been shown that the active principle of this extract lies in the nucleoproteid which can be precipitated from the watery suspension by an acid, and Dr. Berkeley reports good results from the use of this material in human cases. The fresh glands could be used in the same way, but the extract is more convenient and much more easily procured. Reported results differ widely, however, for while Berkeley and a few others apply it with enthusiasm, many, including Pineles and Escherich, have found no result from giving parathyroid by mouth. In experimental animals I have never been able to observe much effect from its administration in this way.

Blind efforts have been made for years and are still being made to cure tetany by feeding thyroid extract—sometimes apparently with good results. The explanation that parathyroid material is included in the dried thyroid seems, however, absurd, for the doses would be infinitesimal.

Soluble calcium salts will stop the symptoms of tetany after parathyroidectomy very promptly if injected intravenously, and even if given by mouth in large doses, and it is possible in that way to keep such an animal alive for a long time. It does not cure the condition, however, but only masks the symptoms which appear again when its effect is worn off. Its use must then be, like that of strontium or magnesium, to tide over in emergencies the period of danger, or in protracted cases of a milder type, to relieve the symptoms. Often, after an operation in which the destruction of the parathyroids has not been complete, the remnants will recover their function and hypertrophy so as to be practically adequate to maintain health, and it is in this period of recovery that calcium may be especially useful. In the spontaneous cases of severer character, some writers have reported good results from its use, but others have observed no effect whatever.

Naturally the ideal therapeutic measure would be to implant with their circulation complete new parathyroid glands to take the place of those which were destroyed or to add their influence to that of the relatively insufficient glands, but on account of their small size, this is impossible. Nevertheless, they have been implanted, without reestablishing their circulation, in the sheath of the rectus muscle and other places; and sometimes, even though the central part becomes necrotic, the more superficial layers remain alive. Dr. Halsted has experimented with this method and has succeeded in keeping a dog alive and well for months with such a graft. Its efficiency was proved by the fact that the dog quickly died of tetany when the graft in its turn was excised, and at autopsy no other trace of parathyroid was found. Dr. Halsted states that it is impossible to get parathyroids from animals of another species to grow and very difficult to succeed with glands from another animal of the same species; further, that even with the transplantation of one of the animal's own glands, it is necessary that there should be an actual need of parathyroid function before the graft will take. Still, these are the conditions which exist when the surgeon suddenly realizes that he has excised the parathyroid with the thyroid, and much may be hoped from their immediate reimplantation. Several cases have already been reported in which this and even the implantation of a gland from another person have been successful.

In conclusion, then, it becomes evident that we are very imperfectly informed concerning the parathyroids. It is certain that they exercise a peculiar and very important function in preventing the appearance of an extraordinary change in the circulating fluids, which in turn

produce an extreme hyperexcitability of the whole nervous system. What metabolic process is responsible for this change we do not know, but it sometimes makes itself felt in spite of the parathyroid glands. There is much evidence that it produces or even consists in a disturbance in the metabolism of calcium which may well be the cause of the heightened nervous irritability. That the parathyroids control this is shown by the curative effects of injecting their extract or implanting them, and we must hope that in the near future we may be able to perfect this method so as to gain the mastery of the disease.

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THE INTERNAL FUNCTION OF THE PANCREAS *

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The view that the pancreas produces an internal secretion has been generally accepted. No one, however, has been able to obtain from the pancreas an internal secretion and proof of its existence is not complete.

Before reviewing the evidence at hand it would be well to describe briefly the nature and actions ascribed to the internal secretions. The internal secretions are defined as the products of a specific activity of an organ or tissue which pass through the blood to other organs or tissues in which they exert a stimulating or inhibitory influence on the material or energy stored up in the cells. These chemical bodies which form the internal secretions are called hormones, a term derived from a Greek verb, meaning to awake or excite. They are divided by Biedl into the assimilatory and the dissimilatory hormones. The former aid in the upbuilding of the living substance in the cells, the latter in the breaking down of the living substance. Both regulate the activity of the cells.

The internal secretions, unlike the external secretions, are not formed exclusively in epithelial cells. Epinephrin is produced in the chromaffin tissue which is closely related genetically with the sympathetic nervous system, and there is evidence that the internal secretion of the testicles is formed in the interstitial tissue. Little is known of the chemical constitution of hormones except that it probably varies greatly with the secretion, and may be a simple or complex body. As all internal secretions are stimulatory substances and do not furnish nutritive material to the cells they are able to exert their specific action when present in very small quantity.

The existence of an internal function of the pancreas, although not necessarily an internal secretion, has been a justifiable assumption since the discovery of von Mering and Minkowski¹ that total removal of the pancreas of dogs always produces a severe and rapidly fatal diabetes. The glycosuria reaches its maximum in two or three days, and persists even when the animal is on a diet free from carbohydrates, or when no food is given. Depancreatized dogs die within a few weeks. The symptoms resemble those of severe human diabetes, and acidosis, although not common, may develop.

After partial pancreatectomy, if more than one-tenth of the pancreas is left behind in the body, glycosuria

* Read in the Symposium on Internal Secretions in the Joint Meeting of the Sections on Practice of Medicine and Surgery of the American Medical Association, at the Sixty-Third Annual Session, held at Atlantic City, June, 1912.

1. Arch. f. exper. Path. u. Pharmacol., 1880, xxvi, 371.

may not result. Sandmeyer² showed that mild diabetes would gradually develop if the greater part of the pancreas was extirpated and at the same time the pancreatic ducts were tied. Lamson, Marks and myself³ found that a rapid sclerosis and atrophy of the pancreas were produced by separating the pancreas from the duodenum after all the ducts had been tied. Later Spooner and I⁴ discovered that in dogs this atrophy was associated with a diminished tolerance for carbohydrates. The limit of assimilation did not fall so low that glycosuria developed on a non-carbohydrate diet. In a hitherto unreported experiment we found that the removal of the processus lienalis and the processus uncinatus, amounting to nearly two-thirds of the entire pancreas, was followed by no lowering of the limit of assimilation for glucose. Both before and after the operation the dog could take up to 125 gm. of glucose without the appearance of sugar in the urine.

Important evidence in favor of the view that the pancreas produces an internal secretion is furnished by the results of the transplantation of pancreatic tissue. Minkowski,⁵ Hédon,⁶ and others have shown that if a portion of the pancreas (processus uncinatus) with its mesenteric attachment be drawn out of the abdomen and placed beneath the skin it will prevent the development of diabetes after extirpation of the remainder of the organ. The removal of the graft is promptly followed by a fatal diabetes.

The extirpation experiments would seem to offer convincing evidence that the diabetes that follows the removal of the pancreas is due to the lack of pancreatic tissue. Pflüger,⁷ however, maintained that it might be the result of cutting the nerves that pass to the pancreas. He attempted to explain the prevention of diabetes by a subcutaneous graft as dependent on the presence of nerves in the mesenteric stalk running to the graft. When the mesenteric attachment was cut, lack of blood-supply caused necrosis of the transplanted piece of pancreas, and diabetes resulted. So Pflüger's claim was difficult to disprove.

In three instances reported by Hédon⁶ and in one experiment of Lombroso⁸ the stalk was cut without diabetes resulting. In Lombroso's animal the autopsy showed that a blood-vessel from the skin had grown into the graft. The external secretion produced in the subcutaneous graft escapes through an opening made in the skin. The absence of diabetes after the loss to the body of all the external secretion indicates that diabetes is not due to any change in the pancreatic juice. This was clearly proved in our experiments in which all the pancreatic juice was excluded from the intestine. Five of the dogs that lived from five months to two years after the operation were found at autopsy to have almost total atrophy of pancreatic tissue, so that in addition to an absence of pancreatic juice from the intestine there was little or no production of pancreatic juice in the body during a period of many months.

Martina,⁹ of Greifswald, an assistant of Payr, transplanted a portion of the pancreas into the spleen. Removal of the remainder of the pancreas resulted in diabetes, but of a less severe type, it was claimed, than that seen in depancreatized dogs. The animal lived the

unusually long time of three months after the onset of the diabetes. At the autopsy living pancreatic tissue was found in the spleen. Details of this experiment were not published owing to the death of this young investigator. Minkowski, the great student of experimental diabetes, at the time a professor in Greifswald, and in a position to judge of the accuracy of Martina's observation, regarded the work as furnishing important evidence against the neurogenic hypothesis and in favor of an internal secretion.

A more successful and more convincing experiment than that of Martina has been made by Murphy and myself. The greater part of the processus uncinatus of a dog was placed in the spleen. The artery which entered the distal end of this portion of the pancreas was not cut. Ten days later the remainder of the pancreas was extirpated. At this second operation the site of the transplantation into the spleen was occupied by an abscess about 4 cm. in diameter. The pus was removed and the mesenteric stalk which carried the blood-vessels to the graft was cut. We feared that all the pancreatic tissue had been destroyed by the suppurative process. The dog, however, rapidly recovered from the operation and the urine remained free from sugar. There was the usual rapid loss of weight and strength seen after excluding the pancreatic juice from the intestine. The weakness became so extreme that it was necessary to feed fresh pancreas. As a result the dog regained its strength in fair measure and lived for six months. Its tolerance for carbohydrates dropped to a low level (glycosuria followed the feeding of 40 gm. of glucose) but true diabetes did not develop.

At the autopsy, a large thick-walled abscess was found, from one side of which projected the remains of the spleen. A cone-shaped mass of fibrous tissue occupied the lower part of the spleen with its base formed by the abscess wall. On microscopic examination a small amount of pancreatic tissue was found imbedded in the fibrous tissue. The pancreatic graft was 1 cm. or less in length and 1 to 3 mm. in width. It was composed of small areas of epithelial tissue, separated by fibrous tissue which contained nerves and ganglion cells. There were distinct well-formed acini, but no structures that resembled islands of Langerhans.

No other pancreatic remains were found either attached to the duodenum or elsewhere; hence the internal function of the pancreas must have been performed by this small bit of the gland in the center of the spleen. Does not the conclusion seem justified that this small collection of pancreatic cells produced an internal secretion which prevented the development of diabetes? That this internal secretion was regulated by nervous impulses is probable and does not militate against the theory of an internal secretion. I know of no other reasonable explanation of our findings.

Pflüger quoted Hédon as saying that he would not accept the view that the pancreas produces an internal secretion, until pancreatic diabetes could be checked by administering some pancreatic product. The fact that in depancreatized dogs no diminution of the glycosuria has been produced by injecting or feeding fresh pancreas is not a valid argument against the existence of an internal secretion. The chromaffin tissue forms an internal secretion which contains a definite and well-recognized chemical substance, epinephrin, yet the administration of epinephrin or the fresh adrenal gland does not lessen the symptoms of adrenal insufficiency in Addison's disease.

2. *Ztschr. f. Biol.*, 1894, xxxi, 12.

3. *Tr. Assn. Am. Phys.*, 1900, xxiv, 226.

4. *Arch. Int. Med.*, 1911, vii, 665.

5. *Arch. f. exper. Path. u. Pharmacol.*, 1893, xxii, 271.

6. *Arch. d. Physiol.*, 1892, iv, 617.

7. *Arch. f. d. ges. Physiol.*, 1907, cxviii, 267.

8. *Ergbn. d. Physiol.*, Wiesbaden, 1910, ix, 11.

9. *Deutsch. med. Wchenschr.*, 1908, No. 1, 45.

As already stated, all attempts to obtain from the pancreas an internal secretion have failed. Spooner and myself⁴ have published evidence which seems to indicate that the gland removed from the body does contain an internal secretion. A dog with atrophy of the pancreas produced by separating the gland from the duodenum was under observation for nearly three years. After the limit of assimilation for glucose had fallen to a low level fresh sheep pancreas was fed. The tolerance slowly rose to the normal and remained there for several weeks after the administration of pancreas was discontinued. It then slowly fell a second time to a low level. About a year later the tolerance was raised by feeding pig's pancreas, and it was maintained at a high point as long as the gland was fed. Two attempts to increase this dog's assimilation for glucose by feeding the gland in summer failed, possibly owing to changes in the pancreas due to decomposition, although the glands were placed in cold storage as soon as received from the abattoir.

In other dogs, in which the administration of pancreas was begun a shorter time after the onset of atrophy, the increase in tolerance has been less marked. Evidence was sought to decide whether or not the property of the pancreas to raise the tolerance was due to a thermolabile substance, but the results were inconclusive owing to the fact that this test was made in summer with pancreas that may have been inactive before it was heated.

In considering our feeding experiments it should be remembered that our dogs, unlike those of other investigators, did not have severe diabetes. When on a non-carbohydrate diet the urine was free from sugar. In depancreatized dogs it has been asserted that the absorption of fat and protein is not increased by the feeding of pancreas; but in our animals the absorption of food material was greatly improved and there was a striking gain in weight and strength.

Can the increase in the assimilation of glucose be attributed to the improved general condition of the animal? There is no evidence known to me that supports such a view. No matter how excellent is the health and nutrition of a dog, total pancreatectomy is always followed by glycosuria within from twenty-four to forty-eight hours and the output of sugar reaches a high point a few days after the operation.

As already stated, the increased tolerance had persisted at the maximum level for several weeks after the feeding of pancreas was discontinued; in one instance, it continued to rise for a short time thereafter. The view that the improved condition of nutrition favored the hypertrophy of the atrophic remains of the pancreas and that this increase in pancreatic elements explains the greater power to assimilate glucose seems untenable because the increased tolerance soon fell to a low level after the feeding of fresh pancreas was discontinued. That the pancreas fed to the dog contained an internal secretion which was absorbed from the intestine into the blood is a justifiable assumption.

The theory that there is an internal secretion essential to carbohydrate metabolism is the only one that seems to explain these findings. The results of these feeding experiments speak even more strongly against the neurogenic theory than do those of the organ-transplantations.

In the dog that lived thirty-four months with an atrophied pancreas the autopsy showed that the entire pancreas had become converted into a small thick strand of fibrous tissue, the outlines of which merged into the surrounding mesentery. The corpus pancreatis was reduced to a nodule the size of a bean. Microscopic examination

of different parts of this pancreatic remains showed neither acini nor islands of Langerhans, but only scattered groups of epithelial cells interpolated between bundles of connective tissue. The main pancreatic duct, somewhat dilated, was found near the center of the sclerosed tissue. The evidence is convincing that these small groups of cells, although so changed as no longer to be recognizable as pancreatic epithelium, were able to functionate so effectively as to prevent the development of glycosuria. In four other dogs and in two cats no islands of Langerhans were found in the atrophied pancreas, but acini were easily demonstrable. None of these animals developed diabetes.

Much has been written on the islands of Langerhans and their relation to the internal secretion and to diabetes, and excellent studies have been made. The structure of the islands of Langerhans favors the view that their function is to furnish an internal secretion in diabetes and the alterations in the islands described by Opie and others point to this conclusion. Weichselbaum asserts that by use of special methods changes in the islands of Langerhans can be found in every case of diabetes. His observations and conclusions lack confirmation. Too much has been claimed by the supporters of the island theory. The incorrect statement is found repeatedly in the literature that the acini atrophy and disappear after the pancreatic ducts are tied, but the islands remain intact. The observations made in our laboratory clearly prove that both structures undergo progressive atrophy and destruction and become greatly diminished in number.

Some interrelation of the several organs of internal secretion is probable; although this is a domain rich in hypothesis it is poor in fact.

The view that the pancreas inhibits the action of epinephrin in mobilizing sugar has rested chiefly on the results of Zuelzer's¹⁰ experiments. This investigator found that when epinephrin was mixed with pancreatic extract its power to produce glycosuria was lost. Now we know, thanks to the work of von Fürth and Schwarz, that the absence of glycosuria was not due to any inhibitory action of the pancreatic extract, but to the toxic action of the injected pancreatic extract (foreign protein) on the kidneys.

I wish to report two recent observations which seem to indicate a chemical correlation between the pancreas and two organs of internal secretion—the thyroid and the sexual glands.

In three dogs in which at the time of death chronic pancreatic insufficiency had existed from five to thirty-four months I found the thyroids so altered in microscopic appearance as to be scarcely recognizable. The size, color and consistency of the thyroids were natural, but histologic study showed either a partial or total disappearance of colloid and in its place were desquamated epithelial cells, so numerous as to fill many of the alveoli. The cells varied in size, but large ones predominated. Their nuclei took the stain deeply and uniformly.

So far as I know, this change in the thyroid has not been hitherto described. Whether it indicates a compensatory action on the part of the thyroid or is simply a degenerative change can probably be decided by extirpation of the thyroids in animals with pancreatic insufficiency in which the atrophy of the pancreas is extreme and of long duration.

Atrophy of the pancreas was induced in a female puppy about 6 months old. This animal was under

10. Berl. klin. Wehnschr., 1907, p. 474.

11. Wien. klin. Wehnschr., 1911, xxiv, 115.

observation for nearly three years after the separation of the pancreas from the duodenum. She never menstruated and the nipples and external genitalia did not develop. It seemed to be a clear case of sexual infantilism of pancreatic origin. The dog in its actions remained a puppy to the end of her life.

The association of sexual infantilism with hypofunction of the pancreas is another bond which binds the pancreas to the undoubted organs of internal secretion, the thyroid and the glandular part of hypophysis cerebri. My observation is difficult to explain in any other way than that the pancreas furnishes something to the blood which influences the development of the secondary sexual characteristics, in other words, an internal secretion.

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THE ANATOMIC AND PHYSIOLOGIC EFFECTS OF IODIN ON THE THYROID GLAND OF EXOPHTHALMIC GOITER *

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The major interest in the pathology of the exophthalmic goiter syndrome still hinges about the thyroid gland as it has done in an indefinite manner since 1840 and in a specific way since Gauthier and Möbius in 1886 and 1887 advanced the hypothesis that the symptom-complex was dependent on hyperactivity of the thyroid gland with a resultant thyroid intoxication.

But, notwithstanding the large amount of study and experiment that has been directed to this subject during the past twenty-five years, the thyroid hypothesis of the etiology of the exophthalmic goiter syndrome still remains an hypothesis.

In recent years the clinical evidence, especially that of surgical therapy, tends to support the thyroid hypothesis, while at the same time the evidence from pathologic anatomy, chemistry and pathologic physiology rather suggests that the thyroid does not play a primary rôle in the production of the symptom-complex.

I. ANATOMIC CHANGES IN THE THYROID

From the standpoint of pathologic anatomy the changes are body-wide and highly variable. The most striking and most constant are those of the lymphoid and thyroid tissues.

Confining ourselves to the thyroid changes, widely different views have been expressed as to their significance. Thus Virchow,¹ summarizing the literature to 1863, stated that there "was neither a distinct variety nor a distinct size nor yet a distinct stage of goiter associated with the symptom-complex," and concluded that such changes could not be considered as causal or primary.

Beginning particularly with the development of the thyroid hypothesis of Gauthier and Möbius and the operative treatment of exophthalmic goiter, the thyroid changes were more extensively studied and the trend of opinion favored the view that the morphologic changes were constant and characteristic. Thus the published

studies of Greenfield,² Haemig,³ Farner,⁴ Lewis,⁵ Ewing,⁶ Wilson⁷ and many others strongly supported such a view.

On the other hand, the studies of Virchow,¹ A. Kocher,⁸ Reinbach,⁹ Brissaud,¹⁰ MacCallum,¹¹ and Simmonds¹² have shown a wide range of morphologic changes in the thyroid.

My own experience during the last seven years includes careful anatomic examinations of 137 operative and autopsy specimens of the thyroid from patients with exophthalmic goiter. The results of part of this series have already been published,¹³ and those still unpublished will not materially alter the proportion or types of changes then noted. I found that the symptom-complex as at present diagnosed was not associated with either constant or characteristic changes in the thyroid, although in about three-fifths of all cases some degree of active hyperplasia was present at the time of removal.

Thus, as larger series of cases have become available for study, opinion is again returning to the view of Virchow, that the symptom-complex may be present with the thyroid in any anatomic state—normal, actively hyperplastic, colloid, in glands the seat of tumors, benign or malignant, or with high degrees of atrophy. These changes, as has long been known, are those common to goiter in general, irrespective of their clinical association but with this difference that the proportion of glands showing active hyperplasia (developing goiter) at the time of operation is at present higher in a series of exophthalmic goiters than in ordinary goiter.

II. IODIN CONTENT OF THE THYROID

Turning to the iodine contents of thyroids in relation to goiter formation, it is now established that the iodine content varies with the amount of visible colloid and inversely with the degree of active epithelial hyperplasia. This relation has been found constant for all mammalian thyroids thus far studied.

The effect of iodine on active thyroid hyperplasia has also been studied in some detail and in all the so-called simple hyperplasias of man and the lower animals it has been found that following the administration of iodine there is a rapid storage of iodine in the thyroid in association with the accumulation of colloid and a progressive involution (throughout three to five weeks) of the active hyperplasia to its colloid or resting stage.

With these facts concerning the iodine relations established for simple thyroid hyperplasia (goiter) and with the anatomic similarity of the hyperplasia found in exophthalmic goiter with that occurring spontaneously in simple goiter or in experimentally induced hyperplasia, it is of importance to ascertain whether iodine induces the same effects on the hyperplasia of exophthalmic goiter. Clinically both good and bad results have followed the use of iodine in exophthalmic goiter and it is still the prevailing opinion that iodine should not be used in this disease, although clinicians generally have noticed a reduction in the size of the thyroid following

2. Greenfield: Brit. Med. Jour., 1897, II, 1261.

3. Haemig: Arch. f. klin. Chir., 1897, IV, 1.

4. Farner: Virchow's Arch. f. path. Anat., 1896, cxliii, 509.

5. Lewis: Surg., Gynec. and Obst., 1906, III, 477.

6. Ewing: Tr. Assn. Am. Phys., 1906, xxi, 507.

7. Wilson: Am. Jour. Med. Sc., 1908, cxxxvi, 851.

8. Kocher, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, IX, 1; Arch. f. klin. Chir., 1910, xcii, 442; Virchow's Arch. f. path. Anat., 1912, cxviii, 86.

9. Reinbach: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1901, VIII, 247.

10. Brissaud: Semaine méd., 1895, xv, 326.

11. MacCallum: THE JOURNAL A. M. A., Oct. 5, 1907, p. 1158.

12. Simmonds: Deutsch. med. Wchnschr., 1911, xxxvii, 2164.

13. Marine and Lenzart: Arch. Int. Med., 1911, VIII, 265.

* Read in the Symposium on Internal Secretions in the Sections on Practice of Medicine and Surgery of the American Medical Association, at the Sixty-Third Annual Session, held at Atlantic City, June, 1912.

1. Virchow: Die krankhafte Geschwülste, 1863, III, 74.