THE INFLUENCE OF THYROIDECTOMY, GONADECTOMY, SUPRARENALECTOMY, AND SPLENECTOMY ON THE THYMUS GLAND OF RABBITS.

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Plates 17 and 18.

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Investigations of the ductless glands during the past 10 years which have required removal of the thyroid, parathyroids, thymus, spleen, suprarenals, and gonads alone, or in several combinations, have afforded us the opportunity of studying some of the effects of such insufficiencies on the remaining tissues of rabbits. The material accumulated under our immediate direction now seems sufficiently extensive to permit of certain statistical studies. In this paper we will report only the data relative to the effect of thyroidectomy, splenectomy, suprarenalectomy, gonadectomy, and combinations of these gland removals on the thymus gland as measured by its involution, persistence, or regeneration.[1] Lymphoid tissues other than the thymus are also affected and will be referred to briefly. The data of 373 protocols have been included in this study. In sorting the material, protocols have been discarded for one or another of the following reasons: (1) animals with chronic infections (except snuffles), (2) animals which survived a given operation less than 2 weeks, (3) animals for which the notes of the gross or microscopic examination of the necropsy tissues were incomplete, and (4) animals on which the operation or necropsy was performed by individuals other than the authors. Of more importance than all of these factors of elimination in determining the value of such records, of

[1] All operations were performed under ether anesthesia.

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course, are the skill and experience of the operators and the personal daily after care of the animals. In all the experiments on which these studies are based two of the authors took part in the operation and subsequent necropsy, thus insuring uniformity of methods and records. It should be emphasized that in so simple a matter as surgical technique, training and experience are essential and these prerequisites cannot be acquired any more easily for an animal than for man. The literature of experimental pathology and physiology is glutted with reports based on insufficient numbers of experiments, on inadequate technical skill and facilities for the operation in question, and on a lack of experience and uniformity in the after care.

The material has been condensed into Table I, arranged according to the several glands removed and arbitrarily divided into four age groups: (1) rabbits under 7 months of age, (2) rabbits from 7 to 13 months of age, (3) rabbits from 13 to 19 months of age, and (4) rabbits over 19 months of age. The value of the age groups may be estimated from the fact that 257 of the 373 rabbits were born and reared in the laboratory (Medical Department of Western Reserve University and Laboratory Division of Montefiore Hospital). In the remaining 116 the age was estimated. The age under which each animal is listed was determined by its age at the time of the first operation. The anatomical condition of the thymus found at necropsy and checked in every instance by microscopic examination is listed under one of the four arbitrary groups. Each of these groups is illustrated in the accompanying photomicrographs. Thus, $+-$ (Fig. 1) indicates complete involution and $+++$ (Fig. 4) represents the large, firm, lobulated, very cellular and fully active organ, while $++$ (Fig. 3) and $+$ (Fig. 2) represent early and moderate involution. At present one cannot tell with certainty whether a given thymus (celloidin sections stained with hematoxylin and eosin) is involuting from a more active stage or regenerating from a less active stage. It will be recalled that the same difficulty applied in the case of the thyroid gland until this shortcoming in interpreting thyroid morphology was overcome by means of iodine determinations. In many cases the appearance of the medulla and the presence or absence of mitotic figures make the distinction in the case of the thymus fairly certain.

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TABLE I.

Glands removed.	No. of rabbits.	Condition of thymus.															
		Under 7 mos.				7–13 mos.				13–19 mos.				Over 19 mos.			
		+−	+	++	+++	+−	+	++	+++	+−	+	++	+++	+−	+	++	+++
Normals	122	2	6	4	27	16	18	14	9	13	6	2	2	3	0	0	0
Thyroidectomy	66	3	2	1	2	10	5	4	0	16	8	1	0	10	3	1	0
Gonadectomy	18	1	0	0	3	0	2	3	3	1	1	0	1	1	0	2	0
Suprarenalectomy	89	0	3	0	14	9	2	11	28	2	2	6	8	1	0	1	2
Thyroidectomy and suprarenalectomy	27	0	0	0	0	7	4	3	0	8	1	1	0	2	1	0	0
Gonadectomy and suprarenalectomy	15	0	0	0	0	0	0	0	8	0	0	0	3	1	0	0	3
Gonadectomy and thyroidectomy	25	0	0	0	0	2	5	3	0	4	2	0	0	4	4	1	0
" thyroidectomy, and suprarenalectomy	11	0	0	0	0	1	0	0	0	3	0	2	1	1	0	0	3

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Analysis of Data.

Thymus in Normal Rabbits.—122 normal rabbits including 23 with splenectomy have been tabulated to show the normal variations in thymus involution in relation to age. The youngest rabbit was 110 and the oldest 631 days of age. The earliest age at which complete thymus involution was noted was 5 months and the oldest rabbit with active thymus was 448 days of age. Thymus involution in this series of rabbits occurred more frequently between the 7th and 9th months. It is hastened by pregnancy. Very wide variations both in the time interval between onset and completion of involution occur—a fact which in itself affords the best general proof that growth, persistence, and involution of this organ depend on the chemical interaction of many other organs. Some of the important functional interrelations with the thymus as revealed in this study will be pointed out in the sections that follow.

The Thymus in Splenectomized Rabbits.—71 of the 373 rabbits were splenectomized. Splenectomy alone was performed in 23; splenectomy plus thyroidectomy in 20; splenectomy plus gonadectomy in 7; splenectomy plus suprarenalectomy in 1; splenectomy plus gonadectomy plus thyroidectomy in 6; splenectomy plus gonadectomy plus suprarenalectomy in 2; splenectomy plus thyroidectomy plus suprarenelectomy in 8; and splenectomy plus thyroidectomy plus suprarenalectomy plus gonadectomy in 4. No definite influence on the thymus could be detected and on this account all splenectomized rabbits have been included either under normals,—when splenectomy was the only operation,—or under the associated gland when splenectomy was combined with other organ removals.

The Thymus in Thyroidectomized Rabbits.—Thyroidectomy alone was performed in 43 cases and combined with splenectomy in 23 cases. Of the 8 rabbits under 7 months of age 5 had involuted thymuses, while of 39 normal rabbits under 7 months of age only 8 had involuted thymuses. In rabbits over 7 months old the thymus is normally involuting. This fact makes it difficult to evaluate the hastening effect of thyroidectomy on thymus involution. Reference to the table, however, shows that the percentage of thyroidectomized rabbits with involuted thymuses is much greater than in normals of

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corresponding age groups. No difference referable to sex was detectable. Further, it should be pointed out that it is often difficult to remove the thyroid entirely in rabbits. About 20 per cent of the rabbits of this series that survived longer than 1 month had unremoved thyroid fragments, but in spite of this involution-inhibiting factor, there is an obvious increase in the number of involuted thymuses.

One may conclude definitely that thyroidectomy in the rabbit hastens thymic involution.

Our data, therefore, confirm the observations of many other investigators, including Jeandelize (1), Jeandelize, Lucien, and Parisot (2), Hofmeister (3), Boccio (4), Hammett (5), and others. Hammett working with rats could not eliminate the possible additional influence of the parathyroids. It is possible to do this in rabbits and the results show that thymic involution occurs when the external parathyroids are intact and therefore may be quite independent of the parathyroid factor. Positive evidence of the thyroid-thymus interrelationship has also been obtained from feeding thyroid to animals. Hoskins (6) noted thymic enlargement in guinea pigs, Kahn (7) observed thymic enlargement in tadpoles, and Courrier (8) reported similar findings in white rats. Further evidence of the relationship has been furnished by Gudernatsch (9) and confirmed by Uhlenhuth (10), who observed that thymus feeding delayed and even prevented metamorphosis of frog and salamander larvæ.

No systematic studies of the effect of thymus removal on the thyroid have been made. Lucien and Parisot (11) removed thymuses in 6 rabbits, MacLennan (12) also working with rabbits and Soli (13) working with guinea pigs concluded that no positive thyroid reaction results. Dustin and Zunz (14) and Scammon (15) working with small series of human cases failed to find evidence of a thyroid-thymus interrelationship.

Pineles (16), Schilder (17), Erdheim (18), Rocaz and Cruchet (19), and others have pointed out that the thymus is atrophic in infantile myxedema associated with atrophy or absence of the thyroid. Simple goiter occurring after puberty in both man and animals is not usually associated with persistent thymus. There are many reports in the literature to the contrary but careful study suggests either that the association occurred before normal thymic involution had begun or that other factors than the involution-preventing effect of thyroid were present. The enlargements of the thymus classically present in Graves' disease, in Addison's disease, in acromegaly, and in status lymphaticus, while without doubt requiring the presence of an active thyroid, are more immediately dependent upon the partial loss of suprarenal and gonadal function, as will be pointed out later.

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The Thymus after Gonadectomy.—Gonadectomy alone was performed in eighteen cases. The series, though small, clearly shows that gonadectomy delays thymic involution in both males and females.

This fact had already been established through the work of Henderson (20), Calzolari (21), Goodall (22), Gellin (23), and others (13). Regarding the important question of regeneration of the thymus following gonadectomy, our data are insufficient. That gonadectomy does tend to cause hypertrophy and regeneration of the thymus seems likely, but this stimulus in itself is too weak to do more than cause slight further enlargement (if done during the growing stage) and delay involution. Gonadectomy will not permanently prevent thymic involution. There is some evidence that thymectomy hastens slightly the onset of sexual maturity in rabbits (24, 25), but this effect is too slight and the variations are too great to be established with certainty by the methods used. The involution that sets in after sexual maturity may be hastened by pregnancy. A corresponding hastening of involution associated with increased sexual activity in the male is not so readily demonstrable.

The Thymus after Suprarenalectomy.—89 cases with bilateral suprarenalectomy (done in two stages) are included in this series. As mentioned above, only those that survived the removal of both suprarenals 15 days have been included. An outstanding fact is revealed—that only 12 of the 89 cases had involuted thymuses irrespective of the age of the rabbits at the time of removal, and in 52 of the 89 cases markedly hyperplastic thymuses were present. Thymus hyperplasia occurs after suprarenalectomy in all age groups; that is, in rabbits known to be over 19 months old, as well as in those under 7 months of age at the time of removal of the second suprarenal. There occurs, therefore, not only an arrest of involution but actual regeneration of the thymus. No difference referable to sex was made out. Involution is permanently delayed if the suprarenal insufficiency is permanent, but as surviving rabbits always have accessory interrenal glands there is a gradually increasing compensation and after months it may be sufficient to initiate thymic involution. We have, however, repeatedly seen fully active thymuses in rabbits 6 months after suprarenalectomy that with crude test of clinical behavior seemed fully compensated. This regeneration includes both the medulla and the cortex, though it begins in the medulla. The medulla seems to act as a specialized

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type of germinal center somewhat analogous to the medulla of regenerating lymph nodes. The lymphoid tissues throughout the body (regional lymph nodes, intestinal, intrathyroid, and peribronchial) also undergo enlargement as pointed out by Crowe and Wislocki (26). This enlargement is of the same general nature as that of the thymus. The anatomical condition closely resembles that present in status lymphaticus. Unilateral suprarenalectomy was performed in 31 rabbits and does not ordinarily create sufficient suppression of the suprarenal function to elicit thymus hypertrophy.

Thymectomy, according to Soli (13), in chickens and guinea pigs, causes no detectable change in the suprarenals. The literature relative to experimental regeneration of the thymus after suprarenal injury is very meager and contains little positive evidence of this striking reaction. It has been reviewed by Jaffe (27) in connection with his quantitative studies on thymic regeneration in the rat.

The Thymus after Thyroidectomy Plus Suprarenalectomy.—27 rabbits are included in this series. The protocols of 15 of these were published in connection with studies on the effect of suprarenalectomy in thyroidectomized rabbits on heat production (28). This series reveals another striking fact, namely that 17 of the 27 cases had completely involuted thymuses, while in the series with suprarenalectomy alone only 12 of 89 cases had involuted thymuses. The thyroid hormone is, therefore, necessary for thymus hyperplasia which usually follows sufficient but sublethal injury of the suprarenal function. It has already been pointed out that thyroidectomy alone brings about thymus involution. In several of these cases fragments of thyroid were present at necropsy, but in spite of this, thymic regeneration was inhibited. On the other hand, 4 cases were discarded because of marked regeneration of the thyroid before suprarenalectomy and in these thymic regeneration had occurred. Thyroidectomy within a few days after suprarenalectomy was unsuccessful on account of the great mortality in attempting further operations on suprarenalectomized animals.

The Thymus in Gonadectomized and Suprarenalectomized Rabbits.—15 cases survived the removal of these glands more than 15 days. The mortality from suprarenalectomy is very much greater in gonadectomized rabbits than in normals. This, we believe, is due to

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the removal, with the gonads, of accessory interrenal masses which for the most part occur in the lower part of the spermatic cord or about the upper pole of the ovary. The mortality is still greater when gonadectomy or any other operation is done after suprarenalectomy. 11 of the 15 cases which survived more than 15 days were suprarenalectomized after gonadectomy. In all but 1 case there was present at necropsy extreme regeneration of the thymus. All these rabbits were over 7 months of age before either operation was performed and 4 were over 19 months of age. While it is true we do not know the actual condition of the thymus in these rabbits before operation, we cannot doubt the occurrence of thymic regeneration, especially when the results are compared with those obtained in the other groups described. Gonadectomy alone delays thymic involution. It is too weak a stimulus to bring about regeneration. Suprarenalectomy alone not only delays involution, but usually causes regeneration. Gonadectomy and suprarenalectomy result in certain regeneration of the thymus in the rabbit with intact thyroid at any age. The combined effect of both gonadectomy and suprarenalectomy is greater than that of either of these operations alone. The combined operation in the rabbit permanently prevents thymic involution provided the suprarenal insufficiency is also permanent. Both gonadectomy and suprarenalectomy appear to exert qualitatively similar effects on the thymus, the difference being one of degree. As already pointed out the lymphoid tissue throughout the body also undergoes hypertrophy with the thymus which in some ways at least is analogous to that present normally in sexually immature animals.

The Thymus after Thyroidectomy and Gonadectomy.—25 cases are included in this group—all over 7 months of age. In 6 the spleen was also removed. Only 4 of the 25 had hyperplastic thymuses, while 12 of the 18 in which gonadectomy alone was performed had enlarged thymuses. When compared with thyroidectomy alone, thyroidectomy plus gonadectomy gives a larger percentage with hyperplastic thymuses. Gonadectomy can, therefore, offset to some extent the accelerating influence of thyroidectomy on thymus involution. The percentage with enlarged thymuses is also slightly higher than in the group with thyroidectomy and suprarenalectomy. The

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reason for this apparent discrepancy, we think, is that thyroidectomy was done in most cases after gonadectomy and in several of these rabbits marked regeneration of the thyroid had occurred.

The Thymus after Thyroidectomy, Gonadectomy, and Suprarenalectomy.—11 cases are included in this group, of which 4 were also splenectomized. Thyroidectomy was performed in all cases before either gonadectomy or suprarenalectomy and a detailed analysis of the series shows that when regeneration of the thyroid occurred gonadectomy and suprarenalectomy caused thymic regeneration, thus strengthening the belief that the thyroid secretion is necessary for thymic regeneration even in the presence of the most powerful stimulus for thymic regeneration; namely, the combined effect of gonadectomy and suprarenalectomy.

DISCUSSION.

Four striking facts have been brought out by this statistical study of the condition of the thymus in 373 rabbits following the removal of other organs of internal secretion. (1) Thyroidectomy hastens involution of the thymus and other lymphoid tissues. (2) Gonadectomy delays thymus involution. (3) Sublethal but sufficient injury of the suprarenal function with intact thyroid prevents thymus involution and causes regeneration even of the involuted thymus. It also causes hypertrophy of other lymphoid tissues. (4) Thyroidectomy prevents thymus regeneration following suprarenalectomy, probably for the same reason that thyroidectomy hastens normal thymic involution.

The first and second of these facts were already known and our studies mainly provide confirmation on a large scale, except that they eliminate the parathyroid factor as influencing the effect of thyroidectomy on the thymus of rabbits.

Recently there has been a tendency to drop the thymus from the group of ductless glands (Sharpey-Schafer (29)) on the grounds that no evidence of an internal secretion exists and that as regards its physiological and pathological reactions it resembles the general lymphoid tissue. While both these statements are true at the present time they indicate our lack of knowledge of this organ rather than a basis for excluding a possible internal secretion. The remarkable con-

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stancy with which thymic and general lymphoid hyperplasia follow sublethal injury of the suprarenals and gonads and the constancy with which thyroidectomy prevents it suggest specific chemical interrelationships between the thyroid, thymus, suprarenals, and gonads of both physiological and pathological significance.

These relationships are involved not only in diseases like exophthalmic goiter, acromegaly, Addison's disease, and status lymphaticus, but also in the normal lymphoid hyperplasias of childhood. In all these conditions thymic and lymphoid hyperplasia are prominent features. We have repeatedly pointed out the striking resemblance between the effects of experimental suprarenal injury in rabbits and exophthalmic goiter, especially as regards the thymic and lymphoid hyperplasia and metabolism (30). It is our belief that the constitutional defect underlying the development of exophthalmic goiter, one manifestation of which is lymphoid hyperplasia, is dependent upon partial suppression of a function of the interrenal and sex glands. It is known that this constitutional anomaly may be congenital (inherited?) (31) or acquired, and is either identical with or closely related to status lymphaticus.

Status lymphaticus has been the subject of controversy since Plater (32), in 1614, pointed out that the thymus was often enlarged in individuals dying suddenly without other assignable cause. Kopp (33), in 1838, advanced the view that death was due to the mechanical effects of the enlarged gland. This was vigorously denied in 1858 by Friedleben (34). Paltauf (35), in 1889, first clearly defined the syndrome and advanced the hypothesis that it was a manifestation of a constitutional defect of a chlorotic-lymphatic nature which so lowered the resistance that such individuals were unable to withstand unusual shocks or strains. The work of Hedinger (36) and of Wiesel (37) pointed to the chromaffin tissue as the seat of the primary lesion.

The observations and experiments included in this paper clearly indicate that the essential features of status lymphaticus—abnormal overgrowth of the thymus and lymphoid tissues, lowered resistance, and relative lymphocytosis—have been reproduced experimentally in rabbits. Contrary to the views of Hedinger and Wiesel, we believe that this syndrome develops as a result of insufficient functional activity of the interrenal and sex glands. This insufficiency may be acquired late in life, as shown by its experimental production

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in animals and its occurrence in previously normal individuals in association with exophthalmic goiter and Addison's disease, or the functional insufficiency of the interrenal and sex glands may occur during fetal life or infancy. The latter form of insufficiency is responsible for status lymphaticus.

The normal prominence of the lymphoid tissues in infancy and childhood is probably also a manifestation of a functional underdevelopment of the interrenal and gonadal systems and the abnormal hyperplasias of the thymus and lymphoid tissues (status lymphaticus) seen in infants and children are the reactions resulting from more marked insufficiencies of these tissues. It should be pointed out that the prominence of the thymus and lymphoid tissues in infancy is probably related to the normally occurring involution of the interrenal gland in the first few weeks of life (38), which is certainly a powerful stimulus to lymphoid hyperplasia. Status lymphaticus is, therefore, the exaggerated manifestation of a physiological process normal in infants and depends on either a partial loss of or a failure of sufficient development of the interrenal and sex glands.

The thymic and lymphoid hyperplasia occurring in exophthalmic goiter, Addison's disease, status lymphaticus, and even in normal infants has a common cause, and the specific manifestation which differentiates these diseases clinically depends on different degrees of involvement of other specific gland functions. Thus in exophthalmic goiter the disease could be explained as due to a primary interrenal injury with normal or increased functional activity of the chromaffin tissue, both acting to stimulate the thyroid. Addison's disease could be explained as dependent on a combined loss of both chromaffin and interrenal function with possibly, as Wiesel and Hedinger suggest, the chromaffin tissue injury primary. Status lymphaticus is the manifestation of a mild degree of functional underdevelopment of the interrenal, gonadal, and chromaffin tissues.

While we are in the habit of considering exophthalmic goiter as an entity it should be pointed out that the essential symptoms are the recurrence at a later age of physiological processes quite normal for infants. Thus the rate of metabolism and the degree of lymphoid hyperplasia seen in exophthalmic goiter usually do not exceed similar manifestations normally present in infancy.

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SUMMARY.

Thyroidectomy hastens, while gonadectomy delays, but does not permanently prevent, involution of the thymus.

Suprarenalectomy alone not only delays involution of the thymus and lymphoid tissue but may cause their regeneration. Thyroidectomy prevents this reaction even after combined suprarenalectomy and gonadectomy.

Suprarenalectomy plus gonadectomy is a more powerful stimulus for thymus and lymphoid regeneration than either of these influences alone.

The combined effect of these two factors results in certain lymphoid and thymus hyperplasia in rabbits which persists until regeneration of accessory interrenal tissue corrects the physiological defect. The syndrome thus experimentally produced resembles status lymphaticus and is believed to depend mainly on a partial loss of certain functions of the interrenal and sex glands rather than of the chromaffin tissue.

The normal and abnormal lymphoid and thymic hyperplasias of infancy and childhood are believed to be manifestations of a functional underdevelopment of the interrenal and sex glands of varying intensity.

The so called lymphatic constitution which underlies or accompanies exophthalmic goiter, Addison's disease, and acromegaly also appears to be dependent on a partial suppression of certain functions of the interrenal and sex glands.

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EXPLANATION OF PLATES.

PLATE 17.

FIG. 1. Rabbit 3–68. Photomicrograph of thymus in complete involution showing the remnants of lobules widely separated by fatty areolar tissue. Indicated in table and text as $+-$. $\times$ 30.

FIG. 2. Rabbit 1–224. Photomicrograph of thymus in advanced involution. Indicated in table and text as $+$. $\times$ 30.

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PLATE 18.

FIG. 3. Rabbit 3–270. Photomicrograph of thymus in state of moderate involution (actually regenerating, as indicated by prominent medulla). Indicated in table and text as ++. × 30.

FIG. 4. Rabbit 3–66. Photomicrograph of thymus in state of complete regeneration. Indicated in table and text as +++. × 30.

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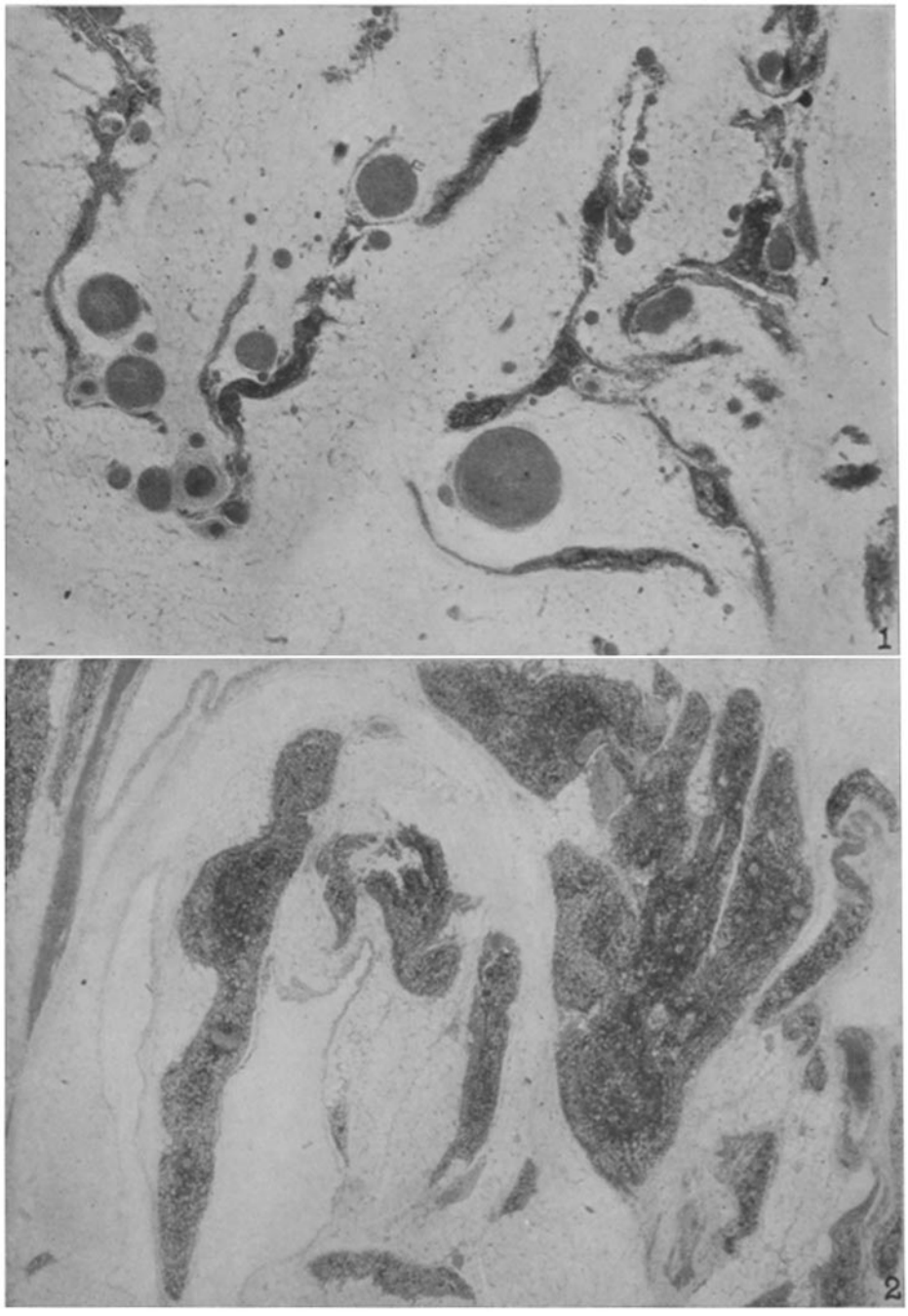

(Marine, Manley, and Baumann: Thymus gland.)

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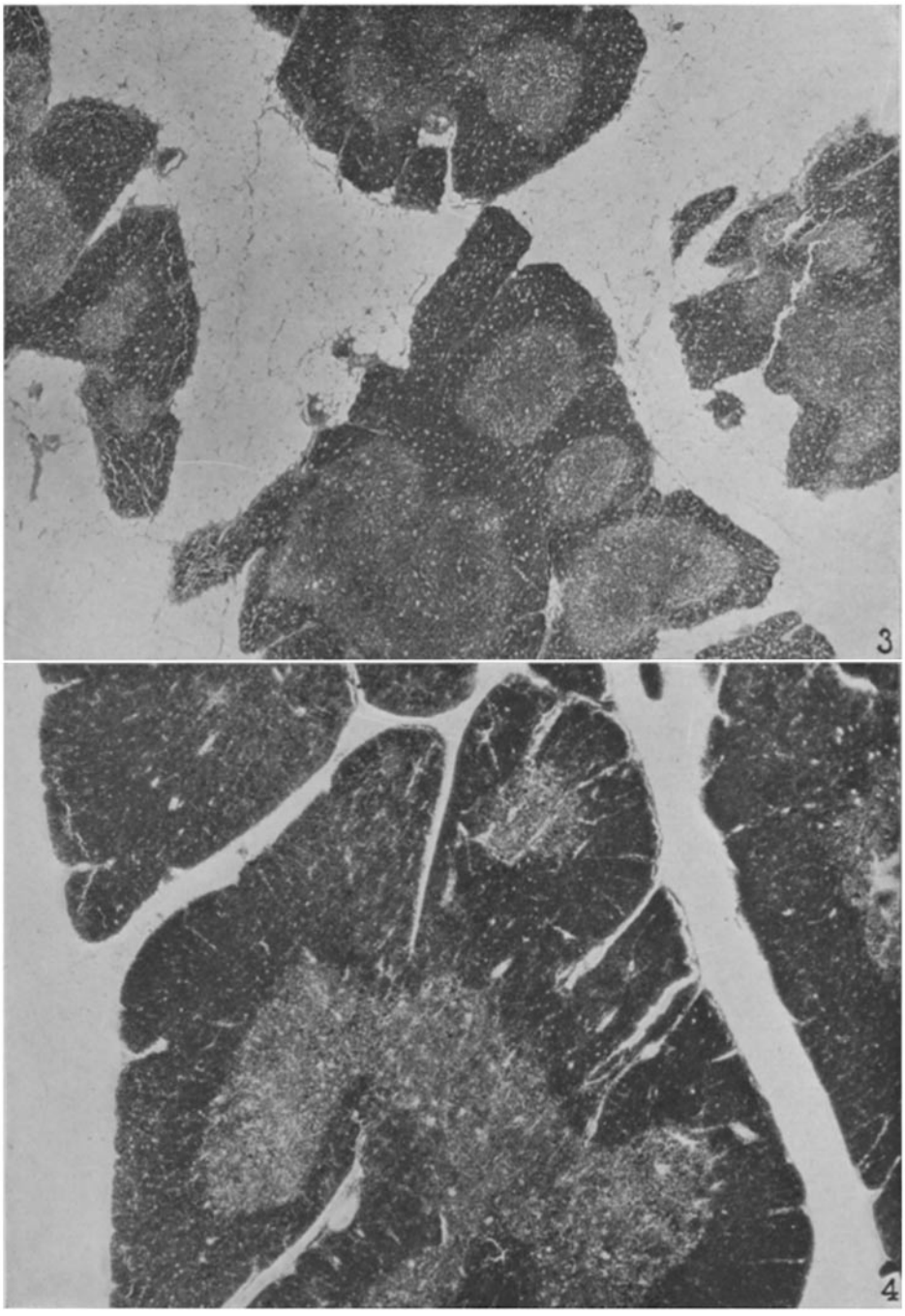

(Marine, Manley, and Baumann: Thymus gland.)

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