>73</td>
<td>60.5</td>
<td>3.5</td>
<td>30.5</td>
</tr>
<tr>
<td></td>
<td>9/23/36</td>
<td>77</td>
<td>3.6</td>
<td>89</td>
<td>34</td>
<td>37</td>
<td>5.4</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>1/24/36</td>
<td>68</td>
<td>3.6</td>
<td>86</td>
<td>30</td>
<td>35</td>
<td>5.4</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
</tr>
<tr>
<td>H. O.</td>
<td>75</td>
<td>7/19/46</td>
<td>66</td>
<td>2.9</td>
<td>0.8</td>
<td>111</td>
<td>33</td>
<td>33</td>
<td>4.2</td>
<td>55</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>DOCA 2 mg intramuscularly daily. Testosterone propionate 25 mg intramuscularly daily for 11 days, thereafter every other day. Reticulocytes increased to a maximum of 5.6% on 7/18/46. 8/14/46</td>
<td>68</td>
<td>3.1</td>
<td>2.0</td>
<td>98</td>
<td>34</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
<td>5.5</td>
<td>35</td>
</tr>
<tr>
<td>Three 75 mg pellets of testosterone and one 75 mg pellet of DOCA implanted subcutaneously.</td>
<td>3/6/47</td>
<td>78</td>
<td>3.7</td>
<td>95</td>
<td>33</td>
<td>35</td>
<td>5.2</td>
<td>35</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. B.</td>
<td>39</td>
<td>7/31/45</td>
<td>70</td>
<td>3.0</td>
<td>1.0</td>
<td>33</td>
<td>35</td>
<td>4.2</td>
<td>55</td>
<td>9</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Desiccated thyroid, 31 mg daily. Implantation of three 75 mg pellets of testosterone and one 75 mg pellet of DOCA</td>
<td>5/15/47</td>
<td>69</td>
<td>3.5</td>
<td>92</td>
<td>31</td>
<td>33</td>
<td>8.1</td>
<td>60</td>
<td>4</td>
<td>33</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>E. J.</td>
<td>68</td>
<td>7/31/46</td>
<td>68</td>
<td>3.3</td>
<td>1.0</td>
<td>33</td>
<td>4.3</td>
<td>5.6</td>
<td>90</td>
<td>1.0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>S. K.</td>
<td>69</td>
<td>1/25/46</td>
<td>77</td>
<td>3.0</td>
<td>1.0</td>
<td>33</td>
<td>4.3</td>
<td>6.1</td>
<td>69</td>
<td>0</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Desiccated thyroid by mouth and DOCA and testosterone propionate by intramuscular injection.</td>
<td>3/24/47</td>
<td>92</td>
<td>3.4</td>
<td>93</td>
<td>27</td>
<td>30</td>
<td>5.4</td>
<td>91</td>
<td>27</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


* Determinations carried out by ward laboratories.

† Determinations carried out by Hematology Laboratories, Mass. Memorial Hospital. Dr. Chester Keefer has kindly consented to the inclusion of these data.

100 cc. A glucose tolerance test was within normal limits. The basal metabolic rate was—16 per cent. X-ray examination of the chest, upper and lower gastrointestinal tract and sella turcica were within normal limits.
Table 1, Part III. Hyopituitarism Secondary to Neoplasms

<table>
<thead>
<tr>
<th>Case</th>
<th>Duration of Disease, Year</th>
<th>Age</th>
<th>Date</th>
<th>% Hb</th>
<th>% Hb 100 g</th>
<th>Erythrocytes X 10^6/mm</th>
<th>% Reticulocytes</th>
<th>M.C.</th>
<th>M.C.H.</th>
<th>M.C.H. Conc.</th>
<th>Total Leukocytes</th>
<th>Eosinophils</th>
<th>% Lymphocytes</th>
<th>% Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. B.</td>
<td>0.5</td>
<td>58</td>
<td>6/12/38</td>
<td>75*</td>
<td>3.5*</td>
<td>88</td>
<td>5.5</td>
<td>65*</td>
<td>0*</td>
<td>32*</td>
<td>34.5</td>
<td>3.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3/19/45</td>
<td></td>
<td>3.8</td>
<td>88</td>
<td>5.5</td>
<td>65*</td>
<td>0*</td>
<td>32*</td>
<td>34.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. R.</td>
<td>1</td>
<td>34</td>
<td>75*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G. M.</td>
<td>2</td>
<td>42</td>
<td>1/21/44</td>
<td>59*</td>
<td>3.6</td>
<td>88</td>
<td>5.5</td>
<td>68.5</td>
<td>3</td>
<td>19.5</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4/18/44</td>
<td></td>
<td>88</td>
<td>4.4</td>
<td>89</td>
<td>31</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. N.</td>
<td>5</td>
<td>38</td>
<td>3/17/44</td>
<td>69*</td>
<td>3.2</td>
<td>88</td>
<td>5.5</td>
<td>89</td>
<td>37</td>
<td>4.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3/31/42</td>
<td></td>
<td>85</td>
<td>4.1</td>
<td>89</td>
<td>32</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. S.</td>
<td>6</td>
<td>46</td>
<td>3/19/43</td>
<td>95*</td>
<td>4.8</td>
<td>91</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


* Determinations carried out by ward laboratories.
‡ Diagnosis established at operation.

A high protein diet with vitamin B complex was given. In addition she received iron, liver and desiccated thyroid separately and in combination for intervals of several weeks without a reticulocyte response.
or improvement in her anemia (see figure 4). Removal of some badly infected teeth seemed to improve her general condition. The patient was discharged from the hospital in April 1935.

She was seen by Dr. Juda Groen in September 1936 at the Boston City Hospital at which time she reported slight improvement in appetite and strength, although she had failed to take desiccated thyroid regularly. Signs of myxedema were evident and the absence of axillary and pubic hair was recorded. The blood findings were much the same as before.

At this time the patient failed to return for further treatment and continued to live a restricted life at home. Fatigue and somnolence became increasingly incapacitating until by 1941 she was almost bedridden. Anorexia became almost total and in November 1941 she had an episode of confusion and disorientation and because of this she was sent to the Massachusetts Memorial Hospital. She was found to be acutely dehydrated and in poor condition on admission. Numerous petechiae were present over the right arm. The blood pressure was recorded as 108 mm. of Hg systolic and 78 diastolic. After adequate repair of her dehydration it was evident that her anemia was practically identical to that observed seven years previously. The red blood cell count was 3.78 million and the hemoglobin concentration was 65 per cent. The white blood cell count on admission was 6,400, with 43 per cent lymphocytes present. The platelets numbered 171,000. Aspiration of bone marrow was performed and the following cell distribution was found:

- Polymorphonuclear leukocytes: 3 per cent
- Band forms: 12 per cent
- Myelocytes: 30 per cent
- Myeloblasts: 6 per cent
- Nucleated red blood cells: 16 per cent
- Erythroblasts: 8 per cent
- Stem cells: 3 per cent
- Lymphocytes: 9 per cent
- Monocytes: 3 per cent

**Figure 4. Changes in Red Blood Cell Count and Hemoglobin Concentration in Case 2.**

Data have been plotted as averages for ten day periods. Note the apparent absence of response to many different forms of treatment.
No follicle stimulating hormone was found in the urine upon testing for 10 rat units per twenty-four hours. The patient excreted 0.2 mg. of 17-ketosteroids per twenty-four hours. An insulin tolerance test, using 0.05 units of insulin per kilogram of body weight, intravenously, demonstrated moderate hypoglycemic unresponsiveness. A "water" test was positive, but a salt deprivation test was negative.

The basal metabolic rate was -13 per cent.

On January 9, treatment was begun with desiccated thyroid, 32 mg. daily, and this was progressively increased to 160 mg. daily. Two pellets of desoxycorticosterone acetate, 155 mg. each, and two pellets of testosterone, 150 mg. each, were implanted subcutaneously. The patient was much improved by this treatment as far as her general condition was concerned, but no improvement in her anemia occurred, and she was discharged from the hospital in May 1941.

In November 1941 she entered the Boston City Hospital for replenishment of her therapy. She was given ferrous sulfate by mouth and desoxycorticosterone acetate and testosterone propionate by intramuscular injection. Therapy with desiccated thyroid was continued. Unfortunately, after a month in the hospital she developed virus pneumonia and died after a brief stormy course.

At postmortem examination the pituitary was very small and fibrotic. Microscopic study showed only a few acidophilic, basophilic and chromophobe cells scattered in dense scar tissue. The thyroid gland was one half normal size and the acini were very atrophic. Extensive adrenal atrophy and fibrosis was found. Microscopic examination of the bone marrow was interpreted as showing less than normal erythropoiesis. There was no evidence of a defect in maturation. Cells of the granulocytic series appeared to be normal except for a questionable increase in the eosinophilic series. Megacaryocytes were of the usual number.

Comment: The etiology of the pituitary fibrosis in this case remains obscure. The onset of symptoms following influenza suggests that this may have been the etiologic factor. The anemia in this patient was normochromic and normocytic and remarkably constant in severity. It was unaffected by raw liver by mouth, liver by injection, iron in several forms and by hormonal replacement treatment.

Postpartum necrosis of the pituitary associated with a moderately severe normocytic and normochromic anemia with improvement after hormone therapy.

Case 1. H. O. N. (Details of this case have been reported elsewhere.79, 80): A housewife, aged 41, was admitted to the Boston City Hospital in May 1941 with the signs and symptoms of myxedema. Twelve years prior to entry she had had a severe hemorrhage due to a placenta previa. Following this episode, menstruation never recurred and symptoms of hypometabolism were noted. She was treated by several local physicians for hypothyroidism and anemia but the details are not available. She took desiccated thyroid only at irregular intervals and at the time of entry the classic features of myxedema were present, with marked mental and physical retardation. However, her nutritional status was good. Pubic and axillary hair was absent. A hypotension of 90 mm. Hg systolic and 50 diastolic was present. The laboratory findings confirmed the diagnosis of Simmonds' disease. The basal metabolic rate was -45 per cent. Plasma protein bound iodine was less than 1 microgram per cent. Marked sensitivity and hypoglycemic unresponsiveness was demonstrated by an insulin tolerance test (0.04 units of insulin intravenously per kilogram of body weight). No follicle stimulating hormone was found in her urine when tested for 10 rat units per twenty-four hours. Free acid was not present in the gastric juice even after the administration of histamine.

Hematologic data: The red blood cell count was 3.45 million, the hemoglobin was 71 per cent, and the hematocrit was 30 per cent. Calculation of the blood indices showed a mean corpuscular volume of 87 cu. microns, a mean corpuscular hemoglobin concentration of 37 per cent, and a mean corpuscular hemoglobin of 32 micro-micrograms. Two-tenths of one per cent of all erythrocytes were reticulocytes. The white blood cell count was 2,100. The differential count was as follows: polymorphonuclear leukocytes 51 per cent, band forms 14 per cent, eosinophils 2 per cent, basophils 4.5 per cent, lymphocytes 19 per cent, young lymphocytes 19 per cent, monocytes 7.5 per cent.

The patient received several pituitary hormones without clinical or hematologic improvement. There was a decline of the red blood cell count and hemoglobin concentrations, as shown in figure 5. Replacement therapy with nonpituitary hormones was begun on December 29, 1941, with the adminis-
treatment of methyl testosterone, 30 mg. a day by mouth, desiccated thyroid 30 mg. a day by mouth and desoxycorticosterone acetate 2 mg. a day by intramuscular injection. At a later date pellets of testosterone and desoxycorticosterone acetate were implanted subcutaneously. Details of therapy are indicated in figure 5.

There was a remarkable improvement in the patient's general condition on this therapy. Prior to treatment, the basal metabolic rate was -53 per cent and it rose to normal after treatment for 1 month. The myxedematous changes disappeared and there was a progressive improvement in her energy and strength. The red blood cell count and hemoglobin concentration on January 17, 1942 showed even lower values than previously. The mean corpuscular volume on this occasion was 111 cu. microns. One month later the red blood cell count had increased to 4.05 million, with a decrease in the mean corpuscular volume to normal size, 85 cu. microns, and 4.5 per cent of the erythrocytes were reticulated. On March 20, 1942 the red blood cell count and hemoglobin had returned to normal levels. On follow-up examination the improvement in the blood picture was largely sustained, despite the fact that additional pellets of testosterone could not be procured for replacement.

The patient re-entered the Boston City Hospital in January 1944 with pneumonia and, in spite of treatment with sulfathiazole, adrenal cortical extract, desoxycorticosterone and testosterone propionate, she died four days after admission.

At postmortem examination the pituitary was found to be very small and appeared on microscopic examination to be composed largely of fibrous tissue, with rare nests of basophilic cells. Marked atrophy of the thyroid was present and no tissue recognizable as adrenals was found. On microscopic examination the vertebral marrow appeared hypoactive. Red blood cell and white blood cell precursors were present and showed no evidence of a defect in maturation.
Comment: The onset of symptoms in this woman following a severe hemorrhage complicating a placenta previa strongly suggests that the atrophy and fibrosis of the pituitary observed at autopsy was due to postpartum necrosis. A moderately severe normocytic anemia was present on admission and became more severe during the period of observation. The macrocytosis observed in January 1942 may have been related to an increase in the severity of her thyroid deficiency as manifested by a basal metabolic rate of $-53$ per cent in December 1941. On combined hormonal treatment the red blood cell count and hemoglobin concentration returned almost to normal in the course of about three months. It seems likely that testosterone propionate was the agent causing the improvement in the blood picture.

Summary and Conclusions

Evidence has been presented that the gonads, thyroid, adrenal cortex and pituitary glands have a definite influence on blood formation. The normal sex difference in erythrocyte levels in animals, and probably in man, can be obliterated by castration and restored by appropriate replacement therapy. Hypothyroidism results in a moderately severe anemia in animals. In the uncomplicated form, the anemia is slightly macrocytic and associated with a hypoplastic bone marrow. In clinical experience the anemia may be complicated by the secondary effects of achylia gastrica leading either to iron deficiency or to a deficiency in the anti-pernicious anemia factor. Hyperthyroidism causes some alterations in the white blood cells, but has little effect on the red blood cell series. Hyperactive states of the adrenal cortex may be associated with a mild polycythemia. Adrenal steroids also have a marked lymphocytic effect, causing the release of beta and gamma globulins from lymphoid tissue. A mechanism involving the anterior pituitary and adrenal seems to exist, controlling the release of antibodies under certain conditions. It is suggested that other mechanisms also exist which control the number of circulating lymphocytes.

Deficiency of the anterior pituitary secretions results in anemia in animals and man. The anemia in animals is usually microcytic and hypochromic and may respond to several types of replacement therapy. In man anemia develops slowly and is rarely severe. Moderate reductions in the red blood cell count occur and the color index varies. There is hypoplasia of the bone marrow. The anemia in man does not respond uniformly well to the therapy now available, but improvement often occurs with the replacement of "end-organ" hormones.

The preponderance of evidence indicates that the regulation of blood formation is not primarily under hormonal control. The effects noted in various glandular disorders are due to alterations in metabolism produced in the bone marrow as well as all other body tissues.

References

ENDOCRINOPATHIES AND BLOOD


Castradale, D., Dierhaum, O., Helwig, E. G., and MacBryde, C. M.: Comparative studies of the effects of estradiol and stilbestrol upon the blood, liver and bone marrow. Endocrinol. 29: 363, 1941.


DAUGHDAY, WILLIAMS AND DALAND 1365

37Albright, F.: Cushing’s syndrome, its pathological physiology, its relationship to the adrenogenital syndrome and its connection with the problem of the action of the body to injurious agents ("alarm reaction" of Selze). Harvey Lectures 38, page 123, 1942-43.
ENDOCRINOPATHIES AND BLOOD


76——: Simmonds' disease due to post-partum necrosis of the anterior pituitary. Quart. J. Med. 8: 777, 1939.


THE EFFECT OF ENDOCRINOPATHIES ON THE BLOOD

WILLIAM H. DAUGHADAY, ROBERT H. WILLIAMS and GENEVA A. DALAND