

THE INTERRELATION OF THE ORGANS OF INTERNAL SECRETION.¹

II. THE PITUITARY

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THE PITUITARY. It has seemed best to discuss the pituitary as a single organ, since it is very generally so treated in the literature; but this is on the score of convenience merely since in its two lobes we are dealing with entities of distinct origin and different functions. This structure will be considered in relation to the thyroid, the reproductive organs, the adrenals, and the pancreas.

Pituitary-thyroid Hyperpituitism. The effect of experimental hyperpituitism upon the thyroid has been as yet but little studied—largely, probably on account of the difficulty of obtaining pituitary material. That a condition parallel to true hyperactivity of the normal gland can be secured by the injection of extracts or by feeding gland substance is by no means so sure as in the case of the thyroid. Hallion and Alquier² subjected five rabbits to prolonged ingestion of extracts of the pituitaries of cattle, using the whole gland. At autopsy the thyroids were found to contain less than the usual amount of colloid, and the cells were somewhat more nearly columnar than normal. Rénon and Delille³ obtained the same results, using intraperitoneal injections of extracts of the gland. They found that the use of the posterior lobe alone had effects similar to the use of the whole gland. This result is incidentally in harmony with the usual results reported by other investigators, who have uniformly found extracts of the anterior lobe without physiological effect. Both sets of experiments indicate that the active substance of the pituitary has a slightly stimulating effect on the thyroid. Lucien and Parisot,⁴ however, have repeated the experiments of Rénon and Delille and obtained somewhat different results. They noted a hypertrophy in the thyroids of from 10 to 40 per cent., with an increased amount of colloid—an appearance “hardly indicating increased activity, but rather resembling a simple goitre.” Sandri⁵ found in guinea-pigs that feeding or injecting pituitary extracts caused in other organs no demonstrable effect whatever. Similar results have been obtained by the writer in case of nineteen young guinea-pigs. The evidence, therefore, on the whole, is inconclusive.

¹ Concluded from page 385.

² Comp. rend. Soc. de biol., 1905, lxx, 5.

³ *Ibid.*, lxx, 499.

⁴ *Ibid.*, 1909, lxxi, 675.

⁵ Arch. ital. de biol., 1909, li, 337.

Hypopituitarism. The little existing evidence as to the effects of deficiency of pituitary secretion upon the thyroid, is positive and clear cut. Cushing,⁶ after an extensive study of the results of hypophysectomy in young dogs, states explicitly that the operation causes acute hypertrophy of the thyroid. An instructive study has been made by Exner,⁷ of two of Hoehnegg's surgical cases, that were essentially experiments bearing directly upon this point. In both instances the pituitary had been extirpated for the relief of akromegaly, and later there was found, among other results, an undoubted hypertrophy of the thyroids.

These results bear a suggestive similarity to the effect of thyroidectomy upon the pituitary and justify an extension of the theory of vicarious activity to include both glands. The theory implies that the glands are more or less synergic. The hypothesis is further supported by the observations of Soli⁸ that after castration in all but 5 of 25 cases, hypertrophy of the pituitary occurred; in these 5, the thyroids were enlarged. Taken altogether, the evidence supports a theory that the two glands are synergic and either can to some extent, in case of need, function vicariously for the other.

Pituitary; Gonads. Clinical observers have noted that disturbances of pituitary function—either by tumors in the gland itself, or by pressure of brain tumors near it—are frequently associated with sexual anomalies.^{9, 10} Cessation of menstruation in the female and impotence in the male are recognized initial symptoms of akromegaly,^{11, 12} and the same effects are noted when neoplasms exert pressure upon the hypophysis.¹³ The two previously mentioned cases of akromegaly described by Exner are especially significant in this connection. The onset of the disease in each instance was marked by the development of amenorrhoea. The restoration of menstruation after the removal of the tumors indicates a specific causal relationship of the pituitary conditions. Thumin¹⁴ has reported the case of a young woman whose sexual functions became erratic with the development of a pituitary tumor, and whose ovaries atrophied as the disease progressed. Other cases of adults of both sexes, in whom atrophy or aplasia of the gonads (infantilism) has been associated with pituitary tumors, have been described by Cushing,¹⁵ Schuller,¹⁶ Kon, v. Eiselsberg, and

⁶ Jour. Amer. Med. Assn., 1909, liii, 249.

⁷ Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, xx, 620.

⁸ Arch. ital. de biol., 1910, lii, 353.

⁹ Kon. Beitr. z. path. Anat., 1908, xlv, 233.

¹⁰ Church. Jour. Amer. Med. Assn., 1909, liii, 97.

¹¹ Cagnetto. Virch. Arch., 1908, clxxxvii, 197.

¹² Kon. Beitr. z. path. Anat., 1908, xlv, 266.

¹³ Axenfeld. Neurol. Centralbl., 1908, xxvii, 608.

¹⁴ Berl. klin. Wochensh., 1909, xlv, 631.

¹⁵ Amer. Jour. Nerv. and Ment. Dis., 1906, xxxiii, 704.

¹⁶ Neurol. Centralbl., 1907, xxvi, 965.

v. Frankl-Hochwart,¹⁷ Rénou, Delille, and Mouier-Vinard,¹⁸ and by Schloffer.¹⁹ A particularly instructive case has been reported by v. Eisel berg;²⁰ a young man, aged twenty years, developed a typical case of *degeneratio adipogenitalis*, with a tumor of the pituitary, and infantile sex organs. The tumor was successfully removed, and a year later, marked genital development had occurred.

Clinical evidence of this nature supports rather convincingly a conclusion that there is some sort of coördination between the activities of the hypophysis and of the gonads. The actual significance of the data, however, is obscured by the uncertainty that prevails as to the etiology of akromegaly. The disease is usually ascribed to hyperplasia of the pituitary, that is, to *hyperpituitism*, but the effect upon the gonads is often the same as that of obliterative tumors, that is, of *hypopituitism*.

Hyperpituitism. As mentioned before, few experimental observations upon the effects of hyperpituitism have been reported. None in which the gonads were considered are known to the writer, except those previously discussed by Hallion and Alquier, Rénou and Delille, and Sandri. As regards the sex glands, negative results were reported in each case.

Hypopituitism. The evidence as to hypopituitism is likewise meagre. Although many partial and complete hypophysectomies have been made, but little attention apparently has been paid to the effects upon other organs of internal secretion. Cushing, however, has noted that after extirpation of a part of the anterior lobe, the gonads often atrophy. It is interesting to note that a tendency to obesity, such as is observed after castration, also occurs. This evidence, together with the observed effect of obliterative tumors in the hypophysis region, indicates that the pituitary normally supplies a secretion that stimulates the sex glands to activity. More definite experimental evidence is needed, however, before a final conclusion can be reached.

Pituitary; Adrenals. The observations regarding a relationship between the pituitary and the adrenals are few. Hallion and Alquier have noted hyperplasia of the adrenal cortex after prolonged feeding of pituitary extract. After intraperitoneal injection of a similar extract, Rénou and Delille have obtained the same result. In both cases the posterior lobe alone was effective. No other data upon this relationship have been found in the literature. Any valid conclusion, therefore, in regard to the matter is obviously impossible.

Pituitary; Pancreas. Whether there is any direct relationship between the pituitary and the pancreas is doubtful. Glycosuria

¹⁷ Wien. klin. Wochens., 1908, xxi, 1115.

¹⁸ Bull. et Mem. Soc. Med. de hôp. de Par., 1909, xxvi, 204.

¹⁹ Wien. klin. Wochens., 1907, xx, 621.

²⁰ Neurol. Centralbl., 1907, xxvi, 994.

frequently occurs in akromegaly. Sternberg²¹ regards this as due to changes in the pancreas. Benda,²² however, thinks that there is no constant change in the pancreas in akromegaly, even in diabetic cases.

The evidence as a whole, indicates a mutual relation between the thyroid and the pituitary such that deficiency of the one leads to increased activity of the other. This is due to the vicarious assumption by the one, of the depressed function of the other. A tentative conclusion that the pituitary exercises a normal stimulating effect upon the sex glands is justified. The meagre data available indicate that the adrenals are stimulated by pituitary secretion, but give little weight to the conclusion. Whether the pituitary has any direct relation with the pancreas is questionable.

THE ADRENALS. The so-called "adrenal gland" consists of two parts, the cortex and the medulla, which are very probably physiologically independent structures. The only known active substance that has been demonstrated in the adrenals is produced entirely by the medulla. The two parts are of different embryonic origin, and in some of the lower fishes, they remain distinct throughout life. A separate consideration of the two parts would be desirable, therefore, in this work, but this would not be feasible because in the literature a distinction has not been consistently observed.

Adrenals; Gonads. A theory that the adrenals are related to the sex function was proposed by Meckel,²³ as early as 1806. It was based upon the following grounds: (1) In certain aborted fetuses he had noted that both the adrenals and the gonads were lacking; (2) in animals in which sexuality is marked, such as the guinea-pig, the adrenals are notably large; (3) in birds and amphibia the gonads and adrenals are closely associated in position, and (4) he had noted adrenal degeneration in several cases of diseases of the genitalia. Meckel's evidence has been controverted by various writers, notably by Nagle,²⁴ but the idea has persisted and at the present time there exists considerable evidence in its favor. This is partly clinical and partly experimental.

In cases of hermaphroditism, marked hypertrophy of the adrenals is sometimes observed. Instances of this association of conditions have been reported in detail by Crecchio²⁵ and by Marchand.²⁶ v. Neugebauer²⁷ in an extensive review of the literature of hermaphroditism published in 1908, was able to find record of 13 cases in which this association was mentioned. As evidence these few instances have no great weight, but they are suggestive.

²¹ "Akromegaly," Notlingel's Handbuch d. spec. Path. u. Ther., vol. vii, Band 2.

²² Cited by Dock; Osler's Modern Medicine, 1909, vi, 468.

²³ Cited by Nagle.

²⁴ Müller's Arch., 1836, p. 365.

²⁵ Wien. med. Presse, 1866, p. 763. Cited by Bullock and Squiera.

²⁶ Festschrift f. R. Virchow, i, 554.

²⁷ Hermaphroditismus beim Menschen., Leipzig, 1908, p. 688.

Bullock and Sequiera²⁵ have been able to find in the clinical literature 12 cases of children showing sexual precocity; who at autopsy, were found to have enlarged adrenals; 10 of these were females, from two to eleven years of age, and 2 were males, aged five and fifteen years respectively. In view of the fact that comparatively a small proportion of such cases come to autopsy at a time when the condition is recognizable, these findings are of some weight as indicating adrenal activity as a condition of sexual development.

Various other instances of associated sex and adrenal anomalies have been recorded. Otto²⁷ noted in a patient a simultaneous hypertrophy of the gonads and the adrenals. Wiesel²⁸ and Karakaschew²⁹ have each reported an instance of adrenal atrophy accompanied by sex depression, and Bullock and Sequiera mention 3 others. Borz³⁰ and Thumin³¹ have recently described 2 cases of young women who had been sexually normal up to the age of sixteen years and in each of whom then, menstruation ceased; the voice became coarse, and an extensive growth of hair upon the body occurred. At autopsy both were found to have markedly enlarged adrenals. In Thumin's case, the ovaries were somewhat atrophic.

The clinical literature taken altogether indicates that there is a correlation between the adrenals and the gonads. It further suggests, too, a theory that the adrenals furnish a stimulus to the gonads. Such a theory, however, is susceptible to the general objection that associated conditions in the two organs may be effects of some common influence, and neither the cause of the other.

The truth of the theory has been tested but little by experimentation. It has been noted by Bossi³² that goats can go through pregnancy and give birth to normal young after the removal of one adrenal. Hultgren and Anderson³³ have found the same to be true of the guinea-pig. The writer has noted, however, that from a given number of guinea-pigs so treated, even though they appear perfectly healthy, the number of offspring secured in the course of a year is notably below normal. Landau³⁴ states that adrenal extirpation is without demonstrable effect upon the ovaries of adult rabbits. Since bilateral adrenal extirpation is rapidly fatal, however, and unilateral extirpation is notably ineffective

²⁵ Trans. Path. Soc., London, 1905, iv, 159.

²⁷ Pathol. Anat. Beobachtungen, p. 139. Cited by Bullock and Sequiera.

²⁸ Virch. Arch., 1904, clxxvi, 103.

²⁹ Beitr. z. path. Anat., 1904, xxxvi, 401.

³⁰ Arch. f. Gyn., 1909, lxxxviii, 445.

³¹ Berl. klin. Wochenschr., 1909, xlii (1), 103.

³² Arch. f. Gyn., 1907, lxxxiii, 505.

³³ Skand. Arch. f. Physiol., 1899, ix, 73.

³⁴ Experimentelle Nebennieren-studien, Dorpat, 1908.

negative results are of slight significance, and scarcely modify the conclusion reached from a study of the clinical literature.

Adrenals; Thymus. The relation of the adrenals to the thymus has apparently received little attention, and there is some likelihood that the clinical evidence is defective simply for this reason. In 1902, Pansini and Bonenati described a case of Addison's disease in which in addition to the characteristic adrenal degeneration there was a marked hypertrophy of the thymus. In 1904, Wiese described a second case. In his report he discussed at some length the association of adrenal hypoplasia and thymus hypertrophy, and claimed priority for the discovery that such an association is common in cases of *status lymphaticus*. In view of this asserted relationship, Hedinger,³⁷ in 1907, made a study of all the material from cases of Addison's disease available in the pathological institutes of Berne and Basel, and found in a majority of the cases a recognizable condition of *status lymphaticus*. Other cases of this association have since been reported by Hart,³⁸ Pappenheimer and Kahn.³⁹ The clinical data are consistent so far as they go, but further observations are needed.

Very little experimental work upon the subject has been done. Boinet⁴⁰ at the autopsies of rats that had survived for a considerable length of time the extirpation of both adrenals found that 11 of 50 individuals showed thymus hypertrophy. Auld,⁴¹ in 1899, in an investigation of "compensatory hypertrophy" found in each of four cats upon which he had performed unilateral adrenal extirpation a "very great hypertrophy" of the thymus. Other investigators who have performed epinephrectomies seem not to have paid attention to the condition of the thymus. The possible results in the thymus after this operation may have been overlooked because the animals either die within a short time, or if they survive long, become more or less cachectic. In the first condition, time would not have been allowed for hypertrophy to occur, and in the second, any tendency to hyperplasia would be masked by the marked tendency of the thymus to atrophy in case of deficient nutrition.⁴²

On the whole, it appears that adrenal deficiency is frequently associated with hypertrophy of the thymus, and so far as the evidence bears upon the point, that is, in Addison's disease, and in experimental adrenal deficiency, that the condition in the adrenals is primary to that in the thymus. More evidence is needed, however, before any final conclusion can be reached.

³⁷ Verhandl. d. deutsch. path. Gesellsch., 1907, xi, 29.

³⁸ Wien. klin. Wochensh., 1905, xxi, 1110.

³⁹ Virch. Arch., 1910 (June).

⁴⁰ Comp. rend. soc. de biol., 1895, xlvii, 163.

⁴¹ Brit. Med. Jour., 1899, p. 1327.

⁴² Jomseri, Arch. f. mikr. Anat., 1909, lxxiii, 390.

Adrenals; Pituitary. The observations as to a relationship between the pituitary and the adrenals have been few. Boinet, in experiments previously mentioned, found pituitary hypertrophy following epinephrectomy in 4 only of 50 cases. Alquier observed also, in a dog, slight evidence of hypertrophy after the same operation. A similar effect in the guinea-pig, dog, and cat, has been noted by Marenghi.⁴³ Landau has found that in the adult rabbit adrenal extirpation is entirely without effect upon the hypophysis. At present, therefore, there is little evidence of any relationship of the adrenals to the pituitary.

Adrenals; Thyroid. Whether a demonstrable result in the thyroid follows adrenal extirpation is questionable. Boinet found hypertrophy of the thyroids in 12 of 50 cases. Landau, however, who has investigated the matter at some length, states that in his experience, adrenal extirpation has upon the thyroids no effect whatever. Parhon and Goldstein⁴⁴ noted in three dogs an augmentation of colloid in the thyroids after a short course of treatment with adrenalin. No definite conclusion in regard to this relationship is yet possible.

Adrenals; Pancreas. Previous mention has been made of Eppinger, Falta, and Rudinger's hypothesis that the chromaffin system and the pancreas are mutually antagonistic. An adequate discussion of the theory would necessitate a review of a long series of researches such as the scope of the present work scarcely permits. Their conclusions as regards the pancreas are based upon the fact noted by Blum, Zülzer and others that the injection of adrenalin causes glycosuria. The theory has the weakness inherent in our ignorance of many of the details of carbohydrate metabolism. It is supported by the observations of Rudinger, Falta, Eppinger, Pollak, and Porges⁴⁵ that in Addison's disease the dextrose limit is high. A final evaluation of the theory, however, must await the accumulation of more evidence.

In summary it appears that the theory of an association between the activities of the adrenals and the gonads is well supported, and there is some reason to believe that the former glands may stimulate the latter. Adrenal hypoplasia and thymus hyperplasia are frequently associated; probably the former condition stands in causal relationship to the latter. There is little evidence of a relationship of the adrenals to the pituitary. The theory that the adrenals stimulate the thyroids has some evidence in its favor but more data are needed; the same is true of the hypothesis that the adrenals inhibit the pancreas.

THE GONADS. While it is probable that the testes and ovaries, considered as organs of internal secretion, have little in common, it will be more convenient to consider them together.

⁴³ Lo Sperin., 1903, Ivii. Cited by Alquier, p. 494.

⁴⁴ Rev. neurol., 1909, xvii, 1143.

⁴⁵ Zeit. f. klin. Med., 1910, lxx, 243.

*Gonads; Pituitary; Hypergonadism.*⁴⁶ No evidence has been found of any effect of activity of the male sex organs upon the pituitary. In the female, pregnancy has been observed to cause an increased activity of this gland. Launois and Mulon,⁴⁷ Morand, and Guerrini,⁴⁸ and Laignel-Lavastine have reached that conclusion from cytological studies. The matter has recently been determined conclusively by Erdheim and Stumme,⁴⁹ who have found from a careful comparison of the weights and cytological condition of the pituitaries from 85 pregnant women with 13 from nulliparæ that both pituitary hypertrophy and increased cellular activity accompany pregnancy. Whether this effect, however, is due to sexual activity *per se* is open to question. The increased activity may be simply a reaction to the changed metabolic conditions that undoubtedly occur during pregnancy. Laignel-Lavastine states that hyperemia and hypertrophy of the pituitary can be demonstrated during menstruation, but the assertion lacks corroborative evidence. Rénon and Delille⁵⁰ have reported that ovarian extract "moderates the pituitary" but their evidence is not convincing. No definite conclusion, therefore, can as yet be reached as to whether or not hyperactivity of the sex glands has any effect upon the pituitary.

Hypogonadism. The effects of castration upon the pituitary have been studied by several investigators. Cecca⁵¹ has reported entirely negative results in both sexes; since, however, the details of his research are not given, a critical consideration of his work is not possible. Fischera⁵² has studied the matter in 65 animals—cocks, 50; buffalo, 5; cattle, 5; guinea-pigs, 2; and rabbits 3 cases—and has found that castration in both sexes is followed by an undoubted hypertrophy of the anterior lobe of the pituitary, with a hyperplasia of the eosinophile cells. In three cases he found that injections of testicular extracts caused a rapid disappearance of the eosinophilic substance. Fischera's results seem well established and have been generally accepted as valid. His findings have been confirmed by Tandler and Gross,⁵³ by Soli, and by Schutz,⁵⁴ on animals and somewhat doubtfully by Kon in a study of the pituitaries of 7 women, and of 1 man, after surgical castration. The effects of this operation seem to be confined to the anterior lobe. These observations suggest that the pituitary may normally be held in check by secretions of the gonads, and

* "Hyper-" and "hypogonadism" are proposed as terms to indicate conditions due to excessive and depressed secretory activity, respectively, of the gonads considered as organs of internal secretion.

⁴⁷ Arch. de gyn. et l'obst., 1904, p. 1.

⁴⁸ Zeit. f. allg. Path. u. path. Anat., 1905, xvi, 177.

⁴⁹ Beitr. z. path. Anat., 1909, xlv, 1.

⁵⁰ Comp. rend. soc. de biol., 1909, lxxvi, 59.

⁵¹ Arch. ital. de biol., 1905, xliii, 403.

⁵² Presse Méd., 1904, xii, 341.

⁵³ Wien. klin. Woch., 1908, xxi, 280.

⁵⁴ Cited by Cushing; Amer. Jour. Med. Sci., 1910, cxxxix, 478.

that when this inhibition is removed, the pituitary manifests increased activity, leading to altered metabolisms and thus to an overgrowth of different parts of the body, such as occurs both in akromegaly, and after castration.

Gonads; Thymus. The evidence of a relation between the gonads and the thymus is not extensive, but is entirely concordant. That the thymus persists until puberty, when the sex glands undergo a physiological hypertrophy, has long been known. It would be *a priori* likely, therefore, that castration, would tend to prolong the persistence of the thymus. The facts bear out the supposition. Calzolari⁵⁵ apparently was the first to investigate the matter experimentally. In six castrated rabbits he found that the thymus invariably attained greater weight and persisted longer than in normal animals. Henderson⁵⁶ investigated the matter in 114 cattle that were being slaughtered for beef. They had, of course, been castrated while young. They were found generally to have persistent thymuses. The same fact was noted by Henderson in guinea-pigs and rabbits. It was noted, also, that in cattle of both sexes, that had exercised the reproductive function, the normal thymus atrophy was accelerated. Godall,⁵⁷ in a histological study of the effects of castration in the thymus of the guinea-pig, noted that both the lymphoid tissue and the corpuseles of Hassal share in the delayed atrophy. Soli in 10 rabbits and 15 capons has noted a similar thymus persistence after castration, and Tandler and Gross have found the same effect in roebucks, dogs, and goats. These writers state also, that persons with hypoplastic gonads retain their thymuses longer than normal. It can, therefore, be definitely asserted that the gonads exert a depressing effect upon the thymus.

Gonads; Adrenals. The effect of conditions in the gonads upon the adrenals has not been studied to any great extent. Guicysse⁵⁸ and Marrassini⁵⁹ have noted that in guinea-pigs the adrenals enlarge during pregnancy, but as pointed out previously, the interpretation of this condition as primarily a sex phenomenon is questionable. Cecca, Marrassini, and Tehodossiet⁶⁰ have reported that hypertrophy occurs in the adrenal cortex after castration just as it occurs in the pituitary after the same operation. These observations have been confirmed by Soli. He has noted further that the hypertrophy is succeeded by an atrophy. This paucity of data, however, permits no final deduction as to the effects of conditions in the gonads upon the adrenals.

Gonads; Thyroid. But little is known of the effects of the gonads upon the thyroid. So far as has been discovered in the present

⁵⁵ Arch. ital. de biol., 1898, xxx, 71.

⁵⁶ Jour. Physiol., 1904, xxxi, 222.

⁵⁷ Comp. rend. soc. de biol., 1899, xlix, 898.

⁵⁸ Arch. ital. de biol., 1906, xlv, 73.

⁵⁹ Russky Vritsch., 1906, No. 5. Cited by Borz.

⁶⁰ Jour. Physiol., 1905, xxxii, 191.

investigation the effects of testicular extracts upon this gland have never been studied. Ovarian extract injected intraperitoneally has been observed by Rénon and Delille to cause congestion or even hemorrhage in the thyroid; such an observation, however, is probably of slight significance as indicating any definite relation between the two glands. The thyroid often hypertrophies during menstruation and pregnancy, and this is sometimes interpreted as indicating a relation between the ovaries and the thyroid. Most observers have failed to note any effect of castration upon the thyroid, but Cecea and Delille, have noted in both sexes a hypertrophy. Soli observed no effect upon the thyroid of this operation in cocks, but in rabbits for the first three months there was a slight augmentation, followed later by a depression of the thyroid weights. The evidence altogether is too meagre in quantity, and conflicting in tenor to permit any conclusion as to a possible effect of the gonads upon the thyroid.

It appears that hypogonadism leads to hypertrophy of the pituitary possibly by removing a normal check upon it; activity of the sex glands seems to lead to depression of the thymus. A few observations indicate that the adrenal cortex hypertrophies after castration. The evidence as to the effects of activities of the sex glands upon the thyroid is meagre and not concordant.

THE THYMUS. Despite a great deal of work upon the subject, little is known of the function of the thymus, and of the data available few observations bear upon the relation of the organ to other glands. Previous mention has been made of the hypertrophy of the thymus that occurs in cases of Addison's and of Graves' diseases but the significance of the condition is unknown.

Thymus; Gonads. Paton⁶¹ has reported that removal of the thymus in young guinea-pigs causes a more rapid growth of the testes than normal. Soli, however, has obtained in cocks and rabbits exactly the opposite effect. Whether the thymus, therefore, has any influence upon the sex glands remains an open question.

Thymus; Thyroids. Aside from a report by Lucien and Parisot⁶² that a series of rabbits killed at varying periods after thymectomy had in every case smaller thyroids than the controls, there is no evidence known to the writer of a relation of the thymus to the thyroid. Soli after a series of 34 thymectomies found no demonstrable effect in the thyroids. In some cases he observed a slight but probably negligible augmentation of the weights of the pituitaries, and of the adrenals.

THE PANCREAS. Previous mention has been made of Falta's theory of the antagonism between the pancreas and the thyroids. There is little direct evidence that the pancreas does depress thyroid activity. Licini⁶³ has noted in dogs, however, a pro-

⁶¹ Jour. Phys., 1904, xxxii, 28.

⁶² Deutsch. Zeit. f. Chir., 1909, cl., 522.

⁶³ Comp. rend. soc. de Biol., 1909, lxxi, 406.

gressive hypertrophy of the thyroids with an increase in the colloid content after pancreas extirpation. The histological appearance of the thyroids in his opinion indicated an increased functional activity.

THE PARATHYROIDS. There is but little known of the relationships between the parathyroids and other endosecretory organs. Marinesco and Parhon⁴⁴ have noted after thyreoparathyroidectomy a marked increase in the fat-like material in the cells of the adrenal cortex. This change they at first ascribed to the removal of the thyroid, but after a repetition of their experiments, concluded that it was caused mostly or wholly, by the loss of parathyroid tissue. Caro and others have postulated an antagonism between the parathyroids and the thyroids, adrenals, and pituitary, on the grounds that the parathyroids depress the irritability of the nervous system, carbohydrate metabolism, calcium, and magnesium metabolism, and blood pressure. There is, however, little or no direct evidence on the point.

THE PINEAL BODY. There is some slight evidence that the pineal body may have an influence on the development of the gonads. Raymond and Claude⁴⁵ have recently reported in detail one instance and cited a few others of pineal tumors associated with sexual precocity. Such instances are too rare, however, to have any great significance.

In this work little mention has been made of the possible mechanism by which the various effects described have been produced. Very suggestive is the work of Falta, Kostlivy, Caro, and others, which indicates that many of the symptoms of endosecretory disturbances are due to stimulation of the sympathetic and general autonomic nervous systems—sometimes acting concordantly, sometimes antagonistically. Other effects may be reactions to endotoxins due to perverted metabolisms. Others are probably due to direct hormone stimulation of various organs. Before the mechanisms of the various interactions can be fully understood, a much greater number of definite data must be secured.

The writer is aware that in the attempt to collect the evidence from such widely scattered sources, some significant observations may have been overlooked. He ventures to hope, however, that not enough has been missed to alter substantially the conclusions reached.

It is a sincere pleasure to acknowledge many obligations to Professor Walter B. Cannon for his helpful criticisms of this work.

⁴⁴ *Doumanie Med.*, 1908, Nos. 10 and 11, 19 and 20.

⁴⁵ *Bull. acad. med.*, 1910, lxxiv, 261.