feeble heart beat. On the clinical side these results agree well with the observation that in Addison's disease, which is accompanied by a lesion of the adrenals, there is also marked asthenia with feeble heart beat and loss

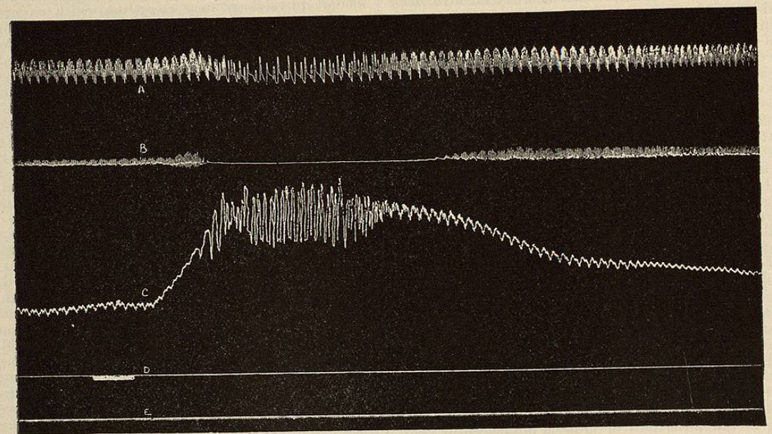

FIG. 4171.—Curve to show the Effect of Intravenous Injections of Extract of the Adrenal, when the Vagi are Intact. The time of the injection and the duration are represented by the white space on line *D*; the effect on blood pressure and pulse rate is represented by line *C*; the effect on the contractions of the ventricle and the auricle are represented respectively by lines *A* and *B*; *E* gives the time in half-seconds. (Schaefer.)

of vascular tone. As in the case of the thyroids physiological investigations of recent years tend to show that the adrenals produce an internal secretion of importance in metabolism, particularly the metabolism of the muscular tissues. Extracts of the medulla of the gland injected into the circulation of a normal animal cause a marked slowing and strengthening of the heart beat and a rise of blood pressure. The heart effect, so far at least as the slowing of the beat is concerned, is due to an action of the extract on the inhibitory centre of the vagus, since

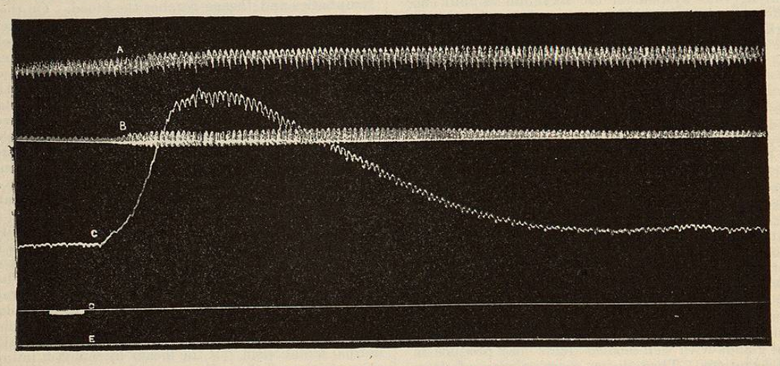

FIG. 4172.—Curve to show the Effect of Intravenous Injections of Extract of the Adrenals when both Vagi are Cut. The designation of the curves is the same as in the preceding figure. (Schaefer.)

it disappears on section of these nerves or after the administration of atropin. After section of the vagi injection of the extracts causes a quickening of the heart rate and a great rise of blood pressure. The effect on blood pressure seems to be due to a direct action on the musculature of the small arteries and veins, causing a contraction and therefore an increase in peripheral resistance. This effect is only temporary; in a few moments the pressure returns to normal, showing that the active substance is quickly neutralized or destroyed within the body. This active substance in the medulla of the glands is normally secreted into the adrenal veins, since blood collected from these veins and injected into a normal animal gives the effects described above. There is some evidence that the secretion of this substance is under the control of secretory nerve fibres. A number of investigators have attempted to isolate the active substance. Abel has succeeded in preparing from the extracts a basic substance to which he gives the name of epinephrin and to which he assigns the formula $C_{17}H_{11}NO_3$. The salts of this substance, when injected even in minute doses, give the characteristic effect upon the heart and blood-

vessels. Other crystalline products—adrenalin and suprarenalin—have been prepared from the extracts of the glands and used upon a commercial scale. They show very active physiological properties, but their exact composition and their relations to epinephrin are at present not fully determined. The conclusion commonly drawn from the above facts is that the adrenals secrete continually into the blood a substance that is normally necessary to the proper metabolism of the muscular tissues. When it is completely absent, as in removal or disease of the adrenals, a perverted metabolism ensues, and this expresses itself in a marked loss of muscular tone. The fatal result may possibly be attributed directly to the effect on the circulation, the feeble heart beat, and the loss of vascular tone, giving a condition analogous to that caused by vascular shock. It should be added that some physiologists give a different interpretation to these facts. They hold that the normal function of the adrenals is to produce an antitoxic secretion capable of neutralizing or destroying certain poisonous products of body metabolism, particularly the metabolism of muscular tissue. According to this view the fatal result of removal of the adrenals is due not to the absence of the normal stimulating or regulating action of their secretion, but to the accumulation of toxic products. This theory is designated sometimes as the auto-intoxication theory, but no convincing proof has yet been produced to show that in animals deprived of their adrenals there is present any toxic substance in the blood or the tissues. Attempts to use adrenal extracts therapeutically in cases of Addison's disease, that is, to substitute injections of the extracts in place of the normal secretion, have given negative or uncertain results. This failure may be due to the fact mentioned above, namely, that the effect of injections is quite transient. According to Battelli, continuous injections of adrenal extracts fail to prolong life to any noticeable extent in animals whose adrenals have been removed experimentally, and Christiani reports that grafts of the adrenals under the skin or in the peritoneal cavity fail to ward off the rapidly fatal results of extirpation. The explanation of this last result, however, seems to lie in the fact that when the organ is grafted the medullary portion undergoes a retrogressive change, although the graft as a whole may seem successful. The marked effect of adrenal extracts in causing vascular constriction has been utilized practically in producing local blanching of vascular membranes in the case of the eye, nose, throat, etc.

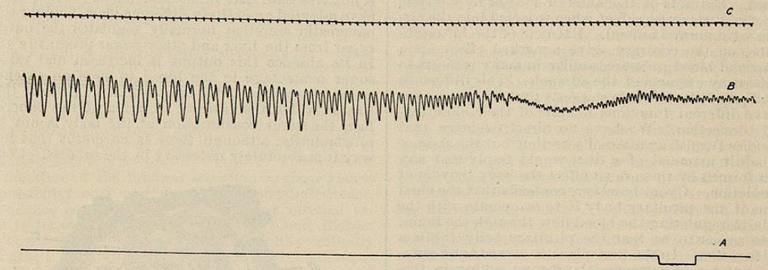

FIG. 4173.—Curve showing the Effect upon Blood Pressure and Heart Beat of an Injection of an Extract of the Infundibular Body when the Vagi are Intact. The point of injection is shown upon line *A*; *B* is the blood-pressure record and *C* the time record in seconds. (Howell.)

The Pituitary Body.—The pituitary body so called consists in reality of two quite distinct structures that possibly have different functions. The anterior lobe or the hypophysis cerebri is a glandular structure that develops in the embryo from the epithelium of the mouth cavity. The posterior lobe or the infundibular body is a mixed structure of nerve cells and glandular cells which develops from the infundibular process of the brain. It is very difficult to experiment upon these structures owing to their position. Vassale and Sacchi state that removal of the entire pituitary body is followed soon by a group of symptoms resembling those caused by thyroidectomy, namely, muscular tremors and

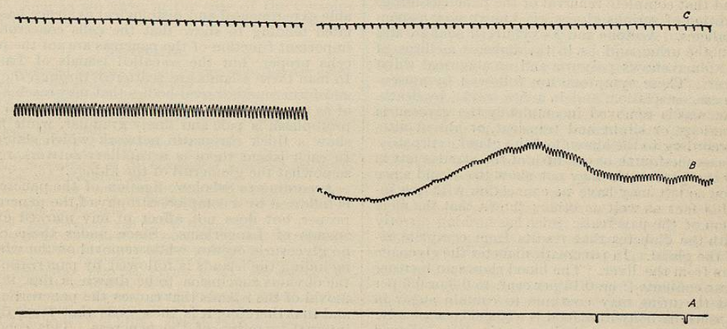

FIG. 4174.—Curve showing the Initial and Final Effect of an Injection of Extract of the Infundibular Body when the Vagi are Cut. The designation of the curves is the same as in the preceding figure. (Howell.)

spasms, apathy and dyspnœa, which soon result in death. It has been suggested, therefore, that the functions of this body may be related to those of the thyroid tissues, but no convincing evidence is at hand to make this view probable. On the clinical side it has been asserted that the peculiar disease known as acromegaly is associated with lesions of the pituitary body, but a causal connection between the two is still very uncertain. Injections of extracts of the body give results that vary with the lobe used. Extracts of the anterior lobe or hypophysis proper give little or no effect when injected into the circulation of a normal animal. Extracts of the infundibular lobe, on the contrary, give a marked effect upon the heart and blood pressure similar in many respects to that caused by extracts of the adrenals. This difference in the effect of the extracts suggests that the two bodies may have different functions in spite of their close anatomical connection. We have no direct evidence that these bodies furnish an internal secretion, but the absence in the adult mammal of a duct would imply that any product formed by them must affect the body by way of the circulation. Cyon, however, contends that the chief function of the pituitary body is to co-operate with the thyroids in regulating the blood flow through the brain. His idea seems to be that the pituitary body fulfils a double function. In the first place it serves as an automatic regulator of intracranial pressure, acting in two ways—mechanically, in that a rise of intracranial pressure stimulates the pituitary body and brings about a slowing and strengthening of the heart beat, and chemically, by secreting substances which act upon the vagus and accelerator centres. In the second place it affects general metabolism also by an action of these last-mentioned substances on the vagi and sympathetic. For the experiments which lead him to this somewhat elaborate theory it will be necessary to consult the original paper, a reference to which is given at the end of this article.

Internal Secretion of the Pancreas.—Few discoveries in physiology have been more interesting and significant than that made by von Mehring and Minkowski regarding the internal secretion of the pancreas. Briefly stated, they found that complete removal of the pancreas brings on a condition of serious glycosuria known now as pancreatic diabetes. Acetone and β-oxybutyric acid are also present in the urine, and, as in the diabetes mellitus of man, the animal shows polyuria and an abnormal thirst and hunger. These symptoms are followed by muscular weakness, emaciation, and in a few weeks by death. If the pancreas is removed incompletely the glycosuria may be serious, or slight and transient, or absent altogether, according to the amount of the gland extirpated. If so little as one-fourth or one-fifth of the gland is left in the body the glycosuria may not show itself, and since the portion so left may have no connection with the intestine, this fact as well as others shows that the mere suppression of the pancreatic juice has nothing directly to do with the diabetes that results from complete removal of the gland. In pancreatic diabetes the glycogen disappears from the liver. The blood shows an increase in its sugar contents from 0.15 per cent. to 0.3 or 0.5 per cent., and the urine may continue to contain sugar in quantity when carbohydrate food is withheld completely. On the basis of these and similar results it is believed that the pancreas forms an internal secretion which is given off to the blood. This internal secretion is supposed to play an essential part in the metabolism of the carbohydrates. It has been suggested, for instance, that the internal secretion contains an enzyme of some kind which is necessary for the dissociation or oxidation of the sugar of the body, so that in its absence the sugar accumulates in the blood and is lost through the urine. A specific form of this hypothesis has been advanced by Lepine. It has long been known that sugar in the blood disappears on standing, and Lepine has shown that this glycolytic action of the blood is due probably to the presence of a definite enzyme. He assumes that this glycolytic enzyme is formed *intra vitam* from the leucocytes of the blood, but that its formation is a function of the internal secretion of the pancreas. When the internal secretion is prevented the blood loses its glycolytic power, and the sugar escapes oxidation. This hypothesis would seem to demand that in diabetes mellitus the glycolytic power of the blood, when tested out of the body, should be absent or distinctly below the normal. Several observers who have tested this point state, on the contrary, that the glycolytic action of diabetic blood is not less than that of normal blood. Other observers have adopted an entirely different view, holding that the pancreatic secretion normally regulates the output of sugar from the liver and other sugar-producing tissues. In its absence this output is increased and raises the sugar percentage in the blood to such an extent as to cause glycosuria. We must admit at present that the way in which the internal secretion of the pancreas affects the sugar consumption of the body is not known satisfactorily, although there is no doubt that in some way it is absolutely necessary in the process. Consider-

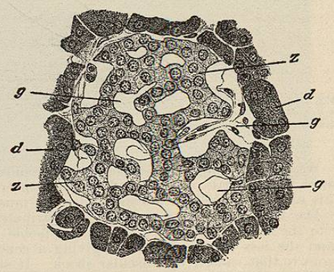

FIG. 4175.—Section Through an Island of Langerhans. *d*, The gland cells of the surrounding pancreatic tissue; *g*, blood capillaries; *z*, the columns of cells composing the island. (Kölliker.)

able experimental and nistological evidence has accumulated tending to show that the cells concerned in this important function of the pancreas are not the pancreatic cells proper, but the so-called islands of Langerhans. In man these islands are scattered through the pancreas and form round or oval bodies that may reach a diameter of as much as 1 mm. The cells are polygonal and their protoplasm is pale and finely granular, while the nuclei show a thick chromatin network which stains deeply. In each island there is a capillary network resembling somewhat the glomeruli of the kidney.

According to Ssbolew, ligation of the pancreatic duct is followed by a complete atrophy of the pancreatic cells proper, but does not affect to any marked extent the islands of Langerhans. Since under these conditions no glycosuria occurs, while removal of the whole organ including the islands is followed by pancreatic diabetes, the obvious conclusion to be drawn is that it is the removal of the islands that causes the pancreatic diabetes, and that therefore it is these cells that form the normal internal secretion of the pancreas. This conclusion is further corroborated by pathological results upon the lesions of the pancreas in human beings in connection with diabetes mellitus. A number of recent observers (Opie, Ssbolew, Herzog, *et al.*) find that in diabetes mellitus the islands are markedly affected. They show signs either of hyaline degeneration or of atrophy, and indeed may in severe cases be absent altogether.

The Reproductive Glands.—The general interest in the subject of internal secretions in recent years was aroused largely by the work of Brown-Séquard upon the effect of testicular extracts (1889–92). The results of his experiments seemed to indicate that these extracts possess a marked stimulating or dynamogenic action upon the neuro-muscular apparatus. The effect was said to be

pronounced not only upon sexual power but upon general muscular and mental vigor. Pohl claims to have obtained from such extracts a definite substance, spermin, to which he assigned the formula $C_5H_{14}N_2$, and which he believes has a general tonic effect upon body metabolism. Similarly Zoth and Pregel report that these extracts increase the power of doing muscular work when measured quantitatively by means of an ergograph. These and other similar experiments give us some reason to believe that the testes may form an internal secretion of importance in regulating and stimulating the metabolisms of the body. If such a secretion is formed, however, its action is not absolutely necessary to normal metabolism as is shown by the fact that castrated animals live in apparently good health. Our natural inference would be that a secretion of this kind might act as a regulator of sexual desire, but it is very uncertain whether such an effect takes place. In the experiments reported the possibility of suggestion playing a part in the results obtained is not excluded entirely, and we must speak therefore of the internal secretion in these glands as a possibility only and not as a demonstrated fact. The evidence is perhaps stronger that an internal secretion is formed by the ovaries. Loewy and Richter have shown that ovariotomy in dogs results eventually in a marked diminution in physiological oxidations as measured by the amount of oxygen consumed. And when an animal is brought into this condition, the administration of ovarian extract is sufficient to bring the consumption of oxygen to its normal figure or to cause an increase beyond normal. Further probable evidence is found in the numerous gynecological cases involving the removal of the ovaries. Quite frequently in such cases disagreeable symptoms ensue, extreme nervousness, vaso-motor flushes, etc., and these results have been sufficiently marked to cause many gynecologists to be cautious in the removal of both ovaries. If one can be left the after-results of the operation seem to be less serious. This general fact, together with the undoubted influence of the ovaries upon menstruation and probably upon lactation, speaks strongly for the existence of an internal secretion; but we lack at present definite scientific proof, such as we have in the case of the thyroids and adrenals. *William H. Howell.*

REFERENCES.

The following general treatises contain references to the very extensive literature of the subject of secretions:
Heidenhain in Hermann's Handbook der Physiologie, vol. v., part i., 1883.
Langley, Edkins, Paton, Starling, Schaefer, Reid: Schäfer's Text-book of Physiology, vol. i., 1898.
An American Text-book of Physiology, vol. i., 1901.
Howell, Chittenden, Adami, Putnam, Kinnicutt, Osler: Internal Secretions. Transactions of the Congress of American Physicians and Surgeons, fourth session, 1897.
Pawlow: Die Arbeit der Verdauungsdrüsen, 1898. Contains the literature of the special work of the St. Petersburg laboratory, also English translation, 1902, by Thomson.
Oppenheimer: Die Fermente und ihre Wirkung, 1900.
Recent literature of importance not found in the above sources, and used in the preparation of this paper are as follows:
On the Mechanism of Pancreatic Secretion. Bayliss and Starling, Journal of Physiology, 1902, vol. xxviii., p. 325. See also Comptes rendus de la Société de Biologie, 1902, vol. liv., No. 9.
Cohnheim's Discovery of Erepsin. See Zeitschrift f. physiol. Chemie, 1901–1902, vol. xxxiii., p. 451 and vol. xxxv., p. 134.
Beddard: On the Secretion of Urine. Journal of Physiology, 1902, vol. xxviii., p. 20. See also Gwaritch: Archiv f. d. ges. Physiol., 1902, vol. xci., p. 71, and Cushny: Journal of Physiology, 1902, vol. xxvii. p. 429.
For Cyon's theories regarding the hypophysis see Archiv f. d. ges. Physiologie, 1901, vol. lxxxvii., p. 565.
For the recent work on the Relation of the Pancreas to Diabetes mellitus see Opie: Journal of Experimental Medicine, 1901, vol. v., pp. 397 and 527. Also Ssbolew: Virchow's Archiv, 1902, vol. 168, p. 91.

SEDATIN, para-valeryl-amido-phenetol, para-valeryl-phenetidin, $C_6H_4.OC_2H_5.NH.C_4H_9CO$, is obtained by the action of valeric acid on para-amido-phenetol. It is insoluble in water, sparingly soluble in ether, chloroform, and benzin, and readily soluble in hot alcohol. It is analgesic and antipyretic in dose of 0.2–0.7 gm. (gr. iij.–x.). Sedatin is also an old name for antipyrin. *W. A. Bastedo.*

SEGMENTATION OF THE BODY.—Segmentation of the body, or metamerism, is an expression used to convey the idea that the body is composed of a series of segments, also called *metameres*, or *somites*, that are arranged in a series along the principal axis, and in each one of which the principal organs are repeated. Familiar examples of metamerism are furnished by the earthworms and tapeworms. A better example is a typical marine annelid like Polygordius or Nereis, in which each somite, beside the integument, ventral nerve cord, main blood-vessels, and gut, which are continuous through the length of the body, has its own body cavity separated by a partition from its neighbors fore and aft, a pair of limbs (parapodia), a pair of nephridia, a pair of gonads, and several pairs of lateral blood-vessels and nerves, the same arrangement being found in each somite except the terminal ones.

In the vertebrates there is an indication of a similar metamerism. Thus in all vertebrates the vertebræ, the ribs, and the spinal nerves are arranged metamerically, and in the fishes the trunk muscles are divided by transverse tendinous plates into myotomes, which are likewise metamerical in arrangement. This metamerism of the musculature is present to a less degree in the amphibia, but in the higher vertebrates, including man, it has almost disappeared in the adult, as the result, doubtless, of adaptive modifications. But in the embryo metamerism is very evident, even in the highest forms, and has its foundation in the primitive segmentation of the mesoderm, forming the so-called protovertebræ. The divisions of the body being thus outlined at an early stage the spinal nerves, lateral blood-vessels, vertebræ, ribs, and the primitive nephredial tubules are developed in definite relation to them.

The body of a vertebrate may be divided into three main regions—head, trunk (extending from the first cervical vertebra to the anus), and the tail. The segmentation of the trunk and tail is very evident in the embryo, if not in the adult, and the number of segments may be counted. Thus in man there are thirty-seven or thirty-eight originally, of which four or five are caudal segments that disappear during the second month of fœtal life.

The segmentation of the head is not so clear, even in the embryo, and has been a subject for earnest investigation and discussion for a long time. While it is evident that the head is a segmented structure, the actual number of segments and the organs appertaining to each one can be determined only after very minute comparative study of the development of the whole complex of muscles, nerves, ganglia, sense organs, and other structures composing the head, and it is not surprising, therefore, that there should be considerable difference of opinion. Thus Rabl denies that the head contains any segments in front of the ear that can be regarded as homologous with the trunk segments. This opinion is contrary to that of Minot and Hertwig, who regard the whole head as composed of homologous segments. But Hertwig estimates the number as nine, while Minot makes it thirteen.

The segmentation of the body in vertebrates has been held to indicate the descent of this group from the annelids. Comparative anatomy shows, however, that the most primitive known allies of the vertebrates present no likeness to the annelids, but, on the contrary, resemble in some respects the echinoderms, or rather their larvæ; therefore the annelid theory of the origin of the vertebrates seems of very doubtful validity. It is more probable that the metamerism of the body arose independently in the primitive forms of the two groups in adaptation to a similar mode of life.

Robert Payne Bigelow.

BIBLIOGRAPHICAL REFERENCES.

Froriep, A.: Entwickelungsgeschichte des Kopfes. Erg. Anat. und Ent., vol. i., 1892, *loc. cit.*, iii., 1894.
Gaupp, E.: Die Metamerie des Schädels, *loc. cit.*, vii., 1898.
Kupffer, C. von: Entwickelungsgechichte des Kopfes, *loc. cit.*, ii., 1893; *loc. cit.*, v., 1896.