PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF THE PAST TWO YEARS ON THE ORGANS OF INTERNAL SECRETION

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The review which follows is intended to cover those parts of the literature on internal secretions of the past two years which have seemed to the writer to be especially important or interesting. It was found impossible to master the entire literature that has sprung up about this fruitful subject, much less to include it in its entirety in a review, so that some important work may receive no mention. Certain organs known to have an internal secretion, the genital glands and pancreas, and others thought by some to possess an internal secretory function, such as the kidney, have been purposely omitted from consideration for lack of time and space for adequate treatment. On the other hand, the pineal and carotid glands, which have been much exploited recently, have been discussed in some detail, although no certainty exists that they are organs of internal secretion. Pende's "new organ of internal secretion" has been included.

The citations of the literature are not absolutely complete. Certain references which seemed to be of little value have been purposely omitted from the list, and doubtless some important references have been accidentally passed over.

THE SUPRARENALS

Thomas,¹ and Elliott and Armour,² both writing in 1911, described the histologic changes which occur in the cortex of the suprarenal shortly after birth. It is well known that the suprarenal of the newborn child is considerably larger, relatively speaking, than the suprarenal at a later period of childhood or in adult life. At the third post-natal month it actually weighs less than at birth (Elliott and Armour), although the body weight has increased by one half or two thirds. According to Elliott and Armour the cortex of the suprarenal at birth is composed of a narrow outer rim of cells, from which develops

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1. Thomas, E.: Beitr. z. path. Anat. u. z. allg. Path., L, 283; cited by Pappenheimer.

2. Elliott, T. R., and Armour, R. G.: Jour. Path. and Bacteriol., 15, 1911.

the adult cortex, and between this rim and the medulla an enormous mass of fetal cortex, destined almost immediately to disappear. The medulla at birth is a thin core, not much more than a line in thickness, which increases in size progressively as age advances. The largest part of the chromaffin tissue of the new-born child lies outside the suprarenals in the paraganglia of the sympathetic. But these paraganglia dwindle as the medulla of the suprarenal increases. "Generalizing roughly, one may say that the fetal cortex, which was so large, and the fetal paraganglia perish and are replaced by a new cortex and a new medulla, which constitutes the adult gland" (Elliott and Armour). The fetal portion of the cortex of the suprarenal contains at birth blood vessels, but not the lipoid substance, which seems to be the characteristic product of the permanent cortex. Immediately after birth it undergoes fatty degeneration and vanishes, but the outer rim, which contains the characteristic lipoid even before birth, increases in size and forms the permanent cortex of the gland.

Lewis and Pappenheimer³ have studied the suprarenal gland in a large series of children dying within the first three weeks of life. According to them the degenerative changes appear in the cortex very soon after birth, and are practically complete by the end of the second week. They cause an abrupt diminution in the breadth of the cortex. No regenerative process can be detected during the first three weeks of life. They think the fibrous tissue which in the mature gland separates the medulla from the cortex is formed simply by the collapse of the connective tissue framework of the fetal portion of the cortex as the result of the degeneration and disappearance of its parenchymatous cells. Neither prematurity nor inanition modify the course of the involution.

Kern, who has looked for these changes in the suprarenals of pigs, rabbits, calves, sheep, rats and horses, has been unable to find them. If his observations are correct, the process seems to be peculiar to human beings. Elliott and Armour also state that the suprarenals of animals (they have not examined the suprarenals of the monkey) are smallest at birth and increase in size progressively as age advances, a fact which speaks against the occurrence in the suprarenals of animals of the cortical changes in man.

The active principle of the suprarenal (epinephrin) McCord demonstrated in very young beef fetuses by means of the uterus strip method.

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3. Lewis, R. W., and Pappenheimer, A. M.: A Study of the Involutional Changes Which Occur in the Adrenal Cortex During Infancy, *Jour. Med. Research*, 1916, xxxiv, 81.

J. H. Lewis⁴ on the other hand, failed to detect epinephrin in the suprarenals of human fetuses, even at term; and Elliott could discover only a trace of the epinephrin in the suprarenals of new-born children, although he found definite evidence of epinephrin in the paraganglion aorticum, a mass of chromaffin tissue situated close to the suprarenals. The epinephrin content of this ganglion was 1/500 of its weight. Similar negative results in human beings have been reported by Moore and Purinton,⁵ 1900, and Svehla,⁶ 1900, using the older, less accurate chemical methods. The method which Lewis employed for the detection of epinephrin was the chemical method advocated by Folin, Cannon and Denis.⁷

Cannata⁸ could find no epinephrin in the blood of new-born children—an experimental result to be anticipated.

Fulk and Macleod⁹ report that acid extracts of retroperitoneal chromaffin tissue of man, the dog, cat, rabbit, guinea-pig, white rat, calf, sheep and pig have the same physiologic action on excised strips of intestine and uterus as the active principle of the medulla of the suprarenal gland.

Stewart, Rogoff and Gibson¹⁰ have been able to detect epinephrin in the blood after stimulation of the peripheral end of the splanchnic nerve, according to the method of Joseph and Meltzer. These last-named investigators found that when one cervical ganglion was removed in the rabbit and several days later the peripheral end of the splanchnic nerve stimulated, there occurred an unmistakable dilation of the pupil on the ganglion-free side. Removal of the ganglion of the sympathetic had rendered the pupil on that side far more sensitive to epinephrin. Stewart, Rogoff and Gibson found that this characteristic response was obtained when epinephrin was injected into the blood stream and was not obtained when the splanchnic was stimulated after the suprarenals had been removed, or when the circulation was interfered with in such a way that epinephrin could not reach the eye. The latent period for liberation of epinephrin from the suprarenals

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4. Lewis, J. H.: Presence of Epinephrin in Human Fetal Adrenals, *Jour. Biol. Chem.*, 1916, xxiv, 249.

5. Moore, B., and Purinton, C. O.: *Am. Jour. Physiol.*, 1900, iv, 57; cited by Lewis.

6. Svehla: *Arch. f. exper. Path. u. Pharmacol.*, xliii, 321; cited by Lewis.

7. Folin, Cannon and Denis: *Jour. Biol. Chem.*, 1912-1913, xiii, 477; cited by Lewis.

8. Cannata, S.: Sulla presenza di adrenalina, nel sangue del neonato, *Pediatria*, 1915, Series 2, xxiii, 244.

9. Fulk, M. E., and Macleod, J. J. R.: Evidence That the Active Principle of the Retroperitoneal Chromophil Tissue Has the Same Physiological Action as the Active Principle of the Suprarenal Glands. *Am. Jour. Physiol.*, 1916, xl, 21.

10. Stewart, G. N., Rogoff, J. M., and Gibson, F. S.: The Liberation of Epinephrin from the Adrenal Glands by Stimulation of the Splenic Nerves and by Massage, *Jour. Pharmacol. and Exper. Therap.*, 1916, viii, 205.

was exceedingly short, since the eye response seemed to occur at the same interval (a fraction of a second) whether the splanchnic nerve was stimulated or epinephrin injected into the renal vein. Massage of the suprarenal produced a similar eye response to that obtained by splanchnic stimulation. It was not found possible to exhaust the epinephrin supply in the suprarenals by fright, or morphin administration to such an extent that the characteristic effect on the eye could not be produced by splanchnic stimulation.

Hartmann¹¹ found that dilute solutions of epinephrin, for example, 1 to 100,000, caused a fall in blood pressure in the peripheral vessels, even after the latter had undergone dilatation as a result of hemorrhage, but that the same concentration of epinephrin produced a constriction of the splanchnic vessels.

Other investigators have previously reported dual action of epinephrin in dilute as compared with stronger concentration. Brodie and Cullis,¹² for example, found that minute concentrations produced constriction of the coronaries of animals, while stronger concentrations caused dilatation.

Hoskins¹³ has conducted feeding experiments on white rats with desiccated suprarenal gland. The animals numbered forty-five, twenty-six serving as controls. Controls and experimental rats were of the same litters. The feedings were kept up from two to nine weeks. Hoskins found that the testes of the suprarenal fed animals showed definite hypertrophy, in accordance with the clinical evidence that the suprarenal cortex exerts a stimulating influence on the growth of the testes. No other effects of the suprarenal feeding were found. There were no disturbances in the growth or development of the rats.

Stilling,¹⁴ in 1888, discovered that when one suprarenal is removed, the remaining gland undergoes compensatory hypertrophy and that it is the cortical and not the medullary portion which is affected. Biedl¹⁵ in 1899 demonstrated by extirpation experiments in fish that the cortical and not the medullary element is essential to life. Crowe and Wislocki¹⁶ have now found that after partial extirpation of the suprarenal, the part of the cortex which is left undergoes hyper-

11. Hartman, F. A.: The Differential Effects of Adrenin on Splanchnic and Peripheral Arteries, *Am. Jour. Physiol.*, 1915, xxxviii, 438.

12. Brodie and Cullis: *Jour. Physiol.*, 1911-1912, xliii, 313.

13. Hoskins, R. G.: The Effects of Suprarenal Feeding, *Arch. Int. Med.*, 1916, xvii, 584.

14. Stilling, H.: *Rev. de Méd.*, 1888, T9, 459; cited by Crowe and Wislocki.

15. Biedl, A.: *Innere Sekretion, ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie*, 1913.

16. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on the Suprarenal Glands with Especial Reference to the Functions of Their Internal Portions, *Bull. Johns Hopkins Hosp.*, 1914, xxv, 287.

trophy, chiefly in the fascicular zone, while the medullary portion shows no change; either gross or microscopical. After almost total removal of both suprarenals, the animals developed subnormal temperature, frequent convulsions, and entered into a condition analogous to shock. If recovery occurred, it was gradual, but ultimately became complete. Although they found that an autoplasmic transplant of suprarenal might take, the cortical cells surviving while the medullary cells died, such a transplant appeared to have no functional value. The authors had one dog under observation for a year after reduction of the suprarenals to a minute rest, which promptly died with the symptoms mentioned when this rest was removed. The following experiment is particularly instructive. On Nov. 13, 1912, Crowe and Wislicki removed from a dog nine-tenths of the right and one week later the entire left suprarenal. The dog survived. Six months later they ligated the vessels supplying the small piece of the right suprarenal which had been left. The ligation was followed by convulsions, subnormal temperature, etc. The animal surviving, on May 14, 1913, one-third of the rest was removed. Death then occurred in twenty-four hours after characteristic symptoms. The hypertrophy of the cortical portion of the rest was extreme, while the medullary portion showed no hypertrophy.

Elliott¹⁷ has made an extensive study of human suprarenals in health and disease. Among the numerous observations which he has made the following are of particular interest: The lipoids of the suprarenal, which are normally found in the cortex, are stored and consumed under conditions entirely different from those which govern the storage and consumption of the body fat; for example, while the body fat disappears in starvation, the cortical lipoid of the suprarenal persists. The cortical lipoid vanishes rapidly, however, during acute infections and is diminished in chronic infections and anemias. The lipoid content of the cortex and the epinephrin content of the medulla have no relation whatsoever to each other. Elliott suggests that the function of the cortex may be to maintain the cholesterin ester content of the blood, which it is known becomes diminished under the same conditions as those under which the cortical lipoid of the suprarenal becomes diminished. He suggests also that the cortex of the suprarenal has a relationship to growth and sexual maturation. He points out the interesting fact that, morphologically, the cortical cells of the suprarenal are akin to the interstitial cells of the testis.

Turning to the consideration of the medullary function of the suprarenal, he finds no evidence that high blood pressure depends on an increased epinephrin secretion. The epinephrin content is at its

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17. Elliott, T. R.: Pathological Changes in the Adrenal Glands, *Quart. Jour. Med.*, 1914-1915, viii, 47.

lowest "in the afebrile acute cardiac failure associated with mental distress in the struggle to live," but is not lower or higher in diseases accompanied by high blood pressure than in others.

Jump, Beates and Babcock¹⁸ have collected from the literature seventeen cases of precocious sexual development associated with suprarenal tumor, all of which were confirmed by necropsy. It is interesting to note that fourteen of the seventeen patients were girls. In all the cases there was an overgrowth of pubic hair; in fourteen of them hair was present on the face; and in five there was axillary hair. Overgrowth of the body as a whole occurred in all. Precocious menstruation and breast development appeared in only one. The majority of the children showed diminished intelligence, but some appeared to be unusually bright. There seemed to be a tendency toward the assumption of the masculine type of sexual development in all the females and an exaggeration of the normal in the sexual development of the males. The tumor always involved the suprarenal cortex.

Baldwin¹⁹ adds another case, a boy 5 years old, whose face was like that of a man and had been shaved for some time. The father thought that the premature sexual development had been evident at about the 18th month. Hair on the pubis and face appeared at 3, and at that time it was noticed the voice was like that of a man. The genitalia resembled those of the adult, except that the testes were small and not completely descended. Necropsy showed a large hypernephroma of one suprarenal and a small one of the other. The other organs of internal secretion were normal.

Van der Bergh reports still another case of hypernephroma of the suprarenal in a girl of 3 years with somatic changes analogous to those just described. The girl was from 4 to 5 inches taller than the average, and her general aspect and the appearance of her genital organs suggested the adult state. There was no indication of pineal or hypophyseal tumor. The hypernephroma was removed and weighed 2,000 gm. Van der Bergh reviews the literature. The ages in his group of cases ranged from 14 months to 14 years; two girls of 5 and 9 years had beards; extreme obesity occurred in several cases.

THE CAROTID "GLAND"²⁰

Luschka, in 1862, gave the first accurate histologic description of the carotid bodies and expressed the view that they were glands and

18. Jump, H. D., Beates, H., Jr., and Babcock, W. W.: Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, *Am. Jour. Med. Sc.*, 1914, cxlvii, 568.

19. Baldwin, J. F.: Adrenal Precocity; Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, *Jour. Am. Med. Assn.*, 1914, lxiii, 2286.

20. Betke's article, on which this review is based, contains a complete bibliography and discussion of the entire subject.

not nervous tissue. Arnold, on the other hand, considered them actually to be blood vessels which branched and developed high epithelium in such a manner as to cause histologic resemblance to glandular tissue.

Embryologists have derived the carotid bodies from the third branchial cleft (from the thymus), from the thyroid anlage and from the sheath of the carotid vessels. Kohn first recognized that the carotid bodies were composed of chromaffin tissue, and consequently their relationship to the sympathetic system.

In man the carotid bodies are two minute structures, 5 to 7 microns in length by 2.5 to 4 microns in breadth, each of which lies on the medial side of the corresponding common carotid artery at its bifurcation.

The only clinical importance of the carotid bodies is that they occasionally give rise to tumors, more than thirty-nine cases of which have been reported, the youngest in a 16-year-old girl. These tumors have never been accompanied by constitutional disturbance.

The function of the bodies has been investigated by Vassale, Frugoni, Schmidt and Betke. Frugoni injected extracts into animals and obtained results which are now recognized as the effects of tissue extract, such as fall in blood pressure, collapse, etc. His conclusion was that the carotid bodies were organs of internal secretion, having a depressing influence on blood pressure.

Schmidt excised the carotid bodies in two stages by first removing the bifurcating portion of the carotid artery on one side with its carotid body and subsequently the carotid artery and body of the other side. Since he obtained no symptoms or pathologic changes as a result of his extirpation experiments, he concluded that the bodies are functionless rudiments.

Betke²¹ repeated Schmidt's experiments on dogs and cats. He noted no changes for from four to eight weeks, but after that latent period had elapsed, there occurred retardation in growth, increasing weakness and cachexia, which led after a few months to death. The necropsies showed no cause of death in either abdomen or thorax. The chief pathologic changes were found in the skeleton and the spleen. The skeleton showed both microscopic and macroscopic evidences of rickets; the spleen showed a disappearance of the follicles, in some instances accompanied by an increase in the connective tissue; large cells of the megalokaryocyte type were numerous. The bone marrow was characterized by atrophy of the marrow cells.

Betke concluded that the carotid bodies are essential to life and

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21. Betke: Experimentelle Untersuchungen über die physiologische Bedeutung der Glandula carotica, Beitr. z. klin. Chir., 1915, xcv, 343.

are, therefore, to be considered among the most important organs of internal secretion, belonging to the group which presides particularly over the growth of bone, and that they probably have some influence on blood formation.

It is interesting to note that Betke's experiments were published from Rehn's clinic in Frankfort, where the experiments of Klose and of Flesch on the thymus were also performed. All three investigators, the one extirpating the carotid bodies, the other two the thymus, obtained almost identical results. The coincidence in the results of such widely different experiments suggests that some common factor, unrelated to the removal of either thymus or carotid bodies, may have been operative, such as infection, confinement, poor care, or improper food, or a combination of these, giving rise to illness characterized by the gradual development of rickets and ending finally in death, making its appearance among those animals subjected to operation.

In any event, it is difficult to imagine that the carotid bodies can be essential to life, if it is true that they are merely aggregations of chromaffin tissue, when it is considered that chromaffin tissue is widely distributed in the body and even the comparatively immense mass of chromaffin tissue comprising the medullary portions of the adrenal glands is not essential to life.²² Further proof must be offered before Betke's work can be accepted.

THE PARATHYROIDS

Not much important literature on the subject of the parathyroid glands has appeared during the past two years.

Thimm²³ points out that the presence of more than two parathyroids on a side does not mean that the anlagen were more than their usual number.

In almost all the higher mammals parathyroid III is the lowermost, that is, the more caudally situated of the two parathyroids, but since it takes origin from the third pharyngeal pouch, while parathyroid IV, as its name indicates, develops from the fourth pharyngeal pouch, its original position in the embryo was above (cephalad to) that of parathyroid IV. The explanation of the more caudal position of parathyroid III lies in the fact that during its development it descends from its place of origin at the third pharyngeal pouch in company with the thymus cord, also derived from the third pharyngeal pouch, in the course of the migration of the latter downward (caudalward) toward the thorax, and comes to rest in most species of animals near the lower

22. Biedl: *Innere Sekretion*, 1916.

23. Thimm, L.: *Zur Kenntnis der Epithelkörperchen (Glandulae parathyreoideae)*, Arch. f. Kinderh., 1914, lxiii, 321.

pole of the thyroid, but in the rabbit descends farther, so as to lie often considerably below the thyroid, usually in the substance of the thymus gland. Parathyroid III is the larger and more constant of the two parathyroids.

To return now to Thimm's paper: When there are more than two parathyroids on a side, the meaning is that parathyroid III was drawn out during its fetal descent into a thin cord, which became either actually broken up into a number of fragments, each forming a separate parathyroid, or else so thinned in places as to give the appearance of several separate parathyroids, when in reality thin strands of parathyroid tissue (often so minute as to be capable of demonstration only on microscopic examination of serial sections) joined them together in a continuous chain.

There is rarely, if ever, more than one parathyroid derived from the fourth pharyngeal pouch on a side, and not always even one. For example, in the guinea-pig parathyroid²⁴ IV is frequently absent or rudimentary.

Fulci and Giannuzzi²⁵ extirpated some of the parathyroids in rabbits and studied the parathyroid tissue that remained for resulting histologic changes. Though the rabbits died five or six days after the operation, with the symptoms of parathyroid tetany, the investigators were able to detect in the parathyroid rests signs which they interpreted as regeneration. Epithelial strands passed from the main mass or masses of parathyroid tissue into the surrounding connective tissue, like the extensions from a neoplasm; some of the cells of the strands were undergoing division and young blood vessels were visible. They observed the same signs of regeneration in the parathyroid tissue of older animals after incomplete parathyroidectomy, as well as in the parathyroids of younger animals.

Thimm's work suggests that Fulci and Giannuzzi might have mistaken the strands connecting separate masses of parathyroid tissue for regenerating parathyroid. In any event, their work is not very convincing.

Jackson²⁶ investigated the effects of inanition on the parathyroids of rats. The parathyroids did not appear to be reduced in young rats by inanition, but in older rats to an extent commensurate with the loss

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24. Ruben, R.: Zur Entwicklung der Thymus und der Parathyreoidea beim Meerschweinchen, *Anat. Anz.*, Jena, 1911, xxxix, 571.

25. Fulci, F., and Giannuzzi, A.: Ueber die Regenerationsfähigkeit der Parathyreoidea (Vorläufige Mitteilung), *Centralbl. f. allg. Path. u. path. Anat.*, 1915, xxvi, 97.

26. Jackson, C. M.: Effects of Inanition on the Structure of the Thyroid and Parathyroid Glands of the Albino Rat, *Anat. Rec.*, 1916, x, 208.

of body weight. He found that the parathyroid is less apt to develop structural changes during starvation than the thyroid and that normal variations in the histology of the parathyroids are less marked than in the thyroids.

By far the most important experimental work on the parathyroids which has appeared during the past two years is that of MacCallum, Lambert and Vogel.²⁷ These investigators performed experiments on dogs to show in a new way that the increased excitability of the peripheral nerves in tetany is caused by the lowered calcium content of the blood. The calcium content of defibrinated dog's blood was reduced in their experiments by means of the dialysis method of Abel, Rowntree and Turner; that is, the blood was passed repeatedly through a series of celloidin tubes immersed in a fluid which had the same inorganic composition as dog's blood, with the exception that calcium was absent. By dialyzing dog's blood against this fluid the calcium content of the blood was reduced, for example, from 0.0364 gm. to 0.0284 gm. per liter. But the dog's blood could not be rendered calcium free by this method.

When the defibrinated blood with its reduced calcium content was perfused through the isolated extremity of a dog, increased excitability of the nerves was obtained, as determined by the galvanic current. But when the calcium-reduced blood was introduced into a living animal, that is, substituted for the normal blood of the animal, no such lowering of the excitability of the peripheral nerves took place, for the apparent reason that the calcium of the tissues of the dog passed over so readily into the calcium-reduced blood as speedily to make up the previously created deficiency in the latter. It is a well-known fact that the introduction of normal blood into an animal suffering from tetany stops the symptoms of tetany for a time. But when calcium-reduced blood was introduced into an animal suffering from parathyroid tetany no improvement of the symptoms resulted, thus demonstrating again the dependence of the symptoms of tetany on the lowered calcium content of the blood.

The authors advance the hypothesis that the function of the parathyroid may be to convert the "nondialyzable calcium into a dialyzable form, which latter is essential for the control of the excitability of the nerves, but which is lost in the excreta and not newly formed in the absence of parathyroid secretion."

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27. MacCallum, W. G., Lambert, R. A., and Vogel, K. M.: The Removal of Calcium from the Blood by Dialysis in the Study of Tetany, *Jour. Exper. Med.*, 1914, xx, 149.

THE PINEAL GLAND²⁸

The pineal gland was selected by Descartes (1628) as the probable seat of the soul, on account of its central position in the brain and its proximity to the ventricles. It has been considered as a possible organ of internal secretion only since other structures of doubtful significance to the body have been found to be glands of internal secretion of vital importance. Embryologically, the pineal gland is the vestigial remnant of the pineal eye of the reptiles and certain other lower forms.

Gutzeit²⁹ in 1896 reported a case of teratoma of the pineal in a 7-year-old boy with precocious sexual development. Oestreich and Slawyk³⁰ in 1899 reported another case and almost simultaneously Ogle³¹ reported a third case of pineal teratoma, both of them in boys less than 7 years old showing precocious sexual development. By 1907 enough case reports of tumor of the pineal had accumulated in the literature for Marburg³² to collect forty-one, including his own. Although only two of Marburg's forty-one cases of pineal tumor showed precocious sexual development, and only a very small number a bodily development exceeding the normal, and in spite of the fact that no experimental work has been done on the pineal which could be used as a basis for speculation (Dandy), Marburg enunciated three clinical syndromes. Hyperpinealism, according to Marburg, gave rise to adiposity; apinealism, to cachexia; and hypopinealism to precocity of sexual development and to hypertrophic conditions of the genitalia.

Since Marburg's publication other cases of pineal tumor have been added to the list, bringing the total number, according to Horrax, to seventy. But in only two of these more recently reported cases have there been the symptoms of precocious sexual development, one, the case of von Frank-Hochwart³³ (1909) in a boy 5½ years old, the other, Horrax's own case (1916). Horrax has reported, in addition to the case of pineal tumor just mentioned which was made certain by necropsy, two additional cases thought to be pineal tumor on purely clinical grounds, but on such slim evidence as to make consideration of them unnecessary.

28. A review of the entire subject by Kidd up to 1913 will be found in the Review of Neurology and Psychiatry, xi, 1-24 and 55-75. Marburg, *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 146, gives a complete discussion of the subject in its clinical aspects. Horrax: *Arch. Int. Med.*, brings the bibliography up to date and gives an excellent résumé of the literature.

29. Gutzeit: *Ein Teratom der Zirbeldrüse*, Diss. Königsberg; cited by Kidd.

30. Oestreich and Slawyk: *Virchows Arch. f. path. Anat.*, clvii, 475; cited by Kidd.

31. Ogle, *Trans. Path. Soc., Lond.*, Vol. 50, p. 6.

32. Marburg: *Wein. med. Wchnschr.*, 1908, xlviii; *Arbeiten a. d. Wiener neurol. Inst.*, 1906, xiii, 288; *Ibid.*, 1909, xvii, 217; *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 146.

33. Frankl-Hochwart: *Deutsch. Ztschr. f. Nervenhe.*, 1909, xx, 455; cited by Horrax.

Horrax³⁴ authenticated case of pineal tumor was that of a boy aged 12 years, who had always been well except for asthmatic attacks until three and one-half months before his admission to the Brigham Hospital. There they noted that the patient was a lean boy, weighing 97 pounds, with some pigmentation of the skin, unequal pupils, choked disk, diplopia on looking to the right, suggestive Romberg, positive Kernig's sign, some stiffness of the neck and ataxia of the left arm. The symptoms, which had been observed during the three and one-half months prior to his admission to the hospital, were dilated and unequal pupils, a staring expression, blurred vision, headache, nausea and vomiting. The case was thought probably to be tuberculous meningitis. When, however, the necropsy revealed pineal tumor, certain other symptoms which apparently had not been sufficiently prominent to attract due attention were recalled. The boy, though lean, had gained 40 pounds³⁵ during the year preceding his acute illness; the pigmentation of the skin was distributed differently from that of sunburn; the genitalia were developed in advance of the age; there was a little pubic hair and the down on his face was in excess of the normal.

The important fact which the clinical study of tumors of the pineal gland brings out is that out of a total of seventy cases reported in the literature, symptoms of precocious sexual development appear in only five, and excessive growth in not more than seven. The study of case reports of pineal tumor, therefore, raises the inquiry whether the pineal gland has in reality anything to do with either sexual or physical development; in other words, whether precocious sexual development or growth occurring in cases of pineal tumor can not be explained by pressure effects on neighboring structures (the hypophysis?).

The most important symptoms of pineal tumor from the standpoint of diagnosis are the focal symptoms produced by the pressure of the tumor against the corpora quadrigemina and underlying structures, with resulting rather characteristic involvements in the distributions of the oculomotor nerves on both sides, and vertigo. The focal symptoms are usually accompanied by general symptoms of tumor. It may be said that if precocious sexual or physical development is present in a given case, unaccompanied by any focal symptoms pointing definitely to the pineal, it is probable that the cause lies elsewhere than in the pineal gland.

Cysts are the most frequent form of pineal tumor and next to cysts, teratomas. All five cases of pineal tumor showing precocious sexual development have been teratomas of the pineal. Hemorrhage into the

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34. Horrax, Gilbert: Studies on the Pineal Gland. I. Experimental Observations, *Arch. Int. Med.*, 1916, xvii, 607.

35. He weighed 114 pounds at the beginning of his illness.

pineal and abscess of the pineal have been reported, and also tuberculous and syphilitic involvements.

The experimental attempts to determine the existence of pineal function have followed the usual lines employed in the determination of the function of organs of internal secretion, namely, feeding and injection experiments and extirpation of the gland.

Extirpation of the pineal gland has been performed by Sarteschi³⁶ in 1910 (rabbits) and in 1913 (puppies and guinea-pigs); by Biedl³⁷ in 1910 (dogs); by Exner and Boese³⁸ in 1910 (rabbits); and by Foà³⁹ in 1912 and 1914 (chickens). Sarteschi had very few survivals from his experiments. One puppy gained more rapidly in weight than the control puppy and at autopsy it was found that the testes were larger than those of the control. Biedl's three surviving dogs⁴⁰ showed no effects. Exner and Boese's six surviving rabbits remained normal. Foà succeeded in his first set of experiments in bringing three pinealectomized cocks and twelve hens to maturity. The pinealectomized cocks crowed and were sexually active from forty-two to seventy-nine days before their controls, and developed hypertrophied combs and testes. In his second set of experiments two male and five female chickens survived. The two males developed in exactly the same way as the males of the first set of experiments. But the females in both sets of experiments remained entirely normal. Foà also removed the pineal gland from a few rats, with indefinite results very similar to those obtained by Horrax.

Adler, attracted by the experiments of Foà, investigated pineal function in the frog. The frog larva seemed to be particularly adapted for demonstration of the effects of extirpation of the pineal. For if the pineal regulates in some special way growth and development, its activity should be intense at the period of metamorphosis from the larval state, and consequently the changes produced by its removal should become very evident as the period of metamorphosis falls due. In the second place the phenomenon of sudden transition from tadpole to frog, at about the tenth to the thirteenth week, afforded a splendid means of measurement of any influence on the development and growth of the animal.

Adler⁴¹ pinealectomized by means of the thermocautery 850 tad-

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36. Sarteschi, U.: *Folia Neurobiologia*, Vol. iv, No. 6; cited by Kidd.

37. Biedl, A.: *Innere Sekretion*, 1913, p. 194.

38. Exner and Boese: *Deutsch. Ztschr. f. Chir.*, 1910, cvii, 182; *München. med. Wchnschr.*, 1911, i, 154; *Neurol. Centralbl.*, 1910, 754.

39. Foà, C.: *Arch. ital. de biol.*, 1912, lvii, 233; *Ibid.*, 1914, lxi, 79; *Pathologica*, iv, 445.

40. Biedl's dogs were fully grown at the time of operation.

41. Adler: *Extirpation der Epiphyse*, *Arch. f. Entwicklungsch. d. Organ.*, 1914, xl, 1.

poles, averaging 21 mm. in length. However, a very small number of them survived the operations and the subsequent period of observation. His operative frogs showed no differences in growth or development, which he felt justified in referring to the removal of the pineal. When he killed the surviving animals two months after the pinealectomy, he was unable to find any changes in thyroid, hypophysis, thymus, or in the testis. He concluded, therefore, that the pineal does not exercise in the frog the functions which were indicated by Foà's experiments in the fowl.

Dandy⁴² (1915) was the first to devise a satisfactory experimental method for removal of the pineal gland in dogs. The methods used by the investigators already mentioned were accompanied by a high mortality, due to hemorrhage from the veins of Galen, which are in close proximity to the pineal gland. Dandy's method depends on an exposure of the pineal by incision through the corpus callosum. He used dogs varying in age from 10 days to 3 weeks, the exact number of which are not stated in his publication. One of his animals was alive fifteen months after the operation; one died of distemper one year afterward; and several survived three to eight months, dying of some condition entirely unrelated to the pineal. Dandy's experiments were hampered by the distemper and mange. He was unable to detect any change in his animals in their sexual or physical development, or in the histology of any of the organs, including the organs of internal secretion. He concluded that the pineal is not essential to life and that removal of the gland in dogs furnishes no evidence that it possesses a function.

The most recent pineal extirpations are those of Horrax³⁴ in guinea-pigs and rats. Out of a large number of guinea-pigs Horrax succeeded in removing the pineal completely in fifteen males and twenty females, which were able to survive the operation. His animals were 2 days to 7 weeks old at the time of the operation, and were kept under observation for periods varying from seven and one-half to fourteen weeks. He controlled his operative animals chiefly but not entirely from the same litters and performed on the controls sham operations, stopping short of removal of the gland. Horrax found that loss of the pineal was not followed by any change in the weight curve. He did find, however, that the testes of the male animals of his operative series outweighed those of the controls, averaging 12.8 gm. as opposed to 9.9 gm., the average weight of the testes of the controls. Between the ninth and eleventh weeks minor histologic changes were found; but in younger animals none were present, and in older animals

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42. Dandy, W. E.: Extirpation of the Pineal Body, *Jour. Exper. Med.*, 1915, xxii, 2.

the changes, if formerly present, had disappeared. The changes noted in the period between the ninth and eleventh weeks were larger tubules and more signs of spermatogenesis than in the testes of the control animals. The seminal vesicles of the operative guinea-pigs also appeared to be the more distended and to contain a colloid substance in greater abundance. The female animals in Horrax' experiments seem to have been essentially unaffected, although he thought he could discern a tendency toward earlier conception.

Horrax' pinealectomies in rats showed really nothing except that the operation was feasible in that species of animals, for his experimental material was killed off in large part by an epidemic.

Horrax draws two conclusions from his experiments, that the loss of the pineal hastens the growth and maturation of the testes and tends to accelerate sexual maturity in the females.

Howell,⁴³ 1908, Dixon and Halliburton,⁴³ 1909, Jordan and Eyster,⁴³ 1911, Ott and Scott,⁴³ 1912, injected pineal extract into animals, obtaining on the whole negative results. Horrax, using pineals from young calves and sheep to make his extract, obtained a fall in blood pressure. McCord⁴⁴ also obtained a drop in blood pressure by injection of pineal extract into animals, and in some instances even death. Both investigators attributed the fall to the physiologic action of the internal secretion of the pineal gland.

Dana and Berkeley⁴⁵ have performed feeding experiments on young guinea-pigs, kittens and rabbits. They found that the animals fed with pineal gained weight more rapidly than the control animals. They then fed pineal glands to defective children, including mongolian idiots, and found that their mental progress was more rapid, though they did not gain in weight so rapidly as the control children.

The most numerous feeding experiments have been done by McCord.⁴⁴ He fed powdered extract of pineals taken from animals of different ages to guinea-pigs, puppies, adult dogs and chicks with remarkable results. He found that chickens fed with the extract of the pineals of young animals gained in weight more rapidly than the control chickens, but that when they were fed extract from pineals of mature cattle, they gained no more rapidly than the controls. In his feeding experiments on guinea-pigs he found a symmetrical overgrowth of the pineal-fed guinea-pig and also an acceleration of sexual

43. For references to the work of these investigators consult Kidd or Horrax.

44. McCord, C. P.: *The Pineal Gland*, Interstate Med. Jour., 1915, xxii, 354; *The Pineal Gland in Relation to Somatic, Sexual and Mental Development*, Jour. Am. Med. Assn., 1915, lxxv, 517.

45. Dana, C. L., and Berkeley: *The Functions of the Pineal Gland*, Med. Rec., New York, 1913, lxxxiii, 835; cited by Horrax. Berkeley, W. N.: *The Use of Pineal Gland in the Treatment of Certain Classes of Defective Children*, Med. Rec. New York, 1914, lxxxv, 513; cited by Horrax.

maturity, as demonstrated by the fact that with but two exceptions young guinea-pigs were born to the pineal-fed females left to breed naturally with pineal-fed males earlier than young were born to the control females bred to control males. McCord's experiments on puppies were rendered of little value because of an epidemic of distemper. Nevertheless, he thought he could detect more intelligence in the pineal-fed dogs than in the controls, as well as increased growth. He remarks that when his experiments were finished only the pineal-fed dogs were in demand as pets.

It seems probable that a mass of experimental literature of a conflicting nature will develop about the pineal body, like that which has sprung up around the thymus and the spleen. It can now be said that the experimental work on the pineal up to the present time has failed to prove that it possesses a function. The results of Foà, which were negative in the pullets and positive only in a few cocks, cannot be regarded as in any way final. The changes which Horrax obtained were so slight as to make it seem remarkable he should have regarded his experiments as positive. If the extraordinary results which McCord obtained by feeding pineal were actually caused by the active principle of the gland, the extirpation experience of Dandy and Horrax ought to have brought overwhelming evidence of pineal function and clinical literature to abound with examples of pineal disease.

THE PITUITARY

Keeton and Becht⁴⁶ found that direct electrical stimulation of the hypophysis caused an increase in the reducing substance of the blood, while stimulation of the brain in front of and behind the hypophysis failed to produce any increase in the reducing substance. The increase did not take place in dogs whose splanchnic nerves had been cut—a finding not in accord with the theory held by Cushing and others that it is the hormone discharged by the hypophysis into the blood which causes mobilization of the glycogen.

Dandy and Goetsch⁴⁷ have shown that fibers from the sympathetic are sent to the pituitary body. By stimulating the cervical sympathetic ganglia Shamoff⁴⁸ obtained glycosuria and diuresis in eight out of fifteen animals tested. All nervous pathways from the stimulated ganglion to the kidneys had been cut. Shamoff, therefore, arrived at the opposite conclusion from Keeton and Becht, namely, that it was the secretion of the hypophysis thrown out into the blood stream as a

46. Keeton, R. W., and Becht, F. C.: The Stimulation of the Hypophysis in Dogs, *Am. Jour. Physiol.*, 1915, xxxix, 109.

47. Dandy and Goetsch: *Am. Jour. Anat.*, 1910, xi, 137; cited by Shamoff.

48. Shamoff, V. N.: Concerning the Action of Various Pituitary Extracts on Isolated Intestinal Loop, *Am. Jour. Physiol.*, 1915-1916, xxxix, 268.

result of stimulation of the sympathetic which produced glycosuria and diuresis, especially in view of the fact that the response obtained was a typical pituitary response, as was indicated by the combination of increased blood pressure, glycosuria and polyuria.

Weed and Cushing⁴⁹ determined that extract of the posterior lobe of the hypophysis introduced intravenously into animals caused an increase in the rate of production of the cerebrospinal fluid. The increase obtained appeared to be independent of respiratory or hemodynamic influences. The authors consequently thought that it was due to the specific action of some substance in the posterior lobe of the hypophysis on the choroid plexus, stimulating it to increased secretory activity.

McCord⁵⁰ found that the pituitary in eight-year-old bovine fetuses showed the presence of the active principle as determined by the method of Dale and Laidlaw.⁵¹ McCord believes the active principle of the pituitary is present in fetal life as early as the gland is capable of macroscopic recognition.

Lewis⁵² found that the quantity of pressor substance contained in the hypophysis of the pig fetus of 175 mm. was sufficient to indicate that a pig fetus of this size is independent of its mother's hypophysial secretion. Lewis discovered evidences of the pressor substance in the hypophysis of pig fetuses 125 mm. long.

Fenger⁵³ attempted to determine by the use of the uterus strip method of Fraenkel whether a seasonal variation in the secretory activity of the posterior lobe of the hypophysis could be demonstrated, but was unable to find any difference in the extracts from summer and winter glands.

The literature of the past two years contains reports of a number of experiments in pituitary feeding which have given quite discordant results.

Pearl and Surface⁵⁴ obtained no evidence that the hypophysis activates the resting ovary of the hen.

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49. Weed, L. H., and Cushing, H.: Studies on the Cerebrospinal Fluid. VIII. The Effect of Pituitary Extract on the Secretion (Choroidorrhea), *Am. Jour. Physiol.*, 1914-1915, xxxvi, 77.

50. McCord, C. P.: The Occurrence of Pituitrin and Epinephrin in Fetal Pituitary and Suprarenal Glands, *Jour. Biol. Chem.*, 1915, xxiii, 435.

51. Dale, H. H., and Laidlaw, P. P.: *Jour. Pharm. and Exper. Therap.*, 1912-1913, iv, 75; cited by McCord.

52. Lewis, D.: The Appearance of Pressor Substance in the Fetal Hypophysis, *Jour. Exper. Med.*, 1916, xxiii, 677.

53. Fenger, F.: On the Composition and Physiological Activity of the Pituitary Body, *Jour. Biol. Chem.*, 1915, xxi, 283.

54. Pearl, R., and Surface, F. M.: Studies on the Physiology of Reproduction in the Domestic Fowl. XIII. On the Failure of Extract of Pituitary Body (Anterior Lobe) to Activate the Resting Ovary, *Jour. Biol. Chem.*, 1915, xxi, 95.

L. M. Clark⁵⁵ found, on the other hand, that feeding of the pituitary gland (the anterior lobe) of young cattle to hens raised the egg production curve at a time when the latter was normally on the decline. The effect was noticed four days after feeding was begun and lasted for a number of days after it had been stopped. He observed, further, that a greater percentage of eggs hatched when both parents had received pituitary feeding than when no pituitary was used.

Pearl,⁵⁶ who also fed desiccated substance of anterior lobe of hypophysis to hens at the period of decline in egg production, could find no evidence that it produced any effect. He came to the conclusion that feeding of the pituitary to growing pullets does not bring about earlier activation of the ovary. The feeding of the anterior lobe to chicks, however, produced a retardation in growth.

Robertson⁵⁷ studied the effects of pituitary feeding on the growth of mice. The administration of 0.125 gm. per day of anterior lobe pituitary tissue to mice, begun in the fourth week, led to retardation of growth during the earlier portion of what Robertson terms "the third growth cycle," that is, between the sixth and twentieth weeks; but from the twentieth to the sixtieth week, in the latter part of "the third growth cycle," to an acceleration of growth, so that the pituitary-fed mice caught up to and surpassed the controls. Robertson further observed that pituitary-fed animals from the thirtieth week onward appeared more compactly built than the controls. Though "weight for weight they were smaller, size for size they were heavier." He also observed that the pituitary-fed animals showed marked belligerency.

Robertson⁵⁸ thinks he has isolated the active principle of the anterior lobe of the pituitary, which affects growth, giving it the name "tethelin." The effects on mice obtained by its administration were identical with those which followed the administration of the entire gland. It is prepared by extracting the dried tissue of the anterior lobe of the pituitary with boiling alcohol and precipitating with ether.

Robertson⁵⁹ investigated the effects of extracts of the anterior lobe

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55. Clark, L. N.: The Effect of Pituitary Substance on the Egg Production of the Domestic Fowl, *Jour. Biol. Chem.*, 1915, xxii, 485.

56. Pearl, R.: Studies on the Physiology of Reproduction in the Domestic Fowl, *Jour. Physiol. Chem.*, 1916, xxiv, 123.

57. Robertson, T. B.: Experimental Studies on Growth. III. The Influence of the Anterior Lobe of the Pituitary Body on the Growth of the White Mouse, *Jour. Biol. Chem.*, 1916, xxiv, 385.

58. Robertson, T. B.: On the Isolation and Properties of the Anterior Lobe of the Pituitary Body, *Jour. Biol. Chem.*, 1916, xxiv, 409.

59. Robertson, T. B., and Burnett, T. C.: The Influence of the Anterior Lobe of the Pituitary Body on the Growth of Carcinomata (Preliminary Communication), *Proc. Soc. Exper. Biol. and Med.*, 1914, xii, 68; *Jour. Exper. Med.*, 1915, xxi, 280.

of the hypophysis on the growth of carcinomas inoculated into rats. He found that emulsion of the anterior lobe of the ox pituitary markedly increased the rate of growth of the primary tumor and that small tumors were affected even more than large tumors. But the acceleration in growth was evidenced only at a certain stage in the growth of the tumor, subsequent to the twentieth day after inoculation.

Goetsch⁶⁰ also has made feeding experiments with the pituitary gland to determine the effects on growth and sexual development. He used white rats, choosing stock of known pedigree, in order to reduce normal variation in his material to the lowest possible point. He conducted separate experiments, using the dried, powdered extract of the entire hypophyses and of the anterior and posterior lobes, respectively.

When dried extract of the entire gland was fed to young rats in excessive doses (0.1 gm. daily), it caused failure to gain in weight, loss of appetite, diarrhea, muscular weakness and tremor. These symptoms Goetsch attributed to the activity of the posterior lobe element. When whole gland was fed in smaller dosage, it caused within from twenty-five to forty days a more rapid growth and development, larger nipples in the females, and a more coarse, harsher coat of hair than in controls fed on the same diet. Some of the controls received ovarian extract in the same dosage as that of the hypophysis. The influence of whole gland feeding on the sex glands of the female was to make the ovaries, tubes and cornua of the uterus larger and more vascular than those of the controls and maturity of the ovary to occur one or two months before the normal time. Maturity of the ovary was indicated by active ovulation and Graafian follicle formation. The effect of whole gland feeding on the genital organs of the male was the production of a more rapid growth and development of the testes, an earlier descent, precocious spermatogenesis occurring at a time when the testes of the controls were still immature.

The feeding of anterior lobe alone caused increased weight, greater and more vigorous body growth and an earlier and more active genital development, but without the diarrhea and nervous manifestations seen at the beginning of whole gland feeding. The period of sexual development was shortened by at least one month. That feedings of the anterior lobe produced earlier and greater sexual activity was demonstrated by the fact that a male and a female fed with anterior lobe over a period of from eight to nine months bred earlier and oftener than a control pair, producing two litters in seven months, while the control pair had no offspring. The effect of continued

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60. Goetsch, E.: The Influence of Pituitary Feeding on Growth and Sexual Development. An Experimental Study, *Bull. Johns Hopkins Hosp.*, 1916, xxvii, 29.

anterior lobe feeding on the sex glands held throughout the life of the animal and was greater, the longer had been the period of administration. Its stimulating effect on the parents was seen in the offspring in intrauterine development and during lactation; and when feeding of the offspring with anterior lobe was begun as soon as lactation from the hypophysial-fed mother had come to an end, the very maximal effects were produced.

Posterior lobe feeding did not stimulate growth or the development of the sex glands; in fact, it seemed to retard the development. In large doses it caused a diarrhea, with loss of weight.

It might be mentioned that ovarian extract, Goetsch found, had a stimulating influence on the sexual development of the female, but a retarding influence on that of the male.

Solem and Lommen⁶¹ have found that injection of pituitary extract causes a decrease in the flow of saliva. In their opinion the decrease is brought about by the constricting action of pituitary extract on the arterioles of the salivary glands, which diminishes their blood supply and also by its specific inhibiting influence on the secretory nerves of the glands.

Simpson and Hill⁶² have studied the effect of pituitary extract on milk production. Their conclusion is as follows:

The administration of pituitary extract, by intravenous, intramuscular or subcutaneous injection, to a lactating animal leads to a marked increase in the quantity of milk secreted and also in its fat content. In the goat, if the injection be continued at intervals over a prolonged period—several months—immunity to its action on the mammary glands appears to be established both in regard to the amount of milk yielded and the percentage of fat it contains.

Livingston⁶³ castrated and spayed rabbits to determine any resulting alterations in the weight of the organs of internal secretion, in particular the hypophysis. He found that though hypertrophy of the hypophysis did not regularly follow spaying or castration, it usually occurred and was a commoner development in females than in males. On the other hand, he discovered that a constant relationship did exist between increase in body weight and hypertrophy of the hypophysis, that is, an increase in the size of the hypophysis was accompanied by increased rate of growth and vice versa. No effect on the suprarenals or thyroid could be detected.

61. Solem, G. O., and Lommen, P. A.: The Influence of the Extract of the Posterior Lobe of the Hypophysis on the Secretion of Saliva, *Am. Jour. Physiol.*, 1915, xxxviii, 339.

62. Simpson, S., and Hill, R. L.: The Effect of Repeated Injections of Pituitary Extract on Milk Secretions, *Am. Jour. Physiol.*, 1914-1915, xxxvi, 347.

63. Livingston, A. E.: The Effect of Castration on the Weight of the Pituitary Body and Other Glands of Internal Secretion in the Rabbit, *Am. Jour. Physiol.*, 1916, xl, 153.

Cushing and Goetsch⁶⁴ have made an interesting study of the organs of internal secretion in seven hibernating woodchucks. They found changes of a minor character in several of the organs of internal secretion, but the most definite changes in the hypophysis. The latter was reduced in size, and the cells of the pars anterior in some of the animals had lost their characteristic staining reactions to acid and basic dyes. After hibernation was over, the gland regained its normal size and the cells their normal staining properties and showed signs of division. Their conclusion is as follows:

On the basis of these observations hibernation may be ascribed to a seasonal physiological wave of pluriglandular activity. The essential rôle may perhaps be ascribed to the pituitary body, not only for the reason that the most striking histological changes appear in this structure, but also because deprivation of the secretion of this gland alone of the entire ductless gland series produces a group of symptoms comparable to those of hibernation.

They base the conclusion just given on an analogy. Human beings with hypopituitarism have shown storage of fat, slow pulse and respiration, extreme somnolence and subnormal temperature. The hibernating animal shows exactly this same group of symptoms. The histologic changes in the hypophyses of both are similar. Since the alteration in the hypophysis appears to be the cause in the one, it must be the chief cause at least of the other. Cushing and Goetsch point out that the theory originated with two Italians, Salmon (1905) and Gemelli (1906), both of whom, however, had, in Cushing and Goetsch's opinion, an incorrect conception of the mode of activity of the hypophysis.

Their conclusion that hibernation is the result of a "wave of pluriglandular inactivity" with the hypophysis playing "the essential rôle" forms an attractive hypothesis.

Fry⁶⁵ has made histologic studies of the pituitary in eight cases of diabetes, two of myxedema, one of cystic goiter, one of Addison's disease and one of status lymphaticus. In the hypophysis of diabetes he found an increase in the chromophil cells, which appeared as adenomatous masses, evidences of conversion of chromophil cells into colloid and, in some instances, degenerative changes which were so extensive that few of the cellular elements in the anterior lobe remained. He believed these changes were not a part of a general reaction of the body tissues to the disease, but indicated that the hypophysis was primarily affected and consequently that it might be primarily concerned in the causation of diabetes. In the case of myxedema he

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64. Cushing, H., and Goetsch, E.: Hibernation and the Pituitary Body, *Jour. Exper. Med.*, 1915, xxii, 25.

65. Fry, H. J. B.: The Pituitary Gland in Diabetes Mellitus and Disorders of the Glands of Internal Secretion, *Quart. Jour. Med.*, 1915, viii, 278.

found the pituitary increased in weight; in the case of goiter showing a hyperplasia of chromophil cells, an increase of colloid in the interglandular cleft, but unchanged in Addison's disease and status lymphaticus. He advanced a theory of explanation of the secretory mechanism of the hypophysis which need not be discussed here.

Riese⁶⁶ reports favorable results⁶⁷ from the use of hypophysis extract in asthma, comparable to those obtained by the use of epinephrin. Similar results had been obtained previously by Borchardt (Riese).

Numerous case reports appear in the literature indicating a favorable effect following the use of hypophysial extract in diabetes insipidus. Grøndahl⁶⁷ reports a case of diabetes insipidus accompanying hypophysial tumor in a 16-year-old subject who showed alimentary glycosuria, as well as polyuria and infantilism, and subsequently developed evidences of acromegaly. The polyuria was reduced from the neighborhood of 6 liters a day to about 2 liters by injections of pituitary extract.

Hoppe-Seyler⁶⁸ reports a case in which the urinary output ranged from 4 to 7 liters daily and the specific gravity of the urine was 1.002, treated by pituitary extract. Subcutaneous injections of pituitary extract repeatedly caused temporary reduction of the total urine to between 1 and 2 liters in twenty-four hours.

Graul⁶⁹ reports a similar case in which extract from the pars intermedia and posterior lobe was given hyperdermically with success.

Metzfeldt⁷⁰ reports three patients with diabetes insipidus, one of whom showed improvement when treated with pituitary extract. This case, which Metzfeldt reports in extenso, is particularly interesting in that the patient appeared to be benefited by taking hypophysial gland by mouth. It was necessary for him to take from five to seven glands

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66. Riese, E.: Zur Wirkung des Hypophysenextraktes bei Asthma bronchiale und zur Asthmatheorie, Berl. klin. Wchnschr., 1915, lii, 768.

67. It is very easy to understand that epinephrin produces a favorable effect in asthma, but it is difficult to understand why pituitary extract should produce a favorable effect. Theoretically it should produce an unfavorable effect, because it constricts smooth muscle quite independently of the innervation. Riese's results cannot be accepted until corroborated.

68. Hoppe-Seyler, G.: Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt, München med. Wchnschr., 1915, lxii, 1633.

69. Graul, G.: Ueber einen mit Hypophysin-Höchst erfolgreich behandelten Fall von Diabetes insipidus, Deutsch. med. Wchnschr., 1915, xli, 1095.

70. Metzfeldt, K.: The Pituitary Gland and Diuresis. I. Diabetes Insipidus and Its Relation to the Hypophysis Cerebri. II. Studies on the Action of Pituitary Extract, Especially on Diuresis, Blood Pressure and Nitrogenous Metabolism in Relatively Healthy Men, Norsk Mag. f. Laegevidensk., 1915, xiii, 1305.

at a time, raw or dried and powdered, in order to obtain an effect comparable to "one quarter of a syringe full of commercial extract."

Von Konschegg and Schuster⁷¹ have obtained well-marked diminution in urinary output by the use of pituitary extract injections in both animals and man. The best results they obtained in human beings suffering from primary idiopathic diabetes insipidus. Their animal material was rabbits.

Pollock⁷² reported four cases of hydrocephalus accompanied by adiposity and tapering hands as probable examples of hypopituitarism, caused by the increased intracranial pressure on the hypophysis.

THYMUS

Badertscher⁷³ finds that the thymus of the pig is of both ectodermal and entodermal origin. The ectodermal derivative, he thinks, is constant and forms the "superficial thymus." Kastschenko⁷⁴ (1887) and Zötterman⁷⁵ (1911) also derive the thymus of the pig from both ectoderm and entoderm.

In the guinea-pig and mole⁷⁶ the thymus has also been traced to both ectoderm and entoderm, but appears to be purely entodermal in the other higher mammals investigated.

Marine⁷⁷ points out the frequency of duct-like spaces or tubules in the thymus of dogs. He was able to find them in 21 per cent. of the animals examined, but in only one human thymus out of a total of 126. Marine believes that these duct-like tubules are closely related in their origin to the Hassall corpuscles, both springing from the "embryonic thymic epithelial tubules and cords." He considers that in the case of the Hassall corpuscles the involutionary change took place before the differentiation into tubules occurred; in the case of the tubules differentiation occurred before the involutionary process began.

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71. Von Konschegg, A., and Schuster, E.: Ueber die Bllinflussung der Diurese durch Hypophysenextrakte, *Deutsch. med. Wchnschr.*, 1915, xli, 1091.

72. Pollock, L. J.: Hypopituitarism in Chronic Hydrocephalus, *Jour. Am. Med. Assn.*, 1915, lxiv, 395. There have appeared in the literature a number of cases of this nature. Indeed the diagnosis of hypopituitarism is frequently made in fat children who are otherwise normal, merely because they are fat. In this connection it is necessary to remember that many mentally defective children, and among them hydrocephalics, lead of necessity vegetative existences and receive diets high in carbohydrates. Consequently, they are especially prone to become fat.

73. Badertscher, J. A.: The Development of the Thymus in the Pig. I. Morphogenesis, *Am. Jour. Anat.*, 1914-1915, xvii, 317.

74. Kastschenko: *Arch. f. mikroskop. Anat.*, 1887, xxx; cited by Badertscher.

75. Zötterman, Agne: *Anat. Anz.*, 1911, xxxviii, 514.

76. Ruben, R.: *Anat. Anz.*, 1911, xxxix, 571.

77. Marine, D.: The Frequency of Duct-Like Spaces in the Thymus Gland with Remarks on the Formation and Fate of Hassall's Corpuscles, *Cleveland Med. Jour.*, 1915, xiv, 186.

Hart⁷⁸ also has made a study of the Hassall corpuscles. He states that they are without doubt derivatives of the epithelial elements of the thymus. On this point there is a very general agreement among all authors, although it has been maintained by some investigators that the Hassall corpuscles take origin from the endothelium of blood vessels (Afanassiew,⁷⁹ Barbarossa⁸⁰). According to Hammer,⁸¹ Hart and others the Hassall corpuscles are formed by a coalescence of the thymus reticulum (the epithelial element) very much as giant cells are formed about foreign bodies. Hart states, further, that Hassall's corpuscles are continually being formed so long as the thymus reticulum continues to exist. In this sense, then, the Hassall corpuscles are an index to the functional activity of the thymus. Hart is careful to state that he does not regard the Hassall corpuscles as the secretory element or representing the secretory mechanism of the thymus, as some writers on this subject have done (Magni⁸² Mensi,⁸³ Livini⁸⁴). He regards the epithelium of the thymus (the so-called reticular cells) as the true secretory element and the Hassall corpuscles merely as the index to the amount of epithelium present. "In a word, it is possible to estimate the functioning energy of the thymus by the kind and number of the Hassall corpuscles . . . and so draw conclusions in regard to the condition of the organ at the time of death." The formation of Hassall corpuscles is most active in childhood, and in pathologic conditions in which the thymus function is increased.

Cases of congenital status thymolympathicus have been reported by Hedinger⁸⁵ (12 cases), Kayser,⁸⁶ Flügge,⁸⁷ Somma⁸⁸ and Durante,⁸⁹ but according to Schridde⁹⁰ it is not certain that they are all true cases, for, in the majority, data essential to the diagnosis are lacking, such as weight of the thymus or evidences of status lymphaticus outside the thymus itself. Schridde's⁹⁰ paper consists of a report of three cases of congenital status thymolympathicus. In one case the thymus weighed 19 gm., in the second 24 gm., in the third 26 gm. The histo-

78. Hart, C.: Thymusstudien. IV. Die Hassallschen Körperchen, *Virchows Arch. f. path. Anat.*, 1914, ccxvii, 239.

79. Afanassiew, B.: *Arch. f. mikroskop. Anat.*, 14, 1877.

80. Barbarossa: *Pediatrics*, 1911, Series 2, xix, 457.

81. Hammar, T. A.: Fünfzig Jahre Thymus Forschung, *Ergebn. d. Anat. u. Entwicklungsgesch.*, 1910.

82. Magni: *Arch. f. Kinderh.*, 1903, xxxviii, 14.

83. Mensi: *Pediatrics*, 1903, xi, 65.

84. Livini: Cited by Mensi (Footnote 83).

85. Hedinger: *Jahrb. f. Kinderh.*, New Series, vlili, 308.

86. Kayser, J.: *Diss.*, Giessen, 1895.

87. Flügge: *Vierteljahrsschr. f. gerichtl. Medizin*, 1899, Series 3, xvii.

88. Somma: *Arch. de patol. infant*, 1884.

89. Hedinger: 310.

90. Schridde, H.: Der angeborene Status thymolympathicus, *München. med. Wchnschr.*, 1914, lxi, 2161.

logic picture of the thymus in all three cases was identical with that described by Schridde as characteristic of the thymus of postnatal status lymphaticus. In all three cases hyperplasia of the medulla of the thymus was present, and the lymph follicles of the spleen were enlarged so that they were visible to the naked eye and in two of the cases the follicles of the intestines were also macroscopically visible. All three were excellently nourished infants. The mother of one of them died of eclampsia soon after the birth of the child and showed at necropsy the lesions of status thymolymphaticus, a coincidence which at once suggested the possibility that the pathologic condition was hereditary. Schridde also examined the thymus gland in about fifty stillbirths not the subject of status lymphaticus and found that the difference in weight of the thymus at birth is considerable, varying from 5 to 20 gm.

The average which Hammar gives for the weight of the thymus in the normally sized child at birth is 13.26 to 14.4 gm.

It is well established that the thymus either continues to persist or undergoes a reviviscence in certain diseases, as, for example, very commonly in exophthalmic goiter and with considerable frequency in Addison's disease and myasthenia gravis.

Hart⁹¹ reports two cases of myasthenia gravis and discusses at some length the relationship of the enlarged thymus to the disease. He thinks the enlarged thymus of myasthenia gravis is a persistent thymus which has undergone hyperplasia, as the persistent thymus, in his opinion, tends to do, and that the aggregations of round cells are lymphocytic infiltrations. He attaches a twofold significance to the enlargement of the thymus in myasthenia. In the first place, he believes it indicates that the affected individual has the lymphatic constitution; in other words, is constitutionally inferior and, therefore, predisposed from birth to the development of such disturbances as exophthalmic goiter and myasthenia gravis. In the second place, Hart believes the thymus in myasthenia gravis exerts a pathologic function and is frequently, if it is not always, the cause of the disease. He states that removal of the hyperplastic thymus cures myasthenia gravis, basing his statement apparently on a single case in which the thymus was removed by Sauerbruch,⁹² but at the same time admits that there are cases of myasthenia gravis without hyperplasia of the thymus, a fact which is well known. He endeavors to extricate himself from the dilemma caused through this admission by saying that after all an enlarged thymus is only one of numerous stigmata of constitutional

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91. Hart, C.: Thymusstudien. V. Thymus befunde bei Myasthenia gravis pseudoparalytica, Virchows Arch. f. path. Anat., 1915, ccxx, 185.

92. Reference not given by Hart.

inferiority and that absence of enlarged thymus does not mean that the subject of myasthenia may not be constitutionally inferior, and in the second place that the thymus, though involuted, may exert a deleterious influence, citing that now well-worn case of von Haberer's, in which great improvement took place in a patient acutely sick with exophthalmic goiter, when a part of the retrosternal fat body was removed. Hart seems to be attempting to transfer his theories of thymus function in exophthalmic goiter to the thymus in myasthenia gravis. His reasoning is not clear and his interpretation of the facts seems to be tuned to his theory. The important point in his article is his statement that removal of a hyperplastic thymus cures myasthenia gravis. The truth or falsity of this statement should be investigated.

Funk and Douglas,⁹³ on the other hand, call attention to the complete disappearance of the thymus in pigeons suffering from beriberi. Their studies are limited to eight pigeons, apparently uncontrolled. Although the thymus is supposed to persist throughout life in the pigeon, Funk and Douglas were unable to find even microscopic rests of the thymus in their beriberi pigeons. In addition to disappearance of the thymus they found changes in other organs of internal secretion. The thyroid showed a marked degeneration in two instances and in a third signs of inflammation. The pituitaries also showed degenerative changes. (Their findings in the pituitaries can scarcely have any value because of their method of preparation for histologic study, which must have made accurate histologic interpretation impossible.) The ovaries were reduced in volume: the testes, atrophied. The pancreas was small and showed areas of degeneration. The spleen also was diminished in size and showed absence of the malpighian bodies. The ages of the birds were not given.

The work of Funk and Douglas was assailed by Williams and Crowell.⁹⁴ These authors found that in human beings having beriberi involution of the thymus does not always occur. In some cases the thymus was found actually enlarged and in others even status lymphaticus present. In a beriberi subject of 13 years the thymus weighed 28 gm.; in another 18 years old, 12 gm. Their experimental study was made on sixteen chickens having beriberi. The thymus had disappeared in seven of the chickens, was atrophied in five, and was slightly if at all altered in four. There was no evidence of a relationship between the severity of the disease and the degree of atrophy of the thymus. Thymus tissue was fed to the beriberi birds without any effect. Williams and Crowell concluded that there is no fundamental

93. Funk, C., and Douglas, M.: Studies on Beriberi. VIII. The Relationship of Beriberi to Glands of Internal Secretion, *Jour. Physiol.*, 1914, xlvii, 475.

94. Williams, R. R., and Crowell, B. C.: The Thymus Gland in Beriberi, *Philippine Jour. Sc.*, 1915, x, 121.

connection between atrophy of the thymus and beriberi, and if a protective influence against beriberi is exerted by the thymus, as Funk in a previous paper had maintained, it is due to the pyrimidon and purin derivatives which are present in large amounts in thymus tissue.

Fenger⁹⁵ has made chemical studies of the fetal thymus to determine whether certain substances are present in it which are found in the postfetal thymus. He discovered that the fetal thymus contains nucleic bodies and phosphates in the same proportions as the glands of young growing animals. For this reason he inferred that the gland is active at least three months before birth. He points out incidentally that fetal animals have more thymus tissue per unit of body weight than animals after birth.

In the two or three years which preceded the period covered by this review, appeared the extensive publications of Klose and Vogt,⁹⁶ Klose, and of Matti⁹⁷ on the physiology of the thymus gland. Their experimental work indicated that the thymus was essential to life, had a profound influence on the growth and development of the body and presided especially over the metabolism of bone. Their thymectomized animals not only showed marked disturbances of growth, but developed rickets and well-marked changes in the thyroid and suprarenals. Klose and Vogt, and subsequently Klose, writing independently, reported in addition extensive lesions in almost all the organs, especially in the nervous system, which they referred to loss of the thymus, and even saw in the behavior of their thymectomized dogs a condition of "thymic idiocy." The work of these investigators has had great influence on scientific opinion and rightly or wrongly has elevated the thymus to a position of great importance among the organs of internal secretion. During the past two years, however, some experimental work has appeared with results at variance with theirs, notably the work of Pappenheimer and Nordmann.

Pappenheimer⁹⁸ removed the thymus from rats, aged 3 weeks or less, controlling from the same litters. His original material consisted of twenty-six litters, making a total of 118 rats, eighty-three of which were thymectomized; but owing to an epidemic of dysentery his material became reduced to twenty thymectomized rats and their controls. The period of observation after operation ranged from forty-five to 131 days. Pappenheimer found that removal of the thymus does not produce disturbance in growth or development. No constant pathologic changes were found anywhere, not in any of the organs of inter-

95. Fenger, F.: On the Size and Composition of the Thymus Gland, *Jour. Biol. Chem.*, 1915, xx, 115.

96. Klose and Vogt: *Beitr. z. klin. Chir.*, 1910, p. 69.

97. Matti, H.: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 1.

98. Pappenheimer, A. M.: Further Experiments on the Effects of Extirpation of the Thymus in Rats, with Special Reference to the Alleged Production of Rachitic Lesions, *Jour. Exper. Med.*, 1914, xx, 477.

nal secretion. He serial sectioned the neck and thoracic tissues of his thymectomized animals for thymus rests, thus proving their absence in the twenty animals which formed the basis of his report. Since his experiments are probably the only ones in the higher mammals in which thymus rests were proved to be absent, his negative results have the value of positive experiments.

Nordmann⁹⁹ had already published two sets of thymus extirpation experiments in dogs. His latest contribution consists of the results of thymectomy experiments performed on eight litters of puppies in the second week of life. He used the operative method of von Basch, which may be called the standard for excision of the thymus, and the intratracheal insufflation of Meltzer. The puppies were fed on a mixed diet and were allowed complete freedom out of doors. He killed them at various periods after thymectomy in order to avoid the error of overlooking transitory changes. Some of them he let live for more than a year. His thymectomized dogs developed no symptoms or pathologic changes of any sort whatsoever. The necropsies revealed no thymus rests in a single instance, although a particularly careful search appears to have been made.

Nordmann's results in this set of experiments have especial importance because in his previous experiments in thymus extirpation he had obtained muscle weakness, abnormal gait with the forelegs thrown wide apart, fatigue, infections of the skin, with loss of hair, and circulatory disturbances, of which dilatation of the heart was the chief. The conclusion which he had drawn from his previous experiments was that the thymus is an important organ of internal secretion, possibly essential to life, having to do especially with the nutrition, regulation of the heart's action and resistance to infections. In the light of his recent work he now concludes that his former results were due to other causes than deprivation of thymus function, for example, infection, and that the thymus is not essential to life and its removal in young dogs is meaningless.

It should be added that Nordmann removed the spleens from several animals, as well as the thymus, without the discovery of any pathologic developments such as Klose described. One female dog deprived of both spleen and thymus bore normal puppies.

Nordmann suggests that the results of the thymectomies obtained by Matti and Klose may have been due to domestication. He charges Klose with the use of an inbred type of dog, particularly liable to the spontaneous development of rickets.

99. Nordmann, O.: Experimentelles und Klinisches über die Thymusdrüse, *Arch. f. klin. Chir.*, 1914, cvi, 172; *Deutsch. med. Wchnschr.*, 1914, xl, 1702.

100. Klose, H.: Thymusdrüse und Rachitis, *Centralbl. f. allg. Path. u path. Anat.*, 1914, xxv, 1.

Klose,¹⁰⁰ however, has come forward with further experiments performed on goats, swine and rats, which have yielded results similar to those obtained by him previously in dogs and rabbits.

The thymus in the swine, as in other hoofed animals, is a large organ situated both in the thorax and neck, which can be removed only with difficulty and never completely (Klose). Whatever changes occur in swine or goats after operation must be, therefore, the result of partial thymectomies. Klose states that swine must be operated on between the fourth and sixth week, if symptoms of thymus deficiency are to be obtained. Signs of rachitis, such as the formation of a rachitic rosary, beading of the ribs, spontaneous fractures of the extremities and disturbances in gait, appear two to three months after the operation, but are transitory, disappearing entirely. Klose's explanation of the transitory character of the symptoms in swine is that the thymus rest which was left, completely regenerating in a short time, raises thymus function to its normal level and, consequently, causes the symptoms due to diminished function entirely to disappear. His results in goats were analogous to those in swine; in goats the thymus must be extirpated in the fourth week, if pathologic changes are to be obtained.

Klose removed the thymus from the rat on the fourteenth day. His first experiments he states were negative, or at least the ensuing changes were transitory. "Many broods behaved in a refractory manner like many kinds of dogs." Klose explained this phenomenon on the ground that thymus rests were present in the thyroid, which underwent functional hypertrophy. Many animals which were free from these rests died of cachexia on an average of from six to ten weeks after the operation and the bones of these animals showed severe grades of rickets.

Klose finds the thymus in the rat is essential to life. If an animal sufficiently young at the time of operation does not die after thymus removal, the thymus, according to Klose, cannot have been completely removed.

Klose had previously advanced the theory that the spleen was closely related in its function to the thymus and normally assumed the function of the thymus when the latter underwent physiologic involution. He explained the failure of thymectomies performed late (after the fourth week) in dogs to awaken characteristic symptoms on the supposition that the spleen had been allowed time enough to assume sufficient of the thymus' function to prevent them from developing. This theory of the interrelationship of thymus and spleen was founded largely on fancy and had already been attacked and disproved and its falsity admitted finally by Klose himself. The object of Flesch's

experiments, which are about to be described, was to investigate the relationship between the thymus and spleen.

The spleen varies in weight very considerably among normal rats, so that a difference of as much as 7 gm. in the weight of the spleens of two rats of equal body weight has no significance, even though the animals come from the same litter (Flesch). Flesch¹⁰¹ used rats, the youngest of which were four weeks old at the time of operation, and killed them from one to four weeks afterwards, or else allowed them to live until death occurred spontaneously in five to seven weeks. Each operative rat had a control.

Flesch found that complete removal of the thymus in the rat is usually impossible because of the presence of microscopic rests of the thymus in the neck, which cannot be found at the time of the operation. But he discovered that the rats having thymus rests did not react differently to a loss of the thymus from those rats in which no rests were found at the subsequent necropsy; for the rats in which cervical rests were present died spontaneously five to seven weeks after the operation, with but two operations, in one of which, when killed eighty days after the operation, an extremely large thymus rest was found, and in the other the spleen showed sufficient divergence from the normal, in Flesch's opinion, to account for the animal's survival! Flesch explained the development of symptoms in the presence of thymus rests by the conjecture that the small thymus particles which escaped removal reached a functional capacity too late to replace the main body of the thymus which had been removed. As might be expected, the thymus rests were found in the neighborhood of the parathyroids.

In this connection it is interesting to note Flesch's statement that the thymus rests sometimes showed signs of regeneration and sometimes degenerative changes. Klose, Fulci and Aschoff have maintained that a microscopic thymus rest left after incomplete thymectomy would regenerate until it reached the size of the original gland.

Flesch corroborated in the main the changes in the rat which Klose had reported. For eleven days after the operation no symptoms appeared ("latent period"); from the eleventh to the twenty-eighth day there occurred the "stage of adiposity," which was followed by the "stage of cachexia," ending in the death of the animal. But Flesch found no characteristic changes in the spleens. Enlargement of the follicles was almost always present and in the end stages an increase in amount of splenic pulp. Often, however, there was terminal sclerotic atrophy. Large cells of the megalokaryocyte type were fairly numerous. Flesch concludes that the spleen in the thymectomized animals

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101. Flesch, M.: Experimentelle Thymusstudien. I. Teil. Thymus und Milz bei der Ratte, Beitr. z. klin. Chir., 1915, xcv, 376.

is in a state of increased function, which is not specific in character, but an expression of a general reaction on the part of the whole body to the loss of the thymus.

Adler¹⁰² studied the relationship between thymus function and development in the frog. He extirpated the thymus by means of the galvanocautery from 950 tadpoles, but encountered an extremely high mortality, so that the number of surviving thymectomized animals fell to thirty-two within a week of the operations, and by the end of three months, to twenty animals. At that time they were killed and examined. The thymus proved to be completely extirpated in only three frogs; in five it was found that only one lobe had been removed and in the remaining twelve frogs that portions of both lobes were still present. None of the operative animals showed abnormal growth or development. The testicles of the three thymus-free animals were larger than the testicles of the controls. The pineals and hypophyses of these three frogs showed no changes, but the thyroids showed hyperplasia, with infoldings of the epithelium and diminished colloid. Adler concluded from his experiments that an interrelationship exists in the frog between thymus and thyroid and between thymus and testis. But since his conclusions are actually based on observations in only three animals, they cannot have much value.

Tongu¹⁰³ performed thymus transplantations in dogs and rabbits. He found the most favorable place for transplantation was in the peritoneal cavity. There an autotransplant might withstand absorption for as long a period as two months. He found the thymus transplanted into the spleen, abdominal wall or subcutaneous tissues was quickly absorbed; no signs of regeneration were evident. In all of his animals he created a thymus deficiency by removal of the gland in whole or in part at the time of or prior to the transplantation. His material consisted of twenty dogs and seventy rabbits, but the number of his successful experiments was exceedingly small.

Although the most extraordinary results have been reported following transplantation of the thymus, it is now well established that even thymus autotransplants cannot escape absorption for more than a limited period of time.

Hewer¹⁰⁴ has conducted feeding experiments on rats using thymus tabloids and the dried gland. She found that large amounts of the

102. Adler, L.: *Metamorphosestudien an Batrachierlarven. I. Exstirpation endokriner Drüsen. B. Exstirpation des Thymus*, Arch. f. Entwicklgsmechn. d. Organ., 1914, xl, 1.

103. Tongu, Y.: *Recherches expérimentales sur la transplantation du thymus (Première étude)*, Mitt. a. d. Med. Fakult. d. k. Univ. zu Tokyo, 1915, xiv, 259.

104. Hewer, Evelyn: *The Effect of Thymus Feeding on the Activity of the Reproductive Organs in the Rat*, Jour. Physiol., 1914, xlvii, 479.

fresh gland were necessary to produce results and that males were more susceptible to thymus feeding than females. The feeding of both parents produced marked retardation in the sexual maturity of the offspring, but the length of the period of gestation was unchanged. If large doses of the thymus were given to the male rats, the structure of the testis was affected, degenerative changes taking place in sexually mature animals and retardation in development of the testis in animals not yet sexually mature. By giving large amounts of thymus Hewer was able to produce a condition which she calls "hyperthymism." The testes of these animals showed an absence of the Sertoli cells, and in the later stages degenerative changes in the sperm cells with diminished numbers or complete absence of spermatozoa. To produce the condition of "hyperthymism" from 2 to 5 gm. per day of thymus substance was given. No breeding took place if either the male or the female had been treated with large doses of thymus.

M'Neil¹⁰⁵ advances the hypothesis that status lymphaticus is an anaphylactic condition. He regards individuals having status lymphaticus as constitutionally anaphylactic and as reacting in an exaggerated manner to all infections. "Status lymphaticus is an abnormal condition in the body in which, if anaphylactic phenomenon occur, they do so in an exaggerated way." M'Neil furnishes no experimental evidence in favor of his hypothesis, which is pure speculation.

Paton had previously found that the testes of young guinea-pigs hypertrophied and Soli that they atrophied after thymus extirpation. Halnan and Marshall¹⁰⁶ in their turn have investigated the relation of thymus to testis in guinea-pigs and found that neither hypertrophy nor atrophy takes place after removal of the thymus. They confirmed the well-established fact that castration is followed by thymus persistence. Their thymectomized animals showed no abnormalities of growth or development, nor did removal of both thymus and testes in young guinea-pigs alter the growth of the animal up to the time of sexual maturity.

Hatai¹⁰⁷ has conducted a very painstaking investigation in the white rat of the effects of castration on the growth and the weight of certain organs, among them those of internal secretion. The most marked effect of castration on any of the organs of internal secretion was on

105. M'Neil, C.: Anaphylaxis and Status Lymphaticus: Their Relation to Intensified Types of Disease in Infancy and Childhood, *Edinburgh Med. Jour.*, 1914, New Series, xiii, 38, 120.

106. Halnan, E. T., and Marshall, F. H. A.: On the Relation Between the Thymus and the Generative Organs and the Influence of These Organs on Growth, *Proc. Roy. Soc.*, 1914, xxxviii, Series B, 68.

107. Hatai, S.: The Growth of Organs in the Albino Rat as Affected by Gonadectomy, *Jour. Exper. Zool.*, 1915, xviii, 1.

the hypophysis. No change in the weight of the hypophysis was noted after spaying or semispaying, but after castration a marked increase in weight took place. No obesity occurred in castrated animals if compensatory growth of the hypophysis had developed. Hatai noted the same tendency of the thymus to persist after castration that has been noted by other authors.

Bompiani¹⁰⁸ confirms the findings of Fulci¹⁰⁹ in regard to the capacity of the thymus to regenerate after pregnancy. Pregnancy causes the thymus to involute, but, as soon as pregnancy is interrupted, the thymus begins to regenerate. Bompiani shows in addition that lactation causes the thymus to involute, or at least keeps the thymus in a state of involution, but that as soon as lactation is stopped, regeneration makes its appearance. Many authors have described regeneration of the thymus: after Roentgen ray (Rudberg¹¹⁰) (Jonson¹¹¹); hunger (Jonson¹¹¹); pregnancy (Fulci¹¹²); partial extirpation (Friedeleben,¹¹³ Klose,¹¹⁴ Fulci,¹¹² Aschoff,¹¹⁵ etc.). Some investigators have failed to find signs of regeneration in rests left at operation (Hammar,¹¹⁶ Adler,¹¹⁷ Pappenheimer¹¹⁸ and others). The question of the behavior of the thymus after partial excision is open to further investigation.

During the past two years Hammar has made at least three contributions to the subject of thymus pathology. The first paper¹¹⁹ cannot be located and therefore is not included in this review.

The first of the two available papers of Hammar's¹²⁰ is a critical study of fourteen thymus glands taken from cases in which the diag-

108. Bompiani, G.: Der Einfluss des Säugens auf die Restitutionsfähigkeit des Thymus nach der Schwangerschaft (Vorläufige Mitteilung), *Centralbl. f. allg. Path. u. path. Anat.*, 1914, 929; L'influenza dell' allattamento sulla capacità di reintegrazione del timo dopo la gravidanza, *Gazz. internaz. di med.*, 1915, xviii, 65.

109. Fulci, F.: *Centralbl. f. allg. Path. u. path. Anat.*, 1913, xxiv, 968.

110. Rudberg: *Arch. f. Anat.*, 1907, 123; *On Thymus Involutionen* Diss., Upsala, 1910.

111. Jonson: *Arch. f. mikroskop. Anat.*, 1909, lxxiii, 390.

112. Fulci, F.: *Deutsch. med. Wchnschr.*, 1913, xxxix, 1776.

113. Friedeleben: *Die Physiologie der Thymusdrüse in Gesundheit und Krankheit vom Standpunkte experimenteller Erforschung und klinischer Erfahrung*, Frankfurt, 1858.

114. Klose: *Neue Deutsche Chirurgie*, Enke, Stuttgart, 1912.

115. Aschoff: *Tr. Internat. Cong. Med.*, 1913, Lond.; 1914, Sect. iii, *Gen Path. and Path. Anat.*, Part 2, 131.

116. Hammar, J. A.: *Arch. f. d. ges. Physiol.*, cx.

117. Adler: *Arch. f. Entwcklungsmechn. d. Organ*, 1914, xl, 1.

118. Pappenheimer: *Jour. Exper. Med.*, 1914, xx, 477.

119. Hammar himself refers to this article, *Mikroskopische Analyse der Thymus in 21 Fällen Basedowscher Krankheit*, *Beitr. z. klin. Chir.*, 1915, but it is not in that journal.

120. Hammar, J. A.: *Mikroskopische Analyse der Thymus in 14 Fällen sogenannten Thymustodes*, *Ztschr. f. Kinderh.*, 1916, xiii, 153.

nosis of "thymus death" was made, with the special object of determining the truth or falsity of certain of the existing beliefs in regard to the pathologic changes in the thymus in that condition.

For full exposition of the opinions of various writers on the subject of the pathology of the thymus in status lymphaticus the reader is referred to Hammar's original article. Suffice it here to point out that certain pathologists have taken the position that the hyperplastic thymus, or more particularly the thymus of "thymus death," presents typical pathologic changes, consisting in (1) an altered relation of medulla to cortex, (2) a change in the number, size and histologic characters of the Hassall corpuscles, and (3) the composition of the medulla. Hedinger in 1906 directed attention to the occurrence, in cases of "thymus death," of a broad medullary and narrow cortical zone, and Schridde¹²¹ writes that the most important feature of the hyperplastic thymus is hyperplasia of the medulla, with hypoplasia of the cortex, and further, that the Hassall bodies are almost always exceedingly large and composed of fat-containing protoplasm without nuclei. In the more recent edition of Aschoff's book (1911) Schridde distinguishes two types of hyperplastic thymus, one in which medulla and cortex are both hyperplastic; the other, far the commoner of the two, in which medulla is hyperplastic and cortex hypoplastic. The hyperplasia of the medulla is characterized by an actual increase of the reticular cells (the undoubted epithelial element) and by the presence of large forms of Hassall corpuscles, though the total number per unit of thymus substance is diminished. In regard to the thymus of "thymus death," Schridde states specifically that, excepting those rare cases in which the thymus operates mechanically, hyperplasia of the medulla and hypoplasia of the cortex are invariably present. While not entirely accepting Schridde's conclusions, Hart finds medullary hypertrophy and considers the cause to be an active proliferation of the epithelial cells. His views in regard to the excessive production of Hassall corpuscles in conditions of excessive function of the thymus have already been discussed. Though other writers (Wiesel, Pappenheimer and others) have expressed dissenting opinions, nevertheless the dogmatic teachings of the Schridde school have received wide acceptance and are frequently quoted in the experimental literature on the thymus gland (Matti, Klose¹²² and others). It is the truth or falsity of these views which Hammar seeks to investigate.

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121. Schridde: Aschoff's Pathology, Ed. 1.

122. As Hammar points out, the description which Klose gives of the pathologic changes in the thymus of status lymphaticus is Schridde's description almost word for word. See *Neue Deutsche Chirurgie der Thymusdrüse*, p. 113.

Before taking up Hammar's paper, however, it is necessary to call attention to the special methods of study used by him in this investigation, which gives to his results a mathematical accuracy. The exact amount of parenchyma (minus the fat and connective tissue) he was enabled to estimate by means of serial sections and reconstructions and in the same manner to determine the exact relation of medullary to cortical substance.¹²³ The Hassall corpuscles he counted.

At the beginning of his paper Hammar points out that although it is popularly supposed that the enlargement of the thymus in "*mors thymica*" is constant, statistics prove that such is by no means the case, for the weight of the thymus may be normal or even subnormal in that condition. Thirteen of Hammar's series of fourteen thymus glands were taken from children whose ages ranged between 9 days and 16 years. The remaining gland was that of an adult. Of the thirteen children's glands, only two were enlarged; the others showed amounts of parenchyma within normal limits. The two enlarged thymus glands had increased amounts of cortex; the medulla in one was larger than normal, though not in proportion to the cortex, and in the other lay within normal limits. The cortico-medullary index (cortical tissue, medullary tissue) was, therefore, high in both instances. (A high cortical medullary index is normal for childhood.) Both thymus glands showed subnormal numbers of Hassall's corpuscles; the very large and calcified forms were absent. A lymphatic infiltration of the medulla was present in both. Of the eleven thymus glands of normal size, one showed signs of accidental involution and was excluded from further consideration. In the remaining ten glands there was diminished parenchyma in all and a high cortico-medullary index in six. The very large and the calcified Hassall corpuscles were also absent in all. Infiltration of the medulla with lymphocytes was found in eight. In no two of the ten glands were all the characters enumerated the same.

The study of these thirteen glands showed it was not possible to distinguish any fixed type and, in fact, in the majority of the glands the variations were within normal limits. There seemed to be no morphologic ground on which to rest a theory of hyperfunction or dysfunction.

Hammar's second paper is an analysis of the mechanical theory of thymic asthma in the light of the study of the form and topographical relations of the thymus gland. Grawitz in 1888 put forward the idea that it was possible for the thymus to become wedged between the

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123. Hammar, J. A.: *Methode, die Menge der Rinde und des Marks des Thymus, sowie die Anzahl und Grösse der Hassallschen Körper zahlenmässig festzustellen* (unter besonderer Berücksichtigung der Verhältnisse beim Menschen), *Ztschr. f. ang. Anat.*, 1913-1914, i, 311.

upper part of the sternum and the vertebral column in such a way as to compress the trachea at that point, causing death from asphyxia. The space between the upper portion of the manubrium and spine has been known ever since Grawitz's publication as "the critical space of Grawitz." Since then other investigators (Barack,¹²⁴ Strassmann, Flügge¹²⁵) have described a second vulnerable spot, where the trachea may be compressed by the hyperplastic thymus, namely, the point of crossing of the innominate artery. Hart, Wiesel, Klose and others recognize these two points as the places where compression of the trachea by the enlarged thymus is particularly liable to occur.

A considerable number of cases of thymic asthma have been described in the literature, chiefly by surgeons, in which the surgical operation or necropsy demonstrated a large thymus or even a causal relationship between the enlarged thymus and the clinical or pathologic condition. The one most prominent symptom reported in these cases has been inspiratory dyspnea with inspiratory stridor, though in some of them expiratory dyspnea was also referred to. The points of compression of the trachea were thought to be at the "critical points" already mentioned. The inspiratory dyspnea in "thymic asthma" has been explained by assuming that the thymus acts like a ball valve, being forced against the trachea at one of the two "critical points" during inspiration, in such a way as to compress it, but falling away again during expiration, permitting the trachea to expand once more. Surgeons who have operated on these patients with "thymic asthma" have observed that the inspiratory dyspnea ceased when the thymus was drawn upward into the neck, but recurred as soon as the thymus was allowed to resume its former position in the thorax; or that the inspiratory dyspnea was permanently diminished when the thymus was drawn upward into the neck and held in that position by suture of the capsule to the sternum.

Hammar's paper shows, in the first place, that the two so-called "critical points" at which it is thought the trachea may be compressed by the thymus are so close to each other, particularly in the new-born child, as to be almost identical, for the innominate artery crosses the trachea close to the upper border of the sternum. Therefore, it is useless to consider them separately. The statement that the trachea was greatly compressed immediately above the bifurcation where the innominate artery crosses is erroneous, for the innominate artery lies considerably above the bifurcation. If the trachea was actually compressed at that point by the thymus, that part of the thymus lying immediately opposite, just above the base of the heart, must have been

124. Barack: Diss. Berlin, 1894; cited by Hammar.

125. Flügge: Vierteljahrsschr. f. gerichtl. u. öffentl. Med., Sanitätswesen, 1899, Series 3, xvii; cited by Hammar.

responsible. The next point which Hammar makes is that since the thickest portion of the thymus lies at the level of the base of the heart, considerably below the so-called "critical point," the surgical maneuver of drawing the thymus upward not only could not possibly relieve dyspnea produced by pressure of the thymus on the trachea at the critical points, but would actually intensify it, since it would bring a thicker mass of thymus between the top of the sternum and the spine than was there previously. If the ascent of the thymus relieved the inspiratory dyspnea of "thymic asthma," it was proof that the point of compression of the trachea did not lie above the thickest portion of the thymus, but at or below the thickest part, in the neighborhood of the bifurcation. In reality the thymus is not forced upward into the neck with each inspiration, but recedes into the thorax, while it is during expiration that it is forced up into the base of the neck ("Rehn's phenomenon"), so that if it produced dyspnea by compression of the trachea anywhere above its thickest part, it would cause expiratory and not inspiratory dyspnea.

Thus Hammar proves that the existing notions about the mechanical compression of the trachea by the enlarged thymus are largely false. He points out, however, that his anatomical preparations indicate the enlarged thymus may exert pressure on the trachea close to the bifurcation, or on the bronchi, particularly in the new-born child, whose thymus is relatively much broader than at a later period. Hammar is careful to avoid the statement that the thymus does actually compress the trachea at these points.

It is to Hammar's painstaking investigations in regard to the thymus, which have never been shown to be wrong in a single particular, that we owe the greater part of our certain knowledge in regard to that organ. The results of his analysis of the fourteen thymus glands from cases of thymus death are probably worth more than the opinions of all those pathologists who have expressed themselves so positively on this subject, because the latter have dealt with impressions, while Hammar has worked out the facts. It is probable that there is no pathologic condition which is characteristic for the thymus of "thymic death" or status lymphaticus. Hammar makes ridiculous the controversionalists who have split hairs on the subject of the compression of the trachea by the enlarged thymus at the "critical points."

THE THYROID

Halstead¹²⁶ showed by experiments performed in 1887 and 1888 that after excision of a portion of the dog's thyroid the remainder underwent hypertrophy.

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126. Halstead, W. S.: Johns Hopkins Hosp. Reports, 1896, i, 373.

Hunnicut¹²⁷ has repeated Halstead's experiments at Halstead's own suggestion. He removed the thyroid piecemeal from thirty-nine dogs and found that in only one of them did the thyroid rest develop hyperplasia. In twenty other dogs, similarly treated, the wounds were left open to determine whether a relationship existed between hyperplasia of the thyroid and infection; but no hyperplasia resulted. Hunnicutt found that one entire lobe and three-fourths of the other lobe of the dog's thyroid could be removed without affecting the remainder of the gland. In only three of the total fifty-nine animals in which piecemeal removal of the thyroid was done did the remaining piece of gland change from the normal to the hyperplastic state, while in five of the fifty-nine dogs the thyroid, which had been found to be hyperplastic in the first place, reverted back in the interval to the normal state, that is, the thyroid rest at the conclusion of the experiment proved to be normal. Definite increase in the size of the rest was not discovered in any instance.

Hunnicut calls attention to the great variability in the histologic structure of the thyroid of the dog. Sections taken from the thyroids before any operation had been performed showed marked hyperplasia in 32 per cent. of the animals and early signs of hyperplasia in 5 per cent. No partially thyroidectomized dog developed myxedema or tetany.

On the other hand, Basinger, who removed the thyroids from rabbits in order to produce myxedema, found that thyroid rests have a great tendency to undergo hyperplasia. "Care was taken to remove all thyroid tissue, because it is surprising how often small remnants of tissue were hypertrophic." The remnants were never more than one-tenth of the size of one of the lobes of the thyroid.

Douglas¹²⁸ examined the thyroids of pigeons, fowls, rats and rabbits to determine the extent of normal variation in the histologic structure of the thyroid in different members of the same species. He concluded that the histologic picture of the thyroid in different animals of the same species kept under the same conditions is so variable that an interpretation of experimental results based on histologic changes in the thyroid is extremely difficult.

Fox¹²⁹ reports marked variations in the thyroids of wild animals confined in the zoological garden in Philadelphia.

127. Hunnicutt, J. A.: The Absence of Hyperplasia of the Remainder of the Thyroid in Dogs After Piecemeal Removal of This Gland; Autotransplantation of the Thyroid in Partially Thyroidectomized Animals, *Am. Jour. Med. Sc.*, 1914, cxlviii, 207. Halstead, W. S.: *Ibid.*, cxlvii, 56.

128. Douglas, M.: The Histology of the Thyroid in Animals Fed on Various Diets, *Jour. Path. and Bacteriol.*, 1914-1915, xix, 341.

129. Fox, H.: The Pathology of the Thyroid Gland in Wild Animals, *Proc. Path. Soc. Philadelphia*, 1915, New Series, xvii, 20.

McCarrison¹³⁰ has made comparative studies of the thyroid gland of wild rats, of white rats and mice kept in confinement and of goitrous rats, both wild and domestic. It was his observation that goiter was exceedingly rare in wild rats, but that the structure of the thyroid gland varied within wide limits and appeared to be especially influenced by altitude and season. A larger proportion of thyroids of domesticated white rats were in a state of active secretion than was the case with the thyroids of wild rats. A small proportion of white rats confined in cages developed goiter spontaneously.

Jackson investigated the effects of starvation on the thyroids of rats. He found that when young rats were held for several weeks, on a diet just sufficient for maintenance, histologic changes appeared in the thyroid; the follicular epithelium became atrophied and reduced in height, the nuclei hypochromatic and pycnotic, and in extreme cases, fragmented; the cytoplasm was more affected than the nucleus, but in some instances showed no changes, while in others it was vacuolated; the colloid appeared normal in some instances, in others disintegrated and replaced by desquamated epithelial cells. The changes just described Jackson thinks in no wise typical of hunger effects, but such as are seen in the thyroid in numerous pathologic conditions.

Jackson found also that the thyroid of the albino rat lost but little weight in acute inanition of sufficient degree to cause the body as a whole a loss of one-third of its total weight. In chronic inanition, on the other hand, the thyroid lost from 22 to 24 per cent. of its weight.

Bensley¹³² also comments on the variability of the structure of the thyroid in animals and the frequency of environmental changes:

The readiness with which the thyroid gland undergoes hyperplastic changes, its responsiveness to iodine administration, as demonstrated by Marine and his co-workers, the ease by which it may be modified structurally by dietary conditions, as shown by the work of Reid Hunt (1911), Marine, Chalmers, Watson (1907), Tanberg (1900) and Missiroli (1910), and confirmed by my recent studies on the relation of diet to hyperplasia in opossums under domestication, confirm the conclusion that there is a delicate adjustment between the functioning of the thyroid gland and general body conditions, though at present we do not know the means by which this adjustment is mediated.

In 1914 Gudernatsch¹³³ reported the results of his second series of feeding experiments on tadpoles. He found that when tadpoles were

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130. McCarrison, R.: Nervous Cretinism, *Brit. Jour. Child. Dis.*, 1914, x1, 508.

131. Jackson, C. M.: Effect of Acute and Chronic Inanition on the Relative Weights of the Various Organs and Systems of Adult Albino Rats, *Anat. Rec.*, 1915, ix, 90.

132. Bensley, R. R.: The Normal Mode of Secretion in the Thyroid Gland, *Am. Jour. Anat.*, 1916, xix, 37.

133. Gudernatsch, J. F.: Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, *Am. Jour. Anat.*, 1914, xv, 431.

fed large amounts of thyroid, they emaciated rapidly and died, but when fed the proper amounts, remained alive and metamorphosed into frogs on the eighteenth day, although normally the tadpole does not turn into the frog until from 10 to 13 weeks old. The result of the premature transition of tadpole to frog was that frogs in miniature were produced, but which never ate, and died within a few days to several weeks. On the other hand, Gudernatsch found that tadpoles fed thymus or spleen grew rapidly, but showed no tendency to metamorphose into frogs. Not one of several thousands of tadpoles fed on thymus could be made to develop into a frog, though tadpoles fed on liver became frogs at the normal period. Gudernatsch, therefore, concluded that the thyroid contained some substance which specifically stimulated development (differentiation in the frog), accelerating it, but at the same time inhibiting growth, while the thymus contained some substance which accelerated growth but inhibited development, also in a specific manner, and that this substance was likewise contained in the spleen and probably also in lymphatic tissue, though to a less extent than in the thymus. The results of Gudernatsch's experiments were confirmed by Romeis¹³⁴ (Stettner).

Morse¹³⁵ undertook to determine the element in the thyroid gland which caused the changes in growth and development of the tadpole described by Gudernatsch. He excluded the lipid of the thyroid as the possible substance by obtaining the same effects in the tadpole with lipid-free thyroid as with untreated thyroid. He next obtained negative results with "metallic" iodine, potassium iodide, methyl iodide, iodobenzoic acid, etc., showing that inorganic iodine is not the substance in question. Iodine-bearing algae, used to determine the effect of iodine in organic combination, and starch iodate ("colloidal iodine such as exists in starch") were both without effect. Kurajeff's blood protein iodine compound ("iodalbin") was effective, however, and both thyroid derivatives, thyroglobulin and iodothyronine, gave results indistinguishable from those produced by thyroid itself. Iodized amino-acids produced less pronounced yet positive results. Morse concludes that the substance in the thyroid which produces the specific effect "concerns the iodine, which is associated in some way with the amino-acids composing the complex iodized globulin of the thyroid." He explains the effectiveness of the iodized blood albumin by its protein linkage.

134. Romeis, B.: Experimentelle Untersuchungen über die Wirkung innersekretorischer Organe. II. Der Einfluss von Thyreoidea- und Thymusfütterung auf das Wachstum, die Entwicklung und die Regeneration von Anurenlarven, *Arch. f. Entwicklungsmech. d. Organ.*, 1914, xxxvii, 571; *Ibid.*, xl, 571; *Ibid.*, xli, 57.

135. Morse, M.: The Effective Principle in Thyroid Accelerating Involution in Frog Larvae, *Jour. Biol. Chem.*, 1914, xix, 421.

Lenhart¹³⁶ also studied the effects of thyroid feeding on tadpoles. He gave the experimental tadpoles on alternate days desiccated thyroid taken from sheep, cattle and man (goiter cases), together with fresh pig liver, while he fed the latter substance daily without admixture of thyroid to the control tadpoles. The idea underlying the experiments was to determine whether the iodine element of the thyroid was the substance which produced the characteristic changes in the tadpoles. Accordingly, Lenhart estimated the iodine content of the thyroid powder in each instance before use. The results of Lenhart's feeding experiments were similar to those of Gudernatsch: large amounts of thyroid caused the tadpoles to emaciate and die before differentiation commenced, but smaller amounts caused differentiation to occur earlier. But Lenhart offered a different interpretation for the results obtained from that of Gudernatsch, namely, that thyroid feeding produced merely an acceleration of the normal metabolism of the tadpole, which in turn manifested itself by a more rapid development and so an earlier metamorphosis.

Like Morse, Lenhart found that nonthyroid iodine, for example, potassium iodide, produced no effect on the tadpole. The effectiveness of the thyroid feeding was, however, always in direct proportion to its iodine content, so that Lenhart concluded the iodine element in the thyroid is the active principle responsible for the changes obtained. No different effect was discovered when the human thyroid was used; if anything, human thyroid was not so potent as the thyroid of the dog.

Stettner¹³⁷ has investigated the effects on tadpoles of feeding thymus, thyroid and genital tissue (ovaries and testes). The thyroid-fed tadpoles were affected exactly like those of Gudernatsch and Lenhart. The thymus-fed tadpoles showed marked irregularities in growth and development. They tended to metamorphose late and develop into malformed frogs with short legs, large abdomens and well-developed musculature. Growth in the majority of the thymus-fed tadpoles appeared to be slightly retarded, but some, receiving extract from a particular thymus (that of a young female calf), attained a giant size. Genital gland feeding produced, in most instances, a late metamorphosis, into a thin frog with slender muscles. The combination of thymus and genital feedings caused metamorphosis at its normal time and led to the production of a normally formed frog.

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136. Lenhart, C. H.: The Influence on Tadpoles of Feeding Desiccated Thyroid Gland in Variable Amounts and of Variable Iodine Contents, *Jour. Exper. Med.*, 1915, xxii, 739.

137. Stettner, E.: Beeinflussung des Wachstums von Kaulquappen durch Verfütterung von Thymus und geschlechtsorganen, *Jahrb. f. Kinderh.*, 1916, lxxxiii, 154.

Stettner saw in the results of his experiments the specific effects of the organs of internal secretion. In his opinion the experiments showed that thymus and genital gland acted in an antagonistic manner and a proper admixture of both was necessary for perfect development, for, though either one given singly caused a retardation in development, their effects were the opposite in other respects. He thought it possible that the deformities of the thymus-fed tadpoles might be rachitic.

The results of the feeding experiments of Gudernatsch, Romeis, Morse, Lenhart and Stettner make certain the effects of thyroid feeding on tadpoles. But the effects of thymus feeding have not been shown so clearly. Though Gudernatsch found that thymus feeding postponed indefinitely metamorphosis in the tadpole, he obtained similar results with splenic tissue, which indicates that the effect of thymus feeding, though definite, was not specific, or at least the active substance was not limited to the thymus, and Stettner's results, which were not exactly like those of Gudernatsch, were not sufficiently uniform to permit of any definite interpretation. The exact effect of thymus feeding on the tadpole should be determined by new, suitably controlled experiments.

Basinger's¹³⁸ experiments, already referred to in connection with the question of thyroid hyperplasia, were undertaken with the view of establishing a biologic test for the active principle of the thyroid, but were actually concerned with the determination of the effects of normal rabbit blood serum, "hyperthyroid" blood serum, standard thyroid preparations, thyroid metaprotein and Kendall's extract B on cretinized rabbits.

He was able to produce cretin rabbits in about eighty-one out of a total of 140 animals. He found certain litters more refractory than others: for example, he succeeded in obtaining cretins in 90 per cent. of some of the litters operated on, while in others in only 25 per cent. The symptoms of experimental cretinism in the rabbit corresponded to the clinical picture of cretinism in human beings. About two weeks after the extirpation of the thyroid the hair became drier, inclined to stand up and could be pulled out easily. In the third week after operation retardation in growth became noticeable. By the tenth week the average weight of the cretin rabbits was 750 gm., while that of the control rabbits was 1,400 gm. The bones showed a "pseudorickety condition" called by Hofmeister "chondrodystrophia thyreopriva" (Basinger). Still later the cretin rabbits developed potbellies and scaly eczematous-like lesions of the skin. They became slow and

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138. Basinger, H. R.: The Control of Experimental Cretinism, *THE ARCHIVES INT. MED.*, xvii, 260.

awkward in their movements and would sit for hours without moving. Sixteen cretin rabbits Basinger kept alive for more than one year.

Normal blood serum transfusions produced no effect on the cretin rabbits. But the blood serum of rabbits fed on thyroid to the point of hyperthyroidism did cause definite improvement, but less than that caused by thyroid feeding. The cretin rabbits, which were fed thyroid the moment symptoms appeared, never grew quite so large as the control rabbits, although the other signs of cretinism disappeared. Kendall's thyroid extract B had no effect. A further interesting point, which Basinger's experiments brought out, was that the cretin rabbits continued to grow after the period when growth of the normal rabbits had ceased.

During the past few years the treatment of cretinism and myxedema by thyroid transplantation has been attempted in several of the European clinics, notably in those of Kocher, Payr and Eiselberg. The transference of thyroid tissue from one individual to another is simple; the difficulty lies in making the transplanted tissue live and functionate. If this difficulty can be surmounted, the cure of cretinism and myxedema can be accomplished, instead of the approximation to complete cure afforded by oral thyroid therapy. Hence the great importance of the attempts to treat cretinism by means of thyroid implantation.

Payr points out that almost all the transplantation work on the thyroid in animals has been done with autotransplants and probably many of the poor results of thyroid transplantation in human beings have been due to the necessity of using homeotransplants. Very little experimental work in homeotransplantation of the thyroid has been done, but as the knowledge about tissue transplantation increases, tissue specificity is becoming more apparent and the number of tissues which permit of homeotransplantation is becoming correspondingly less. Payr believes the outlook for successful transplantation is more hopeful in cases in which the thyroid is deficient than in those in which the thyroid is absent. The best results, he thinks, are obtained by the use of homeotransplants from blood relatives. He advises the use of a large piece of thyroid as a transplant, rather than a small piece or several small pieces. The best sites for the transplants are probably the spleen or thymus, the latter on account of its accessibility. There are undoubtedly cases, he thinks, in which transplantation of the thyroid brought about a favorable result, when oral therapy had failed, and a few cases in which the effect of the transplantation could be followed for years. Payr states that the therapeutic effect from

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139. Payr, E.: Zur Frage der Schilddrüsentransplantation, *Arch. f. klin. Chir.*, 1914, cvi, 16.

thyroid transplantation is more rapid and complete than from thyroid feeding, probably because more elements are present in the internal secretion of the thyroid than can be absorbed through the intestinal tract.

Payr concludes his article with the report of five of his own cases. One of his patients, an eight-year-old cretin, received in the spleen a large piece of her mother's thyroid. In the succeeding half-year she grew 12 cm., when in the three previous years she had grown only 6 cm. and her development in other respects was commensurate with her growth. Two and a third years after the transplantation the patient had a recrudescence of her myxedema, so that the results of the thyroid transplantation were not permanent. Payr's other cases were much less striking than the case just described.

Von Eiselsberg¹⁴⁰ reported two cases of cretinism in which he had transplanted thyroid. In a 13-year-old cretin he had made altogether six implantations of pieces of human thyroid obtained as chance offered. The favorable results following transplantation were only temporary. The other patient was similarly given three thyroid grafts and improved during a short period of observation. Von Eiselsberg also calls attention to the *éclatant* effects produced by transplantation as compared with feeding, the former being much more rapid in their development than the latter.

Kocher¹⁴¹ has contributed his experiences in the treatment of myxedematous conditions by means of thyroid transplantation. The main points in his paper are the following: In no case has a complete and permanent restitution to the normal condition been accomplished in a myxedematous human subject as a result of thyroid transplantation, but in some cases definite improvement has followed, as evidenced by the fact that a smaller amount of thyroid extract was required by the patient, or that the patient himself was conscious of feeling better. He states that before making the transplantation it is necessary to give the patient a preliminary treatment with thyroid, not to make certain of the diagnosis, but to raise the patient's tissues to such a level of nutrition as to enable them to nourish the transplant after it has been received and that the donor must have an active or hyperactive thyroid. Kocher plants either a single large piece of thyroid or a number of smaller pieces and immediately after the transplantation continues the thyroid therapy by mouth in order to combat "thyroid hunger."¹⁴²

140. Von Eiselsberg, A. F.: Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen und Nebenschilddrüsen, zugleich ein Beitrag zur post-operativen Tetania parathyreopriva, Arch. f. klin. Chir., 1914, cvi, 1.

141. Kocher, T.: Ueber die Bedingungen erfolgreicher Schilddrüsentransplantation beim Menschen, Arch. f. klin. Chir., 1914, cv, 832.

142. For a discussion of the most favorable sites for the transplants consult Kocher's article (Footnote 141).

Eighteen of Kocher's patients appear to have been improved by the thyroid transplantation, while in the eighteen other patients no improvement of any kind resulted.

The experimental literature in regard to thyroid transplantation, as Payr points out, relates almost entirely to autoplasmic transplantation (von Eiselsberg,¹⁴³ 1892; Enderlen,¹⁴⁴ 1898; Payr,¹⁴⁵ 1906; Salzer,¹⁴⁶ 1909; Cristiani). Cristiani,¹⁴⁷ who between the years 1894 and 1906 wrote thirty papers on the subject of thyroid transplantation, is the only investigator mentioning homeotransplantation (Hesselberg).

Hesselberg's¹⁴⁸ work bears immediately on this subject and consists of the direct comparison of the growth and development of thyroid homeo- and autotransplants. Her material was guinea-pigs, numbering in all seventy-five animals. Autotransplantation and homeotransplantation were performed simultaneously in pairs of animals, so that direct comparison was possible. The experimental animals were killed at various periods after transplantation and the transplanted tissues excised and sectioned. For a short time after the operation no differences in the transplants were observed. Comparatively soon, however, a destruction of the follicles of the homeotransplants was noticeable, due apparently to an invasion of lymphocytes and an ingrowth of connective tissue. The latter grew much more abundantly into the homeotransplants than into the autotransplants, remaining cellular in the latter, while it became fibrous in the former. The autotransplants developed far the better blood supply. At the end of forty-seven days the homeotransplants had practically disappeared, while the autotransplants were not only living, but showed signs of outgrowth into the surrounding tissue.

Whether homeotransplantation of the thyroid is a success or a failure when applied to human beings with thyroid deficiency cannot be answered with certainty until the fate of the transplanted human thyroid is known. Hesselberg's experiments demonstrate that in the guinea-pig the thyroid tissue transplanted from another individual survives only for a short time. The results of the homeotransplantation experiments in myxedematous human subjects, just

143. Von Eiselsberg: *Wien. klin. Wchnschr.*, 1892, v, 81.

144. Enderlen: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1898, iii, 474.

145. Payr: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1906, xxxv, 503; *Arch. f. klin. Chir.*, 1906, lxxx, 730.

146. Salzer: *Arch. f. klin. Chir.*, 1909, lxxxix, 881.

147. Cristiani: For a list of his very numerous publications on this subject, see bibliography at end of article by Hesselberg, Cora: *A Comparison of Autoplasmic and Homeoplasmic Transplantation of Thyroid Tissue in the Guinea-Pig*, *Jour. Exper. Med.*, 1915, xxi, 164.

148. Citation given in Footnote 147.

related, point also to the same conclusion. The treatment of cretinism by thyroid transplantation up to the present time must be considered a failure and in all probability will never succeed until the problem of the overcoming of tissue specificity is solved.

Fenger¹⁴⁹ found that both enlarged and normal-sized human fetal thyroids contain iodine, at least during the last three months of fetal life, as do the thyroids of cattle, swine and sheep. Because the fetal thyroid contains iodine, Fenger assumes that it functionates in fetal life.

The observation was made a long time ago that the thymus is frequently enlarged in exophthalmic goiter, even in poorly nourished adult subjects whose thymus glands under normal conditions are atrophied. In 1858 Markham¹⁵⁰ reported a case of exophthalmic goiter showing large thymus at necropsy and Moebius¹⁵¹ discussed the significance of enlarged thymus in exophthalmic goiter in his well-known monograph on that subject. But the statistical studies of the past few years, in particular those of Thorbecke¹⁵² and Capelle¹⁴³ have shown an incidence of large thymus in exophthalmic goiter previously unsuspected. For example, Capelle's figures revealed an enlargement or persistence of the thymus in 95 per cent. of fatal cases of exophthalmic goiter and in 44 per cent. dying from other causes. Since the coincidence of large thymus and exophthalmic goiter is too frequent to be explained as accidental, the question naturally arose whether the thymus might not be actively concerned in the production of exophthalmic goiter. The possibility that this might be so was strengthened by the experimental investigations of Matti⁹⁷ and Klose,⁹⁸ which indicated, as already pointed out, that the thymus is itself one of the most important of the organs of internal secretion and that a definite interrelationship exists between thyroid and thymus in that the thyroid becomes hyperplastic when the thymus is extirpated. Still further evidence in support of a thymogenic influence in exophthalmic goiter has been supplied by surgeons, who, acting on the theory that the thymus exerted a deleterious influence, have treated patients by excision of a portion of the thymus, as well as the thyroid, or by partial excision of the thymus alone.

Numerous reports that reduction of both thymus and thyroid have caused more favorable results than those obtained from partial thy-

149. Fenger, F.: On the Presence of Iodine in the Human Fetal Thyroid Gland, *Jour. Biol. Chem.*, 1915, xx, 695.

150. Markham: *Med. Times and Gaz.*, May 1, 1858; cited by Hart.

151. Moebius: *Deutsch. Ztschr. f. Nervenhe.*, 1891, i, 5; Nothnagel: *Spec. Pathol. u. Therapie Bas'sche Krankh.*, Wien., 1896.

152. Thorbecke, M.: *Der Morbus Basedow mit Thymus persistenz*, Diss., Heidelberg, 1905; cited by Capelle.

153. Capelle: *Beitr. z. klin. Chir.*, 1908, lviii, 353.

roidectomy alone have appeared in the literature (Garrè,¹⁵⁴ von Haberer,¹⁵⁵ Klose,¹⁵⁶ Sauerbruch¹⁵⁷ and others). In two recent papers von Haberer¹⁵⁸ reports good results in a series of cases of exophthalmic goiter treated by reduction of both organs, and Halstead the beneficial effects of the Roentgen-ray treatment of the thymus in several cases of exophthalmic goiter in which the thyroids had been partially resected without much improvement. But more important with a view to the determination of the part actually played by the thymus in exophthalmic goiter are the cases treated by the excision of thymus alone, of which there are now a number in the literature (Garrè, von Haberer, Capelle and Bayer, Sauerbruch and others). Although the results in these cases of thymus resection alone are reported as favorable, in no instance has the operation been curative, and in at least two of the cases a subsequent partial excision of the thyroid was necessary. Not one of them proves that the thymus can cause exophthalmic goiter, and in fact none furnishes convincing proof that the thymus has anything whatsoever to do with the production of that disease. Nevertheless, Hart and others regard the proof established, chiefly from their interpretation of the results in these cases, that a purely thymogenic form of exophthalmic goiter exists. Hart recognizes three types of exophthalmic goiter, (1) purely thyrogenic, (2) purely thymogenic, and (3) a mixed form, though he admits that the purely thymogenic form is rare. Klose, as usual, takes the extreme position "no thymus, no Basedow."

Two hypotheses have been advanced to explain the rôle the thymus plays in exophthalmic goiter. According to one of them, that advanced by Gebele,¹⁵⁹ the thymus is thought to compensate for the thyroid insufficiency and for that reason to hypertrophy or at least to persist when the thyroid function becomes sufficiently affected; in other words, the thyroid is the primary cause of exophthalmic goiter and the thymus plays a secondary part. According to the other hypothesis, that of Capelle and Bayer,¹⁶⁰ and accepted by Klose,¹⁶¹ Hart and others, the thymus is thought to have an independent pathologic function, which adds to or intensifies the symptoms produced by the diseased

154. Garrè: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1911, No. 1.

155. Von Haberer: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1913, No. 1.

156. Klose: *Berl. klin. Wchnschr.*, 1914, No. 1.

157. Sauerbruch: *Beitr. z. klin. Chir.*, 1912, lxxvii.

158. Von Haberer, H.: *Kasuistisches zur Frage therapeutischer Misserfolge bei Morbus Basedowii*, *Wien. klin. Wchnschr.*, 1915, xxviii, 1; *Over de klinische beteekenis der thymusklier (special met't oog op den Morbus Basedowii en den status thymicus)*, *Med. Weekbl.*, 1914-1915, xxi, 242.

159. Gebele: *Beitr. z. klin. Chir.*, 1910, lxx, No. 1; *Ibid.*, 1911, lxxvi.

160. Capelle, W., and Bayer, R.: *Beitr. z. klin. Chir.*, 1913, lxxxvi, 509.

161. Klose: Footnote 156; Lampé Liesegang. *Beitr. z. klin. Chir.*, lxxvii.

thyroid; that is, the thyroid and thymus share in the production of exophthalmic goiter.

Various pathologic changes in the thymus of exophthalmic goiter have been described, but none of them are constant. It is probably true that no pathologic condition of the thymus characteristic of exophthalmic goiter exists.

Von Haberer¹⁵⁸ states in a recent paper on this subject that results of the treatment of exophthalmic goiter by partial excision of the thymus have failed to show that a purely thymogenic form exists, although they indicate that the thymus exerts an important pathologic influence. He admits that it is not feasible to distinguish the symptoms produced by the thymus and thyroid. The effect in exophthalmic goiter of thymus reduction, in addition to thyroidectomy, is to make the subsequent course more favorable. Undoubtedly cases of exophthalmic goiter exist in which the thymus plays no part.

In the more recent of his two papers on this subject von Haberer¹⁵⁸ reports two more patients with exophthalmic goiter treated by the combined operation on thymus and thyroid. One of the cases had a fatal termination soon after the operation, with the extreme post-operative tachycardia now so commonly regarded as due to pathologic thymus function. Although the occurrence in this case of symptoms referable to the thymus, after a large part of the latter had been removed, appeared to speak against the theory of thymic influence in exophthalmic goiter, the necropsy, according to von Haberer, tended to strengthen the theory, since it revealed 70 gm. of thymus tissue still remaining in the thorax.

Albert Kocher's¹⁶² paper deals with this same subject. The main points brought out are the following: Exophthalmic goiter without hyperplasia of the thyroid is unknown. On the other hand, numerous cases of exophthalmic goiter with a normal thymus have been established. The thymus undergoes late hyperplasia or revivescence in from 45 to 50 per cent. of the cases of exophthalmic goiter. Its enlargement is much commoner in young than in old subjects. The histologic picture of the thymus shows nothing characteristic to distinguish it from the hyperplasia of childhood. Thymus hyperplasia is much commoner in certain neighborhoods and in certain families than in others. If the thyroid is sufficiently reduced, thymus hyperplasia decreases. The operation for reduction of the thyroid is no more dangerous when enlargement of the thymus exists than when no enlargement is present. If the symptoms of exophthalmic goiter are obstinate, with a tendency to exacerbation, part of the thymus may be removed in addition to the

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162. Kocher, A.: Ueber Basedow'sche Krankheit und Thymus, *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1914, xliii, Part 2, p. 567.

thyroid. A pretreatment with thymus preparations or Roentgen ray may be tried, if the cases are found to react favorably to them.

Klaus¹⁶³ reports a case of exophthalmic goiter occurring in a child 9 months old. The evidences of the disease were exophthalmos, noticed by the parents in the third week, well-marked von Graefe's and Stellwag's signs, and a palpable thyroid, thought to be enlarged. The thymus was judged to be considerably enlarged because of an increase in perimanubrial dulness. The child was known to have rickets and tuberculosis. He was given a single tuberculin treatment and was not seen again for a year. But, when examined again, at the end of that time, he showed no signs at all of exophthalmic goiter; the exophthalmos and the enlargement of the thyroid were gone. Klaus reports the case as the earliest instance of exophthalmic goiter on record.

Inasmuch as exophthalmos occurs in anemic, rachitic children quite independently of exophthalmic goiter; and von Graefe's sign is occasionally seen in normal infants, and slightly enlarged thyroids in infants do not necessarily have a pathologic significance; and the size of the thymus cannot surely be determined by percussion, the case can scarcely be accepted as one of exophthalmic goiter, at least on the data furnished by Klaus. The additional fact that all signs of the disease had disappeared spontaneously after a year makes the correctness of Klaus' diagnosis still more doubtful.

The review of the literature on the thyroid cannot close without mention of the experiments of Cannon and his co-workers. In the past two years these investigators have developed at least two new methods of study of the endocrine glands, which may have far-reaching results. They furnish also the first physiologic proof of hormonal interaction between two organs of internal secretion, the suprarenal and thyroid. Their experiments are among the most brilliant that have ever been done in this field of investigation.

Cannon, Binger and Fitz¹⁶⁴ have produced the symptoms of hyperthyroidism in cats by anastomosing the anterior root of the right phrenic nerve to the right cervical sympathetic, so that, after regeneration had taken place, the thyroid might receive a stimulation with each respiration. The six cats that were alive five months after the anastomosis had been performed showed tachycardia, diarrhea, increased excitability and accelerated metabolism. One of the cats developed exophthalmos. In the cat most affected the suprarenals were found to

163. Klaus, O.: Basedow bei einem neun Monate alten Kinde, *Prag. med. Wchnschr.*, 1914, xxxix, 515.

164. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, *Am. Jour. Physiol.*, 1914-1915, xxxvi, 363.

be three times their normal weight. In a recent paper Cannon and Fitz have shown that the symptoms just mentioned could be made to disappear by removing the thyroid on the side on which the anastomosis of phrenic and sympathetic had been originally performed.

Cannon and Cattell¹⁶⁵ confirmed the observation of Bayliss and Bradford, made in 1885, that an electrical change in the submaxillary gland accompanies the act of secretion and that the change is absent when secretion is not taking place. Applying the same method of investigation to the ductless glands, they found that an action current was set up in the thyroid when the sympathetic was stimulated, and similarly an action current in the suprarenal followed stimulation of the splanchnic nerve. The latent period after stimulation of both thyroid and suprarenal was considerably longer than that which followed stimulation of the salivary glands.

Applying this method of study to the thyroid gland,¹⁶⁶ they found again that stimulation of the sympathetic trunk in the thorax produced an action current in the thyroid gland, which did not occur when other nerves were stimulated; and that this action current remained after the superior and inferior laryngeal nerves had been cut. When the cervical sympathetic was cut, the action current still persisted though in a modified form, but disappeared entirely when the inferior cervical ganglion also was removed. Stimulation of the vagus produced no action current. Cannon and Cattell offer these experiments as proof of the sympathetic innervation of the thyroid gland. Anatomists have already traced fibers from the cervical sympathetic to the thyroid, and previous investigators have shown that atrophy of the thyroid follows severance of its cervical sympathetic nerves (Cannon and Cattell).

Cannon and Cattell¹⁶⁷ have also succeeded in experimentally demonstrating an interrelationship between suprarenal and thyroid. They first showed that the injection of small doses of epinephrin into the blood stream of the cat induced an action current in the thyroid. Stimulation of the splanchnic nerve, physiologically separated from the central nervous system, likewise invoked an action current in the thyroid. The action current did not occur, however, after stimulation of the splanchnic if the return of blood from the abdomen was prevented, but took place promptly when the pent-up blood was released.

165. Cannon, W. B., and Cattell, McK.: Some Results of Studies on Electrical Changes in Glands, *Am. Jour. Physiol.*, 1916, xl, 143.

166. Cannon, W. B., and Cattell, McK.: Some Conditions Controlling Thyroid Activity, *Boston Med. and Surg. Jour.*, 1916, clxxiv, 138.

167. Cannon, W. B., and Cattell, McK.: III. Influence of Suprarenal Secretion on Thyroid, *Am. Jour. Physiol.*, 1916, xli, 74.

The electrical change also failed to appear after splanchnic stimulation if the suprarenal glands had been previously removed.

“GLANDULA INSULARIS CERVICALIS”: A NEW ORGAN OF INTERNAL
SECRETION

Pende¹⁶⁸ describes a structure found in the neck of man, the dog and other animals in the last months of intrauterine life and during the first year, but not after that time, which he thinks is a hitherto unnoticed organ of internal secretion. It is made up of numerous small lobular masses, scattered about in the neighborhood of the thymus and thyroid, and especially likely to be present near the upper pole of the thymus or close to the parathyroids. Some of the separate masses are large enough to be seen with the naked eye as grayish, red particles. The total volume of the “gland” is greater than that of the parathyroids. The lobules, which are sharply separated from each other, are composed of epithelial cells, which are larger in some instances, in others smaller, than the cells of the parathyroids. The cytoplasm contains an abundance of basophilic and acidophilic granules, vacuoles and lipoid substances, while the nuclei are large and round, or in some instances small and pale staining. No connective tissue stroma is present.

Pende’s reasons for thinking the structure is an endocrine gland are based solely on histologic appearances. The cells impress him as being epithelial and secretory.

It is thought that Pende’s new organ of internal secretion is embryonal fat tissue. Its scattered and irregular distribution, its complete disappearance soon after birth and the comparison of the illustrations in Pende’s article with sections of embryonic fat from the necks of new-born puppies makes this suggestion highly probable. Dr. Milton Winternitz¹⁶⁹ first expressed this view.

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168. Pende, N.: Ueber eine neue Drüse mit innerer Sekretion (*Glandula insularis cervicalis*), *Arch. f. mikr. Anat.*, 1914, lxxxvi, 1., Abt., 193.

169. Winternitz, Milton: Personal communication to the author.

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