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THE ENDOCRINE ORGANS

PART II

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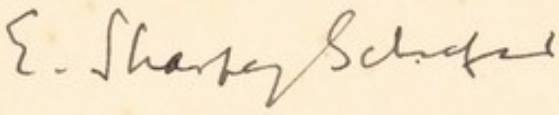

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THE ENDOCRINE ORGANS

AN INTRODUCTION TO THE STUDY OF INTERNAL SECRETION

BY

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SECOND EDITION

WITH NUMEROUS ILLUSTRATIONS

PART II

THE PITUITARY; THE PINEAL; THE ALIMENTARY CANAL; THE PANCREAS, AND THE SEX GLANDS

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ADDITIONS AND CORRECTIONS

Page 7. Evidence is accumulating that special autacoid substances may be produced as the result of stimulation of efferent nerves: such autacoids may assist or prolong the effect caused by stimulation of the nerve. Thus it has been found that stimulation of the vagus or of the sympathetic fibres leading to the heart provokes the appearance of chemical substances in the auricle which, when applied by perfusion to another heart, cause either inhibition and weakening, or acceleration and augmentation of the beat, according to whether the vagus or the sympathetic fibres of the first heart were stimulated. Similarly it has been found that the contraction of both skeletal and of plain muscle is accompanied by the production of autacoid substances—in the latter case possibly cholin—which may themselves cause a prolongation of the contraction. (O. Loewi, *Arch. f. d. ges. Physiol.*, clxxxix. 239, 1921; *ibid.*, cxciii. 201, 1921; *ibid.*, cciii., 1924; Geiger and Loewi, *Biochem. Zeitsch.*, cxxvii. 174, 1922; Brinkman and van Dam, *Arch. f. d. ges. Physiol.*, cxcvi. 66, 1922; L. Jendrassik, *Biochem. Zeitsch.*, cxliv. 520, 1924; Ten Cate, *Arch. néerl. de physiol.*, ix. 588, 1924; H. Fredericq, *Arch. internat. de physiologie*, xxiv. 294, 1925; Brinkman and Ruiter, *Arch. f. d. ges. Physiol.*, cciv. 766, 1924. On the other hand L. Asher (*Zeitschr. f. Biol.*, lxxxviii. 297, 1923), J. F. and C. Heymans (*C. r. soc. biol.*, xciv. 135, 1926), E. and P. Gley (*ibid.*, p. 269), and others have described negative results.

Page 15, line 6 from bottom. This paragraph should read: "Colloid does not make its appearance in them until the ninth or tenth week of fœtal life." According to Tanberg it is not physiologically active until after birth (*Acta med. Scand.*, lvi., 1922), but M. Aron obtained evidence of activity long before this (*C. r. soc. biol.*, xciv. 275 and 278, 1926).

Page 17, footnote 2. "*Queen's Anatomy*" is a misprint for "*Quain's Anatomy.*"

Page 20, footnote 1. "Ambyostoma" should be "Amblystoma."

Page 29, line 11. "~~They" should be "the hairs.~~"

Page 34, line 2. "Tauberg" should be "Tanberg."

Page 49. The effect of thyroid in promoting the metamorphosis of tadpoles can be antagonised by placing them in a solution of quinine hydrochloride of suitable strength. (Lenhart, *Journ. Exper. Med.*, xxii. 739, 1915; S. Hardikar, *Journ. Pharm. Exper. Ther.*, xxiii. 395, 1924; Kroszczynski and Modrakowski, *C. r. soc. biol.*, xciii. 939, 1925.)

Page 49. Add to note 11: Romeis could obtain no effect on the metabolism of various invertebrates (including crayfish) by thyroid feeding. (*Arch. f. Entwickl.-Mech.*, cv. 778, 1925.)

Page 50, line 4. "fig. 25" should be "fig. 27."

Page 56. Romeis found that thyroxin cannot be detected by the tadpole test in blood even a few minutes after it has been injected into a vein (rabbit). It is rapidly destroyed by blood *in vitro*, and also by a suspension of washed erythrocytes. (*Biochem. Zeitsch.*, cxli., 1923.)

Page 57. A special form of goitre which has usually been classed along with exophthalmic goitre is now known to be a distinct affection termed *toxic goitre*. It is characterised physically by the presence in the gland of adenomatous nodules firm to the feel. These can be removed surgically, the operation usually resulting in a speedy cure (85 per cent.). In toxic goitre, although most of the symptoms are similar to those of exophthalmic goitre, *e.g.* loss of weight, tremors, moist skin, tachycardia, and palpitations, there are no thrills or bruits and no acute crises, nor is there exophthalmos, which in true exophthalmic goitre generally supervenes within three months. The blood-pressure is high and also the basal metabolism, but as a rule this is not raised to so extreme a point in toxic as in exophthalmic goitre. The symptoms in toxic goitre come on more gradually, whereas in exophthalmic goitre the onset is usually acute. The two affections are distinct pathologically and clinically: they have a different origin, prognosis, and treatment. In toxic goitre the symptoms are probably due to the production of an excess of thyroxin: iodine is contra-indicated and surgical removal of the adenomata is called for. In exophthalmic goitre there seems also to be an excess of secretion, but it is abnormal (dysthyroidism) and by its action on the nervous system produces characteristic fulminating crises. The affection requires the administration of iodine to restore to the secretion its natural character: this is generally given in the form of Lugol's solution (iodine dissolved in iodide of potassium)—10 drops daily. In most cases the basal metabolism is speedily reduced under this treatment and general improvement results: but the exophthalmos does not disappear. The iodine may be assisted by X-ray treatment. Surgical interference is, as a general rule, not immediately called for in exophthalmic goitre, although it may be required: it is far more hazardous than in the case of toxic goitre. (H. S. Plummer, *Oxford Medicine*, iii. 839, 1921; and *Trans. Assoc. Amer. Phys.*, xxxviii. 251, 1923; H. S. Plummer and W. M. Boothby, *Journ. Iowa State Med. Soc.*, xiv. 66, 1924; W. M. Boothby, *Endocrinology*, viii. 727, 1924; Boothby and Sandiford, *Physiol. Rev.*, iv. 69, 1924; P. Starr and others, *Arch. Int. Med.*, xxxiv. 355, 1924; E. A. Arn, *Endocrinology*, viii. 375, 1924; A. S. Jackson, *ibid.*, p. 525, 1924; J. M. Read, *ibid.*, p. 746, 1924; F. R. Fraser, *Brit. Med. Journ.*, i. 1, 1925.)

Page 65, middle of paper. "Halpenny and Thompson" should be "Mrs F. D. Thompson," and the reference in note 7 should be "*Phil. Trans.*, B, cci., 91, 1910."

Page 79, note 1, line 7. For further notes of this case see *New York Med. Journ.*, April 5th, 1922.

Page 85. J. B. Collip has placed it beyond doubt that the parathyroids produce an autacoid (parathyrin), which seems to regulate calcium metabolism and especially the percentage of calcium in blood. An extract of ox-parathyroids, prepared as free as possible from proteins and other adventitious substances, produces, if injected parenterally in animals, increase of blood calcium, which, if the dose is large, is excessive and is then accompanied by serious toxic symptoms, viz. vomiting, diarrhœa, atonia of muscles, and eventually paralysis and death. On the other hand the tetany which results from removal of the parathyroids and is accompanied by diminution of blood calcium can, as has been previously shown by others, be successfully treated by parenteral injection of parathyroid extract or by the oral administration of calcium lactate: this is also true for idiopathic tetany and for tetany produced in other ways. The nervous symptoms seen in tetany are therefore not necessarily due, as Paton and his fellow-workers supposed, to the presence of an excess of guanidine or methyl-guanidine in the blood, although this may be a contributory factor in promoting their development.

Collip further finds that after injection of parathyrin the blood becomes thick and will not pour readily. (J. B. Collip, *Proc. Amer. Physiol. Soc.*, Dec. 1924, in *Amer. Journ. Physiol.*, lxxii., 1925; Collip and Leitch, *Journ. Amer. Med. Assoc.*, p. 706, 1925; J. B. Collip, E. P. Clark, and J. W. Scott, *Journ. Biol. Chem.*, lxiii. 439, 1925; J. B. Collip and E. P. Clark, "Preparation, properties, and method of standardisation of a parathyroid hormone," *Trans. Roy. Soc. Canada*, xix. 25, 1925; J. B. Collip and E. P. Clark, *Journ. Biol. Chem.*, lxiv. 485, 1925; Hjort, Robison, and Tendick, *ibid.*, lxv. 117, 1925 (confirmatory of Collip). G. Herxheimer (*Deutsch. med. Woch.*, l. 1463, 1924) found that animals deprived of the parathyroids are abnormally susceptible to guanidine poisoning.)

Page 85, line 7 from bottom. "Parathyroid secretion" should be "parathyroid extract."

Page 90, note 8. "1912" should be "1911."

Page 99, note 2. Dr Hurst informs me that his patient lived two years after the grafting operation. During the last three months of life the blood-pressure was below 100 mm. Hg and the hæmoglobin only about 20 per cent. The diagnosis was therefore modified and the case was considered to be one of combined pernicious anæmia and Addison's disease. But at the autopsy both the patient's suprarenals were found to be normal and the graft was almost entirely converted into fibrous tissue, with one group of suprarenal cells remaining. The pigmentation of the skin and buccal mucous membrane was extreme and all the physicians (five in number) who examined the case during life concluded that it was a typical Addison. Nevertheless it was clearly progressive pernicious anæmia and not Addison's disease, properly so called, the essential concomitant of this being destruction of the adrenals.

Page 100, line 12 from bottom. "And which he termed *idiopathic anæmia*." This is wrong. The affection so termed by Addison is that which is now usually spoken of as *progressive pernicious anæmia*. Addison states that he was led to the discovery of the disease which is now known by his name by the study of this peculiar form of anæmia, which it would seem (see previous note) may also be associated with pigmentation of the skin.

Page 102, note 2. "*Ibid.*" should be "*Amer. Journ. Physiol.*"

Page 112, line 3. After "capsules" the words "of the bovine embryo" should be inserted.

Page 112, note 2, should be "*Journ. Biol. Chem.*, xxiv., 1916."

Page 112. Add to note 6: For the relative amount of adrenaline in various diseases see also T. R. Elliot, "Pathological changes in the adrenal glands," *Quart. Journ. Med.*, viii., 1914.

Page 133, add to note 4, "and xxv., 1899."

Page 140. Add to note 1: B. R. Lutz and M. A. Case got evidence of the presence of adrenaline in the suprarenal capsules of the embryo chick on the eighth day of incubation. The test employed was the enucleated eye of the frog. (*Amer. Journ. Physiol.*, lxxiii. 670, 1925.)

Page 141, line 4. Delete the second comma.

Page 156, line 4 from bottom. Delete note 8.

Page 158, lines 8, 9, 10. The paragraph commencing "They calculate" should read "They found the output of the two suprarenals, as the result of reflex stimulation, to be about 0·0035 mg., etc."

Page 158. Add to note 1: In later experiments Tournade and Chabrol employed the denervated spleen of the receiver as an indicator of the outpouring of adrenaline in the donor, the spleen being very sensitive to the effects of

this autacoid. By this method they—in conjunction with Wagner and others—have obtained many interesting results. They have found that cocaine applied to the floor of the 4th ventricle diminishes the secretion of adrenaline, as does section of the cord or of the anterior roots, while excitation of the medulla oblongata or of the cord above the outflow of the splanchnics increases it; that drawing blood from the donor causes an increase of secretion, and transfusion of additional blood a reduction; also that well-marked Traube curves in the donor are responded to by rhythmic contraction of the spleen of the receiver. (*C. r. soc. biol.*, xciii., 1925, several papers. See also Houssay and Molinari, *Rev. asoc. med. Arg.*, xxxvii. 233 and 327, 1924, and *C. r. soc. biol.*, xciii. 1133, 1925.)

Page 159. Add to note 6: Anrep and Daly obtained evidence by means of crossed circulation that the output of adrenaline is increased by acute cerebral anæmia: the increase disappears after denervation of the suprarenal capsules. (*Proc. Roy. Soc.*, B, xcvii. 450, 1925.)

Page 160, line 5. Insert "is" after "acceleration."

Page 162. Add to note 1: E. Zunz and P. Govaerts have obtained results from cross-circulation experiments which are in direct contradiction to those of Gley and Quinquaud. (*Arch. internat. de physiol.*, xxii. 87, 1923.)

Page 213. Administration by intradural injection (lumbar puncture). Molitor and Pick (*Wien. klin. Woch.*, lii. 1392, 1925) find that a far greater and more prolonged antidiuretic action of posterior lobe extract (see p. 244) is obtained by this means than with subcutaneous administration. A. Leimdörfer (*ibid.*, 1926, No. 2), working in Pick's laboratory, further finds that when the extract of posterior lobe is introduced in this manner the effect on blood-pressure also is far greater and more prolonged than with intravenous injection: moreover, the same effect is obtained (and may indeed be more marked) with repeat doses, although these fail to give any result with intravenous administration (tachyphylaxis, p. 220). [A similarly increased effect with intradural injection does not occur with adrenaline.] The result is not obtained if the upper part of the dural canal of the cord is tied off: the action is therefore probably on the bulbar vasomotor centre. Leimdörfer suggests that hypertonicity of the blood-vessels may in this way be produced by abnormal increase of the secretion which passes into the third ventricle (p. 201).

Page 248. Molitor and Pick failed to observe the antidiuretic action of pituitary in animals deprived of the hemispheres or in deep anæsthesia (from paraldehyde): although it was seen in chloretone anæsthesia (*Arch. f. exper. Path. u. Pharm.*, cvii., 1925).

Page 289. According to Brull and Eichholtz, the excretion of inorganic phosphates by the kidney is regulated by the pituitary: if this gland is removed, the phosphates disappear from the urine (*Proc. Roy. Soc.*, B, xcix. 70, 1925).

Page 346. J. J. Abel appears to have succeeded in obtaining insulin in crystalline form (*Journ. Amer. Med. Assoc.*, lxxxvi. 351, 1926). See further, on the chemical nature of insulin, C. Funk, *Proc. Soc. Exper. Biol.*, xxiii. 281, 1926. Funk suggests that it is a polypeptide, and gives 700 as its probable molecular weight.

Page 351. See further, on the nature of blood-sugar, C. Lundsgaard and S. A. Holbell, *Journ. Biol. Chem.*, lxv. 305–370, 1925.

Page 394. Steinach, Keinlein, and Wiesner find that rejuvenation may also be effected by the parenteral administration (in the female) of extracts of ovary and also of placenta, the growth of senile organs being promoted both in entire and in castrated animals (*Arch. f. d. ges. Physiol.*, ccx. 598, 1925).

THE ENDOCRINE ORGANS

AN INTRODUCTION TO THE STUDY OF INTERNAL SECRETION

CHAPTER XXIII

THE PITUITARY BODY (HYPOPHYSIS CEREBRI)

General Structure and Morphology

The next of the endocrine glands to claim our attention is the Pituitary Body or Hypophysis Cerebri. The study of this organ has sprung into prominence within recent years. Regarded as a rudimentary structure of some morphological interest but of little or no physiological importance, nevertheless suspected to be connected with growth phenomena and related pathologically to certain forms of abnormal development, especially of the skeleton, it was not until 1894 that its extracts were found actively to influence certain functions of the body, and not until 1917 that the results obtained by its extirpation seemed to show that it may be essential to life. That it fulfils some important function seems certain from the fact that it occurs throughout the whole vertebrate series, and may, it is thought, even be represented in the ascidian larva by the "subneural gland."

Dimensions and Position.—The pituitary body in man is a small organ the size of a large pea (fig. 87). It is about 9 mm. in antero-posterior diameter, 6 mm. in vertical measurement, and 13 mm. transversely. It weighs about half a gram in the adult male, but a little more in the female. It varies considerably, however, both in weight and dimensions, even under normal conditions.[1]

Rasmussen found the average weight in fifty males of age nineteen to sixty-five, mostly cases of accidental death, to be 0·56 gram: varying from 0·4 to 0·855 gram. E. V. Cowdry [2] gives rather higher average measurements, but it does not appear that they are from original observations. The organ becomes

---

[1] Numerous observations regarding the weight and size in man and animals have been collected from various sources by Livon (Art. "Hypophyse" in Richet's *Dictionnaire de Physiologie*, 1909). A more recent account is that by A. T. Rasmussen (*Endocrinology*, viii., 1924), who has collected the statistics of previous observers and added many original data, including the relative proportion of the weight of the normal gland taken by each of the principal parts. A full bibliography will be found in this paper.

[2] L. L. Barker's *Endocrinology and Metabolism*, i. 705, 1922.

markedly enlarged during pregnancy in the female [1] and also as the result of castration.[2] It is enlarged in myxœdema, in endemic goitre, and in tubercle, but is diminished in size in exophthalmic goitre: the diminution is mainly in the number and size of the oxyphil cells.[3] It is also found to be unusually large after death from cerebral hæmorrhage.[4] Rasmussen [5] finds a distinct relationship between the stature of the body and the weight of the pituitary: tall individuals having proportionately larger glands. As regards age, the gland is found to increase in size up to forty-five years, after which period it gradually decreases. It is distinctly larger in women who have borne children than in nulliparæ.

The pituitary lies at the base of the brain in the sella turcica, enclosed in a

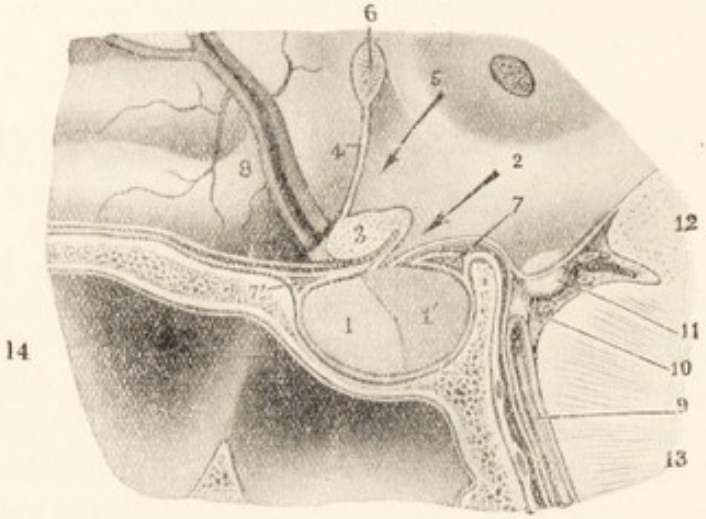

FIG. 87.—Mesial sagittal section showing the pituitary body *in situ* and its relations to the brain and base of the skull (somewhat enlarged).[6]

1, anterior and 1' posterior lobes of hypophysis; 2, infundibulum; 3, optic chiasma; 4, lamina terminalis; 5, optic recess; 6, anterior commissure; 7, 7', circular sinus; 8, anterior cerebral artery; 9, basilar artery; 10, posterior cerebral artery; 11, corpus mamillare; 12, cerebral peduncle; 13, pons; 14, sphenoidal sinus.

sheath derived from the dura mater, except where the stalk connecting it with the third ventricle enters the gland. The sella on the whole varies in size

[1] L. Comte, *Ziegler's Beiträge*, xxiii., 1898; Launois et Malon, *C. r. de l'assoc. des anatomistes*, Liège, 1903; E. Mayer, *Arch. f. Gyn.*, xc., 1910; Gentili, *Arch. d. biol.*, 1920 (cow). Swale Vincent (*Internal Secretion and the Ductless Glands*, 1922, p. 403) states that as the result of pregnancy the pituitary may become two or three times the normal size and the enlargement may persist for a time after parturition. The enlargement of pregnancy affects the anterior lobe almost exclusively.

[2] G. Fichera, *Arch. ital. de biol.*, xliii., 1905; Tandler und Gross, *Arch. f. Entwickl.-mech.*, xxx., 1910. Marrasini and Luciani were unable to confirm this (*Arch. ital. de biol.*, lvi., 1911). Hatai found that in the white rat castration is followed by pituitary enlargement, but only in the male (*Journ. Exper. Zool.*, xv., 1913). W. H. F. Addison (*Journ. Compar. Neurol.*, xxviii., 1917) obtained a like result, and furnishes a number of details regarding the histological changes in the anterior lobe resulting from castration.

[3] E. J. Kraus, *Virchow's Arch.*, ccxlvii., 1923.

[4] For pathological changes in the gland the article by J. J. Simonds, in Barker's *Endocrinology and Metabolism*, i., 1922, may be consulted. The literature of this part of the subject will be found here.

[5] *Op. cit.*, 1924.

[6] From Testut, *Traité de l'anatomie humaine*, by permission of G. Doin, *éditeur*.

with the pituitary, and the relative size of the gland may therefore be inferred from X-ray photographs,[1] but it may happen that a normal sella contains either a smaller or a larger pituitary than normal.[2]

Divisions.—As above indicated, the gland is attached to the floor of the

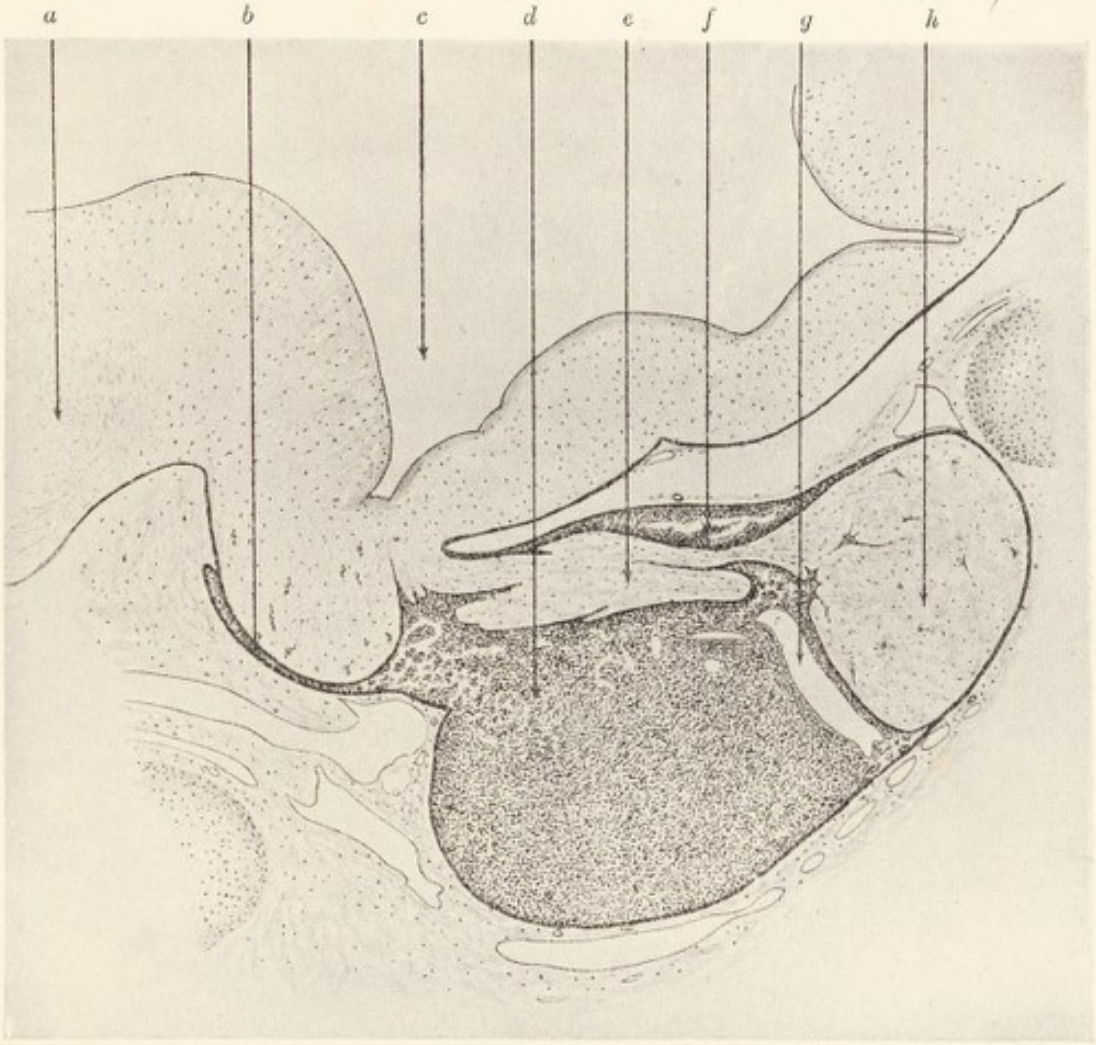

FIG. 88.—Mesial sagittal section through pituitary of a 5th month's human fœtus. (Herring.)

a, chiasma; *b*, pars tuberalis (tongue-like process of Herring); *c*, infundibular extension of third ventricle; *d*, pars anterior; *e*, neck, connecting base of brain at infundibulum with pars nervosa; *f*, extension of epithelium (tuberalis) of pars over neck; *g*, intraglandular cleft; *h*, pars nervosa, separated from cleft by pars intermedia.

third ventricle in man by a short, funnel-shaped *stalk* (*infundibulum*, figs. 87 and 88). In the dead subject and in the supine position during life, especially if the volume of the brain is reduced by injection of a hypertonic solution

[1] For measurements of the sella turcica, see H. Oppenheim, *Arch. f. Psych. u. Nervenkr.*, xxxiv. 303, 1901; D. P. Fitzgerald, *Journ. Anat. and Physiol.*, xliv., 1910; Harvey Cushing, *Harvey Lectures*, 1910 (reprint); A. Keith, *Lancet*, i. 993, 1911. For its relations to the sphenoidal cells—a matter of importance in connexion with the surgery of the gland, which is a frequent seat of cerebral tumours—see W. S. Gibson in *Surgery, Gynæcology, and Obstetrics*, xv., 1912; and W. Blair Bell, "The Pituitary," pp. 18–24, 1919.

[2] Rasmussen, *op. cit.*, 1924.

of salt into the blood, the stalk becomes elongated and stretches across a space occupied by cerebrospinal fluid. The cavity of the stalk, which forms a downward prolongation of the ventricle, stops in man and many animals at its attachment to the gland. The wall of the infundibulum is formed by a prolongation of the nervous tissue of the floor of the ventricle. This prolongation extends into the posterior part of the gland, expanding to form a

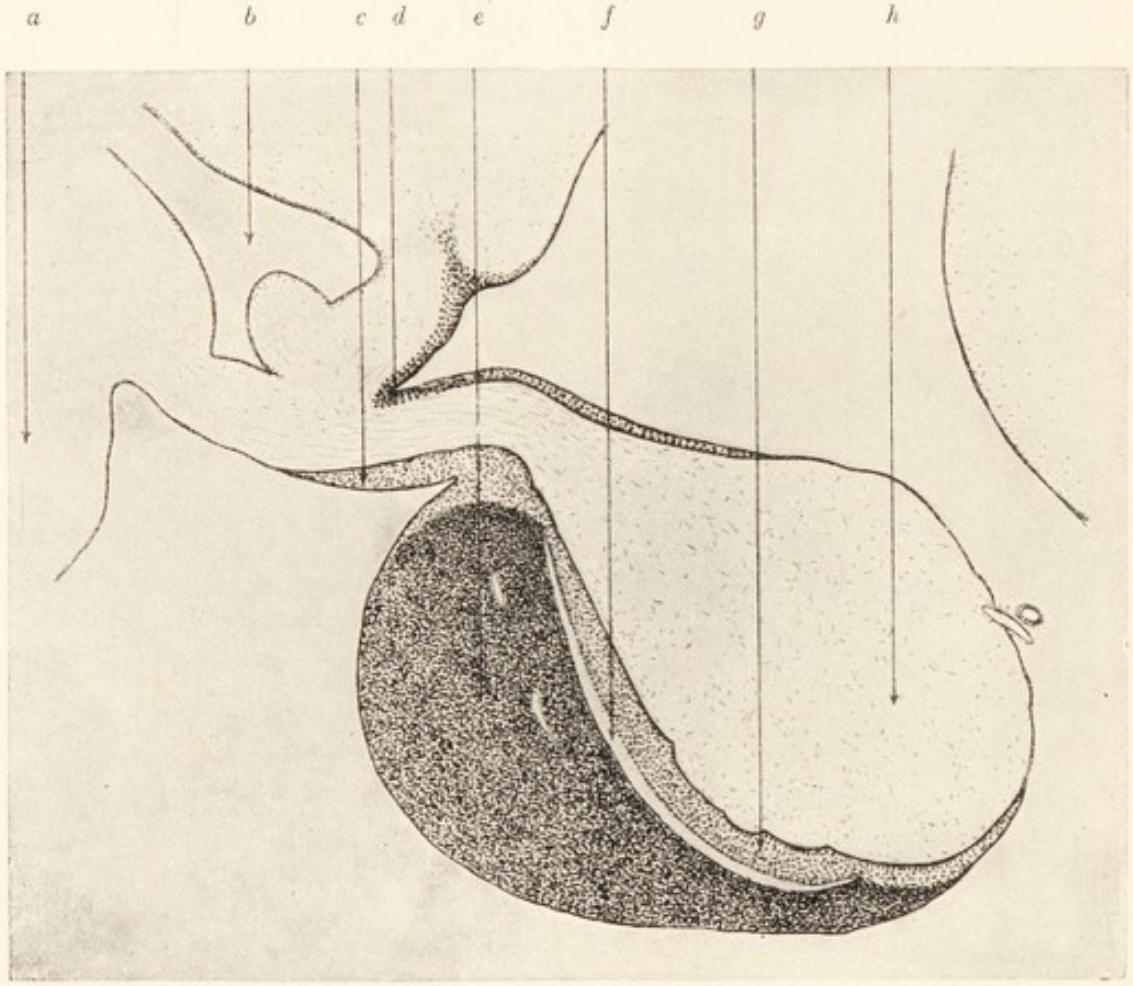

FIG. 89.—Mesial sagittal section through the pituitary body of an adult monkey (semi-diagrammatic). (Herring.)

a, chiasma; *b*, infundibulum; *c*, *d*, pars tuberalis ("tongue-like process"); *e*, pars anterior seu glandularis; *f*, intraglandular cleft; *g*, pars intermedia; *h*, pars nervosa. Notice the blood-vessels entering it behind.

solid mass of what appears to be nervous tissue—*pars nervosa seu infundibularis*—but, when examined by appropriate methods, is found to be mainly composed of neuroglia cells and fibres, nerve-cells being altogether absent, and comparatively few nerve fibres being visible.[1]

The degree to which in different mammals the hollow of the infundibulum extends into the pars nervosa varies greatly, even in nearly allied animals, and gives rise to different types of gland. The three principal types are exhibited in the diagrammatic sagittal sections shown in figs. 89, 90, 91, from the

[1] P. T. Herring, *Quart. Journ. Exper. Physiol.*, i., 1908. See, however, Chapter XXV.

monkey, the dog, and the cat respectively. In the cat the whole of the central portion of the pars nervosa is occupied by a hollow extension of the ventricle: in the monkey, as in man, the cavity stops at the attachment of the stalk to the base of the brain; in the dog it extends to just beyond the neck of the gland. The relation of the various parts of the gland to one another in so far as these can be seen in a saggital section through the middle of the organ are also shown in these figures.

Anterior to and partly enclosing the pars nervosa the pituitary is formed

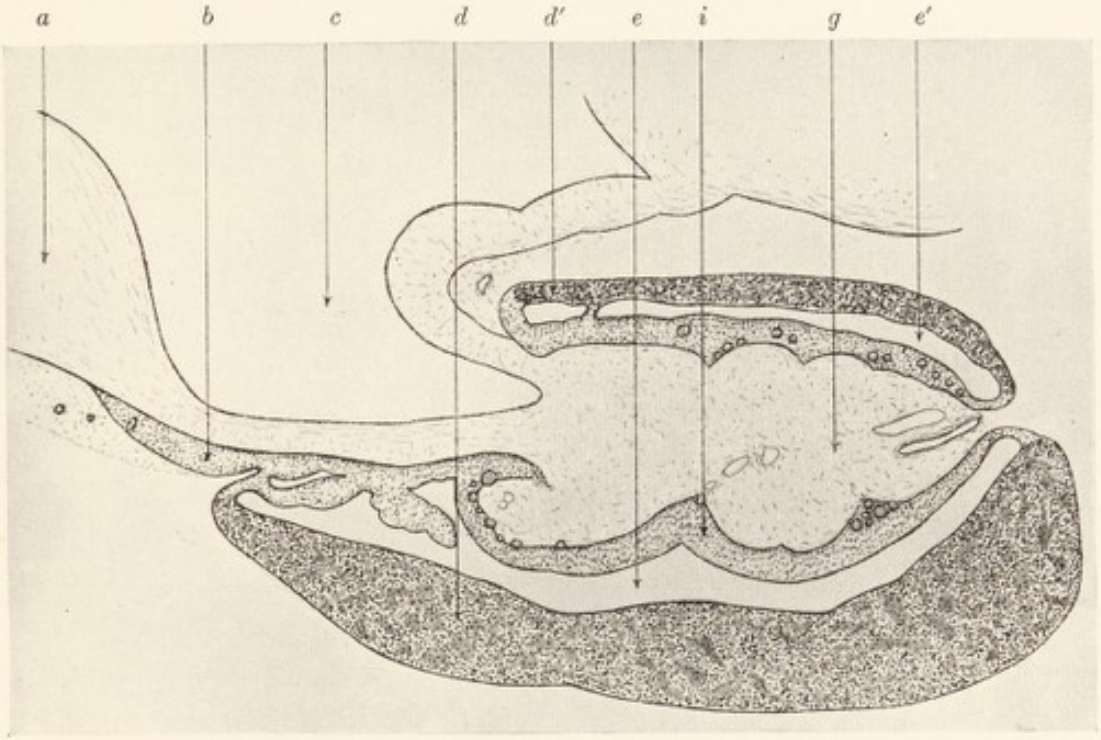

FIG. 90.—Mesial sagittal section through the pituitary body of an adult dog (semi-diagrammatic). (Herring.)

a, optic chiasma; *b*, pars tuberalis (tongue-like process); *c*, third ventricle; *d*, pars anterior (ventral portion); *d'*, pars anterior (dorsal portion). In the dog both the pars anterior and the pars intermedia, with the intraglandular cleft separating them, completely surround the pars nervosa, except behind where the blood-vessels enter and leave this part. *e*, *e'*, intraglandular cleft; *g*, pars nervosa; *i*, pars intermedia closely investing the pars nervosa.

by a mass of epithelium of granular appearance. This mass constitutes what is known as *pars anterior seu glandularis*. It is the most vascular part of the gland, and is rendered conspicuous by its pronounced greyish-red or yellowish-red colour.

Closely associated with the upper surface of the pars anterior, and, like it, very vascular, is a special portion of the gland, which extends along the stalk and over the tuber cinereum and adjacent part of the floor of the third ventricle, to which the name *pars tuberalis* has been applied. As we shall see, this part differs in structure from the other parts and is also developed independently. It forms a sheath around the neck, extending from this in close attachment to the base of the brain. This part was first noticed by Herring and was described by him as a tongue-like extension of the pars intermedia.

Its extent and position are best seen in a reconstruction model (fig. 92). It is shown in sagittal section in fig. 93.

In most animals there is a cleft in the middle of the gland which separates the organ into two lobes, a larger anterior and a smaller posterior. This *intraglandular cleft* is occupied by a variable amount of a glairy, yellowish fluid, which is sometimes consolidated to form a flattened, solid disk with thin edges. In the adult human subject the cleft is generally found to be obliterated, or

FIG. 91.—Mesial sagittal section through the pituitary of an adult cat (semi-diagrammatic). (Herring.)

a, chiasma; *b*, pars tuberalis (tongue-like process) (another portion of the pars tuberalis lies just dorsal to *f'*); *c*, infundibulum of third ventricle; *d*, pars anterior seu glandularis; *e*, intraglandular cleft; *f'*, *f*, cavity extending from infundibulum into pars nervosa; *g*, pars nervosa, near the point of entrance of its blood-vessels; *i*, pars intermedia, in close contact with pars nervosa, which it almost completely surrounds. The vesicular structure of the pars tuberalis and pars intermedia is indicated by circles.

broken up into isolated cysts containing a colloid-like material (fig. 94).[1] In front of the cleft is the pars anterior; this forms the *anterior lobe*: behind it is the pars nervosa, but this is covered by an epithelial layer, which is intimately adherent to it, termed *pars intermedia*. The pars nervosa *plus* pars intermedia together form the *posterior lobe*.[2] The organ is easily separable into the two lobes by splitting it across in the line of the cleft.

[1] Halliburton, Candler, and Sikes, *Quart. Journ. Exper. Physiol.*, ii., 1909.

[2] With regard to the relative size of the principal parts in man, Rasmussen (*op. cit.*, 1924) finds that the pars anterior represents about 72 per cent. of the whole organ; the pars nervosa, 18 per cent.; the pars intermedia, 2 per cent.; the remaining 8 per cent. being capsule and connective tissue. No figure is given for the pars tuberalis, which was not included in the removed glands investigated, but Atwell finds that this may be nearly as extensive as the pars intermedia (see p. 197).

Herring states that in the rabbit it is not uncommon to find the cleft filled with red bone-marrow and fat cells.[1] Watrin has also described hæmapoietic tissue in the pituitary of the guinea-pig.[2] The meaning of this is unknown.

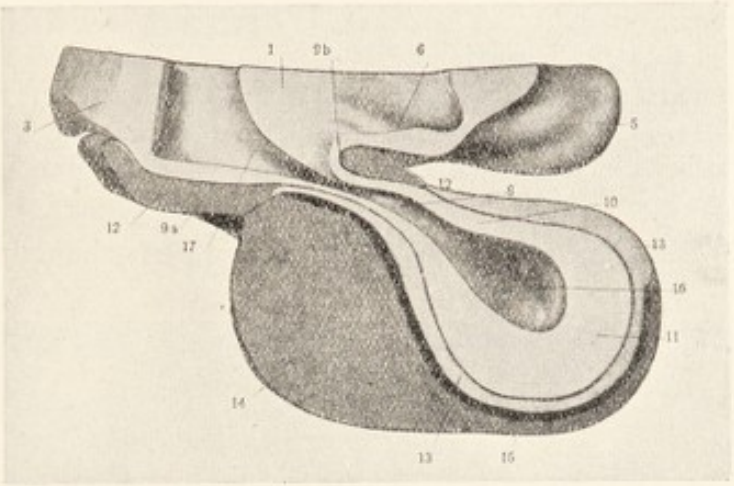

Fig. 92.—Sagittal section of reconstruction model of pituitary and adjacent part of brain of adult cat. (Tilney.)

1, 3rd ventricle; 3, chiasma; 5, corpus mamillare; 6, area premamillaris; 8, neck of recessus infundibularis; 9a, 9b, its lower and upper neural boundaries, passing into 10, 11, pars nervosa of pituitary; 12, 12, pars tuberalis; 13, 13, pars intermedia; 14, pars glandularis; 15, cleft; 16, recessus infundibularis; 17, infundibulum of 3rd ventricle.

Fig. 93.—Mesial sagittal section through the pituitary body of an adult cat. Photograph. (Herring.)

The intraglandular cleft is seen to extend below round the pars nervosa. Notice also the pars tuberalis covering the tuber cinereum in front of the pars anterior and above the neck; also the extension (in the cat) of the infundibulum through the neck into the middle of the pars nervosa.

The cleft is the remains of the original tube which is formed in the early embryo from an outgrowth of the buccal ectoderm. The tube communicated at

[1] *Op. cit.*, p. 182.

[2] *C. r. soc. biol.*, lxxxvii., 1922.

first with the buccal cavity, although the communication became obliterated later.

Cilia have been described on the epithelium of the anterior wall of the cleft in the guinea-pig, as well as on cells which line cyst-like vesicles containing colloid, lying in the pars intermedia.[1] The occasional presence of cilia in the gland of man and of the rabbit had previously been noted.[2] Peremeschko [3] appears to have been the first to describe the three chief parts of the gland, anterior, intermedia, and nervosa. The pars tuberalis was distinguished much later (by Tilney). It usually remains attached to the base of the brain when the gland is removed.

Development.—The development of the pituitary was originally described by

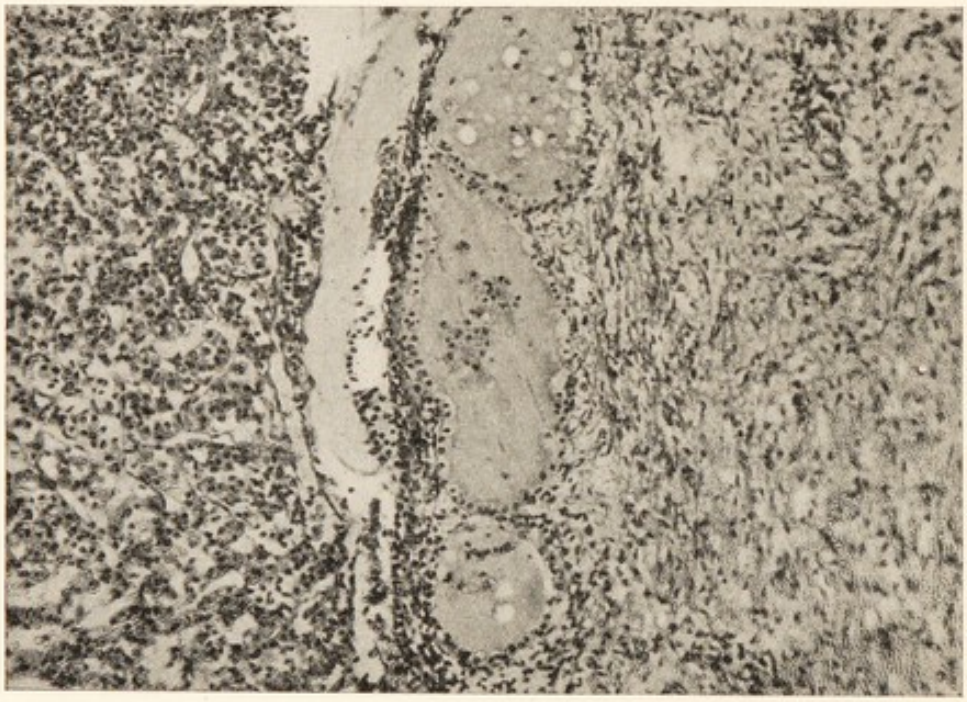

Fig. 94.—Cysts containing colloid, one in the situation of the intraglandular cleft and three in the pars intermedia. From a section of human pituitary. ×120. (Halliburton, Candler, and Sikes.)

Rathke (1838) as occurring in the form of an epithelial invagination at the upper part of the buccal cavity. This invagination was thought by Rathke to be derived from the entoderm. F. M. Balfour (1874) showed that it comes really from the buccal ectoderm (elasmobranch fishes), and this was confirmed by Götte (1875) for Amphibia. The conditions in the chick and rabbit were elucidated by Mihalkowics (1875). More recently the subject has been worked out by Herring,[4] whose description will here be followed.

The first indication of the buccal invagination (*Rathke's pouch*) is seen at

[1] Vanderburgh, *Anat. Rec.*, xii., 1917.
[2] Launois, *op. cit.*, 1904; A. Trautmann, *Arch. f. mikr. Anat.*, lxxiv., 1909.
[3] *Virchow's Arch.*, xxxviii., 1867.
[4] *Quart. Journ. Exper. Physiol.*, i., 1908.

a very early stage[1] just in front of the bucco-pharyngeal septum (fig. 95). This is soon met by another invagination from the neural ectoderm of what

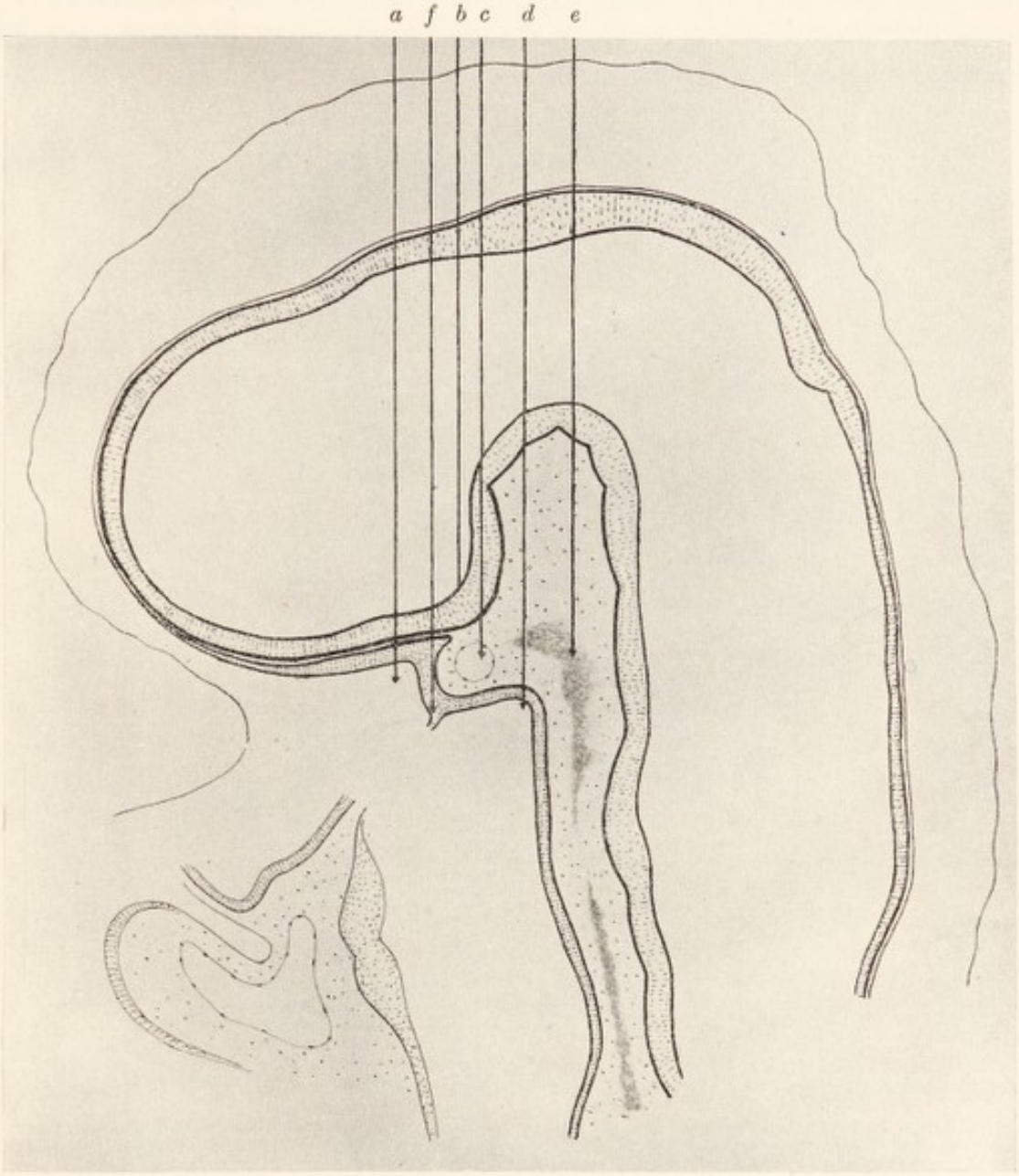

FIG. 95.—Mesial sagittal section through head of 4-mm. embryo of cat (diagrammatic). (Herring.)

a, site of commencement of Rathke's pouch; *b*, part of cerebral vesicle where the hypophysial invagination is about to occur; *c*, blood-channel; *d*, anterior end of foregut (pharynx) with Sessel's pouch (this takes no share in the formation of the pituitary); *e*, notochord; *f*, bucco-pharyngeal septum, ruptured.

will afterwards become the floor of the third ventricle (fig. 96). The two invaginations always maintain close contact with one another. As development proceeds and the basis cranii becomes formed, the upper end of the buccal invagination expands into a considerable cavity, which retains its

[1] In the human embryo before the fourth week, the connexion with the pharyngeal ectoderm being lost by the third month (J. E. Frazer, *Lancet*, ii., 1912).

connexion with the mouth by a narrow stalk. This presently becomes solid, and comes to pass through a canal in the cartilage of the basi-sphenoid (fig. 97). The connexion with the buccal cavity eventually becomes obliterated, but traces of it may persist in exceptional cases even in adult life as the so-called *pharyngeal hypophysis*,[1] which consists of a strand of cells, usually detached,

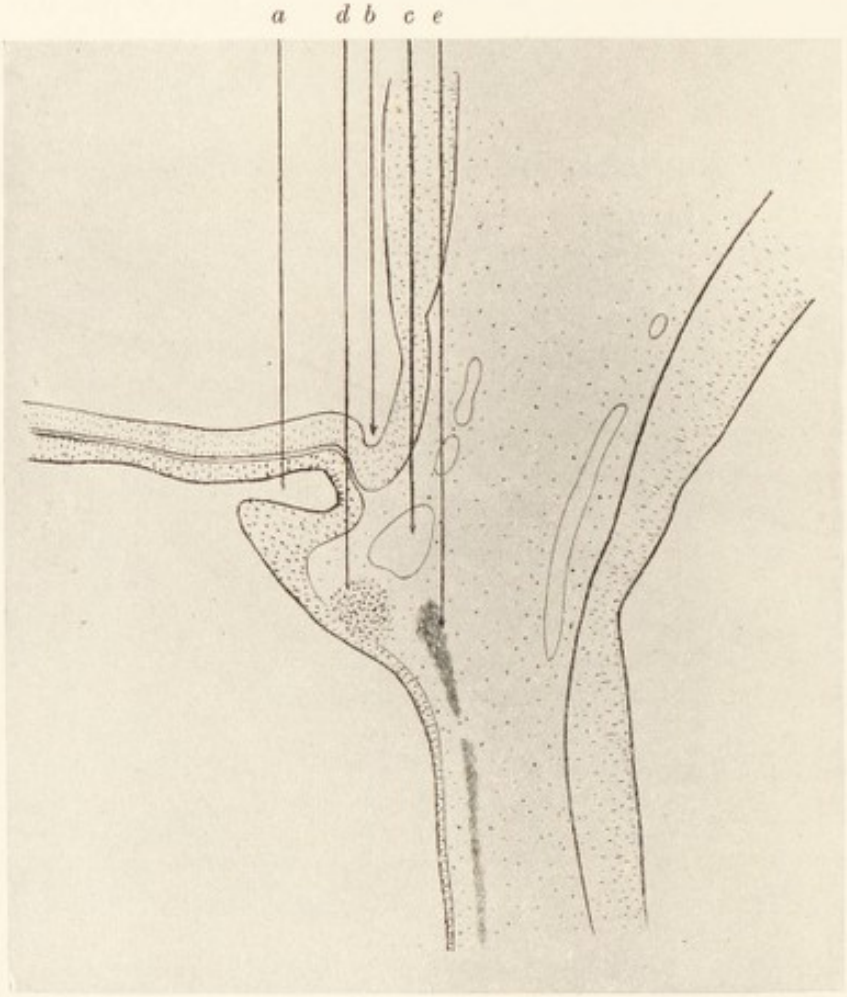

FIG. 96.—Mesial sagittal section through part of head of a 6-mm. embryo of cat. (Herring.)

a, Rathke's pouch (buccal invagination of pituitary which will form pars glandularis, pars intermedia, and pars tuberalis); *b*, neural ectoderm forming invagination for pars nervosa; *c*, blood-channel; *d*, cells at anterior end of foregut; the bucco-pharyngeal septum has disappeared; *e*, notochord.

lying in the submucous tissue between the mucous membrane of the roof of the pharynx and the basi-sphenoid. It is stated that the strand is liable to give rise to tumours.

Nests of stratified (buccal) epithelium sometimes occur amongst the ordinary cells of the gland. They also have been supposed to give origin to tumours.[2]

[1] W. Haberfeld, *Ziegler's Beiträge*, xlvi., 1909; *Frankf. Zeit. f. Path.*, iv., 1910; D. D. Lewis, *Journ. Amer. Med. Assoc.*, lv., 1910; N. Pender, *Ziegler's Beiträge*, xlix., 1910; W. S. Bryant, *Med. Rec.*, xc., 1916.

[2] J. Erdheim, *Ziegler's Beiträge*, xlvi., 1909; D. D. Lewis, *op. cit.*, 1910.

Another vestigial epithelial structure, the *parahypophysis*, with a special blood-supply, may be found between the two layers of the dura mater lining the floor of the sella turcica immediately below the centre of the pituitary,[1] and yet other small accessory bodies containing cells similar to those of the anterior lobe

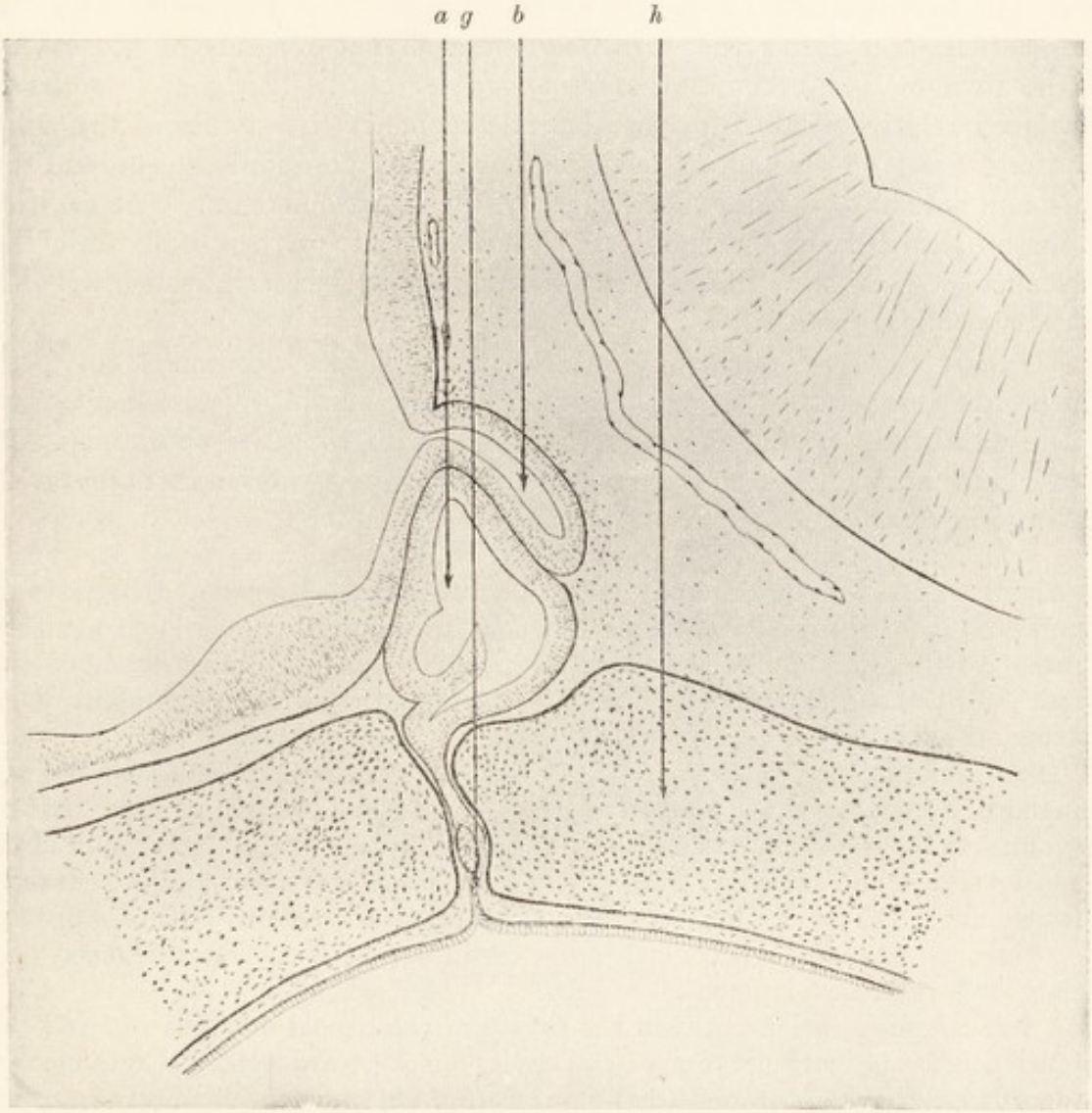

FIG. 97.—Mesial sagittal section through pituitary of 18-mm. cat-embryo. (Herring.)

a, hollow vesicle formed from buccal invagination, from the epithelium of which all the epithelial structure of the pituitary becomes formed, the cavity of the vesicle remaining as the intraglandular cleft; *b*, invagination of neural ectoderm to form pars nervosa; *g*, solid stalk of epithelium connecting *a* with the naso-buccal ectoderm through an aperture in the cartilaginous basi-sphenoid, *h*.

of the pituitary have been described in the track formerly occupied by the stalk of the buccal invagination. It has been suggested that such vestigial structures may undergo hypertrophy after extirpation of the main gland and in part take on its functions.

In the further development of the glandular portion of the organ from the epithelium which forms the walls of the enlargement of Rathke's invagina-

[1] Dandy and Goetsch, *Amer. Journ. Anat.*, xi., 1910–11.

tion, there occurs a considerable multiplication of the cells of the anterior wall which form trabeculæ subdivided later by connective tissue and blood-vessels into isolated clumps. The mass which is thereby produced eventually becomes the *pars anterior* of the gland.[1] The posterior wall is much less thickened, but becomes firmly adherent to and eventually in continuity with the pars nervosa : it forms the *pars intermedia*. What remains of the cavity of the invagination becomes the *intraglandular cleft*. The *pars tuberalis* is developed relatively late from two lateral secondary diverticula of the main pituitary vesicle ; [2] they ultimately fuse together in the middle line around the stalk and spread over the under-surface of the tuber cinereum. The cavities of these diverticula become obliterated and the cells of their walls form the substance of the pars tuberalis : they are often disposed in vesicles, which contain a colloid material.

The *pars nervosa* is developed from the hollow process of neural ectoderm which is in contact with the posterior wall of the buccal invagination : with which, as already stated, it eventually comes into complete continuity. In man and in most animals the cavity of the hollow process becomes obliterated, but in some (*e.g.* cat) it persists throughout life.

Absence of the pituitary body and sella turcica has been noted in cases of anencephaly, many of the features of which (adiposity, hypoplasia of genitals, stunted growth, etc.) might be related to lack of the internal secretion of the gland.[3] But according to D. L. Barlow [4] the gland itself may be present, even although there is usually no sign of sella turcica in these monsters.

The development of the infundibulum and pars nervosa seems to be directly influenced by contact with the buccal ectoderm. P. E. Smith [5] found that if in young tadpoles (4 mm.) the buccal ingrowth is removed, the infundibulum is not developed and the floor of the third ventricle remains membranous. If only a fragment of the epithelium of the buccal ingrowth remains behind, the part of the neural ectoderm with which it is left in contact becomes thickened and undergoes further development.

A free communication between the cavity of the buccal invagination and the extension into the pars nervosa of the cavity of the third ventricle was clearly made out by Herring [6] in one (cat) embryo (fig. 98) and less distinctly in other cases. He regards this as an indication that the cavity of the pituitary may represent an ancestral communication between the stomodœum and the canal of the nervous system, an arrangement which is met with in the ascidian larva.

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[1] M. F. Lucas Keene and E. E. Hewer found oxyphil colloid within vesicles in the pars anterior in an eleven weeks human fœtus. At this stage most of the cells were basiphil. It is only in the later stages that oxyphil cells preponderate as in the adult (*Lancet*, ii. 111, 1924).

[2] F. Tilney (chick and mammal), *Internat. Monatsschr. f. Anat. u. Physiol.*, xxx., 1913 ; W. J. Atwell (Anura, rabbit, man), *Amer. Journ. Anat.*, xxiv., 1918 ; *Anat. Rec.*, xiv., xv., 1918 ; *ibid.*, xviii., 1920 ; E. Baumgarten (reptiles), *Journ. Morph.*, xxviii., 1916.

[3] F. J. Browne, *Edin. Med. Journ.*, xxv. 296, 1920.

[4] *Brit. Med. Journ.*, i. 15, 1923.

[5] *Amer. Anat. Mem.*, No. 11, 1920.

[6] *Op. cit.*, 1908, p. 179.

This view was originally taken by Goodsir[1] although generally ascribed to Kupffer,[2] and if accepted lends important support to Gaskell's theory of the origin

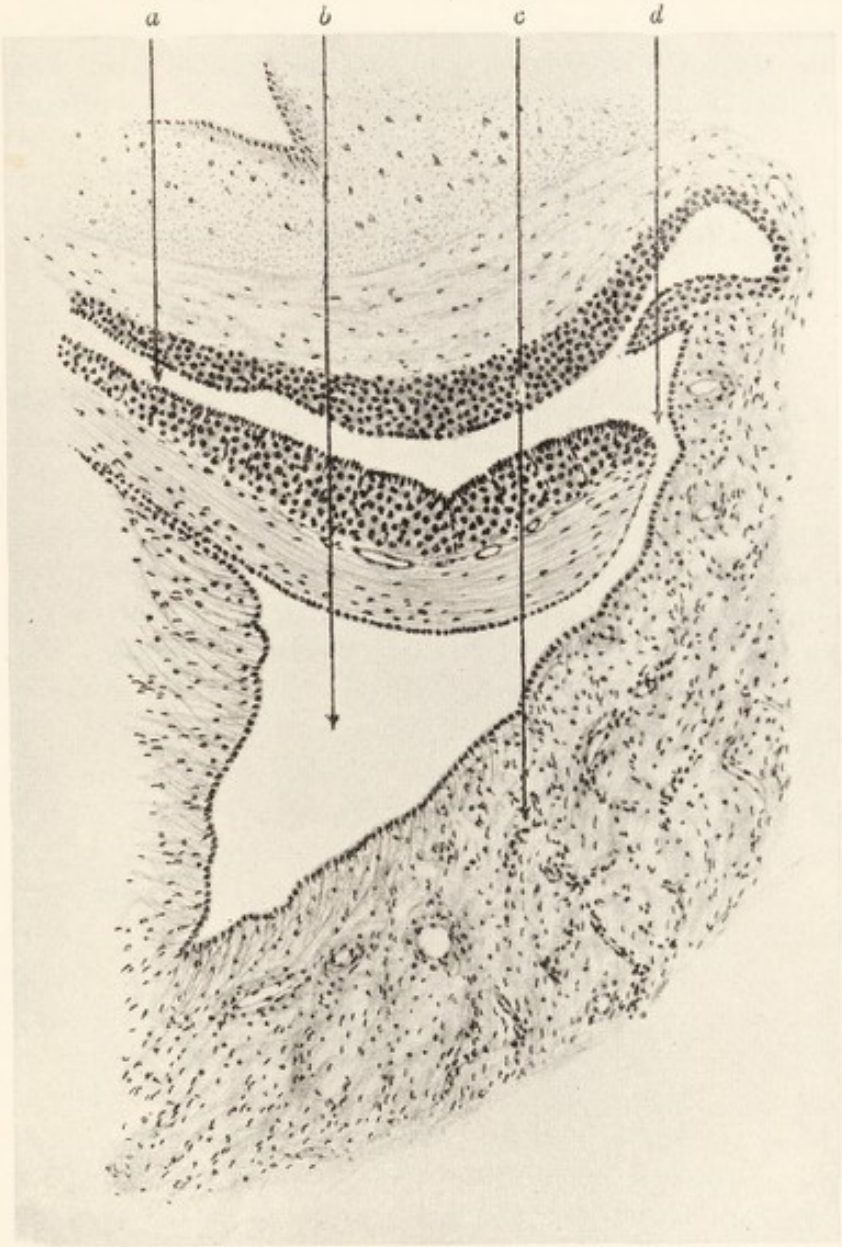

FIG. 98.—Mesial sagittal section through posterior lobe of a kitten near full time. Drawn from a photograph. (Herring.)

a, part of intraglandular cleft ; *b*, cavity in pars nervosa which represents an extension of the infundibulum ; *c*, pars nervosa ; *d*, canal of communication between *a* and *b*.

of vertebrates, which supposes that the central canal of the nervous system represents a primitive ancestral alimentary canal.[3]

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[1] See J. Fraser, *Edin. Med. Journ.*, xxvii., 1921.

[2] " Die Deutung des Hirnanhanges," *Sitzungsb. d. Ges. f. Morph. u. Physiol. in München*, 1894.

[3] *Journ. Anat. and Physiol.*, xxxiv., 1900 ; "The Origin of Vertebrates," London, 1908. For a generalised account of the evolution of the pituitary, see G. R. de Beer, *Brit. Journ. Exper. Biol.*, i., 1924.

In Ammocœtes and in the larva of Amphioxus, Andriezen described a subneural gland consisting of a duct lined by ciliated epithelium, which forms a communication between the buccal and neural cavities.[1]

The existence of cilia in the intraglandular cleft has already been alluded to (p. 184). de Meuron [2] regards certain flattened spaces lined with epithelium occurring in the adult human pituitary as vestiges of the original embryonic vesicle.

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[1] *Brit. Med. Journ.*, i. 54, 1894.

[2] Thèse, Lausanne, and *Trav. d. lab. d'histol. de Lœwenthal*, 1915.

CHAPTER XXIV

THE PITUITARY BODY (*continued*)

Microscopic Structure

Pars Anterior seu Glandularis

The *pars anterior* is formed of epithelium supported by a connective tissue stroma composed of fine trabeculæ continuous externally with a capsular investment of the same tissue. The trabeculæ radiate from two larger lamellated bundles which extend one on each side from the capsule near the substance of the stalk (hilum) into the interior. The stroma has a reticular arrangement. In its meshes are contained cord-like, interconnected or isolated, masses of cells. These cell-masses are usually solid, but sometimes the cells surround a vesicle filled with "colloid" matter, probably secreted by the cells (fig. 99). Some of the finer bundles of connective tissue penetrate into the cell-masses. Numerous thin-walled, sinus-like blood-vessels traverse this part of the gland everywhere, lying in intimate relation to the cells, the secretion of which is probably passed directly into them. The sinus-like vessels are said to be developed like the sinusoids of the liver, the epithelial columns growing into the interior of fairly large blood-sinuses, the endothelial lining of which is pushed inwards by the ingrowth.[1] The great vascularity of the pars anterior is very apparent in the photograph (fig. 101) of an injected gland of the cat.

Characters of the Cells.—The cells of the pars anterior are either clear and non-stainable (chromaphobe, often termed "chief cells") or granular and stainable (chromaphil).[2] The chromaphil cells are divisible into (*a*) those, the granules of which stain with acid dyes (oxyphil, also termed eosinophil); and (*b*) those, the granules of which stain with basic dyes (basiphil): oxyphil cells are normally by far the more numerous. It has been suggested that all three kinds of cell represent different stages of the same cell. There seems to be little doubt that both oxyphil and basiphil granular cells are derived from and may revert, after loss of their secretion, to chromaphobe cells; although, once formed, they appear not to undergo transformation the one into the other[3] but to develop along diverging lines. Both oxyphils and basiphils may show vacuoles containing drops of what is probably secreted material—oxyphil or

[1] E. Gaupp (reptiles), *Arch. f. mikr. Anat.*, xlii., 1893; P. T. Herring (pig), *op. cit.*, p. 172, 1908.

[2] A. Dostoiewsky, *Arch. f. mikr. Anat.*, xxvi., 1886; S. Lothringer, *ibid.*, xxviii., 1886.

[3] P. Bailey, *Journ. Med. Res.*, xlii. 349, 1921. On the characters of the cells at various ages in man, see E. R. A. Cooper, *Oxford Med. Publ.*, 1925.

basiphil—respectively; the material seems to be formed by alteration in and coalescence of their granules.

Launois,[1] by the different affinity they have for certain acid dyes, distinguishes two kinds of oxyphils, but both kinds have their granules darkly coloured by Heidenhain's iron-hæmatoxylin stain (siderophil reaction).

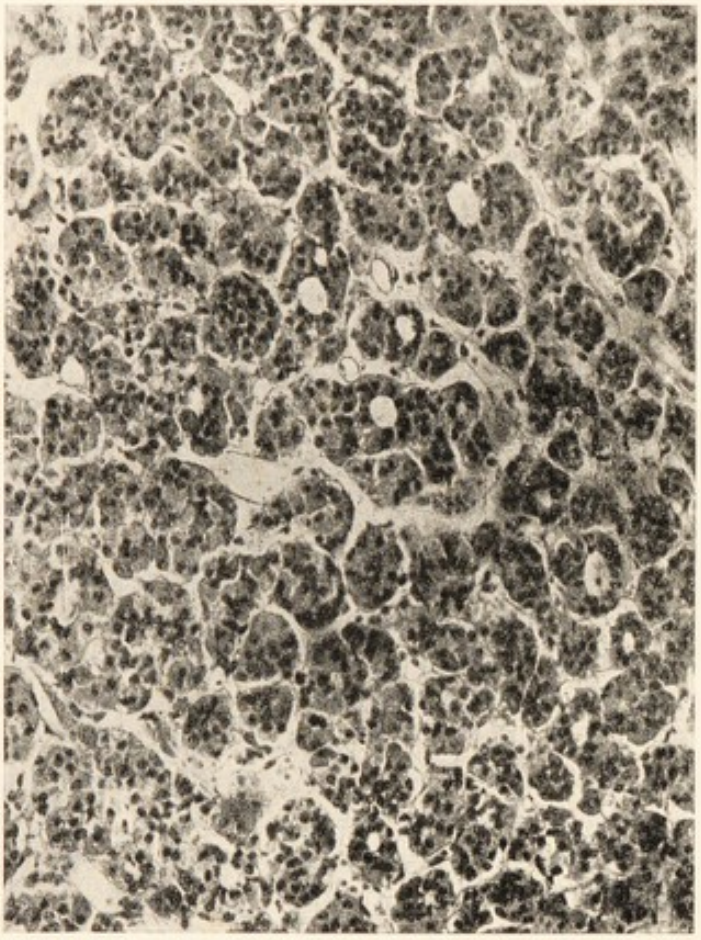

Fig. 99.—Portion of pars anterior of cat's pituitary, showing groups of oxyphil cells with vascular spaces between the groups. Several vesicles, surrounded by cells, are included in the section. Photograph. ×400. (M. Kojima.)

Most of the cells of the pars anterior contain fine fatty or lipoid granules, which can be shown by staining with osmic acid. These are said to increase in number with age.[2]

Tello [3] describes the cells of the pars anterior as containing a reticular structure of mitochondrial nature. This structure is not identical with Golgi's reticulum, which is also present in all the cells,[4] and has been specially studied by P. Reiss [5] with the view of determining the direction taken by the secretion; [6] the Golgi apparatus being, it is believed, always on that side of the nucleus which corresponds with the pole of discharge of a secreting cell. Reiss finds that in the basiphil cell the Golgi reticulum is on the side directed towards the blood-vessels, whereas in the oxyphil cells it is on the side directed towards the centre of the cell-masses, where colloid vesicles are liable to be formed. In the clear (chromaphobe) cells it may be on any side. The observation—if confirmed—is suggestive of two kinds of secretion in the gland, one being stored in vesicles, the other being discharged directly into the blood.

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[1] "Recherches sur la glande hypophysaire de l'homme," Paris, 1904.

[2] L. Launois, *op. cit.*, 1904; Launois, Loeper, and Esmonat, *C. r. soc. biol.*, lvi., 1904; E. J. Kraus, *Ziegler's Beiträge*, liv., 1912; Blair Bell, *op. cit.*, 1919.

[3] *Trab. d. lab. d. invest. biol.*, Madrid, xix., 1921–22.

[4] A. Gemelli, *Bol. d. soc. med. chir. d. Pavia*, xiv. 231, 1900; W. H. F. Addison, *Anat. Rec.*, 1916, pp. 11 and 317.

[5] *C. r. soc. biol.*, lxxxvii., 1922.

[6] *Cf.* Part I., p. 20, which deals with the reticulum of the cells of the thyroid.

It is generally held that the secretion of the pars anterior passes directly into the thin-walled, sinus-like blood-capillaries, around which many of the cells are arranged, with most of their granules on the side of the cell directed towards the capillaries, although it is not easy to obtain evidence of its presence in these. Colloid material has, however, been described within the vessels of the pars anterior.[1]

The "colloid" of the pars anterior, which is especially abundant after thyroidectomy (Herring) and in myxœdema [2] is not of the same nature as that of the thyroid, for it contains no iodine, even after complete thyroidectomy.[3] It is insoluble in water, alcohol, or ether, but swells and eventually dissolves in acids. It is usually contained in vesicles surrounded by cells but sometimes occurs in a diffuse form.[4]

In elasmobranch fishes the cells of the pars anterior are set like a columnar epithelium round large blood-sinuses. In these fishes there is no marked distinction between pars anterior and pars intermedia. In the tortoise non-granular columnar cells surround closed vesicles containing a colloid material.[5]

During pregnancy large, granular, or fibrillated, oxyphil [6] (siderophil) cells are observed forming masses within the pars anterior,[7] which is always enlarged. They have been termed *pregnancy cells*, although, probably, modifications of the ordinary oxyphils. After parturition they diminish in size and lose their specific appearance, but oxyphil cells always remain in larger number. In some animals (ox) the basiphil cells are collected towards the middle of the pars anterior.

During œstrus in animals basiphil cells become more abundant (Rasmussen). According to Addison [8] this is also the case as the result of castration, although other observers have noted an increase in the oxyphil cells [9] or in the chief cells.[10]

Oxyphils are unusually abundant in the enlarged gland of acromegalic subjects where they are accumulated into considerable masses to form an adenomatous tumour.

In diabetes mellitus also considerable masses of oxyphil cells are seen in the pituitary, and between them there may be large accumulations of colloid.[11]

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[1] Launois, *op. cit.*; P. Thaon, "L'hypophyse," Paris, 1907; A. S. and H. G. Grünbaum, *Proc. Physiol. Soc.*, p. xxviii, in *Journ. Physiol.*, xlii., 1911.

[2] W. Hale-White, *Lancet*, i. 156, 1913.

[3] Sutherland Simpson and A. Hunter, *Quart. Journ. Exper. Physiol.*, iii., 1910, and iv., 1911.

[4] On the characters of the colloid of the pituitary, see R. Pirone, *Arch. d. fisiol.*, ii., 1904; Launois, *op. cit.*; G. Guerrini, *Arch. d. fisiol.*, ii., 1904; P. Thaon, *op. cit.*

[5] For the comparative anatomy and histology of the organ in lower vertebrates, see Gentès, *Soc. sci. d'Arcachon, Trav. des Lab.*, Bordeaux, 1907; F. Tilney, *Mem. Wistar Institute*, 1911; P. T. Herring, *Quart. Journ. Exper. Physiol.*, vi., 1913; W. Stendall, *Arch. f. mikr. Anat.*, lxxxii., 1913; de Meuron, *op. cit.*, 1913; W. Blair Bell, *op. cit.*, 1919.

[6] By some authorities these are described as enlarged chromaphobe cells which have acquired oxyphil characters.

[7] L. Comte, *Ziegler's Beiträge*, xxiii., 1898; Launois et Mulon, *Arch. de gyn. et d'obstetr.*, 1904; H. Joris, *Bull. acad. méd. Belg.*, 1908; Erdheim u. Stumme, *Ziegler's Beiträge*, xlvi., 1909.

[8] *Journ. Compar. Neurol.*, xxviii., 1917.

[9] M. Kojima, *Quart. Journ. Exper. Physiol.*, xi., 1917.

[10] A. Kohn, *Münch. med. Wochenschr.*, lvii., 1910.

[11] H. J. B. Fry, *Quart. Journ. Med.*, viii., 1915.

A condition in which the pituitary appears to be relatively inactive is that of hibernation. In this condition the cells both of the pars anterior and pars intermedia are small, without granules and with deeply staining nuclei.[1] (Rasmussen was, however, unable to confirm this for the woodchuck, although the gland undergoes post-hibernation enlargement. This is, however, not the rutting season in this animal.[2]) In connexion with this it is interesting to note that deprivation of pituitary (hypopituitarism) is usually accompanied by drowsiness. Cushing and Goetsch draw attention to the excessive deposition of fat which occurs both in hibernating animals and in individuals with defective secretion of the gland—hypopituitarism—as in the condition known as *dystrophia adiposogenitalis*. They suggest the condition of the pituitary as the actual cause and not merely an accompaniment of the state of hibernation.

Pars Tuberalis

The larger portion of this forms an extension of the gland forwards over

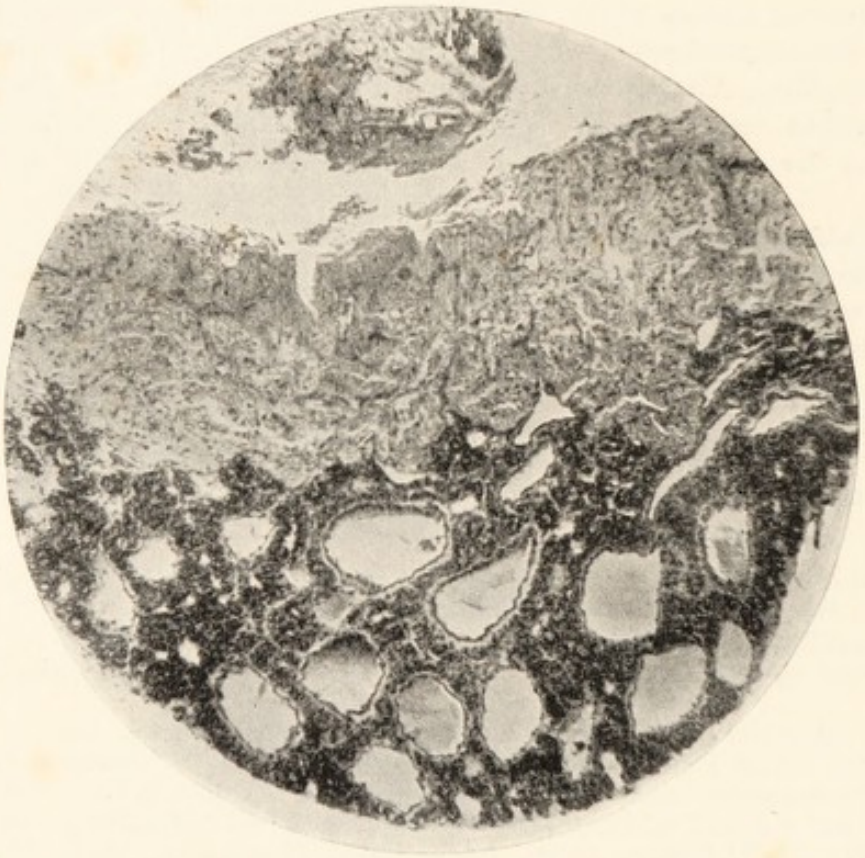


Fig. 100.—Section of pars tuberalis of ox pituitary. Photograph. ×60.

Notice the vesicular structure of the pars tuberalis and its firm attachment to the brain substance of the floor of the third ventricle.

the base of the brain (tuber cinereum), hence the name. This portion corre-

[1] A. Gemelli, *Arch. p. l. sci. med.*, xxx., 1906; Cushing and Goetsch., *Journ. Exper. Med.*, xxii., 1915.

[2] A. T. Rasmussen, *Anat. Rec.*. xviii., 1920.

sponds with what was termed by Herring [1] " the tongue-like process " (fig. 91). He described it as a flattened extension of the pars intermedia ; but alike in structure and development it is distinct from both pars intermedia and pars anterior. Its cells are mostly basiphil, not oxyphil, and generally show a marked tendency to be arranged around colloid contained in vesicles (fig. 100), somewhat similar to those formed in the pars intermedia but more numerous. The vesicular structure is not always apparent ; this may be due to the

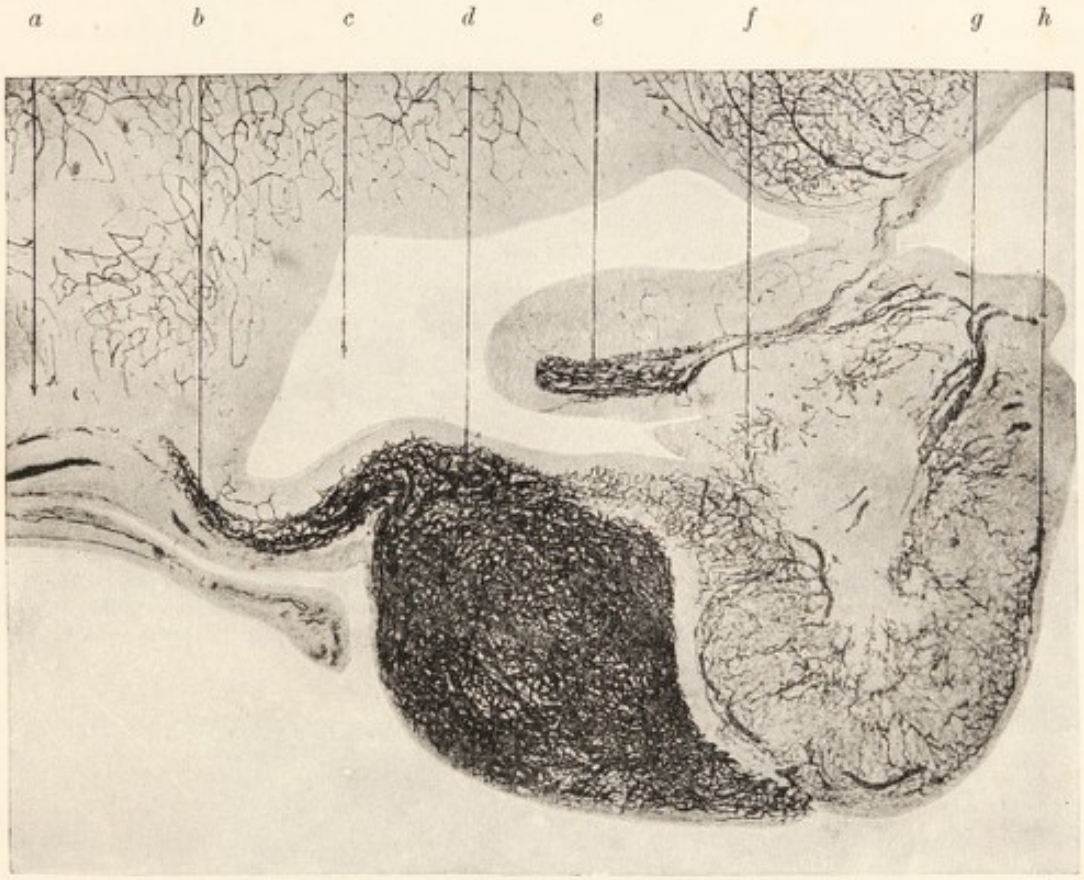


Fig. 101.—Sagittal section of pituitary of adult cat. Blood-vessels injected. Photograph. (Herring.)

a, optic chiasma ; *b*, pars tuberalis (tongue-like process of Herring) ; *c*, infundibulum ; *d*, pars anterior ; *e*, another part of pars tuberalis above neck of gland ; *f*, posterior lobe ; *g*, arterioles and venules entering and leaving posterior lobe ; *h*, vessels near surface of pars nervosa.

vesicles being empty at the time of death, or perhaps to their being only temporarily formed by accumulation of secretion. In vascularity it resembles the pars anterior, so that in an injected specimen (fig. 101) the two closely resemble one another. Its capillaries have a sinusoid appearance like those of the pars anterior (figs. 101, 102). It extends around the neural stalk of the pituitary in the form of a sheath (fig. 103) ending in a disk, perforated for the passage of the neural stalk. It spreads over the adjacent part of the base of the brain (tuber cinereum), especially anteriorly. In sagittal sections it is seen both in front of and behind the neck. It is distinguished from pars

[1] " Histological Appearances of the Mammalian Pituitary Body," *Quart. Journ. Exper. Physiol.*, i., 1908.

FIG. 102.—Sagittal section of cat's pituitary injected, showing part of the pars anterior and the pars tuberalis above it. Photograph. ×35. (From a preparation injected by M. L. Walker.)

The pars tuberalis extends anteriorly (left) over the tuber cinereum (in the preparation it has become detached); posteriorly it penetrates into the brain substance. Notice the extreme vascularity of both pars anterior and adjoining pars tuberalis.

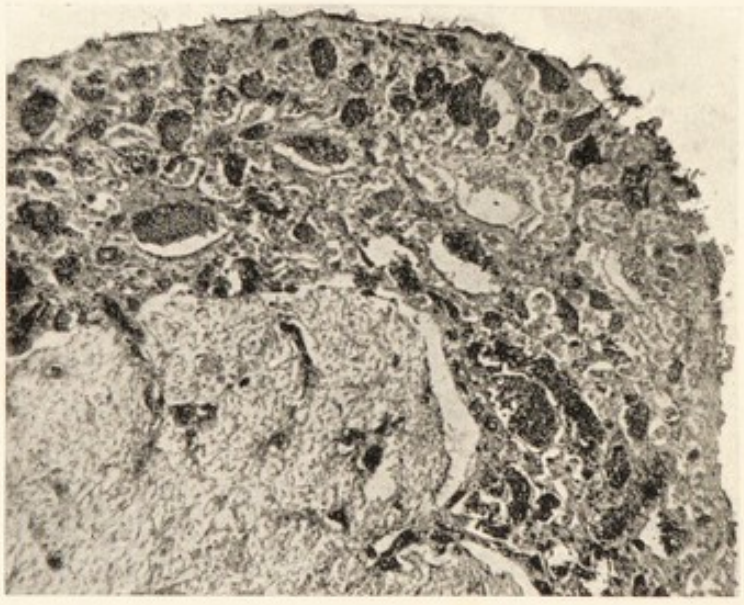


FIG. 103.—Section across stalk of pituitary: human. Photograph. ×80.

Notice the great vascularity of the pars tuberalis encircling the neuroglial portion, which is also very vascular. All the vessels are full of blood, hence their dark appearance. The vesicular structure is not evident in this portion of the pars tuberalis: perhaps because the tissue is not well preserved.

intermedia by its great vascularity ; and from pars anterior, by the different character of its cells and by its usually vesicular structure.

The pars tuberalis may best be described as a nearly flat portion of the gland moulded over the tuber cinereum and the adjacent part of the base of the brain behind the tuber, and ensheathing the stalk of the pars nervosa. Attempts to obtain an insight into its function by investigating the effect of extracts have not so far given any very definite results.[1] Although extracts of the neural stalk—which is covered by pars tuberalis—gave a strong pressor reaction, extracts of pure pars tuberalis gave none. The uterine test reacted to extracts of pars tuberalis but much less so than to an equivalent amount of pars intermedia. Atwell [2] states that in the cat pars tuberalis is nearly equal in volume to pars intermedia. In urodelous Amphibia it is much larger ; in Anura much smaller than pars intermedia.

Pars Intermedia

The *pars intermedia seu juxtanervosa* lies immediately behind the intraglandular cleft (figs. 104, 105), covering and being fused with the anterior surface of the pars nervosa. In some animals it sends an enveloping prolongation around the pars nervosa for a considerable distance (figs. 90, 91). Here and there it shows extensions into the substance of the pars nervosa. These extensions sometimes become cut off from the main portion of the pars intermedia and appear as islets of pars intermedia in the substance of the pars nervosa (fig. 106). The thickness of the pars intermedia varies considerably in different species of animals. In man and the monkey it is relatively thin ; in the cat and dog, thicker ; in the ox, very thick (fig. 104).

In this animal (also in the sheep and pig) there is a cone-like portion of pars intermedia projecting forwards into the intraglandular cleft, which—along with the adjacent pars anterior—fits around it. This cone-like thickening is said by R. Wulzen,[3] who first described it, to resemble in structure pars anterior rather than pars intermedia, and like the former to contain numerous cells with coarse oxyphil granules, which are usually absent from the cells of the pars intermedia.

Herring has drawn attention to the property which the pars intermedia possesses—seen in quite an early stage of development—of penetrating into the thickness of the nervous structures with which it is in contact. He described it as spreading for some distance over the base of the brain, but appears to have confused it here with the pars tuberalis, which was not recognised as a distinct portion of the gland until later and resembles it in this characteristic.

In Ornithorhynchus fine columnar extensions of pars intermedia run through the whole thickness of pars nervosa,[4] but in most animals the extensions only penetrate a short distance, and sometimes they are altogether absent.

Characters of the Cells.—The cells of the pars intermedia are considerably smaller than those of the pars anterior. They resemble more the cells of the pars tuberalis, being devoid of the relatively coarse oxyphil and basiphil

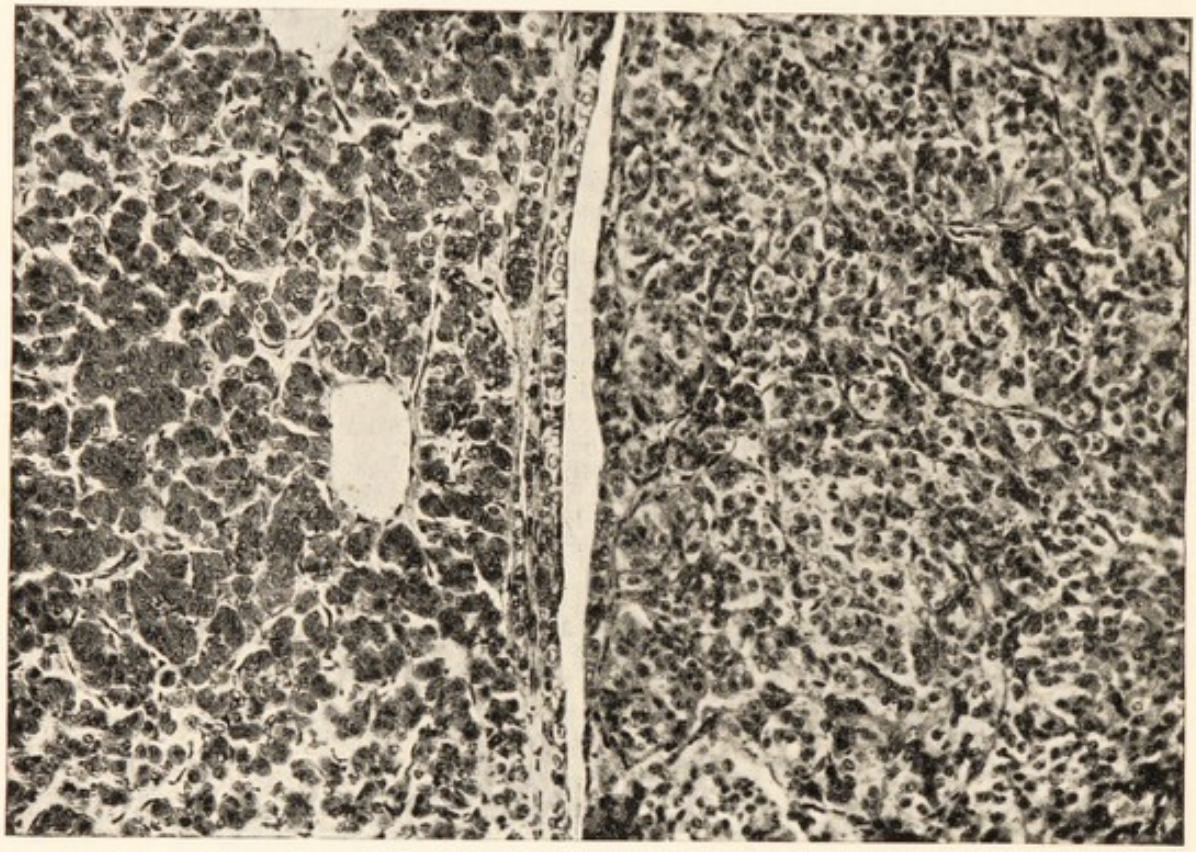
[1] W. J. Atwell and C. J. Marinus, *Amer. Journ. Physiol.*, xlvii., 1918 ; Marinus, *ibid.*, xlviii., 1919.

[2] *Proc. Soc. Exper. Biol. and Med.*, xxii. 499, 1925.

[3] *Anat. Rec.*, viii., 1914.

[4] Blair Bell, "The Pituitary," p. 55, 1919.

granules which characterise many of the cells of the pars anterior : they contain, however, fine granules, staining faintly with basic dyes. Not infrequently the cells of the pars intermedia are seen surrounding circular vesicles occupied by colloid (fig. 105) : such vesicles may occur also, as we have seen, in the pars anterior, but they are more numerous in the intermedia. Whether the colloid is of the same nature as that seen in the pars anterior cannot be stated ;



a *c* *i*

FIG. 104.—Section of ox pituitary at intraglandular cleft (*c*), showing on left side (*a*) a portion of the pars anterior, and on right side (*i*) a portion of pars intermedia. ×200. Stained with hæmatoxylin and eosin. (M. Kojima.)

Most of the cells of the pars anterior are packed with oxyphil granules, staining with eosin : this accounts for their dark appearance in the photograph. They are considerably larger than the cells of the pars intermedia. The two large clear spaces in the pars anterior are venous sinuses. The (empty) blood-channels appear as a network of light spaces between the dark cell-masses.

probably not. Occasionally it is in considerable quantity and the vesicles are correspondingly large. On the other hand, they are sometimes absent. Herring, who described these vesicles, states that those near the intraglandular cleft may take on a tubular character and open into the cleft,[1] and that those which are more deeply situated may have their epithelial investment deficient towards the pars nervosa, as if their colloid were being discharged into the interstitial spaces of that part, in which, as we shall see, isolated masses of colloid material are often found.

[1] Herring, *op. cit.*, p. 149, 1908. See also A. Bevacque, *Anat. Anz.*, xxxviii., 1911.

Herring's Bodies.—Besides such colloid as is contained within the vesicles here described, the pars intermedia often exhibits globular masses of a similar substance, of varying size and not enclosed within vesicles (fig. 106). Some of these masses contain the remains of a nucleus, and have evidently been produced by a chemical transformation of the protoplasm of some of the epithelium cells. These isolated globular masses are sometimes hyaline, sometimes granular

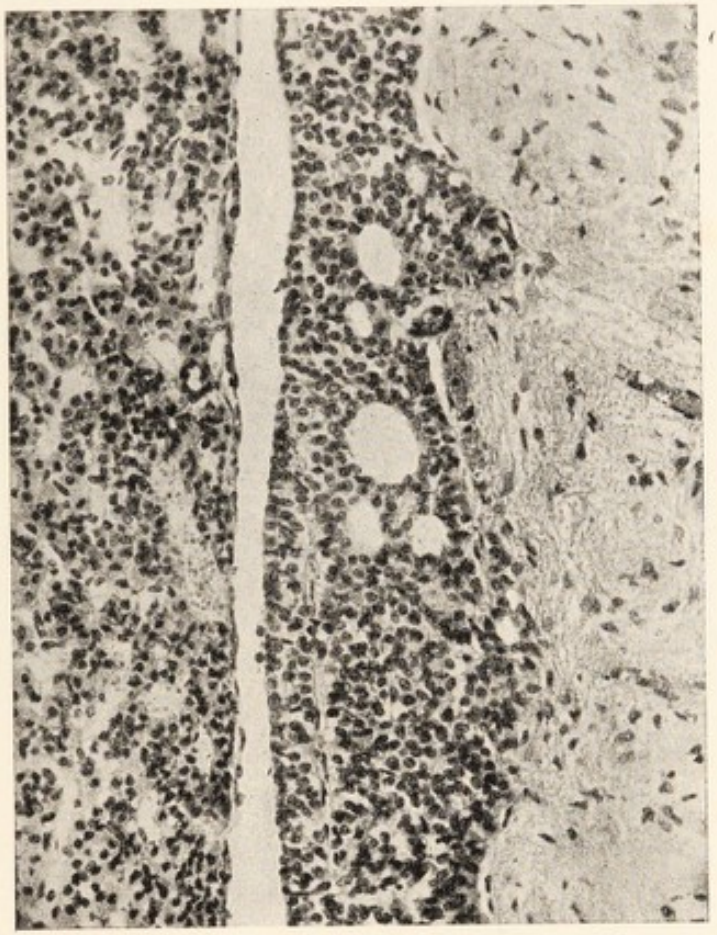


FIG. 105.—Section of pituitary of cat at intraglandular cleft (*c*), showing on the left side (*a*) the highly vascular pars anterior, and on the right side of the cleft the pars intermedia (*b*), in which several vesicles are seen, and which abuts on the pars nervosa (*d*). Photograph. ×200. (M. Kojima.)

in appearance. They are traceable into and through the pars nervosa, and can even be seen passing into the infundibulum of the third ventricle or into its hollow extension (in some animals) into the pars nervosa. Apparently they may undergo a further chemical transformation in their passage, for extracts of pars intermedia alone and of pars nervosa alone show, according to Herring, pronounced differences in their physiological effects. This will be considered later. Similar evidences of secretory activity of the cells of the pars intermedia (pig) have been furnished by D. D. Lewis and S. Maurer.[1]

[1] *Anat. Rec.*, xviii., 1920. According to R. Collin (*C. r. soc. biol.*, xci. 1334, 1924) colloid masses also pass from the pars tuberalis into the tuber cinereum.

In the young mammal (kitten,[1] child [2]) the pars intermedia forms only a thin layer on the surface of the pars nervosa, and its cells are arranged vertically to the surface which bounds the intraglandular cleft posteriorly. At this

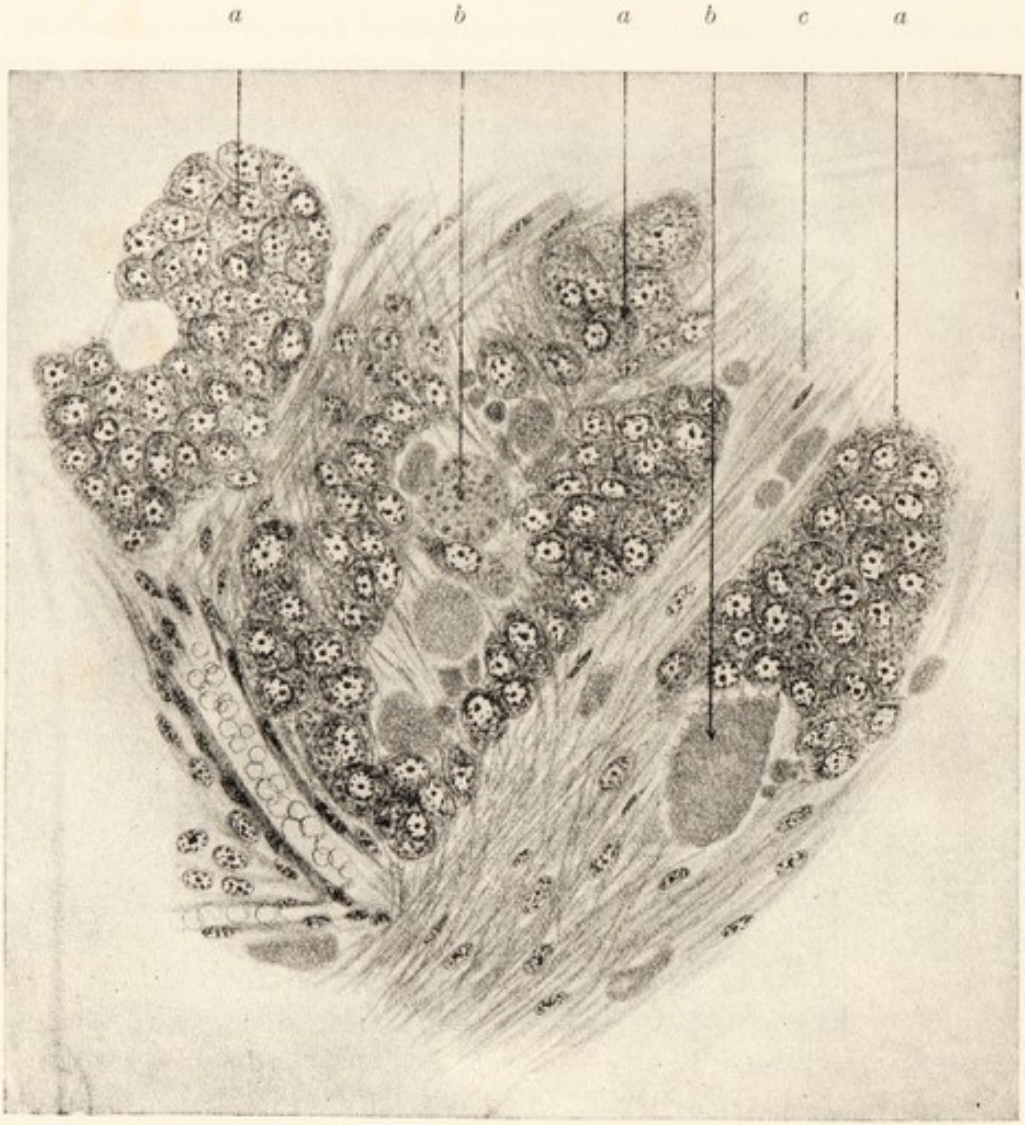


FIG. 106.—Section, including parts of pars intermedia and pars nervosa from pituitary of cat. Drawn from a specimen fixed in Flemming's solution. Highly magnified. (Herring.)

a, *a*, *a*, cells of pars intermedia; *b*, *b*, granular and hyaline masses of Herring, derived from the cells either by degeneration of their protoplasm or by extrusion; *c*, ependyma and neuroglia fibres.

stage of development long spindle-shaped "supporting" cells are seen between the ordinary epithelium cells (fig. 107). But in the adult the pars intermedia in most of its extent is thicker and the cells have a less regular arrangement.

The blood-vessels of the pars intermedia are never very numerous and when the layer is thin may be absent. The capillary vessels are of the ordinary type and not sinus-like as in the pars anterior.

[1] Herring, *op. cit.*, p. 140, 1908.
[2] J. Fraser, *Edin. Med. Journ.*, xxvii., 1921.

Path of secretion from the pars intermedia.—The passage of colloid masses from the pars intermedia into and through the pars nervosa (fig. 108) to be discharged ultimately into the extension of the third ventricle and thus into the cerebrospinal fluid was discovered by Herring. He concluded that the substance of these masses represents the secretion of the pars intermedia, which is thus passed into the ventricle, undergoing in its course certain chemical changes. Herring's observations have been abundantly corroborated by subsequent observers [1] who have used the same methods of fixation and staining. Some authors have expressed the view that the colloid is not a normal but a

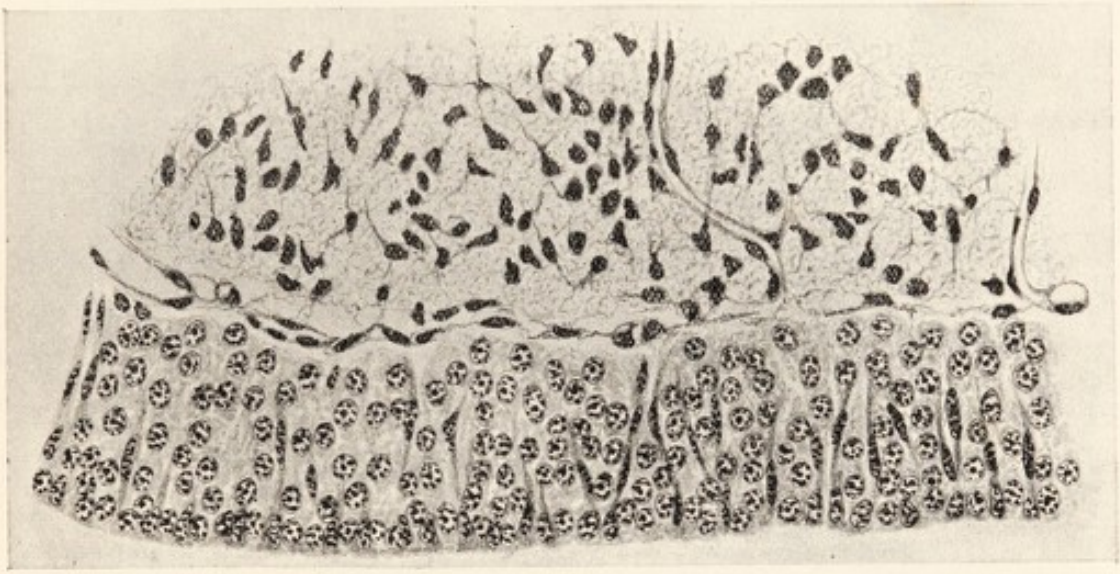


FIG. 107.—Section through pars intermedia and adjacent pars nervosa of new-born kitten. Prepared by Cajal's method. (Herring.)

The pars intermedia contains numerous spindle-shaped cells. The pars nervosa is composed of branched neuroglia cells in a granular-looking matrix. Blood capillaries are seen in the pars nervosa and are especially numerous next to the pars intermedia, but do not penetrate into it.

pathological formation and that it has no physiological significance. But in view of the fact that, if properly looked for, it is found in abundance in perfectly normal animals, and under certain conditions, not necessarily pathological, is greatly increased,[2] this conception is untenable.

Confirmatory evidence is presented by experiments which show the existence in cerebrospinal fluid of the same active principles as can be extracted from the posterior lobe of the pituitary, although normally present in too great a condition of dilution to produce their characteristic effect on blood-pressure until the fluid has been concentrated by evaporation (Cushing and Goetsch [3]). These results have

[1] In man, by Halliburton, Candler, and Sikes, *op. cit.*, 1909.

[2] *E.g.* after thyroidectomy (Herring, *Quart. Journ. Exper. Physiol.*, i. 281, 1908). Cushing and Goetsch obtained a similar result from removal of the pancreas; and also from mechanical injury of the posterior lobe, *Amer. Journ. Physiol.*, xxvii., 1910.

[3] *Op. cit.*, 1910.

been criticised,[1] but since Cushing and Goetsch published their results, it has been conclusively shown by the uterus test—which was not then known—that pituitary autacoids are present even in normal cerebrospinal fluid.[2] Dixon got effects on the uterus from the unconcentrated normal cerebrospinal fluid in nearly every case (dog, cat); although much less than when certain animal extracts are administered beforehand.

Those which are found to be effective are duodenal extract (fig. 109), which takes an hour or more for its effect to appear: and ovarian extract without corpus luteum (fig. 110). With ovarian extract Dixon found that the autacoids appear

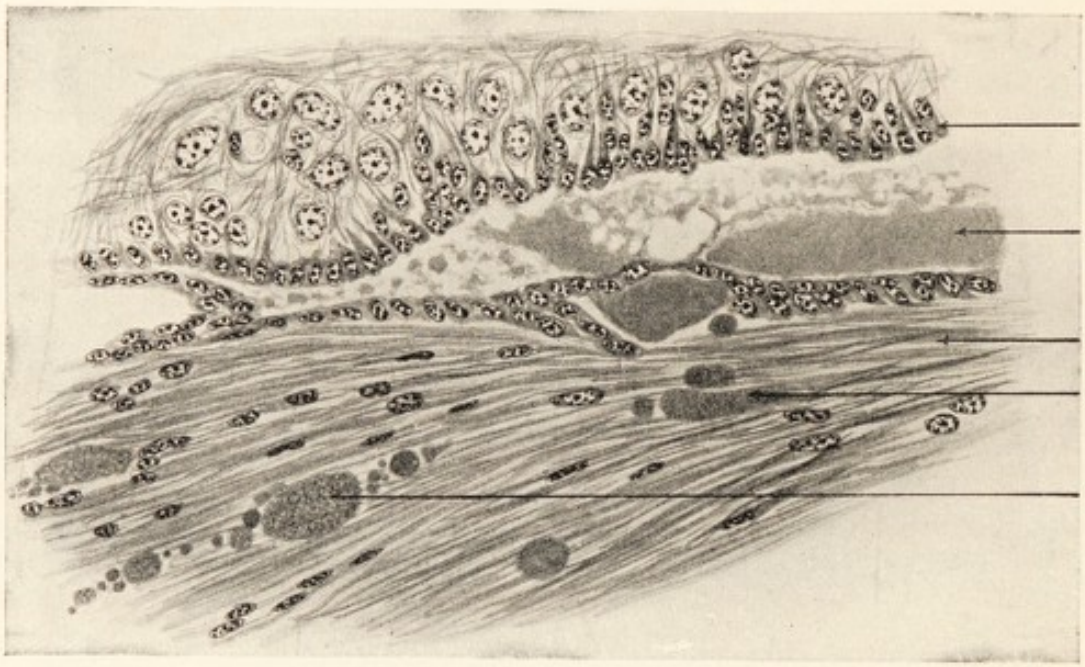


FIG. 108.—Section of posterior lobe of pituitary of cat, including a portion of the central cavity which is continuous with the infundibulum of the third ventricle. (Herring.)

a, ependyma of central cavity; *b*, colloid or hyaline matter in central cavity: some of it is seen passing through the ependyma from the pars nervosa; *c*, ependyma fibres; *d*, hyaline masses and *e*, a granular mass in pars nervosa.

more quickly in the cerebrospinal fluid and sooner disappear. If extract of posterior lobe itself is injected into the circulation its uterine effect is very soon shown by that fluid. Cow found that after extirpation of the pituitary, injection of duodenal extract into the animal produces no effect on the cerebrospinal fluid. ×

Dixon and Marshall have further investigated the effect of ovarian extracts made from the ovaries of the sow at different periods of œstrus and pregnancy. They find that extracts of ovary taken towards the end of pregnancy cause the cerebrospinal fluid to have a strong effect on uterine muscle (fig. 110). This effect of ovarian extract in activating the pituitary is inhibited by corpus luteum extracts and by the presence of corpus luteum in the ovary extracted.[3]

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[1] Carlson and Martin, *Amer. Journ. Physiol.*, xxix., 1911; C. Jacobson, *Bull. Johns Hopkins Hosp.*, xxxi., 1920.

[2] Douglas Cow, *Journ. Physiol.*, xlix. 367, 441, 1915; W. E. Dixon, *ibid.*, lvii., 1923; *Proc. Roy. Soc. Med.*, xvi., 1923.

[3] *Journ. Physiol.*, lix. 276, 1924.

× Dixon & Wadia (B.m.J. 1926 i 820) find that the same effect on the C.S.F. is produced by insulin. And that active pituitrin membrane has an insulin like action on blood-sugar: although they have never got convulsions? The active substance is not secretin since it is destroyed by boiling with dilute acid, whilst secretin is the exact method. It is also destroyed by boiling with NaOH solution

Trendelenburg found that the cerebrospinal fluid obtained by puncture of the fourth ventricle contains an active agent, which produces contraction of the uterus; it is absent if the pituitary had been previously extirpated or its stalk severed.[1] C. and M. Oehme[2] obtained strong vasoconstriction

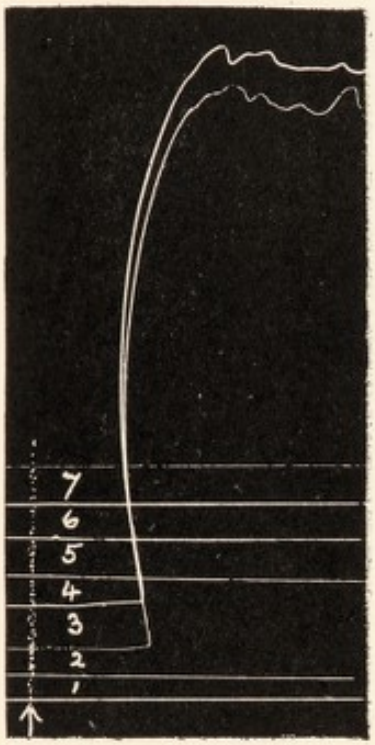

Fig. 109.—Effect of cerebrospinal fluid on uterine cornu of guinea-pig after intravascular injection of duodenal extract. (D. Cow.)

Five and 10 drops of cerebrospinal fluid respectively were added to the 80 c.c. Ringer in which the uterus was immersed to produce the effect shown in 2 and 3. The fluid was collected from 60 to 120 minutes after the injection. The negative results were obtained either with cerebrospinal fluid collected too soon after injection, or with a previously active fluid which had been digested with artificial gastric juice for 18 hours.

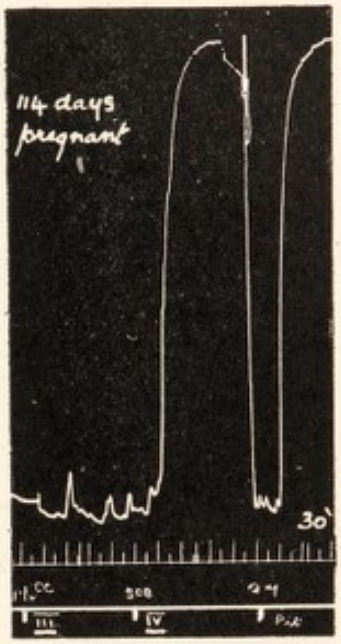

Fig. 110.—Effect of cerebrospinal fluid on uterine cornu of guinea-pig after injection of ovarian extract, obtained from a sow 114 days pregnant and therefore very near delivery, and with the corpora lutea degenerated. (Dixon and Marshall.)

At III. addition to uterus bath of 3 c.c. cerebrospinal fluid collected from 5 to 30 minutes after intravascular injection of extract of ovary (negative result). At IV. addition of the same amount of cerebrospinal fluid collected 30 to 60 minutes after the ovarial injection (strong positive effect). This was followed by the addition of 2 mg. pituitrin to the uterus bath This caused the second strong positive effect.

(rabbit's ear) from perfusion of cerebrospinal fluid obtained by lumbar puncture. A. Mayer found that human cerebrospinal fluid obtained by lumbar puncture during labour (Cæsarian section) stimulates uterine action when injected intravenously into patients with deficient labour pains, and attributes the result to its containing the active principle of the pituitary.[3] Miura[4] has obtained confirmatory results. He found that the effects on the uterus (rat) of the cerebrospinal fluid disappear after extirpation of the pituitary.

[1] *Klin. Wochenschr.*, iii. 777, 1924.
[2] *Deutsch. Arch. f. klin. Med.*, cxxvii. 261, 1918.
[3] *Klin. Wochenschr.*, iii. 1805, 1924.
[4] *Arch. f. d. ges. Physiol.*, ccvii., 1925.

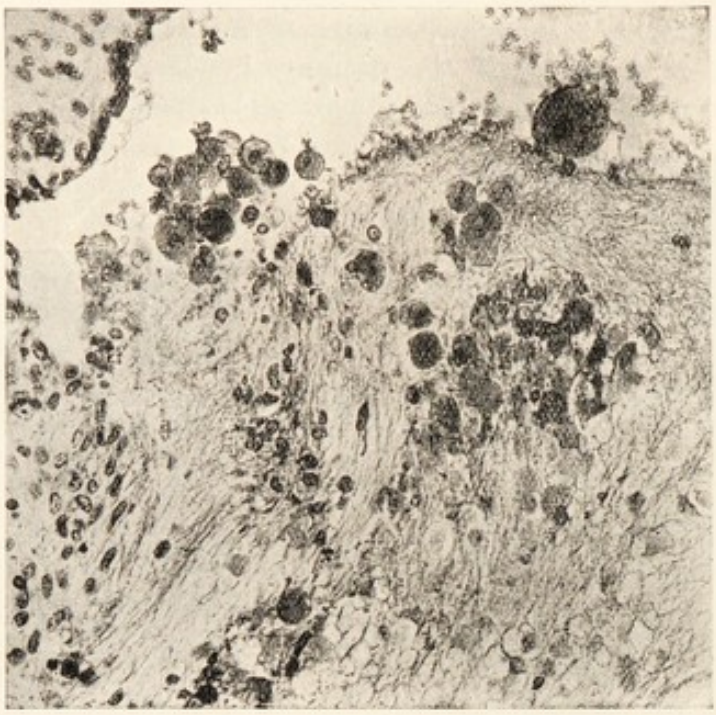

FIG. 111.—Section through infundibular recess and neck of posterior lobe of pituitary of a rabbit killed three months after removal of thyroids. ×200. (Herring.) Cells and colloid bodies streaming through the pars nervosa and passing into the infundibular recess.

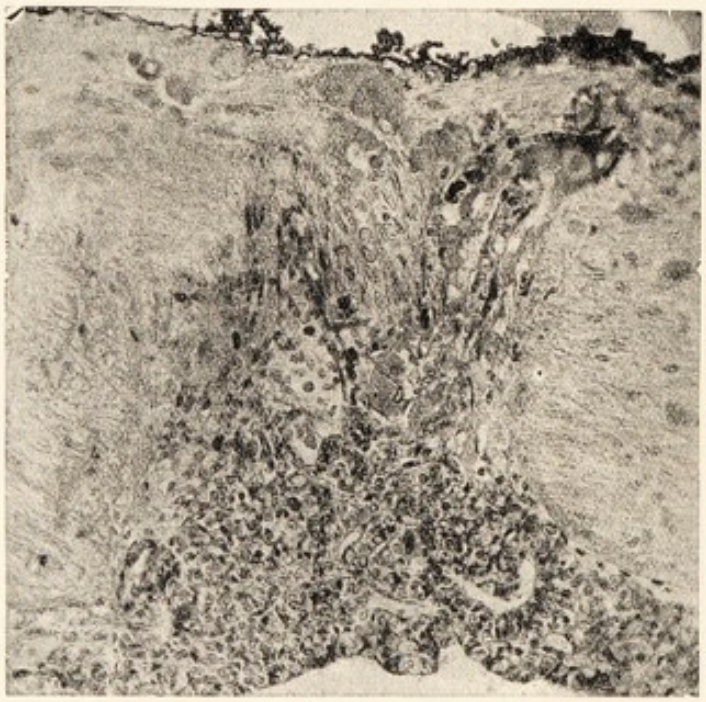

FIG. 112.—Section through infundibular recess (above) and neck of posterior lobe with pars intermedia (below). From the pituitary of a dog, killed 19 days after thyroidectomy. (Herring.) Photograph. ×160.

Cells of the pars intermedia are invading the neuroglial tissue of the neck and producing colloid masses which are streaming towards and into the infundibular cavity.

Pars Nervosa (*Neurohypophysis*)

The pars nervosa is almost entirely composed of neuroglia fibres with glia cells scattered amongst them. Many of the fibres arise from these cells,

Fig. 113.—Section of portion of pars intermedia and pars nervosa of pituitary from a case of myxœdema. (F. W. Mott.)

Groups of cells and masses of colloid are passing from the pars intermedia into the pars nervosa.

others from the ependyma cells of the infundibulum and of its extension into the gland. There appear to be no nerve-cells and not many nerve-fibres.[1]

[1] P. T. Herring, *op. cit.*, 1908. See also p. 180.

A dark brownish-yellow pigment is found in man in both the glia cells and ependyma cells and in the interstices between them.[1] According to Vogel this pigment is peculiar : it is not melanin nor is it of a lipoid nature.[2] It does not contain iron.[3] Between the neuroglia fibres, especially in the neighbourhood of the infundibular stalk, but also in other situations, are to be seen the colloid masses of Herring (fig. 106)—both hyaline and granular—already described under pars intermedia. These masses are traceable, as before mentioned, from the pars intermedia to the ventricular cavity (or its extension into the pars nervosa) ; they may be seen passing through the ependyma and becoming free in the cerebrospinal fluid (fig. 108). Similar masses were found by Crowe, Cushing, and Homans in the neighbourhood of grafts of the pituitary which had been implanted into cerebral tissue.[4] As Herring found, they are greatly increased in amount after thyroidectomy (figs. 111 and 112). Mott has made a similar observation in a case of myxœdema occurring in man [5] (fig. 113).

The enlargement of the gland which is characteristic of pregnancy affects the pars nervosa as well as the rest of the organ. There is also, in this condition, an increase in the number of the cells which pass into pars nervosa from pars intermedia.[6]

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[1] A. Kohn, *Arch. f. mikr. Anat.*, lxxv., 1910 ; F. Tello, *Trab. d. lab. d. invest. biol.*, Madrid, x., 1912.

[2] *Frankf. Zeitschr. f. Path.*, xi., 1912.

[3] J. P. Simonds, *op. cit.*, p. 777.

[4] *Quart. Journ. Exper. Physiol.*, ii., 1909.

[5] *Proc. Roy. Soc. Med.*, x., 1917.

[6] H. Joris, *Mém. de l'acad. de méd. de Belgique*, xix., 1908.

CHAPTER XXV

THE PITUITARY BODY (*continued*)

Blood-Vessels, Lymph-Channels, and Nerves

Blood-Supply

The pituitary is one of the most vascular organs in the body, but its different parts vary considerably in vascularity. The difference is well seen in the photograph of a sagittal section through the injected organ of the cat (fig. 101). The number and size of the sinus-like vessels of the pars anterior cause this part to look almost black in the photograph ; whereas the posterior lobe is certainly not more vascular than the adjacent brain substance, and, as with the brain itself, is least supplied with vessels near the centre and most near the surface. The pars tuberalis (" tongue-like process ") is as vascular as the pars anterior. In the pars intermedia the vessels are few or altogether absent. In the dog the capillaries are more numerous in the pars intermedia than in the cat ; in the monkey they are absent altogether (Herring). And although in most animals the pars nervosa is but little vascular, Blair Bell found that in the ox it has very numerous blood-vessels.[1] The stalk is also very vascular (see fig. 103).

According to the account given by Dandy and Goetsch [2] the pituitary (dog) is supplied by a large number of arterioles derived from the circle of Willis and from a communicating branch uniting the internal carotids (fig. 114, A). These arterioles converge towards the infundibulum and are conveyed to the gland along its stalk. Most are distributed to the pars anterior. Those from the posterior two-thirds of the circle pass over the corpora mamillaria to reach the stalk, along which they also are conveyed towards the pars anterior. The venules from the pars anterior, also very numerous, pass at first to the stalk and thence diverge, uniting to form small veins which radiate outwards and enter a venous circle, roughly corresponding with the arterial circle (fig. 114, B). This venous circle is formed by the cavernous sinuses on each side and by communicating vessels before and behind, those behind draining into the vena magna Galeni. It is clear from this description that severance of the stalk might entail interference with the blood-supply of the gland.

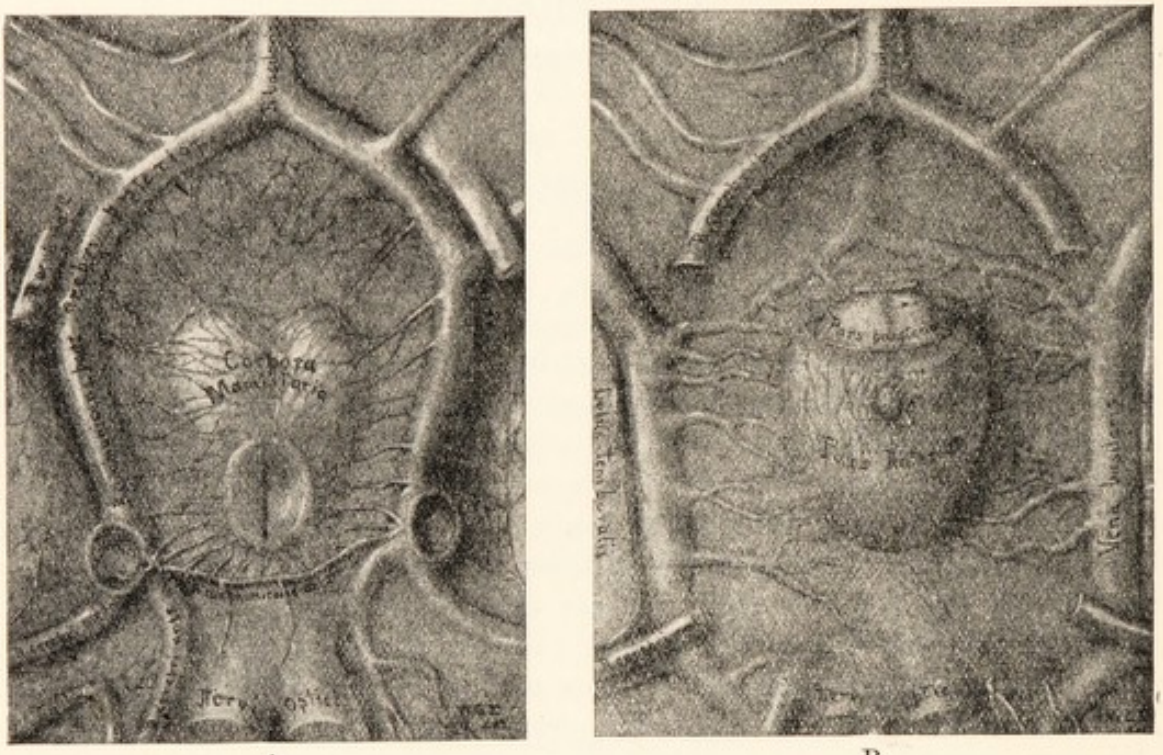
The posterior lobe receives a certain amount of blood from the vessels which are conveyed to it along the stalk. But it has also a special median artery, which enters it posteriorly (fig. 101) and is formed by the union of two small vessels derived from the internal carotids. The branches of this median vessel

[1] *Op. cit.*, p. 61, 1919.

[2] *Amer. Journ. Anat.*, xi., 1910–11.

break up into capillaries in the pars nervosa. These are more numerous near the surface than in the centre; some may penetrate into the pars intermedia. The blood leaves the posterior lobe by a median vein corresponding with the artery and dividing into two which pass one on each side to the lateral sinus.

L. Gentès [1] gives an account which differs in certain respects from that of



A B

FIG. 114.—Blood-supply of the pituitary body (dog). (Dandy and Goetsch.) A. Arterial blood-supply, seen from the ventral aspect. A large number of small arteries are seen converging from the circle of Willis to the neck of the gland (which has itself been removed). B. Venous blood-supply. The principal veins are shown passing from the pituitary to a venous circle, which roughly corresponds with the arterial circle of Willis. Both figures show the parts considerably magnified.

Dandy and Goetsch. He describes the organ in man as being mainly supplied by a small artery on each side derived from the internal carotid, and giving off a number of branches to the gland.[2] Two chief branches of these hypophysial arteries pass on each side, one to the anterior and the other to the posterior lobe, the ventral surfaces of which are covered by their ramifications.

Lymph-Channels

Whether true lymph-vessels occur in any part of the gland is doubtful. Caselli [3] described such vessels in the pars anterior, but Launois, Herring, and

[1] "Les artères de l'hypophyse," *Gaz. hebd. d. sci. méd. de Bordeaux*, 1903. See also Launois, *op. cit.*, 1909.

[2] These are, no doubt, the arterioles coming off from the ramus communicans of Dandy and Goetsch (shown in fig. 114, A), which is itself formed by a branch from each internal carotid.

[3] "Studii anat., etc.," Reggio Emilia, 1900.

others have failed to detect their presence: nor are they usually present where blood-capillaries take the form of sinusoids, as is the case in the pars anterior. Herring, indeed, speaks of "lymph-channels" in the pars intermedia and pars tuberalis ("tongue-like process") as well as in the pars nervosa.[1] But these are more probably interstitial spaces rather than true lymph-vessels. That lymph which is formed in the gland finds its way through such spaces into the third ventricle or its extension is probable.

D. Cow [2] noticed that when China ink was introduced into the ventricular cerebrospinal fluid some of the particles were eventually found in the intra-glandular cleft and others amongst the cells both of the pars anterior and pars intermedia. But he appears not to have succeeded in following the paths by which they travelled.

Nerve-Supply

Very little is known about the origin of the nerves supplying the pituitary. Fibres have been described as passing along the stalk from sympathetic branches on the internal carotids, some of them penetrating to the pars anterior.[3] Such nerves are doubtless derived from the superior cervical ganglion: they are non-myelinated and are probably distributed mainly to the blood-vessels of the glands. But myelinated nerve-fibres have also been described as ending in ramifications amongst the cells of the pars anterior.[4] Some observers have described the pars nervosa as containing many nerve-fibres; Tello [5] traces them into pars intermedia where they terminate in the epithelium. Herring [6] was not able to satisfy himself of the nervous character of the fibres in the pars nervosa and was inclined to regard most of them as ependymal fibres.

Neither Thaon nor Herring was able to detect the presence of nerve-cells in any part of the gland.

[1] *Op. cit.*, 1908.
[2] *Journ. Physiol.*, xlix., 1915.
[3] Berkeley, *Brain*, xvii., 1894; Dandy and Goetsch, *Amer. Journ. Anat.*, xi., 1910; W. E. Dandy, *ibid.*, xv., 1913.
[4] P. Thaon, Thèse, Paris, 1907; F. Masay, Thèse, Bruxelles, 1908; W. Blair Bell, *op. cit.*, 1919.
[5] *Trab. d. lab. d. invest. biol.*, Madrid, xix., 1921–22.
[6] *Op. cit.*, p. 147, 1908.

CHAPTER XXVI

THE PITUITARY BODY (*continued*)

Action of Extracts of Posterior Lobe: General Results

The announcement [1] that extracts of pituitary, as well as of suprarenal, have a remarkable influence upon the vascular system, producing in mammals, when injected into a vein, a great rise of blood-pressure with contraction of arteries and increase in force of heart-beats (fig. 115), led to attention being drawn to this organ, which had until then been neglected by physiologists, although the effects of tumours of the gland had not escaped the notice of pathologists and clinicians. Howell [2] found that the action described by Oliver and Schafer is confined to extracts of the posterior lobe. This observation was confirmed by Schafer and Vincent,[3] who also obtained a depressor effect from alcohol extractives of posterior lobe, but no effect from extracts of anterior lobe.

Some observers [4] have described depressor results upon the circulation from extracts of anterior lobe, but it is doubtful if these are specific, since similar results are obtained from extracts of most glands (see p. 10).

Besides effects produced by pituitary extract upon the circulation, it has been found to influence a number of organs containing plain muscular tissue.[5] The results appear to be direct, and not, as with extract of suprarenal, through the end-substance supplied by sympathetic nerves. One of the most striking effects is the intense contraction of isolated portions of uterine muscle or cornua uteri, discovered by Dale [6] and largely employed as a quantitative test for the activity of commercial and other pituitary extracts. Another effect is to cause contraction, although less strikingly, of the plain muscular tissue of the alimentary canal and of the urinary and generative passages, of the trachea and bronchial tubes (through these it may affect the respiratory movements),

[1] G. Oliver and E. A. Schafer (*Proc. Physiol. Soc.*), *Journ. Physiol.*, xvi., xvii., 1894; *ibid.*, xviii., 1895.

[2] *Journ. Exper. Med.*, iii., 1898.

[3] *Journ. Physiol.*, xxv., 1899.

[4] W. W. Hamburger, *Amer. Journ. Physiol.*, xi., 1904, and xxvi., 1910; Lewis, Miller, and Mathews, *Arch. Internat. Med.*, vii., 1911; C. Jacobson, *Johns Hopkins Hosp. Bull.*, xxxi., 1920.

[5] It is frequently assumed that pituitary extract is a general stimulant for plain muscle, but this is by no means the case: it has a distinctly selective influence.

[6] *Journ. Physiol.*, xxxiv., 1906.

and also of the alveoli of the lactating mammary gland, causing an outpouring of the accumulated milk. Some of the effects produced by the extract can be put down to the action of a non-specific histamine-like constituent, but some are quite specific. Noteworthy amongst these is the effect on amphibian melanophores, which are expanded by the action of a pituitary autacoid. On the secretion of the kidney the effect differs according to the method of administration. When injected into a vein a marked diuresis is the immediate

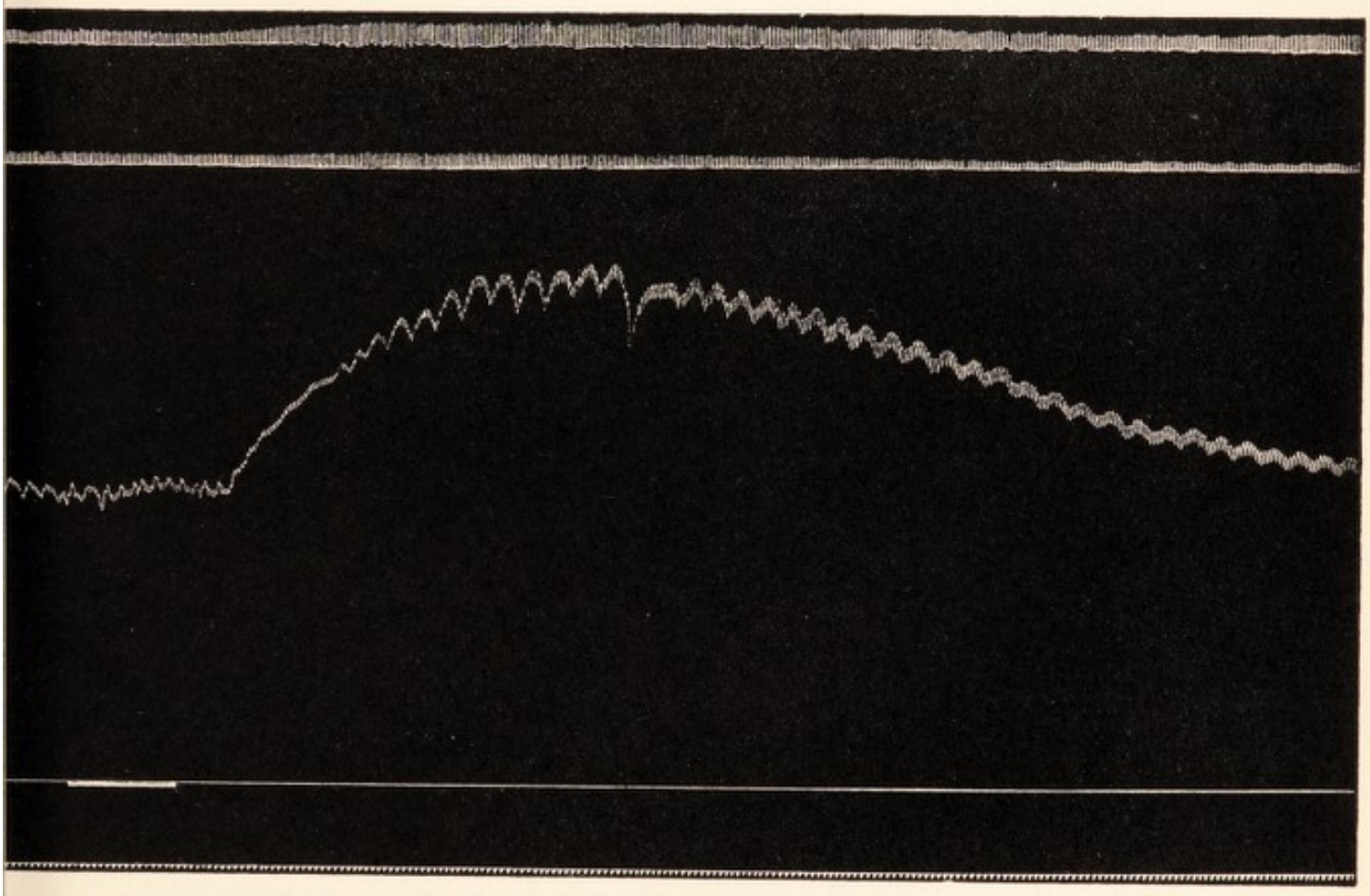


FIG. 115.—Tracing showing the effect of an intravenous injection of extract of posterior pituitary extract upon heart and blood-pressure in a dog anæsthetised with morphia.

A, tracing from auricle; B, tracing from ventricle; C, blood-pressure tracing; D, signal and abscissa; E, time in seconds. The tracing has been reduced to about one-half.

result, giving place to a more prolonged antidiuresis; but when injected subcutaneously the effect is antidiuretic, eventually giving place to diuresis.

As with suprarenal extracts,[1] excessive doses produce strong toxic effects, and may cause death by paralysing the respiratory centre.[2]

[1] Part I., p. 147.

[2] Schafer and Swale Vincent, *op. cit.*, 1899; R. Silvestrini, *Arch. ital. de biol.*, xlv., 1906; Garnier et Thaon, *Journ. de Physiol.*, ix., 1906; Thaon, Thèse, Paris, 1907; Renon et Delille, *C. r. soc. biol.*, lxiv. and lxv., 1908; J. Parisot, *ibid.*, lxvii., 1909; B. A. Houssay, Tésis, Buenos Aires, 1911, and "La accion fisiologica de los extractos hypofisiarios," 1918, and "Nuevos estudios," 1922.

Houssay states that the extract of about 0·17 gram of bovine gland per kilo. weight is toxic if injected into a rabbit's vein ; but a much larger dose is required if administered hypodermically. Parisot found that the extract of ten glands of the rabbit would kill a fair-sized animal of the same species in two minutes. In the rabbit repeated injections on successive days result not only in raising the blood-pressure but in keeping it raised for some days after the last injection. There appears to be no tendency to the production of atheroma such as is caused by repeated injections of adrenaline.[1]

Administered by subcutaneous injection in man, the extract of posterior lobe generally causes a gradual rise of blood-pressure with slowing and strengthening of the pulse,[2] but a fall of pressure has also been recorded.[3] There is often extreme pallor of the skin and stimulation of the intestinal movements ; evacuation of fæces may occur. In women contraction of the uterus is frequently produced.[4]

There need be no fear of the production of toxic effects in man, since the dose which would be required to cause such effects is much greater than is ever likely to be employed therapeutically. In any case the susceptibility of the human subject to the toxic effects of the extract is far less than that of rodents. In carnivora the effects of large amounts administered parenterally is also less than in rabbits, but repeated doses produce metabolic changes leading to emaciation.[5]

It is stated that the toxic effects of posterior lobe extract in rabbits are diminished by simultaneous administration of thyroid extract or of anterior lobe extract, but are increased by suprarenal extract.[6]

In the earlier experiments on the effects of intravenous administration of toxic doses unboiled extracts were used.[7] In such cases the possibility of the production of intravascular clotting must not be overlooked (see p. 11). The immunity which some authors have noted as produced by a first non-toxic dose, followed by one which would otherwise be toxic, may be related to the circumstance that such a result, viz. the production of immunity, as the effect of a prior dose insufficient to cause intravascular clotting, is frequent in cases where unboiled animal extracts are employed.

In nearly all experiments on the action of extracts of the posterior lobe of the pituitary the material used has been exclusively bovine on account of the facility

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[1] G. Etienne and J. Parisot, *Journ. de physiol.*, 1918, p. 1055.

[2] J. Parisot, " Pression artérielle, etc.," Paris, 1908.

[3] R. Porak, " Les glandes surrénales et l'hypophyse," 1922.

[4] The following works deal with the effects which have been observed in man : others will be alluded to under the action on different organs : F. Golla, *The Lancet*, 1902 ; A. Delille, Thèse, Paris, 1909 ; W. Blair Bell, *Brit. Med. Journ.*, 1909, and " The Pituitary," 1919 ; H. Claude et A. Badouin, *C. r. acad. sci.*, cliii., 1911 ; N. S. Heaney, *Surg., Gyn., and Obstetr.*, xvii., 1913 ; J. S. Musser, *Amer. Journ. Med. Sci.*, cxlvi., 1913 ; L. Beco, *Presse méd.*, 1914 ; B. A. Houssay, " La accion fisiol., etc.," 1918 and 1922. The literature of the subject is given by Houssay.

[5] Crowe, Cushing, and Homans, *Johns Hopkins Hosp. Bull.*, xxi., 1910 ; Goetsch, Cushing, and Jacobson, *ibid.*, xxii., 1911 ; Harvey Cushing, " The Pituitary Body and Its Disorders," 1912.

[6] A. Conti and O. Curti, *Boll. d. l'accad. d. sci. med.*, 1906 ; Garnier and Schulmann, *C. r. soc. biol.*, lxxvii. 388, 1914.

[7] Mairet et Bosc, *Arch. de physiol.*, 1896.

with which large healthy ox-glands can be obtained in quantity. But Halliburton, Candler, and Sikes [1] obtained similar results from the human posterior lobe, and Herring [2] has shown that they are obtainable from the pituitary of all vertebrates, exception being made of the glands of elasmobranch fishes, in which certain differences—to be afterwards referred to—have been noticed.

According to Houssay the average weight of the whole gland of the ox is 2·4 grams; of the anterior lobe 2 grams; of the posterior 0·4 gram, *i.e.* about one-sixth of the organ. The posterior lobe of the ox contains approximately the same percentage of active material at all times of the year, so that the results obtained by making a standard extract of the posterior lobe are fairly comparable. Such an extract is therefore recommended for standardisation. The physiological effects generally employed as tests of the activity of an extract are: (1) that on an isolated cornu of the virgin uterus of the guinea-pig, and (2) that on the blood-pressure of the decerebrated cat or rabbit. These tests are known respectively as the "oxytocic" [3] and the "pressor" tests. They will be further discussed later (Chapters XXXV., XXXVI.).

Oral and subcutaneous administration of posterior lobe extracts has usually little or no immediate physiological effect, although the results of intramuscular injections may be well marked. Nevertheless P. Hamill [4] noticed that administration by the mouth to cats in full digestion was followed by certain effects on the intestine and uterus.

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[1] *Op. cit.*, 1909.

[2] *Op. cit.*, 1908.

[3] ὀξυς, quick; τόκυς, birth.

[4] *Proc. Roy. Soc. Med.*, xiv., 1921. See also Rees and Whitehead, *Amer. Journ. Physiol.*, lxv. 90, 1923. These authors find that the principle which stimulates the uterus is not destroyed by the intestinal enzymes.

CHAPTER XXVII

THE PITUITARY BODY (*continued*)

Action of Posterior Lobe Extracts on the Circulatory System

Action on the Heart

Action on the Heart in Situ.—The effect of intravenous injection of posterior lobe extract upon the heart is quite different from that of adrenaline. For, whereas adrenaline—owing to its stimulating influence on sympathetic end-substance—causes marked acceleration, the pituitary autacoid often, but not always,[1] causes slowing. In chloralosed dogs this is very marked. The slowing is not entirely due to a reflex through the vagi produced by the rise in blood-pressure. For even with the vagi cut there may still be slowing, although less than when the vagi are intact. The effect is abolished by atropine.[2] Large doses of the extract are said to affect the conductivity of the A–V bundle, so that the ventricle may then beat more slowly than the auricle ;[3] the beat is, however, strengthened so that no fall of blood-pressure is produced. The slowing is not due to a paralysing effect on the cardiac sympathetic nerves, for these will still cause acceleration if stimulated when the heart is slowed by pituitary.[4] Pituitary extract has the effect of at first diminishing and afterwards increasing the output of the heart in mammals.[5]

Effect on the Isolated Heart.—The effect of the extract upon the isolated mammalian heart is to diminish both the force and the rate of its contractions.[6] This effect can be abolished by atropine. It is more marked upon the auricles than upon the ventricles, but appears to affect both. In the isolated entire frog-heart also Herring[7] obtained diminution in force and rate of the beats, and found the effect to be abolished by atropine, so that after this drug, pituitary extract produced augmentation and acceleration. From this it would appear that the nerve-endings in the auricle are affected, those of the

[1] *Cf.* fig. 115 in which there is no cardiac slowing perceptible, although an increase in force of the beats is very evident.

[2] L. Beco and L. L. Plumier (*Bull. acad. roy. de méd. de Belg.*, 1913) found the slowing of the heart to be abolished by vagus section or atropine ; if the vagi were previously cut the resulting acceleration was counteracted by injection of the extract.

[3] H. Claude and R. Porak ; also H. Claude, R. Porak, and D. Routier, *C. r. soc. biol.*, lxxiv. 205, 360, 1913.

[4] G. Mattirolo and C. Gamma, *Pathologica*, vi., 1914.

[5] C. Tigerstedt and V. Airlie, *Skand. Arch. f. Physiol.*, xxx., 1913, and xxxi., 1914.

[6] L. Beco and L. L. Plumier, *op. cit.* ; Resnik and Geiling, *Journ. Clin. Invest.*, i. 217, 1925.

[7] *Journ. Physiol.*, xxxi., 1904.

vagus the more powerfully: when these are paralyzed by atropine the effect on the sympathetic shows itself.

In the isolated frog-ventricle perfused with Ringer's fluid the addition of pituitary extract to the perfusion fluid was found by Herring to cause, even with moderate doses, augmentation with acceleration, while with strong doses not only was the muscular tone increased, but the contractions succeeded one another so rapidly as to run together. This result is, however, not produced by the pressor autacoid, for Hogben finds that extracts of pituitary from which this has been removed by absolute alcohol have no effect on the frog-heart. It must, therefore, be due to some other factor.

In birds (duck) the extract augments both auricular and ventricular contractions, whether the vagi are cut or intact, to about the same extent; whereas adrenaline affects the auricles only. According to Noël Paton and A. Watson, the pituitary and suprarenal autacoids have an antagonistic action upon the duck's heart.[1]

Action on Arteries

Intravenous injection of aqueous (Ringer) extract of posterior lobe causes a great rise in pressure in the systemic arterial circulation (figs. 115, 116);[2] this may be accompanied by a fall in the pulmonary system,[3] but frequently there is no effect on the pulmonary vessels, or there may be a distinct rise (fig. 120).

This "constrictor" or "pressor" effect in the aortic system may often be seen to be preceded by a depressor or dilator effect. This dilatation is normally only slight but sometimes considerable (fig. 117). When well marked it is accompanied by a rise in the pulmonary pressure. The effect of a second dose administered intravenously within a short time—half an hour or so—of the first is to cause a marked fall of pressure in the aortic and a rise in the pulmonary system (fig. 118); this can be repeated a number of times. The aortic fall is usually, but not always, followed by a slight rise, due to subsequent contraction of vessels (figs. 116, 118).

While the above statements as to the effects of the posterior lobe extract on blood-pressure apply to the anæsthetised cat—whatever the anæsthetic employed—a different result is obtained with dogs anæsthetised with chloralose. This drug appears to have the effect of reversing the influence of the pressor substance, so that intravenous administration of the extract to a chloralosed dog causes a very distinct and prolonged fall of blood-pressure, which may or may not be preceded by a transient rise. The fall in this case is not due to the histamine-like constituent, for it is seen when a preparation is employed which has been thoroughly extracted with alcohol; it is caused by a slowing of the heart's action. The slowing of the heart is abolished by atropine (but not entirely by vagal section); it may occur also with morphia

[1] *Journ. Physiol.*, xliv., 1912.

[2] Oliver and Schafer, *op. cit.*, 1895; Schafer and Vincent, *op. cit.*, 1899.

[3] C. J. Wiggers, *Arch. Int. Med.*, viii., 1911, xxiv., 1919; and L. Hallion, *C. r. soc. biol.*, lxxv., 1914. A fall is more common in the rabbit than in the dog or cat.

anæsthesia, but less distinctly, and here also it is abolished by atropine (fig. 121).

The reversal of effect in the dog caused by chloralose appears to account for the divergence of statements by different authors as to the result of administration of the extract on blood-pressure. *E.g.* Houssay,[1] who seems always to have used chloralose for anæsthetising dogs, almost invariably obtained a fall instead of the rise which usually occurs when morphia is employed.

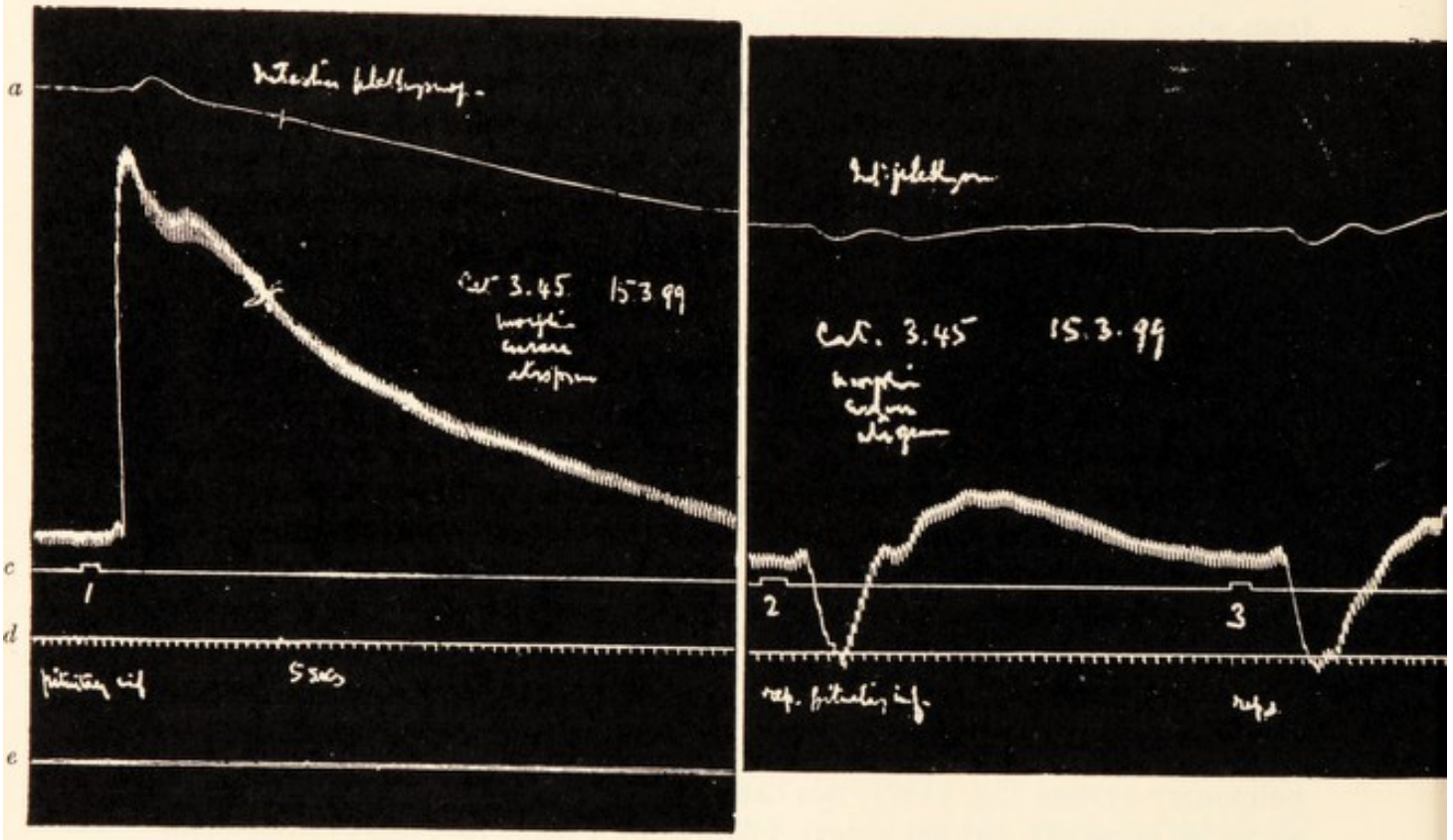

FIG. 116.—Tracing, taken on a very slowly moving surface, to show the effect of successive intravenous injections of extract of posterior lobe of ox-pituitary in a cat. (From Schafer and Vincent, *Journ. Physiol.*, 1899, vol. xxv.) The tracing has been reduced in reproduction.

1, first injection; 2, 3, second and third injections. *a*, tracing of intestinal plethysmograph; *b*, blood-pressure; *c*, signal; *d*, time in five-second intervals; *e*, abscissa of blood-pressure.

The effect of the first injection is to produce a rapid rise of arterial pressure to a maximum, followed by a gradual fall to the original level. The fall is arrested for a short period by a second slight rise. The large oscillations of pressure in the pulsations on the fall of the curve are due to slowing of the pulse-rate. The effect of the "repeat" injections is to cause in each case a marked fall followed by a gradual after-rise. Atropine had been administered, so that the fall is not due to choline, the effect of which is abolished by atropine. It is probably due to histamine (see text).

Fröhlich and Pick [2] state that pituitary extracts remove the paralysis of sympathetic vasomotors which is caused by ergotoxine, but Cow was unable to confirm this. They also describe dilatation of perfused frog-vessels, but Oliver

[1] *Op. cit.*, 1918.

[2] *Arch. exper. Path. u. Pharm.*, lxxiv., 1913.

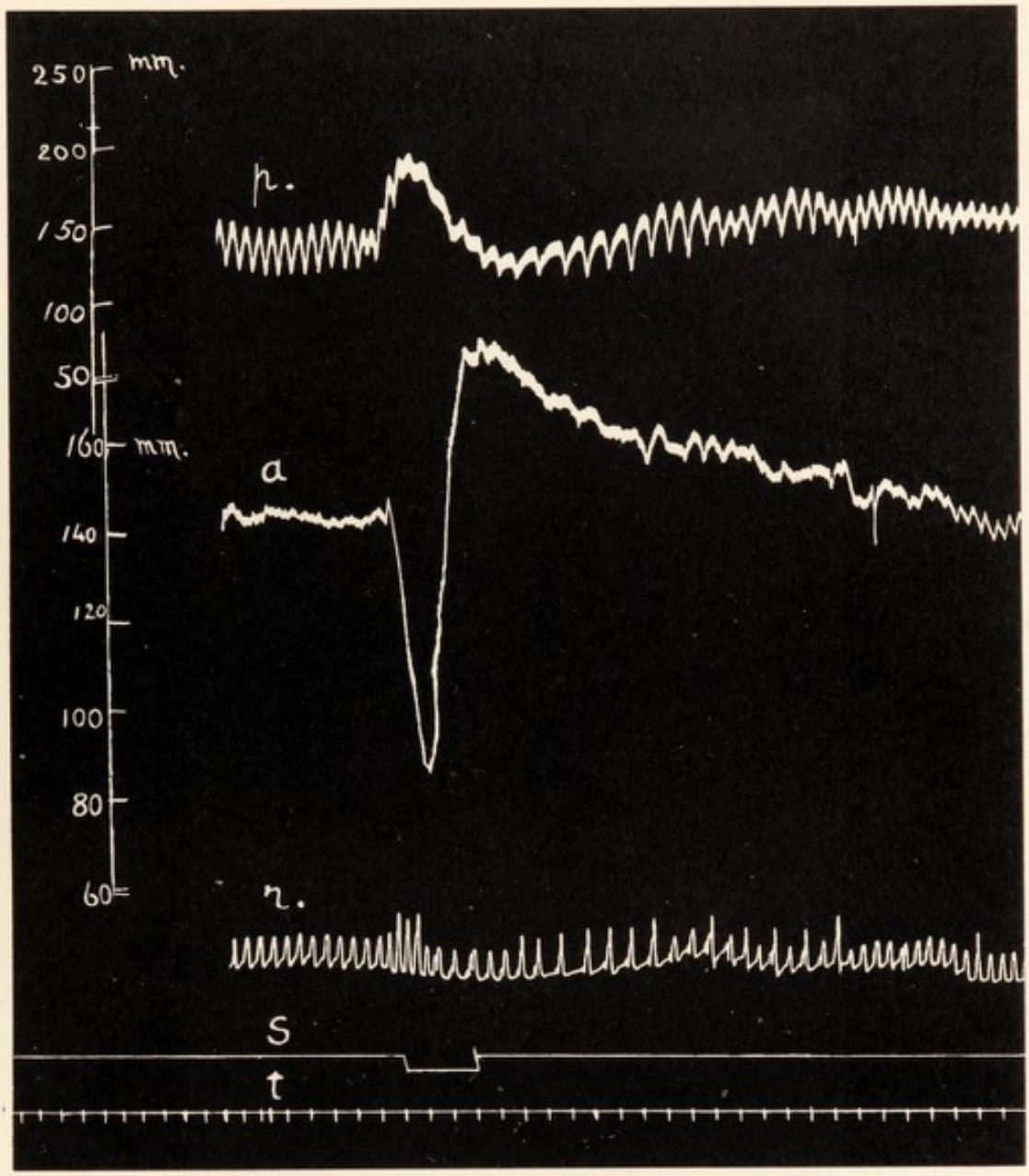

Fig. 117.—Tracing showing the effect upon pulmonary pressure, aortic pressure, and respiration of a first dose representing 5 mg. of dry posterior lobe of ox-pituitary extracted with Ringer's solution, not previously extracted with alcohol (cat, anæsthetised with chloralose).

Notice the well-marked fall of aortic pressure (due to the histamine-like depressor constituent) which precedes the rise (caused by the pressor autacoid). In the pulmonary artery a rise of pressure is seen to accompany the fall in the aortic system. During the rise in the latter the pulmonary pressure shows a slight fall. The respirations are rendered somewhat irregular, but the effect is small.

p, pulmonary pressure (water manometer); *a*, aortic pressure (mercury manometer); *r*, respirations; *s*, signal of injection; *t*, time in ten-second intervals. [The same lettering is used for figs. 118 to 121.] The scales of pressure shown in this figure—the upper in mm. of water for the pulmonary pressure, the lower in mm. of mercury for the aortic—apply also to the tracings in figs. 118 and 119.

The pulmonary pressure was recorded by the method described by Sharpey-Schafer in the *Quart. Journ. Exper. Physiol.*, xii. 133, 1919. After the introduction of the cannula into the pulmonary artery, the chest was sewn up with the lungs distended, and the animal then respired naturally, the respirations being recorded by tambours. [Figs. 117 to 121 are from a paper by Sharpey-Schafer and Macdonald to appear in the *Quart. Journ. Exper. Physiol.*, xvi., 1926.]

and Schafer and most subsequent observers have obtained marked constriction with decoctions prepared directly from fresh glands.[1]

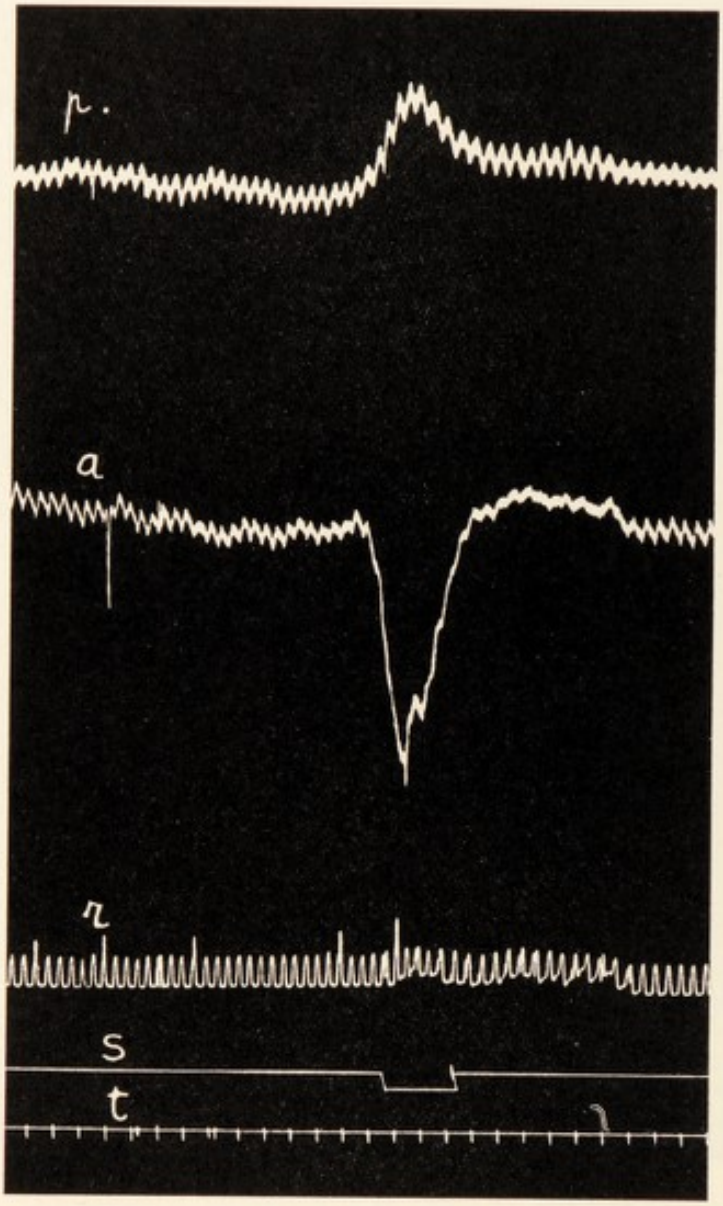

Fig. 118.—Tracing showing the effect of a subsequent dose of the same extract on the same cat as was used in the last experiment; the repeat dose followed the first dose within a few minutes.

There is now merely a fall in the aortic pressure followed by a slight rise, but this is quite different from that caused by the pressor substance, as is shown by comparing it with the effect of the alcohol-extracted material (fig. 120). The aortic fall is accompanied by a pulmonary rise. The respirations are but little affected. There is complete immunity established to the stimulating action of the pressor constituent; this immunity persisted for more than an hour. The depressor effect of the "repeat" dose is exactly paralleled by the effect caused by histamine (fig. 119, B) and by that of an alcohol extract of posterior lobe (fig. 119, A).

[1] Perhaps the preparation used by Fröhlich and Pick contained an unusual amount of histamine. Commercial preparations should, as a rule, be avoided in physiological investigations, since their mode of preparation or additions made to them for keeping purposes may affect the result.

With perfusion of the "surviving" vessels, the extract usually causes contraction of pulmonary vessels [1] as well as of aortic. With such perfusion there is also often seen a tendency to produce rhythmic contractions in the vessels of both systems. The action of pituitary extract upon blood-vessels is not affected by prior administration of ergotoxine.

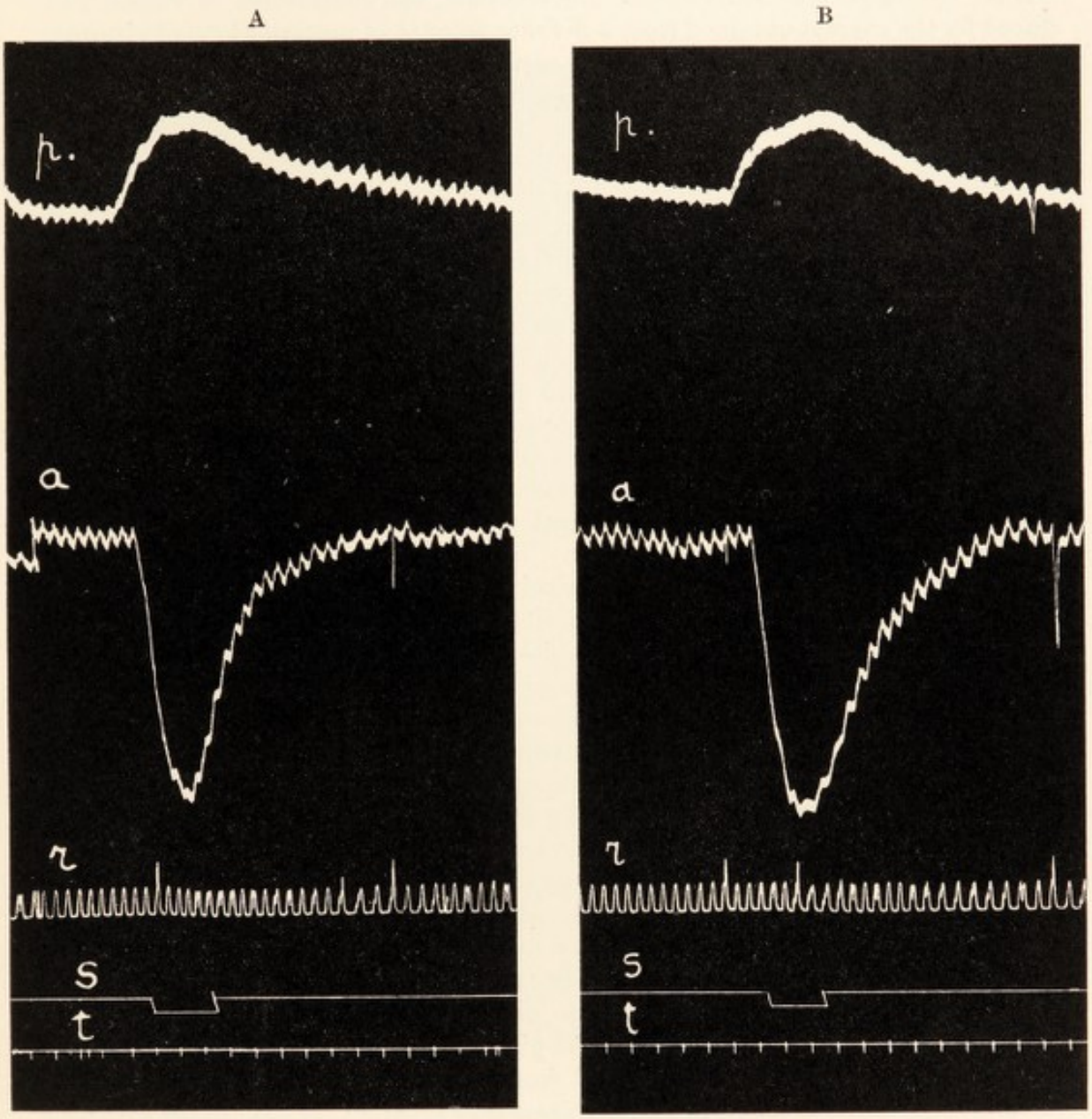

FIG. 119.—Tracings from the same cat taken at intervals of five minutes after that shown in fig. 118 showing—

A, the effect of an intravenous injection of an extract in Ringer obtained from the same preparation of bovine posterior lobe, but using only the portion soluble in absolute alcohol. At the place marked by the signal 2 mg. of the extract dissolved in 1 c.c. Ringer was injected.

B, the effect of an intravenous injection of 0·2 mg. of histamine (ergotamine ~~chloride~~). It will be seen that the effects of A and B are identical, and are similar to those caused by the "repeat" dose of the gland substance, which had not been previously extracted by alcohol (fig. 118).

[1] R. J. S. M'Dowall, *Proc. Physiol. Soc.*, p. i, in *Journ. Physiol.*, lv., 1921.

L. Mummery and W. L. Symes [1] found the pressor effect to last longer in decerebrated than in anæsthetised animals. It lasts much longer than the similar rise caused by adrenaline. Nevertheless, the contraction of vessels produced by the extract obtained from a definite amount of posterior lobe of pituitary is much less than that caused by the extract of a similar weight of suprarenal medulla. This does not necessarily mean that the active principle is weaker, but may be explained by assuming that there is less of it at any one time in the gland. There is indeed reason to believe that when obtained isolated in a condition of purity it will be at least as active, weight for weight, as adrenaline.[2]

Schafer and Vincent concluded that there are two antagonistic principles in posterior lobe extracts, one tending to cause constriction of vessels, the other dilatation. The latter they found to be soluble in alcohol. In some way not well understood the effect of the first dose of the constricting or pressor principle is to produce a refractory condition, which lasts—gradually passing off—for some time, the duration depending upon the original dose. This phenomenon was observed by Howell.[3] The term "tachyphylaxis" [4] has been applied to it. It is not seen in rabbits nor in decerebrated cats and dogs, although always occurring in intact anæsthetised cats, and to a less extent in dogs.[5] Schafer and Vincent [6] found that if the dry posterior lobe substance is first exhaustively extracted by absolute alcohol the depressor effect is not obtained when the dried residue (which now contains only a hormonic or pressor principle) is extracted with water or saline solution (see fig. 120, A); whereas the residue from the alcoholic extract yields to water or saline a chalonic substance which causes inhibition of the tonic contraction of the vessels and hence a pure depressor action which we now know to be exactly similar to that caused by histamine (fig. 119). They considered that this observation supported their view that the posterior lobe contains two autacoid principles acting antagonistically upon the vessels, and probably upon other organs. This view has been criticised by subsequent writers (*e.g.* Abel), who have held that the contrary effects are caused by the same autacoid, its action varying according to the physiological conditions of the tissue. The subject will be discussed more at length when the chemical constituents of the posterior lobe are considered. It will be sufficient to say here that recent work tends to support the view that the posterior lobe of the gland yields more than one autacoid, and that amongst these there is a hormonic or pressor and a chalonic or depressor principle; the former is peculiar to the gland, the latter is probably histamine.

O. Paukow [7] states that if a second dose is given from one to five days after a first dose the effect of the second is, *ceteris paribus*, greater than that of the first both upon the circulation and respiration. But the difficulty of experimenting under precisely similar conditions in the two cases renders the result doubtful.

The extract of posterior lobe tends to produce contraction of most arteries, including the aorta and its principal branches, and the arteries of the heart,[8]

[1] *Proc. Physiol. Soc.*, p. lvi., in *Journ. Physiol.*, xxxvii., 1908.
[2] J. J. Abel, *Harvey Lectures*, 1924.
[3] *Op. cit.*, 1898. [4] ταχύς, quick, and φύλαξις, protection.
[5] L. T. Hogben and W. Schlapp, *Quart. Journ. Exper. Physiol.*, xiv. 229, 1924.
[6] *Op. cit.*, 1899. *Cf.* L. T. Hogben, W. Schlapp, and A. D. Macdonald, *Quart. Journ. Exper. Physiol.*, xiv. 303, 1924. [7] *Arch. f. d. ges. Physiol.*, cxlvii., 1912.
[8] H. H. Dale, *Biochem. Journ.*, iv., 1909; Susanna and Bonis, *Centrlbl. f. Physiol.*, xxiii., 1909; J. Pal, *ibid.*; D. Cow, *Journ. Physiol.*, xlii., 1911; Argyle Campbell, *Quart. Journ. Exper. Physiol.*, iv., 1911.

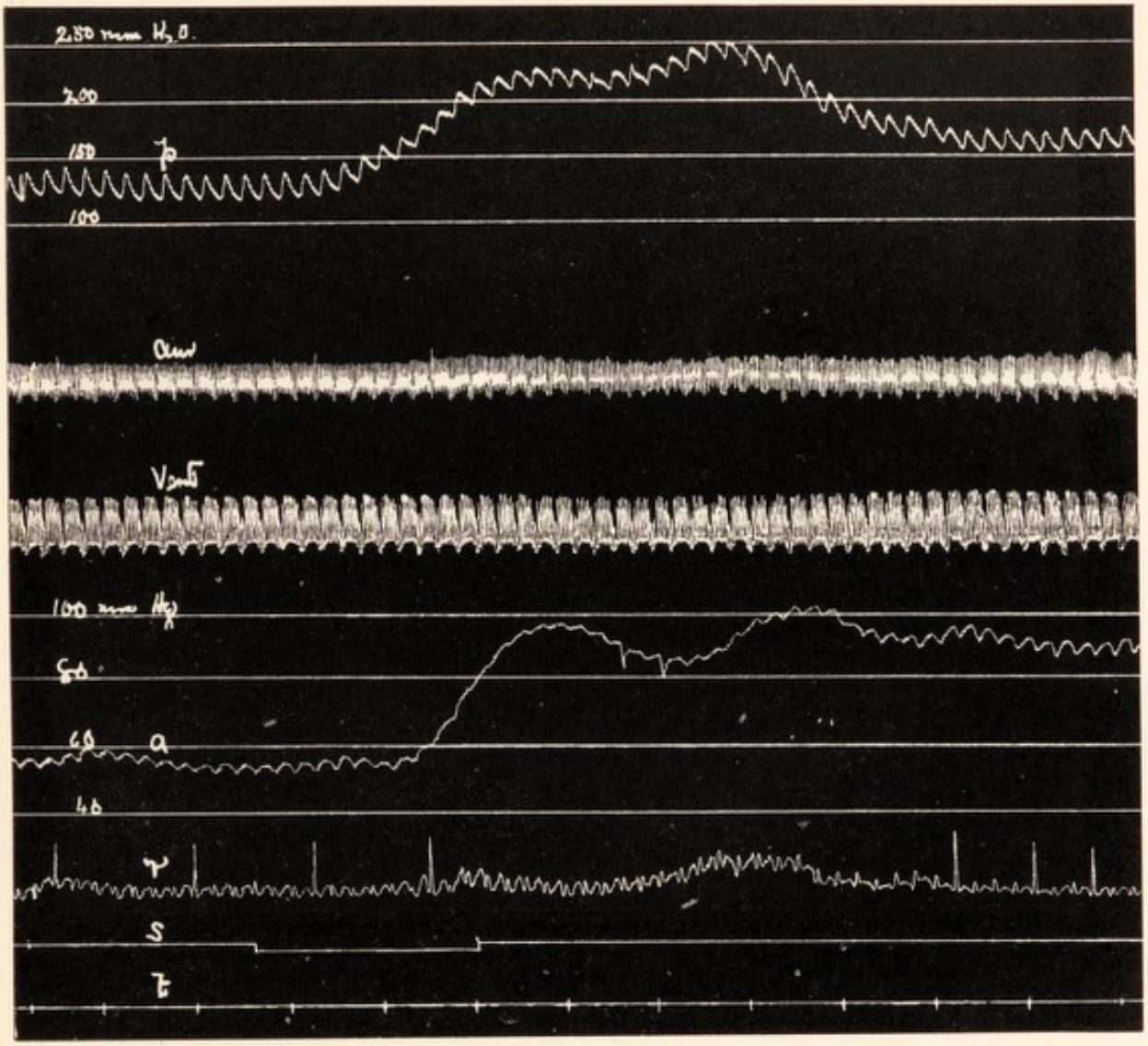

FIG. 120.—Effect of the injection into a decerebrated cat of an extract (in 1 c.c. Ringer) representing 5 mg. of dry bovine posterior lobe which had been extracted with absolute alcohol for six hours in a Soxhlet apparatus to remove the histamine-like substance.

In this experiment the thorax was left open and the heart-movements are recorded. The irregularities on the respiration-curve are caused by spontaneous movements of the diaphragm superposed on the record of the artificial respiration.

p, pulmonary pressure in mm. H_2O; *aur.*, record from auricle; *ventr.*, record from ventricle; *a*, aortic pressure in mm. Hg; *r*, respirations; *s*, signal of injection; *t*, time in ten-second intervals.

lungs,[1] and brain,[2] all of which are little if at all affected by adrenaline. But an important exception shows itself in the renal arteries, the contraction of which is diminished instead of being increased, so that the kidneys swell under the influence of the extract while other organs shrink.[3]

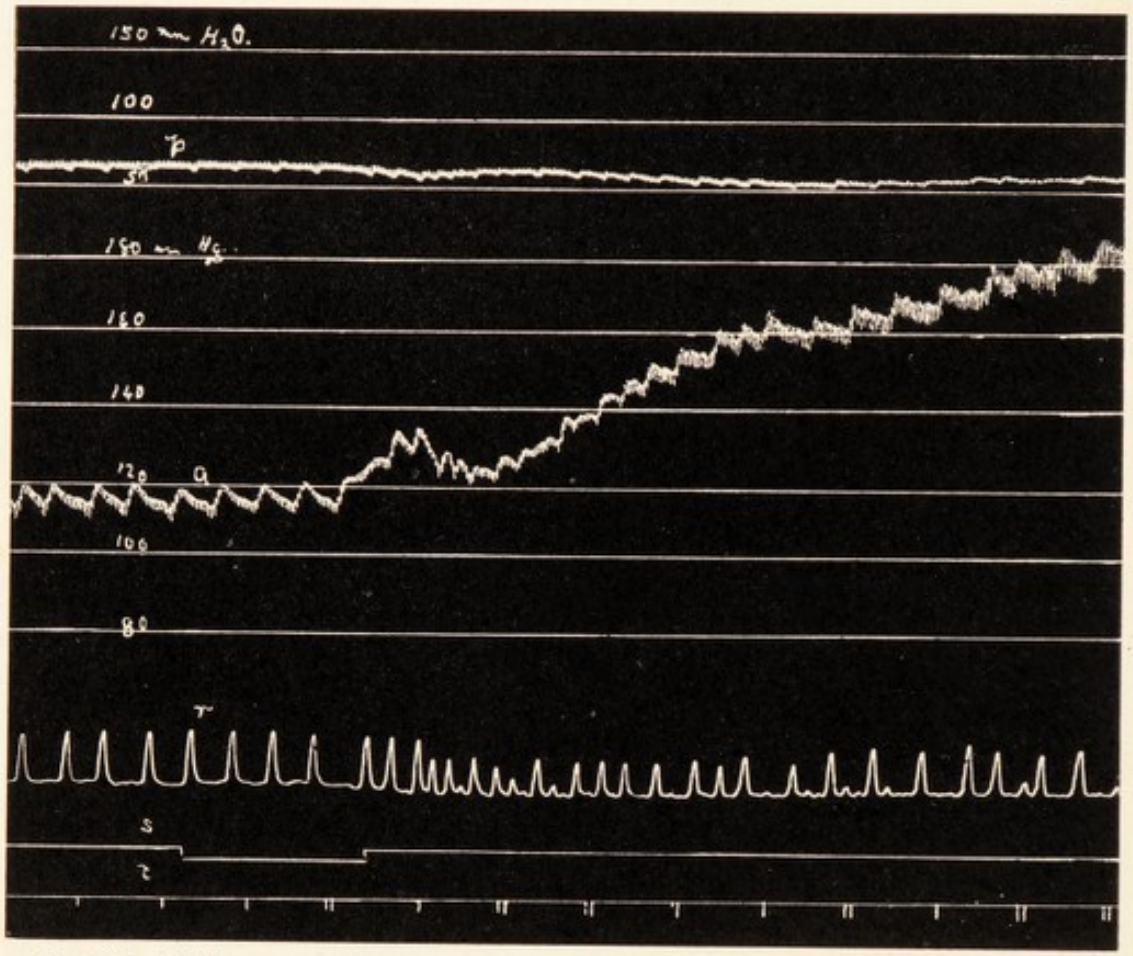

FIG. 121.—Pulmonary and aortic pressures and respiration of dog (8 kilo). Effect of injecting 5 mg. of alcohol-extracted (*i.e.* histamine-free) post-pituitary of ox. Lettering as in figs. 117 to 120. Upper scale shows mm. H_2O: lower scale mm. Hg. This was a second dose: the effect of the first was larger, but it was insufficient to produce complete immunity. (Anæsthetized with morphia, followed by atropine.)

Houghton and Merrill found on perfusing the kidney with Ringer to which pituitary extract was added that contraction was first produced but that this

[1] C. J. Wiggers, *Arch. internat. Med.*, viii., 1911, and xxiv., 1919; *Amer. Journ. Physiol.*, xxxiii., 1914. Wiggers has suggested its use in hæmoptysis, in which it might be administered as a spray. But the effect on the pulmonary vessels is very slight.

[2] L. Fraenkel, *Zeitschr. f. exper. Path.*, xiv., 1914. But H. Florey (*Proc. Physiol. Soc.*, p. lxxxiii., in *Journ. Physiol.*, lix., 1925) obtained no effect on the vessels of the brain from pituitary extract placed directly on the pia mater, the vessels being observed with a microscope. Adrenaline also produced no perceptible result.

[3] Schafer and Herring, *Phil. Trans.*, cxcix., 1908; Argyle Campbell, *Quart. Journ. Exper. Physiol.*, iv., 1911. J. Pal (*Wien. med. Wochenschr.*, 1909) found that pituitary extract causes contraction of a ring from the proximal part of the renal artery and relaxation of one from the distal part. According to D. Cow, this difference is not peculiar to the arteries of the kidney, but occurs with other viscera (*Journ. Physiol.*, xlii., 1911).

rapidly passed off and was followed by swelling.[1] Richards and Schmidt [2] found that pituitary extract at first stopped the circulation in the glomeruli of the frog-kidney, but this action soon became reversed and many more glomeruli became active.

It was found by Argyle Campbell as the result of perfusion experiments on various organs that an extract of posterior lobe of pituitary may cause either contraction or relaxation of the arterial musculature, the result being dependent on the pH of the Ringer solution used. When contraction was caused it always lasted longer than that caused by adrenaline. As for the individual vessels, Campbell found that the coronaries are usually constricted : the renal vessels—both arteries and veins—relaxed.

The pressor principle occurs in extracts from the gland quite early in fœtal life : in the bovine fœtus at about the eighth week,[3] in the pig at about ten weeks.[4] The earliest period in man has not been determined, but it is probably present at the same age as in the bovine fœtus. Keene and Hewer obtained an extract from an eight-week human fœtus which produced expansion of melanophores in the frog [5] although they were not able to get sufficient material to determine a pressor effect in the mammal.

Abel and Geiling [6] obtained both pressor and oxytocic effects from extracts of the nervous tissue of the infundibulum close to the stalk, whereas extracts of brain substance itself have the effect of lowering blood-pressure.

In the bird [7] (duck and fowl) extract of posterior lobe—even after prolonged alcohol extraction [8]—always produces a fall of blood-pressure in the first dose instead of a rise as in the mammal. The fall is antagonised by adrenaline and barium chloride and is abolished by atropine. There is occasionally an after-rise in the fowl. Tachyphylaxis does not occur.

In the tortoise Hogben and Schlapp [9] record also a fall instead of a rise ; it is relatively small and gradual. In the frog there is a slow rise of pressure and no fall.

It seems evident that the effect upon the blood-pressure in the bird must be due to a special autacoid.

Action on Veins

The musculature of the veins also undergoes contraction under the influence of posterior lobe extract when directly applied. But with intravascular injection there may be a fall of pressure in the venous system, due to constriction of the

[1] *Journ. Amer. Med. Assoc.*, li., 1908.
[2] *Amer. Journ. Physiol.*, lix. 489, 1922. See also Richards and Plant, *ibid.*, p. 191.
[3] C. P. M'Cord, *J. Biol. Chem.*, xxxiii., 1915.
[4] D. Lewis, *Journ. Exper. Med.*, xxiii., 1916.
[5] M. F. Lucas Keene and E. E. Hewer, *Lancet*, July 19, 1924.
[6] *Op. cit.* A slight pressor effect from extracts of the floor of the third ventricle was described by Houssay and Giusti (*Argent. med.*, 1912).
[7] Noël Paton, *Journ. Physiol.*, xliv., 1912.
[8] Hogben, *Quart. Journ. Exper. Physiol.*, xv., 1925.
[9] *Ibid.*, xiv. 229, 1924.

arteries and capillaries. This applies to the portal vein, in which the pressure falls during the arterial rise and recovers as the arterial pressure comes down.[1]

Action on Capillaries

A. Krogh and P. B. Rehberg[2] found that the addition of a commercial pituitary extract (pituitrin) to Ringer's fluid containing 3 per cent. of gum arabic causes a local contraction of the capillaries of the frog-web and prevents the œdema which comes on in a short time if such fluid is employed without pituitrin. This effect on the capillaries is obtained with a solution of 1 in 500,000, a strength which does not affect the arteries. On changing over to Ringer without pituitrin the capillaries dilate and œdema commences. Krogh expresses the opinion that this is a normal function of pituitary secretion, and that its presence in the blood serves to regulate capillary action.

Action on the Spleen

The spleen is contracted under the influence of intravascular injections of pituitary extract, and the volume of the organ thereby diminished.[3] This effect is produced by the action of the extract upon the splenic vessels. The splenic capsule is not contracted by it. A detached spleen suspended in warm Ringer solution does not react on the addition of pituitary extract.[4]

[1] F. A. Bainbridge and O. W. Trevan, *Journ. Physiol.*, li., 1917.

[2] *C. r. soc. biol.*, lxxxvii., 1922. See also A. Krogh, "The Anatomy and Physiology of the Capillaries," 1922.

[3] Magnus and Schafer, *Journ. Physiol., Proc. Physiol. Soc.*, xxvii., 1901–1902.

[4] S. de Boer and D. C. Carroll, *Journ Physiol.*, lix. 381, 1924.

CHAPTER XXVIII

THE PITUITARY BODY (*continued*)

Action on Plain Muscle of Viscera

Alimentary Canal.—Blair Bell and Hick [1] noticed that strips from the musculature of the small intestine are stimulated by posterior lobe extract. The same result is obtained with strips of muscular tissue from the stomach and œsophagus as well as from the gall-bladder.[2] It is also seen with the organs *in situ* on injecting the extract into a vein. The contrary result has also been described, viz. relaxation or inhibition.[3] A. W. Young [4] found that the extract may produce not only a general increase of tone of the intestinal strip but also a striking increase in the force of the "pendulum" contractions (fig. 122A). The action of posterior lobe extract on the intestinal strip is, in any case, far less pronounced than on the uterus. Moreover, A. D. Macdonald [5] finds that the effect of extracts which have been made from posterior lobe previously extracted with alcohol is no greater but may be even less than those made from other (indifferent) organs—such as heart and brain—whereas the histamine-like substance of the alcoholic extract has a powerful action on intestinal muscles (fig. 122B). The extract cannot, therefore, be looked upon as a specific for stimulating plain muscle in general, as it unquestionably can for uterine muscle. The principle which acts upon intestinal muscle is soluble not only in water but also in alcohol and ether; it is, moreover, alkali-stable. In these respects it differs from the specific oxytocic and pressor principles; there is little doubt that it is histamine.

[1] *Brit. Med. Journ.*, i. 517, 1909; Blair Bell, *ibid.*, ii. 1609.

[2] B. A. Houssay (frog, rabbit), *Argent. med.*, 1911; F. Bottazzi (fowl), *Arch. ital. de biol.*, lxv., 1917; J. C. Galan, *C. r. soc. biol.*, 1920. B. Zondek, *Arch. f. d. ges. Physiol.*, clxxx., 1920, obtained a similar result on the intestine *in situ*. For observations by X-rays on the effect of the extract on the movements of the stomach and intestine in man, see H. K. Pancoast and A. H. Hopkins, *New York Med. Journ.*, cv., 1917. Other literature in Houssay, "La accion fisiol., etc.," *op. cit.*

[3] Beyer and Peter, *Arch. f. exper. Path. u. Pharm.*, lxiv., 1911; Parisot and Mathieu, *C. r. soc. biol.*, lxxvi., 1914; R. G. Hoskins, *Journ. Amer. Med. Assoc.*, lxvi., 1916; V. M. Shamoff, *Amer. Journ. Physiol.*, xxxix., 1916; J. A. Waddell, *ibid.*, xli., 1916; L. M. Degener, *ibid.*, lx., 1922. In the dog Galan (*op. cit.*) obtained as a first effect relaxation of the pylorus.

[4] *Quart. Journ. Exper. Physiol.*, viii., 1915.

[5] *Ibid.*, xv., 1925, and *Proc. Physiol. Soc., Journ. Physiol.*, 1925. Degener (*op. cit.*) ascribed a stimulating action to extracts of anterior lobe also when applied to the isolated intestinal strip, but the effect was less than that of posterior lobe. Some effect was obtained with other organ extracts, but less than with posterior lobe extract. Macdonald's results do not corroborate this statement.

Administered parenterally, as by subcutaneous or intramuscular injection, the action of whole posterior lobe extract in increasing intestinal tone is generally admitted: this action is, no doubt, due to the histamine it contains. It is in common use by clinicians in cases of loss of intestinal tone as the result of abdominal operation and shock from whatever cause, its effect being often striking.

W. E. Dixon [1] states that the (whole) extract, while increasing the tone of the small intestine, diminishes that of the large intestine. Nevertheless under some

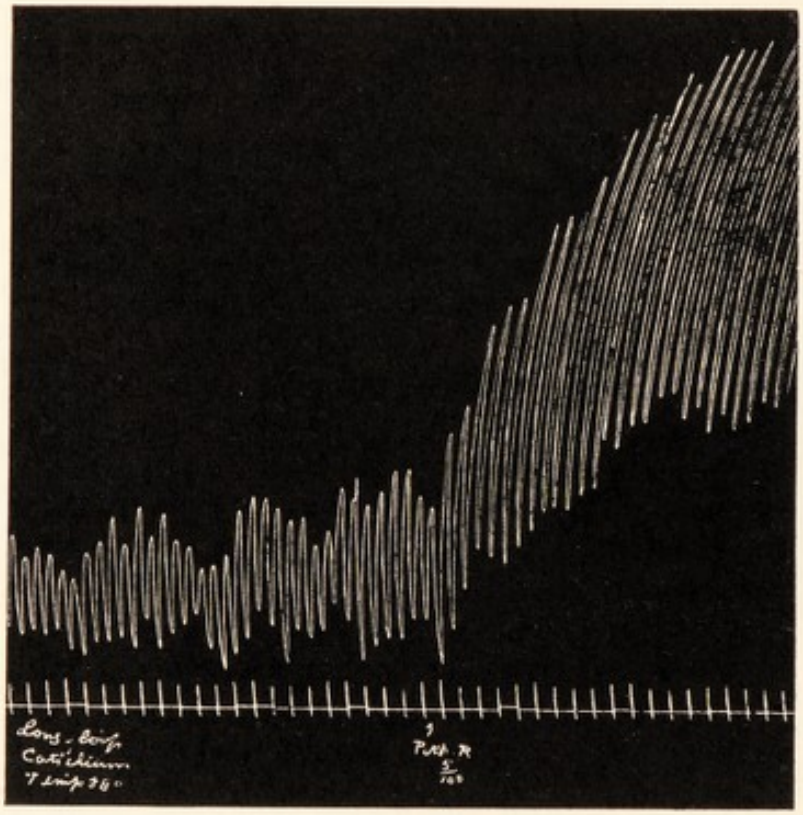

FIG. 122A.—Tracing showing the effect upon a longitudinal strip of intestinal muscle (from ileum of cat) of the addition of extract of bovine posterior lobe, not previously extracted with alcohol, to Ringer's fluid in which the muscle was suspended. (A. W. Young.)

At the arrow a small quantity of the extract was introduced. This produced both an increase in force of the rhythmic contractions and a general increase of tone of the muscle.

circumstances commercial preparations undoubtedly cause defæcation;[2] this is probably due to their containing a considerable amount of the histamine-like principle.

Urinary and Generative Passages.—The *urinary bladder*,[3] both *in situ* and in surviving strips, is powerfully contracted by the extract, and the same is

[1] *Journ. Physiol.*, lvii., 1923.

[2] This seems to have been first noticed by Foderà and Pittau (*Arch. ital. de biol.*, lii. 370, 1909), and by Blair Bell (*op. cit.*, 1909).

[3] L. v. Frankl-Hochwart and A. Fröhlich, *Arch. f. exper. Path. u. Pharm.*, lxiii., 1910.

the case with the isolated *ureter* and with the *m. retractor penis* of the dog.[1] J. A. Waddell [2] obtained no effect on the *vas deferens*, although he got stimulation of the *uterus masculinus* in the rabbit.

The Uterus, Vagina, and Fallopian Tubes.—A very striking result is that which is obtained upon the uterus.[3] This, whether pregnant or non-pregnant, is strongly stimulated : the effect is obtainable both when the extract is injected into the circulation or when it is applied to a " surviving " portion of uterus (fig. 123).[4] In the latter case a very minute dose will produce a powerful effect. On this account a cornu of the uterus of the virgin guinea-pig is the most generally used test-object for the physiological standardisation of pituitary

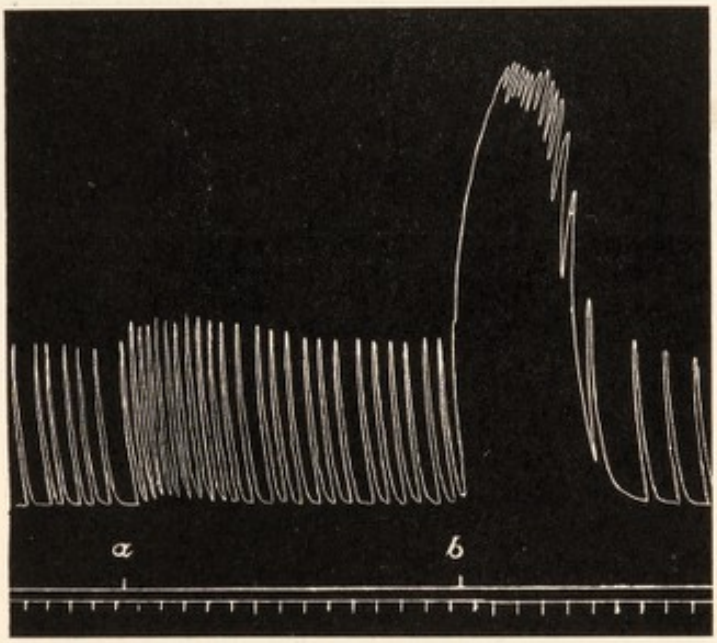

FIG. 122B.—Tracing showing the effect on muscle of cat's ileum (*a*) of extract of 5 mg. posterior lobe which had previously been extracted with absolute alcohol; (*b*) of 2 mg. of the alcohol extractive obtained from 25 mg. of the dry glandular substance. Time in minutes. The mode of conducting the experiment was similar to that shown in fig. 77. The tracing shows that the effect on intestinal muscle is caused by the histamine constituent and not by the " pressor " autacoid.[5]

extracts (fig. 124).[6] Its extreme sensitiveness contributes the chief objection to its use for this purpose, since it will react to a solution representing one part

[1] F. Bottazzi, *op. cit.*, 1916.

[2] *Journ. Pharm. and Exper. Therap.*, viii. and ix., 1916.

[3] H. H. Dale, *Journ. Physiol.*, xxxiv., 1906 ; *Biochem. Journ.*, iv., 1909 ; Blair Bell, *Brit. Med. Journ.*, 1909 ; P. T. Herring, *Quart. Journ. Exper. Physiol.*, viii., 1914 ; M. Itagaki, *ibid.*, xi. 40, 1917.

[4] Charteris, *Glasgow Med. Journ.*, lxxxvii., 1917, obtained contractions of "surviving" strips of human uterus, both non-pregnant and pregnant.

[5] Tracing made by A. D. Macdonald, not elsewhere published.

[6] Dale and Laidlaw, *Journ. Pharm. and Exper. Therap.*, iv., 1912 ; H. Burn and H. H. Dale, *Rep. Med. Res. Council*, 1922 ; E. E. Nelson, *Journ. Lab. and Clin. Med.*, viii., 1923 ; L. Hogben and de Beer, *Quart. Journ. Exper. Physiol.*, xv. 163, 1925. For a discussion of the uterine methods of standardising pituitary extracts, see M. J. Smith and W. T. M'Closky, *Hygienic Lab. Washington Bull.*, No. 138, 1924.

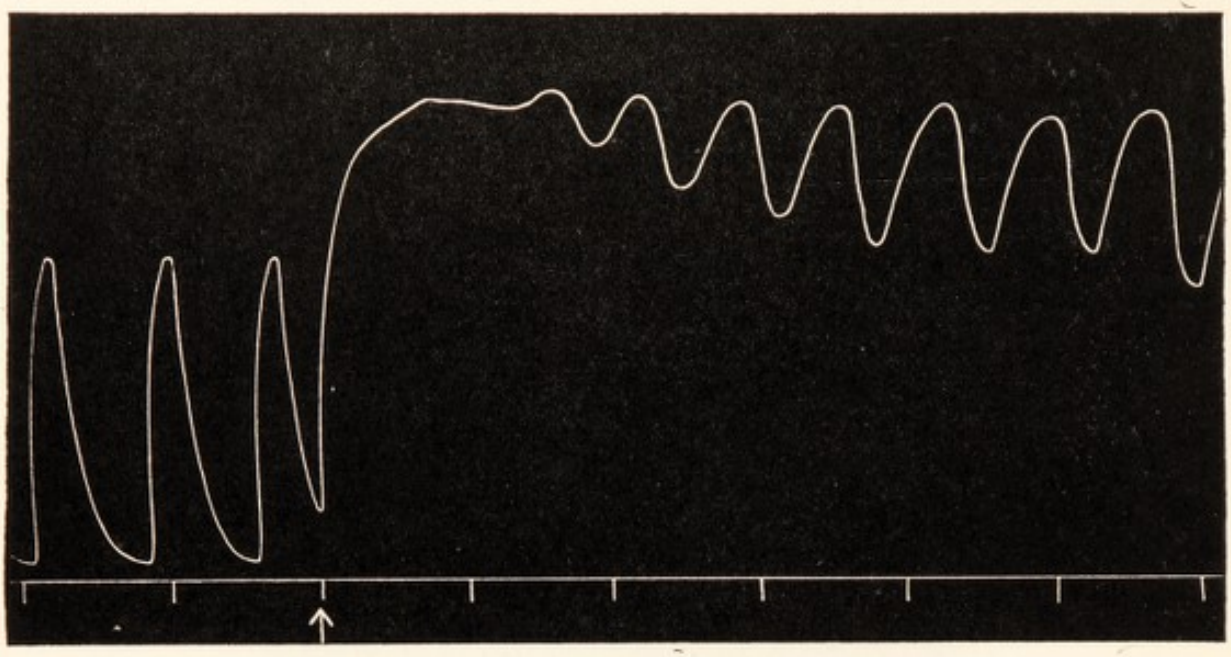

FIG. 123.—Tracing showing the effect on uterine muscle of adding extract of posterior lobe of ox-pituitary to Ringer-Locke fluid in which a cornu of rat's uterus was suspended. Time in minutes. (M. Itagaki.)

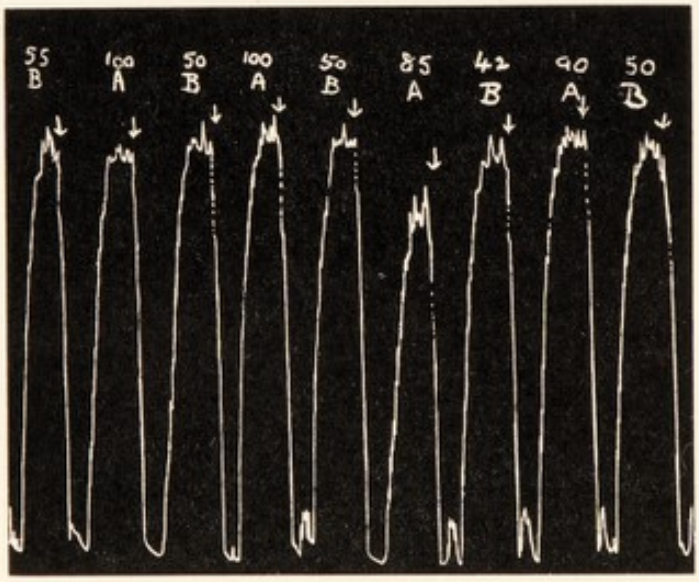

FIG. 124.—To illustrate the "uterus" method of estimating the oxytocic effect of an unknown extract (in this case one of pars intermedia of ox) by comparison with that of an extract of pars nervosa, the oxytocic strength of which had been previously ascertained. (Hogben and de Beer.)

The uterus of a virgin guinea-pig was used. The extract of pars nervosa (A) was of a strength 1 : 1100 ; that of pars intermedia (B) 1 : 112.

As shown in the tracing quantities of 0·55 c.c., 0·50 c.c., and 0·42 c.c. of B were added to the 125 c.c. Ringer solution in the uterus bath, and compared with the effects produced by the addition of 1·00 c.c., 0·90 c.c., and 0·85 c.c. of A.

The oxytocic ratio was found to be 1 pars intermedia : 5 pars nervosa. The corresponding blood-pressure ratio was 1 : 12.

of posterior lobe (bovine) to several million parts of Ringer's solution. Moreover, histamine, with which these extracts are often contaminated, has a similar action on the uterus of the guinea-pig—although less marked. On the other hand, the uterus of the rat is not affected by histamine and is less sensitive to minute amounts of pituitary than that of the guinea-pig. For both reasons it is for some purposes to be preferred.

The extract also causes contraction of the muscular tissue of the *vagina*, but not that of the *Fallopian tubes*.[1]

D. Cow [2] found that under certain conditions pituitary extract may *relax* the circular fibres of the uterus, and that previous treatment with pituitary extract may reverse the normal adrenaline effect.

The effect that extract of posterior lobe has upon the uterus has led to its use in promoting the expulsion of the uterine contents in parturition; it should, however, not be used until the os is fully dilated and there is no other obstacle to delivery. Otherwise the powerful contractions induced may lead to rupture of the uterus. Repeated administration during pregnancy may produce abortion, or at the end of pregnancy may initiate labour.[3] This subject will be again referred to when the therapeutic use of pituitary extract is considered.

According to Riddle [4] injection of posterior lobe extract into birds (ring-dove) causes the eggs to be laid prematurely.

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[1] J. A. Gunn, *Proc. Roy. Soc.*, B, lxxxvii, 1914.
[2] *Journ. Physiol.*, lii., 1919.
[3] Gallie and Scott, *Canadian Medical Monthly*, 1920.
[4] *Science*, liv., 1921.

CHAPTER XXIX

THE PITUITARY BODY (*continued*)

Action of Extracts of Posterior Lobe on Iris, Striated Muscle, Respiratory System, Blood, Cerebrospinal Fluid, and Lymphatic System

Action on the Iris

Injected into a vein, post-pituitary extract causes either no effect or contraction of the pupil, which quickly passes off.[1] This is different from the action of adrenaline, which produces dilatation[2]—a sympathetic action—although in the dog it has been noticed to cause constriction.[3] Instilled into the conjunctiva, pituitary extract usually causes dilatation of the pupil.[4] This dilatation was obtained by Pollock in 94 per cent. of his experiments. It was increased by previous section of the cervical sympathetic and the third nerve, and still more by removal of the superior cervical sympathetic and ciliary ganglia or by section of the post-ganglionic nerves. The contraction of the pupil which follows intravascular injection is ascribed by Pollock to a central stimulation, by the heightened blood-pressure, of the nervous centre regulating the sphincter pupillæ. If the third nerve is cut, dilatation is produced. W. Cramer[5] found that the excised eye of a frog shows dilatation of the pupil if placed in Ringer's solution to which posterior pituitary extract had been added, whereas in Ringer's solution without any addition, or with the addition of extract of anterior lobe, it exhibits constriction. This observation has been confirmed by subsequent authors.[6]

[1] H. H. Dale, *Biochem. Journ.*, iv., 1909; Frankl-Hochwart and Fröhlich, *op. cit.*, 1910. See also Fröhlich and Pick, *Arch. f. exper. Path. u. Pharm.*, lxxiv., 1913 (who employed ergotoxine with pituitrin); Houssay, *op. cit.*, 1911; Githens and Meltzer, *Journ. Pharm. and Exper. Therap.*, ix., 1917.

[2] Part I., p. 136.

[3] *Cf.* T. R. Elliott regarding the effect of adrenaline in the dog (*Journ. Physiol.*, xxxii., 1905).

[4] R. Argañaraz, *La sem. med.*, xx. 517, 1913; W. B. J. Pollock, *Brit. Journ. Ophth.*, March, 1920. This paper contains, besides original observations, a review of previous work.

[5] *Quart. Journ. Exper. Physiol.*, i., 1908.

[6] L. Borchardt, *Zeitschr. f. klin. Med.*, lxvi., 1908; J. Pal, *Zentrlbl. f. Physiol.*, xxiii., 1909; G. Bayer, *Wien. klin. Wochenschr.*, 1909; S. J. Meltzer, *Proc. Soc. Exper. Biol.*, ix., 1912. According to Bayer, the autacoid which dilates the frog pupil is alcohol-soluble, in which case it would not be the same as that which produces a rise of blood-pressure but is probably histamine.

Action on Striated Muscle

The effect produced by extract of posterior lobe on excised striated muscle of the frog is somewhat similar to that of adrenaline.[1] The onset of fatigue is deferred and the recovery of a muscle stimulated to complete exhaustion is accelerated.[2]

The muscle curve in mammals is very little or not at all affected by the posterior lobe autacoids,[3] nor have they any effect on the fibrillations produced when the nerve of a muscle is cut and allowed to degenerate, although adrenaline diminishes these fibrillations.[4]

Action on the Respiratory System

Extract of posterior lobe causes contraction of the muscular tissue of the trachea and bronchioles, acting therefore antagonistically to adrenaline.[5] According to Kolls and Geiling [6] this effect is due to histamine in the preparation; if this is removed little or no effect is obtained (as with intestinal muscle, see p. 225).

With regard to the movements of respiration, these become restricted in extent and generally rendered rather more rapid and somewhat irregular (see figs. 117 to 121). It must be stated, however, that a considerable dose is required to cause much effect. The respirations sometimes show a Cheyne-Stokes character. The effect on respiration lasts a shorter time than that on the circulation. The result is not affected by previous division of the vagi. The restriction of movement is sometimes preceded by deep respiratory movements. Whether these effects are caused by a direct influence on the respiratory centre or not is uncertain; in any case the respirations must be modified by the constriction of the bronchioles caused by histamine in the extract.[7]

Action on the Blood

Various observers have described changes in the number of erythrocytes and in the relative number of the several kinds of leucocytes following subcutaneous

[1] See Part I., p. 145.

[2] J. Joteyko, *Journ. méd. de Bruxelles*, 1903; B. A. Houssay, *op. cit.*, 1911 and 1918. Negative results have been obtained by some observers, but Houssay's records appear conclusive on this point.

[3] F. Bottazzi, *Arch. ital. de biol.*, lxv., 1916.

[4] J. N. Langley, *Journ. Physiol.*, li., 1917.

[5] P. L. Mummery and W. L. Symes, *Brit. Med. Journ.*, 1908; B. A. Houssay, *Presse méd.*, 1912, p. 1011; Dixon and Halliburton, *Journ. Physiol.*, l., 1916; J. Roca, *Journ. Pharm. and Exper. Therap.*, xviii., 1921.

[6] *Journ. Pharm. and Exper. Therap.*, xxiv., 1924.

[7] Besides the papers already enumerated the following may be referred to as bearing on this subject: H. Fühner, *Münch. med. Wochenschr.*, 1912; Fröhlich and Pick, *Arch. f. exper. Path. u. Pharm.*, lxxiv., 1913; Guggenheim, *Med. Klin.*, 1913; Nice, Rock, and Courtwright, *Amer. Journ. Physiol.*, xxxiv. and xxxv., 1914; B. A. Houssay, *Journ. de physiol.*, xvii., 1917; F. Roberts, *Journ. Physiol.*, lvii., 1923; Lewis, Mills, and Mathews, *op. cit.*

injection of posterior lobe extract, but it is doubtful if such action is specific, since changes of the same character are produced by extracts of other glands.[1] J. G. Priestley [2] noted a slight increase in the water and chlorides of the blood as a result of intramuscular injections. E. Ponder [3] found that the extract, when injected into the veins, diminishes the liability of the erythrocytes to hæmolysis by glycocholate of soda. But if the same test is applied to a suspension of isolated erythrocytes *in vitro* the result is negative.

Intravenous and hypodermic administration of the extract is found to increase the coagulability of blood. Extracts of anterior lobe have not the same effect.[4] The increase of coagulability is also seen when blood (man, rabbit) is mixed with extract of posterior lobe *in vitro*.[5]

The extract may be applied locally as a styptic in place of adrenaline. When so used its vaso-constrictor action is aided by the effect on blood-coagulability.

Possible Effects on the Secretion of Cerebrospinal Fluid and of Lymph

From a long series of experiments Dixon and Halliburton [6] came to the conclusion that pituitary extract has no specific effect on the secretion of cerebrospinal fluid, any apparent increase in the flow being due to dyspnœa from bronchial constriction and consequent increased intracranial pressure. In this way they explain the positive results of Weed and Cushing.[7] The correctness of this explanation has been demonstrated by F. C. Becht,[8] who has shown that the effect is purely mechanical and caused by expression of fluid from the skull by the rise of intracranial pressure : this being mainly conditioned by the venous pressure.

Although having no secretory action on cerebrospinal fluid, Becht has shown that the extract is undoubtedly a lymphagogue, for it increases the flow of lymph in lymph-vessels of other parts. This may, however, not be a secretory effect, but is perhaps due to a stimulation of the rhythmically acting musculature of the lymphatics.

[1] R. Feissly, *Presse méd.*, 1922.

[2] *Journ. Physiol.*, lv., 1921. This was perhaps connected with the antidiuretic action of the extract.

[3] *Proc. Roy. Soc.*, B, xciii., 1922.

[4] Ch. Livon, *C. r. soc. biol.*, lxvii. 618, 1909.

[5] P. Emile-Weil and G. Boyé, *ibid.*, p. 428 ; Kahn and Gordon, *Journ. Amer. Med. Assoc.*, lxiv., 1915 ; B. A. Houssay, *op. cit.*, 1922 ; J. La Basse, *C. r. soc. biol.*, xci., 1924. This author finds that extracts of anterior lobe retard coagulation.

[6] *Proc. Physiol. Soc.* in *Journ. Physiol.*, xl., 1910 ; *Journ. Physiol.*, xlvii. 215, 1913 ; xlviii. 128 and 317, 1914 ; l. 198, 1916.

[7] *Amer. Journ. Physiol.*, xxxvi., 1915.

[8] *Ibid.*, li., 1920 ; Becht and Matill, *ibid.*, p. 126 ; Becht and Gunnar, *ibid.*, lvi., 1921. In connexion with the effect of alterations of intracranial pressure on the changes in volume of the cerebrospinal fluid, the article, "The Cerebral Circulation," by Leonard Hill in Schafer's *Textbook of Physiology*, ii. 141, *et seq.*, may usefully be consulted.

CHAPTER XXX

THE PITUITARY BODY (*continued*)

Action of Posterior Lobe Extract on Secretion

The results on salivary, gastric, and pancreatic secretion are doubtful, but definite effects are obtained from intravenous and subcutaneous administration of this extract on the secretion of milk and of urine. These therefore will be dealt with in detail.

With regard to the *salivary secretion*, Oliver and Schafer [1] obtained no effect on the submaxillary secretion of the dog, but Solem and Lommen [2] got diminution, which they found to be independent of the constricting effect of the autacoid on the blood-vessels of the gland.

Effects have also been described upon *gastric secretion*, but the results of the experiments are conflicting. Houssay [3] found that the secretion was excited, but most other authors have obtained inhibition. The varying results may perhaps be due to the fact that histamine, which is commonly found in the extract, stimulates the secretion of gastric juice.

On the secretion of *pancreatic juice* Schafer and Herring [4] got either no effect or a diminished secretion. Pemberton and Sweet [5] found that the secretion of pancreatic juice which was excited by the introduction of acid into the duodenum was inhibited by pituitary extract.

Action on the Secretion of Milk

It was found by Ott and Scott [6] that in the lactating goat an injection of pituitary extract into a vein greatly increases the quantity of milk which can be drawn from the udder in a given time after the injection, as compared with that which could be obtained in a similar period immediately before. This galactagogue action of pituitary extract was confirmed in lactating cats by Schafer and Mackenzie.[7] The method they employed consisted in canalising or

[1] *Op. cit.*, 1895.

[2] *Amer. Journ. Physiol.*, xxxviii., 1915.

[3] Houssay, *La sem. med.*, Buenos Aires, 1913; J. Pal, *Deutsch. med. Wochenschr.*, xlvi., 1916; Rogers, Rahe, Fawcett, and Hackett, *Amer. Journ. Physiol.*, xxxix., 1916; D. Alpern, *Biochem. Zeitschr.*, cxxxvi., 1923.

[4] *Phil. Trans.*, cxcix., p. 25, 1908.

[5] *Arch. Int. Med.*, 1910. See also C. J. Wiggers, *Amer. Journ. Med. Sci.*, cxli., 1911.

[6] *Proc. Soc. Exper. Biol.*, vii., 1910; *Therap. Gaz.*, 1911, 1912.

[7] *Proc. Roy. Soc.*, B, lxxxiv., 1911; K. Mackenzie, *Quart. Journ. Exper. Physiol.*, iv., 1911. See also B. A. Houssay, *Rev. d. l. soc. méd. Argentine*, xxi., 1913, and "L'accion, etc.," 1918, pp. 187–217 (various animals).

incising the nipple of one of the mammæ so as to allow a free passage for any milk which is secreted. The milk is conducted to the side and registered by allowing it to fall upon an electrical drop recorder. This *modus operandi* permits the conditions of the experiment to be controlled and the results to be recorded accurately. In this way it can be shown that even a small dose of

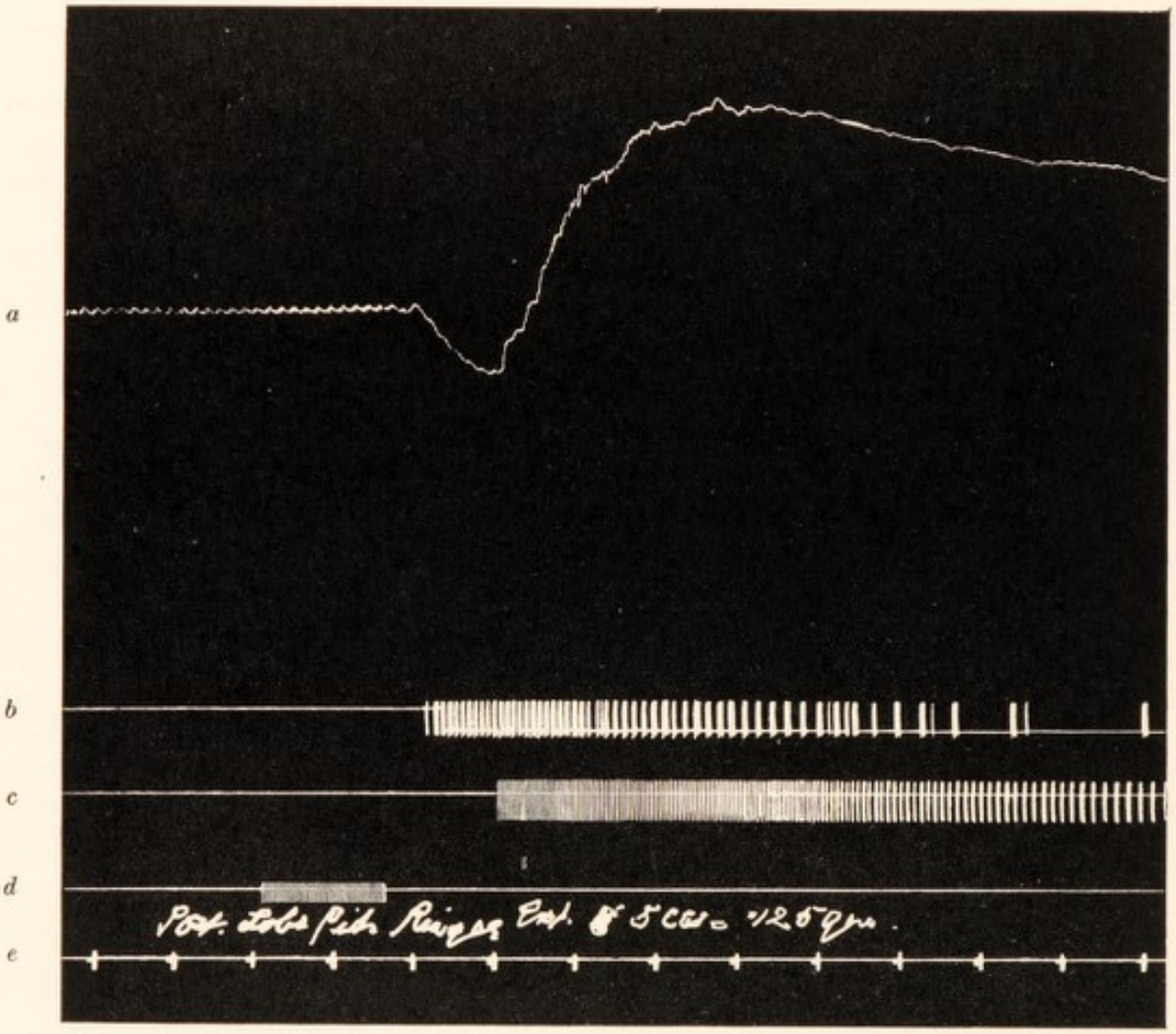

FIG. 125.—Effect on blood-pressure and mammary gland of a lactating cat of injecting extract of 0·125 g. of posterior lobe of pituitary. (K. Mackenzie.)

a, tracing of blood-pressure: notice that the main rise is preceded by a preliminary fall; *b*, electric signal of drops of milk exuding from a fine cannula introduced into one of the lactiferous ducts; *c*, drops of milk exuding from an incised gland; *d*, signal; *e*, time in ten seconds.

the pituitary autacoid will cause milk which has accumulated in the gland to be immediately poured out (fig. 125), whilst a somewhat larger dose will produce complete emptying of the alveoli. If the nipple is not canalised or incised, the resistance which is afforded in the passage through its ducts, controlled as they are by the plain muscle tissue which abounds in the nipple, does not permit of this emptying, and no actual outpouring of the secretion takes place.

Nevertheless under these circumstances the gland swells, doubtless owing to dilatation of vessels and increased flow of blood: the swelling long overlasts any

galactagogue effect which is produced in neighbouring glands with nipples incised. Vaso-dilatation and swelling is also caused in non-lactating virgin glands by intravenous injection of pituitary extract.[1] If an intramuscular injection of pituitary extract is made in the arm of a nursing woman, a feeling of tingling is felt in the mamma and a sensation of milk flowing towards the nipple is experienced like that which occurs when the child is put to the breast, although there may be no actual outpouring of the secretion.[2] But the amount of milk which can be drawn from the gland is materially increased just after such administration.

If in an experiment upon a cat the animal is killed immediately after one of its glands (with nipple incised) has been emptied by an intravenous injection of extract of posterior lobe in the manner above described, and if a portion of tissue comprising parts of two adjacent mammæ—one emptied of its secretion as the result of the injection, the other with its alveoli still full of milk—is fixed and sections are made passing through both full and empty mammæ, the contrast in appearance is remarkable (fig. 126). In the one, where the alveoli are distended with secretion, they are large and rounded and the lining cells are flattened against the limiting membrane, whilst in the other, from which the secretion has been discharged, the alveoli are irregular, shrunken, and empty, their walls are folded and the lining cells stand prominently out from the limiting membrane.[3]

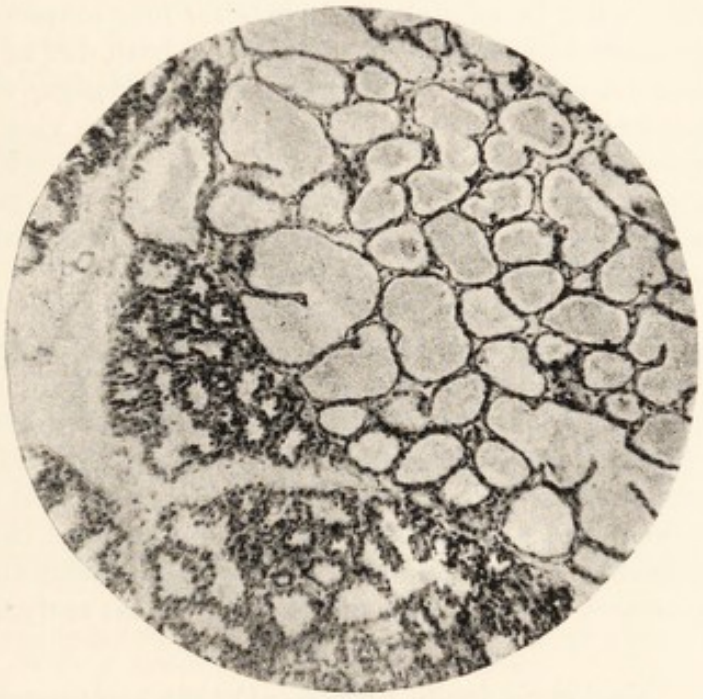

Fig. 126.—Section including the adjacent parts of two mammary glands of a lactating cat. One of them had discharged the whole of its milk as the result of an intravenous injection of pituitary extract, the nipple having been excised to allow the milk to flow out freely. In the other the alveoli are distended with milk. Low power.

If after a full dose of pituitary extract has been given, a second dose succeeds it at a short interval, no further flow of secretion from the exhausted gland can be produced. This is not an instance of tachyphylaxis, but is due to the fact that there is now no milk left in the alveoli. The effect of the autacoid, therefore, is not—at any rate immediately—to cause the cells to form and secrete milk, but only to cause the alveoli to empty themselves of the milk which has previously been formed and secreted within them. The simplest manner in which one can conceive this to occur is by contraction of plain

[1] A similar effect (vaso-dilatation) occurs with other galactagogues, such as corpus luteum extract (Houssay, *op. cit.*, 1918).

[2] Schafer, *Quart. Journ. Exper. Physiol.*, vi., 1913.

[3] Schafer, *ibid.*, viii., 1915.

muscular tissue around the alveoli. In fact, long rod-shaped nuclei can be seen in the walls of the mammary alveoli immediately external to the epithelium. These nuclei resemble those of involuntary muscle-cells and appear to belong to a thin muscular layer which is situated, like the muscular tissue of the sweat glands, between the basement membrane and the epithelium of the alveoli. The contents of the alveoli are therefore discharged by the contraction of this layer of muscle, which is highly susceptible to pituitary extract.

W. L. Gaines [1] injected air into the udder of a non-lactating goat, and found that when he administered posterior lobe extract there was produced increase of pressure and diminution of volume ; both due no doubt to the contraction of the gland musculature. (Of course no galactagogue effect is obtained in a non-lactating animal.) Some authors have taken the view that the galactagogue effect of pituitary injection is due—wholly or in part—to a true secreting effect on the gland cells, such as is produced in the salivary glands by pilocarpine, and in the pancreas by secretin, but the fact that no secretion can be got from an emptied gland renders this view improbable.[2]

Apart from the pouring out of the contents of the alveoli—which when the gland is intact shows itself as a tendency of the alveoli to empty themselves towards the nipple—the pituitary galactagogue has little or no effect on the total production of milk. This at least is the result which was obtained in the cow by Gavin.[3] Later observers (J. Hammond,[4] Hill and Sutherland Simpson,[5] Maxwell and Rothera [6]) have described an increase in the diurnal yield of both goats and cows ; and also an increased amount of fat in the milk produced under the influence of the autacoid. Rothlin, Plimmer, and Husband [7] also obtained an increased secretion in goats, but only in the early stages of lactation.[8]

Mackenzie found (in the cat) that atropine does not arrest the flow of milk obtained as the result of pituitary injection (an observation which has been confirmed for the cow by Houssay). He obtained, however, an inhibitory action both from extract of placenta and from extract of fœtus. Such extracts, when injected into a vein just previously to the injection of pituitary extract, prevent the effect of the latter from influencing the mammary gland. We may conclude from this that placenta and fœtus extracts contain a chalonic autacoid which restrains the outpouring of the secretion of the mamma and antagonises the hormonic action of the pituitary autacoid.

[1] *Proc. Amer. Physiol. Soc.* in *Amer. Journ. Physiol.*, xxxvi., 1915.

[2] For a discussion of this subject, see R. L. Hill and Sutherland Simpson, *Quart. Journ. Exper. Physiol.*, viii. 103, 377, 1914–15 ; and Schafer, *ibid.*, p. 379. Houssay (*op. cit.*, 1918) adduces arguments to prove that both contraction of alveoli and secretory activity of the alveolar cells, as well as increased formation of fat, are caused by pituitary.

[3] *Quart. Journ. Exper. Physiol.*, vi. 13, 1913.

[4] *Ibid.*, p. 311.

[5] *Op. cit.*, and *Amer. Journ. Physiol.*, xxxvi., 1915.

[6] *Journ. Physiol.*, xlix., 1915.

[7] *Biochem. Journ.*, xvi., 1922.

[8] Other papers on the subject are by R. C. Hughes, *Therap. Gaz.*, xxxi., 1915, and A. C. M'Candlish, *Journ. Dairy Sci.*, i., 1918.

Galactagogue autacoids are contained in extracts of other organs besides the pituitary, viz. the corpus luteum of the ovary, the involuting mucous membrane of the uterus after parturition, the lactating mammary gland itself, and to a slight extent the pineal gland. Their effect on the mamma is exactly like that of the pituitary galactagogue, but the effects on blood-pressure are either nil or are different from that of pituitary extract. Their galactagogue action, as well as the effects of extracts of corpus luteum, placenta, of the fœtus, and of ovarian transplants, in promoting the development of the mammary glands, will be described later under the several organs.

The blood, even in non-lactating animals, sometimes contains enough galactagogue autacoid to provoke the mammary secretion of a lactating animal, although other effects of pituitary extract may not be seen. In one experiment as little as 5 c.c. of the blood-serum of a guinea-pig injected into a lactating cat provoked a

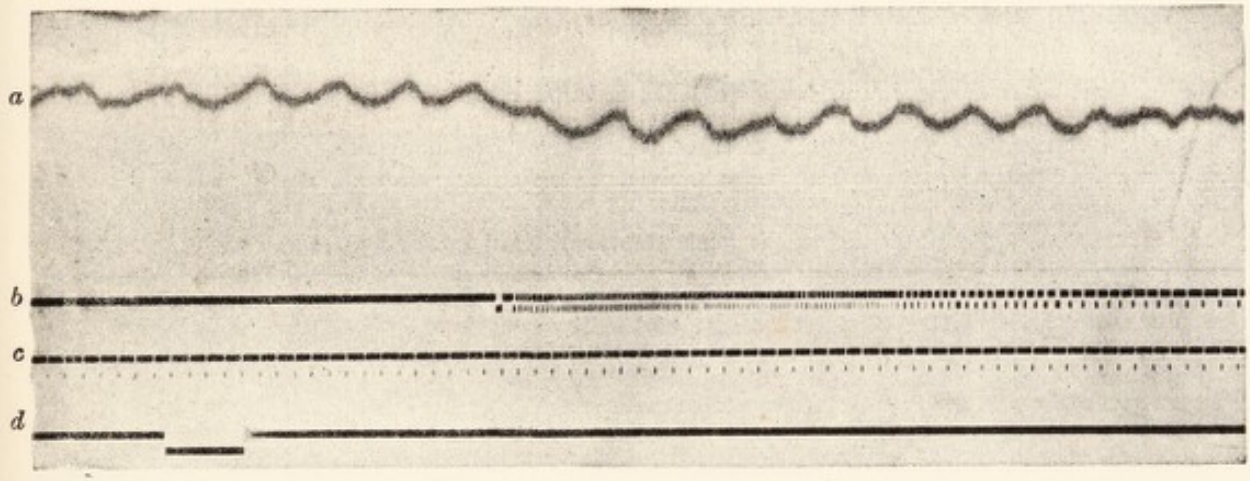

FIG. 127.—Electric change accompanying the flow of milk from the mammary gland under the influence of a dose of pituitary extract administered intravenously.

a, record of string galvanometer: each millimetre of ordinate = 20 microvolts; *b*, record of drops of milk; *c*, time in seconds; *d*, signal of injection. The waves on *a* are respiratory.

marked secretion from a gland, the nipple of which had been incised, without producing any effect on the blood-pressure.[1]

The action of pituitary and other extracts in causing secretion from the gland is accompanied by a change in the electric potential of the organ (fig. 127), so that the alveoli tend to become negative to the duct.[2] This change is somewhat similar to that which is produced in the salivary and other secreting glands.

From what has been stated regarding the mammary gland it is obvious that this is an organ which is singularly under the influence of autacoids circulating in the blood. It is, moreover, well known that its secretion is not directly under the influence of the nervous system. Excitation of its nerves produces no appreciable effect on the secretion, which also continues normal after all nerves are cut.[3]

[1] Schafer, *Proc. Internat. Med. Congress*, London, 1913.
[2] Schafer, *Livre jubilaire du Prof. Ch. Richet*, 1912.
[3] Eckhard, *Beitr. z. Anat. u. Physiol.*, Giessen, 1855.

Drugs which are known to act through nerves and which cause or prevent secretion in other secreting glands have no effect on the mammary gland. Even a gland which has been transplanted to a totally different situation will secrete milk.[1] The case of the ~~pygophagous~~ twins, Rosa-Josepha Blazék, who were united at the sacrum, with anus and vulva in common but with two uteri and vaginæ, is particularly interesting in connexion with this question. For when one of the twins became pregnant the mammary glands in both underwent hypertrophy and eventually secreted milk. The well-known effects of nervous conditions (emotions and the like) upon milk secretion must therefore be produced through the internal secretions of organs such as the pituitary and corpus luteum.

Tumours of the pituitary are sometimes associated with persistent lactation. W. Langdon Brown narrates a case of a woman with such a tumour who showed continuous lactation during seven years.[2]

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[1] Ribbert, *Arch. f. Entwickl.-Mech.*, vii., 1898. For other references, see J. Hammond, *op. cit.*

[2] *Brit. Med. Journ.*, ii. 1052, 1925.

CHAPTER XXXI

THE PITUITARY BODY (*continued*)

Action of Posterior Lobe Extracts on the Secretion of Urine

Diuretic Action

The renal arteries, as we have seen (p. 222), form an exception to the constrictor effect produced by pituitary extract, since they dilate and the kidney swells

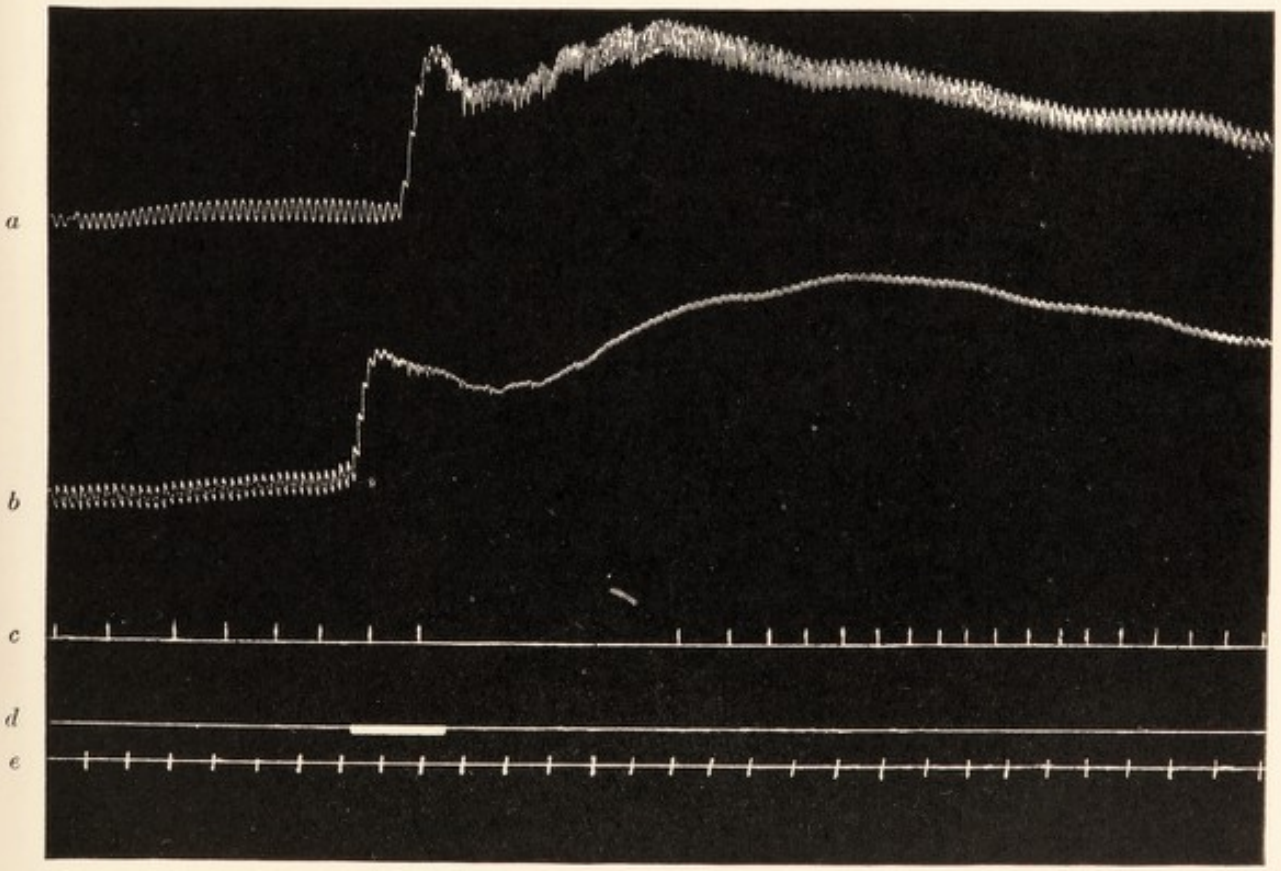

Fig. 128.—Tracing showing the effect on arterial pressure, kidney volume, and urine flow of injecting extract of posterior lobe of pituitary into a vein. (This and the next two figures are from Schafer and Herring, *Phil. Trans.*, 1908, vol. cxcix.)

a, blood-pressure; *b*, tracing of kidney volume (this tracing should be shifted 5 mm. to the right); *c*, urine drops; *d*, signal; *e*, time in ten seconds.

as a consequence of the addition of the extract to the circulating blood (fig. 128): the dilatation is correlated with an increase of secretion of urine, often very

marked.[1] This effect is frequently preceded by a short, slight contraction of the vessels, and the increase of urine by a temporary diminution. The increased secretion may be in part brought about by the increased flow of blood through the kidney vessels due to the circumstance that they undergo dilatation while the other systemic arteries are contracting, so that the blood-pressure in the glomeruli is raised ; but that it is to a certain extent caused by a specific effect of one of the pituitary autacoids, and not merely a mechanical result of increased blood-pressure, is probable from the fact that it may occur in the absence of any obvious vascular change.

Moreover, an increased rate of flow is maintained after the blood-pressure has come back to the level at which it stood before the injection. And the effect of a second and subsequent doses of the autacoid administered soon after the main result of the first dose has passed off is again to produce an increase in the urine flow (see figs. 129, 130), although the blood-pressure as the result of these after-doses does not rise, or falls instead of rising, and although the kidney volume may now be unaffected. This experiment indicates that the autacoid affects not only the blood-vessels of the organ, but also its secreting cells, which it renders more permeable. The secretion must therefore in these circumstances be looked upon as caused by an action on the renal cells, the effect being similar to that of the secretin of the duodenum on the pancreas. In this respect the action of the autacoid of the pituitary is comparable to that of those drugs which act as specific diuretics upon the secreting cells of the kidney, as distinguished from those which produce diuresis by merely increasing the general blood-pressure or the blood-flow through the kidney.

Herring states that the diuretic effect only occurs when extracts of pars nervosa are employed : extracts of pars intermedia and of pars anterior do not produce diuresis.[2]

The diuretic action of the pituitary autacoid is not antagonised by atropine. This may be taken as a sign that it does not act through nerves or nerve-endings, but directly upon the kidney cells ; in this respect also it resembles the action of secretin upon the pancreas.

Although the diuretic effect is most obvious when the extract is injected into the blood, it has also been obtained with hypodermic or intramuscular injection, and even by buccal administration.[3] The diuresis is accompanied by some hydræmia, but is not dependent upon this, since the hydræmia outlasts the diuresis. It is preceded, when the urine is collected from the bladder or the lower part of the urethra, by what appears to be an antidiuretic effect (a short

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[1] R. Magnus and E. A. Schafer, *Proc. Physiol. Soc., Journ. Physiol.*, xxvii., 1901 ; E. A. Schafer and P. T. Herring, *Phil. Trans. Roy. Soc.*, B, cxcix., 1908 ; B. A. Houssay, Tesis, Buenos Aires, 1911 ; R. G. Hoskins and J. W. Means, *Journ. Pharm. and Exper. Therap.*, iv., 1913 ; Stoland and Korb, *Amer. Journ. Physiol.*, lv., 1921. A full literature will be found in Houssay, "L'accion, etc.," 1918 and 1922. See also Mackersie, *op. cit. infra*, and N. S. Craig, *Quart. Journ. Exper. Physiol.*, xv. 119, 1925. According to Dale the active agent is excreted in the urine (*Biochem. Journ.*, iv., 1909).

[2] *Quart. Journ. Exper. Physiol.*, viii. 245, 1914–15.

[3] Stoland and Korb, *Amer. Journ. Physiol.*, lv., 1921.

cessation of flow); this is due to spasmodic contraction of the ureter and can be eliminated by inserting the cannula in its uppermost part.[1]

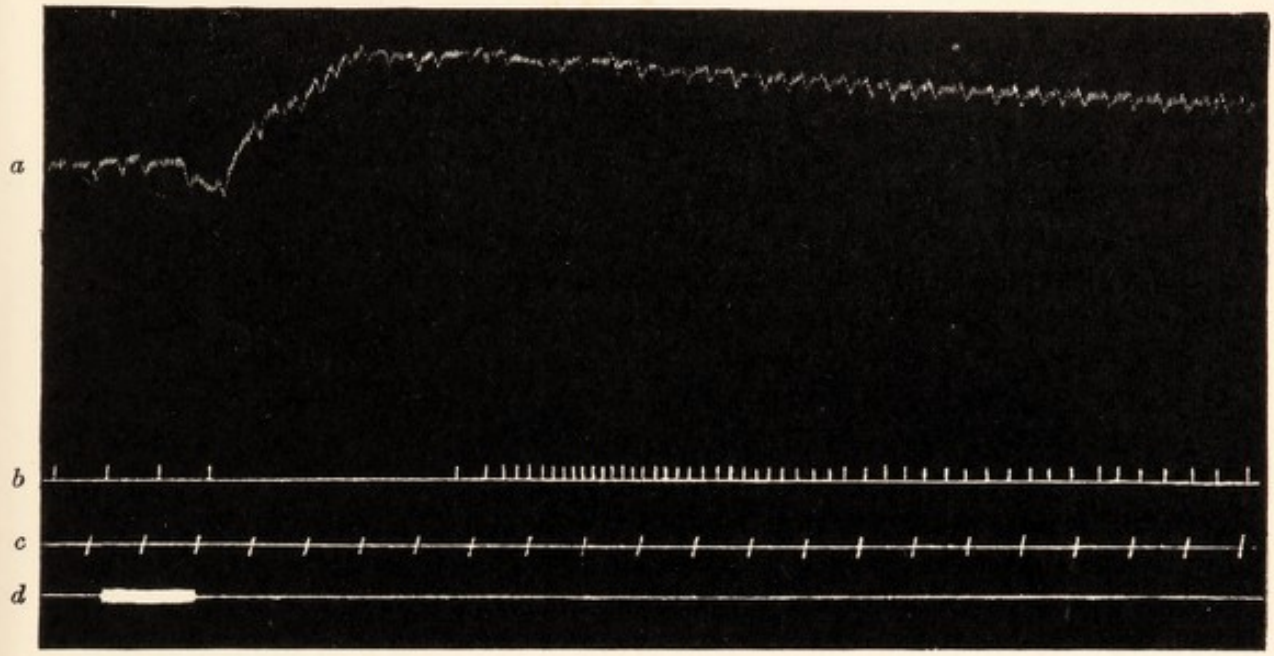

FIG. 129.—Effect of a first dose of pituitary extract on the blood-pressure and urine flow.
a, blood-pressure; *b*, urine flow; *c*, time in ten-second intervals; *d*, signal and abscissa of blood-pressure.

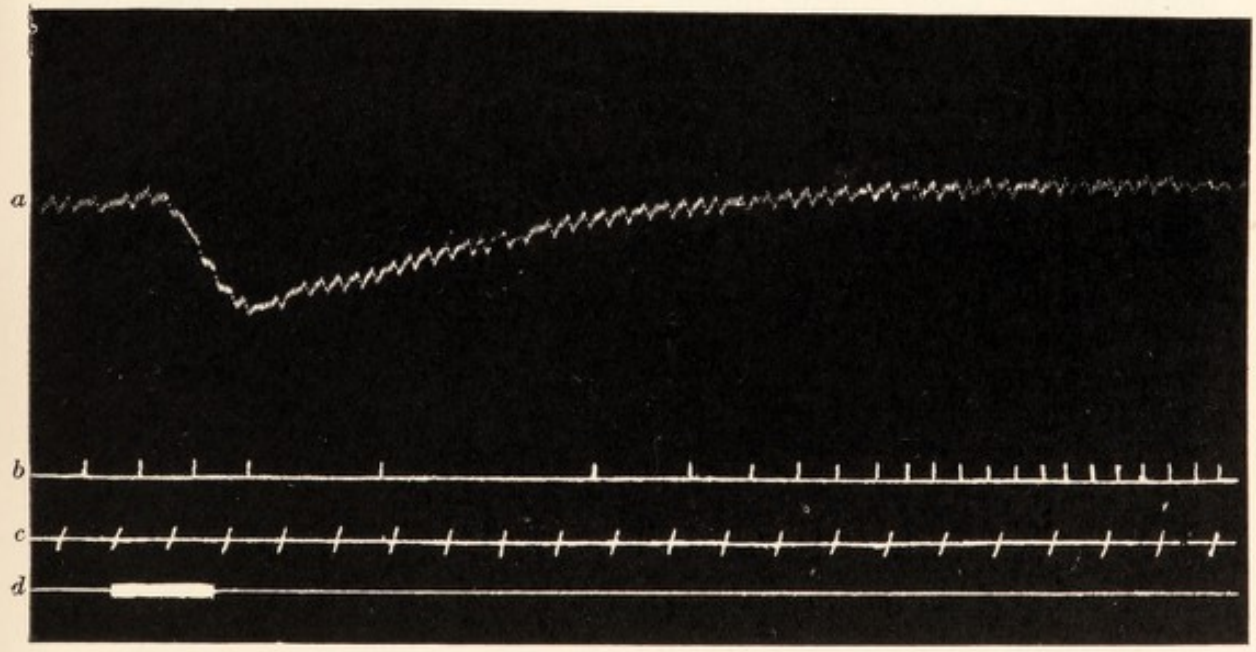

FIG. 130.—Continuation of the experiment illustrated in fig. 129. Effect of a second dose of pituitary extract. Notice that the flow of urine is again accelerated although the blood-pressure is not appreciably raised.

If in place of using an ordinary water or saline extract of the posterior lobe an alcohol extract of the dried substance is employed, not only is a depressor effect

[1] W. G. Mackersie, *Journ. Pharm. Exper. Therap.*, xxiv., 1924.

obtained on the circulation but the urinary secretion is diminished in place of being increased.[1] The substance which produces this effect, being soluble in water as well as in alcohol, is also present to some extent in the ordinary extracts. Its presence in greater or less amount probably accounts for differences which have been met with in connexion with the action of the extract on urine secretion. It is probably histamine.

There has been much conflict of opinion regarding the question whether the diuretic action of pituitary is to be explained by alterations in the blood-flow alone or by a specific action on the kidney cells as well, such as is produced by a solution of urea. That it is not entirely due to the improvement in filtration conditions in the glomeruli caused by the increase of blood-pressure (the arteries of the kidney relaxing whilst those of the rest of the body contract) is shown, as already indicated, by the fact that even under circumstances when no rise of blood-pressure is observable, the autacoid will still bring about an increase in the amount of urine secreted. It must be remembered that although Ludwig observed that the secretion of urine is increased by any drugs or other agencies which cause a general rise of blood-pressure,[2] it was shown by R. Heidenhain that the effect is produced less by increased filtration pressure than by increased blood-flow through the organ. A mere rise in pressure in the kidney vessels, such as is produced by partial occlusion of the renal vein, has the effect of diminishing or arresting the flow of urine, whereas anything which increases the amount of blood flowing through the organ produces an increased flow of urine. Doubtless the blood itself acts as a diuretic, containing as it does urea and other substances which stimulate the kidney cells. That one such substance is the pituitary autacoid is extremely probable,[3] and in accordance with this view it is found that the diuresis which is caused by pituitary extract generally runs parallel with the rate of blood-flow.[4]

It was found by Richards and Plant [5] that in minute doses pituitary extract may decrease the blood-flow through the kidney, although both kidney volume and urine are increased. This they ascribe to a possible slight contraction of the vasa efferentia of the glomeruli producing a rise of pressure in the glomerular capillaries. They find the same to be true for minute doses of adrenaline. They state that an increase of pressure, without any increased flow of blood, will increase the amount of urine excreted, and, with Ludwig, they regard the pressure element as the essential one.[6]

Wearn, Schmidt, and Richards find that application of minute quantities of

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[1] R. Magnus and E. A. Schafer, *op. cit.*, 1901.

[2] But not with those agencies, *e.g.* adrenaline, which contract the kidney vessels as well as all other arteries in the body. Under these circumstances the kidney shrinks and the flow of urine temporarily stops (see Part I., p. 138).

[3] *Cf.* Krogh, *op. cit.*

[4] A. R. Cushny and C. G. Lambie, *Journ. Physiol.*, lv., 1921 (rabbit).

[5] *Amer. Journ. Physiol.*, lix., 1922. See also Richards, *Harvey Lectures*, xvi., 1920–21.

[6] For a criticism of this opinion, together with an account of experiments which favour the "secretory" theory of urine-formation (but without special reference to the action of pituitary extract), see J. M. O'Connor, *Journ. Physiol.*, lix., 1924.

pituitary extract (or of amyl nitrite) to the surface of the frog's kidney causes more glomeruli to become active (normally blood does not pass through all the glomeruli at one time). Subcutaneous injections of urea, salt solution, glucose, and caffeine, all of which have a diuretic action, produce a similar effect. Adrenaline, barium chloride, and large doses of pituitary extract have the opposite effect.[1]

R. G. Hoskins and Means,[2] who employed dogs and always got diuresis, found (in confirmation of Schafer and Herring) no constant relationship between the diuresis and the blood-pressure, and regard the effect as being a direct one on the renal cells.

C. E. King and Stoland [3] found the diuresis to run more or less parallel with the kidney volume, which they ascribe to increased blood-pressure, and they looked upon the diuresis as caused merely by the rise in pressure. Houghton and Merrill [4] took the same view.

But Stoland and Korb [5] found that injection of posterior lobe extract may increase not only the amount of water but also the total nitrogen, urea, and ammonia by 50 per cent.; whilst the total nitrogen and urea of the blood were decreased by 40 per cent.: and even on the following day were 20 per cent. below normal. They consider these results show conclusively that the extract acts as a stimulant to the kidney.

Abel, Rouiller, and Geiling,[6] who worked with a very active extract, obtained a cessation of urine during several minutes, followed by marked diuresis. The cessation was probably due to spasm of ureter.

K. Fromherz [7] found that pituitary extract injected hypodermically has at first a prolonged oligo-uric (antidiuretic) effect. After this has passed off there is not only increased diuresis but also increased elimination of NaCl, which becomes lessened in quantity in the blood. He regards the action as purely renal, due to an alteration in the permeability of the epithelium. This view is supported by the fact that continued injections of the extract produce a toxic effect on the renal cells and an escape of blood into the urine.[8]

Working with the perfused kidney, some observers [9] have obtained a diminution both in blood-flow and in secretion on addition of pituitary extract to the perfusion fluid, whilst others [10] have recorded an increase of urine with or without vaso-dilatation. Knowlton and Silverman [11] found the diuresis caused by pituitary injections to be unaccompanied by a simultaneous increase of O_2 consumption,

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[1] Trans. XIth Internat. Physiological Congress, Edinburgh, in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923.

[2] *Journ. Pharm. and Exper. Therap.*, iv. 435, 1913.

[3] *Amer. Journ. Physiol.*, xxxii., 1913.

[4] *Journ. Amer. Med. Assoc.*, li., 1908.

[5] *Amer. Journ. Physiol.*, lv., 1921.

[6] *Journ. Pharm. and Exper. Therap.*, xxii., 1924.

[7] *Arch. f. exper. Path. u. Pharm.*, c., 1923.

[8] P. Thaon, *C. r. soc. biol.*, lxix., 1910.

[9] H. H. Dale, *Biochem. Journ.*, iv., 1909; Pentimalli and Quercia, *Arch. ital. de biol.*, lviii., 1912.

[10] L. Beco and L. L. Plumier, *Bull. acad. roy. de méd. de Belg.*, 1913; J. Gabriels, *Arch. internat. de physiol.*, xiv., 1914. This author comes to the conclusion that pituitary extract acts on the renal cells.

[11] *Amer. Journ. Physiol.*, xlvii., 1918.

and conclude that the diuresis is dependent on vascular conditions rather than on cell-activity. But this conclusion cannot be safely drawn from their determination, since, however the secretion of urine may be produced, the cells of the gland must play an active part in regulating the passage of water and other urinary constituents either from the blood into the Malpighian bodies and tubules, or, in the case of reabsorption occurring, from the tubules back into the blood.

The probability is that for the secretion of urine there is a direct effect of certain constituents of the blood—of which the pituitary autacoid is one—on the renal cells. It must be borne in mind that although such a condition as is produced by high pressure in the glomeruli is favourable to filtration, no filtration will occur in the absence of a free flow of blood.[1]

Starling and Verny,[2] who worked with the isolated kidney, conclude that the pituitary is normally the regulator of the output of H_2O and Cl in the intact organism. Stehle and Bourne[3] arrive at a similar conclusion from observations on normal animals (dogs).

Antidiuretic Action

Besides the diuretic action of extract of posterior lobe which has been above described, the extract is found under certain circumstances to bring about exactly the opposite condition. With intravenous injection of pituitary extract there is, as we have seen, at first a very temporary diminution of flow of urine followed by a prolonged increase. This increase, however, does not, as a rule, last more than twenty minutes, gradually passing off ; it gives place to a diminution which lasts much longer. On the other hand, with subcutaneous or intramuscular injection, *especially if polyuria is present*, a great diminution in the secretion is produced.

This effect is not obtained with buccal administration, the reason apparently being that the autacoid to which the extract owes its antidiuretic action is destroyed by gastric juice. But if the dessicated extract is made up into pellets coated with salol, it will pass the stomach unchanged, and the active substance will, it is said, then be absorbed from the intestine and exercise its antidiuretic action.

The antidiuretic action was first noticed in clinical cases of diabetes insipidus,[4] in which it has a remarkable, indeed specific, action in controlling the excretion of water by the kidneys and bringing it down to a normal level ; to keep it at that, the injections require to be repeated from time to time. In

[1] *Cf.* C. and M. Oehme, *Deutsch. Arch. f. klin. Med.*, cxxvii., 1918, and C. Oehme, *Arch. f. exper. Path. u. Pharm.*, lxxxix., 1921.

[2] *Proc. Roy. Soc.*, B, xcvii. 321, 1925.

[3] *Journ. Physiol.*, lx. 229, 1925.

[4] F. Farini, *Gazz. Osp.*, 1913; R. v. d. Velden, *Berl. klin. Wochenschr.*, 1913. L. F. Barker and H. Mosenthal suggest that the pars intermedia yields the antidiuretic substance, but the evidence for this is not clear (*Trans. Assoc. Amer. Physicians*, xxxii., 1917).

normal individuals the effect in diminishing the secretion of urine is less striking and may be absent.[1]

Different species of (normal) animals react somewhat differently to subcutaneous injection. In dogs there is often at first an increase of urine: this being followed by a phase in which less urine is excreted. In guinea-pigs and rabbits there is a decrease from the first after subcutaneous injection; although marked diuresis is the result of intravenous administration.[2] Garnier and Schulmann,[3] experimenting on rabbits with extracts of bovine and equine posterior lobe, found the amount of urine passed in twenty-four hours to fall for two or three days to 30 c.c., or even in some cases as low as to 10 c.c. But on the third day polyuria set in and the amount increased to 200 c.c., 300 c.c., or even 500 c.c. The scanty urine during the first period was dark and usually contained albumin, but not blood. In four of the animals some glycosuria was produced.

The rate of urea excretion is also checked by subcutaneous injection of pituitary extract.[4]

Many of the experiments on the antidiuretic action of pituitary extract have been made on "water-diuresis," *i.e.* the polyuria which is produced by ingestion of large quantities of water. Administration of water by the mouth, even in considerable quantity, does not appreciably dilute the blood. The volume of blood is not increased, but the excess of water is immediately absorbed by the protein colloids of the liver and tissues,[5] which gradually give it off again to the blood. The kidneys take it from the blood and pass it on to the urinary bladder, so that in a relatively short time the whole of the excess of water may be got rid of.[6] Probably the greater part of the excess is temporarily stored in the liver. For if physiological salt solution is injected into the blood of an animal with an Eck-fistula—which cuts out the circulation through the liver—the dilution of the blood caused by the salt solution remains for hours, whereas under normal conditions it diminishes rapidly and has wholly dis-

[1] E. E. Larson, J. F. Weir, and L. G. Rowntree, *Trans. Assoc. Amer. Physicians*, xxxvi., 1921; T. Kasa, *Tohaku Gak. Zasshi*, 1922 (abstract in *Endocrinology*, vii., 1923). The literature up to 1919 regarding the antidiuretic action of pituitary will be found in a paper by E. L. Kennaway and J. C. Mottram in the *Quart. Journ. Med.*, xii., 1919. In this paper the authors give a description of two cases of diabetes insipidus treated with pituitary, and a critical discussion of the relation of the organ to urine secretion. The literature is also given by Houssay, *op. cit.*, 1922, and by Mackersie, *op. cit.*, 1924. According to Mackersie the antidiuretic mechanism is probably located in the kidneys.

[2] Houssay, Galan, and Negrete, *C. r. soc. de biol. de Buenos Aires*, 1920; Houssay and Hug, *C. r. soc. biol.*, Paris, lxxxv., 1921.

[3] *C. r. soc. biol.*, lxxvii., 1914.

[4] Addis and Drury, *Journ. Biol. Chem.*, lv., 1923. See also papers by Addis, Shevky, and Bevier, *Amer. Journ. Physiol.*, xlvi., 1918, and by Addis, Barnett, and Shevky, *ibid.*, 1918 (several papers). They find (rabbit) that the blood concentration is increased by pituitary, and that the effect is antagonistic to that of adrenaline.

[5] E. P. Pick, *Wien. klin. Wochenschr.*, xxxvii., 1924.

[6] If physiological salt solution is taken by the mouth instead of water the volume of the blood becomes increased without toxic symptoms being produced, whereas water in excess of the normal salts of the blood is toxic (Haldane and Priestley, *Journ. Physiol.*, l., p. 296, and J. G. Priestley, p. 304, 1916).

appeared in a little more than half an hour. According to Pick, when pituitary extract is administered the effect is the same as with the Eck-fistula: the blood supply of the liver is greatly reduced and the blood remains diluted for hours by the injected salt solution; there is only very slowly a return to normal conditions of urine excretion.

M. H. Rees [1] thought that the check on water diuresis caused by pituitary extract is in part due to delayed absorption from the intestine, but it seems doubtful if this occurs to a sufficient extent to account for the phenomenon.[2]

Motzfeldt,[3] who got an antidiuretic effect (from pituitary extract) in rabbits with water-diuresis, states that the antidiuresis failed when the splanchnics were cut. Larson, Rowntree, and Weir [4] find that in dogs the antidiuretic action shows itself even when all the nerves to the kidneys are severed. This result has also been obtained by others.

If water is administered in large quantity in man soon after a subcutaneous dose of the extract, nausea, vomiting, and headache are produced: in dogs, vomiting, diarrhœa, ataxia, convulsions, and coma; eventually death may result.[5] The effects are increased by repeating the dose.

J. G. Priestley [6] obtained in man from pituitary administration a delay of water diuresis lasting for from four to six hours. After this, diuresis showed itself. K. Fromherz [7] found that administration of the extract to dogs an hour or two before a large amount of water was given by the mouth had no effect in checking the diuresis thereby caused, but tended to accelerate it—although if the extract were given intravenously at the same time that water is taken by the mouth the effect is antidiuretic and lasts six to seven hours. During the antidiuresis there is concentration of chlorides in the urine.[8] At the end of four hours the antidiuretic effect had passed off. Fromherz further found that the diuresis caused in rabbits by intravenous injection of 0·9 per cent. salt solution at the rate of 5 c.c. every ten minutes was checked by the addition of pituitary extract ("hypophysin" eight parts to thirty of the saline solution). Craig,[9] however, working in Cushny's laboratory, found that in the cat the diuresis caused by continuous intravenous injection of 0·9 per

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[1] *Amer. Journ. Physiol.*, xlv., 1918; *ibid.*, lxiii., 1922.

[2] *Cf.* N. S. Craig, *Quart. Journ. Exper. Physiol.*, xv., 1925 (Thesis, Edinburgh, 1924).

[3] *Journ. Exper. Med.*, xxv., 1917.

[4] *Op. cit.*, and *Arch. Int. Med.*, xxix., 1922.

[5] On the effects of the ingestion of water in excess of the excretory ability of the organism, see L. G. Rowntree, Trans. XIth Internat. Physiol. Congress in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923.

[6] *Journ. Physiol.*, lv., 1921. See also M. Brunn, *Zeitschr. f. inn. Med.*, xli., 1920, and M'Brayer, *New York Med. Journ.*, July 6, 1921.

[7] *Op. cit.*, 1923.

[8] Observations (in diabetes insipidus and in "water-diabetes") show that pituitary extract alters the relation of water to salts between the tissues and the blood as well as between the blood and urine. The result of pituitary administration in polyuria is that, while the amount of NaCl excreted by the urine remains constant, its concentration is altered. Thus in a case recorded by E. Frank there was just as much NaCl in 22 c.c. of urine secreted after pituitary, as in 800 c.c. secreted during polyuria. At the same time that the urine becomes concentrated, the blood becomes diluted. Part of the retained water passes into the tissues, part into the stomach and intestine.

[9] *Op. cit.*, 1925.

cent. saline solution at the rate of 2·5 c.c. every five minutes was not only not checked by the addition of pituitary extract to the perfusion fluid, but the amount of urine secreted was greatly increased (fig. 131). If, however, administered subcutaneously to dogs, the extract controlled the diuresis which would normally have resulted from the administration of water or saline solution by the mouth, causing a delay in the onset of the diuresis of at least three hours (fig. 132). It also controlled that produced by the administration intravenously of saline solution at the rate of 4 c.c. a minute. With faster rates (12 c.c. a minute) the diuresis was not prevented by the subcutaneous administration of pituitary. Craig further found that while the blood-volume, as measured by its Hb percentage, was not

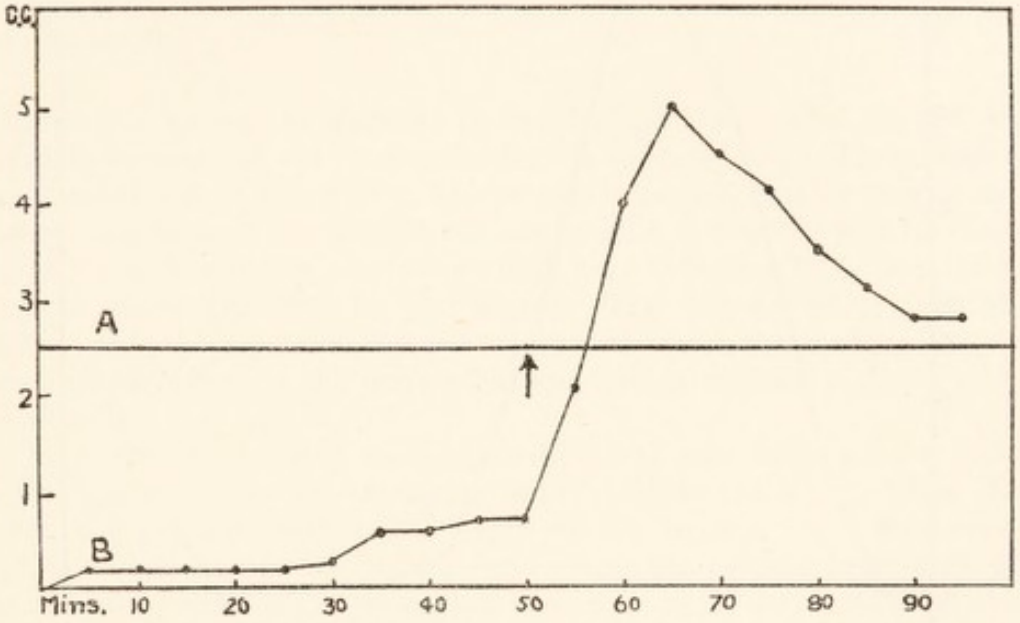

Fig. 131.—Chart showing the amount of urine passed by a cat weighing 2800 g. during intravenous administration of normal saline (0·9 per cent.) before and after the addition of extract of posterior lobe of ox-pituitary to the saline solution. (N. S. Craig.)
The ordinate is marked in cubic centimetres; the abscissa in minutes after the commencement of administration.

A. Line indicating that 2·5 c.c. saline were administered each five minutes. At the point marked by the arrow (fifty minutes after commencement of the administration), saline + pituitary extract replaced the ordinary saline. (The amount of extract reckoned as dry posterior lobe substance added was 1 part to 10,000 saline.) B. Curve of urine passed in c.c. per five minutes.

appreciably affected by drinking large quantities of water, if the drinking is immediately preceded by a subcutaneous injection of pituitary extract there is a definite reduction in the Hb percentage within the first two hours of the antidiuretic period.[1] This seems to suggest that the antidiuretic effect is renal rather than extra-renal.[2] The extract prolongs the diuresis caused by oral administration of urea.

The observations of Molitor and Pick[3] have an important bearing on the mechanism of the antidiuretic action of the extract. They find that the toxic

[1] *Cf.* Priestley, *op. cit.*

[2] Y. Miura (*ibid.*, cvii. 1, 1925) found that after double nephrectomy (in rabbits), pituitary determines an increase both of water and chlorides in the blood, over and above that caused by removal of the kidneys.

[3] *Arch. exper. Path. u. Pharm.*, ci. 169, 1924.

effects which may be caused by pituitary when a large excess of water is administered can be at once removed by the administration of urea, which probably acts by removing water from the tissues and causing its rapid excretion by the kidneys. They found that in dogs a small dose of pituitary posterior lobe (0·0001 gram per kilo body weight) given hypodermically was sufficient to stop for several hours the diuresis produced by administration of 250 c.c. of water, the effect being quite independent of vascular changes and also independent of the liver. The inhibition was removed by intravascular or buccal administration of urea, glucose,

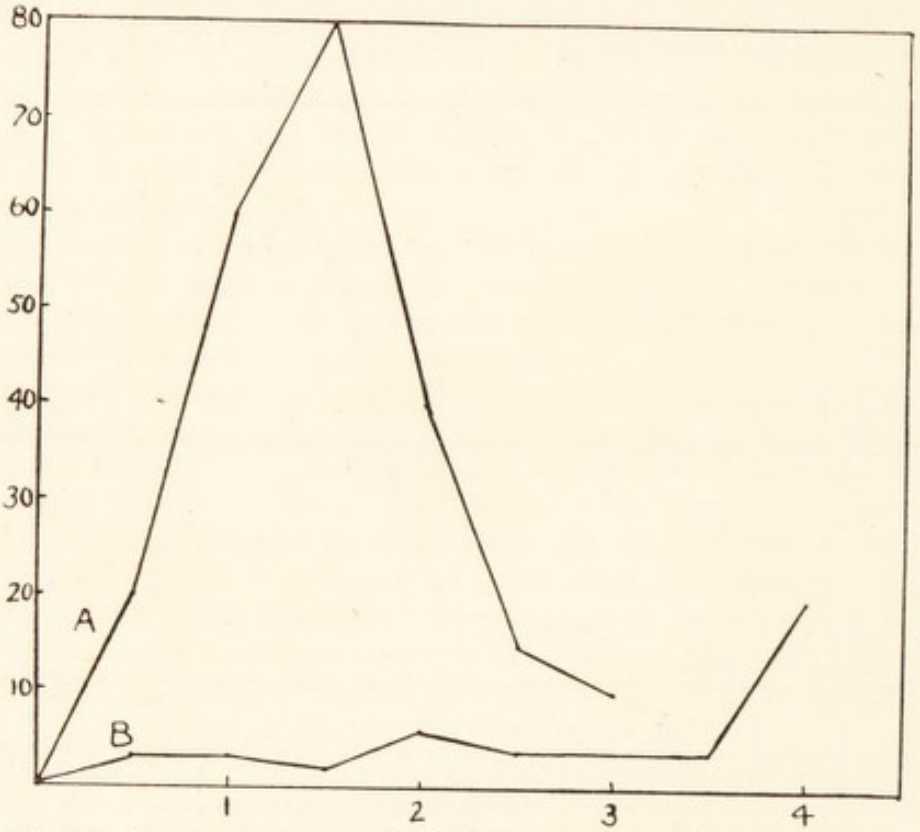

FIG. 132.—Experiment on dog to which 250 c.c. water was administered by stomach tube, the urine being collected by catheter every half-hour after. (N. S. Craig.) The ordinates represent c.c. urine secreted: the abscissa marks the time in hours from the commencement of the experiment.

A. Control experiment without pituitary. B. Experiment (a few days after) with injection of 5 mg. dry posterior lobe extract subcutaneously at the same time as the administration of water by the stomach. It will be seen that the commencement of diuresis is delayed for 3½ hours.

or hypertonic salt solution, but not by calcium salts, nor by thyroid (which generally causes diuresis), nor by increasing the amount of water. They conclude that the antidiuretic action has nothing to do with the renal vessels or with the renal cells, but is an effect on the tissues, perhaps also on the capillaries, and that one of the main functions of the pituitary is to determine the amount of water the tissues can hold.[1]

[1] F. Brunn (*Zeitschr. f. d. ges. exper. Med.*, xxv., 1921) came to the conclusion from experiments on the frog that pituitary promotes the retention of water by the tissues. Poehle (*Arch. f. d. ges. Physiol.*, clxxxii., 1920) states that after extirpation of the pituitary in the frog the animal becomes œdematous. Houssay, Giusti, and Goñalona (*Rev. soc. Arg. biol.*, June 4, 1925) obtained polyuria as the result of ablation of the pituitary of the toad.

The experiments of H. Hofmann had also led him to the conclusion that the posterior lobe of the pituitary serves as a water-regulator for the tissues in general.[1]

With regard to the double action of extract of posterior lobe upon the secretion of urine—and indeed to all actions of this extract upon the tissues—it is necessary to bear in mind that we are probably not dealing, as in the case of adrenaline, with a simple active principle, but in all likelihood with more than one. In the case of urine secretion there is certainly a double action, but whether this is due to two separate and antagonistic autacoids—the effect of the one being to increase urine flow, of the other to diminish it—cannot at present be settled.

The diuretic action was regarded by Schafer and Herring [2] as the direct effect of a specific autacoid on the renal cells, since it appeared to be independent of the vascular conditions of the kidney, except that a certain rate of flow of blood is necessary. As regards the antidiuretic autacoid, it is possible that this does not necessarily act directly on the kidney but may influence it by regulating the amount of water absorbed by the tissues. The diuretic effect may also be connected with the regulation of the amount of water retained by the tissues, although experiments on the perfused kidney rather indicate a direct action on the renal cells.[3]

It may here be recalled that an antidiuretic substance can be separated from the posterior lobe by extraction with absolute alcohol (p. 241). This is, however, not the antidiuretic with which we are dealing, for it was shown by Craig [4] that both diuretic and antidiuretic effects are obtainable from an extract of the residue of dried gland which has been thoroughly extracted with absolute alcohol. But it does not follow that the opposite effects are due to one and the same autacoid, as Abel believes is the case.[5]

Histamine and choline also have an antidiuretic action, but the action of pituitary extract is not due to either of these—which are far less effective and otherwise different.

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[1] *Zeitschr. f. d. ges. Exper. Med.*, xii. 134, 1921.

[2] *Op. cit.*, 1908.

[3] As bearing on this point it may be cited that Monakow has given a description of two cases of atrophy of or injury to the pituitary in which there was degeneration of the cells of the convoluted tubules (*Schw. Arch. f. Neurol. u. Psych.*, 1921).

[4] *Op. cit.*, 1925.

[5] For a further discussion of this question see Chapter XL.

CHAPTER XXXII

THE PITUITARY BODY (*continued*)

Effects of Posterior Lobe Administration on Growth, Metabolism, and Heat Regulation

Growth

The results of administration of posterior lobe on the growth of mammals have either been negative or have shown retardation.[1] Goetsch found also that there was marked retardation of the development of the sexual organs with posterior lobe feeding: he obtained the contrary result with anterior lobe. C. J. Marinus [2] tried the effect of feeding with pars tuberalis, but got little or no effect.

The results obtained with tadpoles have been more definite. B. M. Allen [3] found that tadpoles in which posterior lobe tissue of other tadpoles had been implanted showed distinct retardation of growth. And E. Uhlenhuth [4] noticed that axolotls (larvæ of Amblyostoma) fed with posterior lobe had their growth retarded. We shall see that feeding with anterior lobe produces the opposite result in these animals.

Metabolism

General Metabolism.—J. Malcolm [5] was one of the first to test the influence of pituitary upon metabolism. He investigated in dogs the effect of feeding with the separate lobes on the elimination of nitrogen, calcium, magnesium, and phosphorus. The results which he obtained were somewhat variable, but with posterior lobe feeding there was some retention of N, an increase in P output followed by retention, and an increase of Ca output. The effects were prolonged beyond the period of administration. W. H. Thompson and H. M. Johnston,[6] employing the whole gland, found (in dogs) that metabolism in general was stimulated, both total nitrogen and urea being increased, as well as the urinary phosphates: they ascribe these effects to the posterior lobe.[7] Franchini [8] obtained increase of excretion of calcium, magnesium, and phos-

[1] O. Sandri, *Arch. ital. de biol.*, li., 1909; T. B. Aldrich, *Amer. Journ. Physiol.*, xxxi., 1912; D. D. Lewis and J. L. Miller, *Arch. Internat. Med.*, xii., 1913; E. Goetsch, *Bull. Johns Hopkins Hosp.*, xxvii., 1916.

[2] *Amer. Journ. Physiol.*, xlix., 1919.

[3] *Science*, lii., 1920.

[4] *Proc. Soc. Exper. Biol. and Med.*, 1920.

[5] *Journ. Physiol.*, xxx., 1903.

[6] *Ibid.*, xxxiii., 1905.

[7] See also Falta (with others) in *Wien. klin. Wochenschr.*, 1909.

[8] *Berl. klin. Wochenschr.*, xlvii., 1910.

phates (in rabbits), administering the extract of posterior lobe either by the mouth or hypodermically or intravenously. He also obtained an augmentation of Ca and Mg in the blood, and noticed calcareous deposits in the kidneys, stomach, and intestine.

J. A. Hewitt [1] found that feeding rats with posterior lobe led to increased elimination of ammonia in the urine. Roux and Tallandier [2] noticed an increase of creatinine in the urine of rabbits which were injected subcutaneously with posterior lobe extract. Goetsch, Cushing, and Jacobson [3] found that after repeated injection of posterior lobe extracts the animals (dogs) lost flesh and became emaciated, whereas extracts of anterior lobe had no such effect. R. Coope and E. N. Chamberlain [4] noticed that after subcutaneous injections of the extract in rabbits extending over a prolonged period, the liver became infiltrated with fat without showing any signs of degeneration.

Basal Metabolism.—This is increased by subcutaneous injection of posterior pituitary extract,[5] except in cases where there is reason to believe that the thyroid is insufficiently functioning. This is perhaps an indication that the autacoid acts through the thyroid.

Carbohydrate Metabolism.—The production of glycosuria as the result of injection of posterior lobe extracts was first described by L. Borchardt in the rabbit. Borchardt used a strong extract or decoction, freshly prepared.[6] Hyperglycæmia is first produced. Ott [7] confirmed Borchardt's statement for the rabbit and got a similar result in the cat, but others have failed to obtain glycosuria either in the rabbit or in the dog.[8] Goetsch, Cushing, and Jacobson [9] found that the extract lowers the limit of assimilation for sugar, and that, in consequence, alimentary glycosuria is more readily obtained. The difference in the amount of stored carbohydrate in the experimental animals may be the explanation of the difference in the results obtained by various observers.[10] It would seem that when there is adequate feeding with carbohydrates, injection of posterior lobe in sufficient quantity generally produces glycosuria in normal subjects (both lower animals and man). But the reaction cannot be regarded as specific, like that caused by adrenaline.

The glycosuria sometimes seen in pregnancy may be related to the enlargement of the pituitary which is liable to occur in that condition.

[1] *Quart. Journ. Exper. Physiol.*, viii., 1914.
[2] *Intern. Beitr. z. Path. d. Ernährungsstör.*, v., 1914.
[3] *Johns Hopkins Hosp. Bull.*, xxii., 1911.
[4] *Proc. Physiol. Soc., Journ. Physiol.*, lix., 1924, and *Journ. Physiol.*, lx. 69, 1925; R. Coope (*ibid.*, p. 92) finds that insulin antagonises this effect.
[5] C. A. M'Kinlay, *Arch. int. Med.*, xxviii., 1921.
[6] *Zeitschr. f. klin. Med.*, lxvi., 1908.
[7] "Internal Secretions," 1911.
[8] B. A. Houssay, *op. cit.*, 1911; Carlson and Martin, *Amer. Journ. Physiol.*, xxix., 1911; Garnier and Schulmann, *C. r. soc. biol.*, lxxvii., 1914; Stenström, *Biochem. Zeitschr.*, lviii., 1913; G. Quadri, *Ann. de clin. méd.*, v., 1914.
[9] *Op. cit.*, 1911.
[10] See further on this subject Claude and Baudouin, *C. r. acad. sci.*, cliii., 1911, and *C. r. soc. biol.*, lxxii., 1912; and (with Porak), *ibid.*, lxxiv., 1913.

J. Mellanby [1] found that the glycosuria caused by ether anæsthesia is inhibited by posterior lobe extract. Similarly it has been found that adrenaline glycosuria is also inhibited [2] by the extract. Houssay,[3] on the other hand, obtained a contrary result in rabbits, the addition to adrenaline of posterior lobe extracts enhancing its effect on the amount of glucose in the blood and urine. Although Houssay did not obtain glycosuria from the use of pituitary extract alone, he got in most experiments an increase of blood-sugar.

Heat Regulation

In their dogs injected with posterior lobe extract it was noticed by Harvey Cushing and his fellow workers that there was a rise in body temperature.[4]

This question of the dependence of heat production on the pituitary has been lately subjected to a detailed examination. F. T. Rogers [5] reduced pigeons to a poikilothermous state by removal of the hemispheres and thalami, keeping the animals at an external temperature of 30° to 35° C. He found them to react strongly by a sharp rise of temperature, threatening heat prostration, lasting 12 to 24 hours, to extract of posterior lobe administered intraperitoneally, whereas normal animals showed no such reaction.

M. Hashimoto [6] used mammals—chiefly rabbits but also cats. Operating by the lateral method, he found that removal of the pituitary causes a fall of temperature and reduces the animals to a poikilothermous condition. Injection of extracts of the gland or of posterior lobe only caused a rise to normal, whereas in unoperated animals either no effect was produced or there was a fall of temperature. The hyperpyrexia noted by Rogers in the pigeon does not seem to have been produced. If pyogenic substances which cause fever in normal animals were injected into the hypophysectomised animals no effect was produced unless extract of pituitary (whole gland) were administered just previously. Hashimoto regards it as one of the functions of the pituitary to regulate the body temperature by influencing the excitability of heat centres in the brain. Harvey Cushing has suggested that hibernation may be brought about by a deficiency in its secretion (see p. 194).

As with adrenaline, the effect of pituitary extract upon heat production appears to depend upon the state of nutrition of the animals employed. When these are in the fasting condition, heat production is diminished by both autacoids; when well nourished it is increased; the respiratory quotient also increases (increased combustion of carbohydrate).[7]

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[1] *Journ. Physiol.*, liii., 1919.

[2] J. H. Burn, *ibid.*, lvii., 1923. This had previously been noted by Stenström (*op. cit.*, 1913) and Garnier and Schulmann (*op. cit.*, 1914).

[3] *Op. cit.*, 1918.

[4] *Op. cit.*, 1911. See also H. Cushing, "The Pituitary Body and Its Disorders," 1912. The rise following injection of posterior lobe extract was first noticed by Vassalé and Sacchi (*Riv. Sper. d. Fren.*, xviii., 1891, and xx., 1894).

[5] *Proc. Soc. Exper. Biol. and Med.*, xix., 1922.

[6] *Arch. f. exper. Path. u. Pharm.*, ci., 1924.

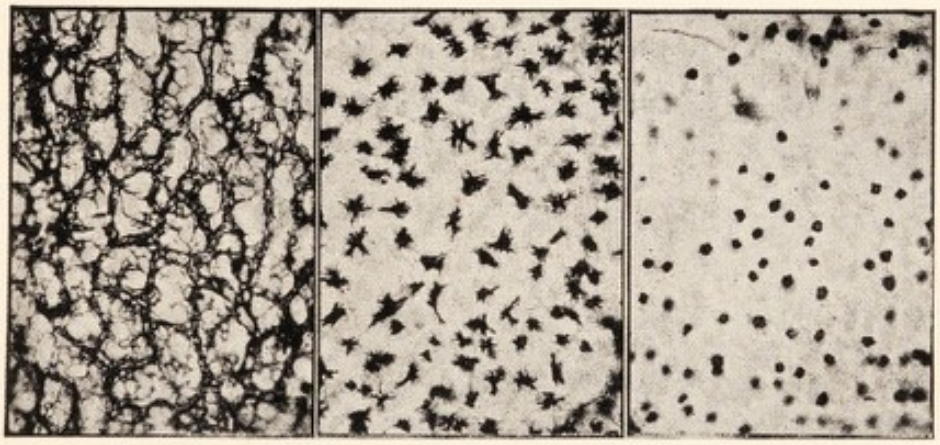
[7] A. Biedl, Trans. XIth Internat. Physiol. Congr. in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., p. 60, 1923.

CHAPTER XXXIII

THE PITUITARY BODY (*continued*)

Effects on Pigment Cells of Amphibia

Experiments on adult Amphibians.—If a frog is kept in a dark moist place at a low temperature (10° C.) it assumes a dark appearance owing to expansion of the pigment in its epidermal melanophores (fig. 133, *a*), and contraction in the subcutaneous xantholeucophores. On the other hand, if kept on a bright background and moderately dry, especially if the temperature is somewhat raised (20° C.), the animal assumes a light appearance: the epidermal melanophore



a *b* *c*

Fig. 133.—Cutaneous melanophores of frog-web (Hogben): *a*, from a dark animal, with the pigment spread out over the whole cell; *b*, in a partially retracted condition; *c*, from a pale animal, with the pigment retracted and concentrated round the nucleus of each cell.

pigment becomes contracted and the xantholeucophore expanded (fig. 133, *c*). These changes are independent of the direct influence of the nervous system and will even occur with blinded frogs exposed to cold and wet or to warm and dry conditions: although if kept at a moderate temperature such frogs show expansion of melanophores whether the surroundings are dry or not.[1]

In all cases of adaptation of the pigment cells of Amphibia to different environmental conditions there is a protracted latent period of from one hour to twenty-four hours or more, whereas with fishes the protective change of colour provoked by alteration in the environment is frequently rapid. The

[1] L. T. Hogben, "The Pigmentary Effector System," 1924.

long latent period in the one case indicates an endocrine reaction : the quick change in the other shows that it is effected under the influence of nerves.[1]

After complete removal of the posterior lobe of the pituitary,[2] a frog becomes and remains pale, whatever the conditions of the environment (even with a dark background and in a cold moist place), and contrasts strongly with a normal animal kept under these conditions (fig. 134). Its melanophores have the appearance of those shown in fig. 133, *c*. The hypodermic injection of posterior lobe extract, whether the frog has been hypophysectomised or not, is followed by a complete change of colour. The animal becomes uniformly dark (fig. 135) ; its epidermal melanophores become fully expanded (like those shown in fig. 133, *a*) and its cutaneous xantholeucophores fully contracted. This condition lasts a certain time, according to the dose employed, the pallid appearance being gradually re-assumed.[3] In normal animals kept in an environment which is optimal for inducing pallor, *i.e.* in a light, warm, dry place, the subcutaneous injection of the extract has the same effect as it has in the hypophysectomised animal. This effect, it may be observed, is exactly the opposite of that caused by adrenaline, which induces extreme contraction of the pigment of the melanophores and expansion of that of the xantholeucophores. Other substances similar in chemical nature to adrenaline produce a similar effect (contraction). But no substance is known, other than that contained in posterior lobe extract, which affects the pigment cells in the same way as the specific melanophore autacoid of that lobe. What this autacoid may be is not ascertained. It is not histamine. It is not antagonised by apocodeine, atropine, curare, or cocaine (Hogben).

These observations tend to show that the " pigmentary effector system " of the frog is controlled on the one hand by the autacoid of the suprarenal medulla (adrenaline) : on the other by an autacoid of the posterior lobe of the pituitary body—probably of the pars intermedia. It seems that in this animal any nervous influences which affect the pigment cells produce their result by stimulating one or other of these glands.[4]

The stimulant for the amphibian melanophores is inactivated by tryptic but not by peptic digestion. It resists boiling. It can be extracted from the pituitaries of all vertebrates examined, but is not yielded by the subneural gland of Tunicata.[5] It was found by Hogben to be present in the pituitary of a

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[1] This does not, however, exclude the participation of internal secretions (see Part I., p. 137) in these.

[2] For the method of removal, see L. T. Hogben, *Quart. Journ. Exper. Physiol.*, xiii., 1923.

[3] Hogben and Winton (*Proc. Roy. Soc.*, B, xcv., 1923) obtained enough extract from a single frog pituitary to affect the pigmentation of fifty-six other frogs. See further on the pituitary regulation of colour in Amphibia (Leptodactylus ocellatus), Houssay and Ungar, *Rev. s. Argent. de biol.*, vi., 1925.

[4] Hogben and Winton, *Proc. Roy. Soc.*, B, xciii. and xciv., 1922. See also Rep. of XIth Internat. Physiol. Congress, 1923, in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923, p. 149.

[5] Hogben and Winton, *Biochem. Journ.*, xvi., 1922.

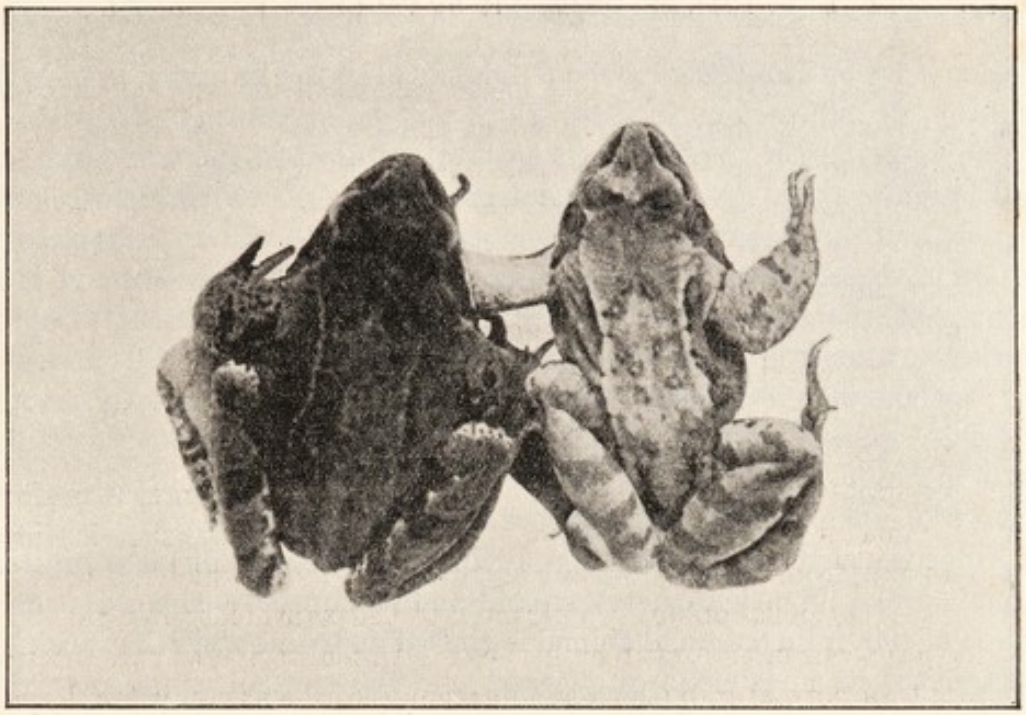

FIG. 134.—Two frogs (*R. temporaria*). That on the left partially hypophysectomised (anterior lobe only); that on the right completely hypophysectomised. (Hogben.)

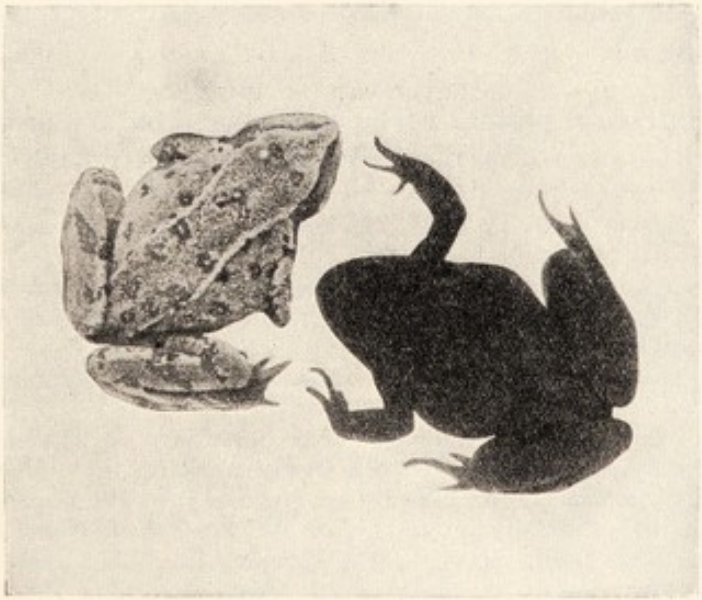

FIG. 135.—Two frogs (*R. temporaria*). That on the right injected six hours previously with bovine pituitary extract; that on the left, control. (Hogben.)

four-months' human fœtus.[1] The retinal pigment cells, which are expanded by adrenaline (Part I., p. 137), are unaffected by the pituitary autacoid.

Experiments on Amphibian Larvæ.—Removal of the pituitary in tadpoles—apart from its influence on growth, which will be afterwards alluded to—has the same effect on the pigment cells as that obtained in the adult frog. The animal becomes pallid from permanent contraction of the cutaneous melanophores in and immediately below the epidermis, together perhaps with a reduction in the number of cells containing pigment and in the amount of their pigment; at the same time there is expansion of the xantholeucophores, producing an almost metallic lustre (experimental albinism).[2] The more deeply seated melanophores remain unaltered. If now the hypophysectomised tadpoles are immersed in an emulsion of pars intermedia of bovine pituitary, the skin melanophores expand while the xantholeucophores contract. Neither pars anterior nor pars nervosa produces these effects.

If a portion of the pallid skin of a hypophysectomised animal is grafted on a normal animal its melanophores expand and its xantholeucophores contract: if a piece of skin from a normal animal is grafted on to one which has been hypophysectomised its melanophores contract and the xantholeucophores expand. These changes occur in about fifteen minutes. Implantation of pars intermedia of a frog into a normal tadpole causes darkening of the skin: into a hypophysectomised tadpole, removal of the albinism. But the grafts gradually degenerate and the effects pass off.[3] Other experiments have been made by Hogben and Winton upon axolotls, the salamander-like larvæ of Amblyostoma tigrinum, which normally retain their tadpole condition and undergo sexual maturity in their larval state. If hypophysectomised, they become and remain pale grey instead of black. A subcutaneous injection of extract of posterior lobe of the bovine gland brings back their colour. The effect lasts a few days, eventually passing off.[4]

Injection of extract of posterior lobe of bovine pituitary produces darkening of the skin in all Anura: the effect can be got with detached pieces of skin

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[1] *Brit. Journ. Exper. Biol.*, i., 1924. Keene and Hewer, however, found it in an embryo of half that age (*Lancet*, i. 111, 1924).

[2] P. E. Smith, *Proc. Soc. Exper. Biol. and Med.*, xvi., 1919. Smith states that experimental albinism can be produced merely by the removal of the part of the gland furthest from the infundibulum.

[3] The pars nervosa has not this action; it causes a peculiar shrinkage of the tadpole (Allen, Swingle).

[4] The history of the subject of the effect of the pituitary on pigment cells, as well as a selected bibliography, is given by Hogben in his work on the "Pigmentary Effector System" already mentioned. The following are some of the chief papers dealing with the question other than those already quoted: Leo Adler, *Arch. f. Entwickl.-Mech.*, xxxix., 1914; B. M. Allen, *Biol. Bull.*, xxxvi., 1907; *Science*, lii., 1920; *Anat. Rec.*, xx., 1921; P. E. Smith, *Anat. Rec.*, ix., 1916; *Amer. Anat. Mem.*, xi., 1920; *Proc. Soc. Exper. Biol. and Med.*, xvi., 1919 (three papers); P. E. and I. B. Smith, *Proc. Soc. Exper. Biol. and Med.*, xx., 1922; *Endocrinology*, July 1923; W. J. Atwell, *Anat. Rec.*, xv., 1918; *Science*, xlix., 1919; *Endocrinology*, v., 1921; W. W. Swingle, *Journ. Exper. Zool.*, xxxiv., 1921; W. H. Cole, *Journ. Exper. Zool.*, xxxv., 1922.

and is specific. The greatest effect is obtained with extracts of pars intermedia, one part to four or five millions of water; with the whole posterior lobe the effect is obtained with one part to one million, while with anterior lobe no effect was got with a more dilute solution than 1 in 500; this may easily have been due to contamination. The authors arrive at the conclusion that the pressor, oxytocic, and melanophore effects are produced by different autacoids (see Chapters XXXV and XXXVI). The effect of injection is equally obtained with amphibians deprived of the pituitary. It is interesting to note that some melanophore action is obtained with mammalian cerebrospinal fluid (see p. 203).

The effects of hypophysectomy and pituitary injections upon toads have been studied by Giusti and Houssay, and Houssay and Ungar.[1] These observers find that removal of the organ in the toad causes not only pallor of the skin but also in every case the formation of a dark cuticle over the surface. In males the operation is followed by testicular atrophy; in females by premature discharge of ova. The complete operation was fatal within forty-five days in 85 per cent. of the animals operated on.

[1] *La sem. med.*, May 29, 1924.

CHAPTER XXXIV

THE PITUITARY BODY (*continued*)

Influence of Nerves and of Direct Stimulation on the Secretion from the Posterior Lobe

Numerous experiments have been made on the results of stimulating the cervical sympathetic or its superior ganglion, and on that of stimulating afferent nerves, such as the vagus, but no constant and unmistakable effect can be shown to be due to such stimulation indicative of an increase or decrease of the passage of active material into the blood or cerebrospinal fluid. Nor has section of the cervical sympathetic or excision of its superior ganglion been found to cause any change in the gland. Weed, Cushing, and Jacobson [1] obtained glycosuria from stimulation of the superior cervical ganglion (rabbit, cat, dog) when there was abundance of available glycogen in storage in the liver, and state that the same effect is produced by direct stimulation of the gland—whether electrical or mechanical—even if the cord is divided at the fourth thoracic segment, *i.e.* above the origin of the splanchnics, but fails if the posterior lobe is previously removed. They even suggest that Bernard's sugar puncture may act through the pituitary. But Rabens and Lifschitz [2] obtained negative results in the same animals as regards hyperglycæmia, glycosuria, and diuresis when they stimulated the cervical sympathetic in the absence of an anæsthetic. On the other hand, V. N. Shamoff [3] got both diuresis and glycosuria in eight experiments out of fifteen, the effects being independent of changes in the blood-pressure or of nervous influences to the kidney, and Keeton and Becht [4] got glycosuria on stimulating the organ directly (dog), but failed to obtain this result if the splanchnics had been divided or the cord cut at the level of the second thoracic segment. They especially note that the effect was only got on stimulating the gland itself, not the brain substance in its proximity. Drugs such as pilocarpine and adrenaline which excite secretion by stimulating nerve-endings within secreting glands have been found to have no effect on the pituitary,[5] although certain animal extracts, and particularly extract of ovary, have a marked effect, acting probably directly on the cells of the pars intermedia (see p. 202).

[1] *Proc. Amer. Physiol. Soc.* in *Amer. Journ. Physiol.*, xxxi., 1913, and *Johns Hopkins Hosp. Bull.*, xxiv., 1913.

[2] *Amer. Journ. Physiol.*, xxxvi., 1915.

[3] *Ibid.*, xxxix., 1915–16.

[4] *Ibid.*, xxxix., 1915–16, and xlix., 1919.

[5] W. E. Dixon, *Journ. Physiol.*, lvii., 1923.

CHAPTER XXXV

THE PITUITARY BODY (*continued*)

Are the Various Effects Obtained from Extracts of the Posterior Lobe Due to Only One or to More Than One Autacoid?

This subject has been already frequently alluded to and will be considered further in the next chapter, in which the chemistry of the gland is dealt with. It will be sufficient here to indicate the physiological observations which appear to bear upon the point.

Without discussing chemical details it may be premised that no autacoid—such as the adrenaline of suprarenal medulla—has been isolated from the posterior lobe in any condition approaching purity, in spite of the prolonged labours of many competent chemists.[1] So difficult has it proved to isolate different autacoids producing the various effects on blood-pressure, uterus, mammary and renal secretion, amphibian melanophores, etc., which have been described in the preceding chapters, that some authors, *e.g.* Abel, have supposed that all the effects are caused by one and the same active chemical principle. There are, however, reasons for believing that this is not the case.

The history of the subject begins with the observation that it is possible to separate by extraction of dry ox posterior lobe with absolute alcohol a substance (*depressor substance*) which has most of the physiological properties of histamine and produces a fall in systemic and a rise in pulmonary blood-pressure in anæsthetised cats, instead of the usual pressor effect yielded by the untreated gland, and given by the residue after such alcohol extraction (*pressor substance*).[2] In the bird such extracts, whether previously treated with absolute alcohol or not,[3] have a purely depressor action,[4] but the mechanism of this action requires further elucidation. It is due to another specific autacoid, which is certainly different from that which produces the depressor effect in mammals, for Hogben finds that extracts of skate pituitary which, as Herring showed, possess no pressor or depressor activity on the circulation in mammals will yet cause a depressor effect in the duck.[5]

That the autacoid which excites the uterus (oxytocic hormone), which is perhaps the same as that which causes emptying of the alveoli of the lactating

[1] *Cf.* G. Barger, *The Prescriber*, xvii. 189, 1923.
[2] Schafer and Vincent, *op. cit.*, 1899.
[3] Hogben and Schlapp, *Quart. Journ. Exper. Physiol.*, xiv., 1924.
[4] Noël Paton and Watson, *Journ. Physiol.*, xliv., 1912.
[5] *Quart. Journ. Exper. Physiol.*, xv., 1925.

mammary gland, is different from the autacoid which causes contraction of the muscular coat of the blood-vessels, appears evident from the fact that the pituitary of the skate yields an extract which has no influence on blood-pressure although it has a marked effect in exciting the uterus and the lactating mammary gland of the mammal (fig. 136), some influence on renal activity, and also, as we have seen, a depressor effect on the circulatory system of the bird. On the other hand, the pituitary of the cod contains autacoids which both raise the blood-pressure and excite the lactating mammary gland (fig. 137) and the kidney, and also depress the avine blood-pressure.[1] Herring has further shown that there are indications of a separation between the autacoids in the two main portions of the bovine posterior lobe. Thus extracts of pars intermedia, while having a marked effect on the uterus, mammary gland, and, it may be added, on

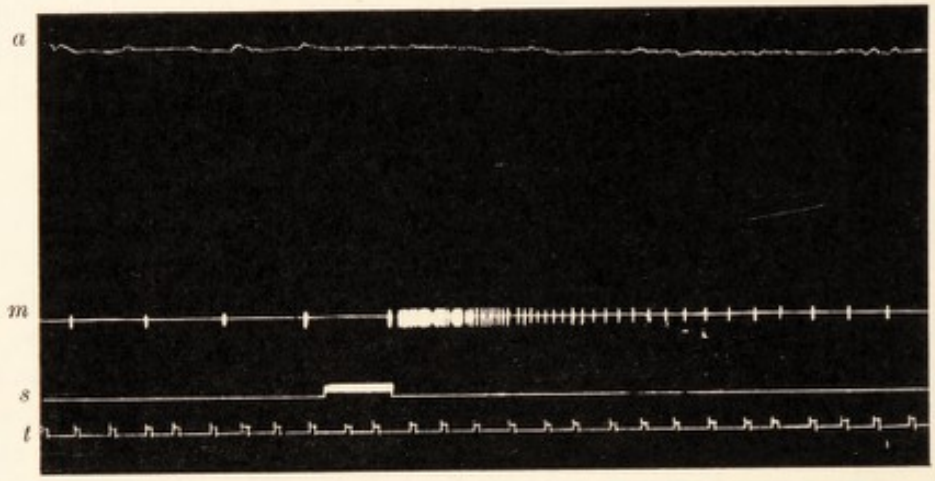


FIG. 136.—Effect of injecting into the jugular vein of a cat 1 c.c. of an extract of the pituitary of the skate. (Herring.) The amount injected represented $\frac{1}{8}$ths of a single gland.

a, blood-pressure; *m*, mammary secretion; *s*, signal; *t*, time in ten seconds. (This extract also has an effect on urinary secretion.)

frog melanophores,[2] contain little, if any, of the pressor principle (fig. 138), which is yielded mainly if not exclusively by pars nervosa;[3] nor do they exhibit a specific effect on the kidney, either in its volume or secretion, such as is caused by extracts of pars nervosa (fig. 139); even if the extract of pars intermedia is a hundred times as strong as a pars nervosa extract. Repeat doses of pars intermedia extract show no tachyphylaxis (this is also the case with extracts of the elasmobranch gland), nor do they hinder extracts of pars nervosa, administered immediately after them, from producing their full effect. On the other hand, extracts of pars nervosa give full effects on all the tissues acted upon (except the amphibian melanophores). Herring found the pressor autacoid to be confined to the pars nervosa, and the

[1] P. T. Herring, *Quart. Journ. Exper. Physiol.*, vi., 1913, and viii., 1914.

[2] Hogben and Winton, *Biochem. Journ.*, xvi., 1922; Hogben, "The Pigmentary Effector System," 1924.

[3] Lewis, Miller, and Mathews (*Arch. internat. Med.*, vii., 1911) obtained a distinct rise of blood-pressure from pars intermedia. It is, however, possible that there was some contamination with pars nervosa.

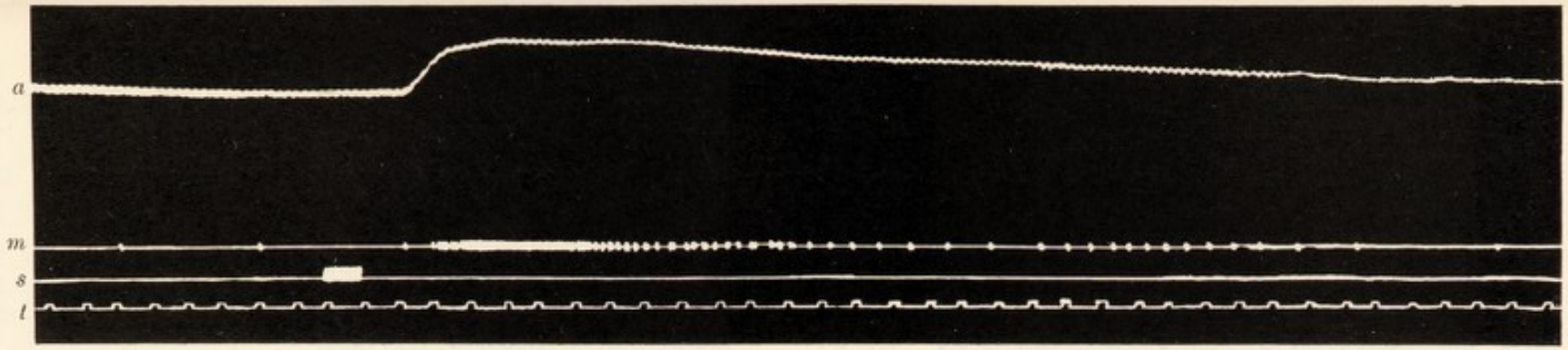


FIG. 137.—Effect of injecting into the jugular vein of a cat 2 c.c. of an extract of posterior lobe (pars nervosa + pars intermedia) of a cod's pituitary. (Herring.) The amount injected represented an extract of $\frac{2}{5}$ths of fresh pars nervosa + pars intermedia of a single gland.

a, blood-pressure ; *m*, mammary secretion ; *s*, signal ; *t*, time in ten seconds. (This extract also provoked urinary secretion.)

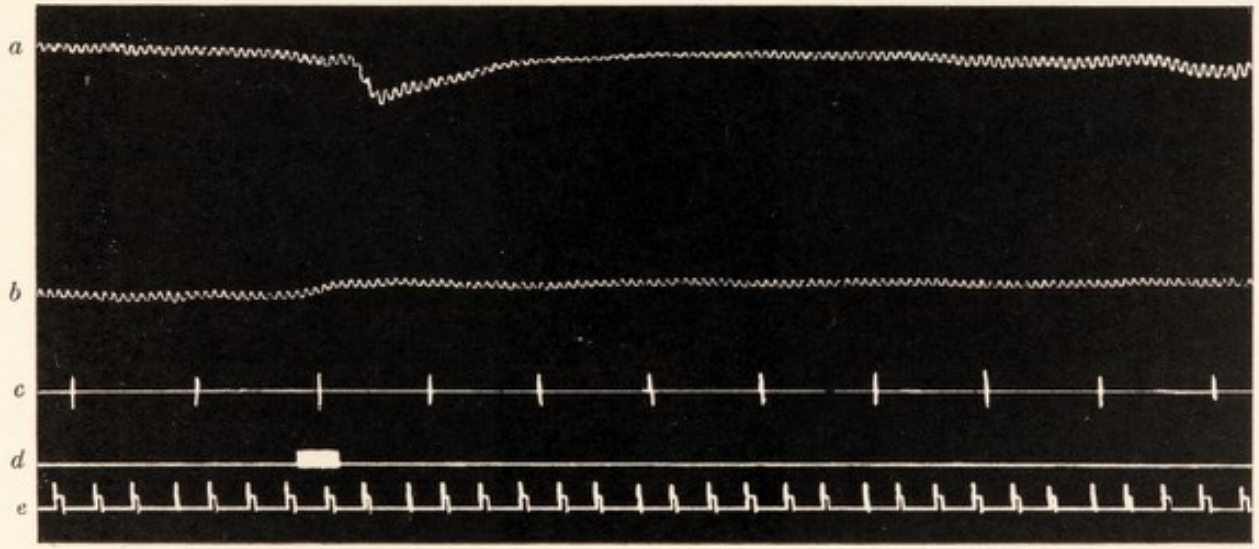


FIG. 138.—Shows slight fall of blood-pressure without change in kidney volume or in urine secretion on injecting 3 c.c. of a 0·25 per cent. extract of pars intermedia of fresh ox-pituitary into the jugular vein of a cat. (Herring.)

a, blood-pressure ; *b*, kidney volume ; *c*, urine drops ; *d*, signal ; *e*, time in ten-second intervals.

oxytocic action, although exhibited by pars intermedia extracts, to be stronger in pars nervosa (from two to five times) (fig. 140). Herring concluded from his

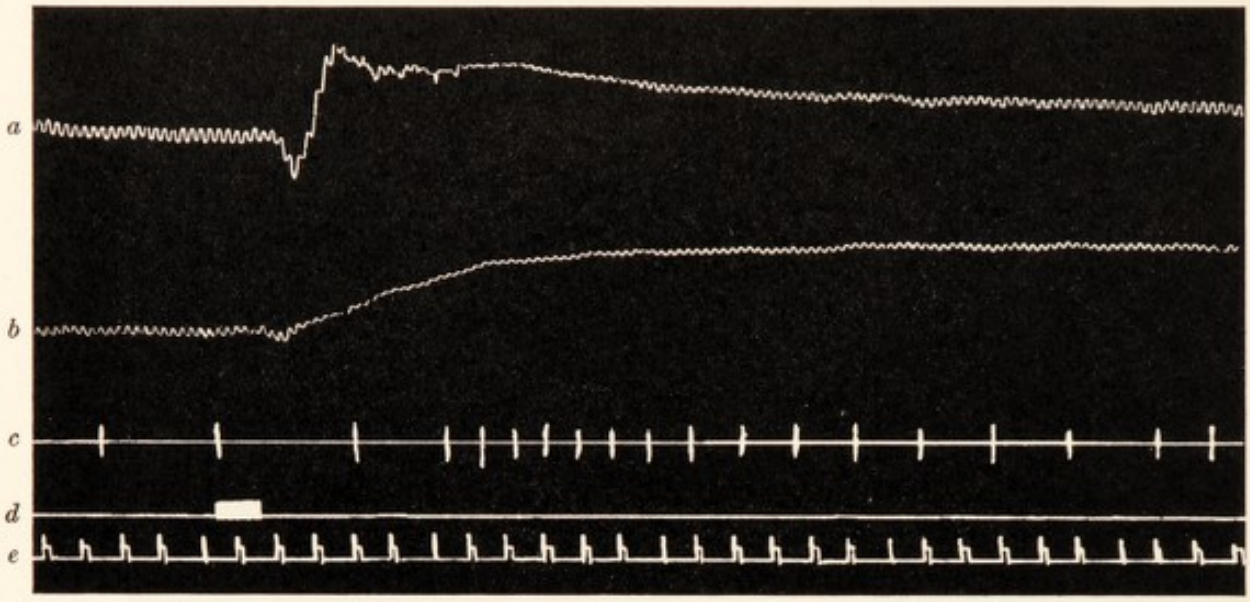
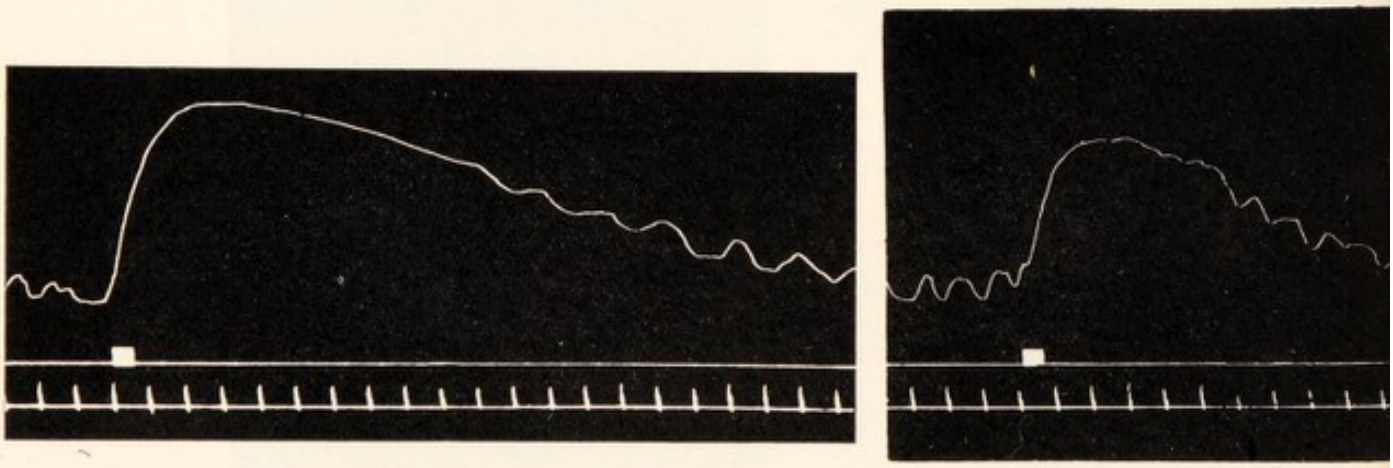


FIG. 139.—Shows marked effects on blood-pressure, kidney volume, and urine flow on injecting 3 c.c. of a 0·25 per cent. extract of pars nervosa of fresh ox-pituitary into the jugular vein of the same cat. This injection was made eight minutes later. (Herring.) Lettering as in fig. 138.



A B

FIG. 140.—A. Tracing showing the effect of extract of pars nervosa of ox-pituitary on isolated muscular tissue of rat's uterus. (Herring.) The strip was acted upon by the extract during the period marked by the signal. B. Tracing made from the same uterus preparation as that employed for A. It shows the effect produced by an equivalent amount of extract of pars intermedia. The resulting contraction is smaller and less prolonged.

observations that there are at least two distinct autacoids in the posterior lobe, one acting on the uterus and mammary gland, the other upon the blood-pressure and kidney. He believed that the material for both is produced by

the epithelium of the pars intermedia, and that this material becomes chemically changed in its passage through the pars nervosa towards the third ventricle. The oxytocic substance is already formed in the pars intermedia, but the pressor substance is a product of the chemical changes in the pars nervosa and is only found fully formed in that part. To this may be added that there are strong reasons, already set forth, for considering that the pressor and diuretic effects are produced by different autacoids.

Hogben and de Beer [1] confirm Herring's statement that extracts of elasmobranch pituitary show no evidence of the presence of a "pressor" autacoid, although producing a well-marked effect on the uterus; they nevertheless think it possible that a pressor autacoid may exist in such extracts but in insufficient amount to produce an appreciable effect, although the oxytocic effect, which is got with a much smaller dosage, is readily obtainable. But the "depressor" effect on the circulation of the duck, which is quite a special result, is obtained from the elasmobranch extract. It seems probable that Herring's opinion that the elasmobranch pituitary does *not* manufacture a pressor substance is correct, and that the pressor autacoid of the mammalian gland is not identical with the oxytocic autacoid, nor with the autacoid which produces a depressor effect in the duck.

The melanophore reaction was not recognised at the time that Herring's observations were made. Although formed in the pars intermedia there are reasons for believing that the autacoid which produces this effect is not the same as the oxytocic autacoid, for although, like that substance, it resists boiling with dilute hydrochloric acid, it can be separated from the oxytocic autacoid by its different solubility in butyl alcohol and by ultrafiltration through collodion, the oxytocic substance alone passing through.[2]

Lewis, Miller, and Mathews [3] differ from Herring in describing a pressor effect from pars intermedia; they also obtained a pressor effect from pars tuberalis. Atwell and Marinus [4] found the slowing action on the mammalian heart was only got from extracts of pars nervosa, not from pars intermedia, but they obtained a strong pressor effect from extracts of pars intermedia and a fairly powerful pressor effect from extracts of the stalk, while extracts of pars tuberalis gave much less result both with uterus and blood-pressure. They agree with Herring that it is probable that the active principles of the pars nervosa are formed by the cells of the pars intermedia.

Abel and Nagayoma [5] found that the pressor effects of posterior lobe extracts are abolished by boiling with dilute hydrochloric acid (0·5 per cent.), whereas the oxytocic and the melanophore effects resist this treatment: the depressor and the broncho-constrictor action is also retained. Roca [6] states that the depressor

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[1] *Quart. Journ. Exper. Physiol.*, xv., 1925.

[2] Glenny and Walpole, *Biochem. Journ.*, ix., 1915; N. B. Dreyer and A. J. Clark, *Proc. Physiol. Soc.*, p. xviii, in *Journ. Physiol.*, lviii., 1924. A partial separation can also be effected by precipitation with lead sulphide (Guggenheim, *Biochem. Zeitschr.*, lxv., 1914; W. Schlapp, *Quart. Journ. Exper. Physiol.*, xv., 1925).

[3] *Amer. Journ. Physiol.*, xxvii., 1911.

[4] *Ibid.*, xlvii. 76, 1918.

[5] *Journ. Pharm. and Exper. Therap.*, xv., 1920.

[6] *Ibid.*, xviii., 1921.

action after such treatment is from seven to eight times as great as that yielded by extracts of anterior lobe. Even after boiling for six hours with the dilute acid the extract retains a powerful oxytocic action—far more than a dose of histamine having an equal depressor effect.[1] The oxytocic autacoid is slowly destroyed by erepsin, but neither it nor the pressor autacoid are affected by papain. Nor is the pressor autacoid affected by peptic digestion [2] although all the active principles are inactivated by tryptic digestion.

W. Cramer [3] found that extracts of posterior lobe which have been kept some time have lost their influence on the pupil of the excised eye of the frog, while retaining their diuretic action. Such extracts also appear to retain a galactagogue action.[4]

The alcohol extract of posterior lobe has been ascertained by Schlapp and Macdonald to be peculiarly potent in its action on the intestinal strip, whereas the residue after such extraction is almost without action on the intestine [5]: nor can the autacoid concerned be destroyed by either acids or alkalies, which is the case with the oxytocic and pressor activities.

Engeland and Kutscher [6] succeeded in obtaining an autacoid which produced a marked action on the uterus but had no effect on blood-pressure.

Further, W. O. Fenn [7] brings forward evidence to show that the melanophore and oxytocic effects of the extract are produced by different autacoids; and also that the pressor hormone is distinct from that which acts on the uterus.

On the other hand, M. I. Smith and W. T. M'Closky [8] found the oxytocic and pressor effects of extracts of posterior lobe to undergo deterioration along parallel lines as the result of keeping at a temperature of 60° C., and conclude that they are produced by a single chemical agent.

Reviewing the above evidence it seems probable that the various physiological effects of extracts of posterior lobe must be caused by more than one autacoid, possibly by several. That it has not been possible to effect a chemical isolation is hardly surprising seeing that such bodies would be separated out together by most precipitation agents, for it is probable there is not much dissimilarity in their chemical constitution.

[1] Dale and Dudley, *ibid.* See also Dudley, *ibid.*, xiv., 1919, and xxi., 1923.
[2] Oliver and Schafer, *op. cit.*, 1895.
[3] *Quart. Journ. Exper. Physiol.*, i., 1908.
[4] B. A. Houssay, *Endocrinology*, i., 1917.
[5] A. D. Macdonald, *Quart. Journ. Exper. Physiol.*, xv., 1925.
[6] *Zeitschr. f. Biol.*, lvii., 1912.
[7] *Journ. Physiol.*, lix. (*Proc. Physiol. Soc.*, p. xxxv), 1924. See also Kraus, Dreyer, and A. J. Clark, *Proc. Physiol. Soc.*, p. xviii. 1925, in *Journ. Physiol.*, lx.
[8] *Hygienic Laboratory, Washington, Bull.*, No. 138, 1924.

CHAPTER XXXVI[1]

THE PITUITARY BODY (*continued*)

The Chemistry of the Pituitary Body

The general chemical composition of the pituitary body has been investigated by J. Malcolm,[2] F. Fenger,[3] and B. A. Houssay.[4] An analysis of both posterior and anterior lobes has been carried out by MacArthur.[5] A detailed account of the methods employed by him and the results obtained cannot be given here; the salient features of his analysis are, however, copied in the following table.

	Anterior lobe.		Posterior lobe.	
	Fresh tissue.	Total solids.	Fresh tissue.	Total solids.
Water . . .	77·23	..	79·68	..
Solids . . .	22·77	..	20·23	..
Proteins . .	17·66	77·53	13·46	66·22
Lipins . . .	3·66	13·67	4·00	19·68
Alcohol-extractives .	1·95	3·73	2·87	14·12

Halliburton, Candler, and Sikes[6] found no iodine in the human or bovine pituitary; Sutherland Simpson and Andrew Hunter[7] none in that of the sheep. E. C. Seaman,[8] who used large amounts of the glandular substance of the sheep, also obtained purely negative results. In man the absence of iodine was long ago determined by E. Baumann;[9] this observation has also been confirmed by W. Denis.[10]

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[1] This chapter is contributed by Walter Schlapp.
[2] *Journ. Physiol.*, xxx., 1904.
[3] *Journ. Biol. Chem.*, xxi., 1915; xxv., 1916; and xxvii., 1916.
[4] "La accion, etc.," *op. cit.*, 1918.
[5] *Journ. Amer. Chem. Soc.*, xli., 1919.
[6] *Quart. Journ. Exper. Physiol.*, ii. 229, 1909.
[7] *Ibid.*, iii., 1910.
[8] *Journ. Biol. Chem.*, xliii., 1920.
[9] *Münch. med. Wochenschr.*, xliii., 1896.
[10] *Journ. Biol. Chem.*, ix., 1911.

Anterior Lobe

We know nothing regarding the chemical nature of the growth-controlling substance of the anterior lobe. The results of its administration have been studied in mammals, in birds, and more recently in amphibian larvæ. Some of the effects obtained in the last named are striking, but the active principle which produces them has not yet been isolated.[1]

According to P. E. Smith [2] the substance which affects the growth of amphibian larvæ is contained in the residues after extraction with boiling water or alcohol.

Posterior Lobe

The investigation of the active principles of the posterior lobe of the pituitary body from a chemical point of view began almost immediately after the discovery of the physiological action of such extracts by Oliver and Schäfer,[3] and although the object of the investigation has not yet been attained, certain facts which throw light upon the nature of the active principles have been elucidated. The efforts of recent investigators have been directed in the main to determine whether the numerous physiological responses evoked by the extracts are attributable to one or to more than one substance (see previous chapter) : and attempts have been made to obtain in a pure state a substance which will evoke one particular response.

H. Fühner [4] described four substances acting differently on various organs and separable in crystalline form, but the opinion of subsequent workers seems to be that none of these represent the active principles in a pure condition.[5]

The fact that it is possible to separate by means of alcoholic extraction a substance which produces a purely depressor response in the anæsthetised carnivore [6] is of the first importance, although largely ignored by subsequent workers. The fact has been recently confirmed by Hogben and Schlapp,[7] who have emphasised the similarity of the depressor response, in both the anæsthetised and decerebrated carnivore, to that produced by histamine. Further confirmation is provided by the statement of Roca [8] that the depressor substance can be removed completely by extraction with chloroform. It is

[1] Mention must, however, be made of the work of Brailsford Robertson, who claims to have isolated the active principle. This will be referred to later.

[2] *Amer. Anat. Mem.*, xi., 1920.

[3] *Journ. Physiol.*, xviii., 1895.

[4] *Deutsch. med. Wochenschr.*, 1913 and 1920 ; *Biochem. Zeitschr.*, lxxvi., 1916.

[5] A concise account of Fühner's methods is given by Houssay, *op. cit.*, 1918, pp. 27, 29. For other methods which have been employed, see A. Baudouin, *C. r. soc. biol.*, 1912, and Bouin and Ancel, *ibid.*, 1914 ; also F. S. Hammett, Article, "Pharmacology of Hypophyseal Extracts," in Barker's *Endocrinology and Metabolism*, i., 1922.

[6] Schafer and Vincent, *Journ. Physiol.*, xxv., 1899.

[7] *Quart. Journ. Exper. Physiol.*, xiv., 1924.

[8] *Journ. Pharm. and Exper. Therap.*, xviii., 1921.

also of importance to notice that although Abel[1] and his co-workers were admittedly mistaken in identifying the chief active principle with histamine,[2] they succeeded in obtaining histamine from posterior pituitary substance.[3] Nevertheless, it seems possible that histamine does not always exist in the perfectly fresh tissue. Hanke and Koessler[4] were unable to detect its presence in glands which were specially preserved, and Hogben, Schlapp, and Macdonald[5] note a total absence of the "depressor" substance in glands which were collected while still warm, frozen at – 10° C., and dehydrated in ice-cold acetone.

Nothing is known concerning the chemical constitution of the active principles, which have never been isolated in a chemically pure condition. The close similarity of their general chemical and physical properties suggests the possibility that if not identical they are at least closely related. The destructive action of trypsin; the, probably hydrolytic, action of dilute acids; the slightly basic properties displayed, and the fact that the most highly purified preparations still give the biuret reaction would appear to indicate a polypeptide structure. A positive Pauly reaction with p-diazobenzene sulphonic acid suggests a connexion with histidine.

Physiological Tests

As the considerations for identity or otherwise of the several principles, which have been put forward from time to time by various writers, must depend for their cogency upon the validity of the physiological methods of standardisation employed, it seems desirable to give some account of these methods.

Uterus.—The uterus or oxytocic test was originally suggested by Dale and Laidlaw,[6] and has since its publication undergone no material alteration. It depends for its efficiency upon the fact that when an isolated uterine cornu of the virgin guinea-pig is suspended in a bath of physiological salt solution, the addition to the bath of pituitary extract produces a contraction of the organ which may be recorded by means of a lever; if the extent of the contraction is just submaximal, equal doses will evoke equal responses. In order to compare the oxytocic activities of two samples of pituitary extract, they are diluted until the responses they evoke are submaximal, and thus a first approximation to the relative strengths may be made. One of the extracts is thereupon selected as a standard, and by increasing or diminishing the amount of the second which must be added to the bath to obtain a contraction

[1] *Ibid.*, xv., 1920.

[2] This had previously been shown by D. Cow (*Journ. Pharm. and Exper. Therap.*, xiv. 257, 1919), and by Dudley, *ibid.*, p. 295.

[3] *Journ. Pharm. and Exper. Therap.*, xv., 1920 (Abel and Kubota, Abel and Macht).

[4] *Journ. Biol. Chem.*, xlii., 1920.

[5] *Quart. Journ. Exper. Physiol.*, xiv., 1924.

[6] *Journ. Pharm. and Exper. Therap.*, iv., 1912. See also H. C. Hamilton and L. W. Rowe, *Journ. Lab. and Clin. Med.*, ii., 1916; Burn and Dale, "Reports on Biological Standards," *Medical Research Council Reports*, No. 69, 1922, and H. Sawasaki, *Pflüger's Archiv*, ccix. 137, 1925.

of the uterus which matches that produced by the standard, a closer estimate of the relative activities of the extracts may be made. The method has been found to give results which are accurate to within 12 per cent. (see fig. 124).

Various standards of comparison have been proposed for pituitary preparations,[1] but probably the most satisfactory is that furnished by the bovine posterior lobe itself, as originally suggested by Dale and Laidlaw. Smith and M'Closky recommend that it be kept as a dessicated powder and extracts made as required.[2]

On account of its application in obstetrical practice a considerable amount of attention has been directed to the oxytocic autacoid, and a number of observations on its properties have been made. Among the physical properties which have been investigated solubility takes a prominent place. Attempts to find suitable solvents have revealed the fact that the hormone dissolves in acidulated methyl and ethyl alcohols, and in water; the potency of the methyl alcohol extract being more than twice that of the water extract.[3] It is also almost completely soluble in acid butyl alcohol (Dudley). The solubility in absolute ethyl alcohol appears to be very slight. The autacoid is insoluble in acetone, ether, petroleum ether, and chloroform, although considerably soluble in a 95 per cent. alcohol-water mixture.[4] Observations have also been made on ultrafiltration and adsorption. As already stated (p. 263) it passes the ultrafilter with fair readiness, and is adsorbed to fine powders such as lead sulphide and talcum. The thermo-stability of the active substance may be inferred from the fact that one author recommends the use of boiling 95 per cent. alcohol for extraction, and it is a matter of routine in some laboratories to subject the extracts to temperatures up to 100° C. for purposes of sterilisation.

With one possible exception no specific chemical reaction has as yet been described. Guggenheim (*op. cit.*) and, later, Abel, Rouiller, and Geiling[5] have called attention to a pink or violet colour which appears on warming with concentrated hydrochloric acid. Other chemical properties which have been described cannot be regarded as specific and only serve to exclude the principle from certain classes of compounds. The numerous attempts which have been made to isolate the autacoids[6] show that the active substance is carried down in precipitates produced in extracts by the addition of salts of heavy metals. Those of mercury have been most commonly employed; but ~~the use of~~ lead, gold, platinum, and aluminium salts have also been advocated.[7] Other

[1] E. E. Nelson, *Journ. Lab. and Clin. Med.*, viii., 1923.

[2] U.S. Public Health Service, Washington, *Hygienic Lab. Bull.*, No. 138, i., 1924.

[3] Fenger, *Journ. Biol. Chem.*, xxv., 1916.

[4] Dudley, *Journ. Pharm. and Exper. Therap.*, xiv., 1919; Fenger and Hull, *Journ. Biol. Chem.*, xlii., 1920; Smith and M'Closky, *Publ. Health Rep.*, Washington, xxxviii., 1923.

[5] *Journ. Pharm. and Exper. Therap.*, xxii., 1924.

[6] A detailed account of these attempts is given by E. C. Dodds and F. Dickens, "The Chemical and Physiological Properties of the Internal Secretions," pp. 74–104, 1925.

[7] Führer, *op. cit.*; Abel, *op. cit.*; Heidelberg, Pittenger, and Vanderkleed, *Journ. Amer. Pharm. Assoc.*, iii., 1914; Crawford, *Journ. Pharm. and Exper. Therap.*, xv., 1920; Houssay, *Endocrinology*, i., 1917.

precipitants, such as phosphotungstic, tannic and picrolonic acids, and cinchonine in alcoholic solution have been used; it is not unlikely that adsorption phenomena underlie some of the results recorded. Tartaric and picric acids have been made use of in the final stages of purification. Abel and his co-workers [1] succeeded in isolating a tartrate which gave the biuret and Pauly reactions and was between 1000 and 1250 times more potent in its action on the uterus than an equal dose of histamine acid phosphate. A solution containing 1 part to 250 millions of Ringer caused contraction of the guinea-pig uterus. This principle, according to Abel, also raises blood-pressure, produces contraction of frog melanophores, and is antidiuretic. Other principles lower blood-pressure: one of these appears to be histamine (see p. 267).

The stability of the oxytocic hormone when acted upon by various re-agents has formed the subject of many researches. It shows no deterioration if its sterilised solutions are kept at 0° C. for a year; very little at temperatures up to 37° C.; more at 45° C.; and nearly complete destruction if kept for three months at 60° C. The pressor principle seems to go hand in hand with the oxytocic in this respect,[2] and may be identical with it as Abel believes, but there are reasons for thinking that this is not the case (see p. 264). The oxytocic hormone is destroyed rapidly by the action of alkali, strong acids, and trypsin (Guggenheim, Dudley); on boiling with dilute acids (0·5 per cent. HCl) the activity gradually diminishes; after six hours some activity (1/200th) remains (Dudley). It is slowly destroyed by erepsin, but is not affected by digestion with papain (Dale and Dudley).[3]

Blood-pressure.—Until recently the position in regard to pressor standardisation has been far from satisfactory. While an initial dose of pituitary extract from which the depressor substance has been previously removed evokes a purely pressor response in the spinal cat, the second and subsequent doses, provided that they are administered at short intervals, produces responses which progressively diminish in extent until what appears to be complete immunity is established. The procedure in comparing the pressor activities of two samples of pituitary extract has consisted in injecting the standard and the unknown alternately into the vessels of a spinal cat in which the state of total immunity was in the process of being established; and of so arranging the dilution of the extract of unknown potency that the responses elicited by its injection form a consistently diminishing series with the responses produced by the alternate injections of the standard. When these conditions are satisfied it is assumed that the extracts were of equal potency. The researches of Hogben, Schlapp, and Macdonald [4] have, however, shown that, provided a sufficient interval is allowed to elapse between the injections, equal responses may be obtained for equal doses. The procedure they employed for com-

[1] Abel, Rouiller, and Geiling, *op. cit.*, 1924. See also Abel, *Harvey Lectures*, 1924; and *Physiological Reviews*, 1924.

[2] M. I. Smith and W. T. M'Closky, U.S. Pub. Health Service, Washington, *Hygienic Lab. Bull.*, No. 138, ii., 1924.

[3] *Journ. Pharm. and Exper. Therap.*, xviii., 1921.

[4] *Op. cit.*, 1924.

paring the pressor activities of two samples of pituitary extract consists essentially in allowing a sufficient interval for recovery between the successive doses. Without entering into details it will be sufficient to say that an accuracy of 12 per cent. can easily be attained ; some experiments have given a 7 per cent. discrimination (fig. 141).

The chemical properties of the pressor hormone resemble in many respects those of the oxytocic, so that many workers have assumed that the responses are due to one and the same substance. Evidence to the contrary has, however, been advanced by Dudley, who has shown that the pressor principle can only be extracted by butyl alcohol to the extent of 50 per cent. Until a well-proved method of standardisation is employed, however, it would be inadvisable to lay undue stress on the results of comparisons of pressor activity. Few workers have as yet carried out systematic experiments with material from which the depressor substance has been extracted, *i.e.* material which does not show the "inversion" effect with a "repeat" injection into the circulation of the anæsthetised carnivore.[1]

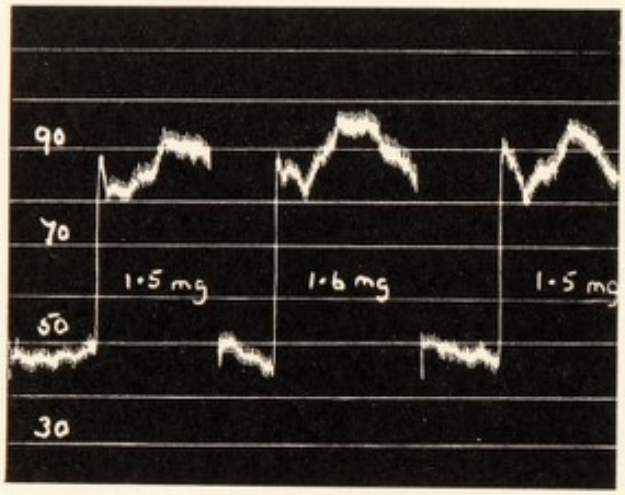

FIG. 141.—Three successive doses of a pituitary extract administered to a spinal cat at hourly intervals. Thirteen previous injections at hourly intervals had been given. (Hogben, Schlapp, and Macdonald.)

In this case the blood-pressure response shows a discrimination between 1·5 mg. and 1·6 mg., *i.e.* about 7 per cent.

Dudley[2] claims to have established the existence of a second pressor principle, which he states to be soluble in acetone, but in view of the fact that the depressor principle has been shown by Hogben and Schlapp to exercise on the blood-pressure of the decerebrated cat an effect which appears to be identical with that obtained from injections of Dudley's second pressor principle, the existence of this as a distinct autacoid must be regarded as doubtful.

C. Heymans[3] has employed in place of blood-pressure a perfusion method of standardisation, using the isolated head of the rabbit.

Frog Melanophores.—Hogben and Winton[4] have elaborated a method for the quantitative physiological assay of the melanophore activity of extracts of the posterior lobe of the pituitary body. The principle of their method lies

[1] Herring employed alcohol-extracted material in his experiments on the action of extracts of the different parts of the bovine gland (see p. 260), and a similar material was used by Hogben and Schlapp in their work on vasomotor activity (*Quart. Journ. Exper. Physiol.*, xiv., 1924), as well as by Sharpey-Schafer and Macdonald (*ibid.*, xvi., 1926).

[2] *Journ. Pharm. and Exper. Therap.*, xxi., 1923.

[3] *C. r. soc. biol.*, xcii., Jan. 1925 (*Soc. belge de biol.*).

[4] *Biochem. Journ.*, xvi., 1922.

in establishing the minimal dose necessary to produce darkening of the frog's skin. A comparison of the dilutions necessary to establish this dose provides a method of assessing the relative melanophore activities of any given pituitary preparations. Provided that a sufficiently large number of frogs is employed, the method is capable of discriminating a difference of 12 per cent. in melanophore activity. These authors were able to show that the autacoid is completely destroyed by trypsin, although it is unaffected by pepsin. They also showed that its activity is diminished only slowly by boiling with 0·5 per cent. hydrochloric acid. Dreyer and Clark [1] have shown that the melanophore stimulant passes the ultrafilter only with difficulty, and they advance evidence in support of the view that it cannot be identical with the oxytocic principle. W. O. Fenn,[2] who confirms this result, standardises for the melanophore autacoid by extracting with butyl alcohol (Dudley) and testing the residue and extract separately for their reactions on the melanophores, blood-pressure, uterus, and kidney.

Kidney and Mammary Gland.—No precise methods for the quantitative study of the substances responsible for the renal and galactagogue action of these extracts have as yet been introduced; but Smith and M'Closky [3] have employed the urine secretion as a method of standardisation, using anæsthetised rabbits, and recording the increased rate of flow. For standardising for antidiuretic action Kestranek, Molitor, and Pick have employed dogs with permanent bladder fistulæ.[4]

Schafer and Herring [5] state that the diuretic principle is stable to boiling, to peptic digestion, and also to hydrogen peroxide, and that it dialyses through parchment paper. Abel, Rouiller, and Geiling [6] showed that the powerfully oxytocic and pressor tartrate which they succeeded in isolating also has a diuretic effect, and that this diuretic effect could be abolished by subjecting the substance to the action of alkali. As already stated, Abel [7] is of opinion that the diuretic and antidiuretic effects—and indeed all the various results obtained from posterior pituitary extracts—may be caused by one and the same chemical substance, acting differently under different circumstances. But, it would appear from the foregoing account there are reasons for believing that the effects obtained are due to more than one autacoid.

[1] *Op. cit.*
[2] *Op. cit.*
[3] *Journ. Pharm. Exper. Therap.*, xxiv., 1924.
[4] *Biochem. Zeitschr.*, clxiv. 34, 1925.
[5] *Proc. Roy. Soc.*, B, lxxvii. 571, 1906.
[6] *Op. cit.*
[7] *Op. cit.*

CHAPTER XXXVII

THE PITUITARY BODY (*continued*)

Effects of Administration of Anterior Lobe

Mammals.—The discovery that in the human subject enlargement of the anterior lobe is associated with increased growth of the body—especially of the skeleton—led to attempts to determine experimentally whether such an effect would follow an increase of anterior lobe substance in animals by implantation or administration with the food or parenterally. The grafting of portions of the gland has, however, offered peculiar difficulties which have rarely, if ever, been successfully surmounted, at least in mammals. Portions of the gland (anterior lobe) have been implanted in various situations (brain, kidney, spleen, bone-marrow, and under the skin), but they do not survive long, and disappear altogether in a short time. The most successful cases appear to be those of Crowe, Cushing, and Homans,[1] who in seven cases out of nine succeeded in prolonging the life of their hypophysectomised dogs (which usually died within forty-eight hours without treatment) for from ten to twenty-six days. Some of the animals were eventually sacrificed to examine the condition of the transplant, which was found to show active anterior lobe cells.

Harvey Cushing has reported one case of successful grafting of the pituitary of a new-born child into a patient suffering from cachexia due to the destruction of his pituitary by cysts. The gland was implanted into the temporal lobe of the brain.

The results of long-continued buccal and parenteral administration in young animals have varied, some observers having observed an increase in rapidity of growth, others a decrease, and yet others no effect at all.[2]

E. Goetsch[3] has recorded a stimulating effect of the administration of anterior lobe substance to young rats—both as regards growth and sexual development (fig. 142)—whereas posterior lobe extract had a retarding effect. In my own experiments—which were carried out on groups of young rats—there was during the first six weeks little or no difference between the pituitary-

[1] *Quart. Journ. Exper. Physiol.*, ii., 1909.

[2] See especially U. Cerletti, *R. accad. sci. Lincei*, 1906–1908. A description and analysis of the work published on this subject up to 1822 will be found in the monograph by B. A. Houssay, "L'accion fisiol. d. l. extractos hipofisarios," 1918–22.

[3] *Johns Hopkins Hosp. Bull.*, xxvii., 1916.

fed animals and the controls—the average weight of both being then 44·25 grams. But at the end of the three months a distinct difference was manifested, the average weight of the pituitary-fed animals being 150 grams and of the controls 131 grams.[1]

Of more recent observations on the effects of administration of anterior lobe may be mentioned those of Sisson and Broyles [2] and those of Evans and Long.[3] The last-named observers describe, in female white rats, well-marked positive results on growth, with large deposition of fat, following intraperitoneal injection of extract of anterior lobe of ox-pituitary. They note that although the ovaries exhibited much luteal tissue, the uterus was considerably smaller than in the control animals (contrary to Goetsch), and œstrus was delayed.

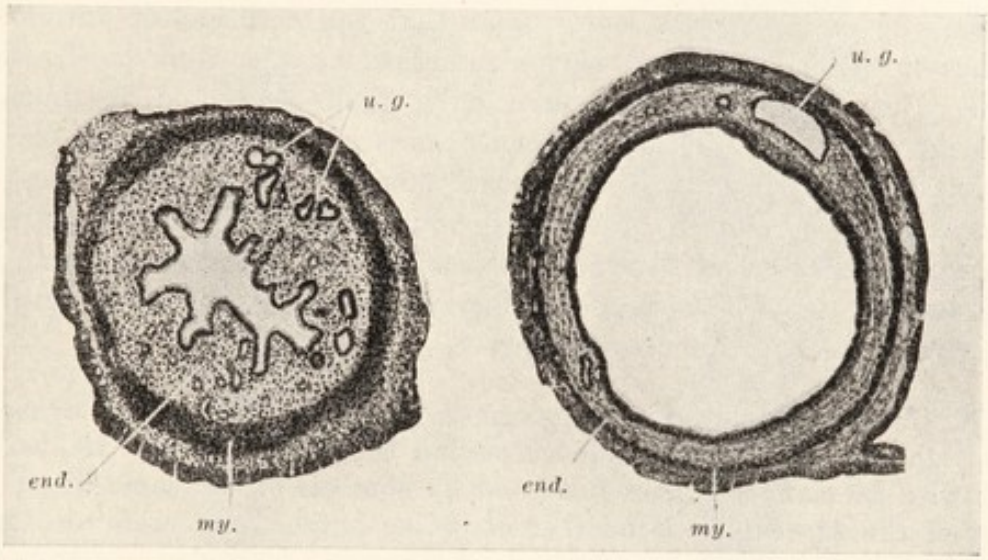

Fig. 142.—Sections of cornu uteri of two rats, 72 days old. (E. Goetsch.[4]) A. Pituitary fed during 30 days before being killed. B. Control, without pituitary.
end., endometrium ; *my.*, myometrium ; *u.g.*, uterine glands.

On the other hand, C. S. Smith,[5] who fed young white rats for a prolonged period with varying amounts of pituitary (whole gland) added to their ordinary food, observed no effect in accelerating either body growth or sexual development. N. M. Dott,[6] however, obtained unmistakable evidence of acceleration of growth and of osseous development of both kittens and puppies as the result of feeding with anterior lobe ; although relatively large amounts (0·3 gram per kilo) were required to obtain a result.

T. Brailsford Robertson believes that the growth-promoting autacoid of the pituitary is a substance to which he has given the name of *tethelin*, which is

[1] *Quart. Journ. Exper. Physiol.*, v., 1912. Other experiments by D. D. Lewis and J. L. Miller (*Arch. internat. Med.*, xii., 1913) yielded variable results, perhaps depending on the age of the animals at which the experiments were commenced.
[2] *Johns Hopkins Hosp. Bull.*, xxxii., 1921.
[3] *Anat. Rec.*, xxiii., 1922 ; *Proc. Nat. Acad. Sci.*, Baltimore, viii. 38, 1922.
[4] *Johns Hopkins Hosp. Bull.*, xxvii., 1916.
[5] *Amer. Journ. Physiol.*, lxv., 1923.
[6] *Quart. Journ. Exper. Physiol.*, xiii., 1923.

present in alcohol extracts of the anterior lobe. He found it to affect the rate of growth of mice differently according to age (in young animals the rate was diminished, in older animals it was accelerated), and to promote the recovery of weight of animals which had been reduced by fasting. He also found that the healing of experimental wounds was accelerated by its administration, which was usually hypodermic.[1]

The *pars tuberalis* may have been included in part at least along with the *pars anterior* in many of these experiments, but Marinus found that this portion, when administered to white rats, had no effect on sexual development as compared with controls, and that the growth rate was somewhat diminished; whereas with anterior lobe feeding the animals exhibited an increased growth rate, accompanied by sexual precocity.[2]

Birds.—Several observers have found that the addition of anterior lobe substance to the food of chicks causes retardation rather than acceleration of growth.[3] But Winternitz,[4] who used only small doses and continued the experiment for five months on eleven chicks (with eleven controls), obtained a striking difference in growth and in the commencement of egg-laying—both being accelerated. Wulzen observed sexual precocity, especially in males; the cockerels began crowing two weeks sooner than the controls, and, later, crowed twenty times as often. R. Pearl,[5] however, who began with older chicks, was unable to obtain similar results.

L. N. Clark[6] announced a truly remarkable result of feeding laying hens (white Leghorns) with anterior lobe substance, the number of eggs yielded being nearly twice as many as those furnished by controls of the same breed. The fertility of the eggs and the number of chicks hatched out were also greatly enhanced. But neither Pearl nor Sutherland Simpson[7] succeeded in corroborating Clark's results. Indeed, A. T. Walker[8] states that intraperitoneal injection of fresh anterior lobe substance inhibits ovulation in hens, although the animals remain in good health. Microscopically an abundance of luteal tissue becomes formed in the ovary.

R. Wulzen[9] found both the growth and rate of multiplication by fission to

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[1] *Journ. Biol. Chem.*, xxiv., xxv., and xxvii., 1916, and *Endocrinology*, i., 1917. See also Robertson's monograph, "The Chemical Basis of Growth and Senescence," 1923, in which the literature is very fully given. Drummond and Canaan state that tethelin has given only negative results in their hands (*Biochem. Journ.*, xvi., 1922). See, however, Robertson, *ibid.*, xvii., 1923.

[2] C. J. Marinus, *Amer. Journ. Physiol.*, xlix., 1919.

[3] R. Wulzen, *Ibid.*, xxxiv., 1914; S. S. Maxwell, *Univ. Calif. Publ. in Physiol.*, v., 1916; R. Pearl, *Journ. Biol. Chem.*, xxiv., 1916. T. Brailsford Robertson states that he is informed by R. Wulzen that one chick which she continued to feed for a prolonged period with anterior lobe substance eventually showed acceleration of growth and surpassed the controls ("Studies in Growth," *Journ. Biol. Chem.*, xxiv., 1916).

[4] *Johns Hopkins Hosp. Rep.*, xviii., 1916.

[5] *Journ. Biol. Chem.*, xxiv., 1916.

[6] *Ibid.*, xxii., 1915.

[7] *Proc. Soc. Exper. Biol. and Med.*, xvii., 1920.

[8] *Amer. Journ. Physiol.*, lxxiv. 249, 1925. *Cf.* Evans and Long, *supra* (rats).

[9] *Journ. Biol. Chem.*, xxv., 1916.

be increased in planarian worms by pituitary feeding—whether anterior or posterior lobe—the principle influencing fission being independent of that influencing growth.

FIG. 143.—Two axolotls of the same age, showing the effect of feeding with pars anterior of bovine pituitary. (Uhlenhuth.) A. Worm-fed control, without pituitary. B. With pituitary. (88 days.)

Amphibia.—A large number of observations have been made on the effect of the administration of anterior lobe of pituitary on the growth and meta-

morphosis of amphibian larvæ. P. E. Smith [1] noticed that with tadpoles thus fed late in larval life there was a relative acceleration in rate of growth and increase of size, as compared with controls. He found this to be true both of normal and of hypophysectomised larvæ. B. M. Allen [2] grafted anterior lobes of pituitaries of adult Rana pipiens into tadpoles of the same species using (*a*) normal, (*b*) hypophysectomised, (*c*) thyroidectomised tadpoles. He obtained acceleration of growth in all, and the animals grew into larger tadpoles than the controls, whereas posterior lobe caused retardation of growth. E. Uhlenhuth [3] used axolotls (Amblyostoma opacum and A. tigrinum), which he fed with anterior lobe after they had undergone metamorphosis (fig. 143). Not only did they grow more rapidly than the controls, but they attained a size far exceeding (by more than 25 per cent.) any dimensions recorded in normal animals of the same species—even the best fed. Posterior lobe feeding restrained growth. W. W. Swingle,[4] using bull-frog and green-frog tadpoles, found grafting anterior lobe of adult animals of the same species to diminish the period of larval life, *i.e.* to accelerate metamorphosis—and at the same time to accelerate development of the thyroid (through which it probably acted). P. E. and I. B. Smith [5] got similar results in frog tadpoles but not in axolotls. On the other hand, L. Hogben [6] got precocious metamorphosis in sexually mature axolotls (Amblyostoma tigrinum) with subcutaneous injection of anterior lobe extract (but not with feeding), even in thyroidectomised animals. E. R. and M. M. Hoskins [7] also got precocious metamorphosis in frog tadpoles, even after thyroidectomy, by administration of anterior lobe of bovine pituitary—which they state contains not more than 1 part of iodine to 200,000. Acceleration of metamorphosis was not observed in tadpoles which had been hypophysectomised, although their growth was accelerated. It is suggested by P. E. Smith and G. Cheney [8] that the acceleration of metamorphosis may have been due to the traces of iodine in the commercial preparation used; they themselves failed to get this result when using fresh gland.

Sutherland Simpson and A. Hunter were unable to detect a trace of iodine in the fresh pituitaries of sheep even after they had long been deprived of the thyroid (which is the only organ in which iodine is stored) and although their food contained an ample amount of iodine.[9] Nor has iodine been shown to occur in bovine pituitaries except in infinitesimal amount.

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[1] *Anat. Rec.*, xi. 57, 1916; and *Univ. Calif. Publ.*, v., 1918.

[2] *Science*, lii. 274, 1920.

[3] *Proc. Soc. Exper. Biol. and Med.*, xviii., 1920; *Journ. Gen. Physiol.*, iii., 1921, and iv., 1922; *Journ. Exper. Zool.*, xxxvii., 1923.

[4] *Journ. Exper. Zool.*, xxxvii., 1923.

[5] *Proc. Soc. Exper. Biol. and Med.*, xx., 1922; *Journ. Med. Res.*, xiii. 267, 1922.

[6] *Proc. Roy. Soc.*, B, xciv. 204, 1923.

[7] *Endocrinology*, iv., 1920. See also E. A. Spaul, *Brit. Journ. Exper. Biol.*, i., 1924.

[8] *Endocrinology*, v., 1921.

[9] *Quart. Journ. Exper. Physiol.*, iii., 1910, and iv., 1911.

CHAPTER XXXVIII

THE PITUITARY BODY (*continued*)

Effects of Complete Removal: Hypophysectomy

A large number of experiments have been made with the view of determining the nature of the symptoms which follow removal of the pituitary. The results of these have been somewhat conflicting in character—due in some measure to the differences of method employed to arrive at the position of the organ, which is obviously a difficult procedure, deeply placed as it is at the base of the brain. Thus, while one set of operators have preferred to approach it (in animals) through the buccal cavity and basis cranii, in order to avoid disturbance of the brain, others have not hesitated to attack it through a large aperture in the side of the skull, another similar aperture being made on the opposite side so as to enable the hemispheres to be pushed over in order to obtain good access to the gland; in the dog, the organ can be got at without much difficulty by this procedure.

The former method has the disadvantages (1) that the operator is working at the bottom of a deep pit from the walls of which blood is constantly oozing so as to obscure the parts, and (2) that it is impossible to secure asepsis. By the use of the lateral method these disadvantages are avoided, but it has been alleged that the serious results which are described as following removal of the organ by this operation are due to shock and paralysis caused by the unavoidable insult to the brain. But if the whole operation is performed exactly as if the pituitary were to be removed, even to manipulation of the gland, but without injuring it, no results follow: the animal—if asepsis is maintained—recovers completely without incident.

Recently it has been suggested that all the symptoms which have hitherto been referred to the hypophysectomy are in reality caused, not by removal of the pituitary body, but by injury to the part of the brain-wall against which it lies, viz. the floor of the third ventricle (tuber cinereum). The evidence which has been put forward in favour of this suggestion is dealt with elsewhere. But in the meantime it will be convenient to assume that the results which follow removal of or injury to the pituitary are in fact due to such removal or injury of the gland itself and not to any concomitant injury to the adjacent part of the brain.

The objection that the brain may undergo injury cannot be raised against another method of destroying or injuring the organ, which can be used for the cat and perhaps for some other animals. Owing to the depth of its sella, the lateral operation, comparatively simple in the dog, is ill-adapted for the cat.

But in this animal it is easily possible to introduce a fine, straight, hollow trocar along the outer margin of the orbit, piercing the conjunctiva at the outer canthus and passing through the sphenoidal fissure into the sella turcica, the point impinging on the dorsum sellæ, and through the trocar to destroy

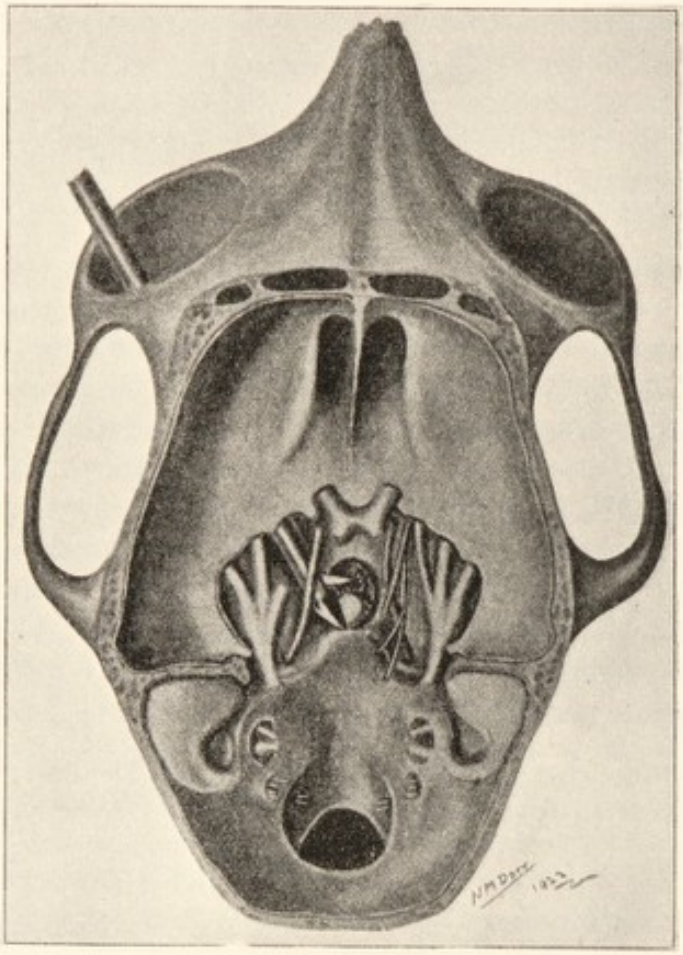

FIG. 144.—Intracranial anatomy of the transorbital electrolytic operation upon the cat. Natural size. (H. M. Dott.)

Observe the position of the trocar. It passes through the orbit (at the outer side of the globe of the eye) and through the sphenoidal fissure; its point lodges in the dorsum sellæ. The projecting electrode is seen piercing the anterior lobe of the pituitary. Note the displaced internal carotid. The nerves entering the sphenoidal fissure have been removed on the left side so as to expose the instrument.

by electrolysis either the whole pituitary or the anterior or posterior lobe only (fig. 144).

The passage of the trocar is guided by a finger placed on the hamulus of the pterygoid process, which is readily felt inside the mouth. In its passage it may press somewhat on the nerves (3rd, 4th, 6th, and ophthalmic division of the 5th) which are entering the orbit, but the internal carotid is displaced upwards and escapes injury. The lumen of the trocar does not extend quite to its point, which is solid, but opens on one side nearer to or farther from the point according to whether the anterior or the posterior lobe is to be electrolysed: the side on

which the opening occurs is marked on the handle. Several such trocars are provided suitable for cats and kittens of different size. The electrode, which should be made the positive pole—the negative pole consisting of a pad moistened with salt solution, applied to the skin of the back—consists of a steel wire with a platinum-iridium end hinged on to it. It is insulated except at the tip by a rubber sheath, and is passed along the trocar, the end emerging at the lateral opening and coming in contact with the part of the gland it is desired to destroy. A current of 10 milliamperes is employed and is passed for from three to ten minutes, according to the extent of destruction desired: the wire and trocar are then withdrawn. The lesion is always confined to the contents of the sella.

The procedure takes only a few minutes, and recovery from the operation and anæsthetic is immediate and complete, except for a certain amount of motor and sensory paresis, caused by the pressure of the trocar on the above nerves, most of which is temporary and all negligible.[1]

Surgical interference with the pituitary in the human subject is an entirely different problem from that involved in operations on animals, access to the gland being usually obtained from the front by an orbital or a nasal route. The chief methods employed are described by Blair Bell.[2] Details of the several methods of operating are given in surgical treatises dealing with the subject.

Effects of Complete Removal.—N. C. Paulesco was the first to state definitely that complete removal is in every case sooner or later fatal. This result was obtained with animals from all classes of Vertebrata.[3] Most of the hypophysectomised mammals died within two or three days. Paulesco's results were confirmed for mammals by Harvey Cushing and his fellow workers,[4] who for the most part restricted their experiments to dogs. They found that adult animals usually succumb after total deprivation in from two to five days, whilst puppies survive longer (ten to thirty days); this difference may perhaps be ascribed to the greater functional adaptability of accessory glandules present in the roof of the pharynx in young animals. In all cases of long survival a fragment of the gland, including some of the anterior lobe, was found *post mortem*; they attributed the survival to such a remnant. On the other hand, they did not obtain a fatal result by severance of the infundibular stalk, a procedure which Paulesco alleged to be fatal. Removal of part only of the anterior lobe leads to certain definite changes in metabolism, which are considered by Cushing to be due to deficient secretion, a condition to which he

[1] A full description of the operative procedure is given by N. M. Dott (*Quart. Journ. Exper. Physiol.*, xiii. 258–264, 1922), who found that complete destruction of the pituitary by this method proved speedily fatal in all the cats he operated on. Control operations involving merely the passage of the trocar, without electrolysis, were performed in two animals, both of which recovered from the operation without any symptoms beyond slight ocular paresis, and survived indefinitely.

[2] "The Pituitary," 1919. See also A. K. Henry, *Dubl. Med. Journ.*, cl., 1921–22; and P. Bassoe, Article, "Acromegaly," in Barker's *Endocrinology and Metabolism*, i. 853, 1922. Also A. J. Walton, *Brit. Med. Journ.*, ii. 835, 1922.

[3] *Journ. de physiol.*, ix., 1907, and "L'hypophyse du cerveau," Paris, 1908.

[4] Cushing and L. R. Lewis, *Johns Hopkins Hosp. Bull.*, xx., 1909; S. J. Crowe, Cushing, and Homans, *Quart. Journ. Exper. Physiol.*, ii., 1909; *Johns Hopkins Hosp. Bull.*, xxi., 1910.

has given the name *hypopituitarism*. Results similar to those of Paulesco and Cushing have been published by Biedl,[1] by B. A. Houssay,[2] by Ascoli and Legnani,[3] by Blair Bell,[4] and by Dott.[5]

The symptoms of complete removal or *apituitarism* (cachexia hypophyseopriva) are described by Cushing as follows: "On the day after the operation the animal (dog) usually appears normal, with fair appetite and no characteristic signs of loss of secretion. Gradually it becomes lethargic, refuses food, and responds slowly or not at all to the voice. Later the respiration becomes slow and the pulse both slow and feeble, the musculature limp, often with tremors and fibrillar twitching; the back is arched and the temperature sub-normal; finally, often within forty-eight hours, the animal becomes comatose and dies in this condition."[6]

Houssay gives the following symptoms as supervening after complete extirpation in dogs: tachycardia, shallow respirations, rapid fall in weight (probably due to refusal of food), increase of N elimination, polyuria in pups, oliguria in full-grown dogs. In adult dogs death usually occurred within forty-eight hours: young animals survived longer and life might be considerably prolonged: when that was the case there was considerable retardation in both general and sexual development, together with development of adiposity. Sometimes a high tolerance for sugar. Somnolence and a low body temperature were almost constant features.

Blair Bell removed the pituitary completely in five dogs: all died within thirty-six hours. They at first showed no symptoms but later became somnolent, with slow respirations: finally coma and death.

Dott effected nine complete extirpations in dogs, the completeness being verified *post mortem* with the aid of the microscope. Most of the animals died within a week: none survived more than two weeks. At first there were no symptoms (latent period): then came signs of profound metabolic depression, the temperature gradually falling. Then ensued a progressive paralysis of the central nervous system, culminating in failure of respiration. Death occurred sooner in adult than in young animals. Hypodermic injections of anterior lobe extract alleviated the earlier symptoms, but had no effect later and never averted the fatal issue.

Most observers agree that removal of the whole of the anterior lobe in the dog has the same effect as complete extirpation of the gland, whereas removal of the posterior lobe alone leads to no definite symptoms. But if one looks at the relations of the parts of the gland to one another in the dog, as they are shown in the diagram given on p. 181, it is obviously difficult or impossible to entirely remove one part without seriously injuring others.

[1] "Innere Sekretion," 1910.

[2] Various papers, mostly published in *C. r. soc. biol.* from 1908 onwards. Also *Nat. Congr. Med. Buenos Aires*, 1916.

[3] *Boll. soc. med.-chir. di Pavia*, xxiv., 1911; *Münch. med. Wochenschr.*, 1912.

[4] *Lancet*, i. 809, 937, 1913; *Quart. Journ. Exper. Physiol.*, xi., 1917; "The Pituitary," 1919.

[5] *Quart. Journ. Exper. Physiol.*, xiii., 1923.

[6] "The Pituitary Body and Its Disorders," 1912, p. 10.

Cushing and his fellow workers found that life was prolonged, but not indefinitely, by transplanting the removed glandular tissue to some other vascular situation (muscle, bone-marrow, cerebrum). Eventually the transplant became disintegrated, but in three animals which were killed on the 24th, 25th, and 26th days respectively, and in which the cachexial symptoms had been steadily improving, the transplanted tissue showed areas of anterior lobe cells.

In some of Cushing's later experiments extirpation of the gland seems to have been less certainly fatal or longer delayed, the animals exhibiting the symptoms rather of hypo- than of a-pituitarism. This may have been due to small portions of the gland having been left behind, or to the employment of younger animals, or to the vicarious activity of some other organ or organs. The fact is interesting because Aschner,[1] who performed a large number of extirpations mainly by the inferior operation (through the base of the skull), did not find the gland to be essential to life—or at least obtained very considerable prolongation of life after its entire removal. It must, however, be regarded as doubtful if it is possible to be certain of effecting complete removal by this operation. Aschner himself, who admits the difficulty, regards the small residue as unimportant. In all his cases, symptoms of hypopituitarism showed themselves. His animals, if young, remained small: their milk teeth were retained and also their lanugo hair and juvenile fat: their epiphyses did not ankylose. The thyroid was enlarged, the thymus persistent, and the cortex of the suprarenal thickened. The development of the sexual organs was markedly retarded.[2] The body temperature was from 1° C. to 1·5° C. below normal.[3] In the adult the chief effect of the removal was the putting on of fat. All the above effects were also obtained by removal of the anterior lobe alone.

The output of carbonic acid was found by Benedict and Homans [4] to be diminished in dogs after removal or partial removal of pituitary. The same is true of frogs.[5] It will occur if the anterior lobe only is removed. The excretion of N is lessened (Aschner).

[1] *Arch. f. d. ges. Physiol.*, cxlvi., 1912; *Arch. f. Gyn.*, xcvii., 1913.

[2] Aschner found removal of the pituitary to be always followed by abortion in pregnant animals. In a more recent publication he states that changes in the sex organs are only obtained after injuries involving the di-encephalon (*Med. klin.*, xx. 1681, 1924).

[3] According to Cushing the normal temperature can be restored by injection of anterior lobe extract.

[4] *Journ. Med. Res.*, xxv., 1912.

[5] F. R. Winton and L. T. Hogben, *Quart. Journ. Exper. Physiol.*, xiii., 1923. Frogs support for a considerable time complete removal of the gland, which is easily effected in them, although the pars tuberalis, which is detached from the rest of the gland, is usually left. The most obvious symptom the hypophysectomised frog exhibits is a permanent pallor of the skin, due to contraction of its melanophores (see fig. 134, p. 255). In toads L. Giusti and B. A. Houssay noticed atrophy of testicles, and in females a tendency to abort. They obtained a mortality of 85 per cent. within forty-five days; whereas controls lived indefinitely (*Rev. d. l. assoc. méd. Argent.*, xxxvii., 1924). Similar results were obtained in frogs by Houssay and Ungar (*ibid.*). A full bibliography is appended to these papers. In the axolotl A. W. Greenwood (*Brit. Journ. Exper. Biol.*, ii. 75, 1925) obtained no effect on the growth-rate if the removal was effected after the thyroid is developed.

The experiments of others have yielded different results. Thus Horsley and Handelsmann,[1] who attempted complete extirpation in a number of animals, chiefly by operation through the base of the skull, state that although a large proportion of their cases died within forty-eight hours, they consider this was due to causes incidental to the operation (shock, hæmorrhage, infection). Those that survived showed none of the symptoms above described as characteristic of apituitarism or hypopituitarism. Camus and Roussy,[2] who have removed the gland, either by the lateral or by the buccal route, from one hundred and twenty-two dogs and twenty-seven cats, have also come to the conclusion that the gland is not essential to life, and indeed that most of the symptoms described by other observers as following hypophysectomy are in no way connected with the pituitary but are due to injury of the tuber cinereum. Nevertheless most of their animals seem to have died within a few days of the removal.

C. G. Brown,[3] who destroyed the pituitary in sixty-six dogs by the buccal operation, also concludes that its loss is not necessarily fatal. But most of his animals also died soon after the operation, whether in consequence of the removal or of septic infection is not clear. Three became somnolent, one showed the Fröhlich syndrome (see p. 284), one developed polyuria, and only five showed no symptoms.

Sachs and Macdonald,[4] as the result of operations on thirty-five animals, came to the conclusion that extirpation of the gland was never fatal unless the infundibular region of the brain was injured; they also attribute accompanying polyuria to a lesion of this region. Only temporary glycosuria was (occasionally) observed in animals, but in a case of acromegaly in man, an operation on the pituitary was followed by well-marked glycosuria lasting eighteen days.

W. E. Dandy and F. L. Reichert[5] removed the pituitary in thirty-one dogs, and afterwards cauterised the base of the brain in the region of the gland. In spite of the extensive lesion, they state that most of the animals survived the operation (from 13 to 138 days).

The varying results obtained by different observers and even at different times by the same observer are difficult of explanation, but may perhaps be related partly to the age of the animals, partly to the completeness of the removal, and perhaps in part to the vicarious action of accessory structures.

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[1] *Neurol. polska.*, 1912.
[2] *C. r. soc. biol.*, lxxxvi., 1922.
[3] *Proc. Soc. Exper. Biol. and Med.*, xx., 1922.
[4] *Arch. Neur. Psych.*, xiii., 1925.
[5] *Bull. Johns Hopkins Hosp.*, xxxvii., 1925.

CHAPTER XXXIX

THE PITUITARY BODY (*continued*)

Effects of Partial Extirpation and of Injury

The results of lesions which have involved only partial destruction of the anterior lobe are even more interesting than those in which the extirpation has been complete, in which the effect is more acute, leading generally to speedy death. The symptoms of such partial lesions have been described by many authors including Cushing, Biedl, Houssay, Blair Bell, and Dott. To their work we must add the important contribution of Aschner, already alluded

Fig. 145.—Twelve-months-old hypophysectomised dog (left) and control of same litter (right). (Aschner.)
The operation was performed at eight weeks.

to. For although Aschner himself believed that the extirpations he effected by the buccal method were for the most part complete, the symptoms agree so closely with those caused by incomplete removal by the lateral method, in which it is possible to see exactly what is being severed, that it will be convenient to consider them as if caused by incomplete destruction of the lobe.

The most striking effect is the retardation of growth of young animals, which shows itself not only in a general diminution in size compared with controls (fig. 145) but in a well-marked delay in the process of ossification and

in the growth of the bones. The sexual organs, both internal and external (fig. 146), long retain their infantile condition : indeed the uterus and ovary, if already advanced in development, may undergo retrograde changes. Mental dullness with a tendency to drowsiness is generally noticeable. The body temperature is below normal. Basal metabolism is diminished. The thymus undergoes diminution in size, or atrophy. The thyroid may show accumulation of colloid. The limit of assimilation of carbohydrate is raised.

FIG. 146.—Young dog, eight months old, four months after removal of the greater part of the pituitary body. (Cushing.)

Notice the tendency to adiposity, and the deficient development of the sexual organs.

But in spite of retardation in general growth and in sexual development there is a marked tendency to fat formation, with large accumulations under the skin, around the viscera, and generally throughout the body. This accumulation may be so large that in spite of its lessened growth the operated animal weighs nearly or quite as much as the controls. In adult animals also obesity is a characteristic feature of partial hypophysectomy. Thus in a dog operated on by Ch. Livon[1] in which only the pars anterior was injured (on histological examination there was found a " lake " of colloid near the seat of injury), the animal, which died eight months after the operation, developed an abnormally thick layer (3 to 4 cm.) of subcutaneous fat as well as a large amount of perivisceral fat. It weighed rather more than before the operation although most of the organs were reduced in size.

There is a tendency in adult animals also to genital atrophy—especially in males, in which the interstitial tissue of the testis is diminished in amount. This condition of adiposity combined with deficient development of the generative organs is known, when observed clinically, as Fröhlich's syndrome or dystrophia adiposo-genitalis (p. 305) : we may employ the expression also for the effects of experimental injury of the gland.

The tendency to adiposity and to genital atrophy after such removal is illustrated in figs. 146 and 147.

Section of the stalk connecting the pars nervosa with the infundibulum of the third ventricle was stated by Paulesco to have the same effects as total

[1] *C. r. soc. biol.*, lxxi., 1911 ; also Livon and Peyron, *ibid.*

extirpation of the gland, but none of his successors have confirmed this statement. The lesion is, however, by no means without effect, for, as Blair Bell has shown, it produces symptoms which are similar to those caused by partial removal of the anterior lobe and especially the condition of dystrophia adiposo-genitalis.[1]

Two bitches in which Blair Bell produced this syndrome by section of the stalk showed complete atrophy of genitalia and of the mammæ, besides exhibiting an enormous deposition of fat. The remarkable changes produced in the general

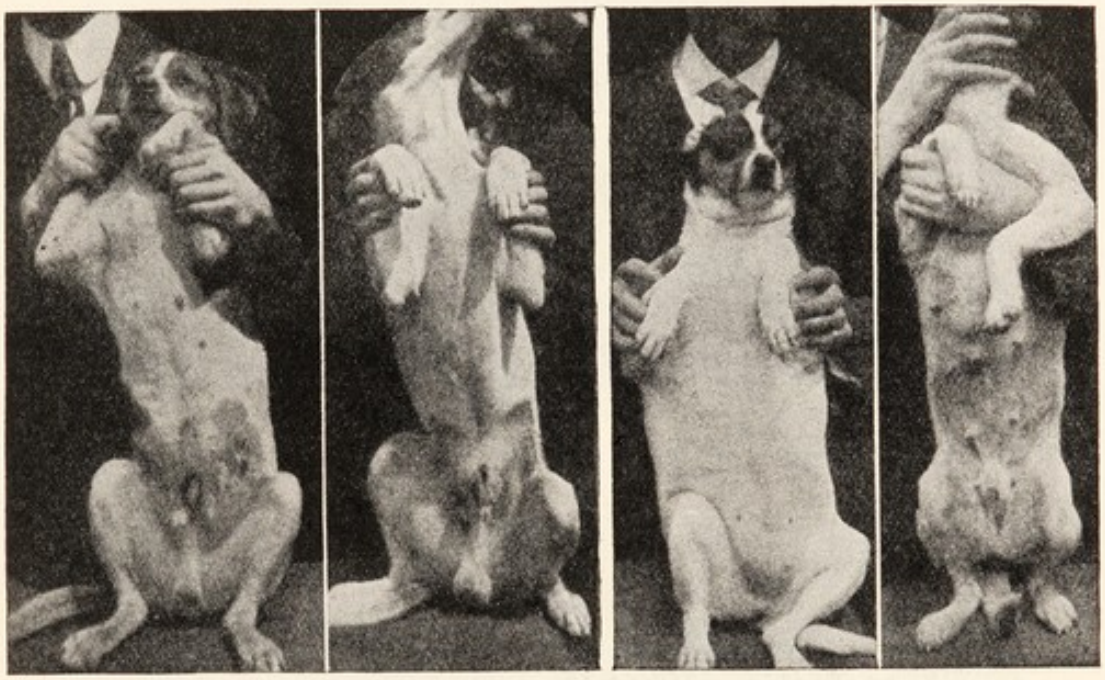

FIG. 147.—Adult dogs, male and female, some months after removal of the greater part of the pituitary body. In each case a control of the same litter is shown on the right of the operated animal. (Cushing.)

The tendency to adiposity is well marked in both sexes.

appearance of such an animal and in the uterus and ovaries are shown in the accompanying figures (figs. 148, 149, 150) and need no further description.

Harvey Cushing and Maddock have obtained similar results in dogs from blocking the passage along the infundibular stalk with a small silver clip. They find that after such a clip is applied, the pars nervosa becomes greatly distended with Herring's colloid bodies, which cannot now pass into the ventricle, and they ascribe the symptoms which are produced (obesity, genital dystrophy) to a consequent deficiency of posterior lobe secretion.[2]

The cells of the pars anterior after section of the stalk were found by Blair Bell to be shrunken and separated by wide spaces, due in all probability to the interference with the vascular supply of the pars anterior.

Dott found that partial removal of the anterior lobe (at least two-thirds), or

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[1] Blair Bell, *Quart. Journ. Exper. Physiol.*, xi., 1917.

[2] Private communication.

of both lobes, as well as section of the stalk, with or without the insertion of a thin platinum plate between the gland and the base of the brain, are all followed by the characteristic syndrome, viz. depression of temperature,

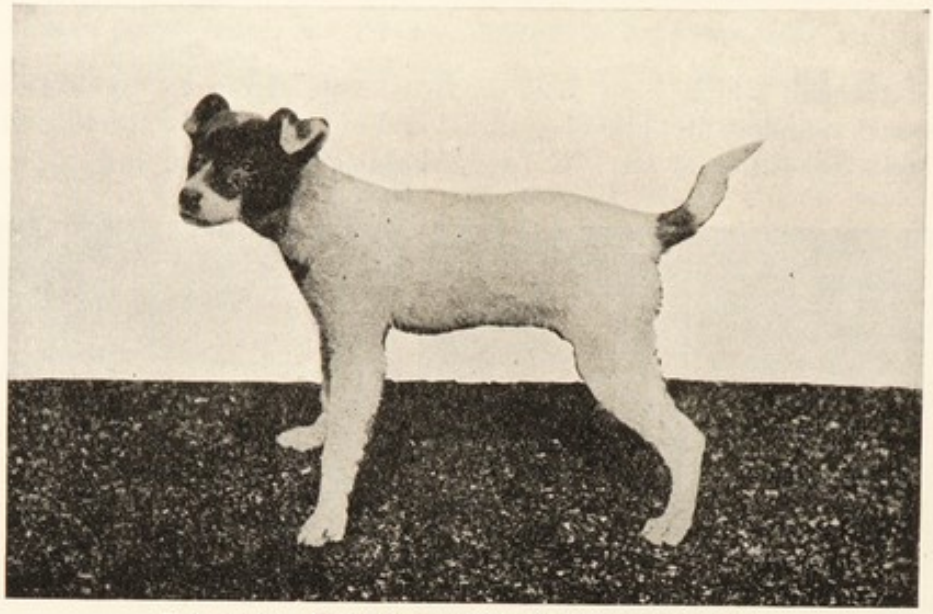

Fig. 148A.—Bitch before operation. (Blair Bell.)

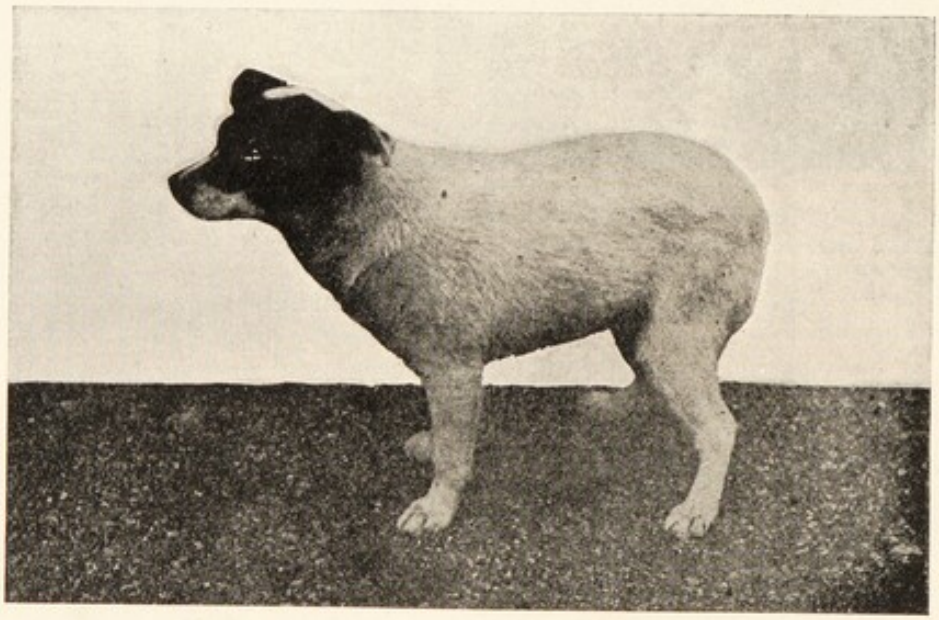

Fig. 148B.—The same bitch 51 days after separation of the infundibular stalk. (Blair Bell.)

lethargy, adiposity, retardation of growth, atrophic changes in the thyroid and in the generative organs.

According to Dott, the constant factor in all cases showing this syndrome is injury to the pars anterior or interference with its blood-supply. The subnormal temperature can be raised by injection of anterior lobe extract. The subnormal temperature of thyroidless animals can also be raised by such injection. And

with continued anterior lobe feeding the temperature of (unoperated) animals is

Fig. 149A.—Section of cornu uteri of bitch shown in fig. 148. This portion of cornu was removed at the time of the operation on the pituitary. (Blair Bell.) ×40.

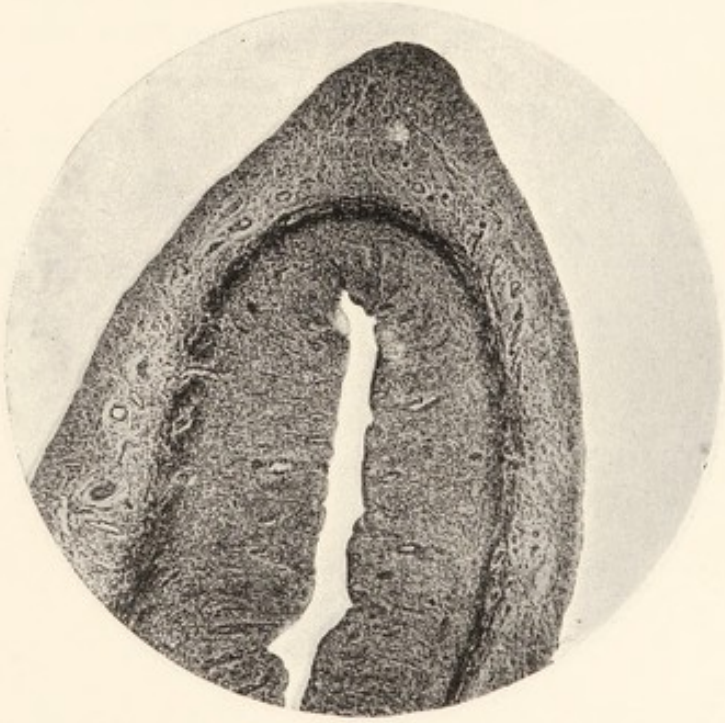

Fig. 149B.—Section of cornu uteri of the same animal removed after death. The animal was killed 128 days after section of the infundibular stalk. (Blair Bell.) ×40.

constantly slightly above that of controls (0·2° to 0·6° F.). The conclusion Dott arrived at was that all the symptoms of anterior lobe removal are those of

metabolic depression. They are independent of any atrophic change in the

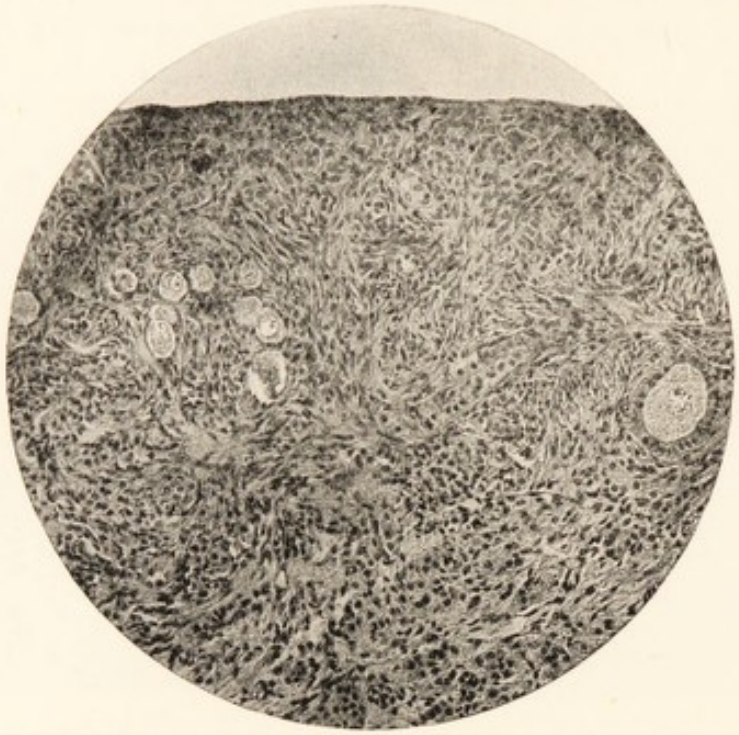

Fig. 150A.—Section of ovary of bitch shown in fig. 148, removed at the time of the operation on the pituitary. (Blair Bell.) ×120.

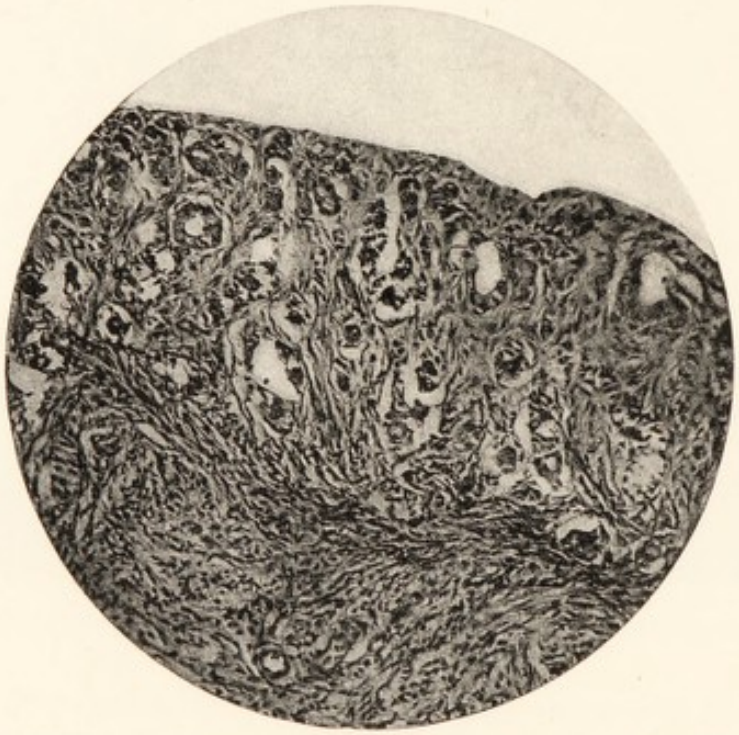

Fig. 150B.—Section of ovary of the same bitch taken after death. The animal was killed 128 days after separation of infundibular stalk. (Blair Bell.) ×120.

thyroid although resembling the effects caused by hypothyroidism: indeed the thyroid is usually hyperplastic after hypophysectomy, complete or partial: this

condition may, however, after a few days be exchanged for one of hypoplasia. Minor symptoms are :—deficiency in the growth of hair : a thin, dry skin : and possibly a lowered resistance to infection. There is marked delay in ossification and a relative diminution in length of the limb bones as compared with controls. In seven experiments Dott found the average diminution due to anterior lobe deficiency to be as much as 57 per cent., whereas in four unoperated animals fed with anterior lobe the average increase was 22 per cent. These conditions were accompanied by histological changes in the epiphyseal cartilages and in the osteogenetic cells of advancing ossification corresponding with the conditions of diminished and increased activity respectively.[1] The above results were obtained from lesions of the anterior lobe or of the stalk. Extirpation of the posterior lobe had no visible effect on growth or development.[2]

Although Dott found—in confirmation of previous investigators—that the condition of hypopituitarism in growing animals tends to produce dwarfism, gigantism was not caused in the normal mammal by pituitary feeding. The animals grew faster and matured sexually earlier but did not ultimately exceed the normal limits of size. Nor did pituitary feeding have any effect on the thyroid.

P. E. Smith and J. B. Graeser [3] injected chromic acid into the pituitary of rats and in seven cases obtained a typical adiposogenital syndrome. The females did not undergo œstrus ; their ovaries were greatly reduced in size ; they contained no recent corpora lutea. The thyroids were also much reduced—to about one-half normal—as well as the suprarenals—to about one-fifth—the cortex being chiefly involved. Sections showed only a small amount of anterior lobe remaining, but a considerable amount of posterior lobe (pars intermedia and pars nervosa). In two females which were treated after operation by hypodermic injection of bovine anterior lobe substance, œstrus was induced and the ovaries became normal.

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[1] In connexion with the effect of lesions of the pituitary on bone development, it may be mentioned that U. Nuvoli has produced rickets in rabbits by treating the pituitary with X-rays for ten minutes a day (*Il Policlinico*, xxx., 1923).

[2] Dott's experiments were made upon young dogs, and the difficulty of removing one part without injury to the rest of the gland applies therefore to them (see p. 280).

[3] *Proc. Amer. Physiol. Soc.*, in *Amer. Journ. Physiol.*, lxviii., 1924; and *Anat. Rec.*, xxvii. 219, 1924.

CHAPTER XL

THE PITUITARY BODY (*continued*)

Polyuria as a Result of Pituitary Lesions

A very common effect of experimental injury of the posterior lobe of the pituitary is polyuria, although removal of that lobe or even of the whole gland is usually stated to have no effect on the secretion of urine. Harvey Cushing,[1] however, records prolonged polyuria after excision of the posterior lobe, and Houssay and Rubio [2] saw marked polyuria following hypophysectomy. Considering that extracts of the posterior lobe produce diuresis when injected into the blood, it is possible that injury of the lobe without removal may produce irritation either of the pars intermedia or of the pars tuberalis, and cause the pouring out of an increased secretion from these. Similarly the polyuria which is often found to accompany fracture of the base of the skull may be due to concomitant injury to the pituitary. Two cases of bullets lodged in the sella have been described in which the accident was followed by persistent polyuria.[3] In Marañon and Pintos' case, a boy of fourteen, the bullet was found to have blocked the infundibulum. Besides marked polyuria, yielding to injections of pituitary extract, there was deficient genital development and a tendency to obesity. And Bailey [4] makes mention of a dog, in which he made a trephine opening through the base of the skull and pressed in gutta percha so as to impinge on the base of the ventricle close to the stalk of the pituitary. This not only produced severe polyuria, but also development of marked adiposity. Mere manipulation of the posterior lobe in the dog, without causing any obvious lesion, will produce polyuria: but exposure of the gland by lateral operation without manipulation or injury has no such effect. The polyuria is sometimes accompanied by hyperglycæmia and even by glycosuria, but these soon pass off and give place to a condition of increased tolerance for carbohydrates, so that it is difficult to provoke glycosuria, even, it is said, if the pancreas is extirpated.[5] The increased tolerance can be promptly lowered by injection of posterior lobe extract.[6] Houssay and Hug [7] state that the polyuria produced by injury to

[1] *Boston Med. and Surg. Journ.*, clxviii., 1913.
[2] *C. r. soc. biol.*, lxxxviii., 1923.
[3] E. Frank, *Berl. klin. Woch.*, 1910, p. 1257; Marañon and Pintos, *Nouv. Icon. d. l. Salpêtr.*, xxviii., 1916.
[4] *Ergebn. der Physiol.*, xx., 1922.
[5] H. Cushing, *op. cit.*
[6] E. Goetsch, Cushing, and Jacobson, *op. cit.*
[7] *C. r. soc. biol.*, lxxxv., 1921.

the pituitary is not diminished by pituitary extract (as is the case with diabetes insipidus in man), but this is contrary to the experience of others.

In an experiment by myself (on a dog) of intentional injury, by a touch with the electric cautery, to the posterior lobe of the pituitary exposed by the lateral method the amount of urine rose immediately from 40 c.c. to 230 c.c. per diem, and then gradually sank ; although for nineteen days it showed an average of 119 c.c. per diem. In another experiment the amount of urine rose from 110 c.c.—the average of the immediately preceding eleven normal days—to 182 c.c.—the average of the eleven days immediately subsequent to the operation. But it was much higher on the third, fourth, and fifth days, averaging on these 266 c.c.[1] D. D. Lewis and S. A. Matthews,[2] and E. B. Towne [3] have also recorded a number of cases of temporary or permanent polyuria produced by injury to the pituitary body or to its stalk. In some of these there were injuries to the adjacent part of the brain. Access to the gland was obtained by Lewis and Matthews by the bucco-pharyngeal route.

Stimulation of the cervical sympathetic or of its superior ganglion was stated by Cushing to cause diuresis. He considered this to be brought about by provoking the secretion of the posterior lobe, since stimulation of the superior cervical ganglion produced no effect if the pituitary were first removed. He therefore concluded that secreting nerves pass through this ganglion to the pituitary. He found excision of the posterior lobe or separation of the stalk to be sometimes followed by prolonged polyuria. According to Weed, Cushing, and Jacobson [4] puncture of the pituitary gives as definite results regarding glycosuria as Bernard's puncture of the fourth ventricle. In both cases there must be "available" glycogen present, *i.e.* glycogen resulting from recent ingestion of carbohydrates. Both this and Bernard's puncture are ineffective after section of the cord at the fourth thoracic level.

Most of the experiments, the results of which in causing polyuria, with or without glycosuria, have been recorded, have taken no account of the pars tuberalis. This part cannot easily be studied separately by reason of the fact that it is intimately united with the base of the brain (tuber cinereum) over which it spreads for some little distance. It may be that injury of this portion of the pituitary is responsible for the polyuria which is frequently associated with injury to the gland. And either injury to the pars tuberalis or interference with the blood-supply of the gland may be accountable for the results which have been recorded by Camus and Roussy.[5] These observers have obtained—in the dog, cat, and rabbit, but not with the same facility in all—polyuria and glycosuria from injuries (by puncture and cautery) of the floor of the third

[1] E. A. Schafer, *Proc. Roy. Soc.*, B, lxxxi., 1909.

[2] *Trans. Chicago Path. Soc.*, ix., 1913. Also Lewis, Article in Barker's *Endocrinology and Metabolism*, i. 721, 1922.

[3] *Proc. Soc. Exper. Biol. and Med.*, xix., 1922.

[4] *Johns Hopkins Hosp. Bull.*, xxiv., 1913.

[5] *C. r. soc. biol.*, lxxv., 1913 ; lxxvi., 1914 (several papers) ; *Presse méd.*, xxii., 1914 ; *C. r. soc. biol.*, lxxxiii., 1920 (two papers) ; *Endocrinology*, iv., 1920 ; *C. r. soc. biol.*, lxxxv., 1921, and lxxxvi., 1922 ; *Journ. de physiol.*, xx., 1922 ; Camus, Gournay, et Le Grand, *Bull. acad. méd.*, June 1924. Leschke, *Zeitschr. klin. Med.*, lxxxvii., 1919, has also described similar results.

ventricle (tuber cinereum) in the immediate vicinity of the pituitary, but apparently without injury to the gland itself. They consider that in all cases the polyuria is due to the brain lesion and not to any effect on or through the pituitary, which can, they state, be removed previously without affecting the result.[1] Camus and Roussy even ascribe the dystrophia adiposogenitalis, and all the other effects which have been put down to lesions of the pituitary, to injuries of the tuber cinereum.

They had one dog with such a lesion under observation for some years: the animal showed polyuria, obesity, and genital atrophy during four years; after that time the testicles began to grow rapidly. In another dog in which the same symptoms had been produced, and in which the testicles and penis were much atrophied and sexual instinct altogether lacking, Camus and Gournay [2] found that administration of large amounts of thymus caused the testicles and penis to greatly increase in size and the animal to exhibit sexual excitement.

Similar results are recorded by Bailey and Bremer [3] as being produced in the dog by puncture with a probe of the base of the brain (hypothalamic region) in the neighbourhood of the pituitary, without in any way directly injuring the gland, the integrity of which was in every case verified histologically. Polyuria resulted from even the smallest puncture: it began, not immediately but within the first two days, and lasted six to eight days or longer, or might be permanent. When permanent polyuria was obtained, the symptoms described as cachexia hypophyseopriva, genital atrophy, and adiposity were also manifested. The permanent polyuria, when it occurred, had all the characteristics of diabetes insipidus in man, such as concentration of urine when intake of water was restricted, excessive polyuria when chlorides were ingested, diminution of urine when posterior lobe extract was injected, absence of effect of theobromine, etc. They found that thirst may precede the polyuria, but does not necessarily do so, and that the renal outflow was independent of the nervous supply to the kidney, or its vascular regulation. Polyuria was never produced by lesions outside the peri-infundibular region; nevertheless, in their opinion, it was not caused by the agency of the pituitary directly or indirectly. They found an extensive lesion of the tuber cinereum to be incompatible with life.

Although there can be no question as to the data recorded by the above-mentioned authors, it is difficult—in view of the numerous observations on the effects of lesions confined to the gland, and of the administration of its extracts—to believe that most if not all of the symptoms described have not been produced through the agency of the pituitary. These observations include the regulation of the output of water by the kidneys, the metabolism of carbohydrates and fats, influences on growth and development, particularly of the generative organs and of the skeleton, and various results which are yielded

[1] It is, however, not possible to include the pars tuberalis in the removal without injuring the base of the brain.

[2] *Paris méd.*, Feb. 16, 1924.

[3] *Journ. Med. Res.*, xlii., 1921; *Arch. Int. Med.*, xxviii. 773, 1921; *Endocrinology*, Nov. 1921; Bailey, *Ergebn. d. physiol.*, xx., 1922. See also G. M. Curtis, *Arch. Int. Med.*, xxxiv. 801, 1924.

by administration of glandular extracts, especially of the pars intermedia and pars nervosa, and appear unmistakably to indicate that the secretions of the pituitary play a fundamental part in the regulation of hydratation and other important functions in the body. It is very difficult to believe that a minute lesion of the floor of the third ventricle—very different in structure and nervous connexions from the floor of the fourth ventricle, and in fact of simpler structure and with fewer nerve connexions than almost any other part of the brain,[1] having no trace of glandular structure except that which is derived from the subjacent pituitary body—should produce *per se* such far-reaching results as those described and hitherto attributed to disturbances of the activities of the pituitary itself. It seems a more rational conclusion that the perihypophyseal lesions effected by Camus and Roussy and by Bailey and Bremer produce their effects by disturbing the normal functions of the gland, possibly through hitherto unrecognised nervous connexions, but perhaps through its vascular supply, or by interfering with the passage of products of the secretion of the pars intermedia into the ventricle, rather than by direct nervous action. The fact that no histological change was recognised in the pituitary as the result of such perihypophyseal lesions is by no means conclusive, since there may easily be disturbance of function without any striking structural change. Moreover, the pars tuberalis has not been taken into account in any of these observations. Any peri-infundibular lesion is bound to injure it and may set up prolonged irritation. It is possible that this portion of the gland plays a more prominent part in the production of polyuria than has been suspected.

Most of the discussion has turned on the question of the production of polyuria from such lesions, although it has, as we have seen, been by no means confined to this question. B. A. Houssay,[2] who confirms the fact of the production of polyuria from lesions of the tuber cinereum, considers that the action may nevertheless be produced through the gland. The fact that polyuria is produced under these circumstances even when the kidneys are completely denervated [3] is an indication that the cause of the polyuria is " humoral " rather than " nervous " : this and the fact that it usually does not make its appearance until the next day or the day after is suggestive of an indirect action through the pituitary rather than an immediate effect of the brain lesion.

Further, Houssay and Hug [4] got normal growth in young dogs with severe lesions of the hypothalamus and tuber, provided that the pituitary was uninjured, whereas extirpation of the gland caused arrest of growth of body and skeleton,

[1] Camus describes two principal nuclei in the tuber cinereum, injury to one of which causes, as he believes, polyuria, and to the other, glycosuria. He states that a lesion of the second causes a graver and more durable diabetes than Bernard's piqûre (Camus, Gournay, et Le Grand, *Bull. acad. méd.*, xcii., 1924).

[2] *Prensa med. Argent.*, May 20, 1915; *Endocrinology*, ii., 1918; Houssay and Romaña, *C. r. soc. biol.*, lxxxiii. 1252, 1920; Houssay and Carulla, *ibid.*, lxxxiii., 1920; *Congr. d. méd. Buenos Aires*, 1922; Houssay and Rubio, *ibid.*, lxxxviii., 1923.

[3] Oehme, *Med. Klin.*, 1919; *Zeitschr. f. d. ges. Med.*, ix., 1919; Houssay and Romaña, *op. cit.*; Stern, Battelli, and Jauffert, *C. r. soc. biol.*, lxxxvi., 1922.

[4] *Rev. asoc. med. Argent.*, xxxiv., 1921; *C. r. soc. biol.*, lxxxix., 1923.

alterations in the structure of the teeth, partial atrophy of thyroid, thymus, and testes, and marked adiposity.

The hypothesis of Camus and Roussy has been subjected to careful examination and criticism by E. Frank, who draws attention to the fact that they and their followers have ignored the existence of the pars tuberalis, with which the diuretic functions of the pituitary are in all probability closely correlated, and points out that the very experiments upon which these observers rely to establish the hypothesis tend rather to favour the supposition that the effects are produced by an interference with the normal functions of the gland. Frank further makes the interesting suggestion that any agency, whether in the form of tumours or experimental injury, which might produce an interruption in the normal slow passage of the secretion along the stalk into the third ventricle, would be likely to cause it to be diverted so that it would be absorbed directly into the blood-vessels and thus tend, as with intravenous injection of the extract, to cause diuresis; while by slow absorption, such as occurs in subcutaneous injections, antidiuresis results.[1] The matter will be further considered in connexion with the occurrence of diabetes insipidus in man.

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[1] E. Frank, *Klin. Woch.*, iii. 847–852 and 895–897, 1924. See also E. Sharpey-Schafer, "On Experimental Polyuria," *Brit. Med. Journ.*, ii. 185, 1925; and *Edin. Med. Journ.*, 1925.

CHAPTER XLI

THE PITUITARY BODY (*continued*)

Effects of Removal in Amphibia

Removal of the pituitary is easily effected in the tadpole or in the adult amphibian through the roof of the mouth without producing injury to the hypothalamus or any other part of the brain.[1] Frogs thus operated on live for a long time, from which it may be concluded that in these animals the organ is not essential to life. The most characteristic external effect is the causation of pallor (fig. 134), the skin becoming light in colour in whatever external conditions the animal may be kept. The pallor begins in six hours and is due to the epidermal and dermal melanophores assuming and remaining in a condition of maximal contraction. The xantholeucophores, on the other hand, display a recticular appearance.[2] Extract of posterior lobe of ox-pituitary injected intraperitoneally speedily reverses these conditions, but the effect gradually passes off and the animals again become permanently pale. The pallor is dependent upon the loss of the posterior lobe (probably of pars intermedia).[3] Lesions of the adjacent brain substance and removal of the anterior lobe have no action on the pigment cells. Similar effects are obtained in the axolotl (Amblyostoma) and in the toad.

Destruction of the buccal rudiment of the pituitary in tadpoles causes the following characteristic symptoms :—(1) Growth is checked and is much slower than in controls ; (2) there is relative atrophy of interrenals, thyroid (fig. 151), and parathyroids ; (3) metamorphosis is suppressed ; (4) the fat-bodies do not diminish in size as development proceeds but undergo hypertrophy ; (5) the melanophores undergo permanent contraction.[4]

Parenteral injection of extract of pars anterior of bovine gland has the effect of reversing all these results, but it may be questioned whether there might not be some contamination with pars intermedia.

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[1] For the method of removal in the frog, see L. T. Hogben, *Quart. Journ. Exper. Physiol.*, xiii., 1923.

[2] In control animals kept in a dark, moist environment along with those which have been hypophysectomised the melanophores are in the expanded reticular condition whilst the xantholeucophores are contracted (see p. 253 and fig. 133).

[3] For a full account of these phenomena and the relative literature, see L. T. Hogben, "The Pigmentary Effector System," 1924.

[4] P. E. Smith, *Univ. Calif. Publ. Physiol.*, 1918 ; *Amer. Anat. Memoirs*, xi., 1920 ; P. E. and I. P. Smith, *Journ. Med. Res.*, xiii. 267, 1922 ; *Anat. Rec.*, xxv., 1923 (*Proc. Amer. Assoc. Anat.*) ; *Endocrinology*, vii., 1923 ; H. M. Evans, Harvey Lecture, April 26, 1924.

Subthalamic lesions in Amphibia produce none of the deprivation effects which are caused by pituitary removal.

The check on growth of tadpoles caused by hypophysectomy is removed by continuous diet of anterior lobe of ox-pituitary, although less readily than with parenteral injections of the extract. The "growth autacoid" or "harmozone" is not contained in either water or alcohol extracts of the

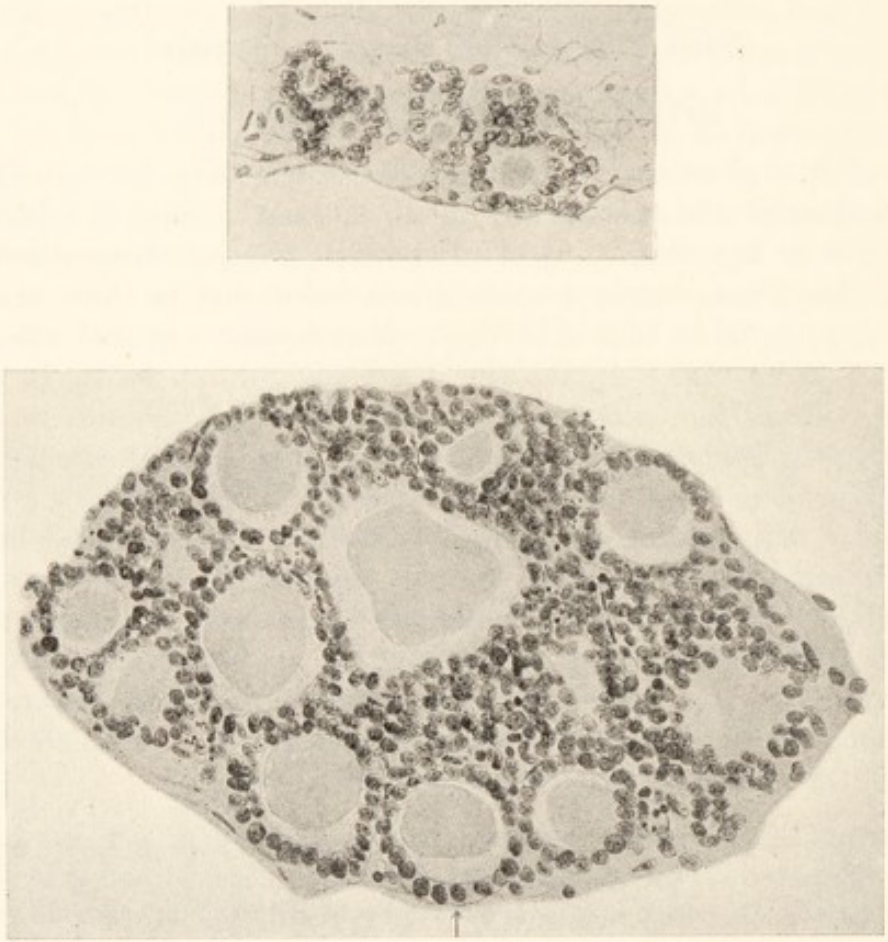

FIG. 151.—Sections across the largest part of the thyroid of a hypophysectomised tadpole, 64 days after the operation (upper figure), and of a normal control of the same age (lower figure). (P. E. Smith.)

anterior lobe, but is present in the residue after extraction with water and boiling alcohol.[1]

B. M. Allen [2] finds that removal of the pituitary in tadpoles of frog or toad has the effect that not only the body generally but also the brain tends to retain its larval characteristics in spite of a general increase of growth.

A. W. Greenwood [3] failed to obtain any effect on the rate of growth of

[1] P. E. Smith, *op. cit.*, 1920. It is therefore not the same as Robertson's tethelin (see p. 273).

[2] *Endocrinology*, viii., 1924.

[3] *Brit. Journ. Exper. Biol.*, ii., 1925.

the axolotl (Amblyostoma tigrinum) if the pituitary were removed after the thyroid had become developed.

P. E. Smith states that injection of anterior lobe extract (bovine) into axolotls produces an increased rate of growth and increase of pigmentation and prevents metamorphosis, which does not occur or is much delayed even if thyroid is given at the same time. Divergent effects may be the result of differences in the proportion of basiphil and oxyphil cells in the lobe or in the part of it used. P. E. and I. P. Smith found that if the centrai part, which contains most basiphils, is employed, the tadpoles metamorphose rapidly, with hyperplasia of thyroid; if the outer part, containing most oxyphils, they grow larger without metamorphosing and the thyroids remain normal.

The effects of removal of the pituitary on growth may be related to the atrophy of the thyroid which is produced by such removal (fig. 151).

CHAPTER XLII

THE PITUITARY BODY (*continued*)

Clinical Evidence

Various clinical symptoms are attributed to alterations in the pituitary body. These alterations may be produced (1) by increase or diminution in size (hypertrophy or atrophy, partial or complete), with corresponding changes in the secretion,[1] (2) by increase or diminution or by changes in the internal secretions of the organ, without any obvious changes in structure, (3) by destruction or injury of the whole or part of the organ caused by traumatisms, by cysts, by degenerative changes, or by pressure of tumours growing from structures adjacent to but outside the pituitary, (4) by changes in the vascular supply, (5) by the agency of nerves supplied to it. Some of these causes can be determined during life by X-ray examination and by intraocular and other symptoms; others can only be made out by anatomical and microscopical investigation of the organ exposed by surgical operation or examined *post mortem*, whilst purely functional changes must be inferred by correlating the clinical symptoms with those which present themselves in animals as the result of experimental interference with the gland. Some of the clinical symptoms have been long described, and their connexion with changes in the pituitary has been generally considered to be well established, whilst others, which have for the most part been more recently noted, are in the opinion of many clinicians not definitely shown to be related to this organ. These differences of opinion will be referred to subsequently.[2]

[1] The increase in size most frequently takes the form of a glandular tumour (adenoma) generally affecting only the anterior lobe, but sometimes involving the posterior. Such tumours are usually benign to begin with, but may later, it is said, become malignant. According to Boyce and Beales 30 per cent. of all cranial tumours are traceable to the pituitary (*Journ. Path. and Bact.*, i., 1893), but Harvey Cushing finds the proportion less than this (Cameron Lecture to the University of Edinburgh, *Lancet*, 1925).

[2] The literature of the pituitary in its clinical aspects is enormous, and very few of the original papers can be referred to in this work. L. Borchardt (*Ergebn. d. inn. Med.*, etc., 1909) and Ch. Livon (Article, "L'hypophyse" in Charles Richet's *Dictionnaire de Physiologie*, 1909) give bibliographies up to that date. Harvey Cushing ("The Pituitary Body and Its Disorders," 1912) describes a number of clinical cases in which the pituitary was believed to be involved, as well as experiments on animals which were correlated with the clinical aspects of the subject, and furnishes numerous references to the literature: this work marks a distinct epoch in the clinical study of the pituitary. Subsequent literature will be found referred to by D. D. Lewis, *Journ. Amer. Med. Assoc.*, Sept. 17, 1910; Blair Bell, "The Pituitary," 1919; W. Engelbach, *Endocrinology*, iv., 1920; Harvey Cushing, *Presse méd.*, xxx., 1922; P. Bailey, *Ergebn. d. Physiol.*, xx., 1922; Dott and Bailey,

Acromegaly and Gigantism

The course of many cases of disorder of the pituitary body is as follows (H. Cushing): Starting with enlargement of the anterior lobe, they are heralded by symptoms of excessive function of this lobe (*hyperpituitarism*). After a variable time—sometimes greatly prolonged—degenerative changes in the enlarged organ may supervene, and there may result a gradual diminu-

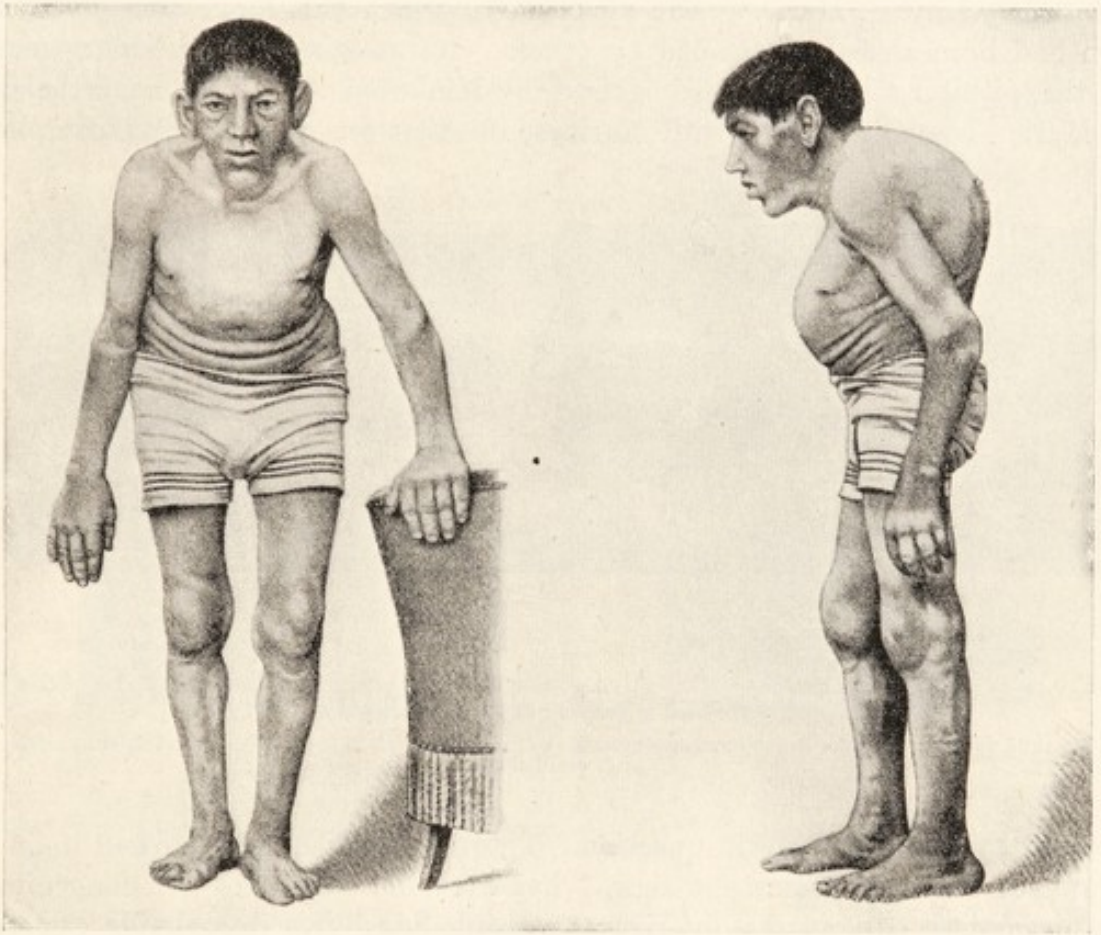

Fig. 152.—Case of acromegaly, front and side view. (Klebs and Fritsche.)
The illustration shows the enlarged hands, feet, and joints, the massive elongated face and thick lips, the dorsal curvature (kyphosis), the apathetic look.

tion (*hypopituitarism*), or even eventually an entire loss of function (*apituitarism*). The primary enlargement may be drawn attention to by diminution of the visual field, caused by the pressure of the enlarging gland upon the optic chiasma; hence these affections often come first under the notice of the ophthalmic surgeon. Although there is loss of vision, this is not necessarily produced by actual destruction of nerve-fibres, for it has frequently been noticed that after

Brit. Journ. Surg., xiii. 314, 1925; as well as in the Articles, "Pathological Anatomy of the Hypophysis," "Acromegaly," and "Dystrophia Adiposogenitalis," in Barker's *Endocrinology and Metabolism*, i., 1922, by J. P. Simonds, P. Bassoe, and H. G. Beck respectively.

operation for removal of the tumour, or alleviation of the pressure produced by it, the patient's vision is speedily restored. The upper temporal part of the field is first affected;[1] then, in order, the lower temporal, the lower nasal, and the upper nasal fields. There is often double hemianopsia with central vision. If the enlargement is more on one side than on the other, the blindness is unilateral. Rarely there may be signs of pressure on the oculomotor nerves.

Accompanying or preceding the visual symptoms certain other signs are developed which point to the advent of a peculiar affection (fig. 152), termed *acromegaly*[2] by P. Marie.[3] The affection to which this name was given by him had been already described by others. Its association with enlargement of the pituitary body was recognised by Minkowski.[4] It is, nevertheless, to Marie—associated later with Marinesco[5]—that we owe the first complete

A B C D

FIG. 153.—Four photographs of the same person showing the gradual development of the facial appearance characteristic of the acromegalic. (Cushing.)

A, at 24 years of age (prior to the commencement of the disease); B, at 29 (onset of disease); C, at 37; D, at 42 years of age.

account of the syndrome in question. The name which he bestowed upon it expresses its most prominent sign, "hypertrophie singulière non-congénitale des extrémités supérieures, inférieures et céphalique"—a remarkable noncongenital enlargement of the limbs and head. The face and head (fig. 153), hands (fig. 154), and feet are especially hypertrophied, the patient finding that he has to provide himself with progressively larger hats, gloves, and boots than he has been accustomed to wear. X-ray photographs show a typical mushrooming of the ungual phalanges (fig. 155). The enlargement is not confined to

[1] A. Josefson, "Studier over Akromegali," 1903; H. Cushing and C. B. Walker, *Brain*, xxxvii., 1915.

[2] ἄκρον, extremity; μέγας, large.

[3] *Revue de méd.*, vi., 1886; *Nouv. Icon. Salpêtr.*, i. and ii., 1888 and 1889; *Progrès méd.*, 1889; *Brain*, xii., 1890. For the history of the subject to 1897, see Sternberg in Nothnagel's "Handb. d. Med.," vii., 1897, and G. Hinsdale, "Acromegaly," Detroit, 1898. For the pathology and clinical features of acromegaly, see G. Peritz, in Kraus und Brugsch's "Pathologie und Therapie," i., 1916, and P. Bassoe, *op. cit.*, 1922.

[4] *Berlin klin. Wochenschr.*, xxxiv. 371, 1887.

[5] *Arch. méd. expér.*, iii. 539, 1891.

the bones of the limbs; it affects the skeleton generally, and indeed all the connective tissues (including the integument), which become thickened and hypertrophied. The skin may become œdematous as in myxœdema. The hair of the face, body, axillae, and pubes may be at first unusually developed but with advance of the disease gradually becomes lost: this is perhaps a secondary effect accompanying diminution of the sexual functions. There is also usually at first considerable activity of the sweat glands, which in later stages disappears. Amenorrhœa in the female and impotence in the male are distinctive features of the affection as it progresses.[1] Headache, deepseated, is a frequent early symptom.[2]

Fig. 154.—Typical hand of acromegalic. (Cushing.)

Notice the broad palm and digits and the relatively small nails, which lack lunulæ.

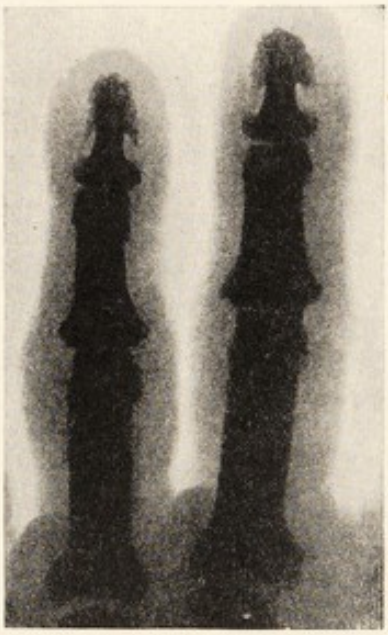

Fig. 155.—X-ray photograph of two digits of an acromegalic patient (Cushing) showing the peculiar mushrooming of the ungual phalanx.

The lower jaw is usually very prominent, also the supraciliary ridges. The face is both broadened and elongated; the features are coarse; the nostrils wide; the lips thickened; the tongue too large for the mouth. The larynx is enlarged,[3] so that the voice becomes deeper. Most of the viscera also undergo enlargement: the heart markedly so.

There is often glycosuria or simple polyuria, sometimes peptonuria; associated frequently with inordinate appetite and thirst:[4] when present,

[1] W. A. Boyd observed sexual impairment in 68 per cent. of male cases and 89 per cent. of females (*Med. Rec.*, lxxxviii., 1915).

[2] L. P. Mark, "Acromegaly: A Personal Experience," London, 1912. An autobiographical account.

[3] C. Jackson, *Journ. Amer. Med. Assoc.*, lxxi., 1918, gives details of the laryngoscopic appearances.

[4] L. Borchardt, *Zeitschr. f. klin. Med.*, lxvi., 1908; J. M. Anders and H. L. Jameson, *Amer. Journ. Med. Sci.*, cxlviii., 1914; Byrom Bramwell, "Clinical Studies," iv., 1915.

these conditions are probably associated with hypertrophy of the pars intermedia as well as of the pars anterior. The tolerance for sugar is usually at first lowered, but as the case advances may be replaced by high degrees of sugar tolerance, due to a subsequent hypoplasia or degeneration of the gland. The sugar tolerance is accompanied by adiposity. According to André Levi, glycosuria occurs in 30 to 50 per cent. of cases of acromegaly. It is interesting to note that in pregnancy also—in which the pituitary is found to undergo enlargement—glycosuria not infrequently occurs. The excretion of urea is sometimes much increased, but usually there is N-retention. Basal metabolism varies but is usually increased in acromegaly, at least in cases in which the disease is progressive, whereas in affections in which there is reason to believe that the secretion of the anterior lobe is diminished there is diminution of basal metabolism.[1]

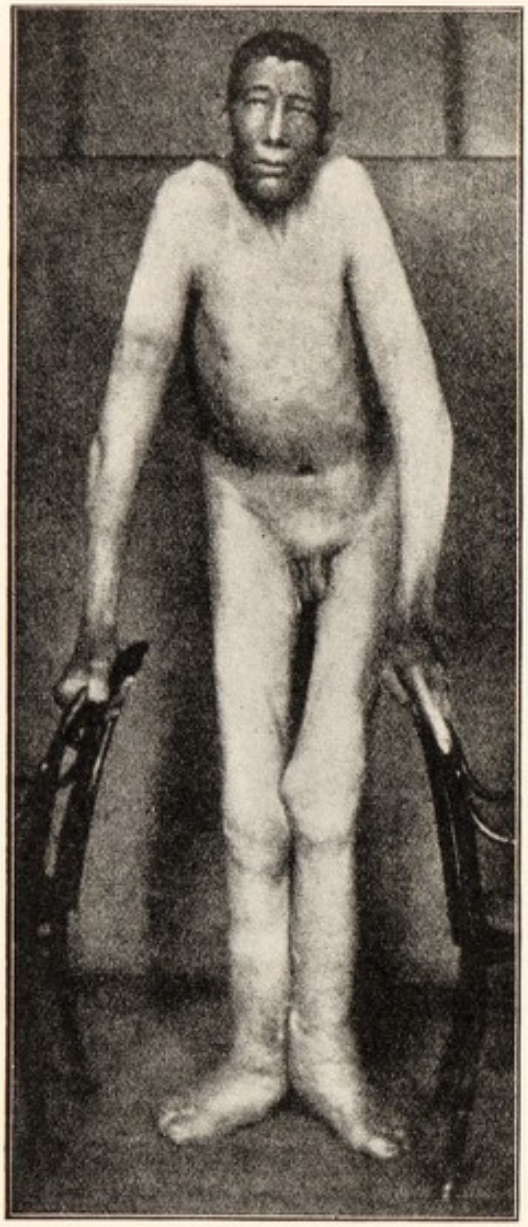

Fig. 156.—Case of pituitary gigantism. (Cushing.) The patient was thirty-six years of age and 8 feet 3 inches high. Notice the large elongated face, the dull heavy expression, the long limbs, narrow chest, enlarged joints, enormous hands and feet, and the deficiency of hair (hypotrichosis). The last is not a constant feature.

In the later stages there may be mental depression and stupor.

There is often very considerable muscular development, the subject being abnormally strong, but later he may exhibit weakness and become easily fatigued.

If the affection does not supervene until adult life is attained, *i.e.* until the epiphyseal cartilages are ossified, the long bones do not grow in length and the height is but little affected, any increase of stature that is produced by increase of the vertebral column being usually more than compensated for by a kyphosis (fig. 152) which supervenes after the disease has made some progress. But if the hyperpituitarism commences whilst the cartilages are still unossified, there is a considerable growth in length of the long bones, so that the patient

[1] C. A. M'Kinlay, *Arch. Int. Med.*, xxviii. 703, 1921; H. G. Hill, *Quart. Journ. Med.*, xv. 331, 1922; Dott and Bailey, *op. cit.*, 1925.

attains an unusual height. This condition is known as *pituitary gigantism* [1] (fig. 156); it is of essentially the same nature and origin as acromegaly,[2] but commences at an earlier age and some of its features are thereby modified.[3]

Both in acromegaly and in pituitary gigantism there is probably always adenomatous enlargement of the anterior lobe of the pituitary forming a tumour; this may attain the size of a Tangerine orange. There is a corresponding enlargement of the sella turcica, which is an indication of the slowness of growth of the tumour. This enlargement is readily detected in X-ray photographs of the basis cranii, and can be noticed in all skeletons of acromegalics and giants in anatomical museums. The enlargement of the sella is altogether out of proportion to the increased size of the skeleton.[4]

In his original papers, Marie, although he drew attention to the enlargement of the pituitary in cases of acromegaly, seemed rather to regard this as an accompaniment than as the actual cause of the affection. Later he inclined to the opinion that acromegaly is due to destructive disease of the gland, since in some cases it was found *post mortem* that the tumour was of malignant character and that the substance of the gland had been destroyed. It was this idea which led to the carrying out by various investigators of experiments for the removal or destruction of the organ, especially in young animals, in order to produce, if possible, an increase of growth. But so far from producing increased growth, this operation led to the opposite result, the development of the skeleton and body generally being retarded and restrained. It is now recognised that all the tumours of the gland which are associated with acromegaly are in the first instance of a glandular (adenomatous) type, the enlargement being due to multiplication of the eosinophil cells.[5] It is therefore held that the characteristic symptoms of acromegaly are due to hyperpituitarism, *i.e.* to increased function, although it may be that there

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[1] There are other kinds of gigantism, without pituitary enlargement (Byrom Bramwell, "Clinical Studies," June 1915; P. Bassoe, Article, "Gigantism," Barker's *Endocrinology and Metabolism*, ii., 1922).

[2] The correspondence between the condition now known as acromegaly and gigantism seems to have been first pointed out by D. J. Cunningham, *Journ. of Anat. and Physiol.*, xii. 294, 1878, and later by Massalongo, *Rif. med.*, viii., 1892; it has since been insisted on by most writers on the subject (Brissaud and Meige, *Rev. neur.*, 1904; C. Tamburini, *Riv. sper. fren.*, xx., 1894, and xxi., 1895; Woods-Hutchinson, *New York Med. Journ.*, 1898 and 1900; Lannois and Roy, "Études biologiques sur les géants," 1904). Rarely gigantism is unilateral; such cases have not been found to be associated with increase in size of the pituitary (Monrad, *Ugesk. f. Laeger*, lxxxiii., 1921).

[3] Nevertheless it is said that true acromegaly may occur in children without the production of gigantism (Barker's *Endocrinology and Metabolism*, vi.; Bassoe, Article "Acromegaly," 1922, p. 813).

[4] Various observers (H. W. Freund, *Volkmann's klin. Vortr.*, 1889; H. Gilford, "The Disorders of Postnatal Growth and Development," London, 1911; and A. Keith, *Lancet*, 1911, p. 993) have called attention to the similarity between the acromegalic skeleton and that of the anthropoid apes and of primitive man. Keith gives a very full description of the growth changes of the skeleton, particularly the skull, in cases of acromegaly. E. C. Case has made the interesting observation that the gigantic saurians of the secondary epoch had a relatively enormous sella turcica (*Journ. Comp. Neurol.*, 1921).

[5] Benda, *Arch. f. Anat. u. Physiol., Physiol. Abteil.*, 1900. Dott and Bailey, *op. cit.*, 1925, find that while tumours associated with acromegaly are characterised by the large number of eosinophil granules in the cells, those associated with Fröhlich's disease and hypopituitarism (simple adenomata) are composed mainly of chromaphobe cells.

is also some degree of perversion of function (dyspituitarism). In later stages, effects of destruction (hypopituitarism) may become apparent and supersede the symptoms of hypertrophy.

Sometimes the tumour of the gland is from the first malignant, but even then many of the cells tend to resemble those of the normal gland (malignant adenoma), and symptoms of acromegaly may still be produced.

Rare cases of acromegaly have been described in which no enlargement of the pituitary was found *post mortem*, and in which the gland has otherwise presented a normal structure. But it is doubtful if these should be regarded as examples of true acromegaly. It is possible, however, that there may have been an increased secretion without a corresponding increase of size.[1]

Not every case of tumour of the pituitary is accompanied by the symptoms of acromegaly. For the disease may from the first be destructive and tend to the opposite condition, viz. hypopituitarism. There is, as we have seen, evidence derived from the results of destruction in animals as to the symptoms which may result from such deficiency. When similar symptoms occur in man, it is therefore natural to conclude that they have the same cause, viz. pituitary insufficiency.

In many cases where the affection begins with hyperplasia of the gland, and subsequent changes produce destruction or degeneration of the enlarged organ, leading eventually to apituitarism, these changes may occupy many years in their development and may even stop at an intermediate stage. If, however, they proceed, the patient ultimately loses strength and gradually wastes. In such circumstances death results under conditions which are analogous to those of *cachexia hypophyseopriva*, described by Paulesco, Cushing, and others in animals operated on by them (pp. 279, 280).

That the acromegalic condition is produced by hypertrophy and over-secretion of the anterior lobe is highly probable, both as the result of partial extirpations in animals and from the effect of operative removal of pituitary tumours in man. One case in particular has been described [2] as having shown within a few days of operation for removal remarkable amelioration of the symptoms, with gradual diminution in size of the enlarged extremities, and eventually complete cure. The thyroid gland both in this and in another instance which was also successfully operated upon by the same surgeon became permanently enlarged. In both, the pituitary tumour was a malignant adenoma. In other cases operated on by Hochenegg, Cushing, and others, in some of which an enlarged anterior lobe only was removed, the results have been less striking than in the above example, but the retrogression of the disease symptoms which resulted from the partial extirpation of the tumour has occasionally been well marked. We are therefore warranted in believing that the enlargement of the skeleton and the other signs which are characteristic of acromegaly are due to hypertrophy of the anterior lobe of the pituitary, with increase of its secretion.

[1] Massalongo, *op. cit.*, 1892. [2] J. Hochenegg, *Wien. klin. Wochenschr.*, 1909, p. 333.

A certain number of cases have been recorded in which acromegaly has shown a tendency to heredity, and cases have occurred in which more members than one of a family of brothers and sisters have developed the disease. But on the whole the hereditarism of the affection is not striking.[1]

Pituitary Nanism

In connexion with the influence of the anterior part of the organ on growth, cases of dwarfs have been described in which the pituitary, or the sella turcica, has been noticeably small and atrophied; although others have been recorded in which this has not been found or the gland has been larger than normal. It may be noted that in more than one such case of a dwarfish stature associated with apparent enlargement of the pituitary, the tumour has been found to be really outside the gland, exercising compression upon it, or to be caused by cysts destroying the anterior lobe.[2] It must be remembered also that increased activity of the natural function of an organ may not necessarily accompany increase in volume: this is exemplified in cases of endemic goitre. There is, on the whole, reason to believe that a dwarfish habit of body is usually associated with diminution either in amount or in activity of the anterior lobe of the pituitary. The change may commence in infancy or even before birth.

It must be borne in mind that there are many factors influencing growth, the pituitary being only one. It is, however, probably the most important organ in this respect; others, such as the thyroid and the gonads, perhaps acting through it.

Dystrophia Adiposo-genitalis (Fröhlich's Disease)

Hypopituitarism appears to be the cause of the syndrome described by A. Fröhlich [3] as associated with the pituitary body, and termed by Bartels [4] "dystrophia adiposo-genitalis." The striking features of the syndrome are adiposity and genital atrophy; with these may be associated either an enlarged or a diminished stature. The symptoms closely simulate those shown by animals which have undergone partial removal or injury of the pituitary, or

[1] *Cf.* Bassoe, Article, "Acromegaly," in Barker's *Endocrinology and Metabolism*, vol. i., 1922.

[2] A case of nanism is described by M. Simmonds (*Deutsch. med. Wochenschr.*, xlv. 487, 1919) in which the anterior lobe was destroyed by cysts, the posterior lobe being normal.

[3] *Wien. klin. Rundschau*, xv. 883, 1901. In considering cases of tumours of the pituitary which are unattended by symptoms of acromegaly, Fröhlich described a case of a fourteen-year-old boy showing the syndrome to which his name has since been attached. He pointed out that similar symptoms had been previously described—the first by Mohr (*Wochenschr. f. d. ges. Heilk.*, vi. 565, 1840). It is interesting to note that as early as 1887 several cases were described—obviously of that affection—of obesity, genital insufficiency, and drowsiness, which were related to changes, for the most part tumours, of the pituitary (*Proc. Ophth. Soc.*, 1887). The history of early cases of the disease is given by H. G. Beck, Article, "Dystrophia Adiposo-genitalis," in Barker's *Endocrinology and Metabolism*, i., 1922.

[4] *Münch. med. Wochenschr.*, lv. 201, 1908. O. Marburg (*Zeitschr. f. Nervenh.*, xxxvi., 1909) seems to have first connected the syndrome with *deficiency* of pituitary secretion.

interference with its blood-supply or of the passage of its secretion into the ventricle, as by severance or blocking of the stalk (p. 285). They are symptoms of pituitary insufficiency, and are the reverse of those ascribed to hyperpituitarism.

Since experiments on the pituitary of animals seem to show that the conditions of sexual atrophy and adiposity are associated with deficiency of the secretion of the posterior lobe, it is probable that the tumours of the gland which lead to the condition of dystrophia adiposo-genitalis cause such deficiency by compressing the posterior lobe or the stalk, and interfere with the blood supply or with the passage of the secretion into the third ventricle.

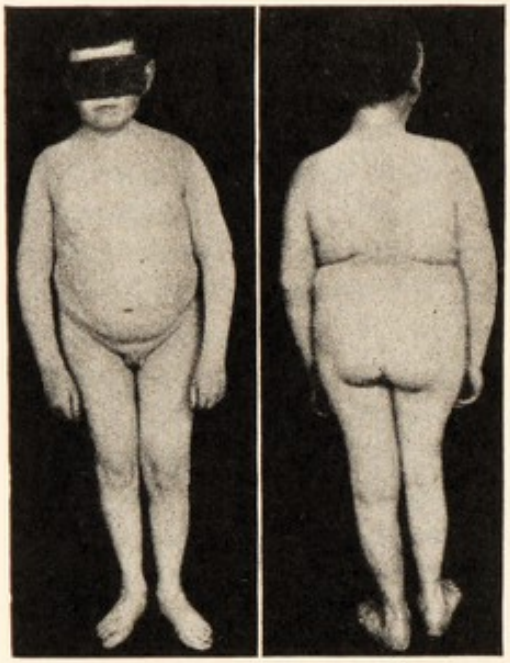

FIG. 157.—Case of pituitary infantilism. (Byrom Bramwell.) The patient was twenty-seven when the photograph was taken. His height was 4 feet $1\frac{3}{4}$ inches. Notice the arrested development of the sexual organs, the deficiency of hair, the adiposity, the slender limbs and digits, and the general approach to the feminine type of body.

If the affection begins before adolescence and there is also deficiency of the secretion of the anterior lobe, as in atrophy of the whole gland, the stature may remain small (as seen in fig. 157) instead of becoming large as in hypertrophy of that lobe; and as there is marked adiposity, the weight of the body may be large relatively to the height. But if the secretion of the anterior lobe is not deficient or is increased, the child becomes much larger than others of the same age (fig. 158).

It is stated that the adiposity of Fröhlich's disease is characterised by being mainly obvious in the lower part of the body, especially the buttocks and thighs, but deposits of fat occur in many other parts and may be general, particularly if the affection occurs in early life. Sexual development is always delayed, and may remain in abeyance, producing a permanent condition of infantilism. In the female the menses are irregular or absent, and in both sexes there is deficient development of secondary sex characters such as the hair on the face (in the male) and over the pubes in both sexes. Such hair as occurs in the last-mentioned situation in the male does not extend to the umbilicus as is usual in that sex, but assumes the disposition characteristic of the female, limited to the mons Veneris. On the other hand, the hair of the head is generally abundant. Nor is the character of the trichosis the only sign of feminism in male subjects affected by hypopituitarism. They usually have a broad pelvis, a certain amount of *genu valgum*, rounded limbs, small feet and hands, tapering fingers, and a tendency to mammary development. Skiagrams of

the bones generally exhibit persistent epiphyseal lines (fig. 159). The skin is smooth and delicate and free from moisture. The nails are small and thin, and the crescents at the base are absent.

Cushing was the first to attribute the tendency to adiposity to deficiency

Fig. 158.—Dystrophia adiposo-genitalis in a boy aged sixteen. (Dr Miller's case.) From a photograph lent to me by Mr A. J. Walton.

in posterior lobe secretion, and later experiments and observations appear to support this conclusion. The occurrence of adiposity in connexion with lesions of the stalk in animals has been already mentioned: it is of interest that it may also be found clinically as a result of tumour principally affecting the stalk.[1]

The condition is generally associated with unusual tolerance to sugar, so that alimentary glycosuria is far less readily obtained than in normal individuals.

[1] J. Fraser, *Edin. Med. Journ.*, xxxi., 1924. For a description of pituitary obesity occurring in adolescents, see H. Gardiner Hill, I. Jones, and J. Forest Smith, *Quart. Journ. Med.*, xviii. 309, 1925.

This means that the assimilation power for carbohydrates is increased: if the excess is transformed into fat, the tendency to adiposity is thus explained. Although the affection is not usually accompanied by glycosuria [1] many cases have been described in which there was excessive polyuria.[2] The basal metabolism is low (16 per cent. to 20 per cent. below normal, Plummer). A sub-

Fig. 159.—X-ray photograph of hand from the case of infantilism shown in fig. 157. (Byrom Bramwell.)

Notice the slender phalanges and the still detached epiphyses. Reduced from 6½ inches.

normal temperature is generally noted, with low arterial tension and a slow pulse. There is also often marked drowsiness and torpidity; [3] so much so that the condition has been compared to that of an animal about to enter into the condition of hibernation: it has been suggested that hibernation is brought about by the agency of the pituitary.[4]

[1] Strada, *Virch. Arch.*, cciii., 1911.

[2] See amongst others, E. A. Graham, *Ann. Surg.*, lxvi., 1917; G. Marañon and A. Rosique, *Trab. d. l. soc. biol. d. Barcelona*, 1917; J. R. Williams, *Endocrinology*, i., 1917.

[3] The fat boy in *Pickwick* is a familiar example of this.

[4] See p. 194.

The duration of the affection depends largely on its etiology. If caused by the growth of a tumour it may prove fatal within a relatively short period unless surgically relieved, but if due to atrophic changes it may become chronic and last indefinitely.

The blood picture shows reduction of hæmoglobin; but little, if any, reduction in the number of red cells. Of the white cells the polymorphs are fewer in number than normal; the oxyphils, lymphocytes, and macrocytes (mononuclears) may show an increase.

In some cases evidences of psychic derangement and occasionally a tendency to epilepsy have been noted.[1]

Hypopituitarism and its accompanying symptoms may result from simple atrophy of the gland, as appears to have been the case in the instance of infantilism shown in fig. 157; in this subject the skiagram showed a small sella turcica. Or, as above stated, it may be caused by destruction of the gland, *e.g.* by the formation of a cyst, or as the result of pressure from a neighbouring tumour,[2] or from accidental injury.

A well-known case described by Madelung in which such symptoms made their appearance was that of a girl of nine years of age (fig. 160) whose pituitary was destroyed by a bullet which lodged in the sella turcica.[3]

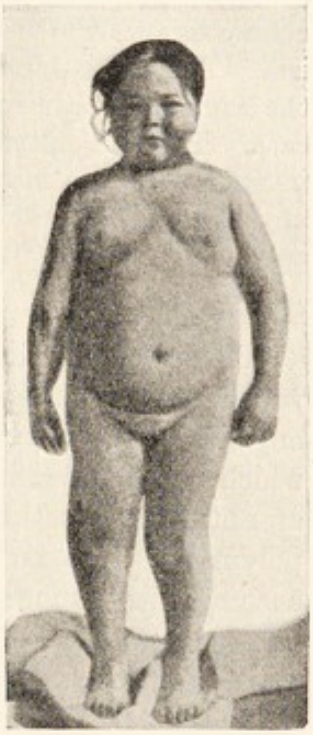

FIG. 160.—Case of bullet wound of pituitary. (Madelung.)

It may here be recalled that a similar syndrome was produced in dogs by Blair Bell and by Bailey, by introducing an artificial "tumour" which pressed upon the pituitary, and by Dott, by allowing a thin platinum plate to rest on the organ (see pp. 286, 290). In these cases the result was perhaps due to an interference with the vascular supply, and hence with the nutrition of the gland, producing hypopituitarism, but it may have been the result of interference with the passage of the secretion of the posterior lobe through the stalk.

When the hypopituitarism comes on after adolescence certain of the above symptoms will be missed; but the tolerance to sugar, the subnormal metabolism and temperature, and the supervention of excessive adiposity are generally present, as well as dryness of the skin and loss of hair. There is also a tendency in the male to adopt the female type of trichosis, even if the male type has already been established.

According to W. Engelbach,[4] when pituitary insufficiency, commencing before puberty, is restricted to the pars anterior, there results sexual infantilism

[1] For classification of cases, see H. G. Beck, *Amer. Journ. Med. Sci.*, clvi. 711, 1918; *Endocrinology*, iv., 1920; and Barker's *Endocrinology and Metabolism*, iii., 1923.

[2] C. N. Armstrong, *Brain*, xlv., 1922.

[3] *Verhandl. d. deutsch. Ges. f. Chir.*, xxxiii. 164, 1904.

[4] *Endocrinology*, iv. 347, 1920, and *Medical World*, xxiii. 218, 1925.

without adiposity, the body and limbs remaining slender, and the stature short (Lorain type of infantilism[1]). It is when the deficiency involves the posterior lobe that both adiposity and sexual infantilism (Fröhlich's syndrome) are manifested.

As has already been stated, the history of some cases of affections of the pituitary shows symptoms characterising hypopituitarism following those characterising hyperpituitarism, although of course little or no retrogression in the growth of the skeleton and body can generally be expected. Thus the occurrence of hyperplasia and hyperpituitarism during adolescence, leading to a general overgrowth of the body and unusual growth of hair, and sometimes accompanied by sexual precocity, may be followed by glandular hypoplasia and diminution of the sexual instinct, even proceeding to impotence; as well as by excessive adiposity and the assumption by the male of some of the feminine characteristics which have been above described as associated with hypopituitarism. This alteration in the signs of disease complicates the clinical features; and the complexity can only be unravelled by a careful study of the history of each case. The difficulties are largely increased by the fact that other glands of internal secretion may be affected by an increase or decrease in the secretion of any one of them.

Diabetes Insipidus[2]

Polyuria (sometimes accompanied by glycæmia and glycosuria) is a symptom which is very frequently associated with affections of the pituitary and might be attributed to the production of an excess of the diuretic hormone which is contained in extracts of the posterior lobe. But these extracts have an antidiuretic action as well, and, when administered hypodermically, restrain polyuria.[3] This fact has led many clinicians to regard the polyuria which accompanies tumours of this region as due, not to an effect upon the pituitary, but to pressure on or injury of the tuber cinereum and the floor of the third ventricle. This position is similar to that arrived at from experiments on animals by Camus and Roussy (p. 291), who showed that a small injury in that region of the brain—to all appearance not involving the pituitary body—will cause copious polyuria, sometimes persistent. Since these results have already been described and discussed, and similar arguments would apply to the effect of tumours as to that of intentional injuries of the perihypophyseal region, it is unnecessary to go over the same ground again. The question must be regarded as *sub judice*, but with a tendency to be settled in favour of the gland itself, which there are strong grounds for believing to be associated with the maintenance of the necessary water-balance of the body (see p. 248).

The literature regarding the clinical aspect of this question is far too abundant to be quoted here. The matter has been discussed at length by various authors,

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[1] E. Levi, *Nouv. icon. d. l. Salpêtr.*, xxi. 297, 421, 1908.

[2] Diabetes insipidus was distinguished from saccharine diabetes (glycosuria) by Thomas Willis in 1674.

[3] Farini, *Gazz. osped.*, No. 109, 1913; R. v. den Velden, *Berl. klin. Wochenschr.*, l. 2083, 1913. See also L. F. Barker and H. O. Mosenthal, *Journ. Urology*, i., 1917.

E. Schulmann and R. Desoutter,[1] Marañon,[2] J. Lhermitte,[3] Lortat-Jacob and Tonquin,[4] Sjövall.[5] Marañon arrived at the conclusion that most cases of diabetes insipidus, as observed clinically, are due to insufficiency of the secretion of the posterior lobe. He states that the amount of urine can be reduced to normal—but not below normal—by injections of posterior lobe extract, and that other forms of diabetes insipidus are unaffected by such treatment.[6] Lhermitte, and Lortat-Jacob and Tonquin conclude with Camus and Roussy that the polyuria of diabetes insipidus depends on some lesion of centres at the base of the brain which regulate hydratation (distribution of water) in the body; while Sjövall suggests that there is, in cases where the affection causing the polyuria is at the base of the brain, an interference with the passage of hormones from the pituitary to this region. Schulmann and Desoutter consider that the testimony of clinical observations fully justifies the theory of the pituitary origin of diabetes insipidus, and hold that it is brought about by functional deficiency of the posterior lobe, extracts of which re-establish the lost secretory equilibrium produced by injury or disease. They repudiate the suggestion of Camus and Roussy that the fact that extracts of pituitary have a specific influence on the excretion of water is a purely accidental coincidence.

Cases have been recorded of diabetes insipidus in which the polyuria disappeared after removal of cerebrospinal fluid by lumbar puncture: [7] such cases seem to indicate a humoral cause for the affection.

Further, cases are on record [8] which point to the active participation of the posterior lobe. In that described by Weber and Schmidt the patient, who was tuberculous, suffered from diabetes insipidus, passing more than 13 litres of urine per diem. It was found after death that the pituitary as a whole was not enlarged, but the posterior lobe had grown round and completely enclosed the anterior lobe: it contained large clumps of cells filled with lipoid granules. In Simmond's case there was a malignant tumour of the pars nervosa extending to the pars intermedia, with marked diabetes insipidus (10 to 19 litres of urine per diem). In a case recorded by Piney and Coats there was a metastatic tumour (from a cancer of the breast) in the posterior lobe, accompanied by marked polyuria.[9] These are apparently cases of the cells of a malignant tumour assuming the functions of the tissues in which they are growing (see p. 39, note 6).

As already pointed out, the fact that the polyuria which is produced in animals by lesions of the tuber cinereum does not make its appearance for

[1] *Rev. méd.*, xxxvii., 1920.

[2] *Endocrinology*, v., 1921. For a review of fifty-six cases treated at the Mayo Clinic, see L. G. Rowntree, *Journ. Amer. Med. Assoc.*, 1924, p. 399.

[3] *Ann. méd.*, xi. 89, 1922.

[4] *Ibid.*, xii. 480, 1922.

[5] *Acta Med. Scand.*, lix. 406, 1923.

[6] This is contrary to the results of experiments with water-polyuria described on p. 246, but perhaps only refers to clinical cases.

[7] J. Herrick, *Arch. Int. Med.*, x., 1912; Graham, *Journ. Amer. Med. Assoc.*, lxix., 1917; John R. Williams, *Endocrinology*, i., 1917. Lhermitte and Fumet (*Bull. et mém. soc. méd. d. hôp.*, xlvi. 322, 1922) obtained the same result in a case of glycosuric polyuria.

[8] E. Frank, *Berl. klin. Wochenschr.*, Feb. 26, 1912; Simmonds, *Münch. med. Wochenschr.*, lx. 127, 1913; F. Parkes Weber and H. Schmidt, *Amer. Journ. Med. Sci.*, clii., 1916.

[9] *Journ. Path. and Bact.*, xxvii., 1924.

some hours or days is also suggestive of a secondary humoral cause through the pituitary rather than of a direct nervous action.

It is further noteworthy that whereas ordinary intracerebral tumours do not as a rule yield favourable results from X-ray treatment, tumours of the infundibulo-hypophyseal region are generally amenable to it.[1]

Camus and Gournay [2] find that diabetes insipidus is characterised by diminution of uric acid and excess of purin bases in the urine. They state that injection of purins in normal animals causes diuresis,[3] and suggest that the polyuria of diabetes insipidus may be caused in this way, in consequence of metabolic effects produced by irritation of the nerve-nuclei of the tuber. But Schteingart finds no parallelism between the diuresis in diabetes insipidus and the urinary purins (although the administration of posterior lobe extract will diminish both) and points out that in some affections (*e.g.* cancer) there may be augmentation of purins without polyuria.[4]

What has been said (p. 293) as to the possible effects of irritation of the pars tuberalis may here be recalled. This part has never been taken into consideration by those who have dealt with the origin of diabetes insipidus : it may prove to be an important factor.

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[1] Roussy, Bollack, Labride, and Lévy, *Rev. neurol.*, ii. 297, 1924. The authors got favourable results from such treatment in cases of acromegaly, of dystrophia adiposo-genitalis, and in ocular troubles caused by pressure of the tumour on the chiasma. E. B. Towne (*Journ. Amer. Med. Assoc.*, lxxxiii., Dec. 1924) records a case of pituitary tumour with diabetes insipidus, treated by X-rays, with disappearance of the polyuria, as well as of the accompanying optic defects caused by pressure of the tumour.

[2] *C. r. soc. biol.*, xci. 1137, 1924.

[3] *Ibid.*, xc. 335, 1924.

[4] *Ibid.*, xciii. 1135, 1925.

CHAPTER XLIII

THE PITUITARY BODY (*continued*)

Relations of the Pituitary with Other Organs

The relationship of the pituitary to other internal secretions and organ-extracts is extensive. Cow [1] showed that the secretion of the posterior lobe is excited by duodenal extract, which, after a somewhat prolonged period of latency, causes its hormones to be poured out in unusual amount into the cerebrospinal fluid. Subsequently the subject was taken up by W. E. Dixon,[2] who found the same for ovarian extract, but with a shorter period of latency. These researches and those of Dixon and Marshall [3] have been already referred to in connexion with the passage of the secretion of the pars intermedia into the third ventricle (pp. 202, 203, and figs. 109, 110). The secretion of this lobe is also related to the glycogenic functions of the liver, and there seems to be a mutual interaction between its autacoids and those of the pancreas, suprarenals, thyroid and sex glands. Further, Ascoli and Legnani [4] found, in dogs which survived for a sufficient time the operation of removal of pituitary, a diminution in volume of the spleen, with disappearance of the Malpighian corpuscles, precocious retrogression of the thymus, enlargement of the thyroid due to accumulation of colloid within its follicles similar to that seen in endemic goitre, and an increase of lipoids in the cells of the cortex of the suprarenals. The relationship with certain of these organs may be considered more particularly.

With the Sex Glands.—The relationship of the pituitary to the sex glands and secondary sex characters has been dealt with in considering the symptoms associated with hypo- and hyper-pituitarism. Besides the effect of these conditions on the state of development of the secondary sex characters and on the activity of the essential organs of reproduction, the latter appear to have some reciprocal effect on the pituitary. Several observers have described enlargement of the gland and increase in the number of large oxyphil cells of the pars anterior as the result of castration. A. E. Livingston finds that in rabbits the effect is greater in the female than in the male.[5] Further, Steinach and Schleidt [6] aver that the changes in the pituitary which would result from castration

[1] *Journ. Physiol.*, xlix., 1915.
[2] *Ibid.*, lvii., 1923.
[3] *Ibid.*, lix., 1924.
[4] *Boll. soc. med. chir. Pavia*, xxiv., 1911.
[5] *Amer. Journ. Physiol.*, xl., 1916.
[6] *Zentrlbl. f. Physiol.*, xxvii., 1914.

are prevented by implantation of either ovary or testis in the castrated animal, and since the generative cells undergo atrophy under these circumstances, they ascribe the result to the interstitial cells of the implanted organs. Moreover, it is found that both menstruation and pregnancy are associated with hypertrophy of the gland. Indeed as the result of pregnancy it may attain to twice or three times its normal weight.

The action of extracts of the pituitary upon the contractile tissue of the sex organs has already been described (pp. 227 to 229).

Clinically, destructive tumours of the pituitary are frequently associated with deficient development of the sex organs and of secondary sex characters. These conditions may be accompanied by atrophic changes in the thyroid.[1]

With the Thyroid and Parathyroids.—That after the removal of the thyroid the pituitary body becomes altered and enlarged was first shown by Rogowitsch.[2] His statements have been confirmed by all other observers.[3] L. Degener [4] finds the increase in weight proportional to the time which has elapsed after removal of the thyroid (in rabbits). The hypertrophy produced by thyroidectomy affects all parts, but most the pars anterior, in which it is not uncommon to observe a considerable development of colloid-containing vesicles not unlike those of the thyroid : the same appearance is seen in myxœdema [5] and other affections involving atrophic changes in the thyroid or interference with its function in the human subject. Livingston [6] found thyroid feeding to prevent the increase in size of the pituitary which would be caused by thyroidectomy.

E. R. Hoskins [7] finds that thyroid feeding (rats) checks the growth of the pituitary in the female and accelerates it in the male. Herring's results confirm those of Hoskins in the female, but tend to show that a similar effect may also be produced in the male.[8]

Another striking effect of thyroidectomy upon the pituitary is increase of hyaline and granular masses in the pars intermedia, and their passage in large amounts through the pars nervosa into the infundibular extension of the third ventricle (figs. 111, 112).[9] This denotes an increased activity of the pars intermedia. The phenomenon also occurs in myxœdema [10] (see fig. 113).

[1] W. H. Good and A. G. Ellis, *Endocrinology*, ii., 1918.

[2] *Ziegler's Beitr.*, iv., 1889.

[3] Hofmeister, *Fortschr. d. Med.*, x., 1892 ; Stieda, *Ziegler's Beitr.*, vii., 1890 ; Gley, *Arch. de physiol.*, 1892, and others. Gley found in one rabbit kept twelve months after thyroidectomy that the pituitary was five times the normal average weight.

[4] *Quart. Journ. Exper. Physiol.*, vi., 1913. The literature up to that date is given in this paper.

[5] W. Hale White, *Lancet*, i. 156, 1913. R. Boyce and C. F. Beadles (*Journ. Path. and Bact.*, 1892) described pituitary enlargement in myxœdema, with the presence of colloid in the blood-vessels of the pars anterior.

[6] *Proc. Soc. Exp. Biol. Med.*, xi., 1914. See also L. Loeb and E. E. Kaplan, *Journ. Med. Res.*, xliv., 1924.

[7] *Journ. Exper. Zool.*, xxi. 295, 1916.

[8] *Quart. Journ. Exper. Physiol.*, xi. 231, 1917.

[9] P. T. Herring, *ibid.*, i. 281, 1908.

[10] F. W. Mott, *Proc. Roy. Soc. Med.*, x., 1917.

Mrs F. D. Thompson [1] described enlargement of the pituitary, and a considerable increase of colloid-containing vesicles in the pars intermedia, as the result of parathyroidectomy also (see Part I., p. 86). This observation was confirmed by Izumi (for the cat).[2] Acromegaly also is often associated with thyroid disturbances, which generally take the form of hypothyroidism.[3]

The microscopic changes in the pituitary which result from thyroidectomy and from parathyroidectomy in the rat and dog have been described in some detail by M. Kojima.[4] In the thyroidectomised rat a number of enlarged cells make their appearance in the pars anterior, and there is a considerable accumulation of hyaline substance between the cells and also within vesicles in this part. After parathyroidectomy there are also a certain number of enlarged cells and the cells of the pars intermedia are large. Thyroid feeding produces an accumulation of hyaline matter both in the intraglandular cleft and in the posterior lobe. In the thyroidectomised dog there appeared an accumulation of hyaline substance between the cells of the pars anterior and many vesicles containing hyaline substance in the pars intermedia and pars nervosa, as well as a considerable appearance of oxyphil and enlarged cells in the pars anterior. Kamo [5] also finds that the hypertrophy of the pituitary which follows thyroidectomy is chiefly of the anterior lobe and is characterised by an abundance of large eosinophil cells in this. On the other hand, removal of parathyroids produces an increase in volume and formation of colloid in the pars intermedia.

The pituitary colloid is not identical with that of the thyroid. It is noteworthy that it does not contain iodine, which is a characteristic component of the thyroidal colloid in all animals. Even many months after thyroid removal Sutherland Simpson and Andrew Hunter [6] were unable to detect the least trace of iodine in the sheep's pituitary. The pituitary cannot take the place of the thyroid in animals affected with cachexia thyreopriva, nor is pituitary extract able to take the place of thyroid extract in the treatment of endemic goitre and myxœdema. There is, therefore, no evidence that these two organs act vicariously. The effect of the injection of their extracts is, moreover, entirely different. But that they show a certain parallelism in relation to growth and development is manifest by the results of their removal in young animals. In both cases growth is slowed or arrested, the development of the body generally and of the sex organs in particular is checked, and that of the higher functions of the nervous system is interfered with. There is also a tendency to adiposity, which is particularly marked in cases of hypophysial deprivation, but is also seen after thyroidectomy and in myxœdema.

Herring [7] found that neither thyroid feeding nor thyro-parathyroidectomy

[1] *Phil. Trans.*, B, cci. 91, 1910.

[2] *Japan Medical World*, ii. 199, 1922 (abstract). Izumi also deals with the histological changes in the pituitary consequent on thyroidectomy and castration.

[3] J. M. Anders and H. L. Jameson, *Trans. Amer. Assoc. Physicians*, xxxvi., 1921.

[4] *Quart. Journ. Exper. Physiol.*, xi., 1917.

[5] *Kyoto Igaku Zasshi*, 1917. (See also *Endocrinology*, ii. 325, 1918.)

[6] *Quart. Journ. Exper. Physiol.*, iii., 1910, and iv., 1911.

[7] *Proc. Roy. Soc.*, B, xcii., 1921. See also Kepinow, *Arch. f. exp. Path. u. Pharm.*, lxvii. 247, 1912.

(in cats) affects the autacoid load of the posterior lobe of the pituitary body as tested on the isolated uterus of the rat and on the blood-pressure of the cat.

With the Suprarenals.—That there is some relationship between the pituitary and the suprarenals appears from the fact that extracts of the posterior lobe of the pituitary and of the suprarenal medulla mutually facilitate one another's action. Thus an immediately prior injection of even a small dose of adrenaline will increase the effect of a dose of pituitary extract, and *vice versa*. This result has been obtained by most observers,[1] although the last part is denied by R. G. Hoskins.[2] Cow found that both the muscular coat of the vessels and the uterine muscle are sensitised for adrenaline by pituitary extract, and not only for adrenaline but for all drugs which act through nerve-endings, such as pilocarpine and ergotoxine; not, however, for those which act directly on plain muscular tissue, such as barium. The uterus is also sensitised by pituitary extract for excitation through the hypogastric nerve. The sensitisation can be obtained by feeding with pituitary. Fröhlich and Pick found that the paralysis of the sympathetic (constrictors) caused by ergotoxine is antagonised by pituitary. Cow considered that the effect of adrenaline on the uterus and blood-vessels is affected by the amount of pituitary substance in the blood. He regarded the increased size of the pituitary in pregnancy as correlated with the fact that whereas (in some animals) adrenaline causes inhibition of the non-pregnant, it produces contraction of the pregnant uterus (see p. 135, Part I.). In animals in which the normal effect of adrenaline on the non-pregnant uterus is to cause inhibition, a preliminary treatment with pituitary extract has the result of reversing this effect and causing adrenaline to produce contraction, in spite of the fact that pituitary alone may cause inhibition. The reversion effect is obtained even more readily with the pregnant uterus. This is also the case with the frog's blood-vessels.[3]

Given by the mouth or injected subcutaneously, pituitary extract inhibits glycosuria and glycæmia whether produced by adrenaline, Bernard's puncture, psychical disturbance, or by caffeine.[4]

R. Hofstätter[5] has investigated, in the rabbit, the effect of posterior lobe injection extending over a prolonged period. One of the chief changes observed was hypertrophy of the suprarenal capsules and of the mammary glands. There was also disappearance of colloid from the thyroid vesicles, but whether this is to be interpreted as an increased functioning of the gland does not appear.

With the Pancreas and Other Organs concerned with Carbohydrate Metabolism.—Hypopituitarism, whether the result of disease or of surgical interference, is

[1] Kepinow, *Arch. f. exper. Path. u. Pharm.*, lxvii. 247, 1912 (blood-pressure and pupil); Fröhlich and Pick, *ibid.*, lxxiv., 1913, and *Wien. med. Wochenschr.*, 1914, p. 1062; H. Börner, *Arch. f. exper. Path. u. Pharm.*, lxxix., 1915–16; Nieulescu, *Zeitschr. f. exper. Path.*, xv., 1914; D. Cow, *Journ. Physiol.*, lii., 1919.

[2] *Proc. Soc. Exper. Biol. and Med.*, xiii., 1915.

[3] Fröhlich and Pick, *op. cit.*, 1913.

[4] T. H. Stenström, *Biochem. Zeitschr.*, lviii., 1913.

[5] *Monatsschr. f. Geburtsh.*, xlix., 1919.

associated with an increased tolerance for sugar. This function is probably connected with the posterior lobe. According to Cushing, animals which have suffered deprivation of this lobe will even bear removal of the pancreas without exhibiting glycosuria. On the other hand, removal of the pancreas increases the amount of hyaline substance passing through the pars nervosa from the pars intermedia to the third ventricle.

There seems to exist a functional correlation between pituitary, suprarenal, pancreas, and liver, so that the disturbance of the function of any one of them may affect the metabolism of carbohydrates through its influence upon others. And to these we may add the thyroid, since, as has already been noticed, the mechanism of carbohydrate metabolism is also affected, in some manner as yet imperfectly understood, by variations in its secretion. For hypothyroidism, like hypopituitarism, raises the assimilation limit for sugar in the body. And, according to Asher and Flack, the presence of an unusual amount of thyroid secretion in the blood acts as an excitant to the suprarenals, causing an increased outpouring of adrenaline, and thus producing a lowering of the sugar assimilation limit.

Subcutaneous injection of pituitary extract diminishes or abolishes the effect of insulin on blood-sugar, and removes the hypoglycæmic symptoms which may have been produced, causing a rapid rise in the blood-sugar. Also as we have seen, the extract inhibits or reduces adrenaline hyperglycæmia and glycosuria.[1] Dogs deprived of the pituitary are much more sensitive to the effects of insulin injections.[2]

In decerebrated cats, the pituitary being intact, insulin does not produce its usual effect on the blood-sugar. This is due probably to an increase of posterior lobe secretion under the influence of the general excitation of the efferent nervous system which accompanies decerebration (*e.g.* decerebrate rigidity). In decapitated animals, or in animals in which the pituitary is removed, convulsions are readily produced by insulin, but not if the spinal bulb is destroyed.[3]

A. W. M. Ellis[4] records a case of tumour, apparently taking origin in the pars intermedia, with marked hyperglycæmia and glycosuria, these disappearing on removal of the tumour. He suggests that the hyperglycæmia was due to increase of pituitary secretion interfering with the normal action of insulin.

Insulin antagonises the action of pituitary extract on the guinea-pig's uterus, if the gland extracts are mixed beforehand.[5]

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[1] J. H. Burn, *Journ. Physiol.*, lvii., 1923.

[2] B. A. Houssay and M. A. Magenta, *Rev. asoc. med. Argent.*, xxxvii., 1924. This is also true for toads (Houssay, Mazzocco, and Rielli, *C. r. soc. biol.*, xciii. 968, 1925).

[3] J. M. D. Olmsted and H. D. Logan, *Amer. Journ. Physiol.*, lxvi., 1923.

[4] *Lancet*, i. 1200, 1924.

[5] G. Joachimoglu and A. Motz, *Deutsch. med. Wochenschr.*, l. 1787, 1924.

CHAPTER XLIV

THE PITUITARY BODY (*concluded*)

Therapeutic Uses of Pituitary Extracts

The employment of pituitary extracts in medicine is chiefly confined to water-extracts of the posterior lobe. These are usually sold—under various names [1]—in hermetically sealed glass containers holding from 0·5 c.c. to 1·0 c.c. of the extract, which should be standardised against an extract of bovine gland of ascertained strength. Unfortunately the standards which have been adopted by different manufacturers vary considerably, so that it is not possible to give a dosage applicable to all.[2]

The extract is usually given by hypodermic or intramuscular injection, but has also been administered as an intranasal spray.[3]

The chief use of the extract is in obstetrics to promote contraction of the parturient uterus. The effect is powerful, and the extract should never be administered unless the os is completely dilated and there is no obstruction to the passage of the fœtal head : otherwise the powerful contractions produced may cause rupture of the uterus.[4]

It is used in post-partum hæmorrhage ; and may also be employed in some other forms of hæmorrhage where adrenaline is contra-indicated, especially in pulmonary hæmorrhage, since it does not raise pulmonary arterial pressure and increases the coagulability of blood.

It is recommended for intestinal stasis, especially that which often follows abdominal operations. Pituitary whole gland, given by the mouth, has been used for treating habitual constipation.[5] But the effects on the intestine appear to be due to the histamine which commercial preparations almost always contain.

[1] *Pituitrin*, *hypophysin*, *infundibulin*, *post-pituitrin*, etc.

[2] For methods of standardising, see Chapter XXXVI. J. H. Burn and H. H. Dale (*Report of Medical Research Council*, No. 69, 1922) recommend that extracts should be standardised to represent 10 per cent. of the fresh posterior lobe, and that the commercial preparations should be tested on a cornu uteri of a virgin guinea-pig, comparing the effect with that of fresh extract of known strength. One cubic centimetre of an extract equal to 1 in 10 of fresh gland may be regarded as an average dose for hypodermic injection.

[3] Blumgart, *Arch. Int. Med.*, April 15, 1922 ; *Proc. Roy. Soc. Med.*, Therap. Sect., 1923.

[4] For its employment in labour, see S. Jervois Aarons, *Lancet*, ii. 1828, 1910 ; B. P. Watson, *Amer. Journ. Obstetrics*, iv. 603, 1922 ; W. Blair Bell, *Brit. Med. Journ.*, i. 1027, 1925.

[5] J. W. Tomb, *Lancet*, Dec. 6, 1924.

It has been recommended to be injected into the heart in asphyxia neonatorum and in heart failure from anæsthesia and other causes in adults, but is probably inferior to adrenaline in such cases.[1]

It has been found beneficial in cases of herpes zoster[2] and serum rashes;[3] also in the collapse and spasm of bronchitis. The extract has been found to influence Graves' disease favourably.[4]

Next to its employment in obstetrics must be set down the influence of posterior lobe extract in controlling the abnormal water-output in cases of diabetes insipidus. This has already been discussed in connexion with the antidiuretic action, and need not be further alluded to. It is also said to be of value in cases of incontinence of urine.[5] It has been recommended for menorrhagia.[6]

For many of the uses enumerated above there appears to be a definite therapeutical advantage in combining pituitary extract and adrenaline.[7]

Preparations of the anterior lobe have for the most part not proved therapeutically useful, although cases of dystrophia adiposo-genitalis have occasionally been treated with them, it is claimed, with some success.[8]

The addition of pituitary (whole gland) to thyroid has been recommended for the treatment of myxœdema and cretinism.[9]

Owing to the fact that Robertson's "tethelin" (see p. 273) is said to have an influence on growth and on the healing of wounds similar to that caused by whole anterior lobe, its therapeutic use has been suggested for the local treatment of indolent ulcers and for the healing of skin lesions produced by burns or otherwise. The results obtained are conflicting, and more extended trials are necessary before a decisive opinion can be pronounced regarding its efficacy.[10]

[1] Toupet, *Journ. de méd.*, 10me mars, 1925.
[2] S. N. Vendel, *Uges. f. Laeger*, lxxxv. 222, 1922.
[3] W. M. Crofton, *Lancet*, i. 124, 1917.
[4] J. Pal, *Deutsch. med. Wochenschr.*, xii. 1537, 1915.
[5] Osborne, "Principles of Therapeutics," 1921.
[6] Blair Bell, "The Pituitary," 1919.
[7] Rohmer, *Münch. med. Wochenschr.*, 1914, p. 1336.
[8] Such cases are described by Tierney in *Endocrinology*, vii. 536, 1923. The effect of anterior lobe administration in redistributing the fat in cases of dystrophia adiposo-genitalis has been noted by H. G. Beck, *ibid.*, iv., 1920, and Article in Barker's *Endocrinology and Metabolism*, i. 913 *et seq.*, 1922.
[9] T. A. M'Graw, jun., *Endocrinology*, v. 691, 1921 (abstract of paper in *Journ. Mich. Med. Soc.*, xx. 27, 1921).
[10] For details regarding these experiments, see F. S. Hammett, "Pharmacology of Hypophyseal Extracts," in *Endocrinology and Metabolism*, i., 1922.

CHAPTER XLV

THE PINEAL BODY

Morphology

The pineal body (*epiphysis cerebri, conarium*) [1] is present in all vertebrates except the lowest, and must therefore be regarded as an organ of considerable morphological, if not physiological, importance. In man it takes the form of a small oval structure of reddish colour, about one-third the

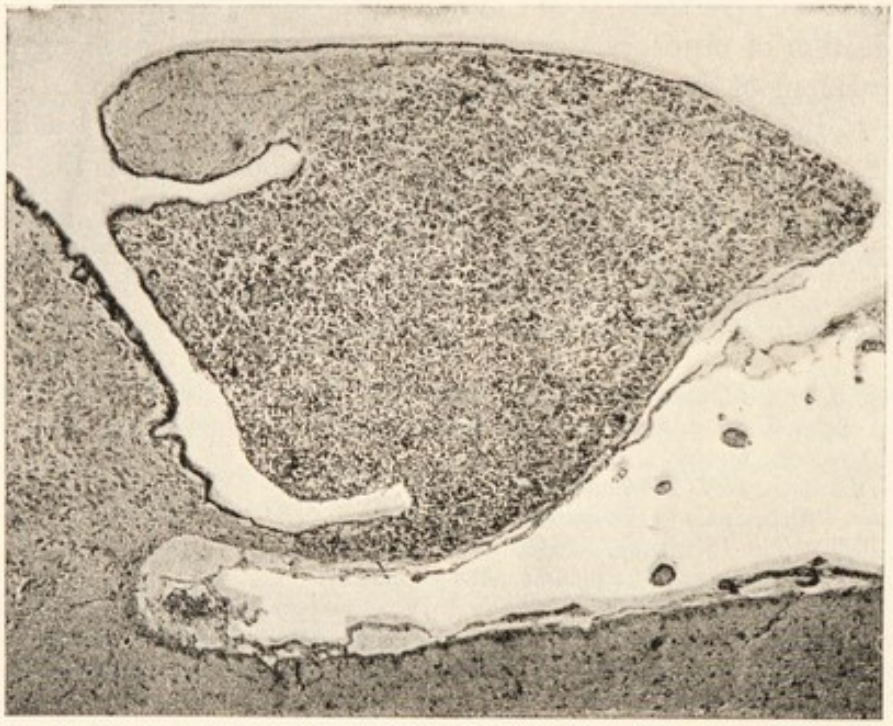

Fig. 161.—Sagittal section of pineal of cat. ×50. Photographed from a specimen by M. Kojima.

size of the pituitary body, projecting from the roof or dorsal wall of the third ventricle over the groove between the two anterior tubercles of the corpora quadrigemina just above the posterior commissure and the exit of the Sylvian aqueduct from the third ventricle. From its position it is apparent that if it undergoes enlargement it may block the passage into the aqueduct and tend to cause hydrocephalus.

[1] Latin *conus pinealis*, a pine cone.

The base of the organ is connected on each side by a short stalk or peduncle with the habenular commissure (fig. 161). In the base is a depression (*pineal recess*)—the remains of an evagination from which the gland was originally developed. The evagination makes its appearance in the human embryo about the fourth or fifth week.

The pineal exhibits considerable variation in size. Its average dimensions are :—Saggital, 8·4 mm. : frontal, 6·3 mm. : from above down, 4·2 mm. Its average weight is 0·180 gram.[1] It is a little smaller in the female than in the male and proportionally larger in the child than in the adult. It is closely invested by pia mater, and usually becomes torn away from the brain if the pia mater is removed.

In many of the lower Vertebrata it is much more developed than in man and mammals. In some a special evagination grows out from it which passes through the skull to reach the integument in the middle line, where a median eye may be formed. This is often quite rudimentary, but in some lizards is well developed and furnished with a cornea, lens, and retina (*parietal eye*), with a median nerve connecting it with the base of the pineal and through this with the corpora bigemina. In the common frog (Rana temporaria) there is an enlargement and thickening of the evagination lying in the middle line of the skull, under the skin, marked by a round spot clear of pigment, lying just between the eyes.

The morphology of the pineal is treated of by Stúdnicka [2] and by Tilney and Warren [3] in elaborate monographs, in which the literature is fully referred to. A short account, which also deals with the physiological and clinical evidence relating to the functions of the organ, is given by Kidd.[4]

Miscroscopic Structure

Sections of human pineal from the young subject show it to be composed of irregularly shaped cells (pineal cells) arranged in loosely disposed trabeculæ (fig. 162) ; the numerous vessels are conveyed in connective tissue continuous with that of the pia mater. In some animals plain and even striped muscle has been described in this tissue. The organ is traversed in its whole length by myelinated nerve fibres : they are said to be traceable to the posterior and habenular commissures. According to Cutore and Ramón y Cajal some at least are derived from the sympathetic ; these doubtless reach the gland along its blood-vessels. Neuroglia cells and fibres are present in abundance, becoming more conspicuous as age advances and the pineal cells proper disappear. In some animals the cells are compactly arranged and the organ has a decidedly glandular appearance. Embedded both in the interstitial connective tissue and

[1] S. Uemura (*Frankf. Zeitschr. f. Path.*, xx., 1917) gives 0·157 gram, G. Cutore (*Arch. ital. anat. embriol.*, viii., 1910) 0·22 gram as an average weight. Both these papers contain many comparative details.

[2] "Die Parietalorgane," in Oppel's *Lehrb. d. vergl. mikr. Anat.*, v., 1905.

[3] "The Morphological and Evolutional Significance of the Pineal Body," *Amer. Anat. Memoirs*, 1919.

[4] *Review of Neurol. and Psych.*, xi., 1913.

in the pia mater covering are small round globules of calcareous matter—*corpora amylacea*, *brain sand*: these are more common in man than in lower animals

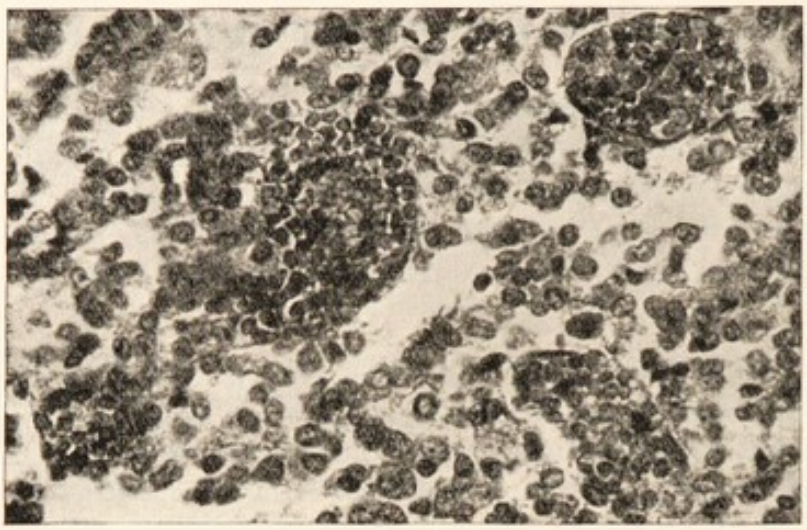

FIG. 162.—Section of pineal, new-born child. Photograph. ×400. Three or four large sinus-like vessels gorged with blood are included in the section.

FIG. 163.—Cells from pineal, showing many different forms. Human adult. (Rio-Hortega.)

and in the adult than in the child. It is doubtful if there are any true nerve-cells in the adult organ, but some authors, including Cajal, have described them in young subjects.

The cells of the organ are not uniform in character. Some are

unbranched, but the greater number are provided with many ramified processes which frequently end in clubbed extremities [1] (fig. 163). Many of the cells have fine oxyphil granules in their protoplasm, but in some the granules are basiphil.[2] The existence of these granules, combined with the extreme vascularity of the organ in young subjects, suggests an internal secretory function of the gland. Many of the branched cells are glia-cells.

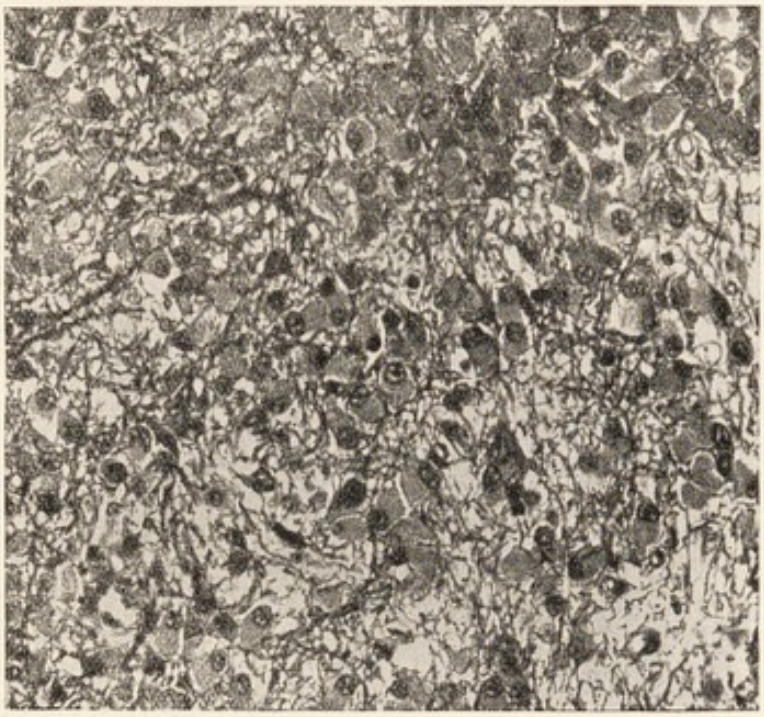

FIG. 164.—Section of pineal of ox, stained with iron-hæmatoxylin. Photographed from a specimen prepared by E. Beard. × 300.

Vesicles containing colloid have been described but are rare. Cysts are, however, not infrequent: they may be pathological. Yellowish-brown pigment granules are often seen in the cells, especially as age advances.[3]

After childhood (seven years) the gland usually undergoes retrogressive changes. The neuroglial tissue hypertrophies and shows a characteristic reticular appearance, whilst its cells become prominent (fig. 164). The pineal cells proper diminish considerably in relative amount.

[1] F. Tello, *Trab. d. lab. d. invest. biol. d. Madrid*, x., 1912; Achúcarro and Sacristán, *ibid.*; Rio-Hortega, *ibid.*, xxi., 1923.

[2] Large secretion granules such as are seen in the cells of the pars anterior of the pituitary are absent from the pineal.

[3] Z. Dimitrova, *Le Nevraxe*, ii., 1901. Dimitrova, who describes three distinct types of nuclei in the pineal cells, states that the nuclei extrude secretion granules into the protoplasm. This recalls a similar observation made by A. Maximow in the cells of salivary glands (see Schafer, *Textbook of Microscopic Anatomy*, 1912, p. 439). The peculiar structural appearance of the nuclei in the pineal is also referred to by O. Marburg (*Arb. a. d. neurol. Inst. Wien*, xvii., 1909) and by K. H. Krabbe (*Anat. Hefte*, liv., 1916).

Effects of Administration of Pineal Extracts

Alcohol extracts of pineal injected intravenously produce a marked temporary fall of blood-pressure accompanied by diminution in volume

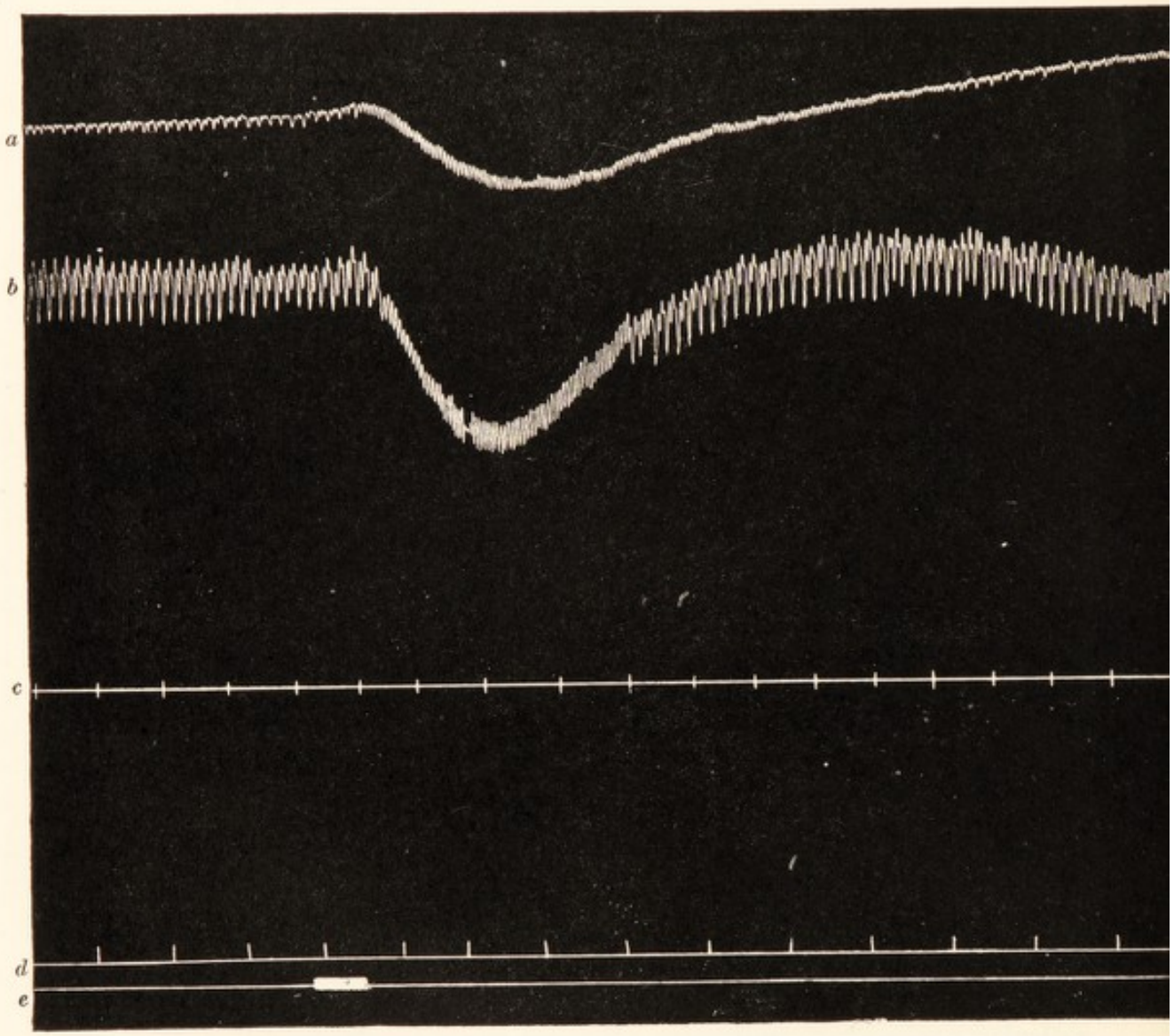

Fig. 165.—Effect on kidney volume and blood-pressure of intravenous injection of a solution in Ringer's fluid of dried alcohol extract of sheep pineal.

a, kidney volume; *b*, blood-pressure; *c*, urine drops; *d*, time in ten seconds; *e*, signal.

of such an organ as the kidney (fig. 165). The respirations are temporarily diminished or arrested. The flow of urine is only very slightly affected. There is a slight discharge of milk from the mammary gland—much less than that caused by pituitary extract.[1]

[1] Ott and Scott, *Monthly Cyclop. and Med. Bull.*, v., 1911 (goat); K. Mackenzie, *Quart. Journ. Exper. Physiol.*, iv., 1911 (cat).

Effects of Feeding with Pineal

Dana and Berkeley,[1] using kittens, guinea-pigs, and rabbits, to the ordinary food of which fresh calf pineal was added, found that the animals so fed increased in weight faster than controls. Their experiments extended over periods of $2\frac{1}{2}$ to 5 months: they describe the results as "certainly remarkable." Similar experiments with dry calf pineal were carried out on guinea-pigs and chicks by M'Cord.[2] The guinea-pig experiments were begun at the second week after birth and continued for ten weeks. At the end of that time the pineal-fed animals had gained 23 per cent. over the controls, but none continued to grow above the normal size. There were also indications of sexual precocity, most marked in males, in which the seminiferous tubules were more mature than in the controls. There was no increase in amount of interstitial tissue of the testicle.

Similar experiments on albino rats have yielded negative results.[3] But in these the dry glandular substance had been extracted with ether, which may have removed the harmozone.

Observations have also been made on the effect of feeding children—especially those lacking in mental or physical development—with pineal: the results were, in the long run, negative.[4]

M'Cord has investigated the effect of adding pineal extract to the culture fluid in which Paramœcium was multiplying, using extracts of muscle and other tissues as controls. The divisions were more numerous in the pineal culture.[5]

Effect on Amphibian Melanophores

A striking effect is produced on the contraction of the integumental melanophores of tadpoles by pineal feeding. As we have already seen, these melanophores are contracted by the autacoid of suprarenal medulla (adrenaline) and expanded by an autacoid yielded by the pars intermedia of the pituitary. M'Cord and Allen[6] find that tadpoles fed with pineal in addition to their ordinary plant food rapidly lose their dark appearance, and even within thirty minutes of the commencement of feeding become clear and translucent (figs. 166, 167), although kept, along with controls, under conditions which would otherwise not favour the assumption of a light colour. This change is brought about by an intense contraction of the melanophores (shown in the insets of fig. 167).

[1] *Med. Rec.*, lxxxiii., 1913.

[2] *Journ. Amer. Med. Assoc.*, lxiii., 1914, and lxv., 1915; *Trans. Amer. Gyn. Soc.*, 1917 (extensive bibliography).

[3] E. R. Hoskins, *Journ. Exper. Zool.*, xxi., 1916; Sisson and Finney, *Journ. Exper. Med.*, xxxi., 1920.

[4] H. H. Goddard, *Journ. Amer. Med. Assoc.*, lxviii. 1340, 1917.

[5] C. P. M'Cord, in Barker's *Endocrinology and Metabolism*, ii. 17, 1922.

[6] *Journ. Exper. Zool.*, xxiii., 1917.

The effect is not obtained at all stages of development. In Rana pipiens it

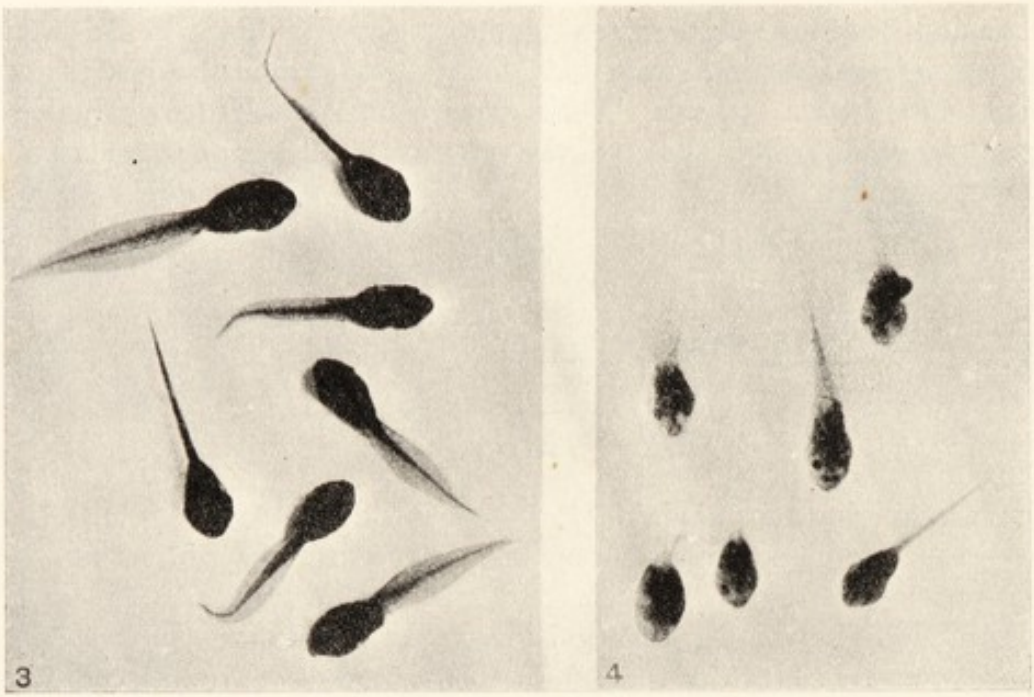

Fig. 166.—Effect of feeding tadpoles with pineal (M'Cord and Allen). Photograph. 3, controls ; 4, after addition of pineal to food.

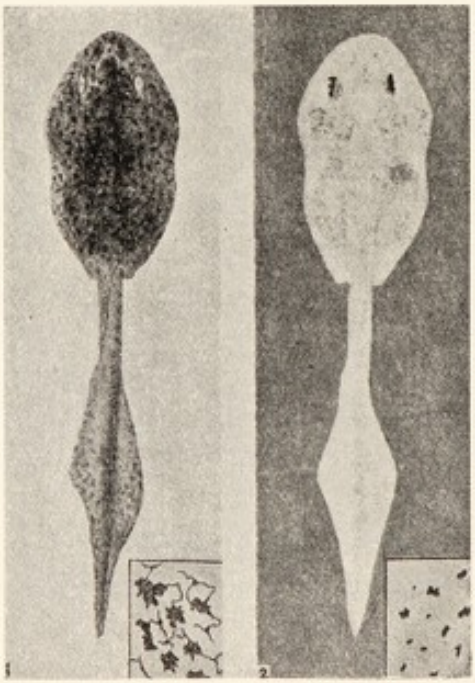

Fig. 167.—The same tadpole (1) just before, and (2) forty-five minutes after pineal feeding. Magnified about 2½ times. (M'Cord and Allen.)

The insets show the conditions of the melanophores more magnified.

occurs in the period between the tenth day of larval life and the time at which the forelimbs begin to protrude. It does not occur with adult frogs, nor with

axolotls.[1] The autacoid which produces this effect is extracted from the dry gland by acetone : on evaporation of the acetone the dry extract can be dissolved in water, and is effective in a dilution of 1 : 100,000. The residue after treatment with acetone has no effect on melanophores but contains an autacoid which stimulates growth.

Relation of the Pineal to the Sex Organs

Effects of Pineal Extirpation on the Sex Organs.—Extirpation of the pineal is a difficult operation to carry through without provoking severe hæmorrhage. The most complete series of experiments on the subject have been those of U. Sarteschi,[2] on young rabbits and puppies, and those of C. Foà,[3] on chicks, and later on young rats. Foà could observe no difference, as compared with controls, in *pullets* in which the gland was destroyed, but in *cockerels* there was a striking difference, shown in an early development of the testicles and of the combs. The changes began to be apparent at five months and were accelerated up to nine months. In male rats there was not only sexual precocity—both the seminiferous tubules and the interstitial tissue being increased—but also a more rapid somatic growth. The results obtained by Sarteschi agree generally with these. Horrax,[4] working with the guinea-pig, found a distinct increase in rapidity of growth of the testicles and seminal vesicles in the male, and noticed that the females operated upon tended to breed earlier than the controls. E. Hofmann[5] obtained enlargement of the seminal vesicles (rat), but could observe no other change. On the other hand, W. E. Dandy,[6] who used puppies and operated by a different, almost bloodless, method, obtained negative results in them.

Effects of Extirpation of the Sex Glands on the Pineal.—The accounts regarding the effect of castration on the pineal are conflicting. Sarteschi obtained negative results in males, whereas Biach and Hulles[7] found that castration of cats—both male and female—produced an atrophic condition of the gland.

Clinical Evidence.—Abnormal growth of the skeleton with precocious development of the sex organs and of secondary sex characters have frequently been noted to be associated with pineal tumours in young boys. Even when the seminiferous tubules have not matured there has sometimes been an unusual development of the interstitial tissue, which is especially associated with the development of secondary sex characters (see Chapter LI.). Since these symptoms are similar to those which have been described as resulting from

[1] L. T. Hogben, "The Pigmentary Effector System," 1924, p. 55.
[2] *Fol. neurol.*, iv., 1910 ; *Pathologia*, v., 1913.
[3] *Arch. ital. de biol.*, lvii., 1912, and lxi., 1914.
[4] *Arch. Int. Med.*, xvii., 1916.
[5] *Arch. f. d. ges. Physiol.*, ccix. 685, 1925.
[6] *Journ. Exper. Med.*, xxii., 1916. In chicks, Badertscher (*Anat. Rec.*, xxviii. 177, 1924) also got negative results, but Isawa (*Amer. Journ. Med. Sci.*, clxvi., 1923) saw acceleration of growth and sexual precocity in both sexes. Very few animals, however, survived the operation.
[7] *Wien. klin. Wochenschr.*, 1912, No. 10.

pineal removal in animals, it has been assumed that the tumours which provoke them have a destructive effect on the pineal tissue and produce hypopinealism.[1] Sexual precocity as the concomitant of pineal tumours is confined to the male sex.

Zandren[2] has described the case of a boy of sixteen who failed to show any sign of puberty and had testicles like those of a child of two. At the autopsy no trace of a pineal gland could be found.

Another condition which has been sometimes observed to accompany pineal tumours is unusual adiposity of a nature somewhat similar to that accompanying hypopituitarism, although not, like that, associated with deficient development of the sex organs. It is suggested that this may be a sign of hyperpinealism.

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[1] A certain number of the tumours of the pineal which are associated with sexual precocity are teratomas (E. Boehm, *Frankf. Zeitschr. f. Path.*, xxii., 1920). The literature of pineal tumours is too extensive to be quoted here, but Bailey and Jelliffe, in describing a case (*Arch. Int. Med.*, viii., 1911), give abstracts regarding all known cases up to that date. More recent developments are dealt with by Boehm. See also the articles by S. E. Jelliffe and G. Horrax in Barker's *Endocrinology and Metabolism*, ii., 1922, and by Horrax and Bailey in *Arch. Neurol. Psych.*, xiii. 423, 1925. The last-named authors observed sexual precocity (in males) in only two cases out of five tumours developing before puberty.

[2] *Acta med. Scand.*, 1921.

CHAPTER XLVI

THE INTERNAL SECRETIONS OF THE ALIMENTARY MUCOUS MEMBRANES

The Duodenal Mucous Membrane. Secretin

Following up an observation of Popielski [1] that the introduction of dilute hydrochloric acid into the duodenum causes a flow of pancreatic juice—an observation interpreted by him as a reflex effect through peripherally situated nerves and ganglia—Bayliss and Starling [2] found that the same result is obtained when a loop of duodenum, completely isolated except by its blood-vessels, is employed. They interpreted this as a proof that a "chemical messenger" is formed in the duodenum under the influence of the acid, and produces a stimulating effect on the pancreas after being absorbed into the blood. They further showed that an acid extract of the duodenal mucous membrane, or even of its epithelium alone, if injected into the circulating blood, causes a copious outpouring of pancreatic juice. This secretion is preceded by a marked fall in the arterial pressure (fig. 168).

Their extract was made by boiling the membrane with dilute acid (0·4 per cent.), neutralising and filtering: the autacoid, which is dialysable, is contained in the filtrate. The active principle has never been obtained in a condition pure enough for chemical analysis.[3] It is destroyed by pepsin and trypsin, and is therefore ineffective if introduced into the alimentary canal. Bayliss and Starling obtained little activity with extracts made with water or saline, and concluded that the active substance (*secretin*) is represented in the tissue by an inactive substance (*pro-secretin*), which only becomes activated or converted into secretin by acid.

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[1] *Arch. f. d. ges. Physiol.*, lxxxvi., 1901.

[2] *Journ. Physiol.*, xxviii., 1902, and xxix., 1903.

[3] For methods of purifying secretin, see Dixon and Hamill, *Journ. Physiol.*, xxxviii., 1908–1909; Dale and Laidlaw, *Proc. Physiol. Soc.*, p. xi. in *Journ. Physiol.*, xliv., 1912; Wertheimer and Duvillier, *C. r. soc. biol.*, lxviii., 1910; Launoy and Oechslin, *ibid.*, lxxiv. 338, 1913; Penau and Simonnet, *Bull. soc. chim. biol.*, vii., 1925. (These authors state that purified secretin has an insulin-like action on blood-sugar.) Dixon and Hamill find that the substance which causes the depressor action can be removed by boiling the dry aqueous extract with alcohol and ether, the secretory action remaining. On the other hand, the secretory action of a duodenal extract is destroyed by peptic or tryptic digestion, but the vaso-dilator action remains (A. B. Luckhardt and E. Blonder, *Proc. Amer. Physiol. Soc.*, in *Amer. Journ. Physiol.*, lxviii., 1924. See also R. Grogan and A. B. Luckhardt, *ibid.*). The depressor action is not due to the presence of histamine in the extract (E. Parsons, *Amer. Journ. Physiol.*, lxxi., 1925). Other references, with details of methods, will be found in Dodds and Dickens, "The Chemical and Physiological Properties of the Internal Secretions," 1925.

They failed to obtain an active material from other parts of the alimentary canal —except a small amount from the jejunum—or from any other organs of the body.[1] But it can be obtained from the duodenum in all animals, and has the same effect in all species investigated. In these respects it resembles other autacoids.

Other acids, even fatty acids according to Babkin and Ishikawa,[2] have a similar effect if introduced into the duodenum.

M'Clure, Montague, and Campbell[3] find that in man the contents of the duodenum are never more than faintly acid, but nevertheless the products of gastric digestion, if placed in the duodenum, will stimulate the flow of pancreatic juice.

Atropine does not, in moderate doses, stop the secretion produced by secretin.

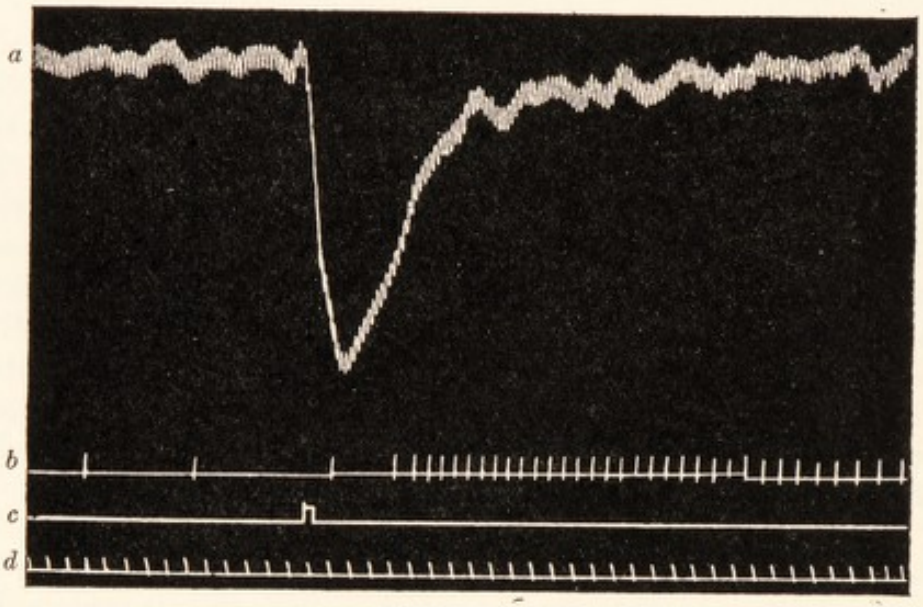

FIG. 168.—Effect on blood-pressure and secretion of pancreatic juice of injecting into a vein extract of mucous membrane of duodenum, made by boiling with dilute hydrochloric acid and subsequently neutralising. (Bayliss and Starling.)

a, blood-pressure: notice the sharp fall followed by return to normal; *b*, drops of pancreatic juice; *c*, signal; *d*, time in seconds.

Probably therefore the hormone acts directly upon the secreting cells and not through secretory nerves.

The pancreatic juice, which is obtained as the result of injecting secretin, differs from that obtained by stimulation of the vagus in the circumstance that the amount of enzymes in it gradually diminishes, whereas the amount of $NaHCO_3$ remains constant during the period of secretion. J. Mellanby, who

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[1] G. W. Volborth states that secretin is obtainable from the contents of a Thiry-Vella intestinal loop and that its presence is also indicated in gastric juice—but not in saliva, bile, or pancreatic juice (*Amer. Journ. Physiol.*, lxxii., 1925). E. Wertheimer (*C. r. soc. biol.*, liv., 1902, and *Journ. de physiol.*, 1905) showed that the effect is obtained by placing acid in a loop of jejunum, all the nerves to which are severed.

[2] *Arch. f. d. ges. Physiol.*, cxlvii., 1912. See also Frouin and Lalou, *C. r. soc. biol.*, lxxi. 189, 1911, and Lalou, *ibid.*, lxii. 518, 1913.

[3] *Boston Med. Surg. Journ.*, cxcii., 1925.

makes this observation, suggests that a main function of secretin is to ensure that the reaction of the juice shall be optimal.[1]

The presence of secretin in the circulating blood two or three hours after a full meal, or after the introduction of dilute hydrochloric acid into the duodenum, is shown by the fact that such blood will excite secretion of pancreatic juice if transfused into a fasting animal, the pancreas of which is not already in activity.[2]

A. Hustin [3] states that while perfusion of the pancreas with blood to which secretin has been added is very effective in causing secretion, if Locke-Ringer is used instead of blood no effect is obtained. He finds that this is not due to lack of oxygen (oxyhæmoglobin) and that the same result is obtained with pilocarpine, which is well known to be an energetic stimulant for the pancreas.

The effect of injection of a given amount of secretin into the blood is less if it is put into the portal vein or femoral artery than into a systemic vein, the explanation furnished being that a part is removed by the liver or the muscles before reaching the general circulation (Djénab).[4] Halliburton and de Souza,[5] who confirm the statement, ascribe the result to dilution with a larger amount of blood. Deuel and Cowgill [6] consider that, while Djénab's explanation holds good for the portal vein, the result with the femoral artery may be explained by dilution.

Duodenal extracts do not act only on the pancreas. They also increase the secretion of bile and of succus entericus, but to a less extent.[7] As a rule they do not affect the flow of gastric juice.[8]

D. Cow [9] has made the interesting observation—already referred to in connexion with the pituitary body—that intravenous injection of duodenal extract causes increased discharge of the secretion of the posterior lobe of the pituitary into the cerebrospinal fluid and eventually into the blood, producing diuresis (see p. 202).

Hypodermic injection of secretin produces an increase in the number of corpuscles—both red and white—in the circulating blood.[10]

That there is an interaction between pancreas and duodenum would appear from the observation of C. Lovatt Evans, who found that pro-secretin disappears from the duodenum in depancreatised animals; but not if enough pancreas is left to prevent the occurrence of glycosuria.

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[1] *Journ. Physiol.*, lx. 85, 1925.

[2] E. Wertheimer, *C. r. soc. biol.*, liv., 1902; Wertheimer and Duvillier, *ibid.*, lxviii., 1910; Enriquez and Hallion, *ibid.*, lv. 233, 1903; M. C. Fleig, *ibid.*, p. 293.

[3] *Arch. internat. de physiol.*, xiii., 1913. Demoor obtained a somewhat similar result on the submaxillary perfused with Locke (stimulation of chorda).

[4] *Berl. klin. Wochenschr.*, liv. 624, 1917.

[5] *Arch. internat. de physiol.*, xviii., 1921.

[6] Trans. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923.

[7] Delezenne and Frouin, *C. r. soc. biol.*, lvi., 1904; Bottazzi and Gabrieli, *Arch. internat. de physiol.*, iii., 1905–1906.

[8] R. K. S. Lim, *Quart. Journ. Exper. Physiol.*, xiii. 91, 1922.

[9] *Journ. Physiol.*, xlviii., 1914.

[10] Downs and Eddy, *Amer. Journ. Physiol.*, 1917 and 1918; also *Endocrinology*, vii., 1923. This paper contains a history and bibliography of secretin.

According to Dixon and Hamill secretin acts upon pro-zymogens in the pancreas, converting them to zymogens, which are discharged with the juice and transformed into enzymes by kinase.[1]

Novva-Santos states that secretin causes hypoglycæmia, and suggests that it does so by influencing the internal secretion of the pancreas.[2]

The Gastric Mucous Membrane: Gastrin

J. Edkins[3] noticed that a substance, appearing to be of nature similar to secretin, but acting on the gastric glands (not on the pancreas), can be extracted from the mucous membrane of the pyloric part of the stomach by boiling water or by dilute hydrochloric acid, or by solutions of dextrin, maltose, or albumose. He failed to get a similar active extract from the mucous membrane of the fundus. Edkins termed the substance in question "gastric secretin" or "gastrin," and supposed it to exist in the mucous membrane in form of a precursor, "pro-gastrin," which is activated by the above reagents. Similar results were obtained by others.[4]

Later, with Tweedy,[5] Edkins found that when dilute acid, dextrin, glucose, or meat-extracts are introduced into the isolated pyloric part, a secretion of gastric juice occurs in the fundus; they considered that such a result could only be the effect of an internal secretion carried by the blood. These results have also been confirmed.[6] Orbeli, however, concluded from his experiments, in which he severed the nerves to a fundus pouch and then failed to obtain a response to food introduced into the main stomach, that the effects obtained by Edkins were nervous rather than humoral.

Other observers, in repeating Edkins' experiments, have found that not only extracts of pyloric mucous membrane, but also of fundus, of intestine, brain, pancreas, and other organs, induce gastric secretion when injected into the blood,[7] and it has also been shown that an active substance can be extracted from vegetables (spinach). Popielski concluded that all the extracts stimulating gastric secretion contain a hydrolytic product of protein disintegration containing CHO and N but no S or P, which he termed "vaso-dilatin." Dale and Laidlaw[8] have pointed out that vaso-dilatin corresponds in most of its

[1] *Op. cit.*, 1908–1909.

[2] *Rev. Sud-Amer.*, viii. 236, 1925.

[3] *Proc. Roy. Soc.*, B, lxxvi., 1905; *Journ. Physiol.*, xxxiv., 1906.

[4] Gross, *Arch. f. Verdauungskr.*, xii., 1906; Krzyszkowi, Thesis, Petersburg, 1906; Orbeli, *Arch. d. sci. biol.*, St Petersburg, xii. 71, 1907.

[5] *Journ. Physiol.*, xxxviii., 1909.

[6] Maydell, *Arch. f. d. ges. Physiol.*, cl., 1913; Ivy, *Arch. internat. Med.*, xxv., 1920, and *Amer. Journ. Physiol.*, lv. 306, 1921.

[7] Popielski, several papers in *Arch. f. d. ges. Physiol.*, 1909 to 1920; Keeton, Koch, Luckhardt, and La Mer, several papers in *Amer. Journ. Physiol.*, 1915 to 1920. Other articles on the subject are enumerated by R. K. S. Lim, *Quart. Journ. Exper. Physiol.*, xiii. 79, 1922.

[8] *Journ. Physiol.*, xli., 1910, and xliii., 1911.

properties with histamine,[1] which is a well-known excitant of gastric juice, can be extracted from many organs of the body, and occurs in the normal gastric mucosa.[2]

Lim [3] determined the potency of extracts of mucous membrane from different parts, and places them in the following order :—(1) pyloric ; (2) cardiac ; (3) duodenal ; (4) fundic. The last gave very little result : extracts from other parts of small intestine none. Whilst confirming Edkins' results as to the effect of pyloric extract, Lim was unable to obtain any secretory effect by passing the blood of an animal in full gastric digestion into a fasting animal, and concludes from this that Edkins' gastrin is not a true autacoid, like secretin, which is passed into the blood, but is a non-specific chemical substance of a histamine-like nature. To this, however, it may be objected that histamine itself may perhaps be regarded as an autacoid.

Lim and Ammon [4] found that if extract of pyloric mucous membrane is injected into the portal vein instead of into the jugular, the effect on gastric secretion is less marked : they ascribe this to removal of some of the exciting substance by the liver.

The effects of extracts and a comparison with that of histamine can be investigated in the human subject by using an Einhorn tube.[5]

Both raw meat juice and, with less effect, extract of meat, if placed in a (denervated) pyloric pouch, produce secretion in the fundus. This seems to imply a humoral effect, although Lim, Ivy, and M'Carthy [6] suggest that increase of vascularity may cause the secretion. It is, however, difficult to understand how a vascular change can be brought about without an autacoidal (chalonic) influence on the vessels if all nervous connexion is severed.

The secretion is also excited by β-alanine—a product of protein hydrolysis—but not by starch, sugar, or fat. It is inhibited by fat introduced into the intestine ; and is also prevented by atropine given hypodermically. It has further been shown by Ivy [7] that a number of substances known to be present in the intestine after a meal, such as peptone and the amino acids, excite secretion of gastric juice when introduced into the intestine by a Thiry fistula. This also occurs if the whole stomach is separated as an isolated pouch, and direct continuity is established between the œsophagus and small intestine, so that food containing these exciting substances can pass straight from the gullet into the intestine.[8] Histamine and

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[1] Histamine is formed from histidine—a protein hydrolytic derivative—by micro-organisms in the intestine (E. Mellanby and Twort, *Journ. Physiol.*, xlv., 1912).

[2] Abel and Kubota, *Journ. Pharm. and Exper. Therap.*, xiii., 1919.

[3] *Quart. Journ. Exper. Physiol.*, xiii. 71, 79, 1922.

[4] *Ibid.*, p. 115.

[5] Matheson and Ammon, *Lancet*, i. 482, 1923 ; Lim, Matheson, and Schlapp, *Quart. Journ. Exper. Physiol.*, xiii. 333, 361, 1923, and Trans. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923 ; Lim and Schlapp, *ibid.*, xiii. 393, 1923.

[6] *Quart. Journ. Exper. Physiol.*, xv., 1925. This paper contains a bibliography as well as a description of the several methods which have been employed for examining the functions of the different parts of the stomach.

[7] With MacIlvaine, *Amer. Journ. Physiol.*, lxiii., 1923. Ivy and Javois (*ibid.*, lxxi., 1925) find that many of the products of acid hydrolysis of proteins stimulate gastric secretion when introduced into the intestine, but not when introduced parenterally.

[8] Ivy, Lim, and M'Carthy, *Quart. Journ. Exper. Physiol.*, xv. 55, 1925.

β-alanine also act when introduced in this manner, but neither meat in the raw state, nor sugar, nor boiled starch produce any effect. Even an entirely non-absorbable substance such as saponin may stimulate secretion of gastric juice if introduced directly into the intestine.

Ivy and Farrell [1] have transplanted a Pavlov gastric pouch into the mammary region of a bitch ; on feeding the animal, gastric juice was secreted into the pouch. This experiment affords positive proof that the secretion may be brought about by humoral means.

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[1] *Amer. Journ. Physiol.*, lxxiv. 639, 1925.

CHAPTER XLVII

THE INTERNAL SECRETION OF THE PANCREAS

The Islets of Langerhans

The pancreas contains, besides its alveoli and the ducts which convey their secretion into the duodenum, a peculiar epithelial tissue occurring in most animals in the form of small isolated masses of variable size interspersed throughout the gland and known from their discoverer as the *islets of Langerhans* [1] (fig. 169).

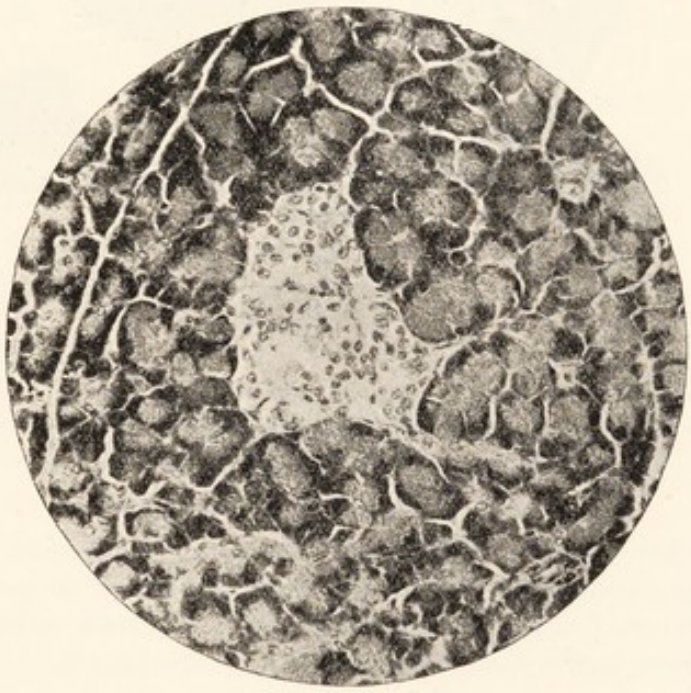

Fig. 169.—Section of pancreas of dog, showing an islet of Langerhans between the alveoli. (Photograph.) ×200.

Although differing both in their general appearance and in the characters of their cells from the alveoli of the gland, the study of their development shows that they grow out, like these, from the budding ducts,[2] and that their cells

[1] *Diss.*, Berlin, 1869.

[2] In the human embryo of 54 mm. (R. M. Pearce, *Amer. Journ. Anat.*, ii., 1903). See also Weichselbaum and Kyrle, *Arch. f. mikr. Anat.*, lxxiv., 1909, and Th. Mironescu, *ibid.*, lxxvi., 1910. Aron (*Arch. d'anat. et d'embryol.*, ii., 1922; *Bull. soc. chim. biol.*, iv., 1922; *Arch. internat. de physiol.*, xxii., 1924) finds that the formation of the islet tissue of the pancreas corresponds in time with the appearance of glycogen in the fœtal liver.

have therefore an origin in common with those of the alveoli. But in the adult they have no open communication with the ducts or alveoli, and are quite distinct from the latter,[1] although in some animals retaining a connexion with the ducts by fine branching cords (fig. 170). These sometimes have a small lumen, but this does not extend into the islets, at least in mammals.[2]

The number of islets in the pancreas varies greatly. This variability has led to inferences being drawn regarding their appearance and disappearance which are probably not justifiable. Thus they have been described as being increased as the result of the injection of secretin and as the effect of fasting.[3] As for the first, it is manifestly impossible that the profound morphological changes involved in the conversion of the acinous into the islet tissue could occur in any very brief period

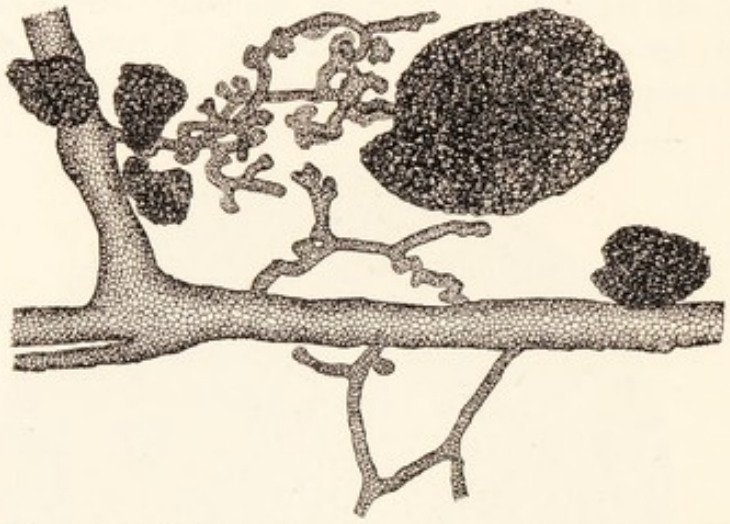

Fig. 170.—Islets of pancreas of guinea-pig, connected with pancreatic ducts by fine branched cords. (R. Bensley.) ×77. Stained *intra vitam* with pyroxin and neutral red.

Two islets are shown directly attached to the ducts.

of time. And the variations in normal individuals are more than sufficient to account for the differences which have been described as occurring in hunger conditions.[4] Rennie found that in a snake which had been without food for many months no increase in the islet tissue could be determined.[5]

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[1] V. Diamare, *Internat. Monatsschr. Anat. Physiol.*, xvi., 1899, and xxii., 1905; *Centrlbl. f. Physiol.*, xix., 1905, xxi., 1908; *Arch. d. fisiol.*, v., 1908, and xxii., 1924: E. Sauerbeck, *Virch. Arch.*, clxxvii., Suppl., 1902: K. Helly, *Arch. f. mikr. Anat.*, lxvi., 1905.

[2] Laguesse, *Arch. d'anat. micr.*, xi., 1909; R. R. Bensley, *Amer. Journ. Anat.*, xii., 1911; E. Clark, *Anat. Anz.*, xliii., 1913. Bensley has shown that the islets can be picked out from the rest of the pancreatic tissue by the facility with which they are coloured by certain *intra vitam* stains, such as neutral red and Janus green.

[3] Lewaschew, *Arch. f. mikr. Anat.*, xxvi., 1886; Statkewitsch, *Arch. exper. Path. u. Pharm.*, xxxiii., 1894; H. H. Dale, *Phil. Trans.*, B, cxcvii., 1905; Vincent and Thompson, *Internat. Monatsschr. Anat. Physiol.*, xxiv., 1907; Laguesse, *Arch. d'anat. micr.*, x., 1909, and *Journ. de physiol.*, xiii., 1911.

[4] de Witt, *Journ. Exper. Med.*, viii., 1906.

[5] *Internat. Monatsschr. Anat. Physiol.*, xxvi., 1909.

Most authors [1] have taken the view that new islet tissue is not formed after the development of the pancreas is completed, and that the acinous tissue is not transformed into the islet tissue or *vice versa*. The importance of this question is obvious, since it is generally agreed that diabetes is the result of a deficiency in the secretion of the islet tissue caused by its degeneration, and if new islets were constantly being formed, one would expect the condition readily to cure itself. This is, however, not found to occur.

The islet tissue forms a far more important part of the structure of the pancreas than would be supposed from the microscopic examination of casual sections. Thus the enumeration of Clark, using the *intra vitam* methods of staining introduced by Bensley, led him to the conclusion that there must be from three quarters of a million to a million and a half islets in the human pancreas (10 to 20 islets in each milligram). In some animals this number may be considerably exceeded. The islets are more numerous at the splenic end than in the duodenal portion.

In elasmobranch fishes the cells of the islets surround a lumen or cavity. In teleostean fishes, instead of being scattered throughout the gland there is a separate mass of islet tissue, forming a distinct organ, encapsuled by connective tissue.[2] It has been shown that this structure yields a considerable amount of insulin,[3] and it was at one time suggested as a fruitful source of that autacoid free from the digestive enzymes of the pancreas. But since methods of extracting insulin whilst leaving these enzymes behind have been elaborated, this source of the active principle of the internal secretion is not likely to supersede the abattoir. Removal of the principal islet in Teleostei (Myoxocephalus) produces marked hyperglycæmia.[4]

Structure of the Islets.—Although the cells of the islets generally remain unstained by the acid and basic dyes ordinarily used in histology, and are therefore frequently spoken of as "chromaphobe," they have, as we have seen, a special affinity for certain *intra vitam* stains. Moreover, although they do not possess coarse granules like those in the cells of the acini, it is possible after fixation to detect the presence within them of granules of two kinds (fig. 171), contained in different cells.[5] Those of the one kind, known as the α cells, have oxyphil granules; those of the other kind, known as the β cells, contain

[1] V. Diamare, *op. cit.*; K. A. Heiberg, *Anat. Anz.*, xxix., 1906, xxxvii., 1910, and *Ergeb. d. Anat.*, xix., 1909; Kuster, *Arch. mikr. Anat.*, lxiv., 1907; Weichselbaum and Kyrle, *op. cit.*, 1909; Bensley, *op. cit.*, 1911; Schafer, "Textbook of Microscopic Anatomy," 1912, p. 562; J. Homans, *Proc. Roy. Soc.*, B, lxxxvi., 1913.

[2] V. Diamare, *op. cit.*, 1899; J. Rennie, *Quart. Journ. Micr. Sci.*, xlviii. 739, 1904.

[3] J. J. R. Macleod, *Journ. Metab. Res.*, ii. 149, 1922; Vincent, Dodds, and Dickens, *Lancet*, ii. 115, 1924; M'Cormick and Noble, *Journ. Biol. Chem.*, lix., 1924. H. W. Dudley (*Biochem. Journ.*, xviii. 665, 1924) finds that the islet tissue of the cod contains, weight for weight, ten times as much insulin as does mammalian pancreas.

[4] N. A. M'Cormick and J. J. R. Macleod, *Proc. Roy. Soc.*, B, xcviii., 1925.

[5] M. A. Lane, *Amer. Journ. Anat.*, vii., 1907; R. R. Bensley, *ibid.*, xii., 1912; Graham and Harris, *Lancet*, 1923; Saguchi, *Amer. Journ. Anat.*, xxviii., 1920. Saguchi describes five kinds of cell, but admits that some may be transitional forms.

basiphil granules. There are also some cells which are devoid of obvious granules.

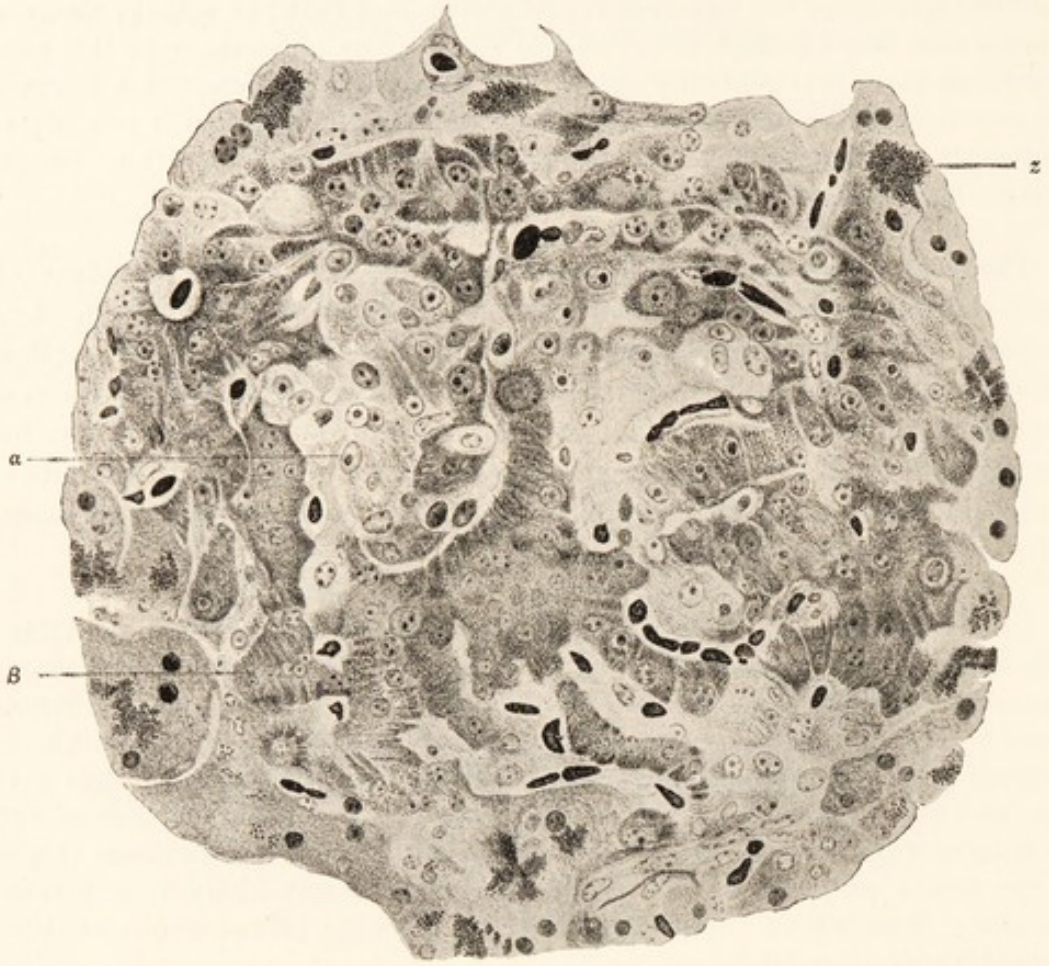

FIG. 171.—Section of an islet of guinea-pig fixed in chrome-sublimate : stained with neutral gentian. (M. A. Lane.) Highly magnified.

z, zymogen granules in an adjoining acinus ; *α*, alpha cells, granules very faintly stained ; *β*, beta cells, granules deeply stained. The dark bodies are blood corpuscles within capillaries.

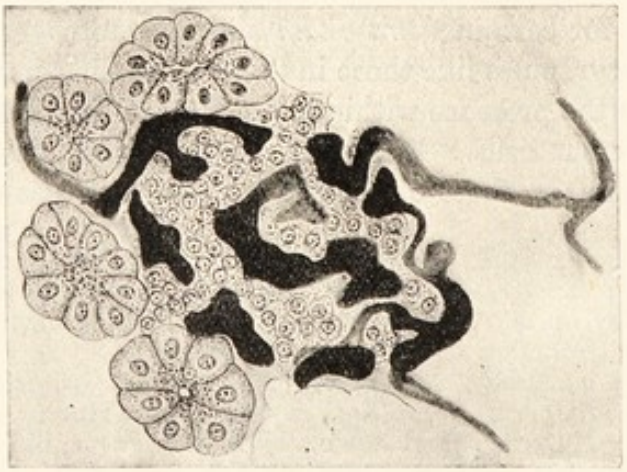

FIG. 172.—An islet of Langerhans of the pancreas, with its blood-vessels injected. (Kühne and Lea.)

The granules of the *β* cells are soluble in alcohol containing a small percentage

of water, in this respect resembling insulin: the α granules are insoluble in alcohol. The nuclei of the islet cells never show mitoses, even under conditions, such as thyroid feeding, which in some animals provoke extensive cell-division in the cells of the acini.[1] Each islet cell contains a well-marked reticular apparatus of Golgi (Ramón y Cajal).

The capillaries of the islets, although continuous with the general network of the pancreas, are very specialised, being dilated into irregular sinus-like vessels (fig. 172) which have a close relationship to the cells.[2] Lymph vessels do not penetrate into the islets; doubtless the secretion of the islet cells is poured directly into the blood.

The islets have an abundant supply of nerve-fibres,[3] both myelinated and non-

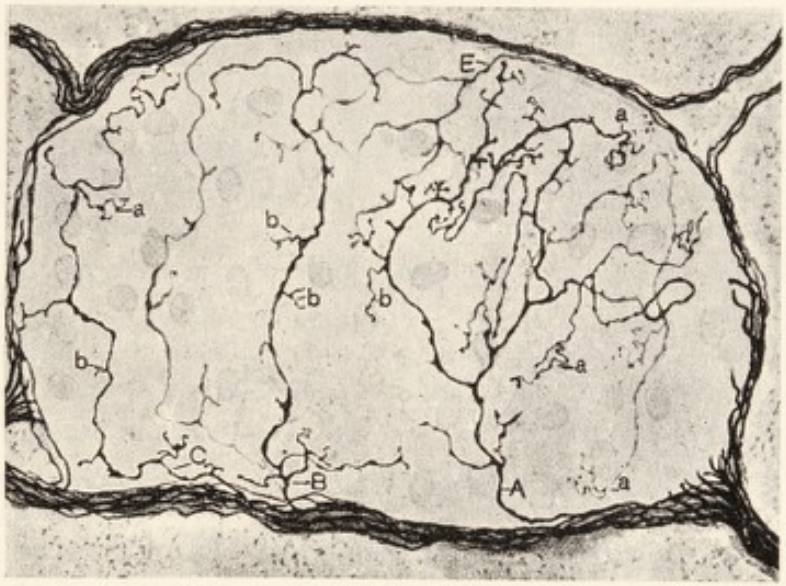

Fig. 173.—Nerves of islet of mouse: Golgi preparation. (F. de Castro.)
The figure shows a peri-insular nerve-plexus, giving off branches (A, B, C, E) which lose themselves in terminal ramifications (a, b) amongst the cells.

myelinated. The nerves form a plexus over the surface of each islet (fig. 173) from which branches penetrate to the interior, ending between the cells in button-like extremities (Gentés). Some are distributed to the blood-vessels.

S. W. Britton [4] finds that in the cat the cells of the islets can be affected by nervous influence through the right vagus. Stimulation of this nerve causes a decrease in the sugar of the blood. No such effect is obtained from the left vagus, nor from the sympathetic nerves to the pancreas. There is no change produced in the blood-supply to the gland.

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[1] M. Kojima, *Quart. Journ. Exper. Physiol.*, xi., 1917. Kojima noticed that zymogen granules are always more abundant in the acini which are immediately adjacent to the islets than elsewhere. Why this should be so is not clear.

[2] Kühne and Lea, *Unters. d. physiol. Instit. Heidelberg*, ii., 1882; Pensa, *Internat. Monatsschr. Anat. Physiol.*, xxii., 1905.

[3] Gentés, *C. r. soc. biol.*, liv., 1902; Pensa, *op. cit.*, 1905; de Castro, *Trav. d. lab. de recherches biol. Madrid*, xxi., 1923.

[4] *Amer. Journ. Physiol.*, lxxiv. 291, 1925.

CHAPTER XLVIII

THE INTERNAL SECRETION OF THE PANCREAS (*continued*)

Effect of Surgical Removal of Pancreas: Diabetes

Since the discovery in 1889 by v. Mering and Minkowski [1] that complete removal of the pancreas in animals, or even of the greater part of the organ, is followed by hyperglycæmia leading to severe and fatal diabetes,[2] whereas this effect is not obtained from mere ligature of the duct (in spite of the disappearance of the alveolar tissue and the complete cessation of formation of pancreatic juice), attention has been especially directed to the islet tissue as the probable source of an internal secretion which serves to regulate carbohydrate metabolism.[3] For the cirrhosed and atrophied gland which eventually remains after ligature of the duct contains none of the ordinary epithelium except in a few remaining enlarged portions of the ducts, but does still contain the islet tissue.[4] Nevertheless the atrophied gland is sufficient to furnish the internal secretion which regulates carbohydrate metabolism, so that this is maintained normal for an indefinite time. But if now the atrophied gland is removed, diabetes at once shows itself.[5] Further, if a portion of pancreas, whether thus atrophied or not, is successfully transplanted to another site and the rest of the gland is then removed, diabetes does not occur—although on removal of the graft it immediately makes its appearance.[6] The evidence for the action of an internal

[1] *Centrlbl. f. inn. Med.*, 1889; *Arch. f. exper. Path. u. Pharm.*, xxvi., 1890: O. Minkowski, *ibid.*, xxxi., 1893. de Dominicis (*Giorn. internat. sci. med.*, 1889) arrived independently at a similar result of pancreas extirpation, but gave an erroneous interpretation of it. R. Lépine (*Lyon méd.*, 1889) repeated and confirmed the observations of v. Mering and Minkowski. E. Gley (*C. r. soc. biol.*, liii., 1901) showed that obstruction of the pancreatic circulation by tying the veins of the organ produces diabetes.

[2] None of their animals (dogs) lived for more than about four weeks. Sugar appeared in the urine in from four to six hours and reached a maximum (5 to 11 per cent.) in twenty-four to forty-eight hours.

[3] The suggestion that the islets may have an endocrine function is due to E. G. Laguesse (*C. r. soc. biol.*, 1893). He described the islets as preceding the acini in development, but thought them to be only temporarily modified parts of the same structures taking on alternately endocrine and exocrine functions (*balancement*). See on this subject, G. van Rijnberk, *Arch. d. fisiol.*, iv., 1907. A. S. Warthin, in Barker's *Endocrinology and Metabolism*, ii., 1922, furnishes a good historical account of the discovery of their endocrine properties. Laguesse's view, that the islets are temporary modifications of alveoli, is still maintained by some authors (*e.g.* Swale Vincent and Dodds, *Lancet*, i. 947, 1924).

[4] Schultze, *Arch. f. mikr. Anat.*, lvi., 1900; Ssobelew, *Virch. Arch.*, clxviii., 1901.

[5] Lancereaux et Thiroloix, *C. r. acad. sci.*, cxv., 1892; E. Hédon, *Arch. méd. exper.*, v., 1893.

[6] L. V. Hédon has shown that temporary blockage of the circulation in such a transplant will also cause hyperglycæmia and glycosuria (*Arch. internat. de physiol.*, xxi., 1923).

secretion yielded by the gland—and in all probability by its islet tissue—and serving to maintain carbohydrate metabolism in a normal condition, is therefore very complete. In support of this conclusion it has frequently been noted in cases of diabetes in man that the pancreas, and especially the islets, have undergone some kind of degenerative change.[1]

The diabetes produced by pancreas removal in animals shows all the symptoms of the affection in man, viz. hunger, thirst, polyuria, muscular weakness, and emaciation.

As above stated, the glycosuria is preceded by hyperglycæmia, which is doubtless the actual cause of the glycosuria.[2] The hyperglycæmia is caused by the inability of the tissues to utilise sugar; nevertheless the demand by them for sugar leads to the mobilisation of the liver glycogen and of most of the glycogen stored in the muscles.[3] Even when carbohydrates are absent from the food and after all the glycogen in the body has been got rid of, sugar is still produced from protein, and appears in the urine together with the urea resulting from the metabolism of the nitrogenous moiety of the protein. When this is the sole source of sugar the proportion of urea nitrogen to dextrose (N : D) in the urine becomes constant.

In the absence of sugar the metabolism of fats is imperfect, and the result is the accumulation in the blood and appearance in the urine of products of such incomplete metabolism of fats as acetone, aceto-acetic acid, and β-hydro-oxy-butyric acid (acetone bodies), which cause acidosis (ketosis) and eventually bring on diabetic coma followed by death.[4] Even if coma does not supervene, the effect of the constant drain on the tissues is that the depancreatised animal loses flesh and rapidly becomes emaciated; eventually death results from inanition and inability to maintain the nutrition and energy of the body. Towards the end there is a marked fall of temperature.

Partial removal, even to the extent of seven-eighths, of the pancreas does not produce diabetes. The severity of the symptoms is in inverse proportion to the amount which remains. Even if sufficient is left to avert diabetes, alimentary glycosuria is more readily obtained. The capacity for assimilating

[1] E. L. Opie, *Journ. Exper. Med.*, v., 1901; M. B. Schmidt, *Münch. med. Wochenschr.*, xlix., 1902; L. W. Ssobelew, *Virch. Arch.*, clxviii., 1901, clxxvii., 1904; *Ziegler's Beitr.*, xlvii., 1909; Weichselbaum and Stangl, *Wien. klin. Wochenschr.*, 1901 and 1902; Weichselbaum and Kyrle, *Arch. f. mikr. Anat.*, lxxiv., 1909; A. Weichselbaum, *Wiener Sitzungsber.*, cxix., 1910. See also J. Homans, *Journ. Med. Res.*, xxx. and xxxiii., 1914 and 1915 (degeneration of islets in experimental diabetes). That human diabetes is caused by a deficiency of the secretion of the islet tissue due to some pathological change in the islets was early suggested (Schafer, "Address to Brit. Med. Assoc.," *Brit. Med. Journ.*, ii. 341, 1895).

[2] According to J. de Meyer (*Arch. internat. de physiol.*, vii. and viii., 1909) the glycosuria is augmented by an increase in the permeability for sugar in the kidneys due to pancreas removal.

[3] But according to Ehrlich the amount of glycogen in the leucocytes is markedly increased.

[4] The appearance of these bodies in urine produces the condition known as ketonuria, which is a sure indication that there is insufficient combustion of carbohydrates (A. R. Southwood, *Med. Journ. of Australia*, Nov. 3, 1923).

carbohydrate can be used as a gauge of the extent of the endocrine function remaining.[1]

It was supposed by R. Lépine [2] that the accumulation of sugar in the blood in depancreatised animals is due to a loss of its glycolytic power, but most recent authorities have failed to obtain evidence of this, and there is no reasonable doubt that the cause of the hyperglycæmia is the failure of the tissues to utilise glucose in the absence of the internal secretion of the pancreas.

In birds, removal of the pancreas does not usually cause glycosuria, although hyperglycæmia is produced. If adrenaline is subsequently administered glycosuria supervenes.[3]

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[1] Numerous observations on partial removal of pancreas and the effects of various conditions (nutriment, environment, age, etc.) on animals with a deficient amount are contained in a series of papers by F. M. Allen, in *Journ. Exper. Med.*, 1920 ; *Amer. Journ. Med. Sci.*, 1920 and 1921 ; and *Amer. Journ. Physiol.*, liv., 1921.

[2] "Nouvelle théorie du diabète," *Lyon méd.*, 1889 ; and papers in *C. r. soc. biol.* and *C. r. acad. sci.*, *Journ. de physiol.* and *Rev. de méd.*, from that date to 1918.

[3] W. Kausch, *Arch. exper. Path. u. Pharm.*, xxxvii., 1896 ; D. Noël Paton, *Journ. Physiol.*, xxix., 1903.

CHAPTER XLIX

THE INTERNAL SECRETION OF THE PANCREAS (*continued*)

Insulin

Historical.—From what has been stated it is clear that the metabolism of carbohydrates is in some way dependent upon the presence of an autacoid which is produced by the islet tissue of the pancreas. To this autacoid the name *insulin* is applied.[1] That insulin is passed into the blood is proved by the fact that if the blood of a normal dog—especially blood coming from the pancreatic vein—is allowed to circulate through the system of a depancreatised dog, the occurrence of hyperglycæmia and glycosuria in the latter is inhibited.[2]

It seemed, therefore, that if a method could be devised to separate the pancreatic autacoid and employ it therapeutically, a means of successfully treating diabetes in man might be furnished. Attempts were in fact made from time to time by administration of extracts of pancreas prepared in various ways, to supply the place of the agent which is lacking in diabetes.[3] Failure to obtain consistent results appears to have arisen partly from the circumstance that the autacoid is destroyed or inactivated by trypsin, partly from the fact that unless given carefully in moderated doses it is highly toxic, causing alarming symptoms (convulsions, coma) and even death.

Some results of a positive nature were obtained. Thus G. Zuelzer,[4] using both water and alcohol extracts of ox pancreas in dogs rendered diabetic from removal of pancreas, as well as in cases of human diabetes, got, from intravenous injection, distinct diminution of urinary sugar. But Zuelzer failed to follow up this clue. Other experiments of a similar kind were from time to time reported.[5] But in most the true cause of the fall in blood and urine sugar was not appreciated, nor were the experiments continued sufficiently to render them of practical value. This does not, however, apply to those of N. C. Paulesco of Bucharest. His experiments, commenced in 1916 but interrupted by the German invasion of

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[1] The term was introduced by de Meyer (*Arch. di fisiol.*, vii., 1909). In ignorance of this it was employed as a convenient term to denote the autacoid of the islet tissue in the first edition of this work, published in 1916. It was independently adopted by the Toronto workers in 1922.

[2] E. Hédon, *C. r. soc. biol.*, lxvi. and lxvii., 1909; lxxii, 1912; lxxiv., 1913.

[3] A short account of these is given by H. Staub, "Insulin," 2te Auflage, Berlin, 1925.

[4] *Deutsch. med. Wochenschr.*, xxxiv. 1380, 1908.

[5] E. L. Scott, *Amer. Journ. Physiol.*, xxix., 1912; Murlin and Kramer, *Journ. Biol. Chem.*, xv., 1913, and xxvii., 1916; I. S. Kleiner, *ibid.*, xl., 1919.

Roumania, were published in 1921.[1] They established that—in dogs rendered diabetic by extirpation of the pancreas and showing all the signs of severe diabetes,—(1) increase of sugar in the blood and its appearance in the urine ; (2) increase of acetone bodies in the blood and their appearance in the urine ; (3) increase of urea in blood and urine—these signs can be made to disappear by intravenous injection of pancreatic extract. The extract he used was made from fresh pancreas with ice-cold distilled water, "stérile autant que possible." It was introduced gradually into a vein of the diabetic dog, and its effect in a short time was to bring down the blood-sugar level to normal or less, and to greatly reduce or abolish the glycosuria.

In later experiments attempts were made by Paulesco to isolate the active substance (termed by him *pancreïne*) by submitting the aqueous extracts to the action of acids and alkalies, of alcohol and of heat. He found that boiling destroys the activity, and that an extract, from which most of the proteins have been precipitated by alcohol or by neutralising the acidified extract by soda, contains the active substance. He further found that no effect was obtained by oral administration.[2]

In the same year that Paulesco published his first experiments, investigations on the subject were commenced by J. C. Banting and C. H. Best,[3] and have led to important practical results. The idea had occurred to Banting that extracts of pancreas had generally failed to influence the course of diabetes in consequence of the destructive action of the digestive enzymes of the gland, and that it might be possible for the extract of a gland, the alveolar structure of which had been destroyed by ligaturing the duct of Wirsung some time beforehand, to prove active. Associating himself with Best and working under the auspices of J. J. R. Macleod in the physiological laboratory of the University of Toronto, Banting was able to show that extracts of such a gland administered parenterally to depancreatised animals enable them to utilise sugar in the same manner as normal animals. Provided the dosage of the extract is conveniently adjusted, the blood-sugar is brought to the normal percentage (0·11 to 0·15) and glycosuria disappears. In normal animals the effect of such an extract is to reduce the percentage of glucose in the blood below normal. If it is reduced in either the normal or the diabetic organism beyond a certain level (0·045) convulsions and eventually death from respiratory failure ensue. The adverse symptoms can be at once removed by

[1] *Arch. internat. de physiol.*, xvii., Aug. 1921. Protocols of his experiments are given by Paulesco, as well as the results of control experiments with extracts of other organs which yielded negative results.

[2] *Ibid.*, xxi., 1923. The later experiments were published subsequently to those of the Canadian observers immediately to be referred to.

[3] *Journ. Lab. and Clin. Med.*, vii., 1922. The pioneer experiments of Banting and Best were preliminary to a long succession of others by various workers, mostly performed in the same laboratory and dealing with different aspects of the problem. A concise record of the development of the subject is given by Macleod in *Physiological Reviews*, iv., 1924. The literature up to date, which is voluminous, is given by A. Grevenstuk and E. Laqueur in the article "Insulin," *Ergebn. d. Physiol.*, xxiii., 1925, which may be consulted for many further details relating to the subject.

injection of glucose, either into a vein or hypodermically, and rather less rapidly by the oral administration of sugar.

It soon became evident—in spite of the success of these experiments—that it would be impossible to obtain a sufficient supply of insulin for the treatment of human diabetes by the method of ligature and degeneration. Although insulin occurs in the pancreas of the fœtal calf (under five months) which contains no proteolytic enzyme,[1] this also would furnish an insufficient amount. The Toronto investigators therefore set to work to discover some ready method of obtaining it from the pancreas of the sheep and ox free from pancreatic enzymes and proteins. In the further prosecution of the research they associated themselves with others who brought to the assistance of the work special skill in chemical and clinical methods. The ultimate result of this combined investigation has been the production of insulin on a commercial scale in a form suitable for the clinical treatment of diabetics. The history of the subject furnishes a striking instance of a notable advance in therapeutics rendered possible by investigations of a purely physiological nature.

Methods of Extraction.[2]—The method of extraction and purification employed by J. B. Collip[3] consisted in treating the fresh pancreas of ox or sheep with cold acidified 95 per cent. alcohol. This leaves behind the digestive enzymes and most of the proteins, but takes up the insulin, which can be precipitated from the clear filtered alcoholic solution by the addition of absolute alcohol. By re-solution and re-precipitation the active material is obtained in a purified form, which can be preserved in the dry state and dissolved in Ringer's solution as required. A better yield is obtained by strongly acidifying the alcohol,[4] and a still better by extracting with cold alcohol rendered alkaline by sodium bicarbonate and afterwards acidified (Dudley and Starling). By some of these methods, about 1800 Toronto units (see p. 347) can be obtained from each kilogram of ox or sheep pancreas. A large amount can be got by simply perfusing the blood-vessels of the pancreas with water acidified with HCl and warmed to 50° C.

Properties.—According to the account given by Macleod (1923),[5] insulin—in the purest form in which it had then been prepared—is a white powder

[1] Ibrahim, *Biochem. Zeitschr.*, xxii., 1909.

[2] The various methods which have been recommended for the extraction of insulin from the pancreas are described in detail by Grevenstuk and Laqueur, *op. cit.*, 1925, and by Dodds and Dickens, *op. cit.*, 1925.

[3] *Journ. Biol. Chem.*, lv., p. xl, 1923; see also Best and Scott, *ibid.*, lvii. 709, 1923.

[4] Doisy, Somogyi, and Shaffer, *ibid.*, lv., p. xxxi, 1923; Doisy and Weber, *ibid.*, lix., p. xxxiv, 1924. For other methods of extracting and purifying insulin, see T. B. Robertson and A. B. Anderson, *Med. Journ. of Australia*, Aug. 25, 1923; Clough, Allen, and Murlin, Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923, p. 88; Mattill, Piper, Kimball, and Murlin, *ibid.*, p. 182; J. R. Murlin (and others), *Journ. Biol. Chem.*, lvi. and lviii., 1923; Moloney and Findlay, *ibid.*, lvii., 1923; N. F. Fisher, *Amer. Journ. Physiol.*, lxvii., 1923; H. W. Dudley, *Biochem. Journ.*, xvii., 1923 (picric acid), and (with W. W. Starling) *ibid.*, xviii., 1924; Dodds and Dickens, *Brit. Journ. Exper. Path.*, v., 1924; Fenger and Wilson, *Journ. Biol. Chem.*, lix., 1924; C. H. Best, *Endocrinology*, viii. 617, 1924; H. Simmonet, *Bull. de la soc. de chim. biol.*, vi., 1924.

[5] Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923.

containing 14 per cent. nitrogen. It is free from phosphorus but contains sulphur. Its solution gives a distinct biuret reaction and also those of Millon and Hopkins-Cole, but only faintly: it also shows the Pauly reaction. It is readily absorbed by kaolin, does not dialyse through collodion membranes, is precipitated by half saturation with ammonia sulphate, by barium salts of weak acids, by picric acid and uranium nitrate. The solubility in water is determined by the H-ion concentration, the iso-electric point being at a pH between 5 and 6. Its aqueous solutions at a pH below 5 can be boiled for some hours without loss of potency, but this occurs rapidly when the pH is about 7. The acid solution is also relatively stable to mild oxydising and reducing agents. According to Fenger and Wilson it is quite soluble in acidulated (pH 5·5) 93 per cent. alcohol. Insulin is also soluble in phenol and the cresols, glacial acetic acid and formamide, but not in most other organic solvents. Its potency is removed by pepsin and trypsin.

According to Dudley insulin is probably of protein nature. Whether really a protein or not, it is significant that all the methods used for its purification are based on reactions characteristic of colloids. Many of these reactions may, however, be due to adsorption by some protein substance, for in a preparation from the pancreas of the skate Best and Macleod [1] obtained by extraction with alcohol a substance which "gave no protein reaction, was not removed by precipitation with alcohol or by adjustment of the iso-electric point, and withstood filtration through a Berkfeldt filter and heating on the water-bath in acid solution for ten minutes without loss of potency, although it was destroyed in three minutes by 100° C., and it was not dialysable."

C. P. Kimball and J. R. Murlin [2] also succeeded in obtaining a purified insulin in the form of a white powder which gave no protein reaction; contained only 4 to 6 per cent. N; was insoluble in neutral distilled water, but soluble in acidulated water and alcohol and in lipoid solvents; was precipitated by amyl alcohol, ammonium sulphate, and sodium chloride; was somewhat dialysable and thermostable; was destroyed by caustic alkalies.

Abel and Geiling [3] state that purified insulin contains no phosphorus, and that its hypoglycæmic activity is correlated with its content of "labile sulphur."

There is some conflict of evidence as to the possibility of the passage of insulin through the placenta. Carlson and Drennan [4] found that a bitch deprived of the pancreas during the later stages of pregnancy does not become diabetic whilst her fœtuses remain *in utero*: this statement has been confirmed.[5] On the other hand, some observers have obtained a different result.[6] The differences may be

[1] *Proc. Soc. Biol. Chem.*, p. xxix., in *Journ. Biol. Chem.*, lv., 1923.

[2] *Journ. Biol. Chem.*, lviii. 337, 1924. See also Mattill, Piper, Kimball, and Murlin, Proc. XIth Internat. Physiol. Congress, in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923; and R. S. Allen and J. R. Murlin in *Amer. Journ. Physiol.*, lxxv. 131, 1925.

[3] *Journ. Pharm. Exper. Therap.*, xxv. 423, 1925.

[4] *Amer. Journ. Physiol.*, xxviii., 1911.

[5] G. Lafon, *C. r. soc. biol.*, lxxv., 1913; Potimada, *Fol. med.*, ix., 1923.

[6] Aron, Stulz, and Simon, *C. r. soc. biol.*, lxxxix., 1923. These authors find that after

related to the age of the fœtuses and the consequent activity or inactivity of their islets.

Standardisation.—Since insulin cannot be obtained in a condition of chemical purity, it is necessary to standardise any sample by the extent of its physiological effect. The Canadian investigators adopted as a physiological unit the amount necessary to bring the blood-sugar in a normal rabbit of average weight (2 kilograms), which had been without food for twenty-four hours, down to a percentage of 0·045, this being the point at which the animal is liable to pass into convulsions.[1] The amount so determined is known as the "Toronto rabbit-unit." For therapeutical purposes it is too large, and one-third of a Toronto unit is now generally referred to clinically as a "unit dose." [2]

Administration.—Insulin is most conveniently administered by subcutaneous injection in aqueous solution, but it may be safely given directly into a vein. It should not be injected intramuscularly. It does not affect the blood-pressure. If taken by the mouth it passes rapidly through the stomach into the intestine, where it is destroyed by the pancreatic juice.[3] In alcoholic solution there is some absorption from the stomach and the effect on blood-sugar may be obtained, but much more slowly than when injected.[4]

The treatment of human diabetes by insulin—which was first attempted successfully in 1922 by Banting and Best and their Toronto colleagues—has given rise to an enormous literature.[5]

The presence of insulin, or at least of a substance which diminishes the percentage of blood-sugar, is by no means confined to the pancreas. Such a substance can be extracted from almost all the tissues and organs of the body as well as from the blood and urine,[6] although it occurs in most organs to a far less extent per cent. than in the pancreas.[7] But it seems probable that the insulin-like substance

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extirpation of the pancreas both mother and fœtuses exhibit hyperglycæmia, and that administration of insulin to a normal mother produces hypoglycæmia in both mother and fœtuses.

[1] The limit may be arrived at, without making blood-sugar determinations, by watching the animals after an injection, since they show restlessness before the more acute symptoms appear. This is especially useful for small animals such as mice and rats.

[2] See on the pharmacological assay of insulin, J. J. R. Macleod and M. D. Orr, *Journ. Pharm. and Exper. Therap.*, xxiii. 137, 1924. On standardisation by blood-sugar determinations, Harrison, Lawrence, and Marks, *Brit. Med. Journ.*, ii. 1102, 1925. On the dosage of insulin, Desgrez, Bierry, and Rathery, *Bull. acad. méd.*, xliii. 478, 1925.

[3] Absorption will occur from a separated intestinal loop (Hachen and Mills, *Amer. Journ. Physiol.*, lxv., 1923).

[4] L. B. Winter and W. Smith, *Journ. Physiol.*, lviii., 1923; Maxwell, Blatherwick, and Sansum, *Amer. Journ. Physiol.*, lxx., 1924. According to Epstein (*Proc. Soc. Exper. Biol. and Med.*, xxii., 1924) pepsin inactivates but does not destroy insulin; trypsin destroys it.

[5] The following textbooks deal with the subject: P. J. Cammidge, "The Insulin Treatment of Diabetes Mellitus," Edinburgh, 1924; E. P. Joslin, "The Treatment of Diabetes Mellitus," Philadelphia, 1924; W. Maclean, "Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes," London, 1924; H. Staub, "Insulin," Berlin, 1925. This book in particular contains a list of the chief works on the clinical aspect of the question.

[6] Best and Scott, *Journ. Biol. Chem.*, lvii., 1923, and *Journ. Metab. Res.*, iii., 1923; J. Ashby, *Amer. Journ. Physiol.*, lxvii., 1923.

[7] Best, Smith, and Scott, *Amer. Journ. Physiol.*, lxviii., 1924. Dodds and Dickens (*Lancet*, i. 330, 1924), however, obtained from the submaxillary gland of the ox as much

yielded by them has been derived from the pancreas. Nevertheless, insulin is not altogether wanting in the tissues and blood of depancreatised animals.[1]

A substance capable of reducing the amount of sugar in the blood has been obtained from many plants,[2] such as beetroot, onions, potatoes, grass, and also from yeast;[3] it has been termed by Collip *glucokinin*. Collip has shown that the effect of its injection can be transmitted from animal to animal by transfusion of blood, and this through several successive subjects without loss of potency. In animals rendered hypoglycæmic in this manner, the injection of glucose has only a temporarily curative effect.

Several observers have obtained from extracts of pancreas, besides insulin—which lowers blood-sugar percentage and the dextrose-nitrogen ratio and raises the respiratory quotient—another autacoid which acts antagonistically, raising blood-sugar percentage and causing a fall in the respiratory quotient.[4]

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as 710 Toronto units per kilo of gland substance; and Baker, Dickens, and Dodds (*Brit. Journ. Exper. Path.*, v., 1924) found as much insulin in the kidney and spleen of man as in the pancreas. The organs of a diabetic also contained an appreciable amount of insulin.

[1] Banting and Best (Proc. XIth Internat. Physiol. Congress, 1923, *Quart. Journ. Exper. Physiol.*, Suppl. Vol.) could obtain none from the blood of depancreatised dogs, but Best, Scott, and Banting (*Roy. Soc. Canada*, May 1923) found insulin in the blood of depancreatised rabbits in large amount.

[2] J. B. Collip, *Journ. Biol. Chem.*, lvi., lvii., and lviii., 1923. Collip kept a totally depancreatised dog alive for sixty-six days with only three injections of glucokinin obtained from onions.

[3] Winter and Smith, *Journ. Physiol.*, lvii., 1923, and (with Hutchinson) *Biochem. Journ.*, xvii., 1923. They also found it in pure cultures of a coliform bacillus obtained from yeast.

[4] Murlin, Clough, Gibbs, and Stokes, *Journ. Biol. Chem.*, lvi., 1923; Petschacher, *Biochem. Zeitschr.*, cxli., 1923; J. Ashby, *Amer. Journ. Physiol.*, lxvii., 1924. H. E. Dubin and H. B. Corbitt (*Journ. Metab. Res.*, iv., 1923) found two similarly antagonistic substances in plant extracts.

J. J. also has obtained insulin in a crystalline form (Ber. B. m. J. 1926 i 666) with an activity of 100 units per mgr. Carnini & Co (Proc. Soc. Exp. Biol. & Med. XXIII, 1926, 281) and Jensen (XXIII, 1926. 401) has also obtained a pure insulin with the probable formula $C_{69}H_{92}O_{22}N_{18}S$ + molecular weight 1565. He believes it to be a polypeptide composed of 15 amino acids. Its toxicity for is 0.08 mgr in rabbits.

CHAPTER L

THE INTERNAL SECRETION OF THE PANCREAS (*concluded*)

Physiological Action of Insulin

When insulin is given subcutaneously in appropriate doses to depancreatised animals it reduces the blood-sugar to the physiological level of from 1 to 1·5 parts per 1000 (0·1 to 0·15 per cent.). Sugar and acetone bodies and excess of urea disappear from the urine and the animal becomes in all respects normal.[1] How long an animal entirely deprived of pancreas can be kept alive by insulin is uncertain. N. F. Fisher [2] failed to do so indefinitely when the depancreatisation was complete, but if any pancreas is left attached to the duodenum, some recovery seems to occur.

The accumulation of fat in the liver and blood which is generally seen after removal of the pancreas (and in human diabetes) disappears with the administration of insulin, especially if carbohydrates are also given—in which case glycogen is deposited in the liver cells.

The gaseous exchanges, which are markedly increased after pancreas extirpation, are not brought back quite to normal by an amount of insulin sufficient to bring blood-sugar to the original level.[3]

In normal fasting animals the effect produced and the rate at which the symptoms supervene depend upon the dose. If this is large enough, glycogen disappears from the liver and muscles, that in the muscles being the first to be utilised. This is what would be expected if insulin promotes the metabolism of sugar by the tissues. Having used their own store, they draw upon that of the liver, and when that store is exhausted they draw upon the proteins of the body, many of which yield carbohydrate when hydrolysed (metabolised). In spite of this access of glucose the blood-sugar level gradually falls, and a condition of hypoglycæmia is produced. As soon as the percentage in the blood falls to 0·045 per cent. (which may occur within half an hour with a sufficient dose) alarming symptoms begin to appear. In rabbits—after a short period of restlessness—there are violent convulsive seizures lasting rather less than a minute, and intermitted by comatose intervals with rapid, shallow respirations. These phases may alternate for an hour or more, the convulsions becoming

[1] Nevertheless acetone bodies often make their appearance in normal rabbits treated with insulin, and there is also in them a decrease in the carrying power of the blood for CO_2 (Collip, *Proc. Soc. Biol. Chem.*, *Journ. Biol. Chem.*, lv., 1923).

[2] *Amer. Journ. Physiol.*, lxvii., 1924.

[3] L. Hédon, *C. r. acad. sci.*, clxxviii., 1924.

feebler and the rectal temperature falling until the animal dies of respiratory failure. The convulsive seizures resemble those of asphyxia.[1] After death from insulin the muscles pass very rapidly into rigor mortis ; this is characterised by an alkaline reaction of the tissue (such as occurs in animals deprived of food for some time before being killed), instead of the usual acidity.[2]

In the dog (and cat) the first signs are rapid respiration and restlessness, often with barking (or mewing) and salivation. There is cutaneous hypersensitivity, muscular twitching, relaxation of sphincters. As in rabbits, there may be alternate convulsive seizures with periods of unconsciousness. The pulse is rapid ; there is muscular weakness and inco-ordination.

Similar symptoms are produced in mice, especially if kept warm. The body temperature in these animals tends to fall very considerably at the ordinary temperature of the room when insulin is administered (Krogh) : this depression of temperature seems unfavourable to the development of convulsions. But even in cold-blooded animals (frogs) convulsions may be caused, although only after very considerable delay.[3]

Administered in a moderate dose to the healthy human subject, the blood-sugar level falls steadily, and in about eighteen minutes has reached the lowest percentage liable to be caused by the dose of insulin administered : it takes about an hour to return to normal.[4] If it is brought down to about 0·075 per cent. the subject experiences extreme hunger and a sense of fatigue : he has an anxious expression and may suffer loss of emotional control. There are no actual muscular tremors, but a sense of tremulousness and some inco-ordination. Almost always profuse sweating occurs, with either flushing or pallor of the skin, accompanied by a feeling of heat or chilliness. At lower levels of blood-sugar the symptoms become serious ; acute mental distress, delirium, and coma, with loss of deep reflexes.[5] The amount which may be administered to the normal subject varies within wide limits : in some individuals 10 units will produce toxic symptoms, whilst in others 20 units may be borne without marked effect.

The fall of blood-sugar begins, in the normal subject, within a few minutes of the hypodermic injection of insulin and progresses steeply and steadily : the curve varying with the dose and the condition with regard to stored carbohydrate. When the effect of a dose begins to wear off, the curve gradually rises to normal. As has been already mentioned, the loss of blood-sugar is not

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[1] Kleitman and Magnus (*Arch. f. d. ges. Physiol.*, ccv. 148, 1924) find, however, that insulin convulsions are not asphyxial but are related to the centres which govern equilibration. See also Russell Brain in *Quart. Journ. Exper. Physiol.*, xvi., 1925.

[2] Baur, Kuhn, and Wacker, *Münch. med. Wochenschr.*, lxxi. 169, 1924.

[3] J. S. Huxley and J. F. Fulton have shown that frogs react to insulin the more readily the warmer their environment (*Nature*, cxiii. 234, 1924). See also Olmsted, *Amer. Journ. Physiol.*, lxix., 1924. The effect appears to be related to the activity of metabolism.

[4] Bodansky and Simpson, *Proc. Soc. Exper. Biol.*, xxi., 1924. These authors injected the insulin into a vein.

[5] A. A. Fletcher and W. R. Campbell, *Journ. Metab. Res.*, ii., 1922. The description here given of the symptoms produced by insulin is largely taken from the address on Insulin by J. J. R. Macleod to the XIth International Physiological Congress in Edinburgh, 1923 (*Quart. Journ. Exper. Physiol.*, Suppl. Vol.).

due to increased glycolysis, for neither blood nor muscle juice *in vitro* with added insulin loses sugar faster than without insulin.[1] It has been suggested with some plausibility that the action of insulin may consist in its causing an alteration in the ordinary α β varieties of glucose,[2] so that they become changed into a less stable kind (γ glucose): this being the form which is supposed to be metabolised by the tissues. In support of this, Winter and Smith found that the sugar in normal blood deprived of proteins rotates polarised light to a less extent than would correspond with its content of ordinary α β glucose as determined by reduction, whereas in diabetic blood the rotation and reduction correspond to those produced by α β glucose. And after administration of insulin to the diabetic subject the sugar conditions of normal blood are resumed.[3]

This explanation of Winter and Smith is, however, by no means universally accepted, and several who have repeated the experiments have either been unable to confirm their results or set them down to changes produced by the method employed.[4] Indeed they have themselves relinquished the idea that the normal blood-sugar is γ glucose.[5] The only positive fact which emerges from a large amount of conflicting evidence is that under the influence of insulin glucose undergoes a change which renders it more readily oxydisable, and therefore better able to be metabolised in the tissues. In the diabetic subject this change does not occur.[6]

It is found that sugar in Locke's solution undergoes some structural change when perfused through the pancreas. Its reducing power is unaffected, but its action on polarised light is altered.[7]

The fall of free blood-sugar is accompanied by a rise in protein-combined sugar, both in normal and diabetic subjects.[8]

Lactic acid in blood is at first increased under the influence of insulin, but is diminished later, both in blood and in the muscles, which, nevertheless, pass rapidly into rigor.[9] The increase is accompanied by a decrease of phosphates and potassium.

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[1] Eadie, Macleod, and Noble, *Amer. Journ. Physiol.*, lxv., 1923.

[2] J. C. Irvine, *Journ. Chem. Soc.*, cxxiii. 898, 1923.

[3] Winter and Smith, *Brit. Med. Journ.*, i. 12, 711, and 894, 1923, and *Journ. Physiol.*, lvii., 1923, and lviii., 1924; G. S. Eadie, *Brit. Med. Journ.*, ii. 60, 1923, and *Amer. Journ. Physiol.*, lxii., 1923; Lundsgaard and Holboll, *Journ. Biol. Chem.*, lxii., 1924. These authors found that a mixture of insulin and muscle diminishes the optical rotation of a glucose solution without affecting its reducing power. A. Fleisch suggests (*Schweiz. med. Wochenschr.*, liv. 1117, 1924) that insulin acts by promoting the formation of lactacidogen —the utilisable form in which glycogen is believed to occur in muscle. See also Audova and Wagner, *C. r. soc. biol.*, xc., 1924.

[4] J. A. Hewitt, *Brit. Med. Journ.*, i. 590, 1923; Van Crefeld, *Biochem. Journ.*, xvii., 1923; M. B. Visscher, *Amer. Journ. Physiol.*, lxviii., 1924; Denis and Hume, *Journ. Biol. Chem.*, lx., 1924; G. Viale, *Arch. ital. de biol.*, lxxiv., 1924.

[5] *Brit. Med. Journ.*, i. 894, 1923.

[6] In connexion with this question the fact may be mentioned that intestinal mucous membrane and other tissues, which have been treated with alcohol and heated to 120° C. to destroy enzymes, have the effect of diminishing the dextro-rotatory action of glucose without affecting its reducing power (A. Richaud and J. Coirre, *Bull. Soc. Chim. Biol.*, v., 1923).

[7] A. H. Clark, *Journ. Exper. Med.*, xxiv., 1916, and *Johns Hopkins Hosp. Rep.*, xviii., 1919.

[8] Bierry, Rathery, and Kourilsky, *C. r. soc. biol.*, xc. 36, 1924.

[9] Briggs, Koechig, Doisy, and Weber, *Journ. Biol. Chem.*, lviii., 1924; Kuhn and Baur, *Zeitschr. physiol. Chem.*, cxli., 1924.

Insulin is found in man to facilitate the conversion into lactose of dioxyacetone, $CH_2OH.CO.CH_2OH$, a triose which in rats and mice is capable of conversion into glycogen by the liver. In cases of severe diabetes in which insulin is lacking, the glycosuria is increased if dioxyacetone is given by the mouth: administration of insulin causes the substitution of lactic acid for glucose.[1]

What becomes of the sugar which disappears from the blood as the result of insulin administration? It is not wholly burnt, although some may be thus accounted for. It has been conjectured that it may be transformed into some other form of carbohydrate (? by polymerisation) or combined with protein or built up into lactacidogen with phosphoric acid. But none of these hypotheses is altogether satisfactory, and it must be confessed that we are still ignorant regarding its fate.[2]

The effect of insulin in diminishing hyperglycæmia is not confined to pancreatic diabetes. It has a similar effect on hyperglycæmia however produced, *e.g.* by Bernard's piqûre, adrenaline, asphyxia, ether, etc.[3]

Liver.—Administered along with glucose to depancreatised animals, insulin causes deposition of glycogen in the liver. But in normal animals with the liver already rich in glycogen there is a rapid reduction in its amount,[4] as well as in that of the muscles. Nevertheless even when the blood-sugar is brought down by insulin to the convulsion level there may still be a considerable amount of glycogen in the liver.[5] This is even more pronounced if the sympathetic supply to the liver is paralysed by ergotamine.[6]

W. Cramer has shown that insulin has a profound effect upon the liver cells. It does not cause rapid mobilisation of their glycogen like thyroid extract, but tends to diminish the transformation of glycogen into sugar by the liver, whilst promoting its combustion by the tissues.[7]

In normal animals the amount of fat in the liver is unaltered by moderate doses of insulin.[8] In depancreatised animals insulin at first leads to the disappearance of fat from the liver, but this afterwards becomes redeposited.[9]

Temperature.—Insulin lowers body temperature: the effect is counteracted

[1] S. Isaac and E. Adler, *Klin. Wochenschr.*, i. 954, 1924.

[2] Häusler and Loewi find that if glucose is added to blood, or to a solution containing tissues in suspension, it is distributed equally between the fluid and the cells. If insulin is now added, more of the glucose is taken up by the cells (*Arch. f. d. ges. Physiol.*, ccx. 238, 1925). Eadie, Macleod, and Noble find that the phosphates of urine are temporarily suppressed by insulin (dog), and that the lactacidogen of muscle is decreased (*Amer. Journ. Physiol.*, lxxii. 614, 1925).

[3] Banting, Best, Collip, Macleod, and Noble, *Amer. Journ. Physiol.*, lxii., 1922.

[4] M'Cormick and Macleod, *Trans. Roy. Soc. Canada*, v., 1923; M'Cormick, Macleod, Noble, and O'Brien, *Journ. Physiol.*, lvii., 1923; and *Proc. Amer. Physiol. Soc.*, *Amer. Journ. Physiol.*, lxviii., 1924.

[5] Dudley and Marrian, *Biochem. Journ.*, xvii., 1923.

[6] J. H. Burn, *Journ. Physiol.*, lvii., 1923.

[7] *Brit. Journ. Exper. Path.*, v., 1924.

[8] Dudley and Marrian, *op. cit.*

[9] Allan, Bowie, Macleod, and Robinson, *Brit. Journ. Exper. Path.*, v., 1924.

by glucose.[1] It also prevents pyrexia.[2] But according to Biedl the first effect of insulin is to increase the production of heat: when the amount of blood-sugar is markedly diminished (at about two hours) the heat production is decreased.[3]

Cramer has shown that the hyperpyrexia which is produced by tetrahydronaphthylamine is prevented by insulin.[4] In point of fact, insulin is one of the strongest antipyretics, even in relatively small doses.

Respiratory Exchange.—In normal animals there is an increase both in O_2 consumption and in the respiratory quotient, which may rise above unity.[5] With the advent of hypernœa and convulsions the rise is succeeded by a fall.[6]

In depancreatised animals, when carbohydrate is also given, insulin causes a rise of the respiratory quotient. In diabetics this is also the case, even in fasting: the effect of a dose lasts three days.[7]

[1] J. J. R. Macleod, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923; H. H. Dale, *Lancet*, i. 989, 1923; Collazo and Händel, *Deutsch. med. Wochenschr.*, ii. 1546, 1923; Noyons, Bouckært, and Sierens, *C. r. soc. biol.*, xc., 1924.

[2] Rosenthal, Licht, and Freund, *Arch. f. exper. Path. u. Pharm.*, ciii., 1924.

[3] Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923.

[4] *Op. cit.*

[5] Dickson, Eadie, Macleod, and Pember, *Quart. Journ. Exper. Physiol.*, xiv., 1924; M'Cormick, Macleod, O'Brien, and Noble, *Amer. Journ. Physiol.*, lxiv., 1923 (*Proc. Amer. Physiol. Soc.*); Eadie and Macleod, *ibid.*, lxiv., 1923 (dogs, rabbits); Macleod, *Physiol. Rev.*, iv., 1924. The opposite effect was obtained in mice and guinea-pigs by Dudley and his co-workers, *Journ. Physiol.*, lvii., 1923 (*Proc. Physiol. Soc.*, p. xlvii.). See also H. H. Dale, *Lancet*, i. 989, 1923. This result in the smaller animals is, perhaps, to be correlated with the marked fall in body temperature which occurs in them. But it must be admitted that there is considerable difficulty in interpreting the variable effects in the respiratory quotient produced by insulin, especially since it usually causes greatly increased pulmonary ventilation. In curarised animals with artificial respiration Krogh obtained no appreciable change in R.Q. as the result of insulin during the first half-hour: this was succeeded by a rise in R.Q. with diminution in O_2 (*Deutsch. med. Wochenschr.*, xlix. 1321, 1923). E. E. Hawley (*Amer. Journ. Physiol.*, lxii. 224, 1925) obtained in rabbits a slight decrease, followed by an increase; the blood-sugar curve was the mirror image of the R.Q. curve.

[6] Heymans and Matton found no increase in the amount of CO_2, nor evidence of increased combustion of sugar (*Arch. internat. de pharm., etc.*, xxix., 1924; *C. r. soc. biol.*, xc. 361 and 1288, 1924). See also Noyons, Bouckært, and Sierens, *ibid.*, p. 365; de Clœdt and Van Canneyt, *ibid.*, xci. 92, 1924; Lesser, *Biochem. Zeitschr.*, cliii., 1924; E. Gabbe, *Klin. Wochenschr.*, i. 612, 1924. Tissue respiration has been found to be increased *in vitro* by insulin (Ahlgren, Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923; *Skand. Arch. f. Physiol.*, xliv., 1923; Büchner and Grafe, *Deutsch. Arch. klin. Med.*, cxliv. 67, 1924; L. Brahme, *Acta Med. Scand.*, lxii., 1925), but some (de Clœdt, Heymans) have obtained negative results.

[7] Fitz, Murphy, and Grant, *Journ. Metab. Res.*, ii., 1922. Laroche, Dauptain, and Jacquet got variable results in diabetics (*C. r. soc. biol.*, lxxxix., 1923). H. W. Davies, C. G. Lambie, D. M. Lyon, J. Meakins, and W. Robson found that the increase of R.Q. was not equal to that demanded by the combustion of the sugar which was utilised under insulin treatment, and conclude that some of the CO_2 formed remains in the blood in combination with soda (*Brit. Med. Journ.*, i., 1923). de Barenne and Burger (*K. Akad. Wetens. Amsterdam*, xxvii., 1924) obtained a marked rise of the R.Q. in decerebrate (fasting) cats, in one animal above unity; this they suggest is due to fat-formation, but as Macleod

Campbell and Dudley [1] injected air under the skin of rabbits, and when it had assumed the CO_2 and O_2 tension of the tissues they injected insulin. This had the effect of increasing the CO_2 tension and diminishing the O_2 tension: the latter followed the blood-sugar curve.

Effect of Insulin on Sugar Consumption by Muscle.—Knowlton and Starling, working by Starling's method with the isolated heart of the dog, found that in the diabetic animal there is a lessened consumption of sugar per gram of heart muscle and per hour than in the normal animal, and that the addition of extract of pancreas to the blood circulating through the heart of the diabetic animal raises its consumption of sugar.[2] Although Starling's later work [3] seemed to throw some doubt on this conclusion, and although Macleod and Pearse [4] obtained a contrary result with skeletal muscle, Maclean and Smedley [5] were able to confirm the original statement of Knowlton and Starling, and A. H. Clark [6] found that if blood or Ringer-Locke solution is first perfused through the pancreas and then through the heart the sugar consumption of the heart is decidedly increased. Similarly Hepburn and Latchford,[7] using Locke's fluid for perfusing the isolated heart of the rabbit, found that when insulin was added, the sugar consumption rose from 0·87 mg. per gram per hour to 3·06 mg. per gram per hour. A similar increase was got by Burn and Dale,[8] who found that the output of CO_2 was not increased in proportion nor is more work done. In the decapitated and eviscerated cat insulin also caused a fall in blood-sugar.[9] This must have been produced in muscle, for besides the heart and muscles, only the lungs were present. The respiratory quotient was always unity.

It was shown by Chauveau and Kaufmann that there is less sugar in the venous blood coming from muscles than in arterial blood. C. F. and G. T. Cori [10] found (in man) arterial blood to contain 5 mg. sugar per thousand more than venous blood. After insulin this difference was trebled. A similar result was arrived at by Ahlgren, who, however, is of opinion that the change of the sugar molecule is not due to insulin alone but is assisted by another (unknown) substance in the extract.[11] E. P. Pick [12] found that with papillary muscle preparations (human) whilst a very small amount of glucose added to the nutrient fluid increased the frequency of the contractions, a large amount reduced both their rate and

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has shown it can be explained otherwise (*Physiol. Rev.*, iv., 1924). *Cf.* also Thurnberg, *Skand. Arch. f. Physiol.*, xlv., 1924; Büchner and Grafe, *Klin. Wochenschr.*, ii. 2320, 1923; Kellaway and Hughes, *Brit. Med. Journ.*, i. 710, 1923.

[1] *Journ. Physiol.*, lviii., 1924.
[2] *Ibid.*, xlv., 1912.
[3] (With Patterson and L. Evans.) *Ibid.*, xlv., 1913, and xlvii., 1914.
[4] *Amer. Journ. Physiol.*, xxxii., 1913.
[5] *Journ. Physiol.*, xlv., 1913.
[6] *Journ. Exper. Med.*, xxiv., 1916, and xxvi., 1917.
[7] *Amer. Journ. Physiol.*, lxii., 1922.
[8] *Journ. Physiol.*, lix., 1924.
[9] See also C. G. Lambie, *Proc. Physiol. Soc.*, xxiii., 1925, in *Journ. Physiol.*, lx.
[10] *Amer. Journ. Physiol.*, lxxi. 688, 1925.
[11] *Klin. Wochenschr.*, i. 1188, 1924.
[12] *Ibid.*, i. 662, 1924.

force. The addition now of a trace of insulin restored and maintained the force and frequency. Eadie, Macleod, and Noble [1] found that the lactacidogen of muscle is, if anything, decreased by insulin, especially if glucose is given; but that insulin is not an important factor in influencing the amount of lactacidogen.

Other Effects.—The excretion of N and urea are diminished by insulin. The inorganic phosphorus is also diminished in the blood and in the urine.[2] The same is the case with potassium.[3] The volume of the blood is increased by insulin, although the osmotic pressure of the serum is unaltered.[4] But with large doses insulin may cause a diminution of volume both in diabetic and normal subjects.[5] It is said to increase the permeability of the erythrocytes to glucose and to chlorides.[6]

Abderhalden finds that insulin inhibits both the growth and metamorphosis of tadpoles.[7]

Neither the heart nor the blood-vessels appear to be directly affected by insulin. Applied to the vessels of the abdominal muscles of the mouse, no change in their calibre is produced.[8]

Insulin in Lymph

It was shown by A. Biedl in 1898 that diabetes is caused in dogs by allowing the contents of the thoracic duct to escape on the exterior of the body instead of being conveyed into the blood, and that a similar result is obtained by tying the thoracic duct. Biedl has further found [9] that if the lymph from the thoracic duct is injected, even in small amount (5 c.c.), into a rabbit it causes, like insulin, a fall in blood-sugar. Biedl concludes that the autacoid passes out from the pancreas by the lymph.

It seems, however, unlikely that this is the explanation. For there are no lymph-vessels in or immediately around the islets of Langerhans—at least none

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[1] *Op. cit.*, 1925. See also note 2, p. 352.

[2] Winter and Smith, *op. cit.*, 1923; Wigglesworth, Woodrow Smith, and Winter, *Journ. Physiol.*, lvii., 1923; Staub, Günther, and Fröhlich, *Klin. Wochenschr.*, ii. 2337, 1923; Eadie, Macleod, and Noble, *Amer. Journ. Physiol.*, lxxii., 1925.

[3] Harrop and Benedict, *Proc. Soc. Exper. Biol. and Med.*, xx., 1923. The authors suggest that the diminution of phosphates and sugar in the blood is related to the formation of lactacidogen in the muscles (see also note 3, p. 351). But the evidence that a carbohydrato-phosphate combination is formed under the action of insulin is not clear (Perlzweig, Latham, and Keeper, *Proc. Soc. Exper. Biol. and Med.*, xxi. 33, 1923).

[4] J. B. S. Haldane, H. D. Kay, and W. Smith, *Journ. Physiol.*, lix., 1924. D. L. Drabkin (*ibid.*, lx., 1925) obtained a contrary effect in the dog and inconstant results in the rabbit.

[5] L. Villa, *Boll. soc. med. chir. Pavia*, xxxvi., 1924.

[6] J. Secker, *Journ. Physiol.*, lx. 286, 1925. According to Olmsted and Logan (*Amer. Journ. Physiol.*, lxvi., 1923) insulin causes the blood both of normal and decerebrate animals to become very dark and to clot easily. It also increases the number of corpuscles (both red and white) per cubic millimeter. This suggests a diminution in the relative amount of water (Levine and Kolars, *Amer. Journ. Physiol.*, lxxiv. 695, 1925).

[7] *Arch. f. d. ges. Physiol.*, ccvi., 1924.

[8] J. Argyll Campbell and H. W. Dudley, *Journ. Physiol.*, lviii., 1924.

[9] Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923, p. 59.

have been described ; and the relation of the islet cells to the blood-vessels suggests a secretion into the blood. This accords also with the results of experiments of perfusion of the blood-vessels of the pancreas.

The Mechanism of Insulin Production

Since insulin serves to regulate the consumption of sugar by the tissues, the amount secreted is probably determined by the demands of the organism for glucose. According to Staub the actual stimulus is furnished to the islets of Langerhans by an increase of blood-sugar. That the formation and secretion of insulin by the pancreas can take place independently of nerves is shown by the fact that a transplanted portion of the organ will keep up a sufficient supply. The amount formed and passed into the blood can be increased by warming the pancreas. This is perhaps due to increased blood-supply.[1] That the nervous system may influence the secretion is suggested by G. A. Clark, who finds that drugs which stimulate parasympathetic nerves (vagus) cause a lowering of the amount of blood-sugar.[2]

The serious symptoms which are produced by an increase of insulin are immediately alleviated and removed by hypodermic or intravenous administration of glucose. Mannose is also effective : fructose less so. Other sugars have either no effect or a very slight one if administered parenterally.[3] Disaccharides can be given effectively by the mouth as well as glucose, since they are converted into that substance and absorbed as such ; naturally, however, the antidotal effect is less speedy. Glycerol is also effective : d-alanin to a less extent.[4]

Relation of Other Internal Secretions and Drugs to Insulin

Adrenaline.—If insulin is administered along with adrenaline the effect produced depends upon the proportion of each autacoid. Also, *ceteris paribus*, it is dependent on the nature of the aliment. If this is predominantly acid (yeast-fed rabbits) the adrenaline effect is more marked : if predominantly alkaline (green-fed rabbits), the insulin effect.[5] If adrenaline is given 1¼ hours after a dose of insulin in rabbits, hyperglycæmia ensues.[6] Adrenaline can be employed to antagonise the toxic effects of insulin, but only if there is a certain amount of glycogen present in the liver.[7]

In diabetic dogs the administration of adrenaline, without insulin, greatly increases the output of sugar and nitrogen.[8]

Various observers have found that after removal of the suprarenals animals

[1] Banting and Gairns, Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923, p. 48 ; *Amer. Journ. Physiol.*, lxviii., 1924.

[2] *Journ. Physiol.*, lix., 1925.

[3] Noble and Macleod, *Amer. Journ. Physiol.*, lxiv., 1923 ; P. T. Herring, J. C. Irvine, and J. J. R. Macleod, *Biochem. Journ.*, xviii., 1924.

[4] Voegtlin, Dunn, and Thompson, *Amer. Journ. Physiol.*, lxxi., 1925.

[5] Abderhalden and Wertheimer, *Arch. f. d. ges. Physiol.*, ccvi., 1924.

[6] Eadie and Macleod, *Amer. Journ. Physiol.*, lxiv., 1923.

[7] J. J. R. Macleod, *Physiol. Rev.*, iv., 1924.

[8] F. M. Allen, *Journ. Metab. Res.*, iii., 1923.

are much more sensitive to the hypoglycæmic effect of insulin.[1] Administered to the intact animal, insulin causes an outpouring of adrenaline into the blood. Ergotoxine prevents this.

Pigeons stand large doses of insulin without showing convulsive symptoms. It is noteworthy that their suprarenals are found to be hypertrophied. Although this is especially evident as regards the cortex, it is probably associated with an increased output of adrenaline from the medulla.[2] Stewart and Rogoff[3] find, however, that the amount of adrenaline in the suprarenal vein is not influenced by insulin.

As already mentioned, frogs and cold-blooded animals generally are relatively resistant to the action of insulin.

If insulin is added to the water in which tadpoles are kept, they become paralysed; occasionally they may show convulsive movements. Eventually they pass into a comatose condition. Addition of glucose or of extract of posterior lobe of pituitary to the water induces rapid recovery.[4]

Pituitary.—Extract of the posterior lobe of the pituitary is directly antagonistic to insulin.[5] After removal of the pituitary in dogs the animals are more readily affected by insulin.[6]

In the decerebrated cat the usual effect of insulin in lowering the blood-sugar is not seen, unless the pituitary is removed: the effect is then well marked and convulsions ensue.[7] In the decapitated cat insulin rapidly brings down the blood-sugar level but convulsions do not occur.[8] It would therefore appear (1) that in decerebrate rigidity there is a greater secretion of the pituitary autacoid (caused perhaps by a general over-activity of the sympathetic system), (2) that the reflex centre for the insulin convulsions is neither in the cerebral cortex nor in the spinal cord but in the bulb.[9]

[1] Sundberg, *C. r. soc. biol.*, lxxxix. 807, 1923 (rabbit); Lewis, *ibid.*, p. 1118 (rat); Magenta and Biassoti, *ibid.*, xc. 249, 1924 (dogs); Houssay, Lewis, and Molinelli, *ibid.*, xci. 1011, 1924; Cannon, M'Iver, and Bliss, *Amer. Journ. Physiol.*, lxix., 1924 (cat); Takashi Akeba, *Tokio Med. News*, Aug. 1924. This hypersensitivity to insulin is also seen in clinical cases which show signs of suprarenal insufficiency (G. Marañon, *Arch. d. med. cir. y espec.*, xxii. 145, 1926).

[2] Riddle, Honeywell, and Fisher, *Amer. Journ. Physiol.*, lxviii., 1924.

[3] *Amer. Journ. Physiol.*, lxv. 342, 1923.

[4] Kroszczynski, *C. r. soc. biol.*, xci. 964, 1924.

[5] J. H. Burn, *Journ. Physiol.*, lvii., 1923; Burn and Marks, *ibid.*, lx., 1925. See also Mochlig and Ainslee, *Journ. Amer. Med. Assoc.*, lxxxiv. 1398, 1925, and Lawrence and Hewlett, *Brit. Med. Journ.*, May 30, 1925. Lawrence and Hewlett found that the antagonism disappears after administration of ergotamine, which paralyses the sympathetic. Given alone pituitary extract produces a rise in the blood-sugar (Partos and Katz-Klein, *Zeitschr. f. d. ges. exper. Med.*, xxv. 98, 1921). In large doses it may cause glycosuria (Goetsch, Cushing, and Jacobson, *Bull. Johns Hopkins Hosp.*, xxii., 1911).

[6] Houssay and Magenta, *C. r. soc. biol.*, xcii. 822, 1925.

[7] According to Raper and Smith (*Journ. Physiol.*, lx. 41, 1925) this is only the case when there is a low glycogen reserve.

[8] Olmsted and Logan, *Amer. Journ. Physiol.*, lxvi., 1923; N. Kleitman and R. Magnus, *Arch. f. d. ges. Physiol.*, ccv., 1924. For the effect on visceral reflexes, see Garrelon and Santenoise, *C. r. soc. biol.*, xc. 470, 1924.

[9] Olmsted and Taylor have since published an experiment in a spinal cat in which strong convulsions were produced (*Amer. Journ. Physiol.*, lxix., 1924): these must have been brought about by a reflex from the cord.

Although insulin is an antidiuretic itself, it inhibits the antidiuretic action of pituitary extract.[1]

Thyroid and Parathyroid.—The action of insulin is increased after thyroidectomy. If the thyroid is removed in dogs with pancreatic diabetes, the blood-sugar falls even without the administration of insulin.[2] Bodansky found (in sheep) that thyroxin does not prevent the blood-sugar lowering effect of insulin but delays the recovery. In most animals the administration of thyroxin tends to antagonise the effects of insulin.[3] But after disappearance of liver-sugar as the result of thyroid feeding (see Part I., p. 45) the insulin reaction is facilitated. Administration of parathyroid subcutaneously along with insulin increases the action of the latter in reducing the amount of blood-sugar and producing convulsions (rabbits).[4]

Kidney.—Administered to phloridzinised dogs, insulin causes a further fall in blood-sugar and a decrease in the sugar and nitrogen of the urine. The respiratory quotient rises and glycogen is stored.[5] But phloridzin administered to a normal fasting animal does not affect the amount of insulin obtainable from its pancreas and other organs.[6]

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[1] Serebrijski and Vollner, *Biochem. Zeitschr.*, clxiv. 1, 1925.

[2] Friedman and Gottesman, *Journ. Amer. Med. Assoc.*, lxxix. 1228, 1922.

[3] A. Bodansky, *Proc. Soc. Exper. Biol. and Med.*, xx. and xxi., 1923; Proc. XIth Internat. Physiol. Congress, *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923: Ducheneau, *C. r. soc. biol.*, xc., 1924: Houssay and Busso, *ibid.*, xci., 1924 (various animals): Burn and Marks, *Proc. Physiol. Soc.*, p. viii., in *Journ. Physiol.*, lix., 1924.

[4] *Journ. Physiol.*, lviii., 1923. The opposite result might have been expected to occur, since J. B. Collip has found that parathyroid extract produces a marked increase in the calcium content of the blood, and completely antagonises the tetany produced by removal of the parathyroids (*Journ. Biol. Chem.*, lxiii., 1925).

[5] T. P. Nash, *Journ. Biol. Chem.*, lviii. 453, 1924; also M. Ringer, *ibid.*, p. 483.

[6] Nash and Benedict, *ibid.*, lxi., 1924 (dogs); G. T. Cori, *Amer. Journ. Physiol.*, lxxi., 1925 (cats).

CHAPTER LI

THE INTERNAL SECRETIONS OF THE SEX GLANDS

The Interstitial Cells of the Testicle

It was noticed by Leydig [1] that the intertubular connective tissue of the testicle is characterised by the presence of strands of epithelium-like cells. These have been termed the *cells of Leydig*, or collectively, the *interstitial gland* (Ancel and

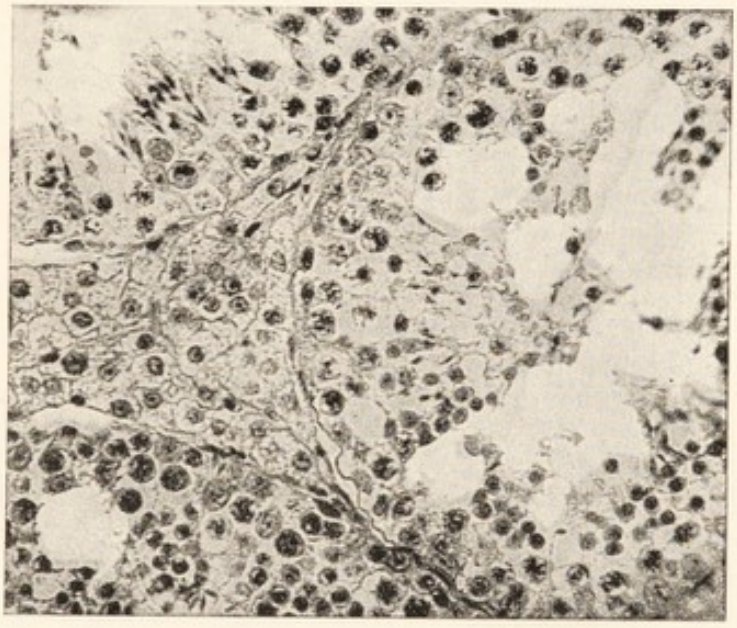

Fig. 174.—Interstitial cells of testicle, cat. × 200. Parts of three tubules are included in the photograph.

Bouin) and the *puberty gland* (Steinach): these two expressions being also applied to certain cells in the ovary which are believed to have similar endocrine functions. This interstitial epithelial tissue of the testicle varies greatly in development in different species of animals, being well developed in the boar and cat (fig. 174), less so in the dog, rat and mouse, and rabbit (fig. 175). In man they form conspicuous, isolated groups (figs. 176, 177). They are less easily shown in Vertebrata below mammals, but appear to be present in all to some extent. In animals which undergo seasonal changes in sexual activity the interstitial cells do not as a rule exactly follow the alterations of the semini-

[1] *Zeitschr. f. wissensch. Zool.*, ii., 1850.

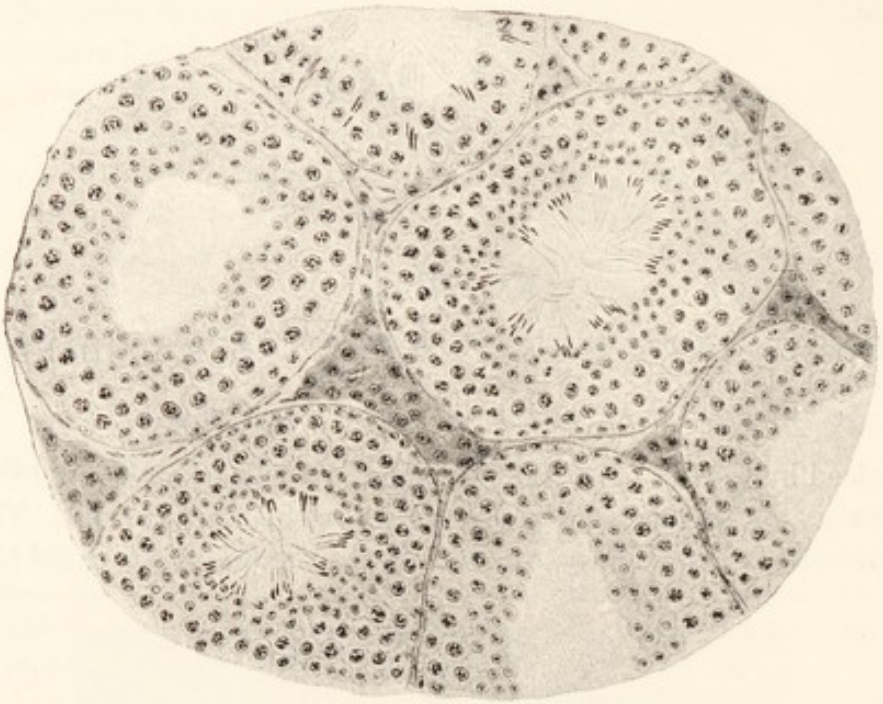

FIG. 175.—Section of testicle of adult rabbit, showing several tubules cut across and the interstitial cells between them. (Bouin and Ancel.) × 250

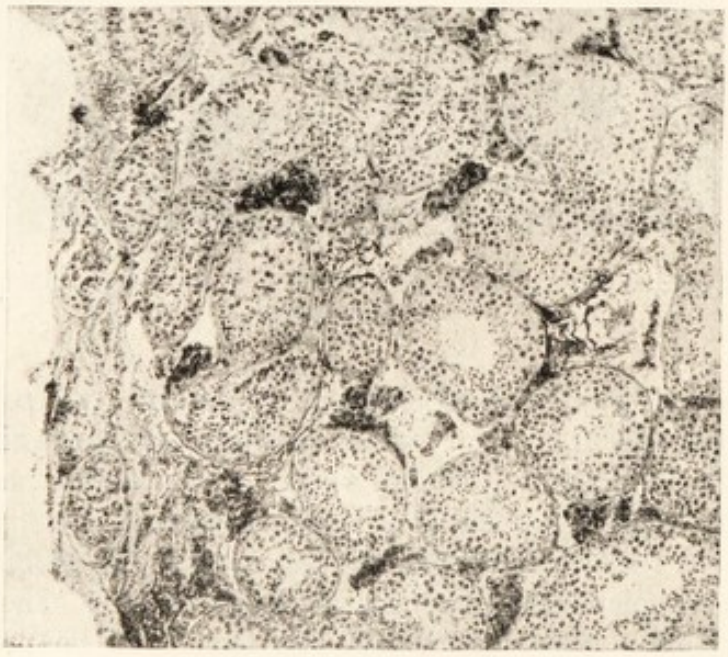

FIG. 176.—Section of testicle, human (executed criminal), showing groups of the interstitial cells between the tubules. × 50.

This and the next figure are photographs from an iron-hæmatoxylin preparation given me by Professor Martin Heidenhain.

ferous epithelium, but nevertheless they run a parallel course, usually preceding the advent of seminal maturity.[1]

In any case an increased development of this tissue appears to be associated with that of the secondary sex characters.

The tissue may be well developed along with atrophy of the contents of the seminiferous tubules, such as occurs in cases of undescended testicle (cryptorchidism) and after ligature of the vas deferens; also after treatment of the testicle with X-rays. In all such cases the masculine secondary sex characters

FIG. 177.—Interstitial cells of testicle, human (decapitated criminal). × 200. One tubule and parts of two others are shown. The groups of interstitial cells lie in loose intertubular reticular tissue.

are just as manifest as when the seminiferous epithelium is intact. If, however, the interstitial cells share the atrophy of the seminiferous epithelium, as occurs experimentally if the whole of the spermatic cord is included in a ligature, so that the nerve- and blood-supply to the testicle is cut off, and also when the whole organ is congenitally atrophied, the condition which results is the same as that which is produced by castration; this condition is termed *eunuchoidism*.

Structure of the Interstitial Gland.—The interstitial cells are polygonal in shape, each with a large spherical nucleus, a well-marked nucleolus, and often a

[1] See on this subject, A. Lécaillon, *C. r. soc. biol.*, lxvi., 1909 (mole); F. H. A. Marshall, *Journ. Physiol.*, xliii., 1911 (hedgehog); A. T. Rasmussen, *Amer. Journ. Physiol.*, xiii., 1917, and *Endocrinology*, ii., 1918 (woodchuck); R. Courrier, *C. r. soc. biol.*, lxxxviii., lxxxix., 1923 (bat).

double centrosome; mitoses are only rarely observed. The cytoplasm often contains lipoid globules and granules of protein nature, which may be either oxyphil or basiphil.[1] There is a distinct Golgi reticulum. In man there are frequently crystals within the cells;[2] the exact nature of these has not been determined.

The cells tend to become accumulated in the angular interspaces between three or four tubules, in masses which surround blood-vessels, with large lymph-spaces separating them from the tubules.[3] But the cell-masses are not especially vascular—indeed far less so than is the case with most endocrine structures.

The interstitial tissue is usually regarded as formed from the (mesodermic) epithelium of the generative cords,[4] but according to some authors it is developed from the cells of ordinary connective tissue.[5] Wagner states that in the guinea-pig it is distinct soon after birth: in the rabbit not until three or four months after birth. In man there is a great increase in the amount of interstitial tissue a little before puberty. In the human fœtus of the latter half of pregnancy there is also a relatively large amount of interstitial tissue, although the cells are less well differentiated than in the adult: from the time of birth to puberty the proportion is diminished.

As already stated, the interstitial tissue becomes hypertrophied under certain conditions. These we may now proceed to consider.

Testicle of the Cryptorchid.—If a testicle fails to descend into the scrotum at puberty but either remains in the abdominal cavity or is held up in the inguinal canal, the seminiferous epithelium remains in an infantile condition, with no development of spermatozoa; indeed it may almost entirely disappear, with the exception of the lining epithelium cells. But the interstitial tissue does not share this atrophy: on the contrary it usually becomes considerably hypertrophied. This cryptorchid condition may occur either unilaterally or bilaterally. If the latter, the individual is sterile but not impotent, and although spermatozoa are not produced, the penis, prostate, and seminal vesicles develop as usual and all the male secondary sex characters (masculine trichosis, masculine growth of body and limbs, enlargement of larynx, and alteration of voice) make their appearance. This is equally true for cases of cryptorchidism occurring spontaneously in animals,[6] or produced by experimental fixation of a testicle in the abdomen.[7] If the other testicle is removed, the retained

[1] F. W. Mott and M. P. y Such, *Proc. Roy. Soc. Med.*, xv., Sect. Psych., 1, 1922. According to Mott they exhibit evidences of division.

[2] Reinke, *Arch. mikr. Anat.*, xlii., 1896.

[3] Duesberg (*Biol. Bull.*, xxxv., 1918) claims to have shown histologically that secretion passes from the cells into the blood-vessels.

[4] Rubaschkin, *Anat. Hefte*, xlvi., 1912; A. Kolm, in Jauregg and Bayer's "Lehrbuch der Organotherapie," 1914; J. Benoit, *C. r. acad. sci.*, clxxvii. 412, 1923.

[5] Kronfeld (and Guillera), *Arch. f. Frauenkr. u. Eugen.*, vii. 242, 1921; Ch. Wagner, *Anat. Anz.*, lvi., 1923.

[6] Regaud and Policard, *C. r. soc. biol.*, liii., 1901: Bouin and Ancel, *Journ. de physiol.*, vi., 1904; *Arch. de zool. expér.*, 1903–1905; also in *C. r. acad. sci.*, and *C. r. soc. biol.*, 1903–1905.

[7] K. Sand, *Journ. de physiol.*, xix. 515, 1921.

organ increases greatly in size owing to hypertrophy of its interstitial tissue (fig. 178).

It has been suggested [1] that the lack of development of the seminiferous epithelium in the undescended testicle is connected with the higher temperature to which the gland is exposed within the body as compared with that within the scrotum. Experiments on animals testing this suggestion [2] have shown that if the scrotum is kept artificially warm, or if a testicle is moved from the scrotum to the abdomen and fixed there, the seminiferous epithelium undergoes atrophy, and

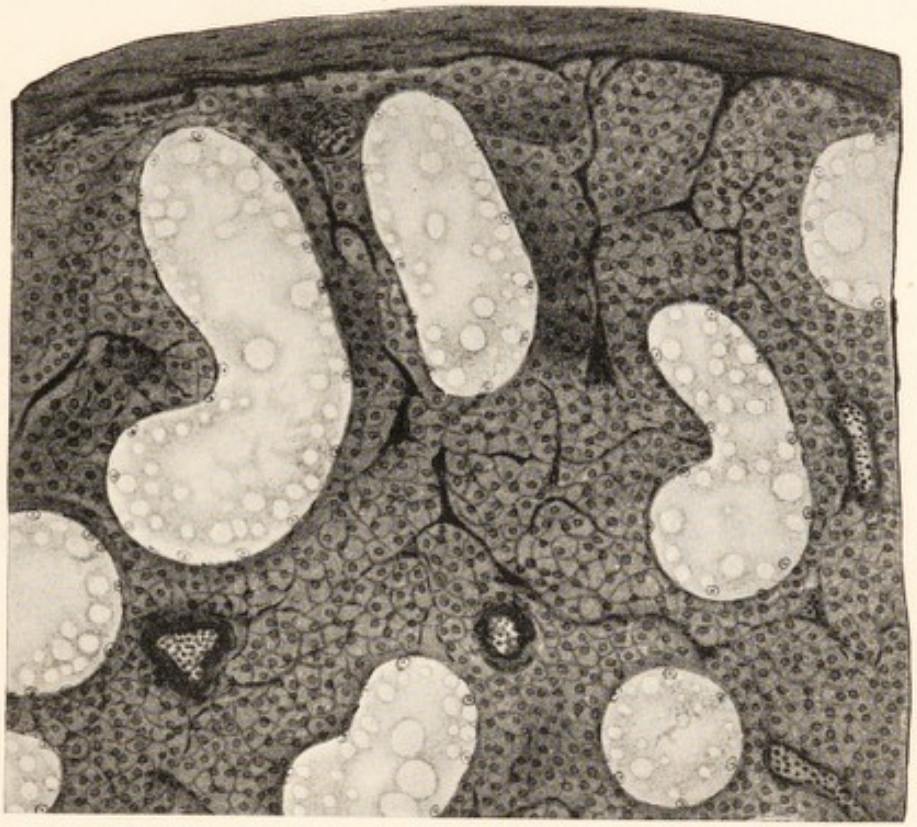

FIG. 178.—Section of undescended testicle of pig, the other (normal) testicle having been removed. (Bouin and Ancel.) × 200.

There is a great increase in the amount of interstitial tissue, the cells of which were stained brown; hence their dark appearance in the photograph. The seminiferous epithelium has disappeared, with the exception of the lining cells.

spermatozoa are no longer formed.[3] Nor are spermatozoa produced in testicles or parts of testicles which have been grafted into the abdomen of animals provided with a scrotum, whereas if successfully implanted in the tunica vaginalis they make their appearance.

But the difference of temperature cannot be the only cause of spermatogenesis. Obviously the suggestion cannot apply to poikilothermous animals, nor to those homoiothermous animals in which the testicles do not descend into a scrotum. In

[1] F. A. E. Crew, *Journ. Anat.*, lvi., 1922.

[2] Fukui, *Japan Med. World*, iii., 1923 (*Acta Schol. Med. Univ. Imp. Kioto*); C. R. Moore and W. J. Quick, *Amer. Journ. Anat.*, xxxiv., 1924.

[3] But if the organ is returned to the scrotum after not too long a sojourn in the abdomen, the seminiferous epithelium becomes regenerated.

any case the development of the interstitial tissue is not hindered, but is rather favoured by the lack of development of the seminiferous epithelium.

The Implanted Testicle.—If a testicle is removed and re-implanted in the same animal (autogenous graft) or in another animal of the same species (homogenous graft) the seminiferous tubules tend to undergo atrophy, and, unless the implantation is into the tunica vaginalis, the formation of spermatozoa ceases. But on the contrary the interstitial tissue of the graft remains, or even undergoes hypertrophy. Such grafts, even if composed of small portions of the organ—

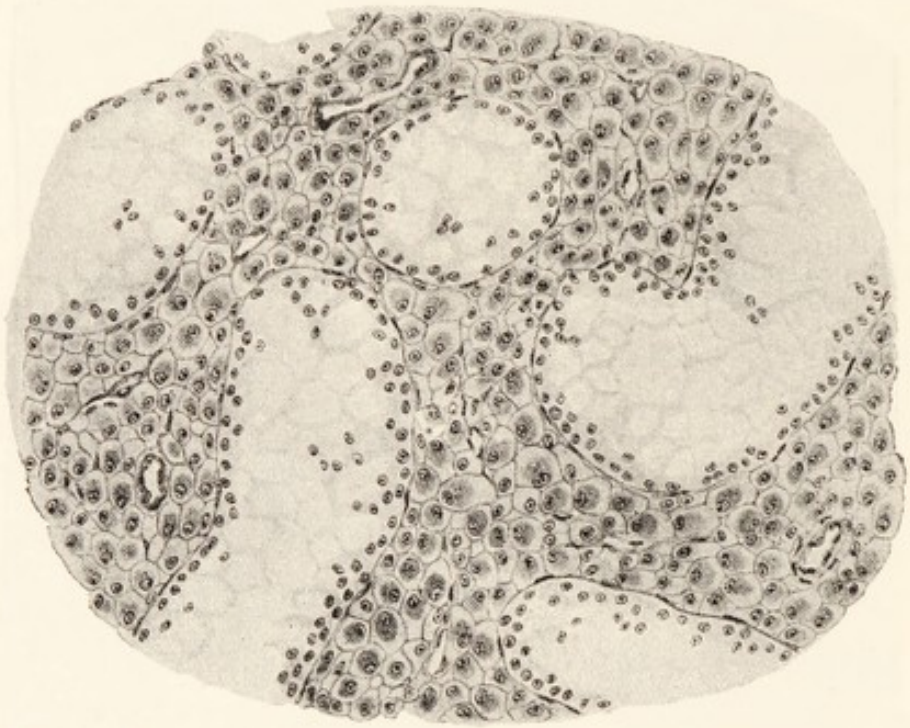

FIG. 179.—Section of testicle of adult rabbit, killed 12 months after tying the vas deferens, the other testicle having been removed at the same time. (Bouin and Ancel.) × 200.
This figure is to be compared with that of the normal testicle shown in fig. 175.

especially if taken from certain parts of it [1]—will entirely prevent the effects upon the secondary sex characters of castration from displaying themselves.

Testicle after tying or cutting (resection) of the vas deferens.—Bouin and Ancel [2] found that after tying the vasa deferentia in adult animals the formation of spermatozoa generally ceases, the seminiferous epithelium, with the exception of the lining cells, disappearing, whereas the interstitial tissue increases in amount. This is especially striking if the other testicle is removed (fig. 179). These observations have been confirmed by subsequent writers, but some have found the atrophy of the seminiferous epithelium less complete and the

[1] Lipschütz, Ottow, and Wagner, *C. r. soc. biol.*, lxxxv., 1921.

[2] *Op. cit.*, 1904. See also Shattock and Seligmann, *Proc. Roy. Soc.*, B, lxxiii., 1904, and K. Sand, *Journ. de physiol.*, xix. 494, 1921, who confirms Bouin and Ancel that the effect is only produced after puberty.

hypertrophy of the interstitial gland less striking than in the cases described by Bouin and Ancel.[1]

The Testicle treated by X-rays.—If the testicle is subjected to the action of X-rays sterility is produced.[2] The seminiferous epithelium disappears, only the lining cells remaining; the interstitial tissue is not diminished but may be increased in amount. The male secondary sex characters remain and the sexual impulses are unaffected. If the irradiation is not strong or prolonged the effect may not be permanent.[3] If the testicles are subjected to the action of X-rays before puberty the epithelium of the tubules remains infantile. But the interstitial cells develop normally, and all the usual somatic sex characters and sexual instincts make their appearance at puberty. The same result is obtained by prolonged exposure to small doses of radium emanation.[4]

In the above cases (cryptorchids, grafts, vaso-ligature, X-rays) only the seminiferous epithelium is affected or atrophied, the interstitial tissue remains. In all of them the secondary sex characters become and remain well developed, and libido sexualis is not diminished but may even be increased.

[1] *Cf.* H. Wheelon, *Endocrinology*, v. 307, 1921. J. F. Nonidez (*Amer. Journ. Anat.*, xxxiv., 1924) failed to obtain an increase of interstitial tissue in cocks as the result of tying the vas; nor did he obtain total degeneration of the seminiferous epithelium. Moore and Quick (*ibid.*) failed to obtain Bouin and Ancel's results in the rabbit within six months.

[2] Albers-Schönberg, *Münch. med. Wochenschr.*, 1903, p. 1859.

[3] Bergonié and Tribondeau, *C. r. soc. biol.*, lvi., 1904, lvii., 1905; F. Villemin, *ibid.*, 1905, p. 1077. See also E. E. Hewer, *Journ. Physiol.*, l., 1916 (rats).

[4] Mottram and Cramer, *Quart. Journ. Exper. Physiol.*, xiii., 1923 (rats).

CHAPTER LII

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*continued*)

The Ovary

The ovary (fig. 180) contains the *Graafian follicles* with their ova, follicular epithelium and liquor folliculi, and the *corpora lutea*. These are embedded in a highly vascular *stroma* formed of a peculiar connective tissue, firm in texture and containing numerous spindle-shaped cells. In most animals the stroma contains groups of cells of a different appearance from the ordinary stroma

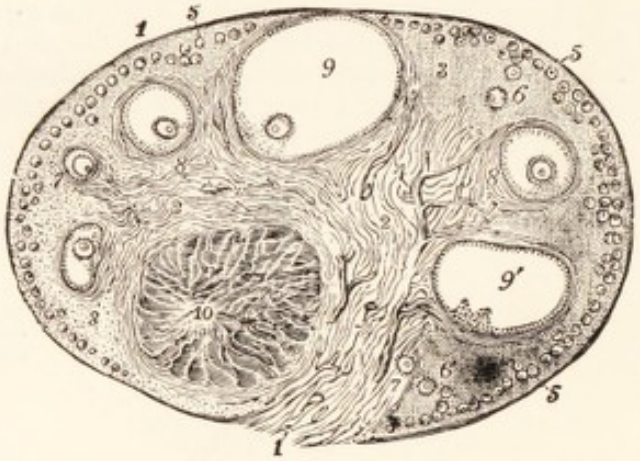

Fig. 180.—Section of cat's ovary. (Schron.) × 9.

1, External surface; 1′, hilum; 2, 2, central stroma; 3, 3, peripheral stroma; 4, blood-vessels passing in from hilum; 5, 5, 5, young Graafian follicles near surface; 6, 6, follicles undergoing enlargement and passing more deeply into the stroma: 7, 8, larger follicles; 9, 9′, follicles which are almost mature; 10, corpus luteum.

cells. These have been named the *interstitial cells*. They are not as distinct in the human ovary as in many animals.

The interstitial cells of the ovary are more readily affected by X-rays than the correspondingly named cells of the testicle, but less readily than are the ova and Graafian follicles. Like the interstitial cells of the testicle, they are regarded as the source of the internal secretion of the gland which regulates the development of secondary sex characters.

The conditions in the ovary as regards internal secretion are more complex than those in the testicle, since the cells of the Graafian follicles, the liquor folliculi, the corpora lutea, the interstitial cells, and the cells constituting the stroma, all play a part in the endocrine functions of the organ.

The Graafian follicles are derived from the epithelium of the germinal ridge;

this epithelium grows into the substance of the ovary in the form of epithelial cords (fig. 181). The cells of these cords are at first alike, but after a time some of them become enlarged to form the primitive ova. The cords presently break up into small nests of cells, each of which eventually contains an ovum with a single layer of flattened epithelium cells surrounding it. After a time these surrounding cells proliferate and form two layers, which soon become multiple. The stroma of the ovary is differentiated around each follicle into two layers, termed the external and internal thecæ : the internal theca is very vascular and contains besides the ordinary stroma cells, which are spindle-shaped and

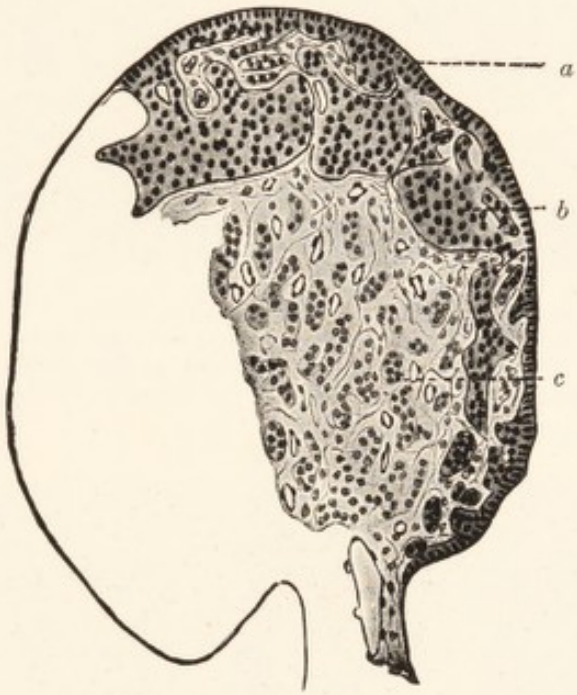

Fig. 181.—Ovary of 28-day rabbit, showing the cords of germinal epithelium growing into the stroma. (Felix and Bühler.)

a, germinal epithelium ; *b*, epithelial downgrowths ; *c*, stroma.

of connective tissue nature, large epithelium-like cells, known as *theca cells* ; these are probably of the nature of interstitial cells (fig. 182).

With the approach of puberty the Graafian follicles become greatly enlarged, partly by multiplication of their epithelium cells, partly by the formation of liquor folliculi within them (fig. 183). This fluid gradually increases in amount until the enlarged follicles, which during their enlargement have sunk deeply in the substance of the ovary, now reach the surface, where they form clear, bulging, cyst-like prominences projecting beyond the general surface. On pricking one of these cysts with a needle the liquor folliculi escapes, and with it the ovum surrounded by a mass of the epithelium cells of the follicle (*discus proligerus*, *cumulus*), leaving behind in the follicle the remaining epithelium cells, which form a layer several cells deep lining the follicular wall (*membrana granulosa*).

In the natural course of events this bursting of a mature follicle and ex-

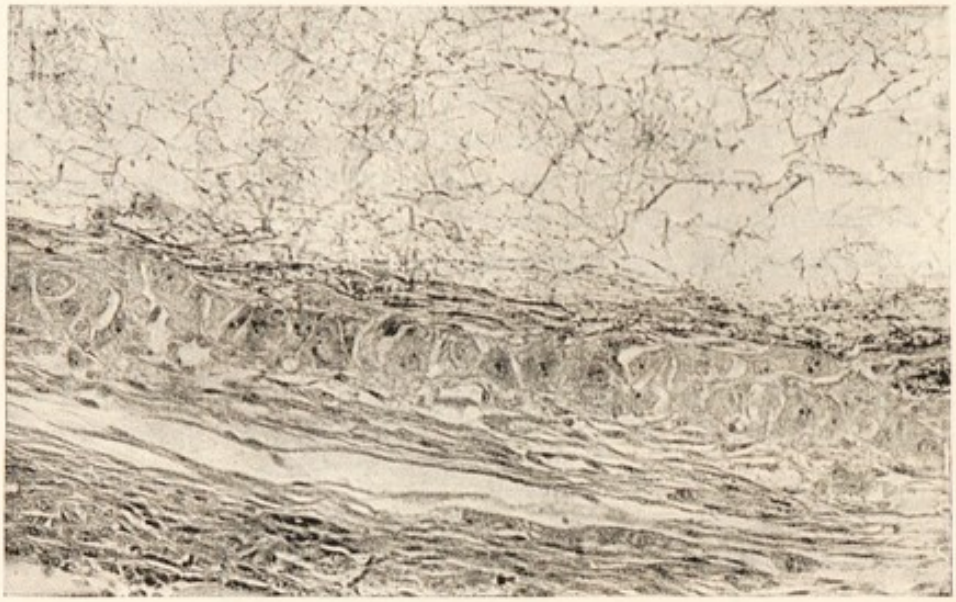

Fig. 182.—Section of the wall of an (atretic) Graafian follicle of the rabbit, from which the ovum and follicular epithelium have been entirely discharged. The cavity of the follicle was occupied by a blood-clot, of which part of the fibrin-network is shown. Notice the large theca cells in the wall of the follicle. Photograph. × 200.

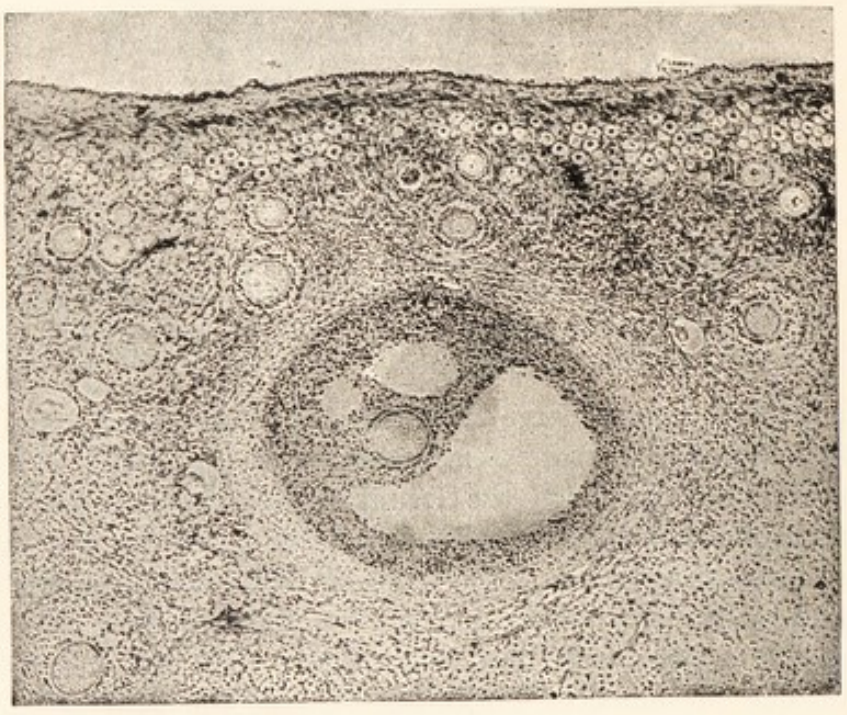

Fig. 183.—Section of rabbit's ovary. Photograph. × 60. Notice the small Graafian follicles near the surface; the enlarging follicles deeper in the stroma. One large follicle, with its ovum and epithelium and surrounded by theca, shows an accumulation of liquor folliculi.

trusion of its ovum (ovulation) occurs spontaneously; in man thirteen to

seventeen days after the commencement of menstruation.[1] The extruded ovum is caught on one of the fimbriæ of the Fallopian tube, and is carried along the tube by the action of its cilia to the body of the uterus. Here, if it should have been fertilised, it becomes attached to the mucous membrane. But whether there is or is not a fertilised ovum the uterine mucous membrane has become modified in such a manner as to facilitate attachment. These modifications in the uterine mucous membrane are preceded by partial disintegration of its substance, with desquamation of the epithelium and rupture of blood-vessels; there is some loss of blood, which, mixed with the uterine secretion, escapes by the vagina. If the ovum is not fertilised it also becomes discharged and lost, and the mucous membrane of the uterus instead of proceeding to the formation of a decidua undergoes a process of

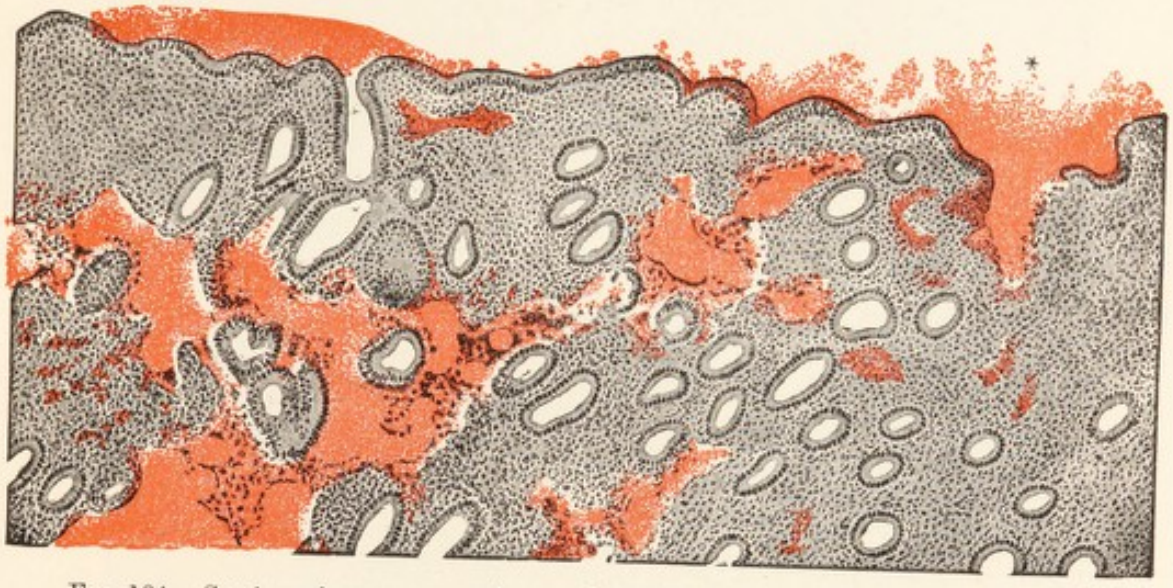

Fig. 184.—Section of mucous membrane of menstruating uterus, human. (Sellheim.) Extravasations of blood are seen both within the mucous membrane and also on its surface.

restitution and reacquires its normal character. These changes in the uterus form what is termed the *œstrous cycle*,[2] which is commonly divided into the period of increased growth and vascularity of the uterine mucous membrane, generally accompanied by escape of blood (fig. 184) (*pro-œstrus*, *menstruation*), the period of proliferation of the cells of the mucosa, or *œstrus proper*, and the period of the return of the mucosa to its inter-œstral condition (*met-œstrus*). Pro-œstrus is always characterised by extreme vascularity of the whole generative apparatus, both internal and external, whether there is an escape of blood or not. A proliferation and desquamation of epithelium occurs in the vagina also; the extent of this has been used to determine the commencement and progress of the œstrous changes.

[1] R. T. Frank, *Journ. Amer. Med. Assoc.*, lxxvii., 1922, and (with Gustavson) *ibid.*, lxxxiv., 1925; W. Shaw, *Journ. Physiol.*, lx. 193, 1925.

[2] W. Heape, *Phil. Trans.*, B, 1897; *Quart. Journ. Micr. Sci.*, xliv., 1901. For a good account of the changes in the œstrous cycle, see P. Bouin, *Presse méd.*, xxxiii. 785, 1925.

In some animals (rabbit, cat, ferret) the cycle is normally arrested at œstrus; in these the act of coitus is accompanied or immediately followed by discharge of ova. In these animals, if fertilisation is prevented by ligature of the vasa deferentia, a condition known as pseudo-pregnancy, characterised by development of corpora lutea and proliferation of uterine mucosa simulating the changes which occur in pregnancy, is produced.

After the discharge of the ovum the emptied Graafian follicle undergoes a remarkable change. Its epithelium (*membrana granulosa*) becomes greatly

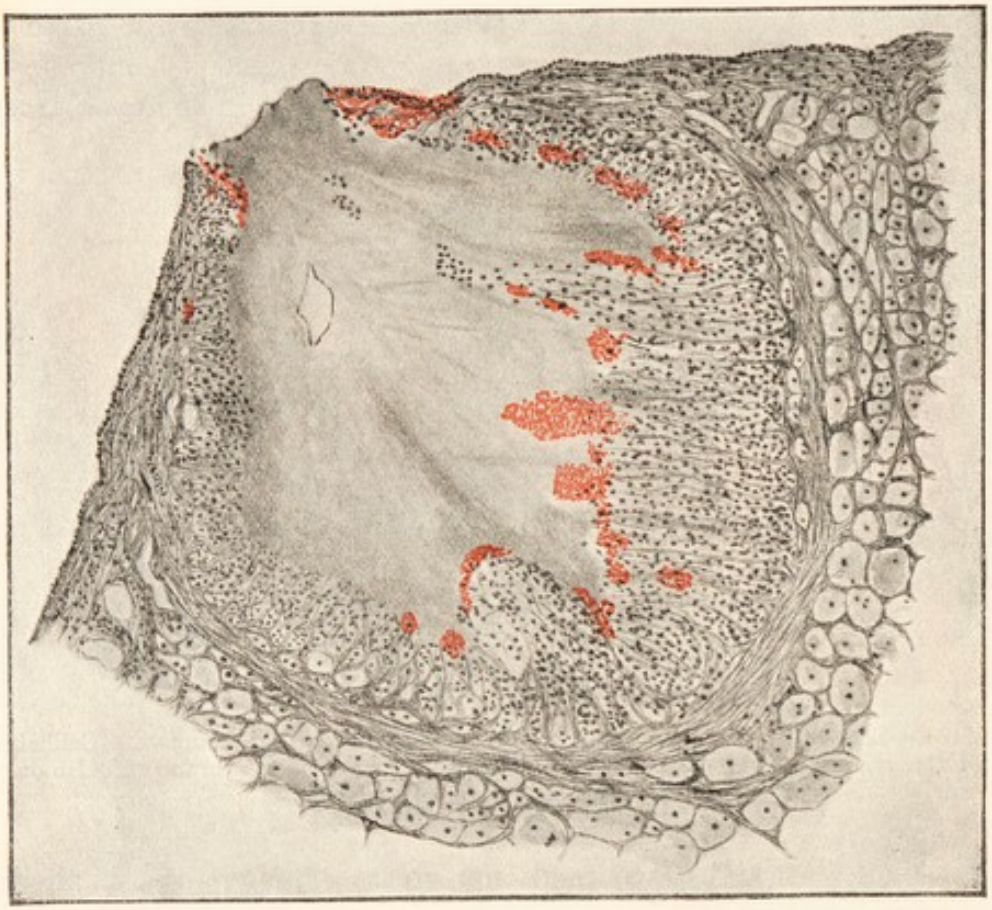

FIG. 185.—Early development of corpus luteum of rabbit. (L. F. Messel.)[1]

The place of rupture of the follicle is still widely open. The membrana granulosa is becoming arranged in columns, with vascular ingrowths from the theca extending between them. Its cells are becoming enlarged. There is some hæmorrhage into the follicle. Large luteal or theca cells are seen outside it.

thickened by enlargement of the cells (with or without their multiplication) and deposition within them of a yellowish lipoid material. They now resemble the epithelium of a secreting gland and collectively form a spheroidal or oval mass known as a *corpus luteum*. Very soon the mass becomes vascularised by the ingrowth from the theca interna of stroma tissue containing blood-vessels (fig. 185): these ingrowths are accompanied by the large "theca cells" before mentioned as derived from the interstitial cells. The theca cells are also

[1] From F. A. H. Marshall, "The Physiology of Reproduction," 1922.

transformed into lipoid-containing cells and become indistinguishable from the original cells of the corpus luteum which were derived from the membrana granulosa. The strands of luteal cells and blood-vessels converge towards a scar-like hilum which is formed at the surface of the ovary at the place where the ovum was originally extruded.

If the ovum remains unfertilised the further development of the corpus luteum ceases relatively early (in man about nineteen or twenty days after the commencement of the œstrous cycle),[1] and about the twenty-seventh or twenty-eighth day it begins to undergo regressive changes resulting in its

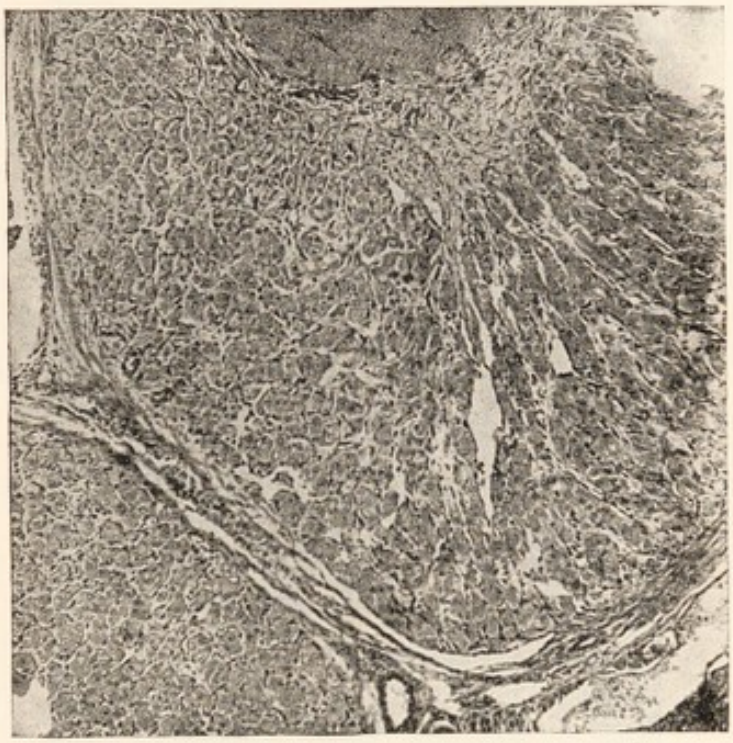

Fig. 186.—A stage in the development of a corpus luteum of the rabbit in which the cells form trabeculæ converging towards the remains of a blood-clot which partly occupied the cavity of the Graafian follicle. × 60.

eventual disappearance. Such a corpus luteum is known as a *corpus luteum spurium*. The sharp distinction between it and the ovarian stroma becomes lost; its cells appearing to migrate into the adjacent stroma. Here they disappear as a distinct tissue, many probably becoming converted into interstitial cells. What is left of the corpus luteum takes the form of a fibrous structure in the stroma of the ovary, known as a *corpus albicans*.

If the ovum becomes fertilised and fixed in the uterus, so that pregnancy supervenes, the corpus luteum undergoes considerable development. It persists in a mature form until the twelfth week of pregnancy in man, becoming greatly enlarged, and forming a large solid prominence at the surface of the ovary, known as a *corpus luteum verum* or *corpus luteum of pregnancy*.

[1] W. Shaw, *op. cit.*

In most animals this appears as a vascular globular mass of yellowish colour, with (in section) strands of cells alternating with sinus-like capillaries (figs. 186, 187). In the human subject and in Primates generally the corpus luteum as it undergoes development has a characteristically plicated appearance. Its cells become greatly enlarged; but they eventually undergo degeneration, forming hyaline masses in which the cell structure has become almost entirely obliterated. The corpora lutea of pregnancy are, like the

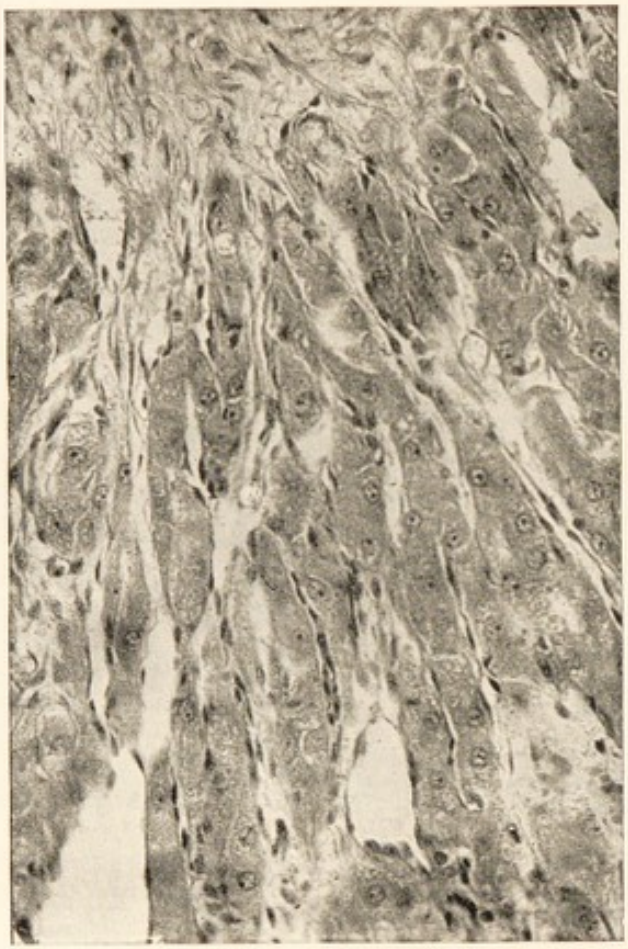

FIG. 187.—Part of the section shown in fig. 186. × 200.

false corpora lutea, ultimately absorbed or merged in the ovarian stroma, but the scar on the surface of the ovary which marks the place where they had been formed long persists.

The corpus luteum appears to be responsible for the premenstrual changes in the uterine mucosa, and, if fertilisation of the ovum takes place, for the formation of the decidua.

The above account of the mode of development of the corpus luteum was originally due to Bischoff (1842) and follows that given by Marshall,[1] who has

[1] "Physiology of Reproduction," 2nd ed., 1922, pp. 137 *et seq.* The literature will be found here.

made a special study of the subject. Marshall brings forward a considerable amount of evidence in favour of Bischoff's view as against that formulated by von Baer (1827). The latter looked upon the corpus luteum as being produced wholly from cells of the theca and stroma, and thought the membrana granulosa was entirely extruded along with the ovum and discus proligerus. Some modern authorities still hold that the cells of the theca interna, which are probably derived from interstitial cells of the stroma, form in certain species of animals, including man, the greater part, if not the whole, of the corpus luteum, the membrana granulosa becoming largely or wholly extruded.[1] According to G. W. Corner [2] both the cells of the membrana granulosa and the theca cells contribute to the formation of the corpus luteum in the pig. Pearl and Boring [3] state that in birds the corpus luteum is formed wholly by large "lutear" cells of the theca interna, without participation of the membrana granulosa.

In any case, if the observation of J. Lane-Claypon [4] is correct that the interstitial cells of the ovary are developed—as well as the epithelium of the follicles—from the germinal epithelium of the ovary, there is no morphological difficulty in supposing the derivation of the luteal cells to be from either or both of these sources.

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[1] W. Blair Bell, "The Sex Complex," 1920; T. Hirose, Tokio, *Igakkwai*, 1920 (Abstract in *Endocrinology*, iv. 623); E. Seaborn and Ch. Champy, *C. r. soc. biol.*, lxxxix., 1923.

[2] *Amer. Journ. Anat.*, xxvi., 1919.

[3] *Ibid.*, xxiii., 1918.

[4] *Proc. Roy. Soc.*, B, lxxvii., 1905. See also A. L. M'Ilroy, *Proc. Roy. Soc. Edin.*, xxxi., 1910.

CHAPTER LIII

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*continued*)

Effects of Castration in the Male

In Man and Mammals.—If the testicles are removed before puberty the secondary sex organs—especially the penis, the prostate, and the seminal vesicles—remain infantile, and the sexual instincts are undeveloped. Such specially masculine characters of the human subject as the development of the male type of chest and pelvis, the enlargement of the larynx and change in the quality of the voice, the growth of hair on the face, chest, and limbs, fail to show themselves. When the pubic hair appears it has the feminine distribution, not rising above the mons Veneris. There is usually considerable development of subcutaneous fat, especially in the gluteal and mammary regions: some castrates, however, remain thin. In the skeleton the epiphyses long remain separate, the limb bones are longer and more delicate than in the average male, and the cranial sutures are slower in becoming ossified.[1] Intelligence has been said to be relatively defective, but there is evidence against this statement. Most of the endocrine organs are affected. The thyroid is diminished in size; the pituitary increased; the thymus gland fails to undergo involution.

Similar alterations are observed as the result of testicle-removal in other young mammals.[2] The secondary sex organs remain infantile. In animals in which special organs—*e.g.* the highly developed horns of the stag and of some sheep[3]—are characteristic of the male, these fail to make their appearance at puberty or only occur in a rudimentary form. If such horns have begun to develop, the growth ceases after castration.[4] There is no appearance of heat or rutting. The combative tendencies of the male—especially in presence of the female—are absent: the disposition is quiet and peaceable. The castrated animal generally lays on fat more readily and, as there is also an increased growth of the skeleton, the body increases in weight and may be altogether larger than the average entire male.

Sutherland Simpson and Marshall found that after prepuberal castration

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[1] H. Sellheim, *Beitr. z. Geburtsh. u. Gynäk.*, ii., 1899; *Zeitschr. f. Geburtsh. u. Gynäk.*, lxxiv., 1913: Tandler and Gross, *Arch. f. Entwickls.-mech.*, xxvi., 1909.

[2] E. Steinach, *Zentrlbl. f. Physiol.*, xxiv., 1910; *Arch. f. Entwickls.-mech.*, xlii., 1916: Lipschütz, *ibid.*, xliv., 1918: N. F. Fisher, *Amer. Journ. Physiol.*, lxiv., 1923.

[3] Arkell and Davenport, *Science*, xxxv., 1912; Marshall, *Proc. Roy. Soc.*, B, lxxxv., 1912; Marshall and Hammond, *Journ. Physiol.*, xlviii., 1914.

[4] For the literature, see Marshall, "Physiology of Reproduction," 1922, pp. 321–332.

stimulation of the nervi erigentes fails to cause erection of the penis in the adult (cat).[1]

If castration is performed after puberty there may be some retrogression of secondary sex characters which have already developed, and the external generative organs may show a tendency to atrophy. In the guinea-pig the secretion of the seminal vesicles, which normally coagulates when it comes in contact with the prostatic secretion, fails to do so in the castrated animal.[2] The vaso-motor system is less readily stimulated (nicotine test), but after a successful testicular graft it returns to normal.[3] R. G. Hoskins finds that the amount of work performed by castrated white rats (revolving cage) is much less than that of normal controls.[4] In most but not in all cases of castration there is a decrease in metabolism, but sometimes—as shown by the gaseous exchanges—there may be an increase: when this occurs the castrate tends to become thin, in place of laying on fat, as is more usual.[5]

The limit of assimilation of carbohydrates is lowered, and alimentary glycosuria more easily produced. Probably the effects on metabolism are caused through the influence which the loss of the testicles exercises on other endocrine organs such as the thyroid and pituitary.

To produce the effects described, castration must be complete. If even a small part of one testicle—not more than one-sixteenth, preferably from the upper pole which contains relatively more of the interstitial tissue—is left, the castration changes do not occur.[6] The portion which is left generally undergoes hypertrophy, the change affecting the interstitial tissue almost exclusively.[7]

In Birds.—In birds the effects of castration are striking. They have chiefly been studied in the domestic fowl—in which, for economic reasons, the process (caponisation) has been long practised—and in the duck.[8] The chief external

[1] *Quart. Journ. Exper. Physiol.*, i., 1908.

[2] Gley and Pézard, *Arch. internat. de physiol.*, xvi., 1921.

[3] Hoskins and Wheelon, and Wheelon and Shipley, *Amer. Journ. Physiol.*, xxxv., 1914, and xxxix., 1916.

[4] *Proc. Amer. Physiol. Soc.*, in *Amer. Journ. Physiol.*, lxxii., 1925.

[5] V. Korenchevsky, *Journ. Path. and Bact.*, xxvi., 1923; *Brit. Journ. Exper. Path.*, vi. 158, 1925.

[6] Occasionally it may happen in such cases that the effect (*e.g.* on the seminal vesicles of the guinea-pig) is unilateral, being more pronounced on the side on which castration is complete (A. Lipschütz, *C. r. acad. sci.*, clxxxi. 75, 1925). This phenomenon is difficult of explanation: it is probably determined by nervous influences.

[7] Lipschütz, Ottow, and Wagner, *C. r. soc. biol.*, lxxxv., 1921; *Arch. f. d. ges. Physiol.*, clxxxviii., 1921: Lipschütz, *Bull. d'histol.*, ii., 1925.

[8] H. D. Goodale, *Biol. Bull.*, xx., 1910; *Amer. Natur.*, xlvii., 1913; "Gonadectomy," *Publ. of Carnegie Institute*, No. 243, 1916: Shattock and Seligmann, *Proc. Zool. Soc.*, 1914: A. Pézard, Thèse, Paris, 1918 (Abstract in *Endocrinology*, iii., 1919): M. Zavadovsky, "Sex and Development of Sex Characters," 1922 (Russian), Abstract by Lipschütz in *Endocrinology*, vii., 1922: Torrey and Horning, *Proc. Soc. Exper. Biol. and Med.*, xix., 1922: J. Benoit, *C. r. soc. biol.*, xc., 1924: A. Lipschütz, "The Internal Secretions of the Sex Glands," 1924.

changes in the capon as compared with the normal cock are in the comb and wattles, which are not only much shorter but relatively thin and much less vascular (fig. 188). The comb of a cockerel castrated at three or four weeks does not even develop to the size of the comb of a hen of the same breed but remains infantile. The spurs are little, if at all, modified from the male type, nor is the plumage deficient: the tail feathers may be better developed than in the "entire" cock. The skeleton is enlarged and far more fat is deposited in the body, so that the weight of the fully grown capon may be 25 per cent. more than that of an average cock of the same breed.[1] The pituitary is greatly enlarged: it may be twice the normal size.[2] The capon does not crow like a

FIG. 188.—Brown Leghorn cock, three years old, castrated as a cockerel. The crest and wattles are undeveloped, but plumage and spurs are masculine. (From Lipschütz.)

cock, will not fight with other male birds, does not tread the hen, and shows no sexual instincts.

In rare instances the testicle may produce an autacoid which, like that of the ovary (see p. 388), inhibits the development of male characteristics. This is the case with certain breeds of fowls (Sebrights and Campines) in which the cocks have normally plumage similar to that of the hens. This "hen-feathering" disappears as the result of removal of the testicles, the castrated cockerels growing in all respects like capons of ordinary breeds, with well developed plumage but with small comb and wattles (fig. 189, A and B).[3] According to Morgan the

[1] H. Sellheim, *Beitr. z. Geburtsh. u. Gynäk.*, i., 1898; ii., 1899; v., 1901; *Zeitschr. f. Geburtsh. u. Gynäk.*, lxxiv., 1913.

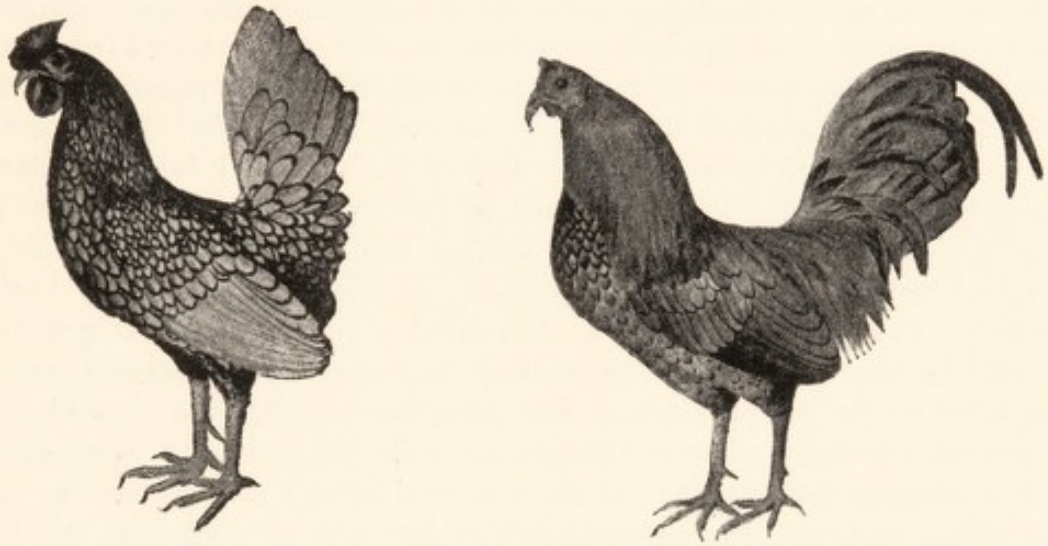
[2] G. Fichera, *Arch. ital. de biol.*, xliii., 1905.

[3] T. H. Morgan, *Proc. Soc. Exper. Biol. and Med.*, xiii. 31, 1915; *Journ. Gen. Physiol.*, i., 1918 (with A. M. Boring); *Endocrinology*, iv. 381, 1920.

chalonic effect is correlated with the presence of lutear cells (like those of the ovary) in the testicles of these breeds.[1]

F. H. A. Marshall [2] has confirmed these results on hen-feathered Sebrights. He also found in three out of six experiments in which only one testicle was removed that cock-feathering made its appearance at first only on the same side, although later it extended to the other side. This suggests that a nervous influence in some way affects the alteration.

If the castration is performed in the adult after the development of masculine characters, some of these soon begin to show retrogression. The comb and wattles diminish in size, the animal ceases to crow and loses its sexual instincts. But the spurs and plumage remain unaffected. If any part of either testicle is left, none of these changes occur.



A B

FIG. 189.—Normal (A) and castrated (B) Sebright cock. (T. H. Morgan.)

Observations regarding the influence of the male gonads on secondary sex characters have also been made in other birds which show marked sexual differences, such as pheasants and ducks.[3] The Rouen drake, which at the end of the breeding season normally replaces brilliant summer plumage by the " eclipse " plumage which resembles that of the duck, fails to do so if castrated. On the other hand, the Rouen duck assumes the bright plumage of the drake after ovariotomy.

It is not as easy in birds as in mammals to show that alterations due to castration are dependent upon the loss of the interstitial cells, for these are not prominent

[1] See further on the lutear cells in the testes, J. F. Nonidez, *Amer. Journ. Anat.*, xxxi., 1922; A. W. Greenwood, *Brit. Journ. Exper. Biol.*, ii., 1925. According to these authors the cells in question are not specially associated with a henny type of plumage.

[2] Quoted from Punnett and Bailey, *Journ. Genetics*, xi., 1921.

[3] In many birds the sexes are similar in plumage; in some the female has the brighter and more developed plumage.

in the bird's testicle ; some authorities even deny their existence.[1] But it seems to be now satisfactorily established that such cells are normally present although obscured in the adult by the enormous growth of the seminiferous tubules.[2] In some birds they have been observed to undergo seasonal changes.[3]

In Amphibia.—In the frog and toad and triton certain secondary sex characters become marked in the male during the breeding season. One of the most striking features in the male frog at that time is the enlargement of a pad on the first digit (thumb) of the fore-limb : the muscles of the limb also undergo hypertrophy. These changes enable the male to clasp the female firmly, the fore-limb of the male encircling the body of the female just below the axillæ and the thumb-pads being pressed against her sternum : the nuptial embrace continues for hours or days, until the spawning is completed. This embrace is a reflex act and can be brought about by contact with inert substances, especially of soft character. As Spallanzani (1786) showed, it continues even after decapitation of the male. It may be inhibited, like many other reflexes, by stimulation of the corpora bigemina (Albertoni, Tarchanoff) : Baglioni finds that under some circumstances it can also be facilitated by such stimulation. Although a clasp reflex is not confined to the spawning time (Busquet) it is specially developed at that period—whether from increase of irritability of the spinal centres or diminished irritability of inhibitory centres, or both, is uncertain—and its development is correlated with the increased growth of the testicles then occurring. Removal of the testicles leads either at once or soon after to its disappearance. But insertion of pieces of testicle under the skin or injections of testicular extract will—for a time at least—restore it. According to Steinach, the testicle to be used for this purpose must be taken from a frog in heat : the autacoid is therefore only produced at this time. That it is also present in the tissues of the nervous system seems to follow from another experiment by Steinach, who obtained a positive result from injecting extracts of the brain and spinal cord of frogs in heat, while extracts of the same organs from castrated frogs produced no result. As we have seen, the thumb-pad does not hypertrophy if the testicles are removed. But its development is also dependent on the nervous system, stimulated perhaps by the testicular autacoid. This is shown by the fact that if the nerves of one forearm are cut just before the time of heat the pad on that side remains undeveloped.[4]

[1] Boring and Pearl, *Anat. Rec.*, xiii., 1917 ; Pézard, *op. cit.*, 1918.

[2] Des Cilleuls, *C. r. soc. biol.*, lxxiii., 1912 ; Reeves, *Anat. Rec.*, ix., 1915 ; A. C. Massaglia, *Endocrinology*, iv., 1920 ; J. F. Nonidez, "The Interstitial Cells of the Fowl's Ovary," from *Libro en honor d. D. S. Ramón y Cajal*, 1922, and *Amer. Journ. Anat.*, xxxi., 1922 ; J. Benoit, *C. r. soc. biol.*, lxxxvii., 1922, and lxxxviii., 1923.

[3] A. Watson, *Journ. Physiol.*, liii., 1919.

[4] See on this subject, Albertoni, *Arch. ital. de biol.*, ix., 1888 : Tarchanoff, *Arch. f. d. ges. Physiol.*, xl., 1887 : Nussbaum, *Ergebn. d. Anat. u. Entwick.*, xv., 1905 ; *Anat. Anz.*, xxx. 578, 1907 ; *Arch. f. d. ges. Physiol.*, cxxvi., 1909 ; *Arch. f. mikr. Anat.*, lxxx., 1912 : Busquet, "La fonction sexuelle," 1910, and *C. r. soc. biol.*, lxviii. 880, 1910–1911 : Steinach, *Arch. f. d. ges. Physiol.*, lvi., 1894 ; *Zentrlbl. f. Physiol.*, xxiv., 1910 : Baglioni, *ibid.*, xxv., 1911 : I. M. Ufland, *Arch. f. d. ges. Physiol.*, ccviii., 1925.

The male triton (Molge cristata) assumes a striking nuptial apparel (crest, etc.) at the breeding time, but if the testicles are previously removed this fails to show itself, or, if already assumed, disappears. It has been shown by Aron [1] that to obtain this result there must be included in the removal a small fatty body of a reddish-yellow colour, lying near the hilum. This body—the *paratestis*—appears to produce the autacoids responsible (there are no interstitial cells in the testicle proper of the triton), for if the paratestis alone is removed, the testicles being left, the effect on the nuptial apparel is the same as with complete castration.

In the male toad, after castration, the " organ of Bidder " has been shown by Ponse [2] to develop ova, which may be shed and fertilised : this organ is therefore not homologous with the paratestis of the newt but is a rudimentary ovary.

Ponse has also shown that in the castrated female toad a testicular transplant causes the appearance of thumb-pads.[3]

In Arthropoda the correlation between the generative glands and the secondary sex characters (which in many species are even more marked than in Vertebrata) does not hold good. Experiments upon caterpillars and crabs show that removal of the generative glands or their complete destruction by parasites has no influence on the development of the sex characters of the imago or adult ; nor do the glands, if transplanted into individuals of the other sex, affect the secondary sex characters or instincts of the host. This need not be taken to mean that the secondary sex characters in these animals are not the result of internal secretion, but may be interpreted by supposing that some organ other than the generative glands furnishes the internal secretion which produces those characters.

It seems clear from what has been stated that the testicle furnishes an internal secretion (probably formed by the interstitial cells) which stimulates the development of certain peculiarly masculine characters. In its absence these fail to develop, or, if already present, undergo retrogression. This particular autacoid or harmozone acts therefore as a stimulant (hormone) for the development of such characteristics. But there is also present in the testicle an inhibitory autacoid (chalone) which prevents the development of essentially feminine characteristics. This is strikingly shown by the " unbolting " experiment of Lipschütz which will be afterwards described (p. 391).

Results of Testicular Implantation or Grafting : Rejuvenation

Birds.—That the testicle secretes a hormonic autacoid which stimulates the production of male secondary characters is also shown by the results of implantation of testicular substance into castrated animals, both male and female. An attempt of this kind seems to have been made by John Hunter in the domestic fowl ; but the fundamental experiment was first performed by Berthold in 1849.[4] " He removed the testicles of several birds : in one of them he replaced the testicles in the abdomen (autotransplantation) : in the abdomen of a second

[1] *C. r. acad. sci.*, clxxiii., 1921, and clxxiv., 1922.
[2] *C. r. soc. biol.*, xcii. 582, 1925.
[3] *C. r. soc. phys., etc., de Genève*, 1923.
[4] *Arch. f. Anat. u. Physiol.*, xlii., 1849.

castrated cock the testicles of another castrated cock were placed (homoio-transplantation). The engrafted testicles ' took ' in different places . . . The appearance of the birds was like that of normal cocks. Two months later Berthold removed the engrafted testicles in one of these ; the bird became a capon." [1] Berthold concluded that the testicles must pass some substance into the blood which reacts on the organism in general.[2]

The experiments of Fogas [3] and Pézard [4] in birds are particularly instructive. The implantation not only of whole testicles but of portions of testicle are found to prevent the effects of castration : the comb and wattles grow again and the birds become fully masculinised. Nor is the presence of the *cells* which produce the autacoid necessary, for male secondary sex characters can be made to appear in young and castrated animals by injections of testicular extracts.[5]

Even in castrated hens repeated injection of testicular extracts will cause the development of male characters.[6]

It is not necessary to use extracts of testicles of an animal of the same species. Pézard [7] got a positive effect on a castrated cockerel by repeated injections of extract of (undescended) pig's testicle. The signs of castration vanished, the bird crowed again and displayed sexual instincts : all these results disappeared on stopping the injections.

The effects of testicular extracts upon the castrated frog may also be recalled.

Lastly, it may be stated that Crew [8] has obtained rejuvenation of aged cocks and hens by feeding them with thyroid gland. The cocks developed " henny " plumage under this treatment. When it was discontinued the symptoms of senility gradually re-established themselves.

Mammals.—The most complete series of experiments with testicular grafts are those of Steinach,[9] Sand,[10] Lipschütz,[11] and Voronoff,[12] and their fellow workers. These experiments have mostly been made on rats, guinea-pigs, and

[1] Quoted from Lipschütz, "The Internal Secretions of the Sex Glands," 1924, p. 81.

[2] Berthold appears to have been the first to attribute the results of castration to the loss of a special secretion, and incidentally he may be regarded as having introduced the idea of internal secretions which now plays so important a part in physiology and medicine.

[3] *Arch. f. d. ges. Physiol.*, xciii., 1903.

[4] *Op. cit.*, 1918.

[5] Bouin and Ancel, *C. r. soc. biol.*, lxi., 1906. Also, according to Loewy (*Ergeb. d. Physiol.*, ii., 1903), by prolonged feeding of caponised cockerels with testicular substance. But Steinach (*Zentrlbl. f. Physiol.*, xxiv., 1910) was unable to produce any effect by feeding castrated rats with testicular substance.

[6] C. E. Walker, *Proc. Roy. Soc. Med.*, i., 1908.

[7] *C. r. acad. sci.*, cliv., 1912.

[8] *Proc. Roy. Soc. Edin.*, xlv. 252, 1925. Crew suggests that the effects on plumage, etc., caused by the gonad hormones may be produced not directly but through their influence on the thyroid. *Cf.* Crew and J. Huxley, " Effect of Thyroid on Growth-rate, Feathering, etc.," *Vet. Journ.*, lxxix., 1923. See also p. 412.

[9] *Arch. f. Entwickl.-mech.*, xlii., 1916.

[10] *Journ. de physiol.*, 1921, p. 305.

[11] Many papers, chiefly in *C. r. soc. biol.*, 1921 and 1922. See also his "Internal Secretions of the Sex Glands," 1924.

[12] *Rep. di med. y chir.*, March 1922, and "Greffes testiculaires," Paris, 1923.

rabbits, but also on other mammals and man. The castrated animals re-develop the lost male characters, after a certain latent period during which the graft is becoming vascularised and recovering its endocrine functions. If a fragment, it becomes hypertrophied, the hypertrophy affecting mainly the interstitial tissue. The effects are manifested not only in external characters but also by behaviour; the animals become vigorous and combative; they are attracted by the female and are not repelled by her, as are castrated animals.

Rejuvenation in the Male.—If the graft is made in aged animals in which the testicles are still present but have become inactive, especially if taken from the testicle of a young animal of the same species, the host in the course of a few weeks or months becomes completely transformed and in a sense rejuvenated: many of the symptoms of senility disappear and are replaced by those of youth and vigour. The sexual instincts which had disappeared are recovered; the animal seeks and may successfully impregnate the female. The grafts, if examined some months after re-implantation, show great hypertrophy of interstitial tissue but complete absence of spermatogenesis—the spermatozoa in cases of fertilisation must therefore have been derived from the senile testicles, which have shared in the general rejuvenation. In certain animals the effects of such grafts have been observed to last two or three years (dog, goat, ram).

Even in young animals (kids) which have been allowed to retain their own testicles the implantation of a testicular graft from another animal of the same species is found to accelerate the development of masculine secondary sex characters, such as the horns and fleece. The operated animals also generally grow faster than controls and are more vigorous.

This principle—of rejuvenation by testicular implantation of young glands—has also been applied in man to combat the symptoms of senility (lack of vigour, etc.) which develop in advanced age and appear to be correlated, *inter alia*, with degeneration or atrophic changes in the testicles. The effects of such implantation are described as being similar to those observed in animals, viz. increase of both physical and mental vigour, recovery of *libido sexualis*, and a general feeling of youthfulness. They recall the observations upon himself of Brown-Séquard, who found at the age of seventy-two that he was able by subcutaneous injection of emulsions of testicular substance from animals to eliminate many of the signs of age and to obtain restored virility with marked improvement of mental and physical powers.[1] The effects of an injection, however, cannot be expected to last more than a few hours or days, and the administration requires to be frequently renewed. Obviously it is otherwise with grafts. But these must be either from the same species or from one which is allied: grafts from alien species will not "take." Voronoff finds that portions of testicle from young anthropoid apes will "take" in man if implanted in the tunica vaginalis, and will survive there indefinitely.[2]

[1] *Arch. de physiol.*, 1889.

[2] For a detailed account of experiments in animals and man on rejuvenation by means of testicular grafts, see "La glande génitale mâle," by E. Retterer and S. Voronoff, Paris, 1921,

Another method of obtaining rejuvenation is ligature or resection of the vas deferens of one side, or, eventually, of both sides. This is advocated by Steinach[1] and has been largely practised both in animals and in man by himself and others.[2] It is claimed for this method that it is as effective in producing rejuvenation as grafting, and far simpler. It was devised by Steinach upon the basis that the operation while producing degeneration of the spermatic tissue causes hypertrophy of the interstitial tissue, which yields the hormone producing the desired result; he supposes that in consequence of such hypertrophy more of the masculine hormone is formed, and an increase in bodily and mental vigour is the consequence of such increased secretion.

This explanation is not accepted by Pézard [3] nor by Lipschütz,[4] who hold that the interstitial tissue has an " all or none " effect and, provided there is already sufficient, an increase in its amount will not increase the result. But Shattock and Seligmann [5] found that the secondary sex characters of partially castrated cocks depend for their development upon the amount of testicular substance left behind, and Lespinasse [6] records similar results. K. Sand [7] also concludes that the force of the hormonic influence is in direct proportion to the amount of hormonic tissue; and Aron,[8] in partial castration experiments on Rana esculenta, finds that the development of secondary sex characters depends upon the amount of interstitial tissue in the remainder, and concludes that the " all or none " principle does not apply. The " all or none " theory is moreover contrary to what is found in other internally secreting organs, in which hypertrophy of the gland generally manifests itself by an increase of functional effect (*e.g.* the pituitary in acromegaly). In any case an attempt at a comparison with the " all or none " doctrine of excitability is illusory, for this is only applicable to individual tissue elements, not to their aggregations. Moreover, drugs act in proportion

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and Voronoff, " Quarante-trois greffes du singe à l'homme," Paris, 1924. L. L. Stanley (*Endocrinology*, v. 137, 1921) describes results obtained by grafting pieces of testicles from young subjects into senile recipients and into patients with various disorders. A short account of most of the experiments on testicle-grafting which have been reported is given by R. G. Hoskins in *Endocrinology*, ix. 277, 1925.

[1] " Verjüngung durch exper. Neubelebung der alternden Pubertätsdrüse," Berlin, 1920, and *Arch. f. Entwickl.-mech.*, xlvi., 1920. A popular account of the results obtained by Steinach is given by P. Kammerer in " Rejuvenation and the Prolongation of Human Efficiency," London, 1924.

[2] K. Sand, *C. r. soc. biol.*, lxxxv., 1921; *Journ. de physiol.*, xix. 494, 1921; and *Acta Chir. Scand.*, lv., 1922: H. Benjamin, *Endocrinology*, vi., 1922: O. Wilhelm, *Rev. méd. de Chile*, 1923: R. Oslund, *Amer. Journ. Physiol.*, lxix., 1924: Retterer and Voronoff, *C. r. soc. biol.*, xc., 1924: K. M. Walker and J. A. Lumsden Cook, *Lancet*, i., 1924. Degeneration of spermatic tissue does not always result from vasectomy (sheep) according to C. R. Moore, *Endocrinology*, viii., 1924, and (with Oslund) *Amer. Journ. Physiol.*, lxvii. 595, 1924: also Oslund, *ibid.*, lxx. 111, 1924 (dogs). In two old cocks in which he tied the vas, F. A. E. Crew failed to observe any sign of rejuvenation, or of increase of the interstitial tissue of the testicle (*Proc. Roy. Soc. Edin.*, xlv. 249, 1925). In any case such increase seems not to be produced in the cock by vasoligation (see note 1 on p. 365).

[3] *C. r. acad. sci.*, clxxii., 1921.

[4] " Internal Secretions of the Sex Glands," 1924.

[5] *Proc. Roy. Soc.*, B, lxxiii., 1904.

[6] Barker's *Endocrinology and Metabolism*, ii., 1922.

[7] *Journ. de physiol.*, 1921, p. 305.

[8] *C. r. soc. biol.*, xlii. 1398, 1925.

to their amount, and the internal secretions must be regarded as acting like drugs (see Part I., p. 5) unless harmozones differ from hormones in this respect.

Cases have been described in young boys, in which tumours of the testicle have been accompanied by early and marked development of male characters (growth of hair on face, axillæ, and pubes, enlargement of penis, and other signs of puberty) which have disappeared on removal of the tumour. This seems to be an instance of tumour cells taking on the functions of normal cells from which they have developed (in this case probably interstitial cells).

To recapitulate :—The development of the secondary sex characters in the male sex is dependent upon an internal secretion of the testicle, and it is highly probable that the active autacoid is yielded, not by the generative cells, but by the interstitial cells. In cryptorchidism, in testicular transplants, also after ligature of the vas deferens and after the application of X-rays, the seminiferous epithelium becomes atrophied while the interstitial tissue remains well developed or is even hypertrophied, yet the secondary sex characters peculiar to the male appear and remain normal. If the interstitial tissue is removed as well as the seminiferous tubules, as in castration, those characters disappear, but reappear with a successful testicular graft.

CHAPTER LIV

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*continued*)

Effects of Castration in the Female

The effects resulting from removal of both ovaries are externally not so striking in mammals as with the equivalent operation in the male. If performed in young animals or if the ovaries are congenitally atrophic the general effect is the production of an intermediate or neutral type, although characters often show themselves which are usually considered distinctive of the male. In the human subject especially there is a tendency towards the male type of trichosis: this is often seen in atrophic conditions of the ovaries.

Constant results of double ovariotomy in the young subject are that the uterus and external generative organs are far less developed than normally: the secondary sexual changes characteristic of puberty do not occur or are greatly modified: there is complete absence of œstrus. When the operation is performed subsequent to puberty the results are less marked; but œstrus ceases, and the uterus, Fallopian tubes, vagina, and mammæ undergo diminution in size.[1] In the human subject the voice tends to become lower in tone after surgical removal of the ovaries, and vasomotor and heart disturbances may be seen (flushing of skin, cardiac palpitations) such as are liable to occur at the climateric when the ovaries lose their activity.

Metabolism is diminished as in the male castrate: there is a tendency to adiposity and a reduction in the respiratory exchange.[2] These effects may be indirect, through some of the other endocrine organs. Administration of ovarian extract brings metabolism back to the normal state.

The suprarenal capsules are said by Hatai[3] to diminish in size in the female white rat as a result of castration, whereas in the male the opposite change results. Hatai finds, on the other hand, that the increase in size of the pituitary which follows castration is far less marked in the female than in the male.

Doubtless the effects of removal of ovaries are due to the loss of their internal secretion. And, reasoning from analogy, one would be disposed to refer the pro-

[1] Carmichael and Marshall, *Proc. Roy. Soc.*, B, lxxix., 1907 (rabbit); Marshall and Jolly, *op. cit.*, 1907 and 1908 (rat); Blair Bell, *Proc. Roy. Soc. Med.*, v., 1912; A. L. M'Ilroy, *ibid.* (man).

[2] Loewy and Richter, *Centrlbl. f. Physiol.*, xvi. 449, 1902; M. Kojima (rat), *Quart. Journ. Exper. Physiol.*, xi., 1917.

[3] *Journ. Exper. Zool.*, xviii., 1915.

duction of this secretion not to the germinative epithelium but to the interstitial cells in the stroma. It is, however, much more difficult to accumulate evidence of this in the female than in the male. For transplanted ovaries or portions of ovary generally contain Graafian follicles and also corpora lutea, although both these may be absent. The chief evidence which can be adduced in favour of the interstitial cells rather than the Graafian follicles furnishing the sex-autacoids is that derived from careful and moderate exposure of the ovaries to X-rays. This treatment if properly graduated will cause complete atrophy of the Graafian follicles (so that incidentally no corpora lutea are formed), whilst the interstitial tissue is unaltered or may be hypertrophied. As a result, even

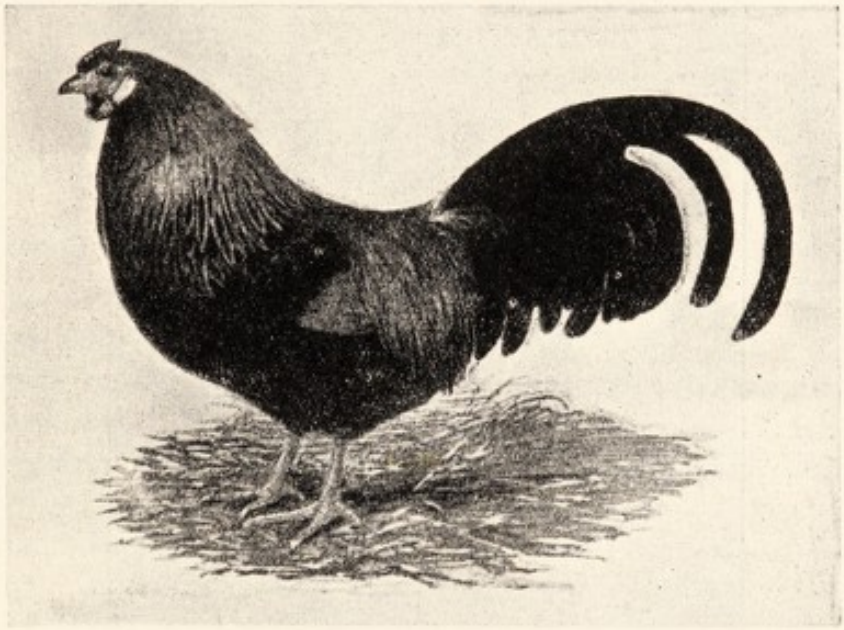

FIG. 190.—Ovariotomised Brown Leghorn pullet. (Goodale.)

The ovary was completely removed on the 66th day after hatching. This figure represents the bird 18 months after operation. An imperfect male plumage was first developed. After the next moult a completely normal male plumage was gradually developed and retained.

in the virgin animal (guinea-pig), the uterus hypertrophies, the mammary gland becomes enlarged as in pregnancy, and the secondary sex characters and sex instincts remain fully developed.[1] But a too prolonged or intense exposure may destroy the interstitial tissue also, and produce the same effects as complete ovariotomy.

Results of Ovariotomy in Birds.[2]— Most of the observations and experiments on female birds have been made, as in the male, on the domestic fowl and duck.

Goodale[3] found that brown Leghorn hens, castrated at from one to four months, acquire spurs and plumage which resemble those of the male, but with even better developed tail feathers (like the capon): they usually grow larger

[1] Steinach and Holzknecht, *Arch. f. Entwickl.-mech.*, xlii., 1916.
[2] In the bird only one ovary—the left—is present.
[3] *Amer. Natur.*, xlvii., 1913; *Carnegie Institute Publ.*, 1916.

than normal hens, but do not crow like a cock ; they lose their sexual instincts. From its external appearance the castrated hen might be taken for a cock, except that the comb and wattles are small (fig. 190).[1] Hens, the ovaries of which—from age or disease—have ceased to function, have also often been observed to acquire plumage similar to that of the cock.[2] The castrated Rouen duck similarly acquires a characteristic plumage not unlike that of the drake.[3] The tendency to masculinity of the castrated female bird seems to be more pronounced than with the mammal. But the general effect of castra-

Fig. 191.—Hen which after 3 years of egg-laying had the ovary destroyed by disease and developed a functional testis on the right side. (Crew.)

tion is to produce a neutral type, with a tendency towards male secondary characters.

Occasionally the masculinity of a hen which has lost its ovary either by operation or disease is more pronounced (Crew), so that the hen becomes in every respect indistinguishable from a cock of the same breed (fig. 191).[4] It not only

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[1] Pézard, *C. r. acad. sci.*, cliii. to clx., 1911 to 1915 (several papers) ; *Endocrinology*, iv., 1920.

[2] Gurney, *Ibis*, vi., 1888 ; Shattock and Seligmann, *Trans. Path. Soc.*, lvii., 1906, and *Proc. Roy. Soc. Med.*, i., 1907.

[3] Goodale, *Biol. Bull.*, xx., 1910 ; *op. cit.*, 1916 : Zavadovsky, *op. cit.*, 1928.

[4] F. A. E. Crew, *Proc. Roy. Soc.*, B, xcv., 1923 (two papers). The histological conditions are described by H. Fell (*Brit. Journ. Exper. Biol.*, i., 1923).

assumes all the secondary characters of the cock, but crows, fights with cocks, pursues and treads hens, and is even capable of fertilising their eggs.[1]

The cases described by Crew exhibited ovarian atrophy: there was also development of seminiferous tubules from generative cords formed by proliferation of the peritoneal epithelium covering the gonad. This seems to be what always happens when the masculine characters become pronounced. It probably means that the embryo chick is at first bi-sexual, but that if and when the ovary develops, this organ produces a chalonic autacoid which inhibits the development of the testicle, an undeveloped rudiment of which is present on the right side. If, in consequence of surgical extirpation or disease, this chalonic influence of the ovary is removed, the testicular rudiment may develop either as to its interstitial cells or as to its seminiferous tubules, or both.

There also frequently occur in birds instances of individuals in which both male and female gonads are potentially present, and according to whether the female or male autacoids predominate, feminine or masculine characters are exhibited.

Effects of Re-implanting Ovaries into Castrated Female Animals

It appears to be easier to get a graft from the ovary to "take" than one from the testicle: probably because it becomes more readily vascularised. As has already been mentioned, the operation has been frequently performed both in mammals and birds, with the result, if the implantation is made at the time of castration of the female, that the signs of castration fail to appear, or, if they begin to show themselves, quickly disappear. If the implantation is made after the changes due to castration are well established, these changes regress and the feminine characters again show themselves. The extent to which this recovery may occur will depend upon the time which has elapsed since the operation of ovariotomy was performed.

Implantation of ovaries has been frequently effected in the human subject. The consequences of castration are thereby averted. The atrophy of the uterus is prevented and menstruation recommences. It is therefore advisable in cases of removal of both ovaries on account of disease to at once re-implant any portion which may be healthy, since even a small piece, which may contain no obvious Graafian follicles, will, if the graft "take," prevent the signs of castration from showing themselves.[2]

[1] Boring and Pearl, *Journ. Exper. Zool.*, xxv., 1918; Hartman and Hamilton, *ibid.*, xxxvi., 1922; Pézard, Sand, and Caridroit, *C. r. acad. sci.*, clxxiv., 1923; Crew, *op. cit.*; J. Benoit, *C. r. acad. sci.*, clxxvii. 1243, 1923, and clxxviii. 1640, 1924; L. V. Domm, *Proc. Soc. Exper. Biol. and Med.*, xxii. 28, 1924.

[2] See on the subject of ovarian grafting both in the domestic fowl and laboratory animals and in man, R. T. Morris, *New York Med. Journ.*, lxii., 1895; *Med. Rec.*, lix., 1901; Knauer, *Centrlbl. f. Gyn.*, xx., 1896, and xxii., 1898; *Arch. f. Gyn.*, lx., 1900; Grigorieff, *Centrlbl. f. Gyn.*, xxi., 1897; J. Halban, *Wien. klin. Wochenschr.*, 1899, p. 1243; Limon, *C. r. soc. biol.*, lvii., 1904; Carmichael, *Journ. Obstetr. and Gyn.*, xi., 1907; V. Magnus, *Norsk. Mag. f. Laeg.*, 1907; C. C. Guthrie, *Science*, 1909, p. 724; Castle and Phillips, *ibid.*, p. 312; Guthrie and Lee, *Journ. Amer. Med. Assoc.*, lxiv., 1915; Unterberger, *Arch. f. Gyn.*, cxvi., 1918; Blair Bell, "The Sex Complex," 1920; K. Sand, *Journ. de Physiol.*, 1921 and 1922; Sippel, *Arch. f. Gyn.*, cxviii., 1923. See also the references on p. 389. J. Halliday Croom

If in a castrated animal which has been thus treated the graft is now removed, the symptoms of castration at once begin to reappear. We may conclude therefore that the stroma of the ovary contains cells which yield an internal secretion of hormonic nature which promotes the production of feminine sexual characters. And since after complete castration there is not only a disappearance of such feminine characters but an appearance of some characters which are pre-eminently of masculine type, and these disappear on the fixation of a successful ovarian graft, we must also conclude that the ovary yields another internal secretion of chalonic nature, which normally restrains the development of masculine characters. We have already seen that the same statement may be made, *mutatis mutandis*, for the testicle (p. 379).

has recorded the birth of a child to a woman from whom both ovaries had been removed and replaced by portions of an ovary from another woman (*Trans. Edin. Obstetr. Soc.*, xxxi. 194, 1905–1906). See also Morris, *Med. Rec.*, lxix., 1906.

CHAPTER LV

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*continued*)

Implantation of Gonads into Animals of the Opposite Sex. Feminisation of Males and Masculinisation of Females

Mammals.—Very interesting are the results obtained by Steinach [1] both from implantation of ovaries or portions of ovaries into castrated male animals and from implantation of testicles into castrated female animals (guinea-pigs and rats). The effect in the first case is to produce feminisation of the male castrate (fig. 192, A, 4). The results are rendered evident in the young male animal by regression in development of the penis, prostate, and vesiculæ seminales, which are even smaller than would result if the castrated animal had not received the ovarian graft.[2] In guinea-pigs the teats and mammary glands become enlarged and resemble those of the female: the mammæ may even secrete milk, and such feminised males have been observed to suckle young animals. If the graft undergoes subsequent atrophy or if it is removed the feminine characters recede. The amount and rate of growth of the feminised male animal is also interfered with by the ovarian graft, so that he ultimately becomes not only much smaller and lighter in weight than the normal entire male but even smaller than the normal entire female. In other words, there is not only feminisation but even hyperfeminisation: this seems to be associated with hypertrophy of the interstitial cells of the graft, which often occurs.[3]

There are also "psychic" changes. The feminised male shows the "tail-raising" and "leg-raising" reflexes exhibited by the female when followed by a male, and is treated in every way by normal males as if it were a female.

The masculinisation of castrated female rats and guinea-pigs by implantation of testicles was also studied by Steinach (fig. 192, B, 4). When a graft "takes" in the young castrated female guinea-pig not only do the teats remain undeveloped and the uterus atrophied, but the clitoris becomes enlarged into a

[1] *Arch. f. d. ges. Physiol.*, cxliv., 1912; *Zentrlbl. f. Physiol.*, xxiv., 1910, and xxvii., 1913. These results have been confirmed by many subsequent experimenters (Athias, *C. r. soc. biol.*, lxxviii., 1915; K. Sand, *Journ. Physiol.*, liii., 1919, and *Journ. de physiol.*, 1921 and 1922; Morse, *Journ. Exper. Zool.*, xxviii., 1919, and xxxiii., 1921). For a full discussion, see Lipschütz, *op. cit.*, 1924.

[2] This illustrates the inhibitory or chalonic influence of the ovarian secretion on the secondary male characters.

[3] Female animals in which, besides their own ovaries, others are implanted do not show hyperfeminisation (Lipschütz and Tiitso, *C. r. soc. biol.*, xcii., 1925).

penis-like organ with a well-marked preputium and hypertrophied corpora cavernosa, and two horny styles develop, like those on the penis of the male

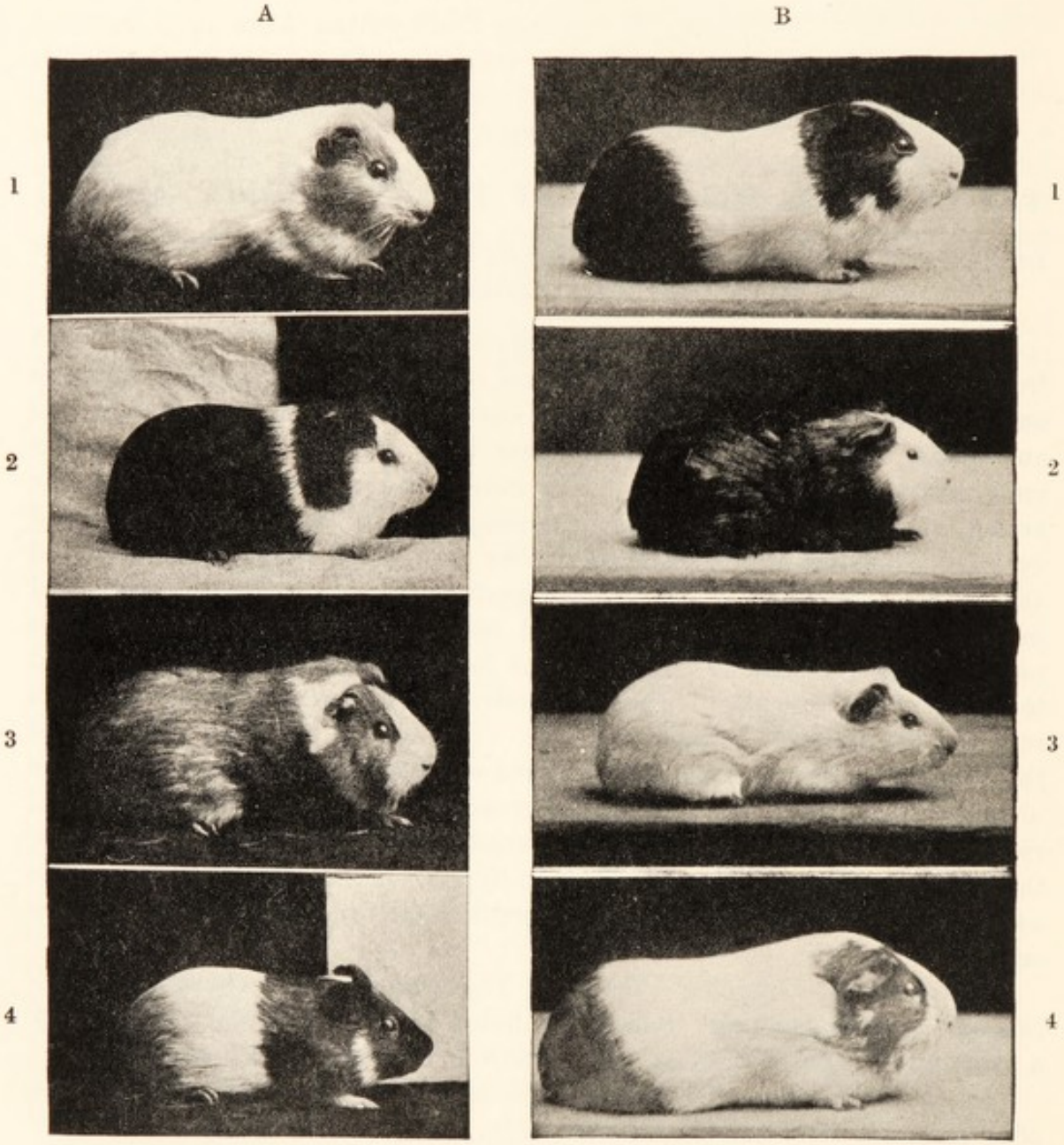

FIG. 192.—Feminisation and masculinisation of guinea-pigs. (Steinach.)

A. From above down. 1, Normal male; 2, normal female; 3, castrated male, 4, feminised male. (All four from same litter.)

B. From above down. 1, Normal male; 2, normal female; 3, castrated female; 4, masculinised female. (All four from same litter.)

guinea-pig. Parallel changes are seen in the masculinised female rat. As regards growth, the masculinised animal surpasses the normal female in size and is even larger than the female castrate: its proportions are those of a normal male; they may even be larger (hypermasculinisation). The coat also becomes

altered in the male direction. The psycho-sexual behaviour is distinctly male. The animal pursues females in heat, emits the characteristic call of the male, and fights with normal males.

Similar changes were noticed by Brandes with a female deer, which was masculinised by implantation of a testicle after castration. The animal showed signs of horn growth in the frontal bones, developed the pomum Adami which is characteristic of the male deer, and behaved like a stag to normal does.[1]

The effects produced by the presence of both gonads in the same individual are shown by the experiment of Sand [2] of implanting ovary into testicle in the guinea-pig. If the graft "takes," whilst the essential masculine characters are all retained—such as size of penis and vesiculæ seminales, coagulability of contents of vesicles by prostatic fluid,[3] etc.—there is also development of certain feminine characters, such as hypertrophy of teats and formation of milk by the mammary gland. The condition is termed "experimental hermaphroditism" or "experimental intersexuality." The animal is partly male, partly female, the extent of each depending upon the relative amount of testicle and ovary. If one testicle is removed at the time of operation the feminine characters develop more quickly. If both testicles are left, and the ovarian graft is implanted in an independent situation, either no effect may be seen, or the effect may only begin to appear after a prolonged period of latency. But if, after the lapse of a few days or weeks without sign of feminisation, the testicles are removed, feminisation begins to show itself, either at once or after a very short period of latency, by hypertrophy of nipples and diminution in size of seminal vesicles and penis. Apparently the ovary was producing sex-autacoids, but the effect of these was inhibited by the male sex-autacoids: these disappear on removing the testicles, and the female autacoids then produce their specific effect.

This instructive experiment, which illustrates the antagonism between the autacoids of the testicle and ovary, is due to A. Lipschütz, who terms it "unbolting." The period of latency of such a graft may be looked upon as divisible into three phases, viz. (1) the vascularisation period, (2) the period of recovery of endocrine function, and (3) the period of action of the internal secretion. In this case (1) and (2) have already been passed through when the "unbolting" is performed.[4]

In the above experiment it took the chalonic autacoids of both testicles to restrain or inhibit the activity of a single implanted ovary. But according to

[1] Brandes (*Berlin Tagebl.*, June 7, 1914) performed a similar experiment on a stag, implanting ovaries after castration.

[2] *Journ. de physiol.*, 1922, p. 472.

[3] See p. 375.

[4] The following papers deal with the subject: Lipschütz and Krause, *C. r. soc. biol.*, lxxxix., 1923: Lipschütz and Voss, *ibid.*, xc. and xci., 1924: Lipschütz, Krause, and Voss, *Journ. Physiol.*, lviii., 1924: Lipschütz, *ibid.*, lix., 1924: Lipschütz and others, *C. r. soc. biol.*, xci., 1924, and xcii., 1925 (several papers); also in *Arch. f. d. ges. Physiol.*, ccviii., 1925. In *Endocrinology*, ix. 109, 1925, Lipschütz summarises his results.

Athias [1] this can be effected by a single testicle (the other being removed), provided the vas deferens has been tied and resected : the testicle, in consequence, acquires more interstitial tissue and furnishes a greater amount of male autacoid.

Yatsu [2] finds that in parabiotic rats, in which a male and a female are conjoined, the testicles of the male are unaffected but the ovaries of the female cease to produce Graafian follicles and corpora lutea.

Cases of true hermaphroditism occur naturally in mammals and in man,[3] although they are not common. Such cases usually show an ovary on one side and a testicle on the other, but sometimes the glands are combined on one or both sides to form an ovary-testicle. Such cases generally tend towards feminism in the external sex characters. But they are occasionally masculine, or there may be a mixture of feminine and masculine characters, presumably according as the influence of the female or male autacoid prevails.

It sometimes happens in apparent hermaphroditism that the secondary sex characters are exactly opposite to those which the gonads present should produce, *e.g.* with both gonads male the external sex characters may be feminine, and with both gonads female the external characters may be masculine. Such cases are difficult of explanation. What has probably happened is that the functions of the interstitial cells have become perverted in the process of development, so that cells producing male autacoids have become developed in the ovaries, and cells producing female autacoids in the testicles. It is possible that perverted sexual behaviour in man may be due to perversion of the internal secretion of the gonads, for it is undoubted that psychical changes are produced by alterations in the character of these secretions.

Birds.—In birds the effects of implanting ovaries or testicles into castrates have also been investigated. If a hen's ovary is successfully implanted into a castrated cockerel the animal acquires the plumage, general appearance, and sexual instincts of a hen.[4] If a cockerel's testicles are implanted successfully into a castrated pullet the bird when it grows to adult size is indistinguishable from a cock of the same breed (fig. 193). If the bird is not castrated, or only incompletely, a graft of a gonad of the opposite sex is less likely to take, but if it does so there may be rhythmic changes in the secondary sex characters, according as the influence of the autacoids of the natural or of the implanted gonad prevail.[5] Such a bird is an experimental hermaphrodite.[6]

[1] *C. r. soc. biol.*, xci. 232, 1924.

[2] *Anat. Rec.*, xxi., 1921.

[3] For an account of such cases, see Blacker and Lawrence, *Obstetr. Trans.*, xxxviii., 1896 ; F. L. Neugebauer, "Hermaphroditismus," 1908 ; E. E. Glynn, *Quart. Journ. Med.*, v., 1912 ; W. Blair Bell, "The Sex Complex," 1916 ; H. H. Young, *Johns Hopkins Hosp. Bull.*, xxxv., 1924. In Young's case there was an ovary with Graafian follicles and corpus luteum on the left side and a testicle in the scrotum on the right side. The secondary characters were mainly masculine.

[4] Pézard, Sand, and Caridroit, *C. r. soc. biol.*, lxxxix. 947, 1923 ; xc. 1459, 1924 ; xci. 1075 and 1146, 1924 : C. C. Guthrie, *Amer. Journ. Physiol.*, xix., 1907 ; *Journ. Exper. Zool.*, v., 1909, and *Journ. Exper. Med.*, xii., 1910.

[5] Pézard, *Ann. d. sci. nat.*, 1922, p. 83 ; Zavadovsky, *op. cit.*, 1922 ; Pézard, Sand, and Caridroit, *C. r. soc. biol.*, xci. 1459, 1924.

[6] For the cause of natural hermaphroditism in birds, see p. 387.

Even without a testicular graft an incompletely castrated hen may show a mixture (mosaic) of male and female feathering, the amount of the ovarian chalone being insufficient to prevent the tendency of the male hormone, which is believed to be always potentially present in the ovary, from exerting its influence.[1]

C. J. Bond [2] has described a pheasant with a left ovary-testicle which showed male plumage on that side and female plumage on the other.

A. W. Greenwood found that gonad grafts inserted in the hen's egg in the later stages of incubation do not influence the determination of sex.[3] In these experiments the gonads of the embryo chick were untouched. G. F. Findlay [4] has made numerous experiments on gonad implantations after castration in newly hatched chicks. These experiments seem to show that although the

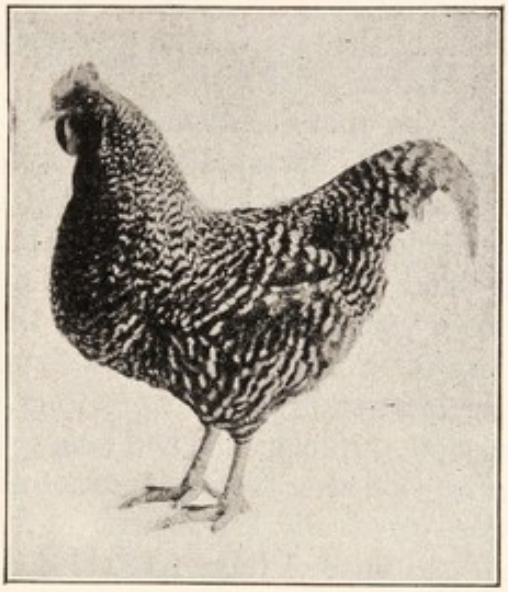

Fig. 193.—Barred rock pullet, the ovary of which was removed at 3 months and two testicles implanted on the ovarian site. Photograph 7 months later. (Lespinasse.)[5]

Note the enlargement of the head, comb, wattles, etc. : the cock plumage, spurs, and hackle.

secondary sex characters follow the gonads, the primary or fundamental sex characters (size and shape of body, spurs, the oviduct in females, voice, and certain psychological differences) are not conditioned by the gonads, but are somatic.

Amphibia.—In Amphibia cases of hermaphroditism or intersexuality are also met with and have been produced experimentally. It will be sufficient to say that they illustrate the same point, viz. that the formation of a male or

[1] Pézard, Sand, and Caridroit, *C. r. soc. biol.*, xci. 1146, 1924, and xcii. 427, 495, 1925.

[2] *Journ. Genetics*, iii. 205, 1914. Other references in Doncaster, "The Determination of Sex," 1914.

[3] *Brit. Journ. Exper. Biol.*, ii., 1925.

[4] *Ibid.*, p. 439.

[5] From Barker's *Endocrinology and Metabolism*, by permission of D. Appleton & Co. of New York, owners of the copyright.

female organism is brought about through the internal secretion of the sex glands.[1] It further appears that the chalone produced by the testicle is powerfully inhibitory of the hormone produced by the ovary, so that even a very small fragment of testicle will arrest the activity of a large mass of ovarian tissue.

Experiments on the Production of Rejuvenation by Ovarian Grafts

We have seen that by implantation of testicular substance of young animals into aged males of the same species a condition may be brought about to which the term rejuvenescence or rejuvenation has been given (p. 381). The same results ensue from cryptorchidism, from resection of the vas deferens, and from moderate X-ray treatment of the testicle. In all these cases there appears to be hypertrophy of the interstitial cells.

In the female some of the above methods are not applicable. But if the ovaries of a young animal are implanted into an aged female of the same species, or if the ovaries of an aged female are treated *in situ* with an appropriate dose of X-rays, similar results are brought about. Thus Pettinari [2] describes the case of a very old bitch with sclerosed and cystic ovaries in which he implanted an ovary from a young bitch. In a short time the character of the animal became transformed. From being completely senile, with slow movements and taking little interest in her surroundings, she became lively in disposition and movements. Although she had long ceased to show œstrus or to display sexual instincts, soon after the implantation she came on in heat, and being put to a male dog, eventually had a litter of five pups, four of which she suckled and reared. As none of these resembled the breed of the animal from which the young ovary was taken, it is concluded that the autacoids produced by this ovary caused the gonads of the aged animal to recover their ovulating function.

Pettinari also obtained rejuvenescence of an old male dog by implanting pieces of the ovary of a young bitch in the testicle and tunica vaginalis. The changes appeared about twenty days after the operation. The animal, which was previously quite feeble, became lively and was able to accompany a bicyclist on long runs : its sexual instincts were completely recovered.

Wang, Richter, and Guttmacher [3] also report increased activity in castrated male rats as the result of ovary implantations.

Similarly Steinach [4] has succeeded in rejuvenating senile female rats by ovarian transplantation. Kolb [5] produced the same result in a she-goat which had pronounced signs of senility, extreme bodily feebleness, loss of hair, and had been sterile for three years. The implantation, under the skin, of ovaries from

[1] F. A. E. Crew, *Journ. Genetics*, xi., 1921 : Harms, *Zool. Anz.*, liii., 1921 ; *Zeitschr. f. Anat. u. Entwickl.-mech.*, lxix., 1923.

[2] *Arch. ital. de biol.*, lxxiv. 57 and 62, 1924.

[3] *Amer. Journ. Physiol.*, lxxiii. 581, 1925.

[4] *Op. cit.*, 1920.

[5] *Wien. med. Wochenschr.*, 1923.

a young animal caused the animal to become lively and robust, to acquire a thick coat of hair, to increase greatly in weight, and four and a half months after the operation to come on in heat. Becoming pregnant, it gave birth in due course to a healthy kid.

Similar results of ovarian transplantation have also been described in women.[1]

The grafting of healthy ovaries or portions of ovary obtained from young subjects is therefore a possible method of treating cases of precocious menopause and senility. But careful administration of X-ray treatment will apparently produce the same effect and may be regarded as an alternative to ovarian transplantation; since this, apart from involving a considerable surgical operation, has other contra-indications against its general employment.

[1] Sippel, *Arch. f. Gyn.*, cxviii., 1923.

CHAPTER LVI

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*continued*)

Functions of the Graafian Follicles and Corpora Lutea

The Graafian Follicles.—The periodical changes which occur in the female appear to be intimately connected with the ripening Graafian follicles. It is found that œstrus can be brought on in adult females (both spayed and entire) by parenteral injection of liquor folliculi of other animals [1] (not necessarily of the same species), especially if the latter are themselves in heat. The injection causes secretion to be poured out in the Fallopian tubes and uterus, and proliferation of the vaginal epithelium. The active substance seems to be of a lipoid nature.[2] It is soluble in alcohol, ether, and acetone.[3] Further, it has been observed that cauterisation of all visible Graafian follicles shortly before the commencement of œstrus prevents this change from occurring.[4]

That œstrus is controlled by endocrine factors is indicated by cases of pyophagus twin girls who menstruate synchronously.

The corpora lutea.—The corpora lutea on the other hand inhibit ovulation and menstruation.[5] Papanicolaou [6] obtained arrest of ovulation and of œstrus

[1] E. Seaborn and Ch. Champy, *C. r. soc. biol.*, lxxxix., 1923 (liquor folliculi of mare injected into rabbits): Allen and Doisy, *Journ. Amer. Med. Assoc.*, lxxxi. 819, 1923; also in *Amer. Journ. Physiol.*, lxviii., 1924, *Amer. Journ. Anat.*, xxxiv., 1924: Doisy, Allen, Ralls, and Johnston, *Journ. Biol. Chem.*, lix., lxi., 1924: G. N. Papanicolaou, *Proc. Soc. Exper. Biol. and Med.*, xxii. 106, 1925: R. Courrier, *C. r. soc. biol.*, xc., 1924. See also L. Loeb, in *Proc. Soc. Exper. Biol. and Med.*, xx., 1922, and R. G. Hoskins, in *Endocrinology*, vii., 1923. Lacassagne et Gricouroff, *C. r. soc. biol.*, xciii. 928, 1925, also used the liquor folliculi of a mare. They injected the fluid subcutaneously into spayed female rabbits, producing characteristic signs of œstrus and acceptance of the male. From three to six injections of 2 c.c. on successive days was sufficient. Allen and Doisy used a protein-free extract prepared by admixture with alcohol and subsequent concentration. They found that the autacoid is obtainable not only from the Graafian follicles, but also from the rest of the ovary, and that it is soluble in lipoid solvents, not in water. They got a similar result from placenta extract. The effect may even be obtained by the employment of extracts from hen's ovaries (Allen, Whitsett, Hardy, and Kneibert, *Proc. Soc. Exper. Biol. and Med.*, xxi. 500, 1924).

[2] R. Courrier, *Arch. de biol.*, xxxiv. 369, 1924; Allen and Doisy, *op. cit.*, 1923; R. T. Frank and R. G. Gustavson, *Journ. Amer. Med. Ass.*, lxxxiv. 1715, 1925.

[3] Dickens, Dodds, and Wright, *Biochem. Journ.*, xix. 853, 1925.

[4] F. H. A. Marshall and W. A. Wood, *Journ. Physiol.*, lviii. 74, 1923.

[5] Beard, "The Span of Gestation," 1897. See also Prenant, *Rev. gén. des sciences*, 1898.

[6] *Op. cit.*, 1924.

in guinea-pigs by hypodermic injection of corpus luteum extracts, and W. P. Kennedy has found that injection of extracts from the corpus luteum of the cow will prevent ovulation in the rabbit.[1] Hermann [2] states that injection of the lipoids of corpus luteum (and of placenta) stops menstruation. It is said that corpora lutea are not found in the ovaries of women during menstruation.[3] Also that if a corpus luteum persists instead of disappearing, sterility results: extirpation of the corpus luteum restores fertility.[4] This operation is practised by veterinary surgeons upon cows, the corpus luteum being expressed from the ovary by the fingers introduced into the rectum. The operation if successful is followed by onset of heat.[5]

W. R. Mackenzie [6] narrates two instances of patients from whom he had occasion to remove a corpus luteum spurium. In both cases menstruation, although not due, came on within two days. He states that removal of the corpora lutea in pregnant women causes abortion.

L. Loeb found that extirpation of the corpora lutea (guinea-pig) accelerates the bursting of ripe Graafian follicles, *i.e.* facilitates ovulation.

The corpora lutea are also believed to be concerned with the final changes in the mucous membrane of the uterus which prepare it for the fixation of the embryo. It was found by Fraenkel and Cohn [7] that if the ovaries of the rabbit are removed or the corpora lutea completely destroyed by galvanic cautery shortly after ovulation and fertilisation of the ovum but before the embryo becomes fixed in the mucous membrane of the uterus, such fixation does not take place and the embryo fails to develop. If the operation is performed after fixation has occurred its development is not hindered. These experiments were repeated (in the dog and rat) by Marshall and Jolly [8] with the same result. They, however, found that destruction of all the corpora lutea by cautery in these animals is equivalent to destruction of the whole ovary. It is therefore desirable that the experiment should be repeated in animals in which there is only a single corpus luteum.

L. Loeb observed that if corpora lutea are present in the ovary, mechanical stimulation of the uterus will set up hyperplasia and decidual formation, but not otherwise. He was unable to replace the functions of the removed corpora lutea by injection of extracts.[9]

Ancel and Bouin [10] showed that there is a close parallelism between the

[1] *Quart. Journ. Exper. Physiol.*, xv., 1925. The literature is given in this paper.
[2] *Monatsschr. f. Geb. u. Gyn.*, liv. 152, 1921.
[3] E. Ramirez, *Endocrinology*, viii., 1924.
[4] Ochsner, *Surg. Gynæc. and Obstetr.*, xxxi. 496, 1920.
[5] J. Hammond, Proc. XIth Internat. Physiol. Congr., Edinburgh, 1923, in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., p. 134.
[6] *Brit. Med. Journ.*, i. 343, 1922. See also M. M. Watrin, Thèse, Liege, 1923.
[7] *Anat. Anz.*, xx., 1901.
[8] *Phil. Trans.*, B, cxcviii., 1905. Other literature in Marshall, "Physiology of Reproduction," 1922.
[9] The relation of the ovary to the uterus and mammary gland is discussed by Loeb in *Trans. Amer. Gyn. Soc.*, 1917. See also L. Loeb, *Amer. Journ. Physiol.*, xxxi., 1912–13.
[10] *C. r. soc. biol.*, lxvi., 1909. See also J. P. Hill and C. H. O'Donoghue, *Quart. Journ. Mict. Sci.*, lix., 1913 (opossum).

development of the corpus luteum and the changes which occur in the uterus, whether pregnancy occurs or not.

The general conclusion from these experiments and observations is that the corpus luteum furnishes an internal secretion which excites the changes in the mucous membrane of the uterus to prepare it for the reception of a fertilised ovum.

According to R. Schroeder [1] ovulation usually occurs in the human subject from the fourteenth to the sixteenth day after menstruation (*cf.* p. 368), and the corpus luteum which is formed prepares the uterus for the succeeding œstrus.

The corpus luteum is also believed to be, at least in part, responsible for the mammary hypertrophy which occurs during pregnancy,[2] especially in the later stages.

Ancel and Bouin state that if in a pregnant rabbit all the corpora lutea are destroyed, the evolution of the mammary gland is arrested. This operation must, however, as we have seen, involve destruction of the whole ovary in the rabbit.

In pseudo-pregnancy in the rabbit, such as follows coitus with a male with the vasa deferentia tied, there is bursting of Graafian follicles without fertilisation of the ova. Corpora lutea become developed and remain a considerable time in the ovaries. As a result œstrus is inhibited and the mammary gland undergoes development. If, however, corpora lutea fail to form, the mammary gland does not undergo development.

According to Hermann and Stein [3] injection of corpus luteum extract into male animals (rats, rabbits) causes retrogression of the sex organs.

There is no clear evidence that, when administered by the mouth, extracts of ovary or of any of the sex organs have any physiological action whatever.[4] Nevertheless, ovarian preparations are often prescribed in various forms of disorder of the generative functions in women, and many physicians believe them to have distinct therapeutic effects.[5]

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[1] *Monatsschr. f. Geb. u. Gyn.*, xxxviii., 1913.

[2] Ancel and Bouin, *C. r. soc. biol.*, lxvii., 1909; *Journ. de physiol.*, xii., 1910, and xiii., 1911: O'Donoghue, *Proc. Physiol. Soc.*, *Journ. Physiol.*, xliii., 1911, and xlvi., 1913: Hammond and Marshall, *Proc. Roy. Soc.*, B, lxxxvii., 1914: Hammond, *ibid.*, lxxxix., 1916.

[3] *Wien. klin. Wochenschr.*, xxix., 1916.

[4] *Cf.* E. P. Durrant, *Endocrinology*, ix. 221, 1925.

[5] See on this subject, W. P. Graves, "Gynecology," second edition, 1918, p. 64; L. Phillips, *Proc. Roy. Soc. Med.*, xvi., pt. iii., 110, 1923, and G. Laroche, "Opotherapie endocrinienne," ch. viii., 1925.

CHAPTER LVII

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*continued*)

Effects of Testicular Extracts

It is claimed that subcutaneous injections of orchitic extracts delay the occurrence of fatigue in the human subject.[1] On the blood-pressure and respiration, aqueous extracts and decoctions, when injected intravenously, appear to have no specific effect, although the vascular depression which is usually caused by glandular extracts is seen. This is due to cardiac inhibition.[2] Alcohol and ether extracts stimulate the vasomotor centre in the medulla oblongata and raise the blood-pressure: this effect does not occur in the spinal animal. Alcohol extracts diminish the activity of the isolated heart: ether extracts increase it. The latter also cause dilatation of capillaries (frog's web).[3]

S. Voronoff states that if testicular pulp is applied to a wound healing is greatly facilitated: no other gland substance has so striking an effect.[4]

Effect of Prostatic Extracts.—Extracts of prostate are said, when injected intravenously, to cause dilatation of the blood-vessels of the penis (dog).[5] Otherwise they have not been found to have any influence on the functions of the sex glands. Macht states that tadpoles fed with prostate in addition to their ordinary food both grow more rapidly and undergo metamorphosis sooner than controls.[6]

Korenchevsky and Carr [7] find that extract of prostate injected into rabbits and dogs causes an increase of nitrogen metabolism (up to 11 per cent.) both in entire and castrated animals.

Effects of Injecting Spermatozoa: Spermatoxins.—Although not coming, strictly speaking, under the head of internal secretion, the fact may be here recorded that the effect of subcutaneous injection of spermatozoa suspended in serum, whether from the same or from different species, into female animals is to cause sterility, which may last for some weeks after an injection.[8] The cause of the

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[1] Zoth, *Arch. f. d. ges. Physiol.*, lxii. 335, 1896; F. Pregl, *ibid.*, p. 379.
[2] W. E. Dixon, *Journ. Physiol.*, xxvi., 1901.
[3] C. Hahn, *Skand. Arch. f. Physiol.*, xlvi. 143, 1925.
[4] "Greffes du singe à l'homme," 1924, pp. 239–251.
[5] Hallion, Morel, and Papin, *C. r. soc. biol.*, lxxiv. 401, 1913.
[6] Barker's *Endocrinology and Metabolism*, ii., 1922.
[7] *Brit. Journ. Exper. Path.*, vi., 1925.
[8] K. Landsteiner, *Zentralbl. f. Bakt.*, xxv. 546, 1899; E. Metchnikoff, *Ann. de l'instit. Pasteur*, xiv., 1900; R. Dittler, *Zeitschr. f. Biol.*, lxxii., 1920; M. F. Guyer, *Journ. Exper. Zool.*, xxxv., 1922; J. L. M'Cartney, *Amer. Journ. Physiol.*, lxvi., 1923; W. P. Kennedy, *Quart. Journ. Exper. Physiol.*, xiv., 1924.

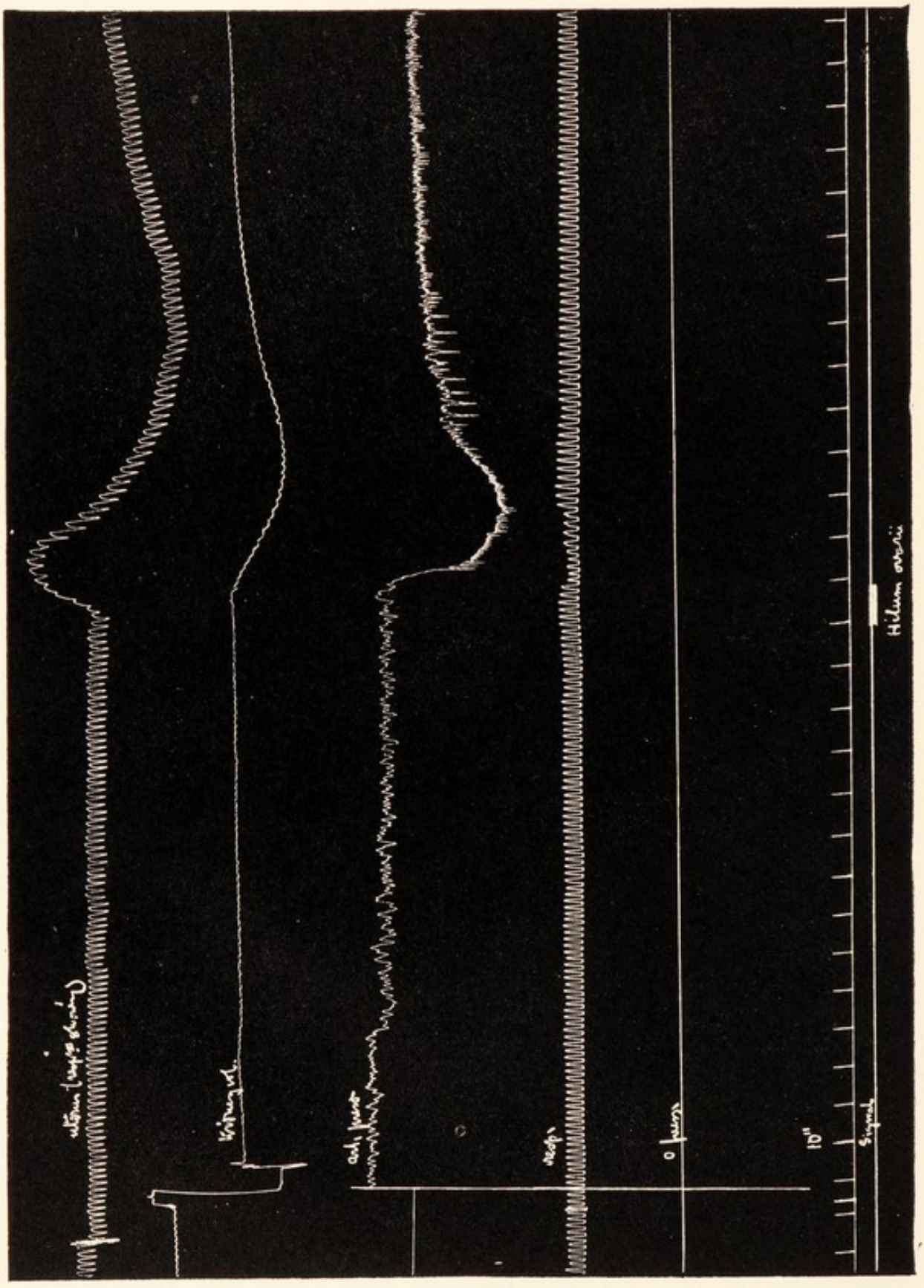

FIG. 194.—Effect of intravenous injection of extract of hilum ovarii on uterus, kidney volume, blood-pressure, and respiration (cat). (Itagaki.)
The small waves on the uterus tracing are respiratory.

sterility seems to be the development of anti-bodies, which appear both in the blood and in the female passages. Similar anti-bodies are produced in the blood in males also as the result of such an injection even if the spermatozoa are from the same individual. It is said that the anti-bodies are also present in the blood after ligature of the vas deferens. These anti-bodies have the effect of producing immobility of spermatozoa, and this is probably the actual cause of the sterility. The œstrous cycle is not affected. Hens thus injected continue to lay eggs as before, but they are always unfertile.

Effects of Extracts of Ovary

Extracts of ovary have a direct influence upon the contractions of the muscular tissue of the uterus and of certain other kinds of plain muscular tissue.[1] Some of these effects are illustrated by the accompanying tracings.

The methods employed to obtain the tracings were (1) injection of an extract into the circulation, and the recording the effect upon the uterus and at the same time upon the blood-pressure, respiration, etc. ; (2) immersion of a length of uterine cornu, or of a strip of uterine muscle, in warmed and oxygenated Locke-Ringer solution, the solution being replaced for a short period of time by the extract to be investigated, which is itself made with the same solution. The extracts were made separately from *corpora lutea*, *Graafian follicles*, *liquor folliculi*, and *hilum ovarii* (*i.e.* stroma without corpora lutea or Graafian follicles, but presumably containing interstitial cells), and always by boiling the tissue, either fresh or dried, with Locke-Ringer (without glucose). Occasionally the dessicated tissue was extracted first with chloroform and then with absolute alcohol ; these extracts were evaporated down and the dry residue extracted with Locke-Ringer ; the remainder of the gland which was left after the chloroform and alcohol had acted upon it being also extracted with Locke-Ringer.

The ovaries of the sheep and cow were used for preparing the extracts : the testing was performed on the tissues of the rat, guinea-pig, rabbit, cat, and dog.

Action on Uterus in situ

A striking effect on the uterus *in situ* is obtained with *extract of hilum* (stroma and interstitial cells). This causes diminution of tone of the uterine muscle, which may be preceded by an increase (fig. 194). Accompanying this change there is a considerable fall in blood-pressure, even in atropinised animals, a diminution in the extent of respiration, and a diminution in volume of such an organ as the kidney.

Diluted with Locke-Ringer (15 parts to 85) the *liquor folliculi* has a very marked effect in depressing blood-pressure (cat) : the effect appears to be due to vagus stimulation, although vaso-dilatation may assist (fig. 195).

Corpus luteum extract injected into the veins causes the uterus, if quiescent, to begin contracting ; if already contracting, to increase its contractions and

[1] M. Itagaki, *Quart. Journ. Exper. Physiol.*, xi. 1–46, 1917.

to assume a more pronounced tone. Little or no effect on blood-pressure or kidney volume is produced by this extract.

Extracts of whole ovary resemble liquor folliculi in causing marked depression of blood-pressure ; the effect is mainly due to dilatation of vessels.

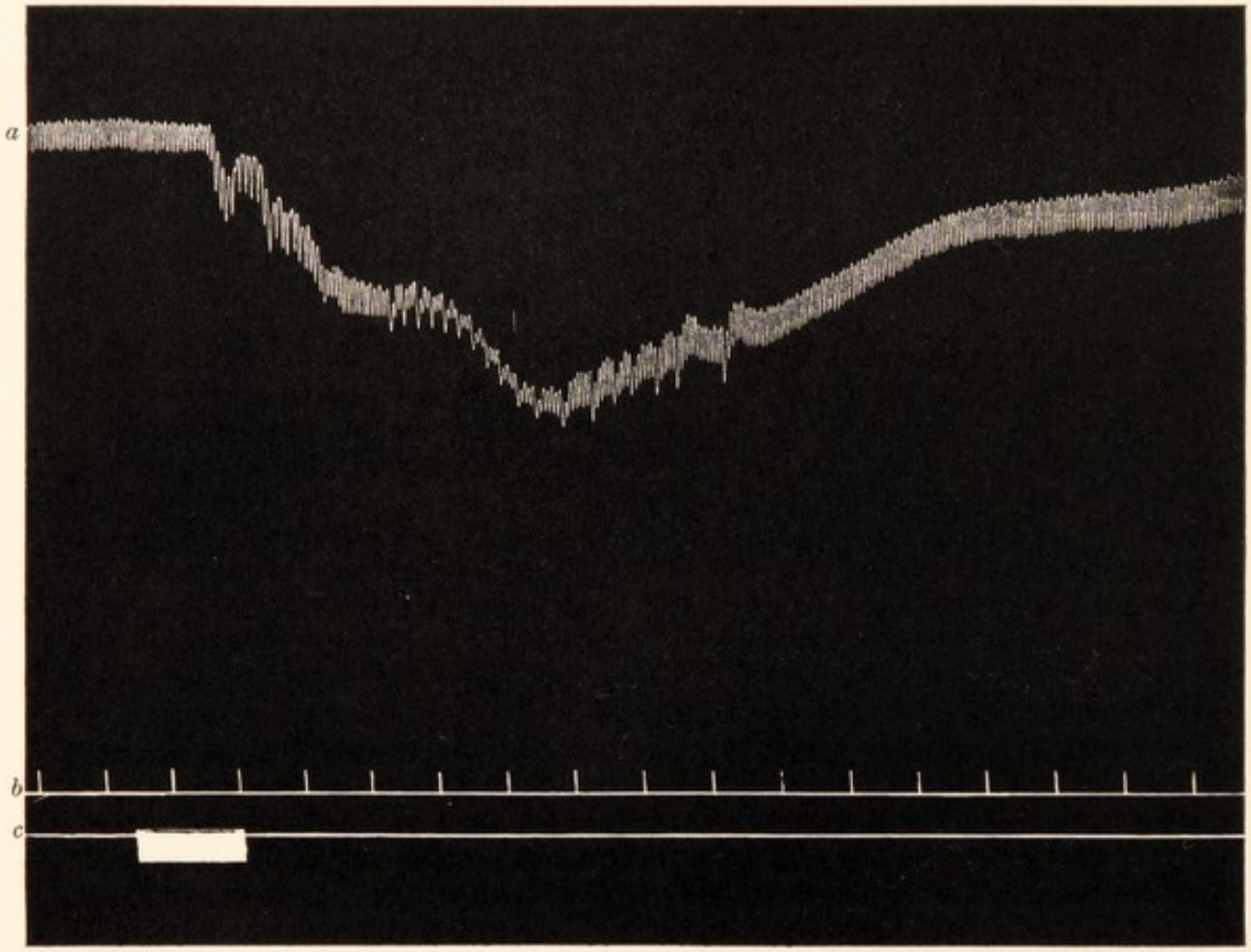

FIG. 195.—Effect on blood-pressure of cat of an intravenous injection of 1 c.c. of liquor folliculi of cow, diluted with Locke. (Itagaki.)

a, blood-pressure tracing ; *b*, time in 10-second intervals : *c*, signal.

Action on Isolated Uterus

The experiments on this were made by a modification of Magnus' method for studying the contraction of strips of the plain muscle of the intestine. A piece of uterine muscle, or of cornu uteri, is placed in a glass tube of the dimensions shown in the accompanying figure (fig. 196). One end is fixed to a hook of gold wire at the bottom of the tube ; the other end is attached by a thread to a myograph lever. The tube is immersed in a large beaker of water kept at a constant temperature, and is fed very slowly through the tube attached to the lower end with Locke-Ringer from a Mariotte flask. This fluid is brought to the same temperature as the water by being allowed to pass through a spiral glass coil within the water-bath. The fluid overflows by the upper side

tube and is led away. The ordinary Locke-Ringer can be replaced at any given time by the same fluid containing a known percentage of the extract to be tested: this also passes through the spiral tube so that it arrives at the tissue warmed to the temperature required. The replacement can be effected without emptying the tube or mechanically displacing the myograph lever, and the temperature undergoes no alteration in changing the fluid. The records are of the contraction of the longitudinal fibres. The preparations usually show (1) rhythmic contractions and relaxations, (2) alterations in the general condition of contraction or "tone" of the tissue. Most of the experiments were made upon the uterus of the white rat.

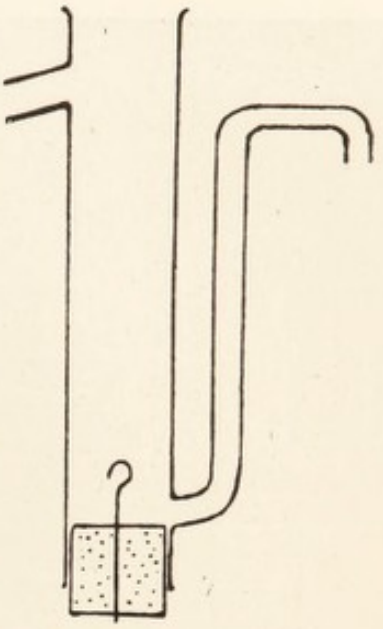

Fig. 196.—Diagram of experimental tube for immersion of uterus or other excised tissue in Ringer's solution, and for replacement of this by the same solution containing organ extracts.

Extracts of Hilum Ovarii.—These are made from the part of the ovary nearest the hilum, free from corpora lutea or obvious Graafian follicles, but presumably containing interstitial cells as well as stroma cells. The usual effect on the rat uterus is to produce marked inhibition (fig. 197) with or without general diminution of tone: only very occasionally is there increase of tone. But the effect in cat and rabbit is usually to cause an increase both of rate of rhythm and of tone.

Liquor Folliculi.—The effect of this upon the rat's uterus is to produce a great increase of tone with cessation of the rhythmic movements

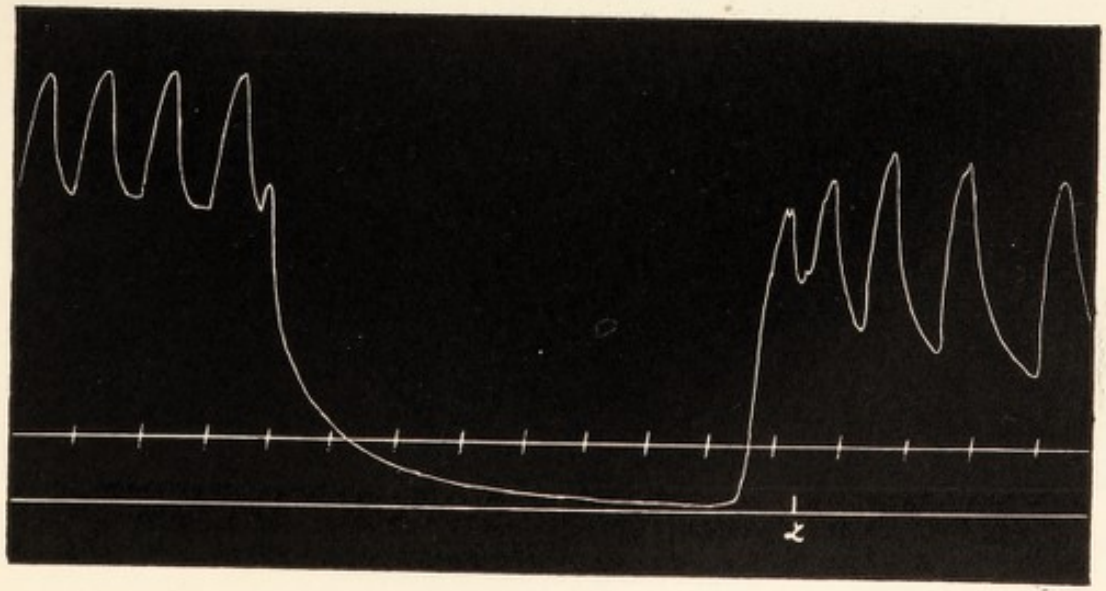

Fig. 197.—Effect of addition of extract of hilum ovarii of cow to Locke's solution in which a cornu of uterus of rat was suspended. (Itagaki.)

Notice the cessation of rhythmic contractions and diminution of tone.

(fig. 198) : the latter effect lasts some little time after the replacement of the extract by normal Locke-Ringer, although the increase of tone disappears

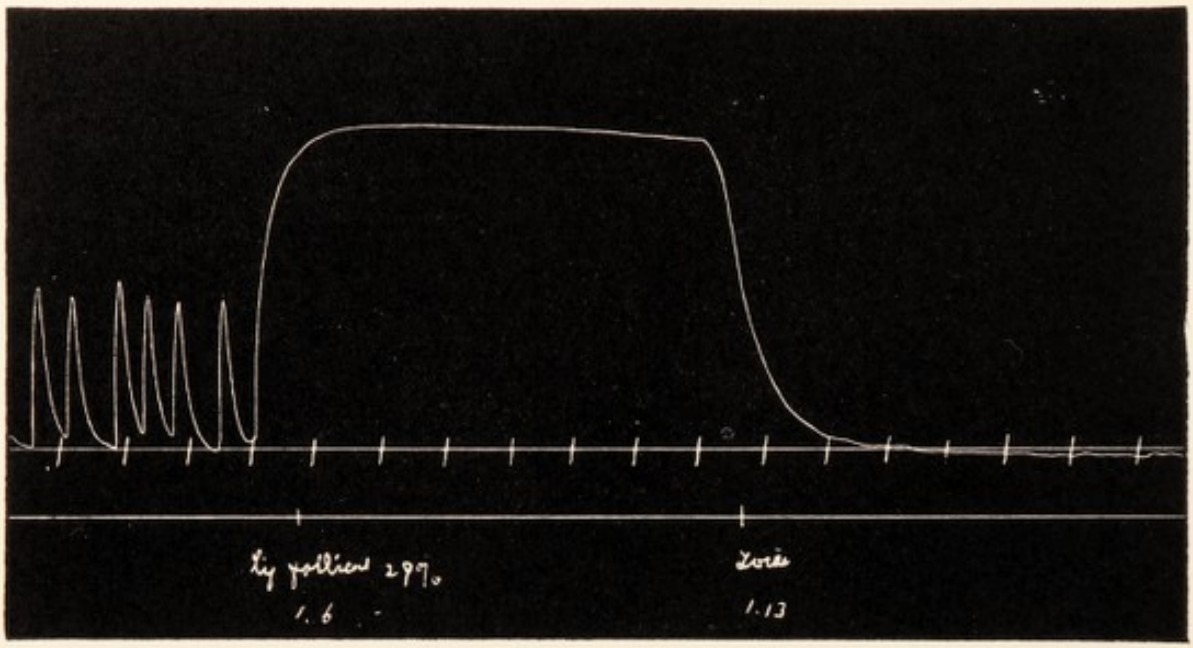

FIG. 198.—Effect of addition of liquor folliculi of cow to Locke's solution in which a cornu of rat uterus was suspended. (Itagaki.)

Notice the increase of tone with cessation of rhythmic movements. At "Locke" the liquor folliculi was removed and Locke's solution substituted.

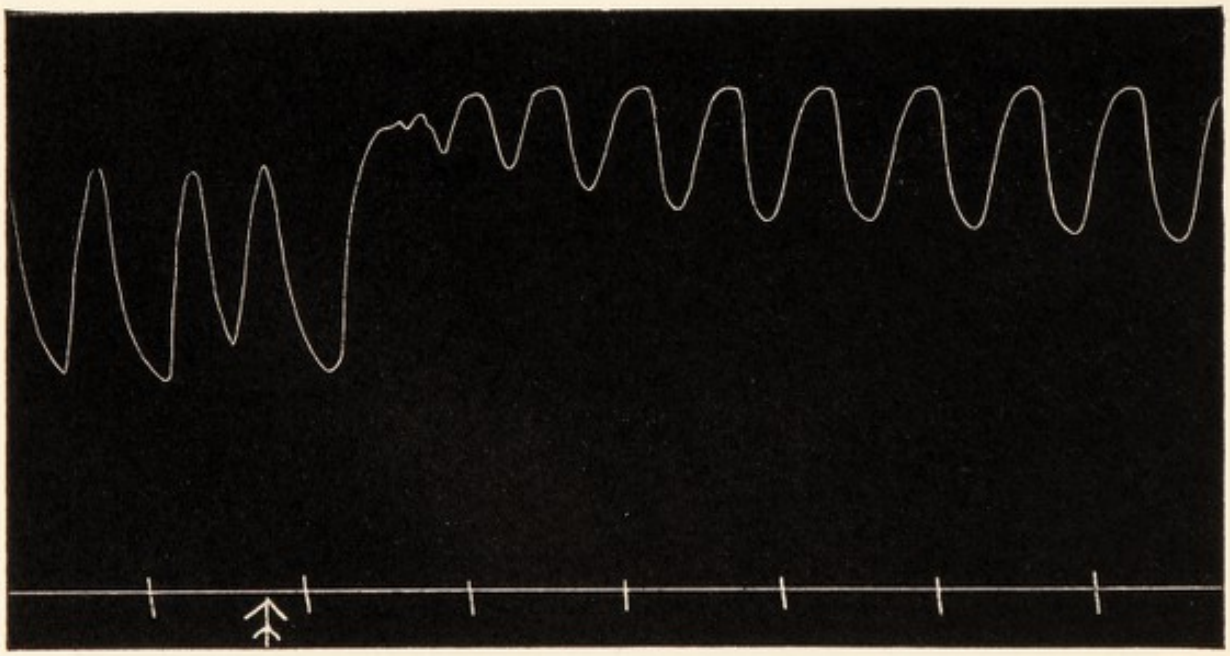

FIG. 199.—Effect of extract of corpus luteum of cow on isolated cornu uteri of rat. (Itagaki.)

Marked increase of tone is produced.

immediately. The effect on the isolated uterus of the rabbit is also to cause an increase of tone but without abolition of the rhythmic movements.

Extracts of Corpus Luteum.—Itagaki found that extracts of corpus luteum produce a distinct increase of tone and increased rate of the rhythmic contractions in the surviving uterus (fig. 199) in nearly all animals examined (rat, rabbit, guinea-pig, cat, dog). Rarely (in seven cases out of sixty-seven) the opposite effect (inhibition) was obtained, but was often followed by increased rate (fig. 200). As a rule the stimulating effect is stronger in extracts made from large than from small corpora lutea. The condition of pregnancy of the uterus made no difference to the result. The condition of pregnancy or non-pregnancy in the animals (sheep) from which the ovaries were taken also made no difference.

Extracts of Young Ovaries, containing neither large Graafian Follicles nor obvious Corpora Lutea.—Itagaki found these extracts to produce inhibition of tone and of rhythmic movements of the rat's uterus and increase in the rabbit's uterus.

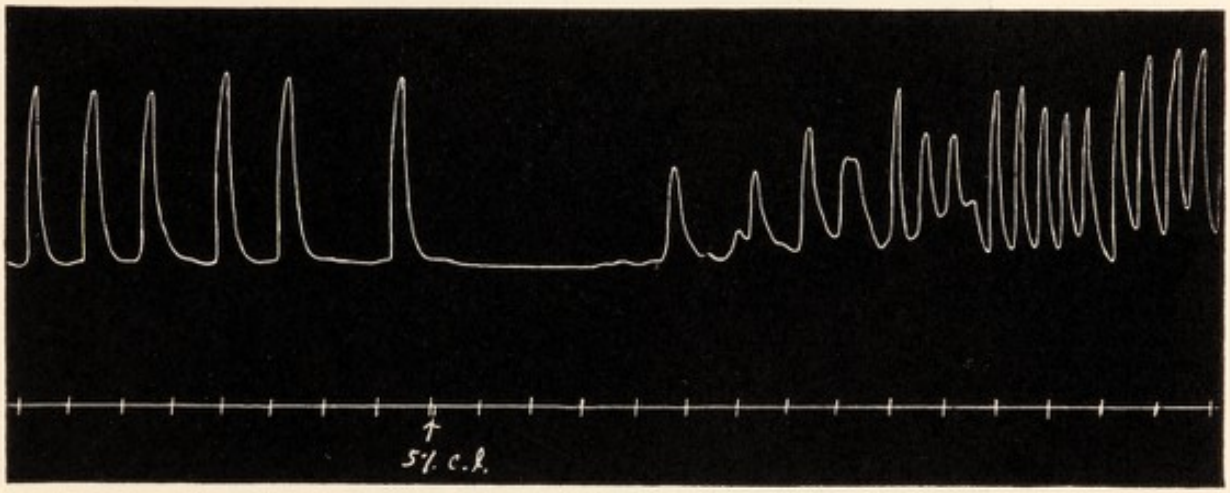

Fig. 200.—Effect of extract of corpus luteum of cow on isolated cornu uteri of rabbit. Inhibition, followed by increased rapidity of rhythm, is produced. (Itagaki.)

Attempts to separate the hormonic and chalonic autacoids by extraction with alcohol showed that the stimulating principle is insoluble in alcohol and lipoid solvents, whereas the inhibitory principle, which is usually small in amount, goes into solution in alcohol. If this alcoholic solution is dried and extracted with Locke-Ringer the resulting extract causes inhibition, whilst the residue left after extraction with alcohol, if dissolved in Locke-Ringer, causes increased contraction.[1]

Galactagogue Action

If an extract of corpus luteum is injected into the vessels of a lactating mammal a free flow of milk is caused,[2] provided the nipple is incised or

[1] An acetone extract is described by D. L. Seckinger (*Amer. Journ. Physiol.*, lxx., 1924) as having a specific action also on the Fallopian tube, increasing both the rate of rhythm and tone of its contractions. Wallis and Williams have obtained from alcohol extracts of corpus luteum a toxic substance which produces, when injected into animals, pathological changes like those seen in toxæmias of pregnancy (*Lancet*, i. 784, 1922).

[2] Ott and Scott, *Proc. Soc. Exper. Biol. and Med.*, viii., 1910 ; Schafer and Mackenzie, *Proc. Roy. Soc.*, B, lxxxiv., 1911 ; K. Mackenzie, *Quart. Journ. Exper. Physiol.*, iv., 1911. Ott and Scott state that they obtained marked development of the mammary glands

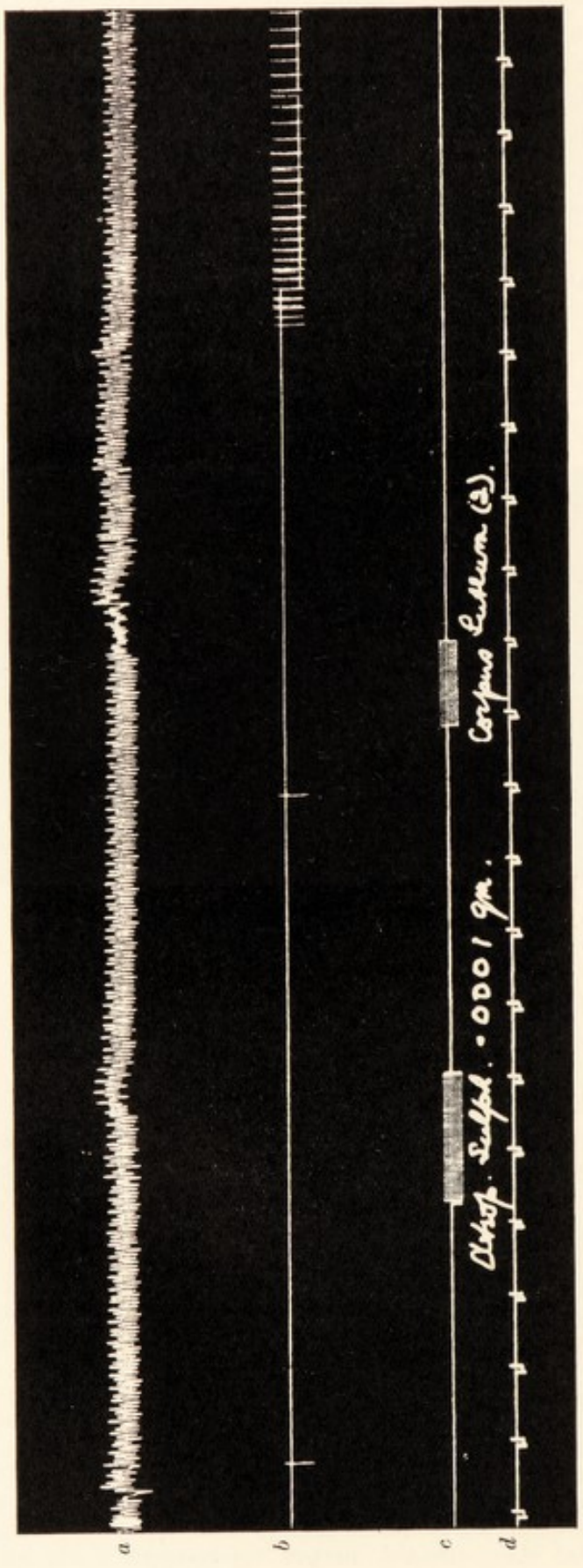

FIG. 201.—Effect of extract of corpus luteum of cow on mammary secretion in lactating cat. (K. Mackenzie.)

a, blood-pressure; *b*, drops of milk fed from an incision in gland; *c*, signal and abscissa of blood-pressure; *d*, time in ten seconds. An injection of atropine sulphate was given one minute before the corpus luteum extract. As will be seen, it failed to arrest the action of the extract.

cannulated. The action is similar to that produced by extract of posterior lobe of pituitary (see p. 233). The effect is obtained even if atropine is administered immediately before (fig. 201). The action was found by Mackenzie to be absent in extracts made from ovaries without corpora lutea.

Action on Intestinal Muscle, on Iris, and on Vas Deferens

The action upon separated strips of intestinal muscle (longitudinal and circular) of liquor folliculi is to cause increase of tone and of the pendulum movements, of corpus luteum extract to produce inhibition of the pendulum movements and loss of tone: this effect is also obtained with strips from the rabbit's bladder.

Macht and Matsumoto find that extracts of corpus luteum cause dilatation of the pupil in the excised eye of the frog: extracts from the rest of the ovary have no such effect. They also obtained stimulation of the vas deferens and seminal vesicles.[1] Itagaki, however, obtained no effect on the frog-iris, and Kennedy none on the vas deferens.

The general conclusion to be drawn from these experiments is that the extracts contain two autacoids of opposite sign—one hormonic and the other chalonic: the effect of the one or other predominating according to the nature of the extract, the part of the ovary used, and perhaps also according to the physiological condition of the tissue investigated.[2]

Extracts of Uterus, Mammary Gland, Placenta

Uterus.—There is some evidence that in certain states the uterus itself may yield an internal secretion. Bouin and Ancel[3] have described an epithelium-like formation in the muscular coat of the uterus of the rabbit and guinea-pig during the latter half of pregnancy which they consider to be related to the development of the mammary glands during the final period of gestation and the production of milk. To this formation they have given the name of *glande myométricale endocrine*. K. Mackenzie[4] found that extracts from the involuting uterus of the cat shortly after parturition cause a free flow of milk from the incised nipple of lactating animals (fig. 202). He obtained no such results from the uterus at other times. He infers, therefore, that it contains a galactagogue hormone only at this period. Blair Bell has suggested that menstruation and ovulation depend on an internal secretion from the uterus, and C. J. Bond has described experiments which appeared to indicate that an internal secretion from the uterus promotes the growth

and even secretion of milk in young virgin rabbits injected subcutaneously at frequent intervals during a month with corpus luteum extract. Frank and Unger (*Arch. intern. Med.*, 1911) failed to confirm this.

[1] *Endocrinology*, iii. 154, 1919; *Proc. Soc. Exper. Biol. and Med.*, xvi., 1919.

[2] *Cf.* C. Bru, *Rév. méd. de l'est*, lii., 1924.

[3] *C. r. assoc. anat.*, xiii., 1911.

[4] *Quart. Journ. Exper. Physiol.*, iv., 1911.

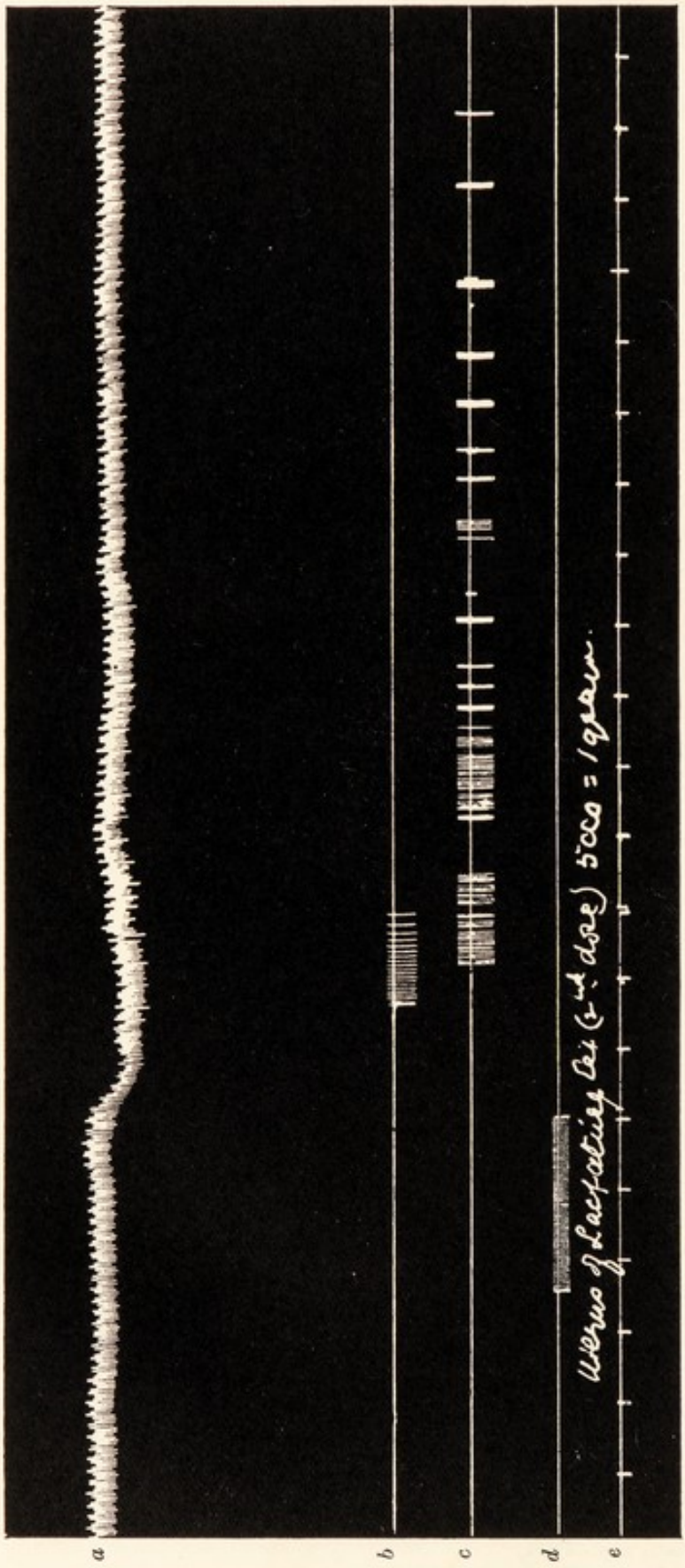

FIG. 202.—Effect of extract of involuting uterus of cat on mammary secretion in lactating cat. (K. Mackenzie.)
a, blood-pressure tracing; *b*, drops from a cannula inserted into nipple; *c*, drops led off from an incision into gland; *d*, signal and abscissa of blood-pressure; *e*, time in ten seconds.

of the corpus luteum.[1] But these views find no support in the experiments of Carmichael and Marshall,[2] who obtained typical development of the ovaries, with ovulation and formation of corpora lutea, in animals (young rabbits and adult rats) from which the uterus had been completely removed.

Mammary Gland.—A galactagogue effect was obtained by Mackenzie as the result of intravenous injection of extract of lactating mammary gland (fig. 203): no result was obtained from the gland of non-lactating animals.

L. Adler[3] found subcutaneous injection of extract of mammary gland to produce enlargement of the suprarenals and increase of adrenaline in the blood, sometimes sufficient to cause glycosuria. He also found it to arrest the development of the embryo, and even to produce abortion in pregnant animals.

Placenta.—Dixon and Taylor have described a blood-pressure raising effect obtained from placenta extract, which they state may be as much as that caused by adrenaline.[4]

Lederer and Pribram[5] state that placental extract has a galactagogue effect. Aschner and Grigoriu[6] found that injection of placental extract into virgin guinea-pigs caused development of mammary glands and secretion of milk. Iscovesco[7] and Herrmann[8] obtained a lipoid from placenta which when injected into virgin animals caused œstrous changes in the whole genital tract. This result has been obtained by others.[9] On the other hand, F. S. Hammett[10] found that feeding with placenta does not affect the growth of the breasts or the amount or quality of the milk. Nevertheless the rate of growth of breast-fed infants was found to be greater when the mothers were fed with dry placenta.

Ludwig states that extracts of placenta cause powerful contractions of plain muscle in general.[11]

Halban suggested that the placenta furnishes the stimulus for the development and growth of the mammary glands, whilst inhibiting the pouring out of their secretion.[12] That the placenta does not form the only stimulus to the growth of the mammæ is indicated by the fact that these glands may become developed and secrete milk in exceptional cases in the virgin, and even in the male sex.[13] The second suggestion has received some support from the

[1] *Journ. Physiol.*, xxii., 1908.
[2] *Proc. Roy. Soc.*, B, lxxix., 1907.
[3] *Monatsschr. f. Geb. u. Gyn.*, xxxvi., 1912.
[4] Proc. VIIth Internat. Physiol. Congress, Heidelberg, 1907.
[5] *Arch. f. d. ges. Physiol.*, cxxxiv., 1910. See also E. M. Pueyrredón, *Arch. Latino-Amer. d. Pediatrice*, xix. 802, 1925.
[6] *Arch. f. Gyn.*, xciv., 1911.
[7] *C. r. soc. biol.*, lxxiii., 1912.
[8] *Monatsschr. f. Geb. u. Gyn.*, xli. 1, 1915.
[9] Giesy, Thesis, Columbia Univ., 1920; Fraenkel and Fonda, *Biochem. Zeitschr.*, cxli., 1923.
[10] *Journ. Biol. Chem.*, xxix. 381, 1917, and xxxvi. 569, 1918. See also *Endocrinology*, iii. 307, 1919.
[11] *Monatsschr. f. Geb. u. Gyn.*, l. 256, 1919.
[12] *Zeitschr. f. Geb. u. Gyn.*, liii., 1904.
[13] This remark is also applicable to the fœtal and to the corpus luteum theories of mammary development.

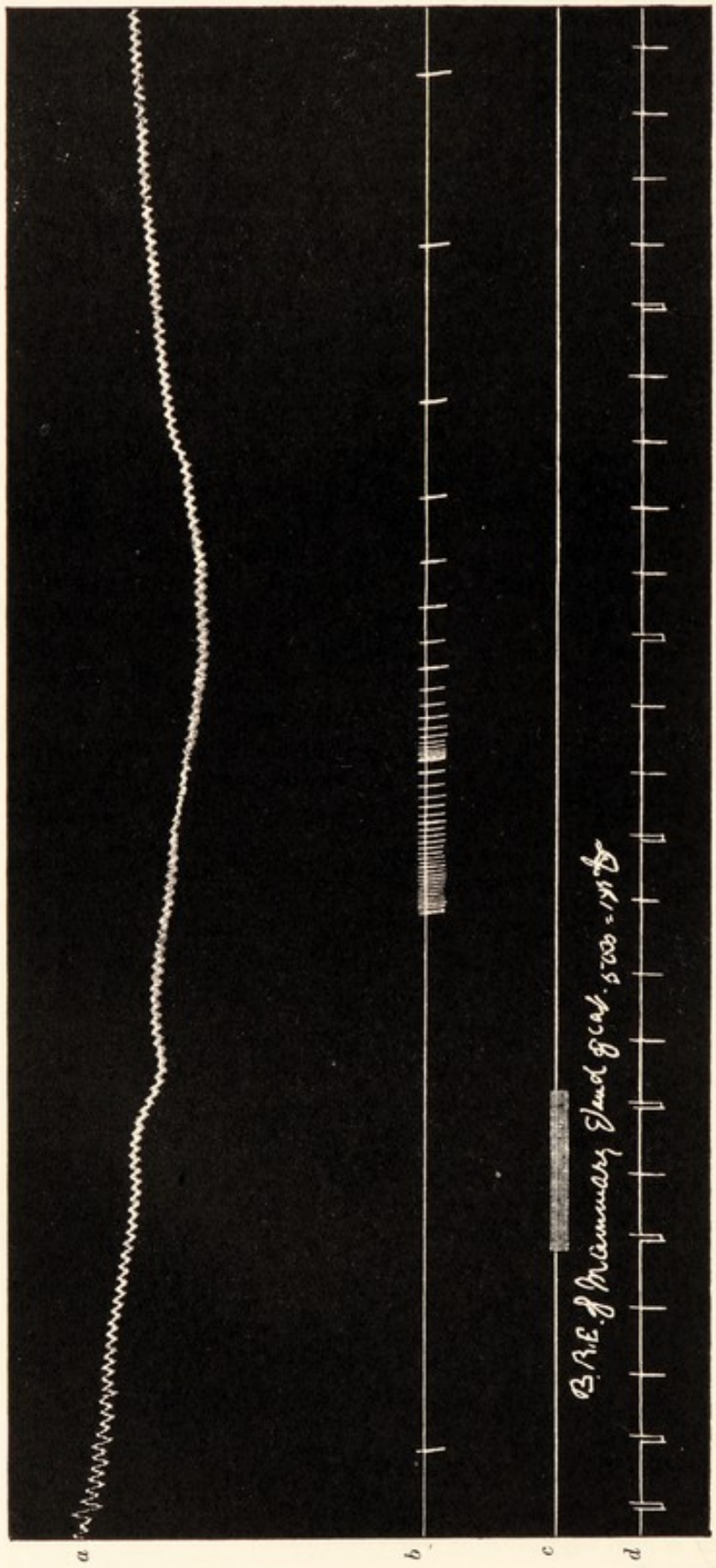

FIG. 203.—Effect of extract of active mammary gland on milk flow in lactating cat. (K. Mackenzie.)

a, blood-pressure tracing; *b*, record of milk drops from incision in gland; *c*, signal and abscissa of blood-pressure; *d*, time in ten seconds.

experiments of Mackenzie,[1] who found that injection of placental extract tends to inhibit the effect of such galactagogue extracts as pituitary or corpus luteum. A similar result was obtained by Mackenzie with extract of fœtus, which has been described (by Starling and Lane-Claypon and by Foà) as promoting mammary development. It would seem, therefore, that both placenta and fœtus produce autacoids which favour the growth of the mammary gland but have an inhibitory effect on milk secretion. As a commentary on this, it may be noted that secretion by the mammary gland does not begin until the removal of any influence which might be derived from placenta or fœtus.[2]

While it is well recognised that the development of the mammary glands is normally dependent on influences affecting them from the uterus and probably also the ovaries, it is also the case that the active secretion of the glands influences the ovaries and the uterus, both of which tend to exhibit signs of atrophy during lactation.[3]

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[1] *Op. cit.*, 1911.

[2] It is certain that the development of the mammary glands is dependent on internal secretions, for the glands will undergo evolution and secrete milk if entirely cut off from their nervous connexions or even if the lumbo-sacral cord (in the bitch) is extirpated (Goltz and Ewald, *Arch. f. d. ges. Physiol.*, lxiii., 1896).

[3] J. Hammond, *Proc. Roy. Soc.*, B, lxxxix. 534, 1917; and Hammond and Marshall, Trans. XIth Internat. Physiol. Congress, in *Quart. Journ. Exper. Physiol.*, Suppl. Vol., 1923.

CHAPTER LVIII

THE INTERNAL SECRETIONS OF THE SEX GLANDS (*concluded*)

Relation of the Sex Glands to Other Endocrine Organs

This subject has been considered in the description of the several organs already dealt with, but certain additional facts may be mentioned here.

Many endocrine organs are modified as the result of castration both in the male and female; it is probable that at least some of the changes which are produced by the operation are the indirect result of these modifications. Further, injury or disease, or extirpation, or stimulation of certain of the endocrine organs (thyroid, cortex of suprarenals, pituitary, pineal) are found to affect the development and functions of the sex organs.

Thyroid.—The effect of thyroid feeding in producing changes in secondary sex characters was studied by Torrey and Horning,[1] who found that hen-feathering in cockerels is induced by thyroid feeding, but not in castrated animals: the harmozone seems therefore to act through the testicles. No effect was got by feeding pullets with thyroid. Although F. A. E. Crew and J. Huxley [2] failed to confirm these observations, Cole and Reid [3] got positive results on adult birds with thyroid feeding: they found in the cock that feathers, formed to replace some that had been pulled out, tended to approach the female type in shape, structure, and coloration.

Suprarenals.—Lespinasse [4] narrates an experiment in which he transplanted suprarenal capsules into a cockerel with the result of producing precocious sexual development.

Bernard has described a hen which developed a cock-like comb and spurs, although the plumage remained feminine: the ovary contained ova. The change was correlated with the formation of a tumour of the suprarenal.

The fact that tumours of the suprarenal cortex are frequently associated with precocious sexual development of masculine type (both in males and females) has already been alluded to. According to Krabbe [5] this is probably connected with the fact that the primitive ovary is fundamentally bisexual [6] and that the part of the germinal epithelium, which may develop into

[1] *Proc. Soc. Exper. Biol. and Med.*, xix., 1922. See also Torrey, Beal, and Horning, *Biol. Bull.*, xlix. 237, 1925, and Torrey and Horning, *ibid.*, 365.

[2] *Veterin. Journ.*, lxxix., 1923.

[3] *Journ. Agric. Res.*, xxix., 1924.

[4] Barker's *Endocrinology and Metabolism*, ii., 1922.

[5] *New York Med. Journ.*, 1921, p. 114.

[6] See A. Kohn, *Arch. f. Entwickl.-mech.*, xlvii., 1920.

the seminiferous and interstitial tissue of the testis, lies in the embryo in close proximity to the cells which form the suprarenal cortex and is liable to be included with them.

There is evidence that enlargement of the suprarenal cortex runs parallel with the development of sex characters and instincts. In animals like the mole, which undergo seasonal changes in the gonads, the suprarenal capsules (cortex)

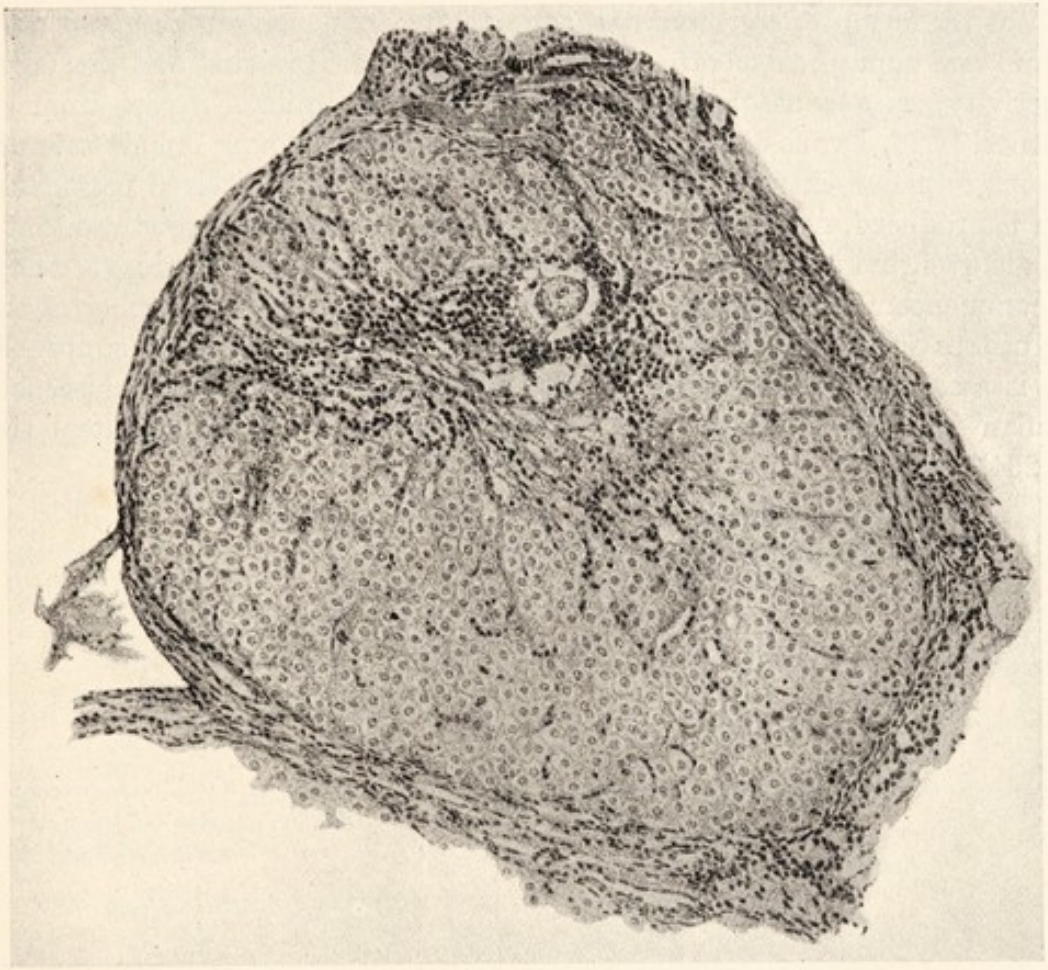

FIG. 204.—A corpus luteum produced from an unruptured Graafian follicle as the result of parenteral administration of extract of anterior lobe of ox-pituitary. (H. M. Evans.)

Notice the retained ovum.

become hypertrophied when the testicles are becoming enlarged.[1] On the other hand, Jaffe and Marine found no change in the testicles of male rabbits in which they had performed adrenalectomy. They obtained, however, marked ovarian enlargement (affecting chiefly the interstitial cells) in female rabbits, similarly operated on, which survived the operation more than thirty days.[2]

W. Kichikawa [3] found, in rats, that the secondary sex changes which result from castration and from implantation of ovaries and testicles show

[1] A. Watson, *Journ. Physiol.*, lviii., 1923.
[2] *Journ. Exper. Med.*, xxxviii., 1923.
[3] *Biochem. Zeitschr.*, clxiii. 176, 1925.

themselves sooner in animals from which the suprarenals have been removed than in controls.

Pancreas.—The alcohol-soluble extractive obtained from the ovary is stated to inhibit the hypoglycæmic action of insulin.[1]

Pituitary.—The influence of this gland upon the development of the sex organs is striking; it is shown by the effects both of removal or injury and of disease. These effects have already been described. It is possible that some of the results may have been due to the influence of the gland on the thyroid and suprarenals, both of which are diminished in size, and presumably in activity, as a consequence of such removal or injury. Apart from such evidence, H. M. Evans and Long [2] have shown that in young female rats, if an aqueous or saline extract of bovine anterior lobe is administered parenterally, there is produced, not only acceleration and increase of body growth so that the animals eventually become abnormally large, but, along with this, a delay in the commencement of œstrus, and a great diminution in the number of times that œstrus will recur, proceeding even to the point of complete suppression. This is associated with the formation of corpora lutea without dehiscence of Graafian follicles, the ova being retained within the mass of luteal tissue (fig. 204).

[1] Dickens, Dodds, and Wright, *op. cit.*, 1925.
[2] *Anat. Rec.*, xxi. 62, 1921.

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- p. 177 line 8 for 1917 read 1907
- 179. Description of fig 88 line 3 should read "of epithelium of parastigmatic"
- 227 Description of fig 122 B line 5: "fig 121" should read "fig 122 A"
267 footnote 2 after "shown" add "to the present".
268 line 2 from bottom - omit "the use of"
269 line 28 - "produces" should be "produce".
- 219 Description of fig 119, line 7 "0.2" should be "0.02" and "agotanine chloride" should read "organic phosphate".
310 line 22 "glycaemia" should read "hyperglycaemia".
314 line 2 insert after "generative cells" "usually".
316 line 9 from bottom "glycaemia" should read "hyperglycaemia"
- 222 footnote 1. "Arch. internat. Med" should read "Arch. Int. Med".
357 letter "Maranon" should be "Marañón".
384 l. 17 insert comma after "diabetes"
- 238 l. 4 "hypothesis" should be "hypophysis"