THE NEW VIEWS AS TO THE MORPHOLOGY OF THE THYMUS GLAND AND THEIR BEARING ON THE PROBLEM OF THE FUNCTION OF THE THYMUS

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It has almost become an established expression in discussing the thymus gland to call it an "enigmatic organ." This may still have been justified a couple of decades ago, when our knowledge of this organ was restricted to certain not very clear data, but nowadays the expression is scarcely more justified for this than for a large number of other organs in the body. It can even with justice be said that in certain not unessential respects our knowledge of the thymus is more thorough than that of the majority of the organs closely related to it functionally. If, nevertheless, the expression in question or the view that it represents reappears not infrequently even in publications of recent date, this is certainly connected with the fact that the knowledge of the results of more recent investigations is still but slightly spread; one often comes across, at least in clinical literature, expositions that start out from older and notoriously incorrect views.

It was accordingly with pleasure that I carried out the wish expressed by the editor of Endocrinology to give a brief exposition of the more recent observations regarding the thymus, especially with respect to its normal morphology. And in doing so one can certainly not altogether exclude certain aspects of the organ during disease nor the question of its function.

Merely from considerations of space, however, it is impossible to give here more than an exposition of certain main features of the subject. Ten years ago I gave a more detailed account of the question (Fünfzig Jahre Thymusforschung, Ergebn. d. Anat. u. Entwicklungsgesch. Jg., 1910) and I can all the more readily refer the reader to this for details because, as far as I can see, no reason to alter in any essential point the view there put forward has arisen since that time. On the contrary this view has of late gained a broader basis in many points, and in several aspects it has become more clearly elucidated than it was then. Due attention will be paid here to certain of these advances.

As it seemed to me desirable to try here especially to elucidate such points as are important for human physiology and pathology and in which the new results contain some new principles, I have given my account chiefly the form of certain leading theses, each of which is developed and illustrated.

1. THE THYMUS IS AN EPITHELIAL ORGAN, INFILTRATED WITH LYMPHOCYTES.

Ever since Kölliker (1879) drew attention to the fact that in an early embryonal stage the thymus has an epithelial anlage and is probably a derivative of a branchial cleft, there came the problem of explaining how from this epithelial germ had arisen the finished structure of the organ, with its combination, resembling the lymphoid tissue, of a reticulum and free lymphoid cells stored in its meshes. It is well known that earlier two different ways of answering this question were attempted.

The *"pseudomorphosis theory"* inaugurated by His (1880) and Stieda (1881) was that the epithelial anlage had elements of connective tissue growing through it, which caused its decomposition and substituted it so that only scattered epithelial remains in the form of Hassall's concentric corpuscles were left, while the rest of the parenchyma was differentiated, like a genuine lymphoid tissue, in the ingrown mesodermal elements. The term "epitheloid" cells introduced by Watney (1881, 1882) in his excellent works on the histology of the thymus and not infrequently used afterwards up to the present day for the hypertrophied medullary cells, arises from a view of that sort, as also does the term "endothelial" or "endotheloid" cells, used by Klein (1880) for the same formations. That these terms do not agree with our present views of the structure of the organ the following will show.

With the "pseudomorphosis" theory there competed from the very first another one, called the *"transformation theory,"* which had already been outlined in its most general features by Kölliker himself. According to this view there was no such regression of the original anlage as the former theory assumed, but the organ as a whole was supposed to appear by a direct transformation of the epithelial anlage. The more detailed consequence of this view was brought out by Stöhr (1905, 1906), who pointed out that, according to this idea, which he himself adopted, the small thymus cells were not lymphocytes, but small epithelial cells.

Both these views had originally been put forward without any detailed investigations as to the histogenesis of the thymus. Neither of them was able to stand this test. In different vertebrate classes it was established that the thymus reticulum appears through a transformation of the epithelial cells of the anlage to a ramified form, while the lymphocytes enter from outside and at first diffusely infiltrate the whole epithelium. The hypertrophy of the central epithelial cells of the organ is only secondary, and the central part, rich in protoplasm, that thus arises, forms the medulla of the organ and the region around the edge, richer in nuclei, its cortex. Within the medulla, on the other hand, there appears later on an increase in the size of separate epithelial cells or groups of cells, giving rise to the medullar differations known under the name of Hassall's corpuscles or their homologues, which are rather different in separate species ("uni-cellular Hassallian corpuscles," "myoid cells," "irregular cell complexes," etc.).

Nowhere does the thymus appear more clearly in its quality of epithelium infiltered by lymphocytes than in certain Teleostei and Ganoids (Hammar, 1908; Ankarsvärd and Hammar, 1913), where at the moment of infiltration the organ still has the character of a thickened surface epithelium—a thymus placode—and in the majority of species investigated the organ also retains this character throughout life, while in other species it is separated secondarily from the surface by ingrowing layer of connective tissue.

In the case of mammals the occurrence of a lymphocytic infiltration of the epithelial anlage during embryonal life was first convincingly shown by Maximow (1909), for birds and reptiles by Vera Dantschakoff (1908, 1910, 1916:1), for Amphibia by Maximow (1912), for Selachia by Hammar (1911), and Maximow (1912). In all cases there are present at first large lymphocytic forms, which secondarily assume the small dimensions characteristic of the thymus lymphocytes only after their entrance into the organ and repeated divisions there.

The proof of the immigration of the lymphocytes into the thymus anlage during development and, in connection with this, the transformation of the latter into an epithelial reticulum; the far-reaching morphological resemblance between the small thymus cells and typical lymphocytes (Laurell;* Pappenheimer, 1913; Pinner, 1920, etc.); the great resemblances between the two kinds of cells from a biological point of view: amoeboid movement (Hammar, 1905; Jolly, 1914:2, 3); great sensibility to Röntgen rays (Heineke, 1905; Rudberg, 1907, 1909; Regaud and Crémieu, 1911, 1912, etc.); the identity of the two kinds of cells from a serological point of view (Ritchie, 1908; Felländer, 1912, etc.) and, finally, the analogous conditions of the lymphocytes in the thymus on the one hand, in the real lymphoid tissue and the blood on the other, during involution and other conditions—about which more will be found below—all these factors form so strong a chain of evidence in favor of the "small thymus cells" having the very much discussed nature of real lymphocytes that even in the latest posthumous editions of Stöhr's own text book his view of them as epithelial cells has now been abandoned.

It ought, however, to be mentioned that this view of Stöhr's is taken up by different investigators (among others Schridde, Dustin, Fulci).

With regard to the details of the histogenesis in man it may be mentioned that the infiltration of the epithelial anlage by lymphocytes begins as early as towards the end of the second month of prenatal life, at an embryonal length of about 30 mm., that the formation of the medulla begins at about the length of 40 mm., and that the first Hassallian corpuscles appear towards the end of the same month at about a length of 50 mm. At the end of the second month the organ already consists of two conical lobes, situated close together in the anterior mediastinum, each with a longer or shorter pointed upper end, the thymus horn, and a basal end usually bent round backwards in the shape of a hook, *the cardiac bends.* Towards the middle of each lobe septa of connective tissue penetrate, especially its thickest parts from all sides, dividing the cortex into so-called cortical follicles. The medulla remains undivided. At the same time

* The myoid cells with cross-striated fibrillae in their interior are regularly found only in inferior vertebrates. In exceptional cases a similar structure has been seen also in individual medullary cells of the human thymus (Pappenheimer 1910, Salkind 1915, Wassjutotschkin 1918).

as the organ continues to increase rapidly in size by mitotic division both of the lymphocytes and the reticulum cells, the formation of medulla—the result of the enlargement of the reticulum cells—encroaches upon the inner parts of the cortical follicles, which consequently assume the character of lobuli, consisting of both medulla and cortex. As, owing to ingrowing connective tissue, these in their turn are undergoing a similar development, and this process is continually repeated, there issues from the originally simple central medullary region of the lobe a central medullary cord, ramified and often exceedingly sinuous; around this are grouped all the thymus lobuli in each lobe, and with it they also subsequently remain connected. Sometimes this central cord also shows at its surface a thin layer of cortex, and it is therefore best to call it *the central parenchymal cord.* In exceptional cases the growing in of the connective tissue causes, especially in the neighborhood of the thin thymus horns, a splitting-off of one or more parts of the parenchyma as an entirely independent division, an accessory lobe, but otherwise the whole parenchymal mass is coherent in each lobe; lobuli bounded on all sides by connective tissue, as described in earlier accounts, do not exist (Hammar, 1911:1).

While in this way a more and more abundant lobulation is developed, the organ grows rapidly during prenatal life. Postponing to another occasion a more detailed account of the results of a numerical analysis that I have carried out on about 80 normal human thymus glands from embryonal life, I shall give here only a few preliminary details.

The analysis that was carried out thus shows how the number of Hassall's corpuscles quickly increases. They are started as small formations of 10-25 μ in diameter, often in the neighborhood of some small vessel. One or two adjacent reticulum cells increase in size and assume a spherical shape. When on this enlargement they reach neighboring cells in the medullary reticulum, the latter cells are thrust to the side owing to the pressure of growth and take up a position close to the central cell or cells, which they concentrically enclose like the scales of an onion. Even the peripheral cells often fairly soon become hypertrophied, so that the formation grows farther and fresh cells are joined to its periphery. When the growth proceeds in this manner two or more corpuscles may reach each other, join together, and continue to grow as a unit. In this way there arise the so-called compound Hassallian corpuscles, which are formed, however, mostly in the later embryonal or postembryonal stages. The lymphocytic and leucocytic forms found in a great number of the Hassall's corpuscles do not take part in the formation, but are as a rule in a more or less advanced state of disintegration. Their number is sometimes so great in a Hassallian corpuscle that it is expanded by them like a little cyst. These Hassall's corpuscles richly invaded by lymphocytes seem to be more than usually numerous in congenital lues.

The majority of Hassall's corpuscles do not normally attain, even in postnatal life, a greater diameter than 25-50 μ. With increasing diameter the larger forms are as a rule more and more rare. It is very rare for any Hassallian corpuscles to attain a greater diameter than 200 μ during embryonal life. Postfoetally, on the other hand, the maximum limit is, as a rule, about 500 μ, i. e., 0.5 mm.; only in some exceptional cases have I found still larger forms postfoetally, up to a diameter of 1 mm. and more.

At the time of birth the thymus in man has a shape that is exceedingly drawn out, transversely. It may occupy a considerable portion of the available space in the thorax. Its lateral surfaces may, with their decidedly convex shape, bend into their respective pleural cavities. With the beginning of pulmonary breathing a change takes place in the shape of the organ; it becomes more elongated, its extension in a sagittal direction increases, while at the same time the sagittal diameter of the thorax increases, its lateral surfaces become planer, even concave and grooved (Hammar, 1916:2; Gräper, 1920).

It forms no part of the plan of this account to enter more closely into the comparative morphogenesis of the thymus. It may be mentioned, however, quite incidentally, that our knowledge of the process of the development of the definitive total form of the thymus, differing in different species, has increased considerably of late year, among others in case of Ammocoetes (Castellaneta 1913, Salkind 1915, Wallin 1917), Elasmobranchii (Fritsche 1910, Hammar 1911, Maximow 1912), Ganoids (Ankarsvärd and Hammar 1913, Castellaneta 1917), Teleostei (Hammar 1908), sparrow (Helgeson 1913), duck (B. Hamilton

1913), Marsupialia (Fraser and Hill 1915, Fraser 1915), pig (Zotterman 1911), cattle (Hagström 1921), rabbit (Hanson 1911), guinea-pig (Maximow 1909, Ruben 1911, H. Rabl 1913), mole (H. Rabl 1909), Prosimii (Nierstrasz 1912), and man (Hammar 1911:1).

It may be said that these investigations afford additional confirmation of the ideas as to the originally branchiogene metameric nature of the organ. Thus circumstances have arisen which make it probable that even in the cases in which a metamerism of this sort does not appear in ontogenesis, the organ has issued from a cell material coming from the entoderm of branchial clefts and thus originally metameric (Ankarsvärd and Hammar).

In addition it has been shown how different are the factors, apparently partly of a mechanical nature, that become active in different species and produce the important differences in position and shape that may characterize the organ even in closely related species (Hagström).

Finally, in the case of mammals it has also been shown that the epithelial thymus anlage itself is by no means equivalent in all cases, as it is certainly, in the majority of known cases, purely entodermal, issuing from the third branchial pocket, but in some species (mole, guinea-pig) it is purely ectodermal, in others, on the other hand, such as the pig, of mixed ecto-entodermal origin. Especially illuminating in this respect is Frasers and Hill's discovery in Trichosurus, where not only together with thymus III, a similarly entodermal thymus IV was shown for the first time in a mammal as a *normal* occurrence, but also, still further, certain parts of the ectoderm of the cervical sinus, about the same as in the pig, are used for the formation of an ectodermal (or ecto-entodermal?) "thymus superficialis."

2. THE THYMUS IS NOT A TRANSITORY ORGAN, BUT PERSISTS AND FUNCTIONS EVEN UNTIL OLD AGE. AT PUBERTY ITS PARENCHYMA BEGINS TO BE REDUCED: "AGE INVOLUTION."

No idea about the thymus gland has perhaps been more widespread and more generally adopted than that the organ is of a transitory nature, that at a certain early age it begins to decline and soon disappears, or at least ceases to function.

It is true that the views as to the time both for the beginning of the regression and the disappearance of the organ have varied to a very great extent. The opinion already upheld by Galenus, that the turning-point in the existence of the organ is at birth, has still found followers in this century (Collin and Lucien, 1905, 1906). Sometimes writers have even wished to assign the entire activity of the organ to embryonal life and assumed that it was spent soon after birth. The most general view during the latter part of last century held, however, that the highest point of the development of the organ was during earliest childhood, 1 to 2 years; opinions were very much divided as to how soon and to what extent the organ atrophied after this time. When in exceptional cases a large thymus was found after the time when it was considered that the thymus would normally have been involved, it was called a "persistence" of the organ, or, later on in such cases, when it was considered that the organ had already been atrophied and had again grown and begun to function once more, a "revivescence."

In the form indicated here the old theory of an "age involution" of the thymus was certainly incorrect.

Although a few earlier anatomists (Cowper, Krause) had already expressed a similar opinion it was Waldeyer (1890, 1891) who drew more general attention to the fact that even in older people (60 to 80 years old) there exists a thymic fat body with considerable parenchymous remains. It may seem strange that this state of affairs could have been neglected so long by the majority of anatomists and that, quite generally, opinions could have been so long divided on an anatomical question of such a kind that one could have supposed the scales should easily have given the decision. The chief reason for this is, however, that it was overlooked how, under the influence of disease or other disturbances in the general economy of the organism, considerable alterations in the conditions of size and structure of the organ regularly occur rather independent of the stage of age involution that was present before the disturbance in question.

Sometimes it is a case of pathological increase of the thymus parenchyma, a hyperplasia of the thymus, but much more often, and as a rule, it is a reduction—not infrequently intense—of the parenchyma, an accidental involution. The greater frequency of the latter is the reason why the average values obtained by a statistical revision of human dissecting material, leaving the conditions mentioned out of consideration, have, almost without exception, given sub-normal values. In the next paragraph I shall deal more in detail with thymus hyperplasia and accidental involution.

If we wish to eliminate this source of error, we may take as the basis of our view as to the normal conditions of the organ in man only organs from persons who have met with a sudden death by external violence, etc., while in good health and in a good state of nutrition. A statistical determination based on these principles and published by the author in 1906 showed that the turning point in the existence of the organ is at the age of puberty (11 to 15 years). Up to this time not only does the size of the organ itself increase, but, what is the essential point, the parenchyma remains undiminished in total volume. After this time, on the other hand, there occurs a rapid reduction of the bulk of parenchyma in the organ, while at the same time the interstitial connective tissue usually assumes the character of adipose tissue and forms a greater and greater part of the organ. With its typical structure retained in principle, the division into cortex and medulla retained, mitotic division of leucocytes and reticular cells proceeding, and with greater and smaller Hassallian corpuscles, the parenchyma remains as a system of parenchymous cords, growing more and more sparse and more and more narrow, quite up to old age. It is only after the age of 55 that among healthy persons who have met with a sudden death we find occasional cases in which a division into cortex and medulla can no longer be established, while, on the other hand, in other individuals it can be demonstrated under similar conditions quite up to 70 years of age.

The circumstances just mentioned, especially the occurrence of mitoses and of small incipient forms of Hassall's corpuscles, and, above all, the retention by the organ of the power to react, as in earlier ages, against disease, etc., by accidental involution of different types, indicate that even at this great age the parenchyma is still functioning.

The old theory of the age involution has thus undergone revision to the effect that the involution does not appear until puberty and that it certainly causes a gradual reduction of the *parenchyma, but in such a way, however, that a functioning parenchyma remains as a rule, even in old age.* In other words, the organ is a factor to be reckoned with throughout life, and not only during childhood. Under such circumstances there can no longer, of course, be any question of a "persistence of the thymus" in the usual meaning of that term. It was obviously in the main just the normal cases that, owing to confusion as to what was normal in this respect and what was abnormal, were put under this heading. Where there is an increase of the parenchyma beyond the normal limits for the age it cannot be termed "revivescence," but here as elsewhere in similar cases, the term hyperplasia is the proper one.

It is not only in man that the involution of the thymus due to age begins at sexual maturity. In various animals it has been possible to establish the existence of similar conditions; thus in the guinea-pig (Goodall, 1905), the rabbit (Söderlund and Backman, 1909), in Raja clavata and Raja radiata (Hammar, 1911:2), in certain Teleostei (Hammar, 1908), in the rat (Jackson 1913, Hatai 1914*). Only in the case of birds are the conditions uncertain. According to Jolly and Levin (1913) involution does not occur in this case until a far later period than sexual maturity. Whether this circumstance may be correlated with the importance that the thymus has, according to Soli (1911) for the normal percentage of calcium in the egg shells of the birds is for the present impossible to determine.

That the sexual glands really play a decisive part in the age involution of the thymus is best shown by the condition of the organ after castration (Calzolari 1898, Henderson 1904, Goodall 1905, etc.). This matter has been examined with special care by Gellin (1910). He found that prepubertal castration does not affect the thymus before the age of puberty, when it allows the amount of the parenchyma in the organ to remain at a higher level than the normal. It is remarkable, however, that this level does not seem to be constant, but with increasing age a reduction of the parenchyma takes place even in the castrated subject, though more slowly and to a less extent than is normal. This circumstance must be considerea as indicating that by the side of the predominant influence that the sexual

* Hatai finds the maximum weight of the thymus of the rat at the age of 85 days, but he does not make any statement as to the period of puberty in his material.

glands exert on the process of age involution, other factors, at present unknown to us, are, though to a less extent, also operative. Interesting in this connection is Gellin's experience that the transmission of Röntgen rays through the sexual glands, which does not cause complete destruction of their endocrine elements, delays, but does not altogether stop, the occurrence of involution.

Of great interest, too, in this respect are the results of Fiore and Franchetti (1911). These authors found a reduction of the thymus of young rabbits and rats before sexual maturity after subcutaneous injections of the blood of full-grown animals of the same species. If a premature age involution and not merely an accidental involution were present, which is not yet certain, this would very likely mean that thymus depressory substances continually occur in the circulating blood of the adult.

During the last 15 years my attention has been directed to an attempt to collect material—normal in the sense previously mentioned—of human thymus glands, and I have analyzed this material according to a specially worked out numerical method, published in 1914. The new material, consisting of about 120 postfoetal cases, has confirmed the fact that age involution in man occurs between the age of 11 and 15 years, but it has also shown that at all ages there normally occur such great individual variations that a very large material is undoubtedly needed if we are to determine with certainty, statistically, when in the prepubertal age the gland, on an average, attains its greatest development.

As the collecting of material is still proceeding I shall put off, even now to another, I hope not very distant occasion, the communication of the absolute and relative values obtained. Among the relative values the relation between cortex and medulla ($\frac{\text{cortex}}{\text{medulla}}$), which is of especially great importance for determining the character of the image of structure, has been separately calculated and is called the *index* of the organ.

The figures show that at the appearance of age involution it is first of all the cortex that diminishes in extent, whereby the index, too, is lowered. It is only later on that the medulla, too, undergoes, on an average, a reduction, which results in an increase in the index value.* The absolute number of Hassall's corpuscles appears often to be somewhat reduced even in the periods 6 to 10, 11 to 15 years; it then decreases with the beginning of the age involution simultaneously with the reduction of the parenchyma. The large forms of Hassall's corpuscles with a diameter of 301 to 400 and 401 to 500 μ do not occur regularly at any age; the earliest age at which they were found was in a two-year-old child; they seem to disappear again as soon as the age of manhood is reached, so that the oldest individual in whom the size of 401 to 500 μ was found among the normal material was 35 and the oldest in whom a size of 301 to 400 μ was present was 38.

In this way the structure of the normal human thymus presents quite a different appearance at different ages, and the following types of structure can be established for the post-foetal period; there are, of course, no fixed limits of age for these, and through numerous individual variations they pass over into one another: (1.) *The type in childhood* (from birth to 10 years of age) with sparse interstitial connective tissue, abundant parenchyma, in which the cortex, consisting of closely united follicles, is predominant; (2.) *The puberal type* (about 11 to 15 years) with broad interlobular septa of connective tissue, but without reduction of the parenchyma. (3.) *The type in youth* (16 to 20 years) with broad interlobular septa of connective tissue, in which the formation of adipose tissue is generally going on to a striking extent, and with reduction of the parenchyma, in which the cortical follicles are now decreased and are separated from each other by wider interfollicular septa of connective tissue; (4.) *The type in the age of manhood* (21 to 45 years) with an interstitial tissue, usually consisting of adipose tissue, parenchymous strands—more or less thrust apart and generally rather narrow—and cortical follicles which are sparse and small, but dis-

*What has been mentioned above is true of age involution of the human thymus. It is now of no slight interest to find that in an animal such as the rabbit, in which the normal percentage of the blood lymphocytes, even post-puberally, is about twice as great as in man, the thymus cortex forms a far greater percentage in the parenchyma than is the case in man. As Gedda (1921) points out, and as is also shown by the figures arrived at by Söderlund and Backman (1909), the medulla and the cortex in the rabbit show a parallelism with regard to the conditions of quantity during age involution, so that even during this period there is a high index in the thymus of the rabbit. It is perhaps superfluous to point out that this difference between species with blood rich and poor in lymphocytes agrees well with what is stated below with regard to the general constitutional character of the variations in the lymphocyte component of the body.

tinct and generally forming rounded prominences on the strand of marrow; (5.) *The type in old age,* with narrow parenchymous strands, atrophied or quite broken off at various places, in which the cortex still is to be seen, not, however, as distinct prominent follicles, but only as patches with more abundant cells here and there in the strands.

By the side of these changes and apparently even before the age involution there occurs, as Strandberg (1917) has shown, even from birth, a growing-in of elements of connective tissue into the parenchyma. This process starts especially from the adventitia of the vessels situated at the boundary of the medulla and cortex and has a progredient character, so that with increasing age a more and more abundant system of fine *circummedullary connective-tissue* bundles arises, connected also with the deepest ends of the interfollicular tissue. This circummedullary connective tissue acquires a certain importance in certain morbid processes, especially in the development of luetic sequestral cysts (the "Dubois abscesses"—see Hammar, 1920).

Microscopical investigation affords us more exact information as to the details of the process of age involution. It appears that in man, as in other species investigated, we are here concerned in the first place with a rarefaction of the lymphocytes in the organ; only in the second place are the reticulum cells and the Hassallian corpuscles involved in the course of the involution in any striking way.

It is the decrease in the number of lymphocytes that is the chief cause of the diminution in the volume of the cortex. They are not situated so close together as before, either, the result of which is that the reticulum cells of the cortex appear with increased distinctness; especially in the periphery of the cortical follicles the elements of the cortical reticulum often join closely, forming a cylindro-epithelial *margin layer* facing the surrounding connective tissue. In the medulla, too, after the beginning of the involution it is easier than before for a joining of the reticulum cells into irregular epithelial cell complexes to take place, a circumstance that need not be of any significance at all pathologically, though it has been interpreted as being so more than once.

It is an obvious assumption to suppose that this rarefication of the lymphocytes in the thymus at the involution of age is connected with the fact that the emigration of lymphocytes from the parenchyma out into the surrounding connective tissue, with its blood vessels and lymphatics, which is a normal occurrence at all ages, is not compensated to the same extent as before by the mitotic division of the lymphocytes in the parenchyma. But this is not yet proved. The countings of mitoses carried out by Syk (1909) for another purpose in the thymus of the rabbit did not include the period of involution.

It is of great importance for our view as to this reduction in the number of the thymus lymphocytes at puberty to know that a similar process goes on at the same time in the real lymphoid tissue (Hellman, 1914) and in the blood (Lindberg, 1910).

With regard to the reduction in the elements of the thymus reticulum, and especially of the medulla, in the age involution it is obvious that it takes place under rather different forms in different species. In certain kinds of animals (dogs, certain Elasmobranchii and Teleostei) in large regions of the medulla the elements revert all at the same time to degeneration and disintegration and then at the places where these *"sequestra"* were situated intraparenchymatous cystic spaces, *"sequestral cysts,"* are developed. In an analogous way there arise in foetuses and children, under the influence of the luetic virus, the often extensive sequestral cysts that are known in the literature under the name of "Dubois's abscesses." In other species, including man, this reduction is usually accomplished cell by cell, and so proceeds under less striking forms. The way in which degeneration takes place in the individual cells also varies; in a number of lower vertebrates a mucous degeneration seems to prevail; in man the cells swell and are filled often with gross granules the nature of which it is difficult to determine.

Normally the regression of the Hassall's corpuscles seems on the whole to take place, both before and after the occurrence of the age involution, in the way that is described in more detail in the next paragraph in connection with a discussion of accidental involution.

In more advanced stages of age involution we find almost regularly atretic changes in the blood vessels of the thymus, culminating in a more or less complete obliterating of certain sections of them. The changes, which are generally found in the thymus veins of middle size, seem to be secondary, produced by the decrease in the supply of blood to the organ that accompanies involution of age.

3. THE THYMUS IS NEVER FOUND IN NORMAL CONDITION IN SUBJECTS WHO HAVE DIED FROM DISEASE; IN THIS CASE THE PARENCHYMA IS GENERALLY REDUCED: ACCIDENTAL INVOLUTION; FAR MORE INFREQUENTLY IT IS INCREASED: HYPERPLASIA OF THE THYMUS.

I have above already touched to some extent on the intimate connection, so very characteristic of the thymus, between its size and structure and the general condition of the organism. This circumstance, which was pointed out by Wharton as early as 1659, has been verified repeatedly by many investigators and never been denied, but it is only lately that its real importance was grasped. As a rule this involution, produced by accidental causes, has been confused with age involution.

Changes in the general condition now occur even within the compass of what is "normal," but to a far greater extent during illness. Everything indicates that in both conditions the changes in the thymus are in many respects similar and often differ only quantitatively. Thus the study of the conditions of the thymus during illness and certain other abnormal influences is an important way of obtaining knowledge about the normal reactions of the organ as well. And it is chiefly from this point of view that I touch on this study here; I shall accordingly deal with the conditions of the organ during various kinds of diseases only so far as it is required for the purpose mentioned.

An accidental reduction of the size and amount of parenchyma in the thymus, i. e., an *accidental involution,* is produced not only by the majority of diseases but also by other sorts of influences—inanition, Röntgen treatment, pregnancy.

None of the different forms of accidental involution is more accurately known than *involution caused by inanition.* Already previously experimentally proved by Friedleben (1859) and the writer (1905), still more light was thrown upon it by Jonson's (1909) detailed experiments on rabbits; his results have been generally confirmed, among others, by Jolly's and Levin's (1911 and 1912) subsequent investigations on birds as well. As this form of involution may be said to be the prototype of the accidental involution, I shall deal with it first here. The account refers to the course at complete, acute inanition or extensive chronic underfeeding; its applicability to man, as well, is substantiated by an analyzed case of congenital pyloric stenosis (Hammar, 1918), and a case of pylorospasm with death soon after the difficulties of nutrition had been overcome; both subjects were children 2½ months old, and there was a great reduction of the amount of parenchyma (1/20 of the average amount at this age). Hart (1917) recently reported a case of acute death from starvation in a 3-year-old child, in which the weight of the thymus was 5 gm. (about 1/5 of the average weight). Here, too, the microscopical report agrees entirely with what is stated below.

In animals as in man the thymus appears to be exceedingly sensitive to the influence of inanition. The changes in the size of the organ are so considerable that the adipose tissue alone is able to compete with it in the extent of the changes of volume. Here, as in other cases, the cortex appears to be the most labile part of the thymus parenchyma. During a state of starvation it is rapidly reduced, while the medulla at first retains its size, the result of which is a lower and lower index in the numerical analysis of the organ. The reduction of the cortex is chiefly brought about by a wholesale emigration of lymphocytes from it. Normally it is principally the septa between the cortical follicles that appear to be infiltrated by leucocytic forms; and among these there are certainly always lymphocytes, but these are mixed with, and often exceeded in number, by larger forms —among others, eosinophile myelocytes and plasma cells (Schaffer). Now under the influence of hunger all the part of the interstitium adjacent to the parenchyma is flooded with lymphocytes; the larger forms of leucocytes withdraw, sometimes apparently almost disappearing altogether. At the same time lymphocytes are found in large quantities in the lymph-vessels and veins situated here. The medulla, too, becomes richer in lymphocytes. Everything points to an extensive mobilization and considerable export of the lymphocytes of the organ.

At the same time the number of mitoses in the parenchyma decreases to a very great extent. Jonson found that after four weeks' underfeeding the number of mitoses had sunk from 10,500,000 in the control thymus to about 3,100; after complete acute inanition for 4 days the numbers were 28,500,000 and 6,500,000, respectively. In no case was the mitotic process in the organ quite extinct. As long as a difference was to be seen between the cortex and the medulla a predominance of the cortex mitoses was found. In extreme stages of involution the remaining mitoses seemed to belong especially to the reticulum cells.

The consequence of this wholesale emigration of lymphocytes is not limited to a reduction of the size of the cortex. It is generally only in the earliest stages of the process that the contrast between cortex and medulla still appears to about the normal degree; subsequently it becomes more and more indistinct and finally disappears entirely. Then the parenchyma has a uniform appearance on an ordinary nucleus-colored preparation, and from an image of this sort one easily gets the impression that the cortex has quite disappeared.

If, however, one follows the process in a section of fresh thymus tissue or tissue treated only with formalin, cut with the freezing method and colored with scarlet-red or sudan, one finds that this is not the case. As has been shown by the investigations of Holmström (1911) and Hart (1912), the cortex of the normal organ is either quite free from fat, or if fat is present, it is only as a few quite fine granules in the immediate neighborhood of the nuclei of the cortical reticulum. This fat is now considerably increased during the course of the accidental involution and at the same time the cortical reticular cell itself swells. In this way small spots, poor in nuclei and recognizable even in ordinary nucleus-stained sections, arise in the cortex; these are sometimes referred to in descriptions by the name of "vacuoles." The mottled appearance that these fat-containing cells, usually occurring in the cortex with a certain regularity, produce in the fat-stained section is seen even after the cortex is not recognizable owing to any predominance in the number of lymphocytes, and shows that the cortical follicle remains far longer than the nucleus-stained specimens suggest. Where the fat droplets are abundant in the cells of the cortical reticulum, there arise, when they are extracted during the processes of preparation, a multitude of pseudovacuoles which may give the cortical region a strikingly transparent appearance. If, at the same time, the medulla is relatively rich in nuclei, we may get the picture of a gland with dark medulla and lighter cortex, described by French investigators as a "glande invertée." This picture appears, however, more often in illness than in starvation.

In involution due to inanition the medulla is undisturbed longer than the cortex; it decreases, however, in the later stages of involution merely because the cell hypertrophy recedes and the size of the individual medullary cells is diminished. To this is added degenerative alterations of separate medullary cells, alterations that are less striking and rather little investigated in detail.

The conditions of the Hassall's corpuscles are the most striking features in the medulla. They are more resistent than the rest of the parenchyma and accordingly collect, as the latter decreases, in a smaller and smaller region, thus becoming *relatively* more numerous. This has led various investigators to assume that an absolute, or real, increase also took place, but, as Jonson showed, this is by no means the case. On the contrary, with the progress of the involution they decrease more and more in number, although, as has been mentioned, far more slowly than the reduction of the parenchyma takes place. As long as it is principally the amount of the cortex that is being reduced, but not that of the medulla, of course countings per mgm. parenchyma, but not per mgm. medulla, give increased values. When, later on, the reduction of the medulla also becomes perceptible, the value per mgm. medulla likewise becomes higher than normally. *Increased relative, and decreased absolute, values of the number of Hassall's corpuscles thus become a characteristic feature of the accidental involution proceeding according to the inanition type,* in its somewhat more advanced stages. In extreme stages of this involution, when the parenchyma has decreased to 1/50 or 1/100 of the normal amount and is represented in the microscopical picture only by narrow stripes poor in lymphocytes, the Hassallian corpuscles may have entirely disappeared.

Even in such extreme stages of involution the process is reversible, as Jonson first showed. The organ is not destroyed, but its parenchyma is reconstituted quickly and completely under the influence of an abundant supply of nutriment to the animal. Jonson's results as to this have been confirmed by Salkind (1915), Jackson and Stewart (1919, 1920), and others. The stages in this reconstruction process are on the whole the same as in the embryological development, first a diffuse lymphocyte infiltration, followed closely by a central medullary differentiation, and finally a reappearance of Hassall's corpuscles in the medulla. The reversible character of involution due to starvation is also shown by seasonal involution that occurs in hibernating animals, which has been investigated in, among other animals, the frog (Hammar, 1905), the chelonian (Aimé, 1921:1), and the mole (Schaffer, 1909).

The *involution caused by Röntgen radiation* is of a different nature. First observed by Heineke (1905), it has been carefully studied by Rudberg (1907, 1909) and, later on, among others, by Regaud and Crémieu (1911, 1912) and Eggers (1913). Instead of an emigration of lymphocytes there occurs in this case, even during the first 2 or 3 hours after the radiation, a wholesale disintegration of lymphocytes, while the reticular cells show themselves to be capable of resistance to a far greater extent. The disintegrating lymphocytes, and especially their nuclei, are to a great extent taken up phagocytically by the reticulum cells and seem there to be digested and dissolved. In a short time the thymus is changed in this way to practically a purely epithelial organ.

Here, too, a reconstitution of the organ is brought about in the course of time, and here it is easier to follow the conditions of the reappearing lymphocytes than after inanition involutions; they seem to appear first in the medulla, probably from its vessels, and from there they spread over the whole parenchyma. In other respects the process of reconstitution seems on the whole to proceed in the same way as after involution due to inanition.

Knowledge of the course of Röntgen involution is of importance, not only because treatment of the thymus with Röntgen rays has of late become a comparatively frequent therapeutic measure, when it has been desired to reduce the size of the organ without surgical interference, but also because our experience of Röntgen involution throws light on certain pictures that are also found in other cases and sometimes even in the normal organ. One finds not quite infrequently without any Röntgen radiation a smaller or greater number of remains, nuclei or parts of these, gathered round the nucleus in the reticular cells of the cortex. Everything indicates that here, too, phagocytosis and disintegration of the lymphocytes has taken place in the same way as in Röntgen involution, although on an incomparably smaller scale than in this case. The correctness of this explanation is shown by the fact that a corresponding phagocytosis has been directly observed in cultures of thymus tissue (Pappenheimer 1913, Wassén 1915).

Certain older anatomists had already observed that an *involution* of the thymus takes place *in pregnancy*. In later times similar observations have been made, among others, by Henderson (1904), Schaffer (1909), Ronconi (1909), Squadrini (1910) and Utterström (1910). The course of the process in certain animals was first studied in detail by Fulci (1913), who also showed its transitory nature. Bompiani (1914), while confirming Fulci's results, has also shown that lactation delays the occurrence of this restitution process.

This involution seems in certain respects to proceed in an analogous manner to inanition involution in its earlier stages; in other respects it differs from this. In two investigated cases of pregnancy in women in which death occurred by poison without any preceding illness, there was found, not only absolutely but also relatively, a marked reduction in the number of newly-formed Hassall's corpuscles and an unusually large number of extensively calcified corpuscles. It is impossible at present to state with certainty whether these findings can be considered characteristic of involution in pregnancy.

From certain cases in which pregnant women have died from disease, it has seemed as if the thymus did not always react during pregnancy in the same way as when pregnancy was not present. This leads one to think of the possibility of a change in the disposition, a "retuning" of the organ in connection with the alteration in the activity of the whole endocrine system, which apparently takes place during pregnancy. This matter is not yet ready for even a brief exposition.

Finally with regard to *the accidental involution* occurring *in disease*, it shows in many cases a course that closely resembles that of the involution due to starvation; here, too, the numerical values are then characterized by a decrease of the thymus index until finally the difference between cortex and medulla is effaced, and by an increase in the relative number of Hassall's corpuscles and a decrease in the absolute number. If an involution of this sort keeps equal pace with the disturbance of the general nutrition that is seldom absent during illness, it is tempting to assume that here, too, as in starvation, the involution is caused merely by the disturbance in the general nutrition, though it is certain that in both cases the possibility of its influence making itself felt in a roundabout way through other, possibly endocrine, organs is at present not excluded. There is not always, however, a parallelism of this sort between the disturbance in the general nutrition and the degree of involution of the thymus. In certain diseases a marked reduction of the gland already occurs even at a time when the general condition, as indicated by the intactness of the adipose tissue and the musculature, is but little affected. This is, for instance, the case in the so-called "Spanish influenze." Such cases suggest the idea that the illness in question has also a more direct depressing effect on the thymus.

In another group of diseases, on the other hand, the accidental involution has a character differing from that of inanition involution, inasmuch as in its course, otherwise fairly similar, it is not connected with a reduction but with an increase of the Hassallian corpuscles and principally the absolute number of small, newly-formed corpuscles. It is especially in acute infections of different kinds that this type is found. It may, therefore, for the sake of brevity, be denoted as *the infection type*. Similar conditions were also found in an analyzed case of snake-bite with death on the third day (Hammar and Lagergren 1918, Hammar 1918). In cases where death has occurred before the thymus involution has obtained any intensive character this increase in the number of the small Hassallian corpuscles is beyond all doubt. Thus the number of these corpuscles in certain investigated cases of death from diphtheria amounts to almost 10 times the *highest* normal value found at a corresponding age. The involution seems as a rule to be accompanied by a relatively small tendency of growth in the individual newly-formed corpuscle, if we are to judge from the fact that in such cases the number of corpuscles in the group of lowest magnitude (Group I, 10 to 25 μ diameter) is the dominating one, and not, as is normal, the number in the next lowest (Group II, 26 to 50 μ) ; this is not only the case in the beginning, but even after longer duration, of the illness. In other words, in infection involution the quotient II/I is decreased and is usually less than 1.0, while normally it is almost always greater than 1.0.

Now we have the remarkable state of affairs that even in infection involution, the more the general condition is disturbed, the more this increase of the Hassall's corpuscles is lessened, so that finally the course of the involution shows, in this case, too, the same character as in inanition involution, i. e., it is accompanied by a reduction in the absolute number of the Hassall's corpuscles. Even in such cases, however, the slight tendency to growth in the corpuscles remains almost to the last, and in this way the quotient II/I is an expression of the effect of the infection for a longer period than the increase of the Hassall's corpuscles itself. This state of affairs is of no little interest as indicating that the excitatory influence of the infection that stimulates the new formation of Hassall's corpuscles, "the cH-excitation," has not ceased, but that it has only been suppressed to a less or greater extent by an antagonistic "cH-depressor" influence, probably caused merely by the disturbance of the general nutrition. I shall return to this question later on.

Even in details much of what has already been mentioned above as regards inanition involution is also true of involution in disease. Here, too, the lymphocytes are rarefied principally by emigration, only in more exceptional cases and to a slight extent by disintegration in loco. Here, too, an increased fat granulation in the reticulum cells of the cortex is a regularly occurring phenomenon. These cells then swell into a more rounded and voluminous shape; at first they retain their processes, but later on they seem to lose them and then they have quite a free position in the parenchyma. If, then, the number of the interjacent lymphocytes is small, the fat-granule reticulum cells may come so near each other that the whole parenchyma at such a place—usually the interior of a cortical follicle—may seem to be in dissociation. Such *"dissociation foci"* are the rule in certain diseases, e. g., Spanish influenza; in others, on the contrary, they do not occur, in spite of the reticulum cells being abundantly filled with fat granules; the reticulum cells are then undergoing the changes just mentioned more separately without any aggregation into foci.

Whether a formation of foci of this sort takes place or not, it is remarkable that these fat-granule cells undoubtedly decrease in number during the progress of the involution, but nevertheless no real signs of degeneration can be detected in them. The nucleus of the cell does not, as a rule, show any such signs; still less can any detritus denoting disintegration of cells be found. On the other hand, in the cases in which there is some more abundant fat granulation in the cells of the cortical reticulum, there also occur rounded fat-granule cells, of much the same aspect, in the surrounding interstitial tissue. The pictures seem directly to suggest that the fat-granule cells are able to release themselves from the cortical reticulum and to pass out from the parenchyma. That this sort of emigration of reticulum cells containing fat granules is a usual phenomenon in cultures of thymus tissue has at any rate been shown by Wassén (1915), by direct continuous observation of the living material. Pappenheimer, too, (1913) seems to have met with similar phenomena in his thymus cultures. As the assumption of the existence of this state of affairs *within* the organism as well is of considerable fundamental importance, caution demands more positive proof than can be given by a fixed material before a view of this sort can be definitely maintained. The question as to whether similar pictures occur in other forms of accidental involution has not been investigated, but at least in the case of inanition involution it seems fairly probable.

In more exceptional cases fat granules are also found in reticulum cells of the medulla, and, in a way that scarcely seems to follow any law, fat can usually be shown to be present in a number of larger Hassallian corpuscles. Whether in these places the fat is autochthonous or whether we possibly have a phenomenon of immigration as well, is at present undecided. In the fibroblasts of the interstitial tissue fat granules are usual in accidental involution; in the thymus lymphocytes, on the other hand, they are found comparatively seldom (e. g. in diphtheria), and even then only in minimum sizes and amounts.

What has been said above will show how a *regression of Hassall's corpuscles* takes place to a great extent in many cases of accidental involution. Such cases are consequently well fitted for the study of the way in which these formations undergo regression, all the more so as corresponding pictures can also be found in normal organs and thus there is a basis for the assumption that the normal regression of these formations proceeds on the whole in a similar manner.

With regard to this I shall at first discuss the so-called *"degenerate Hassall's corpuscles,"* which, usually varying in size between 200 and 500 μ, occur even normally in the human thymus. They consist, as a rule, of a few peripheral layers of flat nucleated cells, and within them a very large number of flattened or shrunken elements without nuclei, often with a more or less distinct concentric stratification around one or several centres, fill up the space in loose arrangement. They often contain calcified parts of a spherical or flake-like shape. Sometimes the contents consist of elements, containing nuclei, resembling swollen leucocytes. These "degenerate Hassall's corpuscles" are as a matter of fact by no means to be looked upon as regressive forms, inasmuch as they are the structural type that human Hassallian corpuscles regularly assume when in their growth they have reached about the degree of magnitude alluded to above. Their disappearance sometimes seems to be preceded by a breaking-up of the peripheral cell-layers and a passing-out of a part of the contents of the corpuscle. This portion seems to be then taken up by the reticulum cells of the surrounding parenchyma and under their influence to be absorbed, while the peripheral cells may remain for a time in the parenchyma, recognizable by their characteristic grouping and their flattened form. Corpuscles of this sort are not infrequently invaded by the surrounding parenchyma, which at its proliferation penetrates the peripheral layers so that the centre of the corpuscle seems more or less filled up with lymphocytes and reticulum cells (Chiari, 1894; Hammar, 1905). The presence of the latter cells shows that the process in these *parenchyma invaded corpuscles* is of a different kind from the leucocytic invasion which has been described above and which as a rule is present in smaller forms of corpuscles.

More often, however, the regression of the large forms seems to take place without any such breaking, by liquifaction of the contents. The fact that, according to the investigations of Kutscher (1901), Jones (1903), Hedin (1906), Rhodin (1911) and others, the organ contains a proteolytic enzyme may perhaps help us to understand these and similar regressive phenomena in the thymus. The corpuscles in question are changed in this way to *cystic forms* with a flat epithelial wall; according as the contents are absorbed the cyst passes from a spherical to a more irregular shape and is finally changed into a narrow cleft with its walls close to each other. Even smaller corpuscles (50 to 200 μ in diameter) not infrequently give rise to cystic forms during their regression. These smaller cystic corpuscles are especially common in the central parenchymal cord, where they are not unfrequently found even in the newly born child.

The *calcified corpuscles,* too, are not to be looked upon as regressive from a morphological point of view, even if, when the calcification affects the whole corpuscle, they are probably of no significance functionally and can then be found not very infrequently partly or quite imbedded in the interstitial tissue as relics of a parenchyma that has already disappeared. Sometimes it seems as if only the lime is absorbed during the regression of a calcified corpuscle, leaving an organic substratum of rather characteristic "mucus-like" staining, while sometimes the corpuscle as a whole may shrink, showing uneven resorption surfaces looking as if they were corroded and resembling those which, in bone resorption, characterize the so-called Howship's lacunae.

The smaller forms of Hassall's corpuscles, almost always preponderating in number, at least as far as they consist of still nucleated living cells, seem chiefly to disappear by a reduction in size of their cells and the resumption by the cells of their character of typical medullary reticulum cells. The process may be called a disaggregation and the loosened corpuscles, engaged in regression, may be called *disaggregation forms.*

THYMUS HYPERPLASIA

The cases in which *hyperplasia* of the thymus is found are relatively rare. Such findings have been made chiefly after castration, in Graves' disease, Addison's disease, myasthenia, acromegaly and the so-called thymus death. Bergstrand (1919) has published two cases of parathyroid enlargement combined with thymus hyperplasia. It is at present impossible to decide whether in these cases the thymus hyperplasia has been produced by changes in the parathyroids. I shall discuss the "thymus death" in the next paragraph. Of the others it is only the hyperplasia after castration and in Graves' disease that have been sufficiently investigated for it to be possible to give some indication of their character here.

With regard to *hyperplasia after castration* I have already mentioned Gellin's results as far as they bear upon prepuberal spaying. It should be added that the same investigator has shown that castration causes hyperplasia of the thymus even when carried out after puberty. It seems from this as if the effect of the castration is less that of checking the process of age involution than that of transferring the regular metabolic processes in the organ, perhaps its production and elimination of lymphocytes especially, to another and higher plane than in the case of intact subjects of the same age. That even in man and even when carried out relatively late postpuberal castration may have an effect of this sort, is shown by a case published by the writer (1918). In a woman, 51 years old, whose ovaries had been removed at 39 and 49 years of age, respectively, there was a distinctly supranormal quantity both of parenchyma and Hassall's corpuscles. At present, however, it is impossible to say whether hyperplasia after castration in man is always of the same type as in the case mentioned.

Best known is *hyperplasia in Graves' disease,* of which I have analyzed numerically 32 cases, 25 of which were already published in 1917. We are here concerned with a hyperplasia that is not infrequently considerable, in which the cortex is to a very great extent, sometimes even exclusively, the region of the parenchyma that is increased and in which the Hassallian corpuscles are increased in number, sometimes to a greater, sometimes to a smaller, extent than the parenchyma, but in typical cases always in a way that is beyond all doubt. The energy of growth in the Hassallian corpuscles newly formed in this way seems to agree more with the normal, so that the quotient II/I is here, as a rule, greater than 1.0 and sometimes is even supranormal.

In uncomplicated cases there is very little fat in the parenchyma of the hyperplastic thymus in Graves' disease, and not infrequently there is none at all. Even the hyperplastic thymus may, however, be affected by accidental involution, often recognizable by the appearance of a somewhat greater amount of fat in the reticulum cells of the cortex. In this involution it is the cortex, as usual, that first reacts by being reduced. Then in certain cases it may turn out that only the medulla, and not the cortex, remains in an increased condition and the quantitative relation between cortex and medulla is obviously altered in favor of the medulla; in other words, a low index appears. It may be assumed that such pictures partly formed the basis of the view maintained in certain quarters (Schridde 1909, 1911; Koch 1911, Klose 1912, etc.) that a hyperplasia of the medulla is, above all, the distinguishing feature of the alterations in the thymus in Graves' disease.

The results obtained by Utterström (1910) by feeding rabbits with thyroid gland indicate that it is noxae issuing from the thyroid gland that are at the root of this hyperplasia. It is true that this investigator never succeeded in his experiments in producing a real hyperplasia of the thymus, but the size of the organ was as a rule so considerable in relation to the animal's greatly reduced state of nutrition and contrasted so decidedly with that of the animals which had been brought to the same degree of emaciation by starvation that we must assume with Utterström that the supply of the thyroid substance had been an item of great importance in the excitation of the thymus. Courrier (1921) has obtained results closely agreeing with these. The thymus reacts differently on thyroid ingestion according to whether the metabolic balance is positive or negative. If it is negative, atrophy of the thymus arises because of the general denutrition. If positive, we generally get thymus hyperplasia, due, as it seems, to specific influence of the thyroid.

Lampé, Liesegang and Klose (1912) consider, however, that this thymus excitation may be caused in an indirect manner by a lesion of the "interstitial gland" in the gonads.

As in the case of age involution, so with the more temporary changes of the thymus discussed here, accidental involution and hyperplasia, it seems also to be true that, as far as they are caused by the conditions of the lymphocytes, they are not peculiar to the thymus but have their analogies in the changed conditions of these cells in other parts of the organism as well. Thus the occurrence of an accidental involution even in the real lymphoid tissue has been shown by Jolly and Levin (1912, 1914:1) and Hellman (1914) and Källmark's investigations (1911) as to the total of leucocytes of different forms in the blood during starvation have thrown further light on the mobilization process of the lymphocytes that takes place under such circumstances. We have less information as to the corresponding conditions in thymus hyperplasia, but still we know that it is often combined with an increase of lymph glands and other lymphoid organs (Hellman*), a fact that has led to the wide-spread conception of a status thymo-lymphaticus—or, perhaps with a more non-committal expression, a lymphocytism (Hammar, 1913)—as existing in these diseases. The occurrence of a lymphocytosis in Graves' disease is likewise a fact well established of late years.

If we are thus justified in assuming that the changes in the number of the thymus lymphocytes in accidental involution and in hyperplasia are, generally speaking, only manifestations of processes that really involve the lymphocytes in the whole organism, then it is an obvious assumption that the same is true on the whole for changes of the same sort lying within the boundary of what is normal.

At any rate it is certain that changes of this sort occur even normally in the thymus. Even in organs from subjects who have died suddenly, for instance from external violence, while in good health and nutrition, on the one hand mitoses are never absent in the lymphocytes of the cortex before old age, and on the other hand there are always lymphocytes present in the interstitial tissue of the organ, especially, as has already been pointed out, in the interfollicular septa. It is also under these circumstances not unusual to find lymph vessels more or less filled with lymphocytes. Everything thus supports the idea of the production and export of lymphocytes even under normal conditions. It seems to be of less importance in this connection whether all the lymphocytes leave the organ unaltered or whether a number of them are already changed interlobularly into the larger leucocyte forms present there (possibly also into erythroblasts), as is maintained by certain investigators (among others Weidenreich 1912, and Weill 1913), though the pictures certainly in many cases encourage a view of this sort. Vera Dantschakoff (1916) has also paid special attention to this process of differentiation, putting it forward as a criterion of the small thymus cells having the character of genuine lymphocytes.

With regard to the epithelial elements of the organ, too, a certain normal lability can be established. Thus even in the reticulum cells mitoses are found long after the general growth of the body has stopped. Normally, too, fat granulation may be found in the reticulum cells of the cortex, though it is far from being a constant character. And all sorts of regressive forms of Hassall's corpuscles also occur normally side by side with those that show themselves by their small size and their close structure to be new formations.

All this serves to form a basis for the conception of the thymus as an organ that not only undergoes great variations in its structure during disease and other extreme states in the organism, but even under normal conditions sensitively reflects all sorts of variations in the organism to an extent which, as far as our present knowledge extends, is not exceeded by any other organ. The losses of substance thereby incurred by the organ through the emigration and degeneration of cells* are more or less completely made good by the processes of mitotic regeneration that normally occur, both in the lymphocytes and the reticulum cells during the whole time the organ is functioning.

* From this point of view Helene Deutsch's statements (1913) as to the "normal" occurrence of a thymolytic ("thymus-abbauende") ferment in human blood are of interest. They are contradicted, however, by the negative results of Bauer (1913), Kolb (1913). Lampé and Papazolu (1913). If the difference in results is not due to technical errors, it is conceivable that the different degree of the processes of reduction in the thymus on different occasions has been of importance (Hammar, 1914 :2). In the case of thyroid disease there are, on the other hand, fairly unanimous positive results with regard to the occurrence of blood ferments of this sort (see Bauer, Kolb, Lampé and Papazolu, Lampé and Fuchs, 1913).

One must admit that it is not in the first place in an organ of this labile nature that one would expect to find traces remaining of an innate abnormal constitution in the cases where this may be looked for. In thus wishing to make a "persistence" or a "revivescence" of the thymus into a specially pregnant expression for such a constitutional anomaly—lymphatism—too little attention has, to my opinion, been paid to what is perhaps the most striking quality of the thymus—its capacity for rapid and powerful reaction.† On the other hand the organ is, just because of this, suited to give valuable indications as to the state of the organism on the special occasion of its investigation. In this respect the trained eye can even now learn from the organ, and it is to be expected that, with extended experience as to the correlative conditions of the organ, these possibilities will be very essentially increased. In the present state of our knowledge there is, on the whole, no other organ in the body that is more fitted than the thymus to illustrate the phenomenon of the correlation of organs.

† I cannot enter here into a discussion on the problem of lymphatism; for this I refer to my earlier statements (Hammar, 1913, 1914:2, 1916, 1917).

EDITORIAL SUMMARY

The thymus gland is fundamentally an epithelial organ infiltrated with lymphocytes. The epithelial components in various mammals are of diverse origin—entodermal in some, ectodermal in some, and combined ecto-entodermal in others. In man the lymphocytic infiltration begins in the second month of intrauterine life.

Contrary to frequent statements the thymus persists as a functioning organ throughout life, although at puberty "age involution," i. e., reduction of parenchyma begins. Five types depending upon age can be differentiated: (1) Type of childhood; (2) Puberal types; (3) Type of youth; (4) Adult type; (5) Senescent type. These types are described.

Descriptions of the thymus gland based upon material from diseased subjects are misleading. Such glands are never normal.

Usually the parenchyma is reduced; occasionally it is hyperplastic. The normal ratio between corpuscles and lymphoid elements is disturbed. Even in healthy subjects the thymus is a very labile gland.

This paper will be concluded in the November issue.—Publishers.