THE PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY

BY
H. B. VAN DYKE

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FOREWORD

THE writing of a monograph of significant value to clinicians and to investigators on the physiology, pharmacology, and functional pathology of the pituitary gland is, today, a herculean undertaking, for the assiduous applications of surgical, biochemical, and physiological investigative methods to this gland, especially during the last fifteen years, have revealed an organ of exceptional importance and complexity. The pituitary-gland literature is very voluminous and, at the periphery, conflicting. The author, himself an active and successful worker on some phases of the pituitary-gland problem, has filtered some five thousand of these research reports through his critical mind. The result, I believe, is clearly on the credit side, in scope, brevity, fairness, and sound conclusions.

Through its chemical messengers, or hormones, the pituitary gland appears to touch nearly all the physiological processes of the vertebrate organism, some more profoundly than others. The growth processes, the ovarian and testes activities, seem most completely under pituitary-hormone control. The rest of the endocrine system and the processes of metabolism are less profoundly affected, while the nervous system is the least influenced, according to the present information. But many of the pituitary-gland products, fractionated by modern biochemical methods, and demonstrated to have physiological or pharmacological actions, have not yet been shown to be true pituitary-gland hormones—that is, to be secreted into the body fluids by this gland in health or disease. That various physical and chemical agents applied to the dead or dying hypophysis may develop specific chemical en-

tities never secreted as such by the living gland is now recognized by most investigators. But, despite the relative crudity of many present biologic methods, the investigator is daily encouraged by the growing body of new and reliable information, rechecked by different workers and by diverse methods. The least encouraging situation today is the clinical application of the experimental findings in the pituitary field. These findings have improved our diagnosis of pituitary disorders in man, but have added little to their control. At least we have not scored a success in the pituitary therapy comparable to that in thyroid, pancreas, and parathyroid disorders. This may be due, in part at least, to the very complexity of the pituitary-hormone relationships. Since none of the hypophysis hormones seems to be significantly active via the oral route, greater success in the therapeutic field is dependent on the quantity production of more pure preparations for parenteral use.

In addition to the ever present challenge of human pituitary therapy, the phylogeny of the pituitary-gland functions is another field of interest as yet inadequately explored. The processes, or factors of growth, metabolism, gonad activity, etc., are common to all the vertebrates. But the hypophysis appears chemically to influence such diverse organs as the mammary gland, the crop glands (present in some birds), the uterus, the chromophores, etc.—organs not present in all vertebrate groups. While we have many instances of the chronologic appearance of hormones so related to processes or structures on which they seem to have specific action as to suggest, at least in some cases, an actual causal relationship, the appearance of "estrogenic" substances in plants, the appearance of CO_2 as a cell product many millions of years in advance of the development of the respiratory center, the as yet questionable hormone status of epinephrine, seem to suggest the reverse process as a factor in evolution—that is,

waste or indifferent cell products, in the course of time assuming hormone significance when additional factors have led to the development of structures or processes where specific "lock and key" relationships obtain.

A. J. CARLSON

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July, 1936

PREFACE

THIS book represents an attempt to describe and evaluate the scientific foundations of our knowledge of the pituitary body in terms of physiology, pharmacology, and their related sciences. Like others interested in this remarkable organ, I am fully aware of the fact that any account of the functions of the pituitary body must plainly show how great is the deficiency of our knowledge. Nevertheless, because of the tremendous amount of work which has been reported, particularly during the past decade, there is great need for a complete and critical restatement of what is known or has been published.

I have attempted to give an adequately documented account of the experimental work on the pituitary body during the past fifteen years (up to and including part of 1935). Clinical observations, in so far as they appear to contribute to knowledge of the functions of the pituitary body, are also discussed. In addition, I have included a discussion of the gonadotropic substances associated with pregnancy and with the growth of certain neoplasms, although it is doubtful whether these substances are actually secreted by the pars glandularis. More than five thousand reports have been consulted; about three thousand of these—many of which must still be considered of doubtful importance—are cited in the Bibliography. To limit the book to a reasonable size, I have found it necessary to condense the subject matter as greatly as possible. However, I believe that references to all phases of the physiological literature are reasonably complete.

I am greatly indebted to the following authors for permission to reproduce illustrations or data: Professor W. J.

Atwell (Fig. 2), Dr. H. H. Cole (Fig. 42), Professor E. T. Engle (Fig. 36), Professor H. M. Evans (Figs. 25–27), Dr. M. S. Gilbert (Fig. 1), Professor C. M. Gruber (Fig. 54), Professor Leo Loeb (Fig. 49), Professor C. R. Moore (Fig. 37), Dr. A. S. Parkes (Figs. 33 and 41), Professor A. T. Rasmussen (Fig. 6), Professor P. E. Smith (Figs. 24, 38, 39, and 45), and Dr. J. M. Wolfe (Fig. 10 and data of Table IV).

I wish also gratefully to acknowledge the permission of the Anatomical Society of Great Britain and Ireland to reproduce Figure 4, which was first published in the *Journal of Anatomy*. To the Verlagsbuchhandlung Julius Springer, I am under obligation for permission to use Figures 5, 40, 43, and 44. The University of California Press kindly consented to my use of Figure 27. Finally, I wish to express my thanks to editors or publishers who permitted me to reproduce illustrations or data from the following journals: the *American Journal of Anatomy*, the *American Journal of Physiology*, the *Anatomical Record*, *Endocrinology*, the *Journal of Biological Chemistry*, the *Journal of Pharmacology and Experimental Therapeutics*, and the *Journal of Physiology*.

H. B. VAN DYKE

PEIPING UNION MEDICAL COLLEGE
1936

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CHAPTER I

THE ANATOMY OF THE PITUITARY BODY

SPECULATIVE interest in the pituitary body has existed at least from Galen's time down to the present. Scientific investigation of this apparently unimportant structure, however, required the microscope, and began with Rathke's (1838) description of some phases of its development. For the next half-century the only clear-cut findings were anatomical. The complex development of the pituitary body as well as the histology and cytology of its main divisions continue to be favorite subjects of anatomical investigation.

THE EMBRYOLOGY AND COMPARATIVE ANATOMY OF THE PITUITARY BODY

The important anatomical divisions of the pituitary body are the following:

Part	Embryonic Origin
Pars glandularis	Rathke's pouch of buccal ectoderm
Pars intermedia	Superior part of caudal portion of Rathke's pouch
Pars tuberalis	Paired lateral lobes at the ventro-nasal end of Rathke's pouch
Pars neuralis	Infundibular process of diencephalon

The term "pars anterior" ordinarily refers to the pars glandularis, but may include part of the pars tuberalis; the term "pars buccalis" usually includes all the structures derived from Rathke's pouch. The term "pars posterior" commonly refers to structures posterior to the residual lumen of Rathke's pouch, and therefore includes the pars intermedia, the pars neuralis, and often part of the pars tuberalis.

The development of the pituitary in the cat is shown diagrammatically in Figure 1. According to modern morpholo-

gists (Kingsbury, Haller, and others), the development of Rathke's pouch and the infundibular process of the dien-

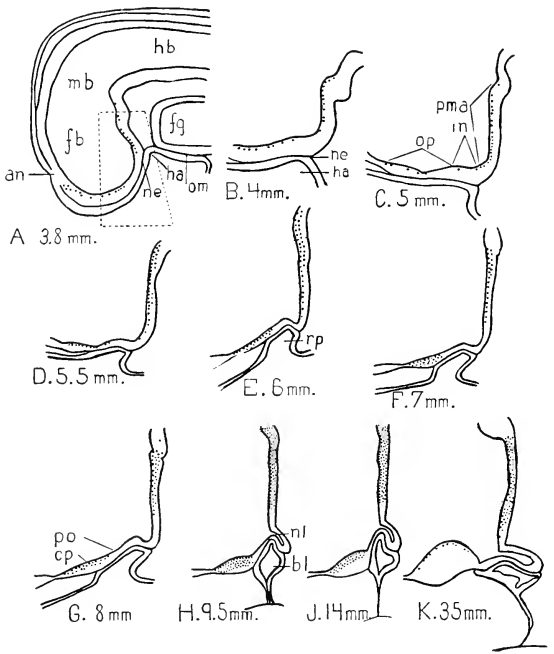


FIG. 1.—The development of the pituitary of the cat in relation to the number of mitoses in the floor of the diencephalon (Gilbert, 1934). Each mitotic figure is indicated by a dot. The dotted lines of *A* inclose the area shown in the other figures. *an*, anterior neuropore; *bl*, buccal lobe; *cp*, chiasmatic plate; *fb*, forebrain; *fg*, foregut; *ha*, hypophysial angle; *hb*, hindbrain; *in*, infundibular region; *mb*, midbrain; *ne*, neuro-ectodermal plate; *nl*, neural lobe; *om*, oral membrane; *op*, optic region, *pma*, premammillary region; *po*, post-optic lamina; *rp*, Rathke's pouch.

cephalon cannot be described as if these were isolated structures, but must be considered from the standpoint of the embryology of the entire region of the head. Among the more

important of these changes are the formation of the neuro-ectodermal plate and the process of cephalization. Very early in life, and throughout development, therefore, the diencephalic floor and the buccal ectoderm, destined to form the neural and epithelial portions of the pituitary, are in contact with each other. According to Gilbert (1934):

. . . . Both the buccal and the neural components of the hypophysis are formed as the result of the mode of development of the head region of the embryo, and not as intrinsic evaginations from the stomodeal and cranial epithelia. That Rathke's pouch is determined by the bending ventrally of the forebrain, and that this pouch is deepened and constricted into a closed vesicle by the condensation of mesenchyme around the pouch has been recognized by most recent investigators. The importance of the firm adherence of the ectoderm to the floor of the brain as the mechanical condition which determines the formation of a pouch in this particular region was early recognized by Minot (1897), and has been further emphasized in this work. This dependence of the pars buccalis on contact with the brain floor has been substantiated by the experimental work of Blount (1932) and Stein (1933), who showed that in both Amblystoma and chick, the pars buccalis will not develop in the absence of contact with the brain floor.

. . . . That the place and manner of appearance of the pars neuralis, and the form which it assumes can likewise be explained as due to the interaction of the growth-processes of adjacent regions on the neuro-ectodermal plate seems to be equally well established by this investigation.

. . . . It seems definitely clear that the original neuro-buccal adherence is not destroyed at any time during the develoment of the hypophysis, but its position with relation to the axis of the pars buccalis is changed by the rotation of the neuro-ectodermal plate around the apex of the buccal pouch as a result of growth pressures set up within the brain. This maintenance of the original neuro-ectodermal adherence is the essential factor in the formation of both the neural and buccal lobes of the hypophysis in the cat.

A model of the pituitary of the rabbit at one stage of its development is shown in Figure 2. This illustrates clearly a phase of the development of the pars tuberalis which was recognized as a separate structure by Tilney (1913). The embryologic hypophysial stalk, from which pharyngeal hypophysial tissue may arise, should not be confused with the stalk by which the pituitary is attached to the tuber cinereum in postnatal life in some mammals like man.

For discussions of the evolution and comparative anatomy of the pituitary the reader is referred to the papers of Herring

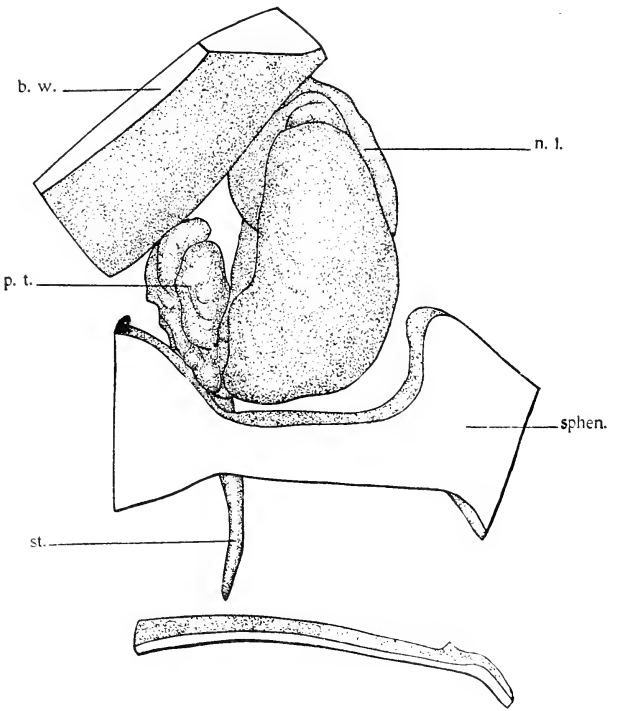


FIG. 2.—Model of the pituitary region of a rabbit embryo 16 days old. Nasal end to the left. From Atwell (1918). *b.w.*, brain wall; *n.l.*, pars neuralis; *p.t.*, pars tuberalis; *sphen.*, portion of cartilage of sphenoid; *st.*, stalk.

(1908, 1913) and to the monographs of Stendell (1914) and De Beer (1926). Diagrams of the pituitary of some vertebrates are shown in Figure 3. In the tortoise, and in most

mammals, the residual lumen of Rathke's pouch can usually be recognized as a space separating at least part of the pars intermedia from the pars glandularis. Often the space is filled with an eosin-staining, homogeneous material resembling histologically—but not otherwise—the colloid of the thyroid.

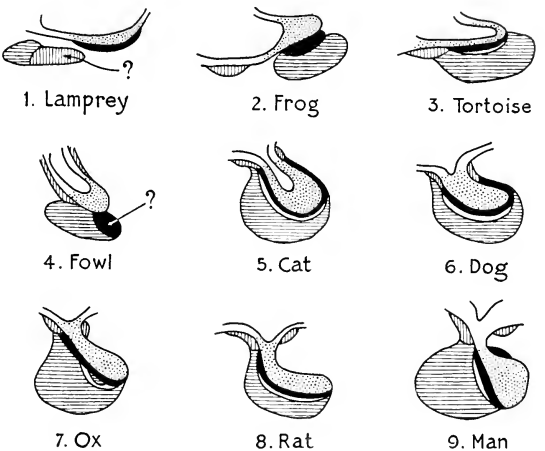


FIG. 3.—Diagrams of the pituitary region in some vertebrates (modified from Atwell, De Beer, and Tilney). Sagittal sections with the nasal end to the left. Pars neuralis, stippled; pars glandularis, horizontal lines; pars intermedia, black; pars tuberalis, vertical lines. No. 1. The "Uebergangsteil" of the lamprey may or may not be homologous with the pars tuberalis of other vertebrates (De Beer). No. 4. De Beer, not confirming Tilney, denied that the fowl possesses a pars intermedia. No. 7. In the ox (and pig) a cone of pars glandularis tissue, attached to the pars intermedia, projects into the residual lumen of Rathke's pouch (cone of Wulzen).

In adult human beings the residual lumen often is not present and the pars intermedia may be identified only with difficulty. It is clear from the diagrams that *complete* hypophysectomy may be very difficult or almost impossible in animals like the rat, in which the pars tuberalis extends a considerable

distance over the surface of the brain. It is easy to understand, also, that great care must be exercised in removing the pituitary so as not to injure the ill-understood but important nerve tracts and nuclei of the overlying tuber cinereum.

A number of investigators have studied the relationship between pituitary weight and body-weight or stature. Such studies, however, do not take into account the complexity of the gland's structure and function. The correlations found depend in a large measure on the heaviest part of the pituitary body, the pars glandularis. Data from more useful studies are summarized in Tables I and II. After puberty the female pituitary is usually the heavier (the woodchuck is an exception). Usually, also, the pituitary of pregnancy is heavier than that of the non-pregnant female. This is particularly true of man. Freeman (1934), as well as others, have studied the relationship of the weight of the whole pituitary of men to weight, stature, and race. He reported that the pituitary weight is better correlated with body-weight than with stature, and that the pituitary of the negro is heavier than that of the caucasian if the pituitary weights of the same sexes are compared. Freeman summarized the literature on the correlation of the pituitary weight with other variables and concluded, *inter alia*, that there may be some decrease in pituitary weight with age but that the change is slight. One of the most elaborate studies in animals is that of Hammar (1932) in the rabbit.

The specific gravity of the adult human pituitary is about 1.054 (Scheele, 1929).

The relationship between the meninges and the pituitary has been studied by Hughson (1922, 1924) in the dog and cat and by Koller (1922) in a number of mammals. According to the latter, a complete dural diaphragma sellae is to be found only in man. The diaphragm is incomplete in the ox, small ruminants, pig, dog, and cat. In the horse there is no dia-

TABLE I

THE WEIGHT OF THE DIFFERENT PARTS OF THE PITUITARY BODY IN MAMMALS

Animal	Age	Sex	Pars Glandularis (mg.)	Pars Intermedia (mg.)	Pars Neuralis (mg.)	Authority
Woodchuck		Male	3.48*	0.22*	3.65*	Rasmussen (1921)
Woodchuck (*Marmota monax*)		Female	2.96*	0.14*	3.03*	
Rat	Adult	Male	6.59	0.54	0.87	Stein (1933)
Rat	Adult	Castrate male	10.52	0.52	0.88	
Rat	Adult	Female	11.65	0.45	0.95	Stein (1934)
Rat	Adult	Pregnant female	11.90	0.49	1.13	
Guinea pig	Adult	Male	7.5	.....	.....	Loeb and Friedman (1933)
Sheep	.....	.....	350	.....	.....	Loeb and Friedman (1933)
Pig	.....	.....	125	.....	.....	Loeb and Friedman (1933)
Ox	.....	.....	1115	.....	.....	Loeb and Friedman (1933)
Rabbit	At puberty	Male	12.2	2.5	3.4	Hammar (1932)
Rabbit	At puberty	Female	12.5	2.7	3.5	
Rabbit	After puberty	Male	13.2	2.6	3.6	
Rabbit	After puberty	Female	18.6	3.3	4.4	
Horse	Adult	Castrate male	1060†	.....	700‡	Saito (1923)
Horse	Adult	Female	1200†	.....	640‡	
Horse	Adult	Pregnant female	1500†	.....	560‡	
Whale	.....	.....	32500†	.....	1400‡	Valsö (1934)
Man	Adult	Male	394	10.8	121	Rasmussen (1928)
Man	Adult	Female	503	9.6	104	Rasmussen (1934)
Man	Adult	Pregnant female	617	6.5	108	Rasmussen (1934)

* × 10^{-1} cc. † Pars anterior. ‡ Pars posterior.

phragm, but a fold of "primary dura" separates the pars intermedia from the pars neuralis. Apparently a somewhat

TABLE II

THE PROPORTION OF THE DIFFERENT PARTS OF THE PITUITARY BODY

(Italics: Percentage of Pars Buccalis [Epithelial Part].
Roman: Percentage of Pituitary Body without Pars Tuberalis)

Animal	Age	Sex	Pars Glandularis	Pars Intermedia	Pars Tuberalis	Pars Neuralis	Authority
Frog			*74*	*25*	*1*		Atwell (1926)
Urodele amphibia			*72–95*	*4–14*	*1–17*		
Mouse	(16.5 g.)	Male	70	19		11	Saller (1933)
Mouse	(20.0 g.)	Female	71	19		10	
Rat	Adult	Male	82	6.7		11 0	Stein (1933)
Rat	Adult	Castrate male	87	4.3		7.4	
Rat	Adult	Female	86	3.4		7.1	Stein (1934)
Rat	Adult	Pregnant female	87	3.6		8.3	
Cat			*75*	*16*	*9*		Atwell (1926)
Man	7–9 mos. fetus		*95*	*2.5*	*2.5*		Atwell (1926)
Man	9 mos. fetus		78	2		20	Covell (1927)
Man	Adult	Male	75	2		23	Rasmussen (1928)
Man	Adult	Female	81	2		17	Rasmussen (1934)
Man	Adult	Pregnant female	84	1		15	Rasmussen (1934)

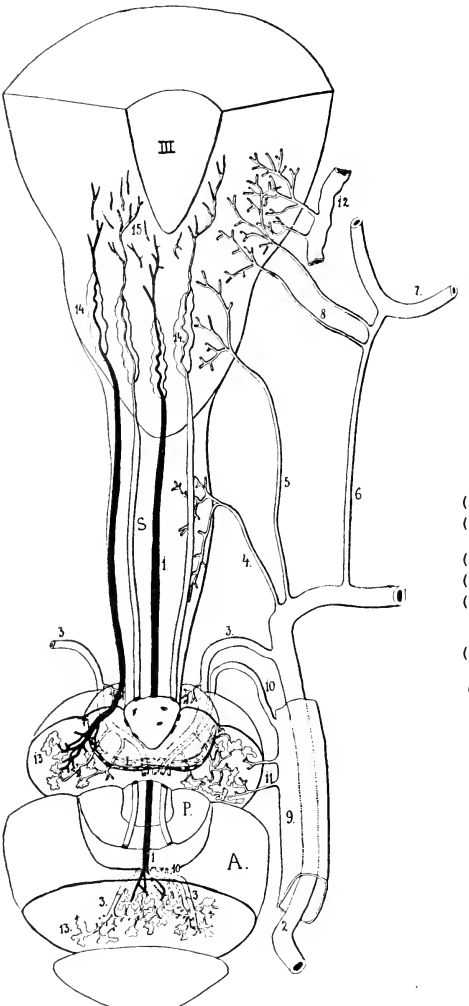
similar separation of the pars glandularis from the pars neuralis occurs in two aquatic mammals, the porpoise (Wislocki, 1929) and the whale (Valsö, 1934, and particularly Geiling, 1935, and Wislocki and Geiling, 1936).

THE BLOOD VESSELS, LYMPH VESSELS, AND NERVES OF THE PITUITARY BODY

The blood vessels and lymph vessels of the pituitary body.— The arterial vessels of the pituitary body of mammals like the dog and man arise from the internal carotids and the circle of Willis. Most of the vessels accompany the stalk, although there may be a small branch supplying the pars neuralis independently (Dandy and Goetsch, 1910; Basir, 1932). Apparently the vascular supply of the pars glandularis is the best. Within the pars glandularis are found large sinusoids lined with endothelium, but no arteries or veins. The pars tuberalis is better supplied with vessels than the pars neuralis, but the pars intermedia is relatively avascular.

Recently, unique veins participating in the circulation of blood in both the pituitary and the hypothalamus have been described by Popa and Fielding (1930). Veins receiving blood from all parts of the pituitary, including the pars tuberalis, ascend in the stalk and enter the hypothalamus where they form a capillary network. These veins were called the hypophysio-portal vessels by Popa and Fielding, and have been recognized in the stalk, at least, by others (e.g., Pietsch, 1930). The diagram of Figure 4, from one of the papers of Popa and Fielding, illustrates the vascular supply of the human pituitary but is distorted to show clearly the course of the hypophysio-portal vessels. 'Espinasse (1933) has studied the embryologic development of these vessels, which he identifies as originating from the arteries of the brain. The arachnoidal sheaths common to cerebral vessels (Virchow-Robin spaces) accompany some of the pituitary vessels (Hughson, 1922, 1924) but not the hypophysio-portal vessels (Basir, 1932; 'Espinasse, 1933; Basir and Reddy, 1934).

Brander (1932) described a communication between the residual lumen of the full-term human fetus and a venous sinus which, almost enveloping the gland, opened into the venous channels of the marrow of the sphenoid bone; this



(1) Hypophyseo-portal vessel
(2) Carotid artery
(3) Hypophyseal artery
(4) Small artery for pars tuberalis
(5) Small artery for tuber cinereum
(6) Posterior communicating artery
(7) Posterior cerebral artery
(8) Small arteries for infundibulum
(9) Cavernous sinus
(10) Hypophyseal vein
(11) Small hypophyseal veins
(12) Basal vein
(13) Sinusoids
(14) Heavy glial sheaths of the hypophyseo-portal veins
(15) Secondary distribution net
(A) Pars anterior of pituitary
(P) Pars posterior of pituitary
(I) Pars intermedia of pituitary
(S) Stalk

FIG. 4.—The blood vessels of the human pituitary body. From Popa and Fielding (1930).

finding was confirmed in the guinea pig (Collin, 1932) but not in other studies of human material ('Espinasse, 1933).

The nerves of the pituitary body.[1]—According to Dandy (1913), the pars glandularis of the dog and cat is supplied with numerous sympathetic fibers arising from the carotid plexus. Pines (1925) found that these fibers finally formed intercellular plexuses from which arose pericellular nets terminating in button-like thickenings on the surface of the cells of the pars glandularis. Possibly of greater importance is the large bundle of non-myelinated nerve fibers passing from the hypothalamus down the stalk to be distributed to the pars neuralis and pars intermedia (perhaps also to the pars tuberalis). The source of these fibers in the hypothalamus was first investigated by Pines (1925), Stengel (1926), and particularly by Greving (1926, 1928, 1930). The cells of origin are considered to be located in the nuclei paraventriculares and, more clearly, in the nuclei supraoptici (see Fig. 5). Both pairs of nuclei can be recognized in a number of mammals (Grünthal, 1933). The axones pass down the stalk as a bundle of non-myelinated fibers (tractus hypothalamo-hypophysius) terminating chiefly in the pars neuralis, but also ending as fibrils, often thickened at the end, about or within the cells of the pars intermedia (Roussy and Mosinger, 1933). It has been argued by Greving, and by Roussy and Mosinger, that these fibers regulate secretion in at least the pars neuralis and the pars intermedia. The best physiologic evidence in favor of this view has been obtained in the case of the pars intermedia of cold-blooded animals like the frog. There is very little evidence that secretory nerves control the activity of the pars glandularis; most experiments designed to demonstrate secretory nerves have either denied their existence or have been inconclusive like those of Vogt (1931).

[1] For the older literature of Cajal's school, see the translation of Cajal's *Histology* by Fernán-Núñez (Baltimore, 1933).

THE MICROSCOPIC ANATOMY OF THE PITUITARY BODY

Not a small part of the enormous literature dealing with the pituitary body chiefly concerns the histology and cytology of the various parts. References to much of the older liter-

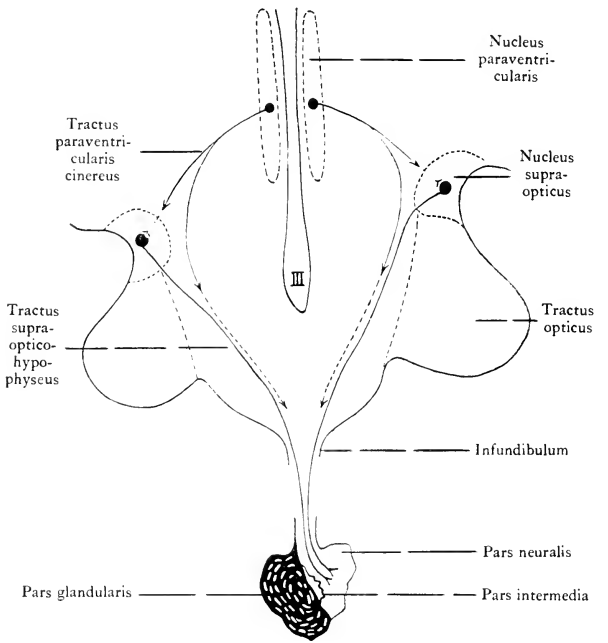


FIG. 5.—The cells of origin of the principal nerve fibers to the human posterior lobe. From Greving, *Klin. Woch.*, VII (1928), 734–37. Continuous line: verified histologically; broken line: hypothetical. The diagram of the brain is from a frontal section.

ature can be found in the paper of Trautmann (1909). The reader is also referred to the articles of Kraus (1914, 1926), Bailey (1921), and Benda (1932), as well as to other papers cited in this chapter.

The pars glandularis.—Three types of cells are usually recognized in the pars glandularis (Schönemann, 1892): (1) reserve cells (chromophobes, neutrophils, chief cells), (2) oxyphilic cells (eosinophils, acidophils, α cells), and (3) basophilic cells (cyanophils, β cells) (see Figs. 6 and 7). Sometimes the cells are classified simply as reserve cells (chromophobes) and chromophilic cells (oxyphils and basophils) (Flesch, 1884). The reserve cells are characterized by a poorly staining, homogeneous cytoplasm. The cytoplasm of the chromophil cells appears to contain granules staining readily

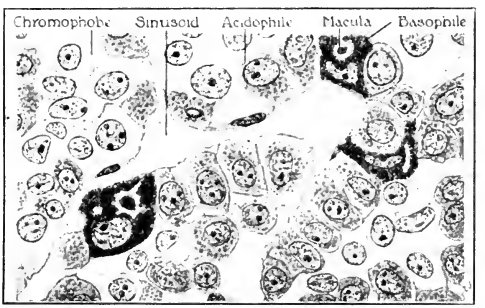


FIG. 6.—Cells of the pars glandularis of the woodchuck (*Marmota monax*). Mallory's stain. ×1,000. From Rasmussen (1921).

with eosin (oxyphils) or with haematoxylin and other dyes, usually but not necessarily basic (basophils). In the human pituitary, the cytoplasmic granules of the oxyphils appear to be coarser and more numerous than those of the basophils. Some authors believe that at least the chromophils can also be differentiated by the morphology of the Golgi body (Reiss, 1922).

Cytogenesis in the pars glandularis.—In the rabbit (Yamakawa, 1933), sheep and ox (Aron, 1929; Zimmermann, 1931), dog (Wolfe, Cleveland, and Campbell, 1933) and man (Cooper, 1925; Roffo, 1933), the first chromophil cell to be

differentiated from the primitive undifferentiated (or reserve?) cells in embryonic life is the oxyphil. In all these mammals, the basophils can be recognized only later; in some, like the dog, basophils cannot be found until after birth. According to Nelson (1930, 1933), the process is reversed in the pig. The principal chromophil cell in pig embryos of 7–10 cm. is the basophil. Oxyphils appear in em-

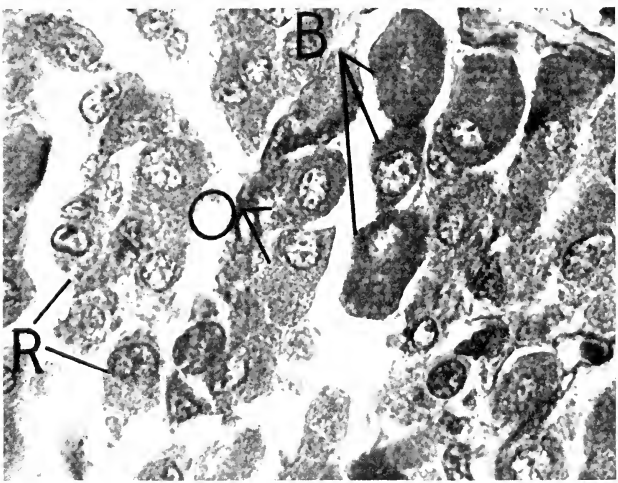


FIG. 7.—Photomicrograph of the pars glandularis of the dog. Mallory's stain. ×1,290. *B*, basophils; *O*, oxyphils; *R*, reserve cells.

bryos about 16 cm. long and tend to predominate in embryos of 20 cm.

The distribution of the three types of cells in the pars glandularis.—In some mammals like the ox, one part of the pars glandularis (in this case the central part) may be richer in basophils than other parts (Smith, 1923). Soós (1934) believed that the number and distribution of basophils varied

among different animals but remained fairly constant in a given species. He found more basophils in man, the pig, and the horse than in ruminants and birds. According to Beato (1935) no basophils are to be found in the pars glandularis of the sheep; but, contrary to the findings of others, Beato also found almost none in the ox gland.

Some of the quantitative studies which have been made are given in Table III. The differences in the results of different workers undoubtedly are partly of technical origin. Probably there are fewer oxyphils in the female rat's pituitary than in

TABLE III

THE PERCENTAGE OF DIFFERENT TYPES OF CELLS IN THE PARS GLANDULARIS

Animal	Sex	Reserve Cells	Oxyphils	Basophils	Authority
Rat.....	Male	58	37	5	Martins and De Mello (1935)
Rat.....	Male	42	52	6	Ellison and Wolfe (1935)
Rat.....	Female	63	32	5	Ellison and Wolfe (1934)
Rat.....	Female	74	23	3	Stein (1933)
Man.....	Male	52	37	11	Rasmussen (1929)
Man.....	Female	50	43	7	Rasmussen (1933)

the male's. Rasmussen's comparisons between men and women were made by a uniform technique. In women, in comparison with men, the proportion of oxyphils was significantly higher, whereas that of basophils was significantly lower. He found that the relative number of reserve cells increased by about 4 per cent in both men and women more than fifty years old; in women the proportion of basophils also increased by 2 per cent. The changes in both sexes occurred at the expense of the oxyphils.

Other aspects of the microscopic anatomy of the pars glandularis.—As a rule, relatively few mitotic figures can be found in the pars glandularis (De Beer, 1926). In the rabbit they are found chiefly in the oxyphils (Majima, 1926).

Much has been written about the relationship or lack of relationship among the different cells. Most investigators believe that the oxyphils and basophils are morphologically different types of cells. There is much less agreement as to the relationship of the reserve cells to the chromophils. The beliefs of different authors have been illustrated and discussed by Severinghaus (1933). On the basis of studies of the Golgi apparatus in the rat, he concluded that the reserve cells were of two types: one ultimately differentiated into an oxyphil cell, the other into a basophil. The most important of other interpretations as well as references to some of the literature of this field can be found in Severinghaus's paper.

The pars intermedia.—The greater part of the pars intermedia of mammals lies between the pars glandularis and the pars neuralis. Usually, also, the residual lumen of Rathke's pouch (Kölliker's space), containing a homogeneous eosin-staining material ("colloid"), separates at least part of the pars intermedia from the pars glandularis. In adult human beings the space may be absent. The pars intermedia is readily identified in children. In adults it appears to be a rudimentary structure at most. In other mammals, the pars intermedia usually is a clearly defined structure. Often cords of cells from the pars intermedia invade the adjacent pars neuralis.

A photomicrograph of the pars intermedia of the monkey is reproduced in Figure 8.

The cells of the pars intermedia have been studied by many investigators by a variety of cytological techniques.[2] Generally they are described as non-granular basophils differing in morphology, however, from the basophils of the pars glandularis. Maurer and Lewis (1922) described two types of

[2] The following are references to some of the recent literature: Dayton, Schönig (1926); Guizzetti, Urasov (1928); Rasmussen (1928–30, 1933); Marburg (1929); Aschoff, Pietsch (1930); Maeda (1931); Kraus (1932); Roussy and Mosinger (1934); and Beato (1935).

cells in the pars intermedia of the pig: one, making up the bulk of the structure, was characterized by a granular cytoplasm; the other appeared to be a colloid-secreting cell. The colloid of the pituitary body, which usually accumulates in the residual lumen or in irregular vesicles and blind tubules lined by cells of the pars intermedia, has been considered by

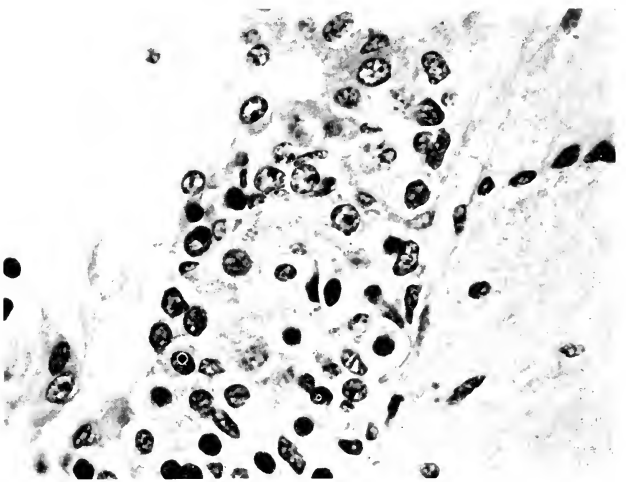


FIG. 8.—Photomicrograph of the pars intermedia of the monkey (*Macaca mulatta*). Haematoxylin and eosin. ×800. Pars neuralis to the right; residual lumen containing colloid to the left.

some to be a true secretion. The evidence in favor of this view is largely histological and will be discussed later. Others, like De Beer, look upon accumulations of colloid as representing "degeneration phenomena." About 1 per cent of the bulk of the adult human pituitary appears to consist of colloid (Rasmussen, 1927–28, 1934).

Considerable amounts of a melanin-like pigment may be found in the pars intermedia of the black or piebald rat,

but not in that of the albino rat (Lehmann, 1928; Parhon and Caraman, 1930).

The pars tuberalis.—Little is known about the physiologic significance, if any, of the pars tuberalis. Anatomically it consists of glandlike cells arranged in acini which have no dis-

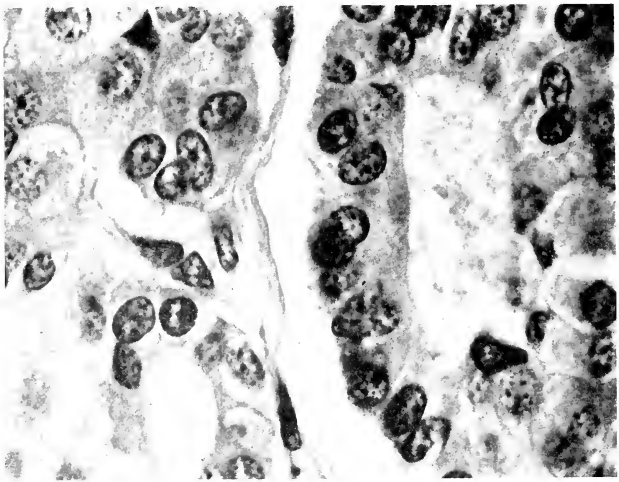


FIG. 9.—Photomicrograph of the pars tuberalis of the monkey (*Macaca mulatta*). Haematoxylin and eosin. ×1,290.

tinct lumen (often in the ox) or may be distended with colloid (cat) (Atwell and Marinus, 1918; Atwell, 1929).

A photomicrograph of the pars tuberalis of the monkey is reproduced in Figure 9. Morphologically the cells of the pars tuberalis are different from those of any other part of the pituitary. Usually they are described as being relatively nongranular, faintly basophilic cells which appear to be colloid-secreting in some animals like the cat. Pietsch (1930) found some oxyphils and basophils in the human pars tuberalis, but

did not regard them as cells typical of that part which he described as being made up of numerous blood vessels, much connective tissue, as well as small cells with pyknotic nuclei and a cytoplasm containing minute basophilic granules.

The pars neuralis.—The pars neuralis is perhaps the least homogeneous part of the pituitary body. It is composed of non-myelinated nerve fibers, neuroglia-like cells, and basophilic cells (rarely oxyphils) as islets or cords of cells growing from the pars intermedia or the pars glandularis. The invasion of the part by basophils, whether originating from the pars intermedia or the pars glandularis, appears to be more frequent in the pituitary of man and the primates than in that of lower animals. "Hyaline material," thought by Herring, Cushing, and others to represent the true secretions of the pars neuralis and to be derived from basophils (holocrine secretion) or colloid, can also be observed.

Various neuroglia-like cells peculiar to the pars neuralis have been described in the pituitary of the ox by Bucy (1930), who named them "pituicytes." Their staining reactions may be similar to those of true neuroglia. Some of these cells contain granules of pigment resembling a lipochrome rather than melanin. Among recent descriptions of the similar cells of the human pars neuralis are those of Hoenig (1922) and Scheele (1929). Stern (1932) believed that a melanin-like pigment could be found among the cell processes in the pars neuralis of many human pituitary bodies.

True nerve cells have not been demonstrated in the pars neuralis.

The nature and significance of the basophilic cells in the pars neuralis are still subjects of controversy. Many doubt the existence of a true pars intermedia in the adult human pituitary, and consider that the basophils, often infiltrating into the pars neuralis from the site of the juvenile pars intermedia, are basophils like those of the pars glandularis. In lower mammals, invasion of the pars neuralis by basophilic

cells is less pronounced; the basophils, however, are (usually) those of the pars intermedia (Herring, 1908). Those interested will find a detailed study of these cells in the human pars neuralis, together with a discussion of the literature, in the paper of Lewis and Lee (1927).[3]

THE PHYSIOLOGICAL ANATOMY OF THE PITUITARY BODY[4]

The pituitary during pregnancy.—As part of his study of the interrelationship of the pituitary and the thyroid, Comte (1898) reported that the pituitary of pregnant or parturient women was greatly hypertrophied in three of six cases. These pregnancy changes were studied in great detail by Erdheim and Stumme (1909), who found that the only important changes were in the pars glandularis. They concluded that (1) the chief histological change consisted of the appearance of "pregnancy-cells" apparently derived from reserve cells, the homogeneous protoplasm of which became enlarged and could be stained with eosin; (2) the number of pregnancy-cells increased as pregnancy progressed so that in the first half of pregnancy only true oxyphils were present in greater numbers, whereas toward the end of pregnancy the predominant cell type was the pregnancy-cell; (3) the changes were more pronounced in the pituitaries of multiparae than in those of primiparae; and (4) even in primiparae, months elapsed before the pituitary histologically resembled that of nulliparae, although there was a reduction in the number of pregnancy-cells a few weeks postpartum.

Most German authors agree with the results and interpretation of Erdheim and Stumme. Rasmussen (1934), however, declared that the proportions of reserve, oxyphilic, and basophilic cells were practically unchanged in his material, although there may have been a slight increase in the number

[3] Also see Pietsch (1930) and Rasmussen (1930).

[4] Other aspects of the physiological anatomy of the pituitary body are discussed in the succeeding chapters.

of reserve cells at the expense of the oxyphils. He found that the increase in the weight of the pituitary of pregnant women, in comparison with that of non-pregnant women, averaged 113 mg. or 18.3 per cent; this difference was entirely due to the hypertrophy of the pars glandularis, which was increased in weight both relatively (pregnant, 84.1 per cent; non-pregnant, 81.4 per cent) and absolutely (increase in pregnancy, 114 mg. or 22.7 per cent). The results were obtained by weighing outlines, traced on paper, of serial sections of the pituitary of twenty-four pregnant women and sixty non-pregnant women.

The anatomy of the pituitary of pregnant animals was investigated as early as 1905 by Guerrini, and Morandi, who obtained results as difficult to interpret as those reported later. The more recent detailed studies of the histology and cytology of the pars glandularis, particularly of pregnant rats, and also of pregnant mice, guinea pigs, rabbits, sheep, and cows, have led to conclusions which are especially contradictory in respect to the origin of the pregnancy-cell. The characteristic cell of the pars glandularis of pregnancy is described as a non-granular oxyphil, more or less resembling the human pregnancy-cell of Erdheim and Stumme, in the mouse (Urasov, 1927; Haterius and Charipper, 1931), guinea pig (Kolde, 1912; Brouha and Desclin, 1931; Desclin, 1932), rabbit (Kolde, 1912; Berblinger, 1914), and cow (Gentilli, 1920; Beato, 1935; and others). Other changes, particularly in the basophils, are reported by Watrin (1922) in the sheep and by Urasov in the mouse. According to Majima (1926), who studied the pituitary of the pregnant rabbit, a marked increase in the number of mitoses could be observed in the chromophil cells—particularly in the oxyphils (pregnancy-cells?).

Atwell (1930) found that the enlargement of the cat's pituitary, occurring in pregnancy, depended upon hypertrophy of all the lobes, the relative sizes of which were unaltered.

Recently, a number of authors have studied the pituitary of the pregnant rat. Oxyphilic cells with homogeneous or finely granular protoplasm are said to be characteristically present in the pars glandularis (Schenk, 1926; Lehmann, 1928; Haterius, 1932; Charipper, 1934; and Desclin, 1934). Wolfe and Cleveland (1933), however, doubted that any particular cell type was peculiar to pregnancy in the rat; they described complex qualitative and quantitative changes in all the cell types. Severinghaus (1934) declared that the pregnancy-cell is a modified (degranulated) basophil which other investigators have confused with reserve cells or with altered oxyphils. The results so far mentioned cannot be reconciled with those of Stein (1933–34), who reported that no qualitative or quantitative change in the cytology of the pars glandularis occurred in pregnant rats. He found that the proportion of reserve cells, oxyphils, and basophils was altered neither in primiparous nor in multiparous normal rats. Unlike the pituitary of many mammals, that of the rat not only does not enlarge during pregnancy (Stein), but also may become smaller (Herring, 1920). According to Stein the pars neuralis may be hypertrophied in multiparous rats.

In the mouse, rat, and guinea pig the pregnancy changes in the pituitary have been attributed to the internal secretion of the corpus luteum (Brouha and Desclin, 1931; Haterius and Charipper, 1931; Haterius, 1932; Desclin, 1932–33; Brouha, 1934; Charipper, 1934). The changes may be produced in non-pregnant females or in males with transplanted ovaries by causing luteinization (with resulting increased corpus luteum secretion) of the ovarian tissue. The administration of corpus luteum extract to normal, castrated, or spayed animals is also said to provoke pregnancy-like changes in the pars glandularis.

Haterius (1932) found that the pituitary of lactation resembled that of pregnancy in the rat. After weaning and with the onset of oestrus, the oxyphil cells with homogeneous

cytoplasm rapidly disappeared. Piccone (1933) found that the pituitary of the lactating guinea pig resembled that of the pregnant animal.

The pituitary after spaying or castration.—Tandler and Gross (1908) examined, by means of X-ray photographs, the sella turcica of castrated men. They observed enlargement of the sella, due, they believed, to a hypertrophy of the pituitary. In the same year Kon studied the pituitaries of a castrated man and several spayed women. He concluded that the hypertrophy, if present, was the result of hyperplasia of the chromophil cells of the pars glandularis. In most of Kon's cases there seemed to be an increase in the number of oxyphils, although in two the basophils also were "especially well developed." In the castrated man there seemed to be a hypertrophy of the reserve cells. Rössle's report (1914) is based on the study of a large number of human pituitaries of which twenty-eight were from women spayed one week to sixteen years previously. According to Rössle, hypertrophy of the pituitary after spaying is less constant than a histological alteration of the pars glandularis. The latter consists chiefly of an increase in the number as well as the sites of formation of oxyphils. However, Rössle did not find such changes constantly nor did he believe that they were specifically related to ovariectomy. In a recent report, dealing in part with the histology of the pituitary of ten spayed women (mostly ovariectomized, but some previously treated by X-rays or radium), Philipp (1930) described a marked increase in the number of oxyphils as well as a similar change in the amount of colloid. Kraus (1932) also was of the opinion that the proportion of oxyphils in the pituitary is increased after gonadectomy in man.

The widely quoted work of Fichera (1905) was the first dealing with the effect of gonadectomy on the pituitary of animals. He concluded that the pituitary became larger and was made up of an increased number of oxyphil cells after

the spaying or castration of fowls, guinea pigs, rabbits, buffaloes, and oxen. In the fowl and buffalo, the pituitary weight was practically doubled. All subsequent work also seems to show that gonadectomy in mammals is usually followed by a hypertrophy of the pituitary due to a growth of the pars glandularis.

Many authors have reported on the changes in the pituitary of rats after castration or spaying. Among the earlier reports may be mentioned those of Hatai (1913) and Addison (1917). Hatai observed a hypertrophy after castration, but was not convinced that a similar change occurred after spaying. Addison studied the microscopic appearance of the gland in normal and castrated rats. The most important histologic change in the pituitary was in the appearance and number of the basophils. Besides appearing to increase in number, these cells hypertrophied and, about two months after operation, became vacuolated. Subsequently the size of the vacuoles as well as the number of vacuolated basophils increased. These constitute the "castration-cells." Addison believed that some basophils were formed from reserve cells and that, months after castration, there was some reduction in the number of oxyphils in part due to dedifferentiation into reserve cells.

Stein (1933) reported that the hypertrophy of the pituitary following castration in the rat was entirely due to the increased size of the pars glandularis, which was found to be increased 63 per cent (castrated, 10.52 mg.; normal, 6.59 mg.). The relative weight of the pars glandularis after castration was 87.2 per cent in comparison with 82.3 per cent in normal rats. Stein emphasized that colloid, practically absent in the pituitary of the normal rat, could be found in great abundance after castration.

The castration-cell may appear like a signet ring when the vacuole has attained a large size, so that the nucleus and the remainder of the cytoplasm appear to have been crowded to-

gether at the periphery of the cell. These cells can also be found in large numbers in the pars glandularis of spayed female rats (see Fig. 10). With Addison's general conclusions as to the changes in the basophils of the rat's pituitary after gonadectomy there is a refreshing agreement among most authors (Nukariya, 1925; van Wagenen, 1925; Schenck,

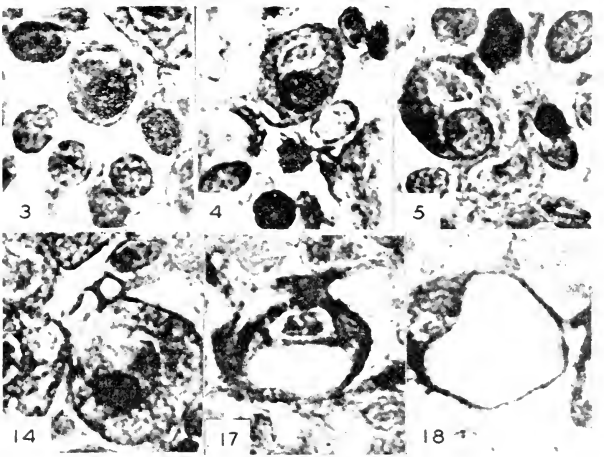


FIG. 10.—The effect of spaying on the basophil cell of the rat (Ellison and Wolfe, 1934). Photomicrographs. ×1,660. Nos. 3, 4, Basophils in the pituitary of normal female rats. Nos. 5, 14, 17, 18, Basophils in the pituitary of spayed rats. Nos. 17 and 18 conform to descriptions of "castration-cells."

1927; Lehmann, 1928; Severinghaus, 1933; and others). Schenck (1929) reported that twenty months after castration no typical castration-cells but intermediate types of basophils could be found. Schultze (1934) believed that the most pronounced changes in the pituitary of gonadectomized female rats occurred in those gaining the most weight after operation. Actual counts of the number of different cell types of the pars glandularis of normal, spayed, and castrated rats

have been made by Ellison and Wolfe (1934–35). Part of their data is reproduced in Table IV and illustrates the striking changes which occur particularly in the proportion of basophils (including castration-cells). Severinghaus (1933) observed that the size of the oxyphils progressively diminished after the castration of adult rats so that 46 days after castration the average sectional area of the oxyphil cell was approximately 54 per cent of that of the normal.

TABLE IV

THE EFFECT OF GONADECTOMY ON THE DISTRIBUTION OF THE CELLS OF THE PARS GLANDULARIS OF THE RAT

(Ellison and Wolfe, 1934–35; the Standard Deviations Have Not Been Included)

SEX	DAYS AFTER GONADECTOMY	CELL-TYPE			
		Reserve (Per Cent)	Oxyphil (Per Cent)	Basophil (Per Cent)	Castration (Per Cent)
Female	Control	62.4	31.8	4.6	.....
	60	39.7	42.4	12.8	4.1
	120	41.8	40.8	6.4	11.3
Male	Control	42.2	51.2	5.5	.....
	55	35.5	45.6	17.0	1.4
	120	30.5	46.0	10.6	10.4

To determine whether the castration changes result from the loss of the germinal epithelium or that of the interstitial tissue, two types of experiments have been performed in rats. Male rats have been made cryptorchid so that considerable degeneration of the germinal epithelium occurs without apparent damage to the interstitial tissue (Desclin, 1934; Ellison and Wolfe, Martins and De Mello, 1935; and others). Usually, but not invariably, the pars glandularis then resembles that of castration, but the changes are never so pronounced as after operative castration. Likewise after irradiation of the testes (X-rays) there may be pronounced degenerative changes in the germinal epithelium, but apparently

no anatomical or functional alteration of the interstitial cells; in such animals, castration changes of a moderate grade are also apparent in the pars glandularis (Schenk, 1927; Witschi, Levine, and Hill, 1932; Desclin, 1933–34). In the female rat, after irradiation of the ovaries, castration changes in the pituitary do not appear unless there has followed a complete suppression of oestrin secretion (Levine and Witschi, 1933). All these observations seem to show that typical castration changes in the pars glandularis depend partly on the removal of the germinal epithelium; data discussed in other chapters, however, indicate that the presence or absence of the interstitial tissue is also of importance.

Unquestionably, among mammals so far investigated, castration changes in the pituitary are most readily, and most constantly, observed in the rat. A summary of the views of different authors can be found in the paper by Stein (1933); not included in his bibliography are the reports of Majima (1926) and Maeda (1931) (rabbit), Werner (1929) (guinea pig), and Andriani (1925) (dog). According to recent reports, no "typical" castration-cells or increased number of basophils can be found in the pituitary of gonadectomized guinea pigs (Severinghaus, 1932), whereas in the pituitary of the spayed rabbit there occurs a marked increase in the proportion of basophils (Smith, Severinghaus, and Leonard, 1933).

Other aspects of the physiological anatomy of the pituitary.—The pituitary of the woodchuck (*Marmota monax*) has been studied by Rasmussen (1921) before, during, and after hibernation. No important difference was found in comparisons of the pituitary before and during hibernation. In the spring, with the appearance of oestrus, however, there was an increase in pituitary size amounting to one-third, despite three months' starvation (hibernation with or without subsequent starvation) and great activity (rutting). There was also found a threefold increase in the number of basophils in com-

parison with the number in the pituitary of animals killed before or during hibernation.

The pars glandularis of the rabbit, dog, sow, and rat has been investigated at different times of the oestrous cycle to determine what qualitative or quantitative histological changes occur.[5] All the authors believed that they had observed changes in the chromophils; and it is not surprising that they were described as differing in different animals. The pituitary of the rat, during the oestrous cycle, was the only one studied in more than one laboratory. Reese found that the oxyphils were intensely stained during metoestrus (vaginal stage of cornification) but appeared to contain fewer granules and to be lighter staining during dioestrus (corpus-luteum phase). He observed no changes in the basophils. Charipper and Haterius described a basophilia during oestrus and a predominance of oxyphils during dioestrus. Finally, Wolfe and Cleveland believed that "qualitative rather than quantitative" cyclic changes could be observed, especially in the oxyphils, similar to those described by Reese. Differences in the appearance or the number of the chromophil cells at different times of the oestrus cycle of the rabbit (including pseudopregnancy), sow, and dog have been described by Wolfe and Cleveland and their co-workers.

Specific cells as sources of the hormones of the pituitary body. —The gonad-stimulating, growth-promoting, and thyrotropic hormones, as well as those more or less responsible for the normal functioning of the adrenals, the pancreas, and probably the parathyroids, seem to be elaborated in the pars glandularis. The hormone responsible for the dispersion of chromatosomes in the chromatophores of cold-blooded animals is produced by the cells of the pars intermedia (and pars glandularis). The site of formation of the oxytocic and vaso-

[5] Charipper and Haterius, Reese (1932); Cleveland and Wolfe, Wolfe and Cleveland, Wolfe, Cleveland, and Campbell (1933); Wolfe, Phelps, and Cleveland (1934).

pressor hormones (including the diuretic-antidiuretic hormone) of the pars neuralis is uncertain; unquestionably the highest concentration of these hormones is found in the pars neuralis. General statements cannot be made with respect to a presumed division of function among different cell types, such as those of the pars glandularis. In a given animal, however, there may be some correlation between histological change and the amount of a hormone.

The oxyphilic cells are thought to secrete the growth-promoting hormone because (1) the symptoms of the most clear-cut disease of the pituitary in man, acromegaly, are apparently due to an excessive secretion of the growth-promoting hormone by the oxyphilic cells of a tumor (adenoma) and (2) growth-promoting effects may be produced by ox pituitary tissue composed of oxyphils and reserve cells, but not by tissue composed of basophils and reserve cells (Smith and Smith, 1923). If we are to accept other evidence, however, the oxyphilic cells also appear to be responsible for the secretion of a gonad-stimulating hormone in man (Philipp, 1930; Kraus, 1932–33) and in the pig. According to Nelson (1930), the pituitary of the fetal pig is characterized by a marked differentiation of the oxyphils only when the crown–rump length is 16–17 cm. The chromophils are predominantly oxyphilic at a fetal length of 20 cm., when Smith and Dortzbach (1929) detected gonadotropic hormone. In the younger fetus (about 10 cm.), the chromophils are chiefly basophilic; pituitary implants then cause growth in hypophysectomized rats but no gonadotropic effect in immature mice.

The data just cited suggest that the basophils in the pig secrete the growth-promoting hormone. More generally held is the view that the basophils specifically elaborate the gonadotropic hormone(s). In the woodchuck, the period of great sexual activity after hibernation appears to be correlated with a marked increase in the number of basophils in the pars glandularis. In the rat and rabbit, castration or spaying is

characterized both by an increase in the number and size of basophils and by an increase in the gonadotropic potency of the pituitary. In the guinea pig, however, no similar morphological change occurs, yet the gonadotropic potency is increased. The injection of oestrin is known to decrease the gonadotropic potency of the pituitary; in the rat, however, the cells of the pars glandularis are said to be characterized by a basophilia after the production of persistent oestrus following oestrin injection (Charipper and Haterius, 1932; but Nelson, 1935, reported that the change consisted of a loss of granules by both oxyphils and basophils). In man, the anterior pituitary of spayed or castrated individuals appears to secrete an increased amount of follicle-stimulating hormone; the anatomical changes, however, concern chiefly the oxyphils. Cytological changes in the pituitary of female rats at different stages of the oestrous cycle also suggest that the oxyphilic cells secrete a follicle-stimulating hormone. Moreover, there seems to be a greater amount of gonadotropic hormone in the pituitary of the male rat than in that of the female (Evans and Simpson, 1929; Lipschütz and Reyes, 1932);[6] this difference may be related to the greater proportion of chromophils—particularly oxyphils—in the pars glandularis of the male rat.

From studies of the pituitary of the frog, Zahl (1935) concluded that changes in the gonads and sexual activity could be correlated with cytological changes chiefly in the oxyphils.

The thyrotropic hormone has been thought to be a secretory product of the basophilic cells in studies of the pituitary of the ox and toad (see chap. vii).

The presence of gonadotropic hormones in parts of the human pars glandularis, thought to consist predominantly of cells of one type, has been investigated by Philipp (1930), Kraus (1932–33), and Zondek (1933). Some of the observations have already been discussed. Apparently gonadotropic

[6] Also see chap. iv.

effects can be observed after the implantation of any cell type, including reserve cells (chromophobe adenoma). Generally, tissues composed mostly of reserve cells produce the weakest response. There is some evidence that luteinization is more readily produced by tissues containing many basophils and that intermediate effects—follicle growth with or without luteinization—follow the implantation of parts chiefly made up of oxyphils. Kraus, but not Zondek, believed that the stalk contained gonadotropic hormone even after the removal of the pars tuberalis. In several reports (Höppli, 1921; Skubiszewski, 1925; Kraus and Traube, Kraus, 1928) an increase in the proportion of basophils in the pars glandularis is said to occur in two-thirds or more of cases of renal disease, particularly if there is an associated hypertension. Kraus even postulated an increased number of basophils in the pituitary of hypersthenic individuals (including hypertension and contracted kidney) and a diminished number in asthenia (Addison's disease, tuberculosis, carcinoma, etc.). He believed (1933) that the oxyphils were concerned in carbohydrate metabolism, and the basophils in fat and cholesterol metabolism. Cushing (1932–33) has described symptoms (abdominal obesity, hirsutism, hypertension, etc.) which he attributes to a basophilic adenoma of the pars glandularis ("pituitary basophilism").

There is convincing evidence that the cells of the pars intermedia of vertebrates other than man secrete the hormone causing dispersion of the black pigment granules in chromatophores.

Investigators of the anatomy of the pars neuralis usually refuse to consider that the specific and transiently powerful hormones of that part are elaborated by its peculiar neuroglia-like cells. Instead, it is oftener postulated that the cells of the pars intermedia or basophils invading the pars neuralis, bearing a greater resemblance to glandular cells elsewhere, secrete the posterior lobe hormones. The physio-

logical and pharmacological support for this view is, however, weak and will be discussed in the chapters dealing with the hormones of the pars neuralis.

The transport of internal secretions from the pituitary body.—The routes by which the internal secretions of the pituitary body may be conveyed to the rest of the organism have been subjected to much anatomical study since Herring's pioneer work (1908). It is generally agreed that most of the secretion(s) of the pars glandularis are removed by way of the rich network of vascular sinusoids, of which probably only a small number empties into the hypophysio-portal vessels. Conceivably some secretion could also escape into the cerebrospinal fluid by way of the arachnoidal sheaths of blood vessels.

The pathways of secretion of the pars intermedia and pars neuralis are matters of controversy lacking satisfactory physiological support (see chap. x–xii). These parts, particularly the pars intermedia, are the least vascular of the whole pituitary body, so that novel routes of conveying the secretion (which is thought to be represented by "colloid" or "hyaline material" [Herring, Cushing, Collin, and Roussy]) have been postulated. Colloid accumulations in the pars intermedia or hyaline material in the pars neuralis have also been considered to represent degenerative changes (Bailey, De Beer, and others). Herring (1908, 1913, 1915) believed that the colloid (of the pars intermedia) and the hyaline material (as a holocrine secretion of the pars intermedia) found their way into the pars neuralis whence, after storage with possible conversion into more active substances, they ultimately passed through the ependymal lining of the third ventricle into the cerebrospinal fluid. This view in modified form is also held by Collin, Roussy, Cushing, and others. A recent paper by Cushing (1933) contains a restatement of his position. Other reports are by Costa (1923, 1925), Collin and others (1924–25, 1929, 1933–34), Florentin (1934), and Roussy and

Mosinger (1933–34). Maurer and Lewis (1922) considered it more likely that the internal secretions of the pars neuralis passed directly into blood vessels. Collin and Roussy speak of the following types of secretion: "haemocrine," into the blood stream; "neurocrine," into the pars neuralis and through the stalk to affect the nerve cells of hypothalamic nuclei; "hydrencephalocrine," into the cerebrospinal fluid; and "haemoneurocrine," through the hypophysioportal vessels into the hypothalamus.

CHAPTER II

THE EFFECTS OF HYPOPHYSECTOMY (WITH REMARKS ON THE EFFECTS OF LESIONS OF THE HYPOTHALAMUS)[1]

THE observation of the effects of the removal of a gland of internal secretion is generally the most important step in the elucidation of the gland's function. In this respect the pituitary body has presented unusual difficulties. In the first place, in mammals at least, the gland is shielded by bone against experimental insults on almost all sides; in addition, it is surrounded laterally by a rich venous sinus. Second, the pituitary body is in intimate relation to the hypothalamus; not only is the infundibular part of the tuber cinereum continuous with the pars neuralis, but a portion of the pars buccalis—usually the pars tuberalis—may also be attached to the floor of the tuber cinereum, especially on the nasal side. Therefore, removal of the gland, so complete that no remnants of pituitary tissue can be found histologically, is almost inevitably complicated by injury to the basal part of the hypothalamus (tuber cinereum). Even the incomplete extirpation of the pituitary body may be attended by injury of the tuber cinereum. Although our knowledge of the physiology of the hypothalamus is very imperfect, there can be little doubt but that it is of decisive importance in some phases of the metabolism of water, fat, and carbohydrates, probably in the regulation of the temperature, and, less directly perhaps, in the nervous control of the respiratory movements and the cardiac rate.

It is therefore not surprising that the literature on hypo-

[1] For references to the older literature the reader is referred to the books or articles of Aschner (1912); Cushing (1912); Biedl (1913); Leschke (1919); and Bailey and Bremer (1921).

physectomy[2] contains many contradictory results largely owing to the failure properly to evaluate complications due not to the removal of the gland but to injury of the brain. The belief that the pituitary body is essential for life—formerly shared by Paulesco, Cushing, Biedl, Blair Bell, and others—certainly is not true of the dog, in which most of their experiments were performed. It is reasonable to conclude that their results depended upon an unrecognized injury of the hypothalamus.[3] The evidence today, from reports of successful hypophysectomy of fish, amphibia, reptiles, birds, and mammals, indicates that the operation is compatible with the survival of animals for weeks or months except in the case of the fowl, which is said to succumb within a few days. For the most part, the data show that the pars glandularis is the only important division of the pituitary body in mammals. In some, but not all, cold-blooded animals the internal secretion of the pars intermedia is necessary for the control of the dispersion of pigment-granules, particularly in the melanophores. Extirpation experiments offer little support for the belief that the pars neuralis is physiologically important.

THE EFFECTS OF THE EXTIRPATION OF THE PITUITARY BODY OF FISH, AMPHIBIA, AND REPTILES

The effects of hypophysectomy in fish.—No detailed studies of the effects of hypophysectomy in fish appear to have been made. Orias (1932) was particularly interested in the carbohydrate metabolism in the dogfish (*Mustelis canis*) after hypophysectomy, after pancreatectomy, and after both operations had been performed. He reported that the concentration of glucose in the blood was much higher after pancrea-

[2] In a strict sense, the term "hypophysectomy" should refer to the removal of the tissues derived from Rathke's pouch; in accordance with common usage, however, it is here used to refer to the removal of the pituitary body.

[3] Dandy and Reichert (1925) pointed out that increased intracranial tension may be in part responsible for post-operative symptoms.

tectomy than after both pancreatectomy and hypophysectomy. Hypophysectomy alone was without effect on the blood-sugar concentration. Matthews (1933) observed that the adaptation of *Fundulus* to colored backgrounds, finally effected by changes in the chromatophores, was not altered by hypophysectomy.

The effects of hypophysectomy in amphibia.—In amphibian larvae (salamander, newt, frog, and toad), the most striking single effect of hypophysectomy is the failure of the animals to undergo metamorphosis. Adler (1914) performed the first experiments in tadpoles (*Rana temporaria*) in which he attempted to destroy the pars glandularis by means of a galvano-cautery. The mortality among the operated tadpoles was enormous. Ten of the surviving animals did not undergo metamorphosis. In some of these no cells of the pars glandularis could be found histologically; there was also an associated atrophy of the thyroid and the gonads. Other experiments of Smith (1916 and later) and Allen (1917 and later) were performed in very young tadpoles from which it was possible to remove the whole buccal anlage without injury of the mouth. Some of the operated and normal animals of Adler and Smith are shown in Figures 43 and 45. In addition to failure to undergo metamorphosis, due to a hypofunction of the thyroid (see chap. vii), a retardation in growth, an atrophy of the adrenal cortex and of the epithelial bodies (homologous with the mammalian parathyroids), a persistent fat-organ, and a change in pigmentation (albinism) follow the extirpation of the pars buccalis in tadpoles.

Tadpoles (*R. boylei*) continue to grow for about two months after the removal of the pars buccalis. Their rate of growth is about the same as that of normal animals until the time of the normal mid-larval period subsequent to which it becomes markedly reduced (Smith, 1916, 1918, 1920). Similarly, tadpoles of *R. aurora draytoni* grow much more slowly after the excision of the pars buccalis than do normal or thyroidecto-

mized tadpoles (Allen, 1928). On the other hand, if salamander larvae (*Amblystoma tigrinum*) are hypophysectomized after the development of the thyroid, their growth-rate (at least for a period of eighteen weeks) is not significantly different from that of normal larvae (Greenwood, 1924). Burns and Buyse (1932) also hypophysectomized immature salamanders (*A. tigrinum*, axolotl variety). Despite the operation, the animals grew as large as normal adults. Such results differ from those obtained in mammalian experiments. In very young rats (less than four weeks old), some growth may occur for a short time after hypophysectomy; in older rats (more than six weeks old), growth ceases almost immediately after hypophysectomy. The excision of the pars buccalis in tadpoles would correspond more to the hypophysectomy of the mammal *in utero*—a feat which has never been accomplished. Therefore, the experiments in which tadpoles were used can hardly be compared with those in mammals. More comparable are the experiments of Burns and Buyse, who hypophysectomized immature salamanders which, however, finally grew as large as normal salamanders.

Regeneration of a limb or the tail occurs as readily in hypophysectomized as in normal axolotls (Kabak, 1931).

Involution of the gonads or failure of the gonads to develop as a result of hypophysectomy can be demonstrated more clearly in immature or adult amphibia than in amphibian larvae. Smith (1916) removed the pars buccalis of larvae of *R. boylei* but found no constant change in the gonads as a result of the operation. Atwell (1932) performed the same operation in tadpoles of *R. sylvatica*. The central part of the ovaries of operated tadpoles contained large ovocytes surrounded by interstitial tissue, whereas the cortical part contained largely ovogonia. It is not clear from Atwell's report, however, to what extent this histologic appearance differed from the normal. Observations on the effect of hypophysectomy on the genital tract of adult female toads have been

made by Giusti and Houssay (1922, 1924), Hogben, Charles, and Slome (1931), and Shapiro and Shapiro (1934). The hypophysectomy of *Bufo marinus* in the spring is followed by an expulsion of the ova. In *Xenopus laevis*, the removal of the pituitary is followed by involutionary changes in the ovary. In salamanders and newts, such as *A. tigrinum* and *Triton cristatus*, the ovaries either develop incompletely (immature) or undergo regression (adult) after hypophysectomy. Atresia of the follicles is particularly striking (Woronzowa and Blacher, 1930; Burns and Buyse, 1932; and Dubowik, 1935).

The extirpation of the pituitary of male toads (*B. marinus*, *B. arenarum*) is followed by atrophy of the testes (Giusti and Houssay, 1923–24; Houssay and Giusti, 1930). Houssay and Lascano-Gonzales (1929) were of the opinion that, in *B. marinus*, complete hypophysectomy brought about a more pronounced testicular atrophy than did extirpation of the pars glandularis. In immature and mature salamanders and newts, the removal of the pituitary causes more marked degenerative changes in the testes than in the ovaries (Woronzowa and Blacher, 1930; Burns and Buyse, 1932). The germinal epithelium of the immature hypophysectomized animal fails to develop, and appears to undergo a gradual degeneration; months after the operation, however, some recovery in the form of a return to the larval appearance may be observed. Degenerative changes in the testes are particularly striking in animals hypophysectomized after sexual maturity. Secondary sexual characters, such as swelling about the cloaca, either fail to develop or undergo regression.

Atrophy of the adrenal cortex without much change in the medulla follows hypophysectomy in the amphibian (Smith, 1920). This is similar to what occurs in mammals. The amount of epinephrin in the adrenal gland of *B. arenarum* was found by Houssay and Mazzocco (1933) to be the same in both hypophysectomized and normal toads. The hypotonia

and asthenia of hypophysectomized toads (Houssay, 1933), as well as the lessened work capacity of the gastrocnemius of hypophysectomized frogs (Deuticke, 1931), may be related to the atrophy of the adrenal cortex resulting from the removal of the pituitary.

The significance of the atrophic changes in the thyroid gland of hypophysectomized amphibia is discussed in chapter vii.

From experiments with toads there is considerable evidence of the importance of the pars glandularis in carbohydrate metabolism. Houssay and his co-workers,[4] who performed their experiments with *B. arenarum* and *B. marinus*, found that hypophysectomy was followed by a reduction in the concentration of the blood sugar and of the hepatic glycogen. Moreover, insulin induced a more marked degree of hypoglycemia than in normal animals. In toads rendered diabetic by pancreatectomy, the subsequent removal of either the pars glandularis or the entire pituitary abolished the glycosuria and reduced the concentration of the blood sugar. Zwarenstein and Bosman (1932) hypophysectomized the clawed toad, *X. laevis*. As a result of the operation, the concentration of the blood sugar was not changed; there was, however, less elevation of the blood-sugar concentration, due to the injection of glucose, than in normal animals.

A striking hypertrophy of the fat body is found in hypophysectomized amphibia, without relation to the sex or to the age (larval, immature, or adult) at which the gland is removed.

Allen (1916) and Smith (1916) were the first to call attention to the striking change in the pigmentation of the tadpole following hypophysectomy (silvery appearance, albinism, Fig. 45). Apparently Adler (1914) did not remove all the pars buccalis in his operations (Fig. 43). Further studies of

[4] Houssay, Mazzocco, and Rietti (1925); Houssay and Biasotti (1930–31); Houssay, Di Benedetto, and Mazzocco (1933).

the pigmentary changes resulting from the removal of the pars buccalis or of some of its parts from both larval and adult amphibia,[5] as well as studies of the effects of extracts of different divisions of the pars buccalis, justify the conclusion that the pigmentary change is the result of the removal of the pars intermedia. The important alteration appears to be due to a "contraction" of the melanophores, i.e., the granules of melanin instead of being diffusely distributed in the pigment-cell and its processes are clumped together in the central part of the cell.[6] As a result, the skin appears to contain less black pigment—the degree of the change depending upon the number and nature of the other chromatophores. In addition, there is observed a marked "expansion" of the xantholeucophores (tadpoles, frogs, and toads). In hypophysectomized tadpoles there is also a reduction in the amount of free melanin and in the number of melanophores in the epidermis (Allen, Atwell, Smith).[7] Hogben and Slome (1931) concluded that the adaptation of *X. laevis* (and perhaps of frogs such as *R. fuscigula*) to a white background could not be accomplished unless the pars tuberalis was intact. The indirect control of the chromatophores by means of nerve fibers, presumably ending in the pars intermedia, is discussed in chapter ix.

Other changes in the skin of hypophysectomized amphibia have also been described. Giusti and Houssay (1921) described a bronzing or blackening of the skin in hypophysectomized toads (*B. marinus*) due to a hyperkeratosis. Later, they found that a similar change occurred as a result of lesions of the tuber cinereum (Giusti and Houssay, 1922; Houssay and Giusti, 1929). The removal of the pituitary or

[5] Tadpoles, frogs, toads, and salamanders.

[6] See Sumner (1933), and Mast (1933).

[7] Allen (1916–18, 1929–30); Smith (1916, 1920–23); Atwell (1921); Hogben and Winton (1923); Houssay and Ungar (1924); Puente (1927); Houssay and Giusti (1929); Hogben and Slome (1931); Zieske (1932); and Adams (1933).

the pars glandularis of *T. cristatus* or other newts brings about an abnormal cornification of the epidermis and an interference with molting (Adams). This change is related to a hypofunction of the thyroid (see chap. vii).

The disturbances in the metabolism of water, which may occur in hypophysectomized frogs or toads, are discussed below in the section dealing with lesions of the hypothalamus.

The effect of hypophysectomy on metabolism (oxygen consumption and carbon-dioxide production) in amphibia is discussed in chapter vii. Charles's experiments with *X. laevis*, however, should be mentioned here. She found that the reduction in the oxygen consumption of operated toads was more pronounced in completely hypophysectomized animals than in those from which only the pars glandularis had been removed. The respiratory quotient was often as high as 1.09 (normal toads, 0.82). In the skeletal muscle of hypophysectomized toads (*B. arenarum*) after nerve section, the amount of total phosphorus and of phospho-creatine is reduced (Marenzi, 1933). In *B. marinus*, hypophysectomy has no effect on the amount of glycogen in skeletal muscle (Houssay, Mazzocco, and Rietti, 1925). In another toad, *B. arenarum*, the operation is followed by a bradycardia and apparently a reduction in the concentration of glycogen in the cardiac muscle (Orias, 1934). The concentration of lactic acid in the resting skeletal muscle of the toad is not affected by hypophysectomy; the amount present after indirect stimulation, however, is much greater in normal toads (129 mg. per cent) than in those from which the entire pituitary (53 mg. per cent) or the pars glandularis (88 mg. per cent) has been removed (Marenzi, 1934). The concentration of calcium and of potassium in the serum of *X. laevis* is lowered as a result of hypophysectomy or removal of the pars glandularis (Hogben, Charles, and Slome, 1931; Zwarenstein, 1933). Shapiro and Zwarenstein (1933) found that an equally great reduction in the concentration of calcium in the serum occurred after

gonadectomy; so far as the removal of the pituitary was concerned, they believed that parts of the gland other than the pars glandularis also were factors in the regulation of the concentration of the blood calcium.

The effects of hypophysectomy in reptiles.—Schaefer (1933) has hypophysectomized garter snakes (*Thamnophis sirtalis* and *T. radix*). He reported that the operated snakes shed repeatedly at irregular intervals apparently because of a hypofunction of the thyroid. Hypophysectomy was also followed by an atrophy and a degeneration of the testes as well as a reduction in the size of the adrenal cortex.

THE EFFECTS OF HYPOPHYSECTOMY IN BIRDS

The pituitary body or the pars glandularis has been removed from the fowl, duck, pigeon, and turkey (Mitchell, 1929; Martins, 1933; Hill and Parkes, 1934). Hill and Parkes concluded that a severe metabolic disturbance, not the result of anesthesia or operative trauma, accounted for the death of their hypophysectomized fowls (80 per cent) about 48 hours after operation. Martins, on the other hand, mentioned that pigeons may survive the operation at least 60 days.

In surviving fowls or in those kept alive by the temporary injection of extracts of the pars glandularis or the adrenal cortex (Hill and Parkes), atrophic changes were found in the gonads and thyroid. Secondary sexual characters, such as the comb and wattles, regressed so that their appearance resembled that of gonadectomized fowls. According to Hill and Parkes, the changes in the plumage were those one would expect in fowls suffering from a deficiency of the internal secretions of both the thyroid and the gonads.

Hill, Corkill, and Parkes (1934) believed that a hypoglycemia following hypophysectomy (normal blood sugar, 200 mg. per cent; in hypophysectomized fowl, as low as 119 mg. per cent) was at most a contributory cause of death. Fowls surviving because of treatment only during the critical period

of 4–6 days after operation, usually molted, lost weight, and became inactive. Their blood still contained less glucose than was normal; but they were not abnormally sensitive to insulin.

THE EFFECTS OF HYPOPHYSECTOMY IN MAMMALS

Successful hypophysectomy, complete except for remnants of the pars tuberalis or, rarely, of the pars intermedia, has been performed in nine different mammals.[8] Many of the discordant results in the literature concern hypophysectomy in the dog, and are due to complications arising from injuries of the hypothalamus. Aschner (1912) recognized the complicating dangers of hypothalamic injuries and, unlike Paulesco, Cushing, Biedl, and Blair Bell, correctly maintained that the removal of the pituitary is not immediately fatal. Hypophysectomy was satisfactorily performed in other mammals after Smith's (1927) successful operations in the rat. All the evidence available from extirpation as well as from other experiments in mammals indicates that the pars glandularis is the important division of the pituitary body. After its removal, the gonads, the thyroid, the pancreas, the adrenals, the parathyroids, and probably the thymus do not function normally. Moreover, growth ceases at once or shortly after operation.

The effects of hypophysectomy in the rat.—Various techniques by means of which hypophysectomy can be performed in the rat are described in the papers of Smith (1927, 1930), Koyama (1930), Thompson (1932), Wehefritz and Gierhake (1932), Collip, Selye, and Thomson (1933), Møller-Christensen (1933), Giragossintz (1934), and Anselmino and Pencharz (1934). The most satisfactory method is probably one by which the gland is approached from below as in Smith's parapharyngeal method. Usually the diaphragm of the sella is not broken and most of the pars tuberalis remains.

According to Smith (1932), more than 90 per cent of the

[8] The cat, dog, ferret, guinea pig, hedgehog, monkey, mouse, rabbit, and rat.

pars glandularis must be removed to produce the changes typical of complete hypophysectomy. If 10–30 per cent of the pars glandularis remains, there appear symptoms of a partial pituitary deficiency. Rats appear to be normal in all respects if 30 per cent or more of the pars glandularis remains.

If hypophysectomy is performed in growing rats weighing 80–100 g. or more, growth ceases almost immediately (Smith); in younger rats, however, growth continues for a time even after complete hypophysectomy (Collip, Selye, and Thomson, 1933). In Figures 11–14, photographs both of hypophysectomized and normal brother- or sister-rats and of the same rats' skeletons are reproduced. The stunting of growth is more striking in the hypophysectomized male rat because the normal male littermate grows to a larger size than the normal female littermate. The infantile appearance of such animals depends not only upon the failure to grow but also upon the persistence of the more delicate hair of the young rat. Cachexia may appear earlier if the rat is older at the time of hypophysectomy. Rats hypophysectomized when young frequently become emaciated after weeks or months; they produce heat at a slower rate and commonly have a lower body temperature than normal rats. Isolated tissues, such as the liver and the cortex of the kidney, if obtained from young rats from which the pituitary body has been removed, consume less oxygen than similar normal tissues (Reiss, Hochwald, and Druckrey, 1933). The spontaneous activity of hypophysectomized rats is markedly reduced (Richter and Wislocki, 1930). So far as the skeleton is concerned, the chief changes are a shrinkage and a degeneration of the epiphysial cartilage with a failure in growth (Smith). The incisor teeth, which normally grow continuously, grow much more slowly after hypophysectomy; the operation also causes a delay in the eruption of the molars and histologic changes in both the molars and the incisors (Schour and

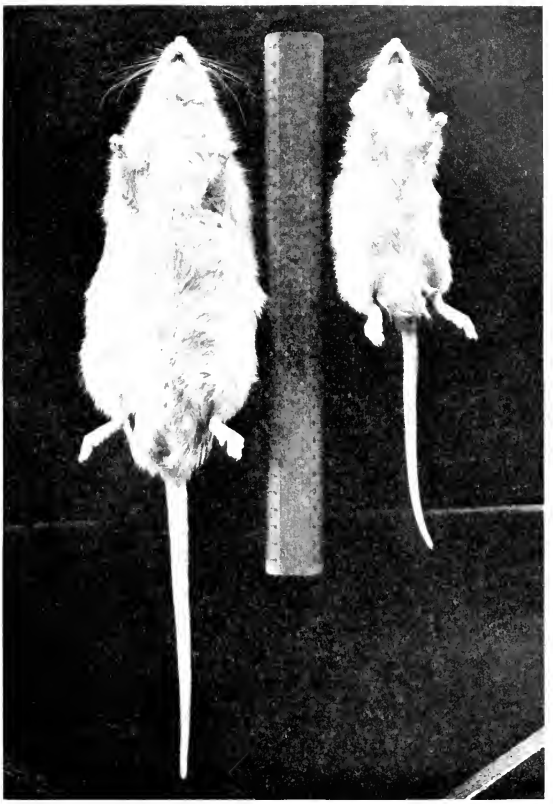


FIG. 11.—Normal (left) and hypophysectomized (right) littermate male rats. The rat at the right was hypophysectomized at an age of 38 days. Both rats were killed at an age of 170 days. Weight of the normal rat, 408 g.; weight of the hypophysectomized rat, 120 g.

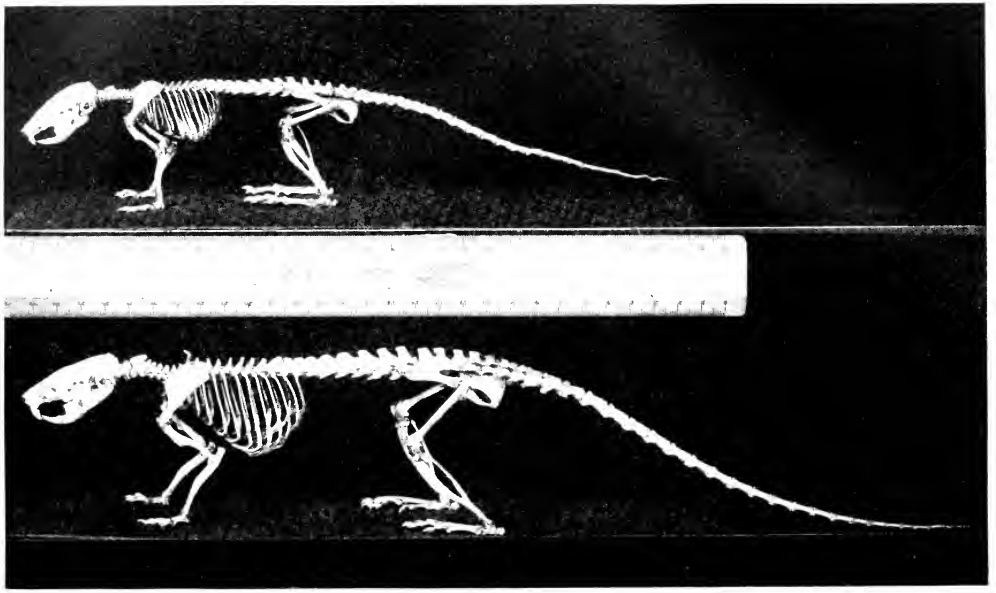


FIG. 12.—The skeletons of the rats shown in Figure 11

van Dyke, 1932). Koyama (1930–31) found that the weight of the brain of the rat hypophysectomized when immature was

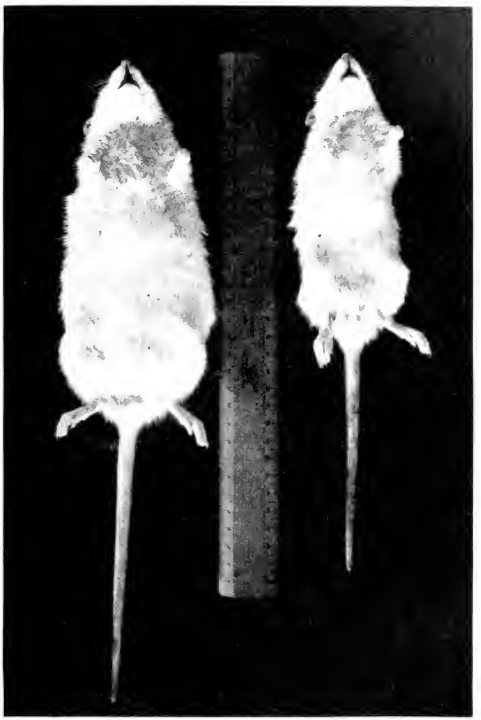


FIG. 13.—Normal (left) and hypophysectomized (right) littermate female rats. The rat at the right was hypophysectomized at an age of 39 days. Both rats were killed at an age of 175 days. Weight of the normal rat, 267 g.; weight of the hypophysectomized rat, 113 g.

the same as that of the normal rat if both were killed some months later. He implied that growth of the brain had occurred in the hypophysectomized rat. A reference to the

data of Donaldson (1924), however, shows that the weight of the brain of an immature rat (50 g.) may be three-fourths that of an adult rat (350 g.).

Smith estimated that, under the most favorable conditions, the life-span of the hypophysectomized rat is about one-half that of the normal rat.

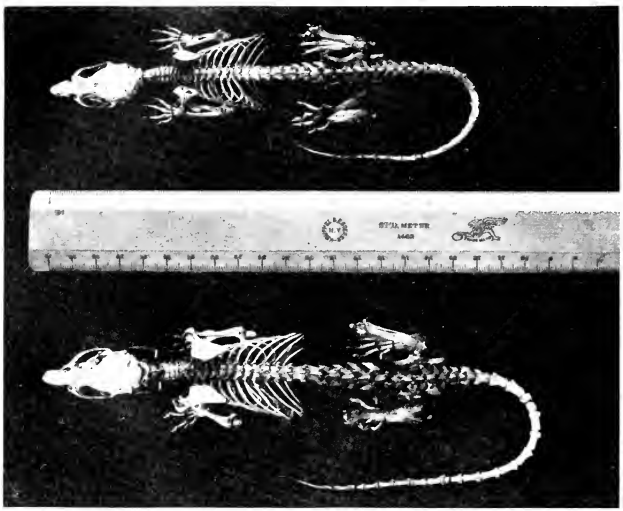


FIG. 14.—The skeletons of the rats shown in Figure 13

As in amphibia, reptiles, and birds, hypophysectomy in the rat is rapidly followed by atrophy and degenerative changes in the gonads and their related structures. The gross and microscopic appearances of the testis of a hypophysectomized and a normal rat are shown in Figures 15 and 16. The regressive changes involve not only the germinal epithelium but also the interstitial cells, so that a marked atrophy of the seminal vesicles, prostate, etc., occurs (see Figs. 17 and 18).

White (1932) found that spermatozoa survived (judged by motility) about three weeks after either hypophysectomy or after hypophysectomy and castration. Reiss, Druckrey, and Hochwald (1933) investigated the metabolism of isolated testicular tissue of rats weighing about 100 g. when hypophysectomized. Even 4 days after operation the oxygen consumption of the isolated testis was reduced. After about 15

FIG. 15.—The testis after hypophysectomy. Left: A testis of the hypophysectomized rat of Figure 11; weight of both testes, 0.577 g. (Note that the *tunicae* were accidentally injured so that some of the *parenchyma testis* is escaping.) Right: A testis of the normal rat of Figure 11; weight of both testes, 2.694 g.

days, the rate of anaerobic glycolysis was reduced. The rate of aerobic glycolysis appeared to increase slowly.

Sexual desire is lost more quickly and more completely after hypophysectomy than after castration (Smith, 1930; Wiesner and Sheard, 1933).

Smith described in detail the changes in the female genital tract of the hypophysectomized rat. Some of the changes in the ovaries, uterus, and vagina are illustrated in Figures 19, 20, 21, 22, and 23. The principal changes in the ovary consist of, (1) an atresia of all follicles, medium-sized or larger,

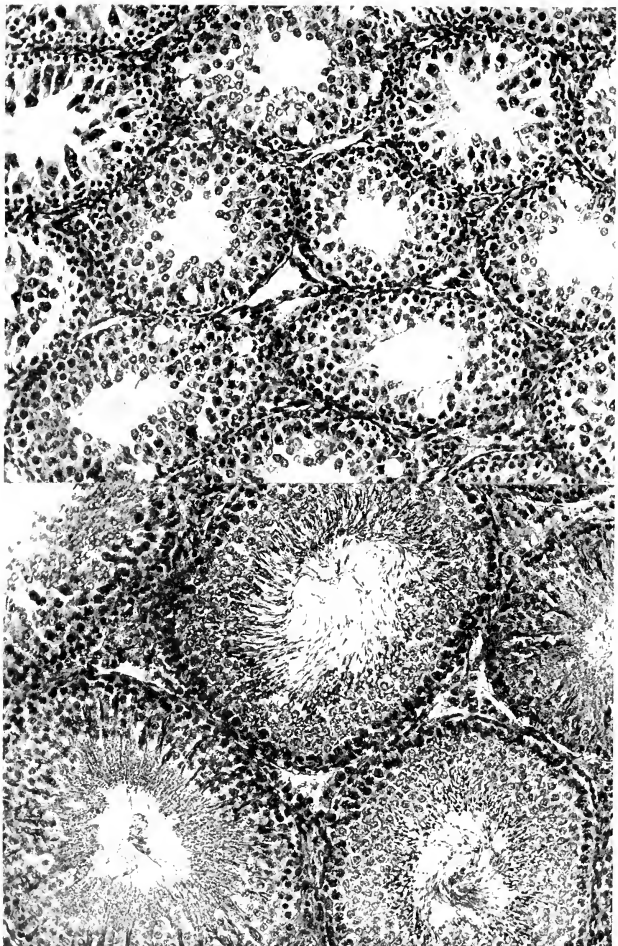


FIG. 16.— Photomicrographs of the testes shown in Figure 15. ×200. Top, testis of the hypophysectomized rat; bottom, testis of the normal rat.

including those continuing to develop from the reduced number of primordial follicles, and (2) an abnormal persistence of corpora lutea (9.5–14.5 months compared with 2.5 months in the normal animal) probably present at the time of hypophysectomy. According to Swezy (1933), the rate of ovogenesis is increased after hypophysectomy. Selye (1933) reported that in rats hypophysectomized at an age of 18 days and killed 10–25 days later the ovaries contained both normal follicles

FIG. 17.—The seminal vesicles of the rats shown in Figure 11. Left, of the hypophysectomized rat; weight, 16.8 mg. Right, of the normal rat; weight, 652.0 mg.

and atretic follicles; the theca-cells about the latter appeared to be undergoing degeneration ("theca-deficiency cells"). Selye, Collip, and Thomson (1933) described the appearance of the ovaries of rats 6–8 months after hypophysectomy, which was performed after the animals had become sexually mature. Much of the ovary seemed to be made up of cells of theca origin, the nuclear changes in which led them to describe the cells as "wheel-cells." Unilateral ovariectomy in the hypophysectomized rat is followed not by compensatory

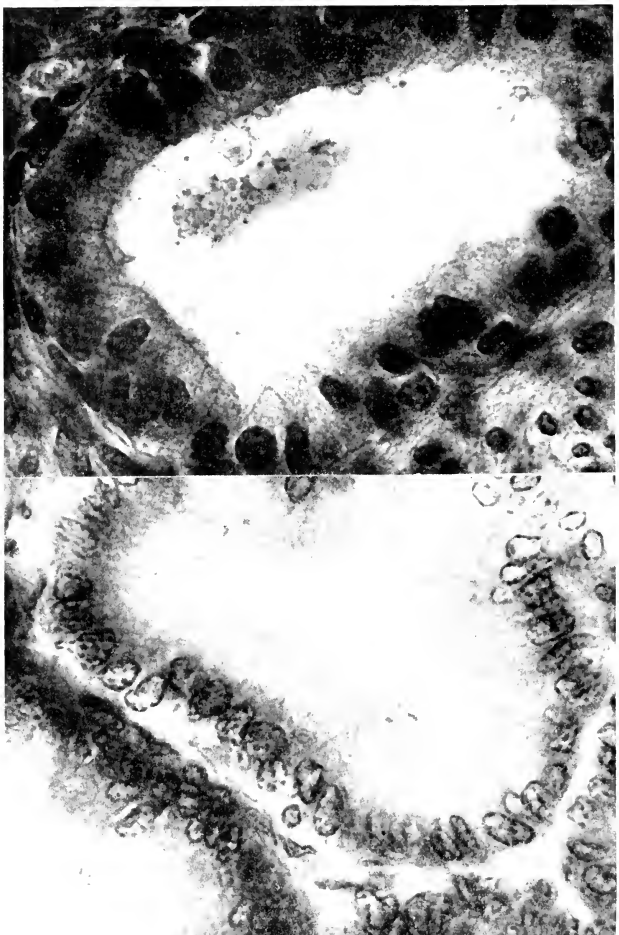


FIG. 18.—Photomicrographs of the seminal vesicles shown in Figure 17. ×1,290. Top, of the hypophysectomized rat; bottom, of the normal rat.

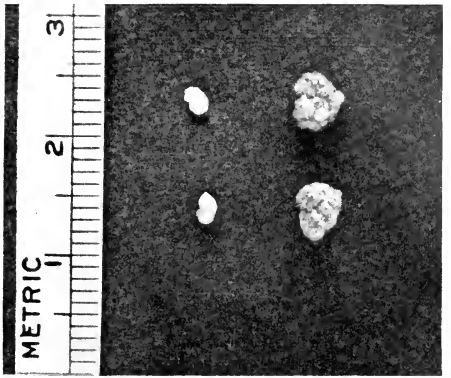


FIG. 19.—The ovaries of the rats shown in Figure 13. Left, of the hypophysectomized rat; weight, 6.0 mg. Right, of the normal rat; weight, 46.6 mg.

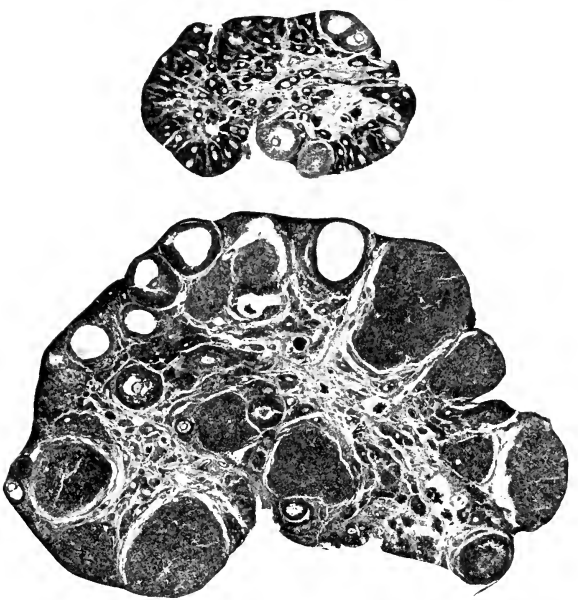


FIG. 20.—Photomicrographs of the ovaries shown in Figure 19. ×22. Top, ovary of the hypophysectomized rat; bottom, ovary of the normal rat.

hypertrophy (as in normal rats), but by further atrophy (Smith, 1930).

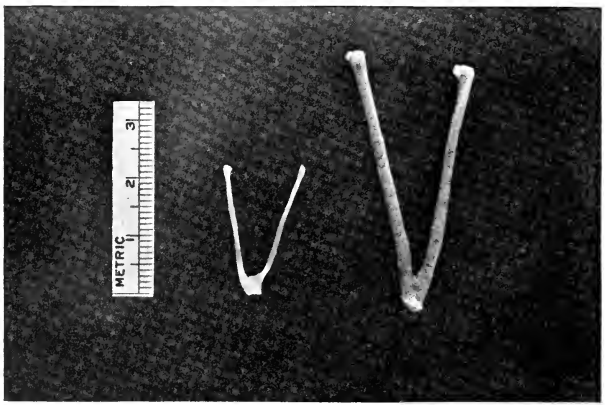


FIG. 21.—The uteri of the rats shown in Figure 13. Left, of the hypophysectomized rat; weight, 34.2 mg. Right, of the normal rat; weight, 283.0 mg.

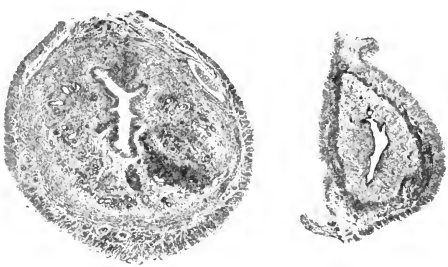


FIG. 22.—Photomicrographs of the uteri shown in Figure 21. ×22. Left, uterus of the normal rat. Right, uterus of the hypophysectomized rat.

Oestrous cycles and probably ovulation do not occur in the hypophysectomized rat. Both the uterus and the vagina undergo a marked atrophy (Figs. 21–23). The characteristic

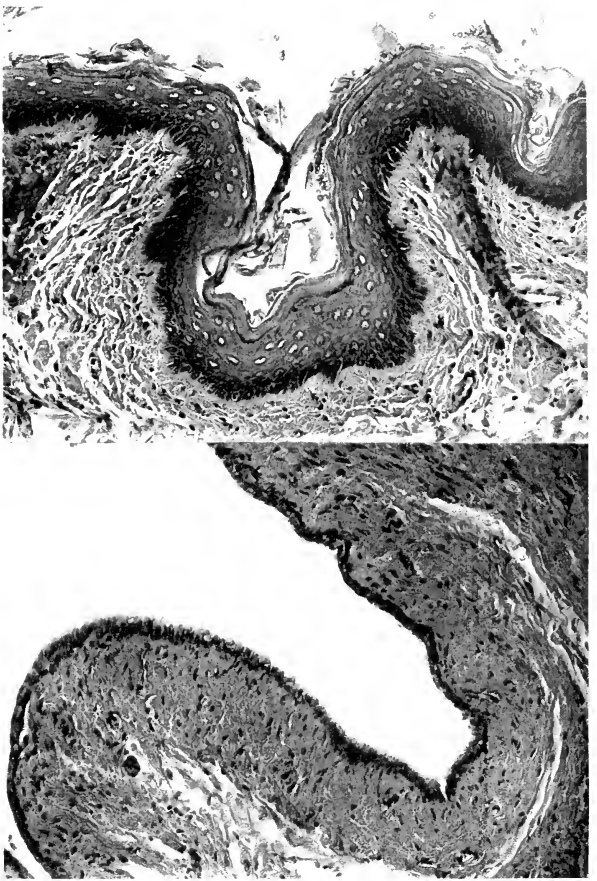


FIG. 23.—Photomicrographs of the vaginae of the rats shown in Figure 13. ×200. Top, vagina of the normal rat; bottom, vagina of the hypophysectomized rat.

changes in both structures following the injection of oestrin, however, are as readily observed in hypophysectomized as in spayed rats (Smith, 1932).

Pregnant rats have been hypophysectomized by Pencharz and Long (1933), Selye, Collip, and Thomson (1933), and Bergmann (1934). Parturition can occur in the absence of the pars neuralis even if the latter has been removed weeks before the termination of pregnancy (Smith, 1932). Implantation is prevented if hypophysectomy is performed not more than 4 days after coitus. Death and resorption of the fetuses occur in rats hypophysectomized 7–10 days after impregnation. Hypophysectomy between the tenth and twentieth days of pregnancy results either in fetal death and resorption or in a prolongation of the pregnancy from the normal period of 21–22 days to a period of 24–26 days. Dead or living young may then be born. Normal parturition occurs in rats hypophysectomized on the twenty-first day of pregnancy. It is not clear exactly why hypophysectomy should lead to a prolongation of the period of gestation. The corpora lutea of pregnancy appear normal histologically. The uterus, however, is said to be less sensitive to the oxytocic principle of the pars neuralis.

The mammary glands of hypophysectomized pregnant rats undergo hypertrophy; the secretion of milk sets in immediately postpartum only to cease a few hours later. If the uterus of the pregnant rat is emptied, lactation sets in and continues for 36 hours, but not if hypophysectomy has also been performed (Collip and others, 1933). If the lactating rat is hypophysectomized, the secretion of milk ceases within 24 hours (Jeffers, 1935). The pituitary, therefore, must be intact if the secretion of milk is to continue; the growth of the mammary gland, however, can occur in the absence of the pituitary.

The changes in the anatomy and physiology of the thyroid

gland following hypophysectomy are discussed in chapter vii. (Also see Figs. 46 and 47.)

Phillips and Robb (1934) reported that the blood-sugar concentration of fasting hypophysectomized rats was low (35–50 mg. per cent). They also believed that the intestinal absorption of glucose was less than that in normal rats and that the rate of storage of glycogen in the liver and in striated muscle was considerably slower than in normal rats.

In rats, as in other animals, the adrenal cortex but not the medulla becomes atrophic after hypophysectomy (see Figs. 50 and 51). The medulla, however, is not as large as that of a normal animal if a considerable time has elapsed after hypophysectomy, but is normal in structure (Smith, 1930). Accompanying atrophy of the adrenal cortex, there occurs a reduction both in the amount of fat and in the amount of cytoplasm of the cortical cells. Perla (1935) observed hemorrhages in the zona reticularis of the adrenal cortex during the first 2 weeks after the removal of the pituitary from adult rats. He concluded that this change preceded an atrophy.

The author is not aware of any study of the parathyroid glands of hypophysectomized rats.

Smith (1930) reported that the thymus of the hypophysectomized rat (weight, 91–149 g. at the time of operation) underwent a more rapid involution than that of the normal rat. In normal and hypophysectomized rats killed months after the operation, the absolute weight of the thymus of the hypophysectomized rat was about one-half that of the normal rat. Opposite results were obtained by Richter and Wislocki (1930), who described a marked hypertrophy of the thymus in hypophysectomized *adult* rats.

According to Wyman and tum Suden (1934), removal of the pars neuralis of the rat affected neither the blood pressure nor the susceptibility to histamine, whereas total hypophysectomy was followed by a lowered blood pressure and an increased susceptibility to histamine. Foster and Smith (1926)

stated that the specific dynamic action of glycocoll, administered by intraperitoneal injection, was abolished by total hypophysectomy but not by the removal of either the anterior or the posterior lobe alone.

The growth of the Walker mammary-gland carcinoma in hypophysectomized and normal rats was investigated by Ball, Samuels, and Simpson (1932), Samuels, Ball, and Simpson (1933), and McEuen (1933). The rate of growth of the tumor was slower, but the area of necrosis in the tumor was greater in the transplants in hypophysectomized rats. These findings suggest that the tumors growing in the hypophysectomized rats were less adequately vascularized than those growing in the normal rats. Reiss, Druckrey, and Hochwald (1933) transplanted the Jensen-sarcoma into young rats before and after hypophysectomy. The operation had striking effects on the growth of this tumor. The removal of all the pituitary body from tumor-bearing animals (provided that the tumor was smaller than a cherry in size) or the successful transplantation of the tumor into hypophysectomized animals was followed by some growth of the sarcoma; however, within 3 weeks, the tumor retrogressed especially in animals losing weight. The retrogression occurred earlier if the tumor was transplanted into rats some months after hypophysectomy.

The effects of hypophysectomy in the dog.—Since Horsley's (1886) first observations on experimental hypophysectomy in the dog, the literature has contained numerous reports of the effects of the removal of the pituitary. The difficulty of the operation is reflected in the discordant results of different investigators. If the number of papers published be accepted as a guide, more attention has been given to hypophysectomy in the dog than in any other animal. Horsley's dogs lived in apparently normal health for months after the removal of the pituitary—an observation which Handelsmann and he (1911) repeated a quarter of a century later. Paulesco (1907), how-

ever, found that the complete removal of the gland was followed by death usually within 24 hours; this result he believed not to be due to operative trauma either of the hypothalamus or of other structures. Cushing and his collaborators, Biedl, Blair Bell, and others were more or less in agreement with this view. For example, Crowe, Cushing, and Homans (1910) reported that complete hypophysectomy in adult dogs was followed by death within 5 days, whereas the performance of the same operation in puppies permitted survival for as long a period as 3 weeks. They, like others, described symptoms of hypophysial deficiency now recognized as characteristic; however, these were frequently complicated by symptoms now believed to be due chiefly to lesions of the hypothalamus and/or increased intracranial pressure. Aschner (1912), Ascoli and Legnani (1912), and Sweet and Allen (1913) all believed that the removal of the pituitary body was not followed by death within a short time. As a result of his elaborate investigation, Aschner concluded that injury of the tuber cinereum was the unrecognized complication responsible for the rapidly fatal issue of the operation as described by Paulesco and later investigators. With few exceptions (Blair Bell, 1917; Dott, 1923), all later work (such as by Benedict and Homans, 1912; Houssay and his collaborators, *after* 1921; Camus and Roussy, 1913, 1922; Brown, 1923; Dandy and Reichert, 1925; McLean, 1928; Koster and Geesink, 1929; Karlik and Robinson, 1931) indicates that hypophysectomized dogs may live for months, but that obesity and transient polyuria with or without glycosuria also frequently occur in operated animals.

In order to gain access to the gland, two types of approach are commonly used: the temporal and the buccal. The temporal approach is aseptic but is more likely to be complicated by direct or indirect injury of the brain. The disadvantage and advantage of the buccal approach are the reverse of those of the temporal approach: asepsis cannot be complete; serious

injury of the brain, however, can be avoided. In the absence of hemorrhage and infection, hypophysectomy in the dog as a rule is quickly followed by the death only of those animals in which the gland has been approached from the temporal side of the cranium. By skilled hands, however, the operation by either approach has been satisfactorily performed (e.g., Aschner, 1912, Dandy and Reichert, 1925; Reichert, 1928; McLean, 1928).

The effects of the removal of the pars glandularis.—In the dog, as in the rat, the important effects of the removal of the pituitary body are due to the removal of the pars glandularis. Those who formerly believed that hypophysectomy was followed shortly by death attributed this result to the extirpation of the pars glandularis. In the cases of some of their dogs, however, they believed that, because of the incomplete removal of the pars glandularis, the animals lived and later exhibited the symptoms of a pituitary deficiency. Aschner (1912) concluded that hypophysectomy in the dog is physiologically complete if no remnants of the pars glandularis can be found grossly; he also stated that no symptoms of pituitary deficiency appear if about one-third of the pars glandularis remains—an estimate very close to that made by Smith (1932) in his study of partial hypophysectomy in the rat.

The principal changes, clearly attributable to hypophysectomy in dogs, resemble those in hypophysectomized rats. As a result of hypophysectomy, puppies cease to grow but may increase somewhat in weight due to the deposition of fat. Unlike normal brothers or sisters, their skeletons scarcely change in size, the epiphyses remain open, and the first dentition persists for months after it has been replaced by the second dentition in normal dogs. The skin and hair remain infantile. The animals are sluggish and inactive.[9] The body temperature is 1–1.5° C. lower than that of normal dogs; the

[9] Conditioned reflexes in hypophysectomized dogs have been compared with those in normal dogs by Kriaschew (1933).

gaseous metabolism takes place at a slower rate. Atrophic changes or other anatomical indications of diminished function are clearly discernible in the gonads and in the thyroid and adrenal glands.

The testes and the male secondary sexual organs either regress (after the removal of the pituitary of the sexually mature dog) or remain infantile (after the hypophysectomy of puppies). The changes in the ovaries and female secondary sexual organs are similar in nature. Aschner hypophysectomized three pregnant dogs. Abortion took place in two (5- and 7-weeks' pregnancies) within less than a week. In a third, hypophysectomized late in pregnancy, parturition occurred 12 days after the operation; the fetuses were born alive, but lived only 2 days. Aschner's protocols, although mentioning lactation, do not indicate that the latter was affected by the removal of the pituitary.

The changes in the thyroid, and the associated alterations in the metabolism, in the concentration of iodine in the blood, etc., are discussed in chapter vii.

A large part of the evidence in favor of an important interrelationship among the pars glandularis, the islet-tissue of the pancreas, and the carbohydrate metabolism, has been gathered in dogs. Sachs and MacDonald (1925), Pickat (1927), and Koster and Geesink (1929) found that the concentration of sugar in the blood was lower in hypophysectomized than in normal dogs. Similar reports were made by others (Kobayashi, 1931; Fujimoto, 1932; Lucke, Heydemann, and Hechler, 1933; and Ichijo, 1934); not all the pars glandularis, however, had been removed from some of the dogs. The most marked changes in the blood-sugar concentration were reported by Biasotti and Houssay (1931–32) and D'Amour and Keller (1933). They found that the concentration of glucose in the blood was frequently very low (34–70 mg. per cent); in some cases, the symptoms of animals dying appeared to be the result of a hypoglycemia. Cowley (1931)

found that the subcutaneous injection of 8–10 cc. of the blood of a starved normal dog into a rabbit (1.5–2.0 kg.) was followed by a reduction in the concentration of blood sugar amounting to 5 per cent; under similar conditions, a greater reduction (23 per cent) in the concentration of the blood sugar followed the injection of the blood of a hypophysectomized dog. This report was not confirmed by Di Benedetto (1934), who injected as much as 20 cc. of blood.

The administration of glucose, by stomach-tube or parenterally, on the other hand, is usually said to modify the glycemic curve of hypophysectomized dogs in the direction of a greater change (increase) and a slower return to normal (Klug, 1928; D'Amour and Keller, 1933; Lucke, Heydemann, and Hechler, 1933; Biasotti, 1934). (Some have stated either that the curve is normal or perhaps rises more slowly [Houssay and Hug, 1921; Houssay, Hug, and Malamud, 1922; Sachs and MacDonald, 1925].) Only Fujimoto (1932) found that less elevation of the glycemic curve occurred in hypophysectomized dogs. Both he, and Lucke and others, reported that the glycosuria following the administration of glucose was less in hypophysectomized dogs than in normal dogs.

The amount of glycogen in the liver and in striated muscle is said not to be affected by hypophysectomy (Aschner, 1912; Houssay, Hug, and Malamud, 1922). Yet epinephrin produces less elevation of blood sugar and less glycosuria in operated animals (Aschner, 1912; Fujimoto, 1932). Such changes do not necessarily indicate a decreased sensitivity of the sympathetic nervous system, as Aschner thought, but may be due to an increased rate in the metabolism of glucose or to other causes.

The administration of phlorhizin to hypophysectomized dogs, in comparison with normal dogs, brings about the following changes (Houssay and Biasotti, 1931; Biasotti and Houssay, 1932; Rietti, 1932): (1) death frequently occurs, the blood-sugar concentration being less than 70 mg. per

cent; (2) the blood-sugar concentration falls faster; (3) less glucose and less nitrogen are excreted in the urine, but the reduction in the excretion of glucose is the greater so that the D/N ratio is lower; (4) the excretion of acetone bodies is reduced. Biasotti and Houssay concluded from these observations that, in the hypophysectomized dog, glucose is formed from protein less readily than in normal dogs.

All authors[10] agree that insulin shock is produced much more easily in hypophysectomized dogs. According to Geiling and his collaborators, even 0.15 clinical unit of insulin per kg. dog produced insulin shock, whereas 2–3 units were required to produce the same symptoms in normal dogs. They believed that this change was due to the extirpation of the pars neuralis, because it was not observed in one dog from which only the pars glandularis had been removed. The completeness of the removal of the pars glandularis, however, was not investigated postmortem. From other observations on the effects of extracts of the pars glandularis (see chap. viii), it seems more likely that the increased insulin-sensitivity of the hypophysectomized dog is principally due to the removal of the pars glandularis.

If both hypophysectomy and pancreatectomy are performed in the same dog, the course of the diabetes is profoundly modified (Houssay and Biasotti, 1930–31; Barnes and Regan, 1933; and others). Such dogs may live without insulin for months; they excrete less glucose (D/N ratio: 0.87–1.85)—sometimes none if they are starved; acetone is found in their urine infrequently; the concentration of sugar in their blood (130–270 mg. per cent) is less than that in the blood of pancreatectomized dogs. The course of phlorhizin diabetes is about the same in hypophysectomized and in pancreatectomized-hypophysectomized dogs. It is of consider-

[10] Houssay and Magenta (1925); Geiling, Campbell, and Ishikawa (1927); Fujimoto (1932); Di Benedetto (1933); and Lucke, Heydemann, and Hechler (1933).

able interest that abnormally high sensitivity to insulin is said still to persist after the removal of the pancreas from a hypophysectomized animal. If this observation is correct, the frequently observed hypoglycemia and increased insulin sensitivity of the hypophysectomized dog cannot be interpreted as merely the results of the removal of an "inhibitory" effect of the pituitary on the pancreas.

Aschner's statement that the adrenal cortex of the hypophysectomized dog is thickened but that the adrenal body is not enlarged because of an atrophy of the medulla has not been confirmed. On the contrary, it appears that the principal change is an atrophy of the adrenal cortex, as in the rat (Ascoli and Legnani, 1912; Houssay and others, 1933). The latter authors found that the adrenal body was about 40 per cent smaller in the hypophysectomized dog in comparison with the normal. The medulla appeared to be unaltered. The whole adrenal contained, in absolute terms, as much epinephrin as the normal gland (colorimetric determinations). In the cortex, owing to the atrophy of the reticulate and fasciculate zones, the glomerular zone appeared to be hypertrophied.

Although degenerative changes can be found in the parathyroid glands of hypophysectomized dogs (Koster, 1930), they are said to occur in only about two-thirds of the cases (Houssay and Sammartino, 1933). However, they are always present in hypophysectomized dogs also subjected to thyroidectomy or pancreatectomy (Houssay and others, 1931, 1933). Koster and Geesink (1929) observed a reduction (0.5–2.8 mg. per cent) in the concentration of the blood calcium. The change was not constant and only infrequently great enough to justify their conclusion that there was a significant reduction. Neither Mazzocco (1927) nor Gerschmann (1931) found any change in the amount of calcium in the blood of hypophysectomized dogs.

Some contend that the thymus is somewhat larger or per-

sists for a longer time in hypophysectomized dogs (Aschner, 1912; Koster, 1930), whereas others find that the gland regresses more rapidly as a result of the operation (Ascoli and Legnani, 1912; Houssay and Hug, 1921; Kapran, 1932). The latest report is that of Houssay and Lascano-Gonzalez (1934). They stated that precocious involution of the thymus occurred in three-fourths of dogs hypophysectomized at an age of 6–10 weeks and killed 5 weeks to a year later. The atrophic changes, if present, involved chiefly the cortex; only few Hassall's corpuscles could be found.

No change in the pineal body occurs after hypophysectomy (Aschner).

The blood pressure of the hypophysectomized dog is 20–30 mm. lower than that of the normal dog (130–135 mm. Hg). It is not altered, however, by the removal of the pars neuralis. After a hemorrhage (1.5 per cent of the body-weight), the blood pressure returns to its former level after 45 minutes in normal dogs, but only after 95 minutes in hypophysectomized dogs (Braun-Menendez, 1932, 1934).

Besides those already mentioned, other constituents of the blood have been studied in hypophysectomized dogs. In nearly every case in which observations have been repeated—sometimes in the same laboratory—there are disagreements in results. The exceptions are sodium and chloride, which are said to be present in the normal concentration (Mazzocco, 1927; Marenzi and Gerschmann, 1935). The concentration of potassium and magnesium in the blood is said either to remain unchanged after hypophysectomy (Mazzocco, 1927) or to be reduced (Marenzi and Gerschmann, 1935). Similarly, the concentration of inorganic phosphate has been reported not to change (Mazzocco, 1927; Gerschmann, 1931; and Marenzi and Gerschmann, 1935), or to fall (Kobayashi, 1931; and Ichijo, 1934). Fukushima (1931) stated that the concentration of total fatty acids, lipoid phosphorus, and cholesterol in the blood was greater in hypophysectomized than in nor-

mal dogs. According to Houssay and Mazzocco (1922), the important non-protein nitrogenous constituents of blood are present in about the same concentration in the blood of normal and of hypophysectomized dogs.

Some of the most important changes in metabolism (particularly the basal metabolism) after hypophysectomy are discussed in chapter vii. It is appropriate to mention here, however, studies of the protein metabolism in hypophysectomized and normal dogs. If the hypophysectomized dog is starved, the excretion of nitrogen is considerably reduced (one-third to two-thirds) in comparison with that of the starved normal dog (Aschner, 1912; Braier, 1931, 1933). Normal and hypophysectomized dogs fed regularly, however, excrete in 24 hours about the same amount of nitrogen in the urine; but during the first 8 hours the operated dogs excrete less (Braier). The hypophysectomized dog is thought to excrete more allantoin and less uric acid and purine bases in comparison with the normal dog (Braier, 1933). The administration of protein to the hypophysectomized dog produces a relatively greater specific dynamic action because the basal metabolic rate of the hypophysectomized dog is considerably less than normal (Artundo, 1931).

From observations of the effects of extirpation of the anterior or posterior lobe of the pituitary body, and from studies of the effects of extracts of the various parts of the pituitary, it may be concluded that probably all the changes so far described are due to the removal of the pars glandularis. There is no evidence that the pars intermedia is physiologically important in the dog. The pars tuberalis is said to undergo hypertrophy after hypophysectomy (Koster, 1928; Koster and Geesink, 1929), but this has been denied (Karlik and Robinson, 1931). In the case of the active principles which can be extracted from the pars neuralis, some investigators have observed in hypophysectomized dogs changes which they attributed to the removal of the posterior lobe. For the

most part these experiments deal with (*a*) the oxytocic principle, and (*b*) the principle responsible for diuretic-antidiuretic effects. However, parturition takes place in the hypophysectomized dog or in the dog from which the posterior lobe has been removed (Aschner, 1912; Dott, 1923). Moreover, the metabolism of water may remain unchanged in the hypophysectomized dog (Houssay and Hug, 1921; Houssay and Mazzocco, 1922). As was mentioned before, the blood pressure of the dog may fall after hypophysectomy, but not after the removal of the posterior lobe. There is, therefore, little evidence in favor of the view that the pars neuralis (or posterior lobe) is physiologically important. The interpretation of the data is intimately connected with the interpretation of the effects of hypothalamic lesions and will therefore be postponed (pp. 71–79).

The effects of hypophysectomy in other mammals.—Selye, Collip, and Thomson (1933) studied the effects of hypophysectomy in pregnant and lactating mice. Apparently normal parturition occurred in mice from which the pituitary was removed in the latter half of pregnancy; the young, which appeared normal, were probably still-born. Milk was secreted by the mothers only for a short time postpartum. Hypophysectomy in lactating mice prevented the secretion of milk within 24 hours after the operation. In hypophysectomized mice, unlike hypophysectomized rats, the corpora lutea did not persist, but regressed rapidly.

The technique of hypophysectomy in the guinea pig has been described by McPhail and Parkes (1933), Anselmino and Pencharz (1934), and Macchiarulo and Amelotti (1934). Pencharz and Lyon (1934) hypophysectomized pregnant guinea pigs. In animals subjected to operation on the thirty-fourth to the thirty-sixth day, resorption of the fetuses began within two days. If the operation was performed on the fortieth to the forty-first day of pregnancy, the period of gestation was not significantly altered (63–67 days); however,

only a slight and transient secretion of milk was observed after parturition. As in the hypophysectomized mouse (but not the rat), the corpora lutea of the hypophysectomized guinea pig rapidly regressed.

Successful hypophysectomy in the rabbit is best performed by employing an orbital (Firor), parapharyngeal (Smith and White), or a buccal approach (White); other methods, such as by the use of a nasal trocar (Kosakae, 1930), of hot wax to cause a necrosis (Krieser and Partos, 1935), or of radon (Lacassague and Nyka, 1934) or X-rays (Mogilnitzky and Podljaschuk, 1928) not only are more likely to damage adjacent structures but also are less likely to effect the complete removal or destruction of the gland. All the effects of hypophysectomy in the rabbit appear to be due to the removal of the pars glandularis.

By means of acute experiments in rabbits from which the pituitary was removed, Fee and Parkes (1929) showed that ovulation, which normally takes place about 10 hours after coitus, could be prevented provided that hypophysectomy was done within less than 1 hour *post coitum*. If the operation was performed later than 1 hour after copulation, ovulation occurred and the corpora lutea underwent normal but perhaps slower development than in control rabbits (Deanesly, Fee, and Parkes, 1930). These observations were confirmed and extended by Smith and White (1931) who found that the corpora lutea continued to grow only for about 2 days; after 8 days they had definitely begun to regress. The early development of the corpus luteum in the rabbit may therefore take place in the absence of the pituitary (but not necessarily in the absence of pituitary secretion).

The other effects of hypophysectomy in immature or adult rabbits resemble those in other mammals (White, 1933; Saito, 1934). White also found a considerable atrophy of the liver and spleen in hypophysectomized adult rabbits. According to Firor and Reynolds (1933), spontaneous contrac-

tions of the uterus due to the injection of oestrone (theelin) are inhibited by actively secreting corpora lutea (pregnancy or pseudopregnancy); this inhibition, however, was not observed 48 hours after the hypophysectomy of rabbits on the fifth or sixth day of pregnancy or pseudopregnancy. Morimoto and Ikeda (1932) stated that the uterus of the hypophysectomized rabbit could be electrically stimulated (technique not described) less readily than that of the normal rabbit. Saito (1934) studied some aspects of the carbohydrate metabolism in hypophysectomized and normal rabbits. Hypoglycemia could be observed particularly in operated animals which were cachectic. In comparison with normal rabbits, hypophysectomized rabbits exhibited a greater susceptibility to insulin and a smaller increase in the concentration of the blood sugar after the injection of epinephrin.

White (1932) and Firor (1933) have investigated the effect of the removal of the pituitary body from pregnant rabbits. Ovulation but not implantation occurred if hypophysectomy was done 50 minutes (White: 60 to 75 minutes) to 3 days after copulation. Hypophysectomy on the fourteenth day *post coitum* caused, as a rule, fetal resorption; the later performance of the operation (17–28 days) usually caused a termination of the pregnancy within 48 to 72 hours.[11] The expelled fetuses were either dead or lived only a few hours. Apparently parturition can occur in the absence of all parts of the pituitary body (Firor).

McPhail and Parkes (1933) have described the technique of hypophysectomy in the hedgehog.

Observations on the technique and effects of hypophysectomy in ferrets have been made by Hill and Parkes (1932–33) and by McPhail (1933, 1935). In the ferret, as in the rabbit and cat, ovulation ordinarily occurs only after copulation. Hypophysectomy prevents ovulation in the ferret provided that it is performed within 1 hour after the beginning of

[11] Firor's control rabbits delivered 30–34 days after copulation.

coitus. Animals hypophysectomized 2 hours after the beginning of coitus ovulate normally (after about 36 hours); the corpora lutea subsequently formed do not grow, but appear immature. There are no signs of pseudopregnancy 8 days after copulation followed by hypophysectomy, in spite of which ovulation and corpus-luteum formation occurred. Atrophy and regressive changes appear in the gonads of both male and female ferrets after hypophysectomy; such changes are perhaps more marked if the operation is performed during the period of anoestrus. If male or female ferrets are placed in artificially lighted quarters, oestrus occurs during the anoestrous period (Bissonnette); in the female, at least, this effect is not observed after hypophysectomy. No differences in the response of the uterus to oestriol is found if normal, ovariectomized, and hypophysectomized anoestrous ferrets are compared.

Pregnancy in the ferret is interrupted by hypophysectomy. If the operation is performed on the twenty-first day (the normal period of gestation is 41–42 days), abortion or fetal resorption occurs; if the operation is performed on the thirty-fifth day, parturition takes place within 3 days. The young may be delivered dead or living; in the latter event, they die shortly after delivery. The secretion of milk by the mother rarely appears postpartum, and never persists. Hypophysectomy during lactation is promptly followed by a cessation of the secretion of milk. The effects of hypophysectomy in pregnant and lactating ferrets therefore resemble those in other mammals.

Gemelli, who apparently was the first (1908) successfully to hypophysectomize cats, recognized that the removal of the pituitary did not immediately cause death but that changes in growth and in the glands of internal secretion followed the operation. Until recently, however, the mortality in operated animals has been high (Camus and Roussy, 1922; Ciminata, 1926). In the later, more successful operations, the approach

to the gland has been transbuccal, parapharyngeal, or retropharyngeal.

Hypophysectomy in the cat is followed by characteristic atrophic or regressive changes in the gonads, thyroid, and adrenal cortex; the liver and spleen are also smaller in hypophysectomized cats (McPhail, 1935). Parturition in pregnant cats can take place normally in the absence of the pituitary body (Allan and Wiles, 1932). The effects of the operation at about the middle of pregnancy or during lactation are similar to those in the rabbit and ferret (McPhail). Hypophysectomized cats are unusually insulin sensitive (McPhail); if they are also pancreatectomized, they lose weight and excrete glucose in the urine. Unlike pancreatectomized cats, however, they may live for weeks without insulin and may not suffer from either an acidosis or a ketosis (Long and Lukens, 1934).

The technique of hypophysectomy in the monkey (*Macaca mulatta*, *M. rhesus*) has been described by Firor (1932).

THE EFFECTS OF LESIONS OF THE HYPOTHALAMUS[12]

The effects of lesions of the hypothalamus in amphibia.—The precise extent to which injury of the hypothalamus is responsible for changes in the absorption, retention, and excretion of water in frogs or toads is not clear from the experimental results of different investigators. Accurate experiments require the careful control of the temperature of the air and water, the period of immersion in water, etc. Some of the papers cited do not state how carefully the conditions of the experiments were controlled. Moreover, the metabolism of other substances, such as salts, may profoundly affect the metabolism of water and yet may be completely neglected.

An increased rate of excretion of water—apparently due to a polyuria—has been attributed to an injury of the tuber

[12] Only those effects, which are often thought to be associated with the removal of all or a part of the pituitary body, are considered.

cinereum by Houssay and his collaborators (1925, 1929). Probably the polyuria following the extirpation of the infundibulum as reported by Tschernikoff (1926) should be classified as a result of an injury of the hypothalamus. Houssay, Giusti, and Gonalons (1925) also found that a retention of water (increased weight) might accompany the diuresis due to an injury of the hypothalamus. An increased weight, interpreted as indicating a retention of water, with or without polyuria, was observed in hypophysectomized frogs and toads by Pohle (1920), Houssay, Giusti, and Gonalons (1925), and Tschernikoff (1926). The extirpation of the glandular tissue of the pituitary (apparently either the pars glandularis or the pars glandularis and the pars intermedia) appeared either to be without effect (Jungmann and Bernhardt, 1923; Tschernikoff, 1926) or to be followed by increased weight and polyuria (Houssay and others, 1925). Jungmann and Bernhardt described diuresis with or without water-retention as effects of injuries of the *Zweihügel* (optic lobes?). Finally, Rey (1935) declared that hypophysectomy with or without injury of the hypothalamus caused no change in the metabolism of water in frogs. The conflicting data cannot be easily interpreted. They indicate the probability that lesions of the brain in the hypophysial region can cause changes in the excretion and perhaps in the absorption and/or retention of water.

Schürmeyer (1926) reported that an injury of the midbrain of the frog caused a persistent darkening of the skin (due to a dispersion of the melanosomes within the melanophores) which he considered to be the result of an increased liberation of hormone from the cells of the pars intermedia. According to Giusti and Houssay (1922–23), both the bronzing of the hyperkeratotic skin and the expulsion of ova in the spring could be produced in the toad either by injury of the tuber cinereum or by hypophysectomy. Among other effects observed by Houssay and his collaborators (1924–25, 1929) in toads with hypothalamic lesions was a lowering of the con-

centration of the blood sugar. Such lesions were not followed by atrophy of the testes.

The effects of lesions of the hypothalamus in mammals.—Aschner pointed out (1912 and subsequently) that the rapidly fatal effect of hypophysectomy in Paulesco's dogs, as well as the condition described by Cushing and his collaborators as a *cachexia hypophyseopriva*, were probably due to an inadvertent injury of the tuber cinereum. Among the effects of injury of the stalk or tuber cinereum mentioned by Aschner were slowing and weakening of the pulse, bradycardia, slowing of the respiratory rate (sometimes with "vagal breathing"), and glycosuria. Aschner believed that young dogs more often survived hypophysectomy without complications attributable to hypothalamic lesions because the pia-arachnoid, being more delicate, could be torn during the operation with less likelihood of injury of the adjacent nervous tissue. Dandy and Reichert also emphasized that increased intracranial tension was probably a major contributory cause of death in the acutely fatal outcome of many hypophysectomies performed in dogs by the temporal route.

Of greater interest today is the part played by the hypothalamus in the metabolism of water, salts, carbohydrates, and fats. For, particularly in dogs, hypophysectomy may be followed by polyuria, perhaps by changes in the distribution of certain inorganic salts, by glycosuria, and by obesity. All these symptoms are probably never observed simultaneously in one animal. The most frequently reported symptom is a polyuria[13] which may be slight and transient if hypophysectomy is performed with great care. Most of the observations have been made in dogs; some experiments have also been performed in rats, cats, and rabbits. In the following account, the statements refer to experiments in dogs unless another animal is mentioned.

The relation between the hypothalamus and the metabolism of

[13] Particularly in young dogs (Houssay and Hug, 1921).

water and salts.—Camus and Roussy (1914, 1920, 1922), Leschke (1919), Houssay, Carulla, and Romana (1920), Bailey and Bremer (1921), and Curtis (1924) have particularly studied the production of polyuria by means of injuries of the hypothalamus. Little can be said about the localization of such injuries beyond the statement that they are best made in the para-infundibular region of the tuber cinereum and may be very minute.[14] It is reasonably certain that the production of polyuria by such lesions is not related to any effect on the pars neuralis, pars intermedia, or pars glandularis, because the same effect can be produced after complete hypophysectomy (Houssay and others, Curtis).[15] In dogs or men with lesions of the hypothalamus associated with diabetes insipidus, the pituitary body may be normal anatomically (Bailey and Bremer, 1921; Fulton and Bailey, 1928–29). On the other hand, if there is extensive destruction of the tuber cinereum, no polyuria is present (Towne, 1922; Bourquin, 1927; Fulton and Bailey). Apparently either polydipsia or polyuria may be the first symptom; both symptoms may then persist for months or may disappear after a few weeks or even after a few days. The polyuria is as readily produced in dogs with denervated kidneys as in those with normal kidneys (Bailey and Bremer, 1921; Houssay and Rubio, 1923).

From acute experiments in which blood from dogs was circulated through isolated kidneys, Verney (1926) concluded that blood returning from the head caused a lessened rate of urinary secretion and an increased concentration of chloride

[14] Hanchett (1922) found that if traction was applied to the stalk, polyuria usually followed.

[15] Richter (1934) reported that a permanent diabetes insipidus was produced in rats if all the posterior lobe and only part of the anterior lobe of the pituitary were removed. His belief that the removal of the posterior lobe is a factor in the experimental production of diabetes insipidus is not supported by the observations (1) that diabetes insipidus can be produced after complete hypophysectomy, and (2) that the removal of the posterior lobe from dogs may not be followed by a polyuria. He had also found previously (1930) that a puncture-injury, located in the hypothalamus at the level of the anterior margin of the pars glandularis, could produce a marked permanent polyuria and polydipsia.

in the urine, as did the addition of posterior-lobe extract to blood which otherwise was without effect. He also concluded that this effect was not observed after hypophysectomy. In criticism of Verney's experiments it may be pointed out that the effect of a lesion of the tuber cinereum was not investigated.[16] Moreover, Fee (1929) has questioned the validity of conclusions drawn from such a use of the isolated kidney. In the acute experiments of Brull and Eichholtz (1925), hypophysectomy *or* injury of the wall of the third ventricle abolished the normal secretion of inorganic phosphate in the urine. This effect occurred independently of the rate of the renal secretion of water or chloride.

The relation between the hypothalamus and the metabolism of carbohydrates.—In both dogs and men with lesions of the hypothalamus, a glycosuria may appear. Experimentally, however, it has been noted much less frequently than polyuria, and is usually more transient.[17] D'Amour and Keller (1933) reported that after the administration of glucose by stomach tube, hyperglycemia and high or prolonged glycemic curves might occur in dogs in which a bilateral transverse lesion had been made at the level of the optic chiasm. Similarly, Biasotti (1934) stated that after the intravenous injection of glucose, the concentration of sugar in the blood returned to its former level more slowly in dogs with lesions of the tuber cinereum than in normal dogs. The changes reported by these authors resemble those in hypophysectomized dogs, but are less pronounced. These effects of hypo-

[16] According to Bourquin (1927–29), diuresis can be produced by extracts of the blood and the urine as well as of the hypothalamus of dogs with diabetes insipidus after an injury of the hypothalamus. She stated that this effect could also be produced by extracts of the hypothalamus (corpora mammillaria) of normal dogs. Trendelenburg concluded that Bourquin's extracts would have produced diuresis-inhibition in unanaesthetized animals (i.e. produced effects like posterior-lobe extract).

[17] Besides the references of the preceding section, see Sachs and MacDonald (1925); Pickat (1927); and Houssay and Biasotti (1931).

thalamic lesions will be difficult to interpret until more data have been secured, but they suggest that functional changes have occurred in the pancreas and/or the pituitary.

According to Davis (1934), a bilateral hypothalamic lesion in the cat may prevent the appearance of both glycosuria and hyperglycemia if pancreatectomy is performed later. His other experiments, from which he concluded that such lesions also prevent glycosuria and hyperglycemia following the stimulation of the cervical sympathetic ganglion, are not convincing.

The relation between the hypothalamus and the metabolism of fat.—Obesity frequently occurs in hypophysectomized dogs, particularly if the operation has been performed in young animals. This is especially true of operations performed by a temporal approach. For example, Aschner, who used the buccal approach, observed much less obesity in his dogs, hypophysectomized when adult, than did Cushing. However, Aschner described a marked increase in the subcutaneous fat of his hypophysectomized puppies (e.g., subcutaneous fat of abdomen, 4–5 cm. thick). On the other hand, only moderate obesity appeared in Reichert's puppies hypophysectomized by a temporal approach.

Lesions of the hypothalamus, without apparent injury of the pituitary body, have caused the appearance of adiposity with atrophy of the gonads in both dogs and men (Camus and Roussy; Bailey and Bremer; Fulton and Bailey). In the rat, Smith observed a pronounced deposition of fat in some animals in which he undertook to destroy the pituitary body by the injection of chromic acid (Fig. 24). In these experiments, Smith used a lateral approach. If, as seems likely, adiposity may appear after an injury of the hypothalamus, little is known as to the mechanism of this effect. Whether or not the pars glandularis or the whole pituitary body is present, apparently makes little difference. "Genital dystrophy" is thought by some to occur merely as the result of a lesion of

FIG. 24.—Adiposity in a female rat (to the left) in which destruction of the pituitary body by the injection of chromic acid had been attempted. Nevertheless, 33 per cent of the anterior pituitary remained—probably sufficient for all the rat's needs (Smith, 1932); the animal was also given daily intraperitoneal injections of a suspension of beef anterior pituitary. Littermate normal female rat to the right. From Smith (1930).

the hypothalamus; however, it is doubtful if it is not then secondary to an additional change in the pars glandularis.

The presence in the hypothalamus and in the cerebrospinal fluid of substances resembling the active principles of the pars neuralis.—As will be pointed out later in chapters dealing with the effects of extracts of the pars neuralis, cerebrospinal fluid has been found to stimulate the isolated uterus and to raise the blood pressure. To the observers, these results have often seemed to prove that the pars neuralis secretes its active principles into the cerebrospinal fluid as postulated by Herring, Cushing, and others. At present, however, the physiological evidence is far too equivocal to permit the acceptance of this belief. For example, the isolated uterus of the guinea pig, which is used extensively for the assay of extracts of the pars neuralis, can probably be stimulated by many organic substances other than histamine and the oxytocic principle of the posterior lobe; apparently the calcium-ion of cerebrospinal fluid also will cause a contraction of the isolated uterus and thus mimic the true oxytocic principle (van Dyke, Bailey, and Bucy, 1929). A pressor principle can be extracted from cerebrospinal fluid, ascitic fluid, and blood (Page, 1935). Its pressor effects, however, disappear after the destruction of the central nervous system; so it cannot be identical with the pressor principle of the pars neuralis.

Geesink and Koster (1928) concluded that the concentration of the oxytocic principle in the cerebrospinal fluid was reduced in hypophysectomized dogs. In the same year, Trendelenburg and Sato reported that an apparently normal amount of oxytocic principle could be found in the cerebrospinal fluid some time after hypophysectomy; they believed that this was vicariously produced in the tuber cinereum from which they were able to make extracts having oxytocic and antidiuretic–chloride-concentrating properties. Such extracts were found to be more powerful if made from the tuber cinereum of hypophysectomized dogs. Sato (1928) also

stated that diabetes insipidus was observed in dogs after the destruction of the tuber cinereum irrespective of the presence or absence of the pituitary body; but others have concluded that polyuria does not occur if the tuber cinereum has been destroyed (see p. 74).

The hormone increasing the dispersion of chromatosomes in chromatophores (melanophores and erythrophores) has been thought to occur in cerebrospinal fluid after hypophysectomy (Sato) or to be present in increased concentration as a result of the faradic stimulation of the hypothalamus (experiments in cats by Karplus and Peczenik, 1930, 1933). The latter authors also believed that the cerebrospinal fluid contained more pressor principle after the stimulation of the hypothalamus.

CHAPTER III

THE GROWTH-PROMOTING HORMONE OF THE PITUITARY BODY

IT IS impossible to state how many hormones are *secreted* by the pituitary body. By means of various crude or refined physico-chemical manipulations, many extracts differing in their physiological or pharmacological effects have been secured. The number of such extracts, however, cannot be taken to correspond to the number of hormones actually elaborated by the pituitary body. Some investigators believe that they may in part be cleavage-products of one or more larger molecules. In the pars glandularis, for example, the properties of the active extracts so far made suggest either that the true hormones are protein-like or that they are closely associated with protein-like substances. For purposes of presentation in this chapter and in those succeeding it, effects which appear to be peculiar to a particular extract of the pars glandularis will be described as if they were due to a particular hormone. From the standpoint of the physiology of the pars glandularis in the normal animal, however, this may not be true.

Often it is not realized how limited a generalization can be made concerning an extract which appears to be specific in its effects. Any generalization as to the action of an extract of the pars glandularis must take into account differences in the response arising from variations in age, sex, race, diet, season, method and frequency of administration of the extract, ease of absorption of the extract, total dose, etc. It must always be realized that very significant inherent differences may appear in the response of other animals—even of animals belonging to the same class and order. A further important con-

sideration is whether the effects are observed in normal or in hypophysectomized animals.

It is well known that the removal of the pituitary body from young and growing animals may markedly inhibit growth. A priori it would be expected that the administration of the pituitary or of extracts made from the pituitary would cause a resumption of growth in animals abnormally small because of a previous hypophysectomy. Furthermore, because gigantism and acromegaly in man appear to be due to a hyperfunction of the pars glandularis, it would be expected that growth at a faster rate and beyond the normal could be brought about by the administration of the pituitary. In certain animals both of these expectations have been realized.

The use of the term "growth," however, requires a brief consideration. Depending upon the investigator, growth is judged by different criteria which usually are narrow and restricted rather than broad and comprehensive. An increase in the weight of the body is frequently taken to be synonymous with "growth." This is an imperfect but nevertheless important indication of growth. An increase in weight is the most characteristic result of the administration of the growth-promoting hormone; in experimental gigantism it often is a more prominent change than an increase in the dimensions of the body or of some of its parts. A truer growth-promoting effect is obtained by the administration of the anterior pituitary to animals hypophysectomized when young; in such animals both the body-weight and the body-size are strikingly increased by the treatment. Other characteristics of growth in relation to growth-promoting extracts of the pars glandularis have been studied much less frequently.

The pituitary is of no importance probably in early embryonic growth; but in later embryonic life it possibly affects the rate of growth. After birth, the rate of growth, the ultimate body-size, and the shape of the body and its parts are dependent only in part upon the normal functioning of the pars

glandularis. Of equal or greater importance is the genetic constitution of the individual. One example may be quoted. Robb (1928) determined the weight of the pituitary body in dwarf (Polish) and giant (Flemish) rabbits. There was no correlation between the weight of the pituitary and the growth-rate or the adult body-weight. In fact, the pituitary bodies of adult rabbits of both breeds weighed about the same, but the relative weight of the pituitary of the giant rabbits was about one-half that of the dwarf race.[1] A hereditary defect of the pars glandularis may be responsible for a marked inhibition of growth and final body-size as in the mice of Smith and MacDowell (1930–31). The inhibition of growth and development of Eidmann's tadpoles (*Rana esculenta*) may have been of both genetic and endocrine origin (Eidmann, 1921).

So far as the glands of internal secretion are concerned, the pituitary is unquestionably the most important and the most essential regulator of growth. Disturbances of growth may also be clearly present after the removal of the thyroid or the gonads. Also, there can be little doubt but that the growth-promoting principle of the pituitary is elaborated in the pars glandularis. The weight of the anatomical evidence is in favor of the view that the hormone is secreted by the oxyphil cells (see chap. i).

To determine the effects of the pituitary body or its parts on growth, the following methods of administration have been employed: feeding (including possibly cutaneous absorption in larval amphibia), transplantation, implantation, and the injection of extracts.

THE EFFECTS OF FEEDING THE PITUITARY BODY OR ITS PARTS

Feeding experiments, employing the pituitary or the pars glandularis as all or part of the food, have been performed in

[1] The weight of the pituitary body, of course, is not necessarily related to the secretory capacity of the gland.

flies, worms, amphibia, the fowl, and mammals. So far as the promotion of growth is concerned, the only satisfactory results were obtained in amphibia.

Feeding experiments in amphibia.—Smith (1918)[2] fed the fresh pars glandularis of the ox to normal and to hypophysectomized tadpoles (*R. boylei*). As a result, normal tadpoles grew more rapidly in the last part of the larval cycle than did normal tadpoles to which anterior pituitary was not fed. Hypophysectomized tadpoles, if not fed anterior lobe, grew about as rapidly as normal tadpoles until the mid-larval period, after which their growth-rate was clearly inferior to that of normal animals. The feeding of pars glandularis caused an acceleration of the growth-rate to the normal level during this latter period. No metamorphosis occurred, and the tadpoles frequently grew for a longer period and to a larger size than normal tadpoles without pituitary feeding. The feeding of the pars glandularis to hypophysectomized tadpoles, unlike the injection of extracts, was not followed by any beneficial effects on the pigmentary changes or on the atrophy of the adrenal cortex, thyroid, and epithelial bodies. Uhlenhuth (1920–23) fed the pars glandularis of the ox to salamanders (*Amblystoma tigrinum*, *A. opacum*) *after* metamorphosis. His experiments, conducted over many months, showed that the feeding of liver or of pars glandularis was accompanied by an increased growth-rate, so that salamanders larger than other animals of the same variety fed on worms were produced. The pituitary-fed animals were the largest—being about 20 per cent larger than the liver-fed animals.[3]

Belkin (1934) concluded that the rate of regeneration of an

[2] Also see Smith and Smith (1922–23).

[3] Křiženecký (1924) and Křiženecký and Podhradský (1926) believed that the growth of tadpoles (*R. fusca* and *R. temporaria*) might be increased by feeding either the pars glandularis or the pars neuralis—the former increasing the weight, the latter, the length. The later report (1926) did not confirm some of the other unusual conclusions reached in the first report (1924).

amputated limb was increased in axolotls if the animals were kept in water containing 0.25 cc. of a pars-neuralis extract per liter. Herrell (1934) studied the regeneration of the tail in tadpoles (*R. clamitans*) 6–8 months old. Apparently he added a solution of anterior pituitary extract ("Antuitrin G") to the water in which the tadpoles were kept. Tail-regeneration took place at a slower rate if the extract was added before or shortly after the partial amputation; regeneration occurred more rapidly and even extended beyond the normal size if the addition of the extract was postponed to the later "proliferative" or "differentiative" phases of regrowth. The extract also brought about an increased growth of the body and tail of normal tadpoles.

According to Wulzen (1916), the fission-rate of planarian worms is increased by feeding any part of the pituitary body. In comparisons of the growth-rate of such worms on diets of liver or of different parts of the pars glandularis, she later showed (1930) that growth was most accelerated in worms fed on a diet of liver; however, a diet of pars glandularis, composed chiefly of oxyphil and reserve cells, produced more growth-acceleration than did a diet of pars glandularis composed of basophil and reserve cells.

The experiments of Thompson (1929), who fed lettuce which had been dipped in an extract of the pars glandularis to silkworms, cannot be evaluated because the experiments were inadequately controlled and not enough data are given. According to Patterson (1925) flies (probably *Sarcophaga sarcena* and *Calliphora erythrocephala*) do not grow or metamorphose more rapidly if their food is restricted to the pars glandularis or to other parts of the pituitary body undergoing decomposition.

Both Wulzen (1914) and Pearl (1916) reported that the feeding of the pars glandularis of the ox to fowls caused a retardation of growth which was manifested by changes in the weight and in the length of bones. Wulzen also observed that

the involution of the thymus took place more rapidly in the fowls which received anterior pituitary. The results of Maxwell (1916), who fed fresh ox pituitary and lamb thymus to growing fowls, were similar.

In spite of earlier reports,[4] some of which were recognized by the authors themselves as being negative or inconclusive, there appears to be no foundation for the belief that growth-acceleration may be caused in mammals by the feeding of the pituitary or the pars glandularis or extracts of these. Aldrich (1912), Sisson and Broyles (1921), Drummond and Cannan (1922), Evans and Long (1922), and C. S. Smith (1923) observed no growth-acceleration in normal mammals. The most conclusive experiments were those of Smith (1927) who fed the pars glandularis of the ox to hypophysectomized rats; the oral administration of two fresh anterior pituitaries each day to each hypophysectomized rat was without effect on the body-weight. Such rats promptly increase in size after the *parenteral* administration of anterior pituitary tissue.

THE EFFECTS OF THE PARENTERAL ADMINISTRATION OF THE GROWTH-PROMOTING HORMONE

The effects of the administration of the growth-promoting hormone to amphibia.—Smith and Smith (1922–23) administered intraperitoneally suspensions of different parts of the pituitary body of the ox to hypophysectomized or normal tadpoles. The hypophysectomized tadpole thereby could be caused to grow even larger than normal tadpoles. In addition, the abnormal atrophic changes in the thyroid, adrenal cortex, and epithelial bodies (parathyroids) were corrected. All these effects were produced by suspensions of the pars glandularis only. A more pronounced effect on growth was caused by the portion made up of reserve and oxyphil cells;

[4] Goetsch (1916); Marinus (1919); Robertson and his co-workers (1916, 1919–20, 1923); Schäfer (1909, 1912); and others.

whereas the portion made up of reserve and basophil cells caused the greater effect on the atrophic thyroid.

Blount (1930) transplanted one or two *Anlagen* of the pituitary (buccal and neural) in the region of the extremity of salamander embryos (*A. punctatum*). As as result, growth was *inhibited* chiefly because of a shortening of the tail. There also occurred shortening and thickening of the extremities. Grafts of the buccal ectoderm alone did not grow and differentiate. Burns (1930), and Burns and Buyse (1931) used young larvae of *A. tigrinum* in their experiments. Neither pituitary transplants from adult axolotls nor the injection of alkaline extracts of the pars glandularis of the sheep or the ox caused much change in body-size. A few animals were slightly longer and had a greater girth and larger heads. It will be recalled that salamanders, subjected to hypophysectomy after metamorphosis, may grow as rapidly as normal salamanders.

The effects of the administration of the growth-promoting hormone to mammals.—Evans and Long (1921) were the first to demonstrate that the growth-rate could be accelerated and that gigantism could be produced in a mammal (in this case, the rat) by the long-continued injection of a simple extract of the pars glandularis. Smith (1927) later showed that an anterior pituitary extract could cause the resumption of growth of hypophysectomized rats. Most of the observations of other investigators have been made in animals (dog, guinea pig, rabbit, rat, man, and mouse) in which the pituitary had not been disturbed. It must be realized that the growth-promoting hormone has not been separated as a pure substance; therefore, some of the statements in the following pages may require modification in the future.

In the early experiments of Evans and Long (1921–22), anterior pituitary tissue of the ox was triturated in a mortar containing sand and Locke's solution. The supernatant fluid obtained from this mixture was then injected daily into the

peritoneal cavity of young growing female rats, 14 days old when the injections were begun. At an age of 75 days, the average weight of thirty-eight injected rats was 228 g., where-

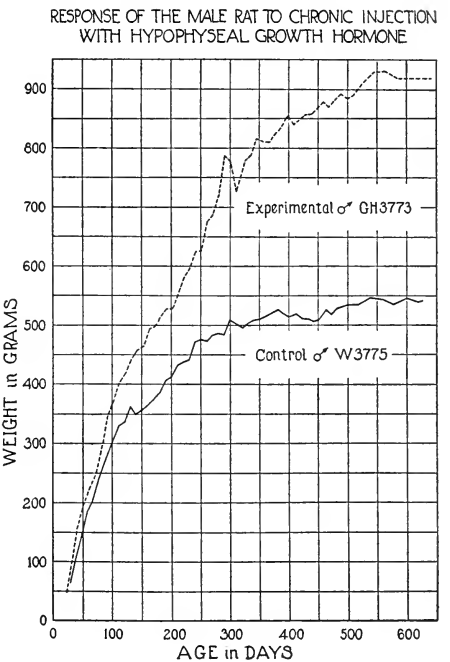


FIG. 25.—The response of the normal male rat to a growth-promoting extract of the pars glandularis. From Evans and Simpson (1931).

as that of thirty-eight littermate control rats was 184 g.; therefore, the average weight of the injected group was already nearly one-fourth greater than that of the normal group. More striking differences were obtained in rats injected for a longer period. This is illustrated in Figure 25, in

which the weights of two male rats—one injected and one normal—are plotted against time, which in this instance amounted to more than 20 months.

Unless large doses of growth-promoting extract are employed, the differences between normal and injected growing rats are not striking until after the age of 75–100 days. Thereafter, normal rats grow slowly, whereas those receiving suitable doses of the hormone continue to increase in weight at a rapid rate so that at ages of 200–400 days the injected rats may be twice as heavy as normal rats—surpassing in size normal rats of any age (Evans, 1924). The important change in such experimental gigantism is in the weight, although the size of the body and its parts, including the skeleton,[5] is increased. As in human acromegaly, the viscera are enlarged. The belief of Evans and Long that an important part of the weight increase is due to the deposition of fat has not been confirmed by others (see below, pp. 100–102).

Crude extracts of the pars glandularis also produce changes in the gonads. The discussion of the gonadotropic effects of such extracts, however, will be taken up in chapter iv.

The administration of growth-promoting extracts to rats which are otherwise normal produces a greater relative change in the weight and size of the female rat (Johnson and Sayles, 1929; Evans and Simpson, 1931; Simon and Binder, 1932; and Rubinstein and Kolodner, 1934). In terms of the absolute weight and size, however, the largest rats produced by the repeated injection of the hormone are males. If the administration of the growth-promoting extract is delayed until the rats are growing very slowly, and if the period of ad-

[5] Handelsman and Gordon (1930) concluded that normal periosteal bone-growth was stimulated by the growth-promoting hormone but that this effect could not be clearly shown except in animals approaching adult weight. Lucke and Hückel (1933) observed proliferative changes in the joint cartilage as well as both proliferative and retrogressive changes in the epiphysial cartilage, all of which they attributed to the administration of a growth-promoting extract. They concluded that the alterations resembled those accompanying the specific arthritis of early human acromegaly.

ministration is about 3 weeks, female rats gain more weight and do so in greater numbers than do males (Evans and Simpson; see Fig. 26).

Smith (1927, 1930) has clearly shown that pituitary implants or the injection of extracts of the anterior pituitary promptly cause the hypophysectomized rat to resume

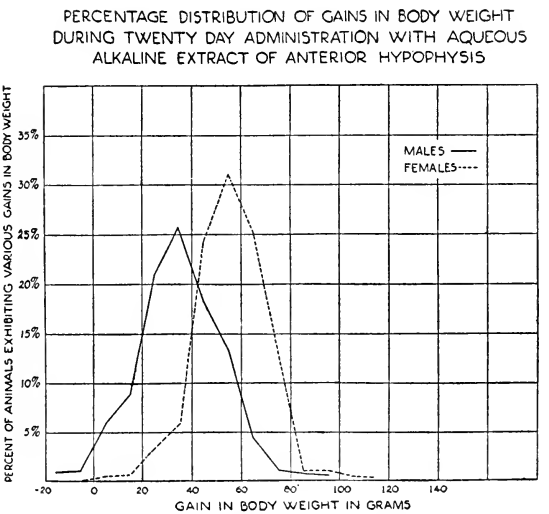


FIG. 26.—A comparison of the response of male and female rats to a growth-promoting extract of the pars glandularis. From Evans and Simpson (1931).

growth. In rats dwarfed because of hypophysectomy, the administration of the growth-promoting hormone produces relatively greater changes in the skeleton than is the case in normal rats receiving the hormone. Pituitary implants do not cause a greater change in weight and size than does the administration of a crude extract of the pars glandularis of the ox. Implants, however, do correct the atrophic changes in

the gonads, thyroid, and adrenal cortex; whereas, crude extracts have no effect on these structures, but may even prevent the beneficial effect of the implants on the gonads.

Hypophysectomized rats respond more readily to the growth-promoting hormone than do normal adult rats (van Dyke and Wallen-Lawrence, 1930; Evans, Pencharz, Simpson, and Meyer, 1933). The aged normal rat may respond poorly to the injection of a growth-promoting extract (Handelsman and Gordon, 1930). Similarly, van Dyke and Wallen-Lawrence found that hypophysectomized rats, 4 months or more after operation, might be completely unresponsive to doses of growth-promoting hormone causing a clear-cut increase in the weight of other rats hypophysectomized more recently. Such animals also might exhibit no weight increase after nineteen homo-implants administered once daily. However, if the growth-promoting hormone was injected for a longer period with no attempt to use doses near a threshold level (for recently hypophysectomized rats), growth could be stimulated in rats 294–336 days after hypophysectomy (Schour and van Dyke, 1932). Similar results were obtained by Evans and his co-workers (1933) in one rat given injections 279 days after operation as well as in four others first treated 128–151 days after operation.

The rate at which the incisor tooth of the rat erupts becomes markedly reduced as a result of hypophysectomy. A growth-promoting extract increases the rate of eruption if an associated general growth-response also occurs. The hormone has no effect on the rate at which the incisor erupts in the normal rat, although it causes an increase in the body-weight (Schour and van Dyke, 1932). Putnam, Teel, and Benedict (1928) reported that the hair grew more slowly after hypophysectomy but that this deficiency could be corrected by the administration of a growth-promoting extract. Snow and Whitehead (1935) made a careful study not only of the condition of the skin and hair of hypophysectomized rats, but also

of the way in which they were altered as a result of the injection of growth-promoting hormone. The hormone restored the skin to normal (after operation, it was atrophic). The hormone also augmented the rate of hair-growth to normal and increased the weight of hair per unit surface to as much as one-fourth above that in normal rats.

The effects of extracts containing the growth-promoting hormone have been investigated in several races of dogs.[6] The prominent general effects in growing puppies or dogs otherwise normal are the following: symmetrical overgrowth of the skeleton and soft parts,[7] including a marked folding of the skin; splanchnomegaly including hyperglossia; various symptoms such as hypotonia (the stance may be plantigrade instead of digitigrade), asthenia, polyphagia, polydipsia, polyuria, and sialorrhea. Emaciation may or may not be associated with glycosuria and hyperglycemia (diabetes mellitus may be diagnosed). Whether or not all these signs and symptoms are to be attributed only to the growth-promoting hormone is not known.

In Figure 27, photographs of two of the pure-bred *Dachshunde* of Evans, Meyer, Simpson, and Reichert are reproduced. One of these littermate males (No. 3) had received injections of a growth-promoting extract over a period of 6 months. As a result, the weight was markedly increased (control, 10.9 kg., injected, 17.1 kg.). The changes in the skin and soft parts are evident. By means of roentgenograms, definite increases in the size of the skull and bones could be demonstrated. The short extremities of the *Dachshund*, which the authors, following Stockard, consider to be due to an achondroplasia, were not affected by the treatment.

[6] Putnam, Teel, and Benedict (1928); Reichert (1929); Benedict, Putnam, and Teel (1930); Downs (1930); Teel and Cushing (1930); Evans, Meyer, Simpson, and Reichert (1932–33); Reichert, Simpson, Cornish, and Evans (1933).

[7] Changes in the jaw and skull may be relatively greater in the bulldog—an exaggeration of what is normal in this race.

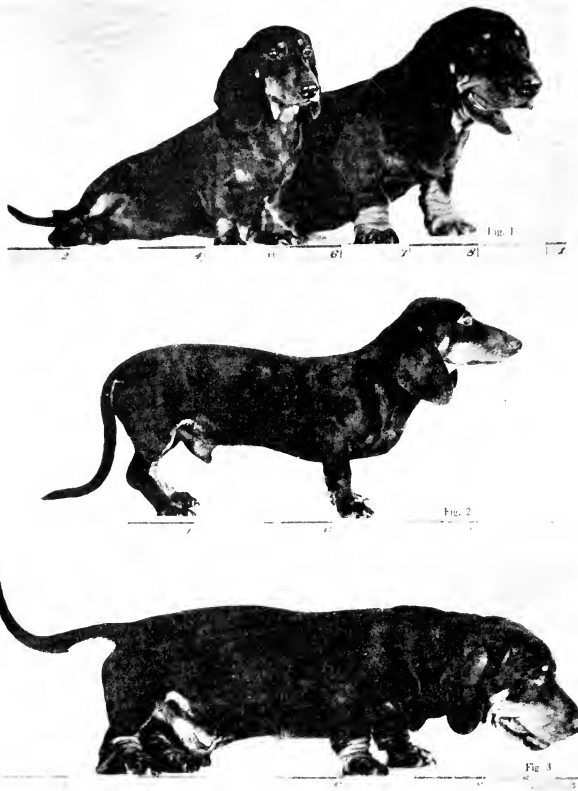


FIG. 27.—The effect of a growth-promoting extract of the pars glandularis on the *Dachshund*. 1. Dog on left, normal littermate; dog on right, injected. 2. The normal dog of 1. 3. The injected dog of 1. From Evans, Simpson, Meyer, and Reichert (1933).

Other experiments have been performed in hypophysectomized dogs. The daily injection of the hormone for weeks may correct the majority of the growth-defects without causing the changes described above. Growth may be as rapid or more rapid in comparison with littermate normal animals. The first dentition instead of persisting is replaced by the second dentition at about the normal time. The epiphyses close only a short time later than those of normal young dogs.

The effects of growth-promoting extract in growing normal mice appear to resemble those in normal rats. Johnson and Hill (1930) believed that the female mouse responded better than the male, although their data were hardly numerous enough to justify such a conclusion. The mice of Smith and MacDowell (1930–31) were dwarfs because of a hereditary defect of the pars glandularis. If they were given implants of fresh pituitary from normal rats or mice they grew to resemble normal mice. Kemp (1934) administered the growth-promoting hormone to similar dwarf mice. The gonads were not normal, but normal growth took place in the body and its other parts with the exception of the thymus, which was markedly hyperplastic. According to Downs (1930), the incisor of the normal mouse erupts more rapidly if growth-promoting extract is administered.

Engelbach and his colleagues (1932–34) have described increases in the weight, increases in the height and other dimensions of the body, and changes in the roentgenograms of bones and joints after the administration of the growth-promoting hormone (often combined with thyroid extract) to dwarfed human beings.

SPECIAL CONSIDERATIONS

The specificity of the effects.—Growth-promoting effects—in the sense in which they have been described in the preceding pages—are obtained only by the administration of tissue or extracts of the pars glandularis of the pituitary body. The

"thymocrescin" of Asher possesses no analogous growth-promoting effect (Simon and Binder, 1932). A similar statement can be made concerning prolan and extracts of other glands of internal secretion.[8]

The part played by diet.—The detection or assay of certain vitamins (A and the B group) may be chiefly based on the failure of animals to grow. Unquestionably, in such cases of experimental vitamin-deficiency, the physiology of the growth-promoting hormone of the pars glandularis is disturbed. Probably there are both "central" and "peripheral" changes—i.e., perhaps the pars glandularis secretes inadequate amounts of the hormone or no normal hormone; if the normal hormone is secreted, the growth-potentiality of the tissues may be so reduced that no response occurs. At present it is impossible to say which of these conceivable changes is the more important; but that the growth-promoting hormone is involved in some way appears to be an incontestable fact.

If growth-promoting hormone is administered either to normal or to hypophysectomized rats, the rate of growth depends upon the adequacy of the diet (Bryan and Gaiser, Thompson and Gaiser, 1932). However, no matter how excellent the diet, the hypophysectomized rat will not grow unless growth-promoting hormone is also administered. Bryan and Gaiser concluded that the diet, more than the inherent growth-potentiality, determined the degree of growth-acceleration produced by the injection of the growth-promoting hormone into normal rats. It is not known what is the maximum possible growth-rate of the rat. By means of improve-

[8] Parhon and his collaborators (1930, 1934), believed that the growth-promoting hormone could be detected in the serum and urine of patients with acromegaly; the data they offer are too few to support this belief. Van Dyke and Wallen-Lawrence (1930) were unable to detect the hormone in either the serum or the urine of the acromegalic subject.

Wehefritz and Gierhake (1932) reported that, by means of an adsorption method, extracts causing growth in normal or hypophysectomized rats could be secured from the urine of pregnant women.

ments in the diet, the rats of Anderson and Smith (1932) were made to grow as rapidly as those of Bryan and Gaiser, which received growth-promoting hormone in addition to the better diet of Bryan and Gaiser. Even the injected rats of Evans and Long (1921) weighed, on the average, 228 g. at an age of 75 days, whereas the rats of Anderson and Smith weighed 300 g. at an average age of 63 days.[9] The male injected rat of Evans and Simpson (Fig. 25) weighed 500 g. at an age of 175 days; twelve normal rats of Anderson and Smith weighed the same at an average age of 123 days. The experiments with growth-promoting extract, therefore, do not indicate the maximum possible growth-acceleration which can be obtained.

Gough and Silva (1933) found that the pars glandularis of the ox contained 40–50 international units of antiscorbutic vitamin (C) per gram of fresh tissue. They also studied the reducing properties of the pituitary as well as other glands in different animals by applying a solution of silver nitrate to the fresh tissue. Their results suggested that the pars glandularis might contain considerable amounts of ascorbic acid. Later (1934), Gough concluded that the pars glandularis of the ox is the richest known source of ascorbic acid—containing even more than the adrenal cortex or the corpus luteum (pig). From a study of the reduction of silver nitrate by the anterior lobe tissue of human hypophyses, he concluded that the concentration of ascorbic acid in the pars glandularis is greater in young than in aged individuals, and is low (or almost nil) in individuals dying in an emaciated condition after a long illness. From their study, using Tillmanns' technique, Giroud and others (1934–35) found that the pars glandularis (ox) contained the largest amount of ascorbic acid (1.65 mg.

[9] In this comparison, account must be taken of three facts: Anderson and Smith used only male rats which naturally grow larger and for a longer period than females; Evans and Long used female rats which, however, respond to the growth-promoting hormone better than males; the rats were not of the same race.

per g. fresh tissue) but that the concentration was higher in the pars intermedia (2.01 mg. per g. fresh tissue). The pars neuralis contained about one-third the concentration found in the pars glandularis. That the substance with reducing properties is in any way associated with the growth-promoting hormone is doubtful (Salter, Green, and Putnam, 1934).

The growth-promoting hormone and the glands of internal secretion. 1. *The pituitary body.*—Evans and Simpson (1928) found that the gonadotropic effects of extracts of the pars glandularis were prevented by the injection of a growth-promoting extract; they concluded that the gonadotropic effects were antagonized by the growth-promoting hormone. Lipschütz and Kallas (1929) came to a similar conclusion. All the authors pointed out that sexual activity is diminished during the period of rapid growth. Targow (1933) castrated young rats at weaning and then injected growth-promoting hormone to a part of the group for about 40 days. Although both the pars glandularis and the pars neuralis (posterior) were smaller in the injected rats, yet the gonadotropic potency of the pituitary was as great as in uninjected littermate rats which had also been castrated. There is no direct evidence that the growth-promoting effects of anterior pituitary extract are antagonized by the injection of gonadotropic extracts of the pars glandularis. Evans and others (1933) found this also to be true of prolan and pregnant mare's serum.

According to Rubinstein (1934), who administered a growth-promoting extract to adult rats for more than 5 months, the weight-response was relatively greater in the female rats. The weight of the pituitary body of the female rats was not changed; but, as in normal rats, it was greater than that of the injected male rats. In the injected male rats, however, the pituitary body was significantly heavier in comparison with that of normal males.

Evans, Meyer, and Simpson (1932) concluded that "sex-free" growth-promoting hormone markedly potentiated the

gonadotropic effects of prolan. However, they later withdrew the conclusion that this effect was due to the growth-promoting hormone (Evans, Simpson, and Austin, 1933).

2. *The gonads.*—It has been shown repeatedly that, as a result of the administration of a growth-promoting extract, female rats exhibit a greater response relatively (and often in absolute terms) than do males. Evans and Simpson (1931) reported on the manner in which gonadectomy affected the response.[10] They concluded that the order of susceptibility was the following: the spayed female, the normal female, the castrated male, and, lastly, the normal male. By itself, this statement suggests that the internal secretions of the gonads antagonize the growth-promoting hormone. Gonadectomy, however, influences the rate of growth and the ultimate size—factors which doubtless also affect the response to the hormone.

If a daily injection of 10–20 rat units of oestrone is given to rats from an age of 3–4 weeks to an age of 11–22 weeks, the growth in weight (and to a lesser extent, the growth in bone-length) is inhibited as much as 20–25 per cent. The pituitary body of the injected rats appears normal histologically. If the injections are stopped, rapid growth promptly sets in. The normal growth in weight may occur in rats receiving both oestrone and the growth-promoting hormone (Spencer, D'Amour, and Gustavson, 1932). In experiments lasting only a few days, Engel (1934) was not able to find any change in the response of rats to growth-promoting hormone, if either oestrone or testicular hormone was also administered.

The effects on the course of pregnancy and on the young, which may follow the administration of a growth-promoting extract of the pars glandularis, are not necessarily attributable to the growth-promoting hormone. They will be discussed in chapter iv.

[10] Also see van Wagenen (1928).

3. *The thyroid.*—Young female rats which have become dwarfed because of thyroidectomy will grow at a normal rate if growth-promoting hormone is administered (Flower and Evans, 1924). Similarly, female rats, thyroidectomized when adult, respond to growth-promoting hormone both qualitatively and quantitatively like normal adult female rats (Margitay-Becht and Binder, 1934). Smith, Greenwood, and Foster (1927) reported that the injection of a suspension of fresh thyroid gland of the sheep promoted the growth of the thyroidectomized, but not of the hypophysectomized (or normal) rat. In later experiments, Smith (1933) performed both hypophysectomy and thyro-parathyroidectomy in rats; in such animals the effect of a growth-promoting extract was improved by the addition of thyroid extract to the rats' diet. In hypophysectomized rats, the thyroid glands of which were intact, the injection of both thyroid extract and growth-promoting hormone produced no greater rate of growth than did the administration of the growth-promoting hormone alone (Smith, 1930). All these findings suggest the following conclusions: (1) if failure to grow is due to a complete deficiency of the pituitary secretion, no replacement therapy can be effected by the administration of thyroid extract; (2) if dwarfing occurs as a result of thyroidectomy, it probably is due to the insufficient secretion of the growth-promoting hormone; and (3) the growth-promoting effects of an extract of the pars glandularis may in part depend upon a stimulation of the thyroid gland (conceivably, a growth-promoting extract, free from thyrotropic hormone, would be equally effective in hypophysectomized rats whether or not a thyroidectomy had also been performed).

Lee, Teel, and Gagnon (1929), and Lee and Gagnon (1930) studied the gaseous metabolism of normal rats which had received injections of growth-promoting extracts over long periods. The respiratory quotient after starvation was the same (0.72) in both the normal and the injected rats. In about

60 per cent of the injected rats, the basal metabolism (computed in terms of the body surface) was reduced 10–40 per cent. If the injections were stopped the basal metabolism might remain low for 1–2 weeks. Szarka[11] (1933) obtained different results, perhaps partly due to the presence of considerable amounts of thyrotropic hormone in his extracts. He found that an *elevation* (9–29 per cent) in the basal metabolism of female rats occurred if the growth-rate was increased by the injection of an extract of the pars glandularis. If no growth-response was obtained or growth ceased, the basal metabolism often fell (to 18 per cent below normal), provided that the thyroid had not been removed; in the latter case, no change in the basal metabolic rate was observed.

The diuretic effects of some growth-promoting extracts may be the result of a thyroid-stimulation (see chap. vii).

4. *The adrenals.*—Evans and his colleagues (1932) concluded that the growth-promoting extract used in their experiments probably abolished the cachexia of hypophysectomized rats because it favored the restoration of normal function on the part of the cortex of the adrenal glands. The extract also aided in the restoration of thyroid function. Gonadotropic hormone(s) did not produce such effects. In the experiments of Smith (1930), however, a cruder extract of the pars glandularis caused growth in hypophysectomized rats without altering the atrophic changes in the adrenal cortex and in the thyroid. Evans, Pencharz, Meyer, and Simpson (1933) reported that the injection of a growth-promoting extract of the pars glandularis did not favor the survival of adrenalectomized rats. Similar results were obtained by Shumacker and Firor (1934), who found that if the pituitary was implanted into adrenalectomized rats, there was no effect on the loss of weight, the failure of growth, or the survival period.

[11] S. Szarka (*Ber. ges. Physiol. exper. Pharm.*, LXXIV [1933] 189) appears to be the same investigator who (A. J. Szarka) worked in Evans' laboratory.

5. *The thymus.*—If anterior pituitary tissue is fed to the fowl, growth is inhibited and the thymus undergoes a more rapid involution (Wulzen, 1914). Kemp (1934) injected a growth-promoting extract into mice dwarfed because of a hereditary defect of the pars glandularis. Growth in normal proportions occurred in the body and all the organs except the thymus, in which an unusually marked proliferation of the parenchyma was observed.

6. *The epiphysis.*—Engel (1934) concluded that alkaline extracts of the human epiphysis antagonize the growth-promoting effects of extracts of the pars glandularis of the ox. This conclusion was based on experiments of a few days' duration in the rat (assay-technique of van Dyke and Wallen-Lawrence); the extract of 1–2 human epiphyses appeared to prevent the weight-increasing effects of 2 g. of the fresh pars glandularis of the ox.

Experimental obesity and the growth-promoting hormone.—Evans (1924) reported that the marked obesity which Smith produced in rats, probably by injuring the hypothalamus, was not affected by the repeated injection of the growth-promoting hormone.

Biochemical changes following the administration of the growth-promoting hormone.—Although Evans and Long (1922) were of the opinion that, following the injection of the growth-promoting hormone into normal, growing rats, the "Increase in weight results to a great extent from a storage of fat, but is not solely due to this, ... ," subsequent work has shown that the amount of fat in the bodies of injected rats is reduced. The accompanying table summarizes what is known about the composition of the rat caused to grow at an increased rate and for a longer period by means of repeated injections of the growth-promoting hormone (see p. 101).[12]

From their careful investigation, Lee and Schaffer conclud-

[12] From the data of Schäfer (1931); Bierring and Nielsen (1932); and Lee and Schaffer (1934).

ed that the most striking changes were in the amounts of the total nitrogen and of the dry tissue free from ash and fat. The reduced amount of fat suggested that the injected animals oxidized more of the available fat than did the normal animals (all the rats received the same amount and kind of food). The chemical composition of the injected rats resembled that of littermate rats analyzed when the injections were begun (average weight, 190 g.) and was likewise similar to that of an immature or growing mammal (Moulton, 1923).

Percentage of				
Water	Ash	Protein or Total N	Fat-Free Dry Tissue	Fat
Increased	Increased	Increased	Increased	Diminished

It is not clear what is the significance of the increased amount of water in the bodies of animals receiving growth-promoting hormone. Targow (1934), who used castrated rats which were still young (fifty-six days old) at the end of the period of injection, concluded that the skin was the only tissue which clearly contained more water. Downs and Geiling (1929) and Downs (1930) observed a considerable increase in the amount of water in the bodies of mice which had received injections of the growth-promoting hormone. Wadehn (1932), using a more refined extract, did not confirm this finding or Downs's report that injected mice were composed of more ash and fat; on the contrary, his results suggested that less fat and less ash (in the skeleton but not in the rest of the body) were present in the carcasses of injected mice.

Metabolic studies in dogs before and after the administration of growth-promoting hormone have consistently revealed changes in the metabolism of nitrogen-containing substances (Teel and Watkins, 1929; Teel and Cushing, 1930; and Gaebler, 1933). The non-protein nitrogen of the blood falls to the extent of 20–30 per cent; this is largely due to a re-

duction in the amounts of urea and amino acids. Apparently there is less combustion of protein and more combustion of fat because (1) the nitrogen balance is shifted in a positive direction (due to a reduction in the excretion of nitrogen in the urine), and (2) the respiratory quotient falls from about 0.90 to about 0.79.

According to Teel and Cushing, the injection of a growth-promoting extract into the normal dog may cause a diminished excretion of phosphorus and an increased excretion of calcium. However, the administration of a similar extract to hypophysectomized rats, on a low-calcium ration and with a negative calcium balance, causes a retention of calcium (positive balance) in association with growth (Pugsley and Anderson, 1934).

Growth-promoting extracts of the pars glandularis of the ox may cause polydipsia and polyuria in the dog. This effect (and possibly other effects described above) is not observed in thyroidectomized dogs.

The effect of the growth-promoting hormone on the amounts of glutathione and ascorbic acid in the liver and striated muscle of rats was studied by Gregory and Goss (1934) and Goss and Gregory (1935). Reiss, Hochwald, and Druckrey (1933) investigated the metabolism of the isolated liver and kidney of hypophysectomized rats, to some of which they administered a growth-promoting extract.

Does the growth-promoting hormone affect the growth of neoplasms?—D. Engel (1923) as well as P. Engel (1934) studied the rate of growth of Ehrlich's adenocarcinoma in mice; in both reports it was found that the injection of an extract of the pituitary caused an increase in the rate of growth, although the extract used by D. Engel probably contained no growth-promoting hormone. In his report, P. Engel (1934) also concluded that the effect of the pituitary extract could be antagonized by the injection of an extract of the pineal body. According to Reiss, Druckrey, and Hochwald (1933),

the Jensen-sarcoma grows slowly in hypophysectomized rats and even begins to retrogress 1–3 weeks after transplantation. If, however, growth-promoting hormone is administered to tumor-bearing, hypophysectomized rats, the sarcoma begins promptly to grow. Tumor-growth parallels body-growth to some extent.

Hofbauer (1930) attributed a proliferation of the squamous epithelium of the portio vaginalis of the cervix to the administration of implants or extracts of the pars glandularis of the ox. He believed that the changes produced resembled a leukoplakia. He stated that implants or extracts produced the same effect *after* bilateral ovariectomy. Hofbauer's experiments were performed in guinea pigs.

The assay of growth-promoting extracts of the pars glandularis.—Most attempts to assay the growth-promoting hormone have been made in rats, although mice have also been used by a few investigators. A more or less qualitative recognition of the presence of the hormone in an extract can be accomplished without much difficulty. For such a purpose either young hypophysectomized rats of either sex or normal adult female rats should be used. For clear-cut results a greater number of the latter is required. If injections are to be made only for a few days, as by the method of van Dyke and Wallen-Lawrence (1930),[13] it is best to use at least twenty rats; if injections are carried on for a period of 3 weeks, five or six rats are sufficient (Evans and Simpson, 1931). Obviously it is necessary to make certain that no growth (hypophysectomized rats) or very slow growth (normal adult female rats) is taking place before any injections are made. It is also necessary that all the conditions of the experiment (diet, time of feeding, temperature, etc.) be kept as constant as possible. Young animals, provided that they meet the description given above, are more sensitive than old animals. Animals which have never been injected probably respond better than animals which have already been used for assay.

[13] Also see Simon and Binder (1932).

Little is known as to the accuracy with which the growth-promoting hormone can be assayed. Quantitative assay—even by the standards of biological assay—is difficult for a number of reasons. The presence of anterior pituitary hormones, other than that promoting growth, may interfere with the response. For example, the presence of the thyrotropic hormone probably would interfere with the growth-response in animals like the guinea pig; in the rat, this is less important because the normal rat's thyroid appears not to be easily stimulated by this hormone. If the assay technique requires the continuation of injections for a long period, or if the animals are repeatedly used by the technique of short-term injections, the hormone, which appears to be protein-like, may not produce the maximum possible effect because of the production of antibodies or "antihormones" (as postulated by Collip and others). Our knowledge of the relationship between the quality of the diet and the degree of the response is still imperfect. Moreover, injected rats gain weight even if the diet is restricted; it is possible that the response might be less pronounced but more constant under such conditions. It would be desirable, if there were agreement as to the most suitable frequency and total number of injections in an animal like the normal adult female rat, to undertake assays under the following conditions: (1) to employ rats of the same race, age, and approximate weight; (2) to use such rats for assay only once (despite statements to the contrary, it is not known to what extent the response is modified by the use of animals more than once); (3) to use a sufficient number of animals for one dose-level (perhaps thirty); (4) to employ moderate doses which are clearly submaximal (in many of the reported assays, the doses appear to be maximal or supramaximal); (5) to determine the relationship between the dose and the response by observing the effects of multiples or fractions of a dose so that a "unit" could be defined; and (6) to inject, in the performance of routine assays, one group of rats

with a "standard" preparation available to different laboratories so that potency could be stated in terms of a standard preparation.

The only attempts to determine the relationship between the dose and the response in normal rats were those of van Dyke and Wallen-Lawrence (1930) and Evans, Meyer, and Simpson (1933). The former workers gave different doses of one preparation, in proportion to the body-weight, in different orders to a group of thirty-six adult rats most but not all of which were female. The short-term (injection for three successive days) method was used with the following results (given in the order of administration, the relative dose and the percentage increase in weight being indicated in each pair of figures): 2.0:3.58; 1:1.09; 1.5:3.45; 2.3:3.21; 1.25:2.34; 1.25:2.18; and 4:4.14. Seventeen per cent of the animals responded only to the largest dose. Evans, Meyer, and Simpson used four to six adult female rats for each dose, which was given seventeen times over a period of 20 days. In studying the relationship between the relative dose and the gain in weight (from 15–20 g. to 60–70 g.) produced by three different preparations, they found that the logarithm of the change in weight was proportional to the logarithm of the change in dose. In the case of one preparation $\log y = 0.48 \log x + 1.22$, in which y is the change in weight expressed in grams and x is the relative dose expressed as an arbitrary unit. This, however, is not a general expression; in the cases of the different preparations, the intercept, of course, varied. More important is the fact that the slope varied from 0.48 in the case just cited to about 0.26 in the best of the other experiments. In other words, two different preparations do not produce the same proportional change in the logarithm of the change in weight in relation to the logarithm of the change in dose. In the data of Evans, Meyer, and Simpson is an example of the assay of one preparation administered in different doses (preparation K 18, smallest dose, 11.4 mg. given here as a

relative dose of 1). The results, in which the relative dose is given first, and the gain in weight expressed in grams second, were as follows: 1:22; 2:36; 4:36; 8:41; and 16:46. Such results would seem to indicate that their method, as routinely used, has very little quantitative value.

The hypophysectomized rat, operated upon when young, responds much better to a growth-promoting extract than does the normal young adult female rat. The difference between the responses of groups of the two types of animals is not great if the comparison is made several months after operation. Collip, Selye, and Thomson (1933) performed their assays in recently hypophysectomized rats which they preferred not to use repeatedly for such a purpose. They defined their "unit" as the amount of hormone, administered in 1 day, required to produce an increase of 15 g. in weight in a period of 15 days. They used groups of six animals.

The preparation and properties of growth-promoting extracts of the pars glandularis.—Despite numerous attempts, the growth-promoting hormone has been only imperfectly purified.[14] It appears to be a protein or a protein-like substance. The initial extraction of the hormone to produce a crude extract—by using either the fresh pars glandularis of the ox or the same tissue after dehydration by means of acetone, removal of the acetone, and powdering ("acetone powder")—is best done in a dilute aqueous solution of an alkali. One of the following alkalies is most frequently used: NaOH, NH_4OH, $Ba(OH)_2$, or $Ca(OH)_2$. If the extraction of the glandular tissue is undertaken in the presence of even a very low concentration of acid (pH 6.0), little or none of the hormone can be detected in the fluid after extraction.

Subsequent purification of the hormone contained in the

[14] Evans and his co-workers (1921–22, 1924, 1928–29, 1933); Putnam, Teel, and Benedict (1928); Hewitt (1929); Teel (1929); van Dyke and Wallen-Lawrence (1930); Bugbee, Simond, and Grimes (1931); Wadehn (1932); and Collip, Selye, and Thomson (1933).

crude alkaline extract has been attempted by a number of methods. Sodium sulphate can be used to salt out an extract which is less crude (Teel). Several adsorbents (norit, $Al(OH)_3$, and Lloyd's reagent) have been used without success; Collip and others, however, reported that $Ca_3(PO_4)_2$, under proper conditions, adsorbed the hormone and that the elution of the hormone from the adsorbent could be subsequently accomplished. By adjusting the hydrogen-ion concentration either inert substances or the crude hormone may be partially separated from a solution.

Evans, Meyer, and Simpson (1933) described in great detail a number of attempts to purify the growth-promoting hormone such as by the use of phosphotungstic acid, flavianic acid, trichloracetic acid, adjustment of the hydrogen-ion concentration (what they term "iso-electric precipitation"), etc. The physico-chemical changes involved in many of their methods appear to be very complex; consequently, even slight changes in technique might markedly alter the results. They point out that growth-promoting extracts may be extremely labile under certain conditions.

Little that is significant is known about the properties of growth-promoting extracts. They appear not to dialyze (collodion or other membranes) and to be heat-labile. Some extracts in a dilute aqueous solution of alkali will withstand a temperature of 60° C. (but not 80°) for 15 minutes. Others appear to be inactivated at lower temperatures.

How potent and how specific in their growth-promoting effects are various extracts? As to potency, the following remarks can be made. The preparation of van Dyke and Wallen-Lawrence, in a dose of 0.35 cc. per kg. rat or about 0.09 cc. for a female rat of 250 g. per day for 3 days, produced a total increase in weight amounting to 3 per cent. The total dose, 0.27 cc., contained about 2.7 mg. of total solids in part made up of protein (0.88 mg. computed from the total N, 0.14 mg.); probably most of the solids were salts. Evans,

Meyer, and Simpson mention that their purer preparations produced maximal growth (an increase in weight of 40–60 g. or 16–24 per cent, if one assumes that the adult females weighed 250 g. when the injections were started) in a dose of 5 mg. per day administered seventeen times in a period of 20 days. Therefore the total dose used to cause a weight-increase of about 20 per cent in 20 days amounted to 85 mg. All their preparations may have been more potent; only a few were shown to be more potent. What appears to have been the most potent, No. K 18, caused an average weight-increase of 36 g. (about 14 per cent) after the administration of a total dose of 22.8 mg. Collip, Selye, and Thomson stated that their preparation in a dose of 0.5–1.0 mg. twice daily (total daily dose as total solids, 1–2 mg.) caused a marked growth in hypophysectomized rats.

The preparation of van Dyke and Wallen-Lawrence undoubtedly also contained both thyrotropic and gonad-stimulating hormones, although the latter were not shown to be present by injections into immature rats but were by means of the ovulation test in rabbits (Hertz, Hellbaum and Hisaw, 1932) or in a newt (*Triturus viridescens*) (Adams, 1934). Some of the preparations of Evans, Meyer, and Simpson caused no change—even when administered in large doses—in the ovaries of immature rats. To this extent only can they be said to have been free from gonad-stimulating hormone. Collip, Selye, and Thomson reported that they had secured preparations apparently free from gonadotropic and thyrotropic effects. In passing, it may be noted that an extract with growth-promoting properties is not necessarily much refined if it has no effects on the thyroid and adrenal cortex of the hypophysectomized rat; for Smith (1930), who produced growth in hypophysectomized rats by injecting a crude extract or a saline suspension of the pars glandularis of the ox, could find no change in the atrophic thyroid and adrenal cortex.

CHAPTER IV

THE GONADOTROPIC EFFECTS OF IMPLANTS, EXTRACTS, AND SECRETION OF THE PARS GLANDULARIS

THAT there exist significant interrelationships between the pars glandularis of the pituitary body and the gonads is clear. Some of the evidence has already been considered (studies of the physiological anatomy of the pituitary, chap. i; the effects of hypophysectomy, chap. ii). The great importance of these interrelationships has been generally appreciated only during the past fifteen years, particularly since Smith, and Zondek and Aschheim (1926) reported that "precocious sexual maturity" could be produced in immature mice and rats by the implantation of the whole pituitary or of the pars glandularis. Five years earlier Evans and Long had demonstrated that the long-continued injection of simple extracts of the pars glandularis of the ox either prolonged the oestrous cycles or prevented oestrus in the rat. This effect appeared to be the result of an extensive luteinization of the ovary.

The discovery of the gonadotropic effects of implants or extracts of the pars glandularis furnished additional concrete evidence that the gonads are not autonomous structures but depend upon a substance or substances, transported in the blood, for at least part of their development and for their maintenance. Previously, a number of investigators of the physiology of the sexual glands had held the view that a hypothetical substance (Heape called it a "generative ferment"), elaborated elsewhere in the body, was responsible for the growth, maturation, and maintenance of the gonads. In the light of our present knowledge, it may be concluded

that this substance (or substances) is secreted by the pars glandularis of the pituitary and that it (or they) is what today is called the gonadotropic hormone (or hormones). It is generally agreed that gonadotropic hormones directly affect only the primary sex organs (ovaries and testes). Other effects on the generative tract (uterus, vagina, seminal vesicles, prostate, etc.) depend upon the stimulation of the primary sex organs and, therefore, cannot be produced in gonadectomized animals.

Despite the publication of a tremendous number of papers dealing in whole or in part with gonadotropic substances, many questions of fundamental importance have not been answered satisfactorily. Among significant problems not yet solved are the following: (1) The question of the number of gonadotropic hormones secreted by the pituitary body has been answered in the most varied way. Some investigators postulate only one, others, as many as five. This question will be answered—but perhaps not completely answered—when the various hormones thought to exist will have been isolated as pure substances. (2) How are the gonadotropic hormones, secreted by the pars glandularis, related, if at all, to the gonadotropic substances of the body-fluids of pregnant women and horses, to those of the placenta and mucosa of the pregnant uterus (woman and horse), and to those of malignant tumors of the generative tract of men and women? This problem is discussed in chapter v. (3) The physiology, including the comparative physiology, of the pituitary-gonad group of glands of internal secretion will still require much investigation, the progress of which partly depends upon the isolation of gonadotropic hormones as pure substances. Many interesting conclusions rest on a flimsy foundation. As matters now stand, almost every investigator uses a different preparation. The evaluation of results may be further complicated by the use of different methods of administration and by the use of different animals. Diet, care, and age also

affect the results. Only infrequently have studies been made in animals after the removal of the pituitary body; it would be desirable to have all conclusions confirmed by means of experiments in hypophysectomized animals.

THE EFFECTS OF IMPLANTS OF THE PARS GLANDULARIS ON THE GONADS OF THE MOUSE AND THE RAT

Smith and Engle, and Zondek and Aschheim published in 1927 a detailed description of the effects of implanting the pituitary into immature mice and rats. They were able to show that the growth and maturation of the gonads were tremendously accelerated. Not only was the germinal epithelium stimulated (follicle-epithelium and epithelium of the seminiferous tubules),[1] but there also followed an increased secretion of the hormones of the gonads as demonstrated by changes in the secondary sex organs. Gonadectomy prevented any effect on the secondary sex organs; so they concluded that such effects were indirect and depended upon the stimulation of the primary sex organ (ovary or testis). The anterior-pituitary implants produced the same general effects although obtained from animals of different sexes and although they were frequently heteroplastic (from the cat, guinea pig, man, mouse, ox, rabbit, and rat). All the control tissues which they implanted were without effect (skeletal muscle, adrenal, epiphysis, pars tuberalis, posterior pituitary, testis, thymus, and thyroid).

In this section only the general effects of implanted anterior-pituitary tissue will be considered.

The effects in female animals.—The first external evidence of ovarian stimulation in immature mice and rats is the opening of the vaginal orifice and the appearance of nucleated or cornified epithelial cells, without leucocytes, in smears of the vaginal contents. There are therefore present all the external

[1] In the hypophysectomized but not the normal immature male.

signs of oestrus. Such a precocious oestrus can be produced in mice 15 days old (after five implants) or in rats 22 days old (after eight implants).[2] Older animals invariably respond more quickly.

The changes in the ovaries of immature mice or rats receiving implants are the most striking part of the effects. They may be enormously increased in size, weighing ten (rat) to nineteen (mice) times as much as ovaries of normal littermate animals. The implanted anterior-pituitary tissue liberates hormone(s) which appear initially to cause ovarian hyperemia, and follicular growth and maturation. Many follicles may become fully ripe at the same time, rupture, and liberate as many as forty-eight ova (superovulation of Smith and Engle). On the other hand, only follicular growth without ovulation frequently occurs (Zondek and Aschheim). Corpora lutea are then formed either from ruptured or unruptured follicles. In the latter case the lutein cells are largely derived from the granulosa and grow about the degenerating ovum, thus forming corpora lutea atretica.[3] The increased ovarian weight is due both to follicular growth and to the formation of corpora lutea (see Fig. 28).

The completion of vaginal canalization and the appearance in the vaginal smear of the nucleated and/or cornified cells characteristic of oestrus are due to the liberation of the follicular hormone (oestrone, oestradiol?). This hormone likewise causes a marked hypertrophy of the uterus, largely due to a distension by fluid, which is also characteristic of oestrus. There is unquestionably a marked increase in the amount of the uterine tissue; for the uterine weight is increased 2.5–6.0

[2] "Sexual maturity" probably does not occur in normal female mice at an age of less than 28 days. In normal female rats the earliest age of sexual maturity is probably 34 days. In some colonies the average ages of sexual maturity were found to be: mice, 35 days; rats, 72 days (Engle and Rosasco; Long and Evans).

[3] Swezy (1933), like others, believed that most of the lutein cells of corpora lutea atretica arise from the theca interna.

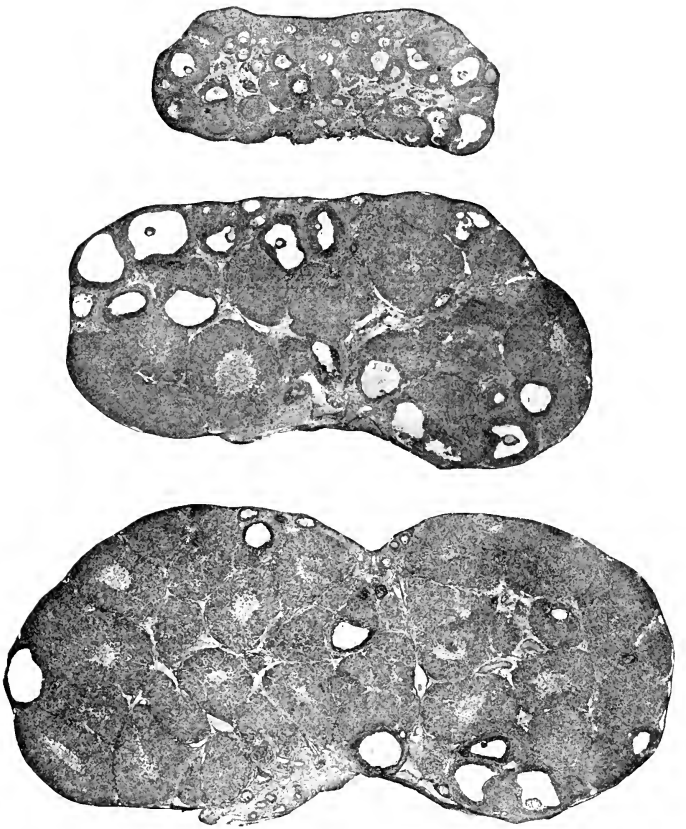


FIG. 28.—Photomicrographs of the ovaries of littermate rats, 26 days old. ×19 (also see fig. 29). Top: ovary of normal rat. Weight of both ovaries, 17.1 mg. Body-weight, 57 g. Middle: ovary of rat receiving a total dose of 2 mg. of an extract of human whole pituitary. 0.5 mg. of the extract was given once daily for 4 days (21–24 days). Weight of both ovaries, 79.8 mg. Body-weight, 55 g. Bottom: ovary of rat receiving a total dose of 6 mg. of an extract of human pituitary. 1.5 mg. was given once daily for 4 days (21–24 days). Weight of both ovaries, 150.5 mg. Body-weight, 54 g.

times in animals killed in the succeeding dioestrus when the uterus is not distended by fluid (see Fig. 29).

Immature mice in which implants of the anterior pituitary have caused sexual maturity will mate (Smith and Engle).

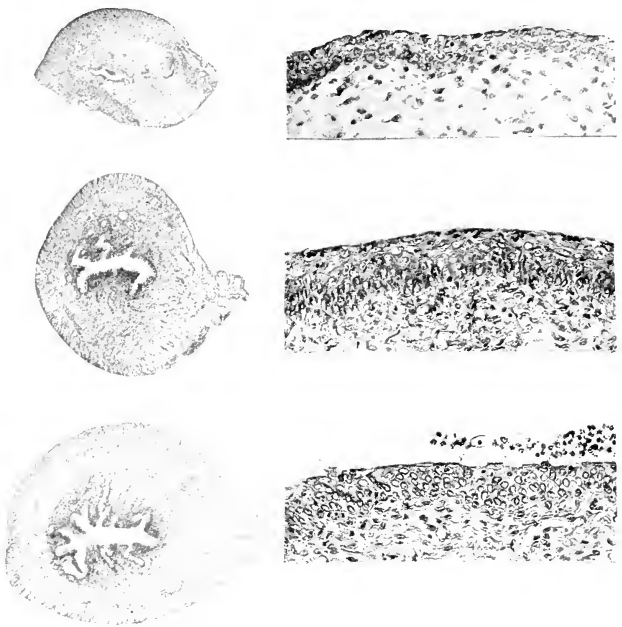


FIG. 29.—Photomicrographs of the uteri (×24) and the vaginal mucosae (×200) of littermate rats, the ovaries of which are shown in Figure 28. Top, of normal rat. Middle, of rat receiving 2 mg. of extract. Bottom, of rat receiving 6 mg. of extract.

Implants of the anterior pituitary of immature, adult, and senile rats are about equally effective in producing a precocious sexual maturity (Smith and Engle). On the other hand, the implantation of anterior pituitary tissue into senile mice will cause oestrus and the formation of corpora lutea (Zondek

and Aschheim). The lack of complete development of the immature ovary and the atrophic changes in the senile ovary are therefore not clearly due either to an absence of gonadotropic hormone in the anterior pituitary or to an inability of the ovary to respond to the hormone. It may be that an insufficient quantity of gonadotropic hormone is available, or that the hormone is liberated at a slower rate than in young adult animals.

Adult female mice respond in much the same way as immature mice.[4] In adult female rats, however, the predominant effect is a stimulation of follicular growth with the formation of numerous cysts, both small and large. The ova in such cystic follicles undergo degeneration. After maximum follicular growth has occurred, lutein cells may be formed from the theca interna and the granulosa; the corpora lutea finally grow to a size greater than that found in the normal adult rat (Engle and Smith, 1929).

Smith (1927, 1930) has shown that the administration of homo-implants to hypophysectomized rats restores the atrophic female gonads to normal.

The effects in male animals.—Smith and Engle studied the effects of implants of the anterior pituitary in immature and mature male mice and rats. In immature male animals the effects on the gonads were much less pronounced than in immature female animals. Five or six implants, administered as one implant each day to immature male rats, had no effect on the size of the testis, but did cause an increase in the size of the rest of the genital tract amounting to about 50 per cent. After ten or more implants, similarly administered, there was a definite increase in the size of the testis as well as a much more pronounced effect on the size of the rest of the genital tract. In the accessory organs there was histological evidence

[4] Engle (1927) mated adult female mice into which he had implanted mouse pituitary tissue. When the mice were killed 9–10 days after mating he could find as many as 19–29 nidation-sites in the uterine horns of a single mouse.

of increased secretory activity—particularly in the seminal vesicles and the coagulatory gland of the prostate. In the testis, precocious spermatogenesis was not produced, nor did the interstitial tissue appear to have undergone a greater growth than the seminiferous tubules (see Figs. 30–32).

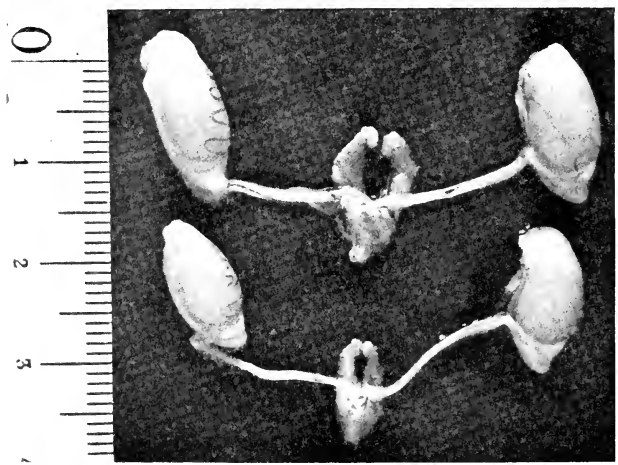


FIG. 30.—Part of the genital tract of littermate male rats, 28 days old. Scale in cms. Upper: testes, etc., of rat receiving a total dose of 36 mg. of an extract of sheep pituitary injected as 2 mg. twice a day for 9 days (19–27 days). The "unit" of this extract in the immature female rat was 3.5 mg. Weight of both testes, 523 mg. Weight of seminal vesicles, 31.0 mg. Body-weight, 60 g. Lower: testes, etc., of normal rat. Weight of both testes, 384 mg. Weight of seminal vesicles, 11.5 mg. Body-weight, 66 g.

Implants of the anterior pituitary of the guinea pig were without effect on the genital tract of the immature male rat (two animals).

The only effect of implants (14–35 days) in adult male mice and rats appeared to be an increase in sexual activity. The experience of others[5] who have investigated the effects of

[5] Steinach and Kun, Voss and Loewe (1928); Martins (1929); Borst and Gostimirović (1930); Evans and Simpson, Moore and Price (1931); and Engle (1932).

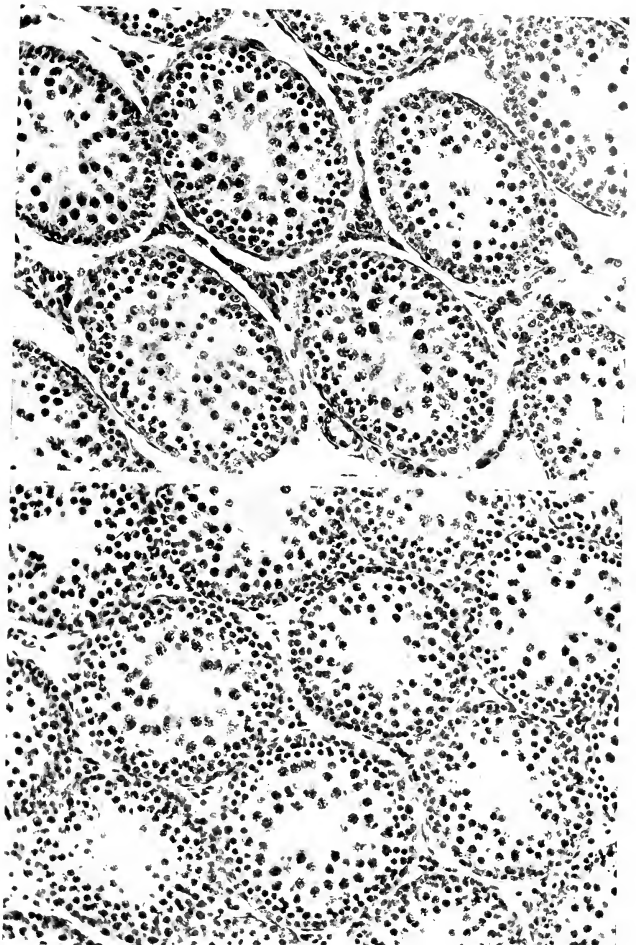


FIG. 31.—Photomicrographs of the testes shown in Figure 30. ×200. Upper: of the rat receiving pituitary extract. There appears to be a greater development of the interstitial tissue than in the testis of the normal rat. Lower: of the normal rat.

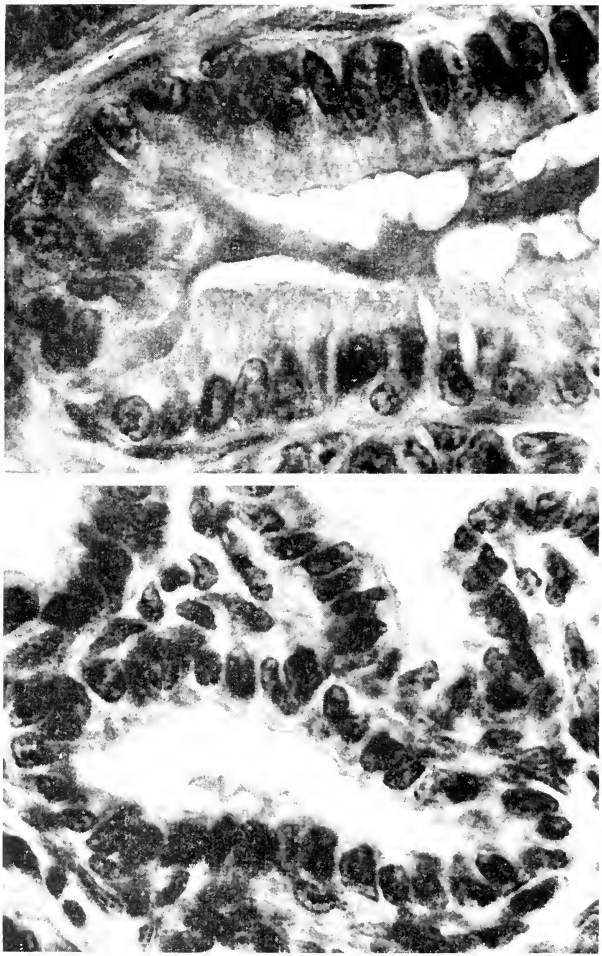


FIG. 32. Photomicrographs of the seminal vesicles shown in Figure 30. ×1,290. Upper: of the rat receiving pituitary extract. Lower: of the normal rat.

implants or extracts of the anterior pituitary on the gonads of immature, young adult, and senile male mice or rats indicates that the chief effect is on the interstitial cells. As a result of treatment, an increased amount of testicular hormone is liberated, the secondary sexual organs become larger, and the *libido sexualis* is increased. Some extracts, such as those of the pars glandularis of the ox, may have the opposite effect—delaying the growth and maturation of the testis and other parts of the genital tract, and lessening sexual activity; the action of such extracts is discussed in the section following this.

The most striking effects of implants in male animals were obtained by Smith (1927, 1930) in hypophysectomized rats. The whole genital tract, which prior to treatment was atrophic, was restored to a normal size and appearance. Not only did the implants bring about normal secretory activity on the part of the interstitial tissue of the testis, but there was also a restoration of spermatogenesis so complete that fertile matings occurred between normal female rats and the hypophysectomized males which had received homo-implants.

THE COMPARATIVE PHYSIOLOGY OF THE GONADOTROPIC HORMONE(S) OF THE ANTERIOR PITUITARY

The comparative physiology of the gonadotropic hormone(s) of the anterior pituitary not only is of scientific interest in itself but also is of importance because of the evidence it is thought to provide in favor of the existence of several gonadotropic hormones. Moreover, it is impossible to attempt correctly to evaluate the assay of gonadotropic hormone(s) without bearing in mind how different the response of the gonads—both qualitatively and quantitatively—may be in different animals. Frequently it is difficult to say to what extent differences are apparent rather than real. For example, the metabolism of a gonadotropic hormone, admin-

istered as a foreign tissue or as an extract of a foreign tissue, conceivably may differ markedly from that of the animal's own anterior-pituitary secretion. Moreover, observations are usually made in animals with intact hypophyses.

The gonadotropic effects of implants or suspensions of the anterior pituitary in fish.—Houssay (1931), Cardoso, and Pereira and Cardoso (1934) have administered homo- or hetero-implants (of other fish) or saline suspensions of the pituitary to fish. Ovulation (spawning), in 1–3 days, was produced in *Cnesterodon decemmaculatus* and in *Prochilodus*. In sexually immature specimens of *Pimelodus clarias*, Cardoso produced ovarian or testicular hypertrophy by administering pituitary implants. Ovarian hypertrophy was more easily produced than testicular hypertrophy.

The gonadotropic effects of implants or extracts of the anterior pituitary in amphibia: 1. *Anuran amphibia.*—Ovulation sometimes without oviposition (spawning) has been produced in a number of frogs (*Rana catesbiana*, *R. clamitans*, *R. pipiens*, *R. temporaria*, and *R. vulgaris*.[6] In male frogs, likewise at times other than the normal breeding season, implants or extracts can produce amplexus and the discharge of spermatozoa. Thus, by administering anterior-pituitary implants or extracts to frogs of both sexes, it is possible to obtain fertilized ova at all times of the year. To produce such gonadotropic effects, homo-implants, hetero-implants (of other frogs and of toads), and extracts of the anterior pituitary of the ox have been employed.

Lipschütz and Paez (1928) and Martins (1929) were unable to cause ovarian stimulation in immature mice and rats by the implantation of the frog pituitary. Lipschütz and Paez used the pituitary of the 230–280 g. Chilean frog, *Calyptocephalus*, and implanted as many as two pituitaries each day for 6 days into the immature mouse. Martins used

[6] Wolf (1929); Dubowik (1930); Adams (1931); Bardeen (1932); Bellerby (1933); and Rugh (1935).

the pituitary of *Leptodactylus ocellatus* and implanted, in some cases, nine pituitaries in a period of 3 days. The frogs which he used as donors, unlike those of Lipschütz and Paez, were killed during the stage of sexual activity.

Houssay, Giusti, and Lascano-Gonzalez (1929) showed that homo-implants of the pituitary produced ovulation and oviposition in female toads (*Bufo arenarum*). In male toads of the same species, implants caused an increase in the size of the testes as well as the appearance of the clasping reflex. They were unable to produce such changes by the administration of hetero-implants obtained not only from various mammals but also from the fowl, the frog, and the snake. Although others[7] also have been unable to cause ovulation in toads (*B. vulgaris* and *B. americanus*) by implanting frog pituitary, but could do so by means of homo-implants, Wills, Riley, and Stubbs (1933) caused ovulation in *B. americanus* by implanting the pituitary of the frog (*R. pipiens* and *R. sphenocephala*) or of fish (garpikes, two varieties of *Lepidosteus*). Even extracts of mammalian anterior pituitary bring about ovulation and oviposition in the South African toad, *Xenopus laevis*, and in Fowler's toad, *B. fowleri* (Hogben, Charles, and Slome, 1931; Bellerby, 1933; Rugh, 1935). It is therefore not possible to generalize on the "zoölogical specificity" of the response of the toad's ovary as some have done.

In hypophysectomized toads (*B. arenarum* and *B. marinus*), homo-implants of the pituitary restore to normal the atrophied gonads of both male and female hypophysectomized toads (Houssay and others, 1929). As a result of castration in mammals, the pituitary enlarges and produces an increased gonadotropic effect; however, the pituitary of the toad (*B. arenarum*), even 90 days after castration, is neither enlarged nor more potent in causing ovulation in female toads (Novelli, 1929). Bellerby (1933), using extracts of the anterior pituitary of the ox, studied the effects of environ-

[7] Adams (1931), and Bardeen (1932).

mental temperature and of dose on the production of ovulation in *X. laevis*. At higher temperatures (23.5–31.5° C.) ovulation occurred earlier but not more frequently than at lower temperatures (14.0–18.5° C.). Changes in dose produced principally a change in the proportion of toads ovulating rather than a change in the number of eggs extruded. Defining a "unit" as the amount of hormone given to each toad so as to cause ovulation in 50 per cent of a group of toads each weighing about 35 g., he calculated that a kilogram of fresh anterior lobe of the ox contained 750 "toad-units."

2. *Urodele amphibia.*—Blount (1930) transplanted pituitary *Anlagen* from other embryos into embryos of *Amblystoma punctatum*. There later occurred a swelling of the cloaca which, he believed, probably indicated a stimulation of the gonad due to the excessive production of gonadotropic hormone. Burns and Buyse[8] performed experiments in immature male and female salamanders (*A. tigrinum*). By means of homo-implants or alkaline extracts of the sheep pituitary, they produced a marked stimulation of the germinal tissue of the testis so that the testicular tissue hypertrophied (500–600 per cent) and precocious spermatogenesis occurred. In immature female salamanders, the injections did not produce such clear-cut results; however, the anterior pituitary extract did cause oviposition.

According to Adams (1930, 1934), ovulation out of season can be produced in *Triturus viridescens* by homo-implants or by extracts either of the pars glandularis of the ox or of the pituitary of the sheep. In this same newt, Stein (1934) produced ovulation by the administration of implants or saline suspensions of the pars glandularis of the fowl. Patch (1933) administered implants of the pituitary of *T. dorsalis* or of a frog (*R. pipiens*) to newts (*T. viridescens*). Ovulation was produced, but the extruded ova were of low fertility; if ferti-

[8] Burns (1930); Buyse and Burns (1931); and Burns and Buyse (1934).

lization occurred, developmental abnormalities frequently appeared.

The gonadotropic effects of implants or extracts of the anterior pituitary in reptiles.[9]—In the snake, *Xenodon merremi*, Houssay (1931) found that the administration of homo-implants (five) was followed by the expulsion of eggs after less than a week. According to Cunningham and Smart (1933), the lizard, *Lacerta viridis*, can be made to extrude fully developed eggs after the injection of an extract of the pars glandularis. The most complete experiments in reptiles appear to have been those of Forbes (1934), who studied the gonadotropic effects of extracts of the sheep pituitary in immature alligators (*Alligator mississippiensis*). The extract caused a hypertrophy of the gonads more marked in the male. In both sexes the hypertrophy appeared to be due chiefly to a proliferation of the germinal epithelium. The disappearance of the Wolffian ducts in the female, and of the Müllerian ducts in the male, was accelerated.

The gonadotropic effects of implants or extracts of the anterior pituitary in birds.—The interrelationship between the pituitary and the ovary or testis of the bird has been investigated in the fowl, the pigeon, and the duck. In the majority of the experiments different varieties of fowls have been used.

1. *The female fowl.*—In 1915, Clark reported that the feeding of the pars glandularis of growing mammals appeared not only to cause an increase in the number of eggs laid by hens but also, in the case of fertilized eggs, to increase the number of chicks hatched. The only author who in part confirmed Clark's results was Gutowska (1931), who believed that the oral administration of an acetone-desiccated anterior-lobe powder daily for a month caused hens to lay a slightly increased number of eggs which were larger than those of normal hens. This effect was most clearly obtained late in the winter. All other attempts to repeat Clark's work have failed

[9] Also see Herlant (1933).

(Pearl and Surface, 1915; Pearl, 1916; and Simpson, 1923). It may be concluded that the feeding of the anterior pituitary has no effect, or at most a very slight effect, on the production of eggs by the hen.

Although Dubowik (1930) found that homo-implants appeared to increase egg-production by hens (or to cause a resumption of egg-laying), other investigators obtained the opposite result by injecting crude extracts of the anterior lobe of the ox. Walker (1925) showed that the intraperitoneal injection of a saline extract of the pars glandularis of the ox inhibited ovulation apparently by causing a follicular atresia which interfered with the development of the ova. Noether (1928, 1930–31) fully confirmed the experiments of Walker. Inasmuch as the effect could be produced only by extracts of the pars glandularis, Noether suggested that extracts could be assayed in terms of their ability to inhibit ovulation. He found that the minimal effective dose was equivalent to about 0.2 g. of fresh anterior lobe of the ox. According to Renoult (1931), anterior-lobe extracts which cause luteinization of the ovaries and growth in mammals inhibit ovulation in the hen, whereas extracts causing more typical gonad stimulation in mammals accelerate ovulation so that eggs without a shell may be laid.

Bates, Lahr, and Riddle (1935) stated that an extract of the anterior pituitary, specifically affecting lactation in mammals ("prolactin," see chap. vi), antagonized the follicle-stimulating effects of other extracts on the fowl's ovary. They also found (Riddle and others, 1935) that the extract, "prolactin," seemed to provoke broody behavior particularly in fowls actively laying eggs.[10]

In the immature fowl, Domm (1931, 1933) and Domm and van Dyke (1932) showed that either homo-implants or a gonadotropic extract of the sheep pituitary caused the fol-

[10] They stated that this effect was produced by extracts previously kept at 100° C. for one hour.

lowing effects.[11] The head furnishings grew rapidly so that the pullets resembled males. No ovulation was produced, but the oviducts became enlarged. As a result, especially of the injection of the extract, the ovary, the rudimentary right gonad, and the Wolffian ducts underwent hypertrophy. All these effects were prevented by the removal of the ovary (left gonad). Domm concluded that a stimulation of the medulla of the ovary caused a liberation of "testicular" hormone so that the head furnishings grew to resemble those of the male; the growth of the oviduct he attributed to a liberation of ovarian hormone from the cortex of the ovary.

2. *The male fowl.*—Domm (1931–33) caused a marked stimulation of the testis of the fowl (3–12 weeks old) by administering a homo-implant once daily for 19–28 days. The head furnishings became swollen and red, and grew markedly. Older cockerels were observed to crow and tread. Not only did the implants bring about a testicular hypertrophy, but spermatogenesis was also precociously accelerated so that mature spermatozoa were formed. Domm had the impression (as in his experiments with pullets) that implants taken from capons were the most effective, whereas those from cocks and hens—particularly the latter—were less effective. All the changes were prevented by gonadectomy. Likewise, all the foregoing effects, except the production of mature spermatozoa, were produced by the repeated injection of a gonadotropic extract of the sheep pituitary (Domm and van Dyke, 1932). Dingemanse and Kober (1933), who employed an extract of the anterior lobe of the ox, produced comb growth but no testicular change in cockerels. On the other hand, Vacek (1934) concluded that the injection of an extract of the pars glandularis of the pig actually caused a testicular regression with failure in the development of the head furnishings. Schockaert (1932) proposed that the

[11] Mitchell (1932) was unable to cause changes in the ovary or oviduct of young pullets receiving implants of the pars glandularis of the chick.

growth of the comb and testes of cockerels be used as a means of assaying the gonadotropic hormone.

3. *The pigeon.*—Riddle and Flemion (1928) produced a marked stimulation of testicular growth in immature doves by injecting repeatedly a glycerin extract of the anterior lobe of the ox. The extract caused no clear-cut change in the size of the ovaries of immature females. Homoplastic implants brought about little, if any, change in the gonads of both male and female birds. Riddle later (1931) concluded that the injection of an extract of the mammalian pituitary into the pigeon stimulated testicular growth far more than ovarian growth. According to Evans and Simpson (1934), the testis of the immature pigeon is one of the most sensitive and specific test-objects for the gonadotropic hormone(s) of the pars glandularis.

The anterior-pituitary hormone causing lactation ("prolactin") brings about an involution of the testis of the pigeon (Riddle and Bates, 1933).

Smith and Engle (1927) observed no change in the ovaries of immature mice which had received one implant of the pigeon pituitary each day for 5 days. Likewise, Lipschütz, Kallas, and Wilckens (1929), although administering from six to twelve pituitary glands of pigeons to immature mice, produced uterine hypertrophy but no change in the ovaries except in one mouse, in the ovaries of which there appeared to be some growth of follicles.

4. *The duck.*—All the experiments in ducks have been performed in drakes. Schockaert (1931) injected various extracts of the anterior lobe of the ox. In the immature drake this treatment provoked a tremendous hypertrophy of the testis (35–40 times the normal size) which might be accompanied by precocious but complete spermatogenesis. The most marked changes were produced in ducks 2.5–4 months old, when the testis normally begins to grow rapidly. Benoit and Aron (1934) were of the opinion that the testicular hypertro-

phy, following the administration of anterior-pituitary extracts, could be most readily demonstrated in drakes 5–8 months old. Ducks 1–4 months old were the least sensitive, whereas adult ducks (at times other than the breeding season) were of intermediate sensitivity.

The gonadotropic effects of implants or extracts of the anterior pituitary in mammals.—The comparative physiology of the gonadotropic hormone(s) in mammals is a treacherous field in which many observations have been made. Too often these observations are of doubtful value even from a qualitative standpoint, especially when they are thought to suggest the existence of different gonadotropic hormones. In the cases of some mammals it is necessary to consider (1) the gonadotropic effects of pituitary extracts in the animal itself as well as (2) the gonadotropic effects of the animal's pituitary in other mammals.

Until there is agreement as to the real number of gonadotropic hormones, little can be said regarding the adequacy of the various tests for a gonadotropic effect now in use. If one chooses to disregard the qualitative aspects of the question, one finds that the most sensitive test-object is probably the ovary of the immature mouse. The production of ovulation in the rabbit in oestrus is a very sensitive test for the presence of a gonadotropic hormone. The testis of the immature pigeon is said to respond more readily than the immature rat's ovary provided that one is using material obtained from the pars glandularis. Of the four test-objects mentioned, the ovary of the immature rat appears to be least sensitive.

So far as the qualitative peculiarities of the gonadotropic effects are concerned, probably the most that can be said is that the pars glandularis of the guinea pig, of the horse (especially if castrated), and possibly of the adult female rat produces chiefly a growth of follicles when tested in immature mice and rats.

So far as the concentration (disregarding qualitative ef-

fects) of gonadotropic hormone is concerned, the following statements appear to be at least approximately correct. Judged by its ability to produce ovarian changes in immature mice and rats, the pars glandularis of the ox contains the lowest concentration of gonadotropic hormone(s). The concentration of the gonadotropic hormone(s) in the pituitary or anterior lobe of other animals appears to vary as follows: horse (especially if castrated) > sheep > pig; rat > rabbit > guinea pig; non-pregnant woman > pregnant woman. Another type of assay—the production of ovulation in the rabbit in oestrus—yields different results. According to this test (Hill), the following relationships appear to hold: sheep > or = horse = pig but far > ox. Differences in potency depending upon sex (cat, dog, guinea pig, rabbit, and rat) are considered later.[12]

The discussion of the comparative physiology of the gonadotropic hormones either as assayed by using the animal's own pituitary or as determined by the response of the animal's gonads will be divided according to the following groups of animals: (1) the ox, sheep, pig, and horse; (2) the mouse, rat, and guinea pig; (3) the rabbit, cat, and ferret (animals which normally ovulate only after coitus); (4) the dog, ground-squirrel, and whale (a miscellaneous group); and (5) the monkey and man.

1. *The ox, sheep, pig, and horse.*—In only one animal of this group (the pig) has any attempt been made to study the effect of extracts of the anterior pituitary on the gonads.

All investigators agree that the concentration of gonadotropic hormone(s) in the pars glandularis of the ox is very low (typical effects ordinarily are detected only by the most

[12] The statements so far made are based on the reports of the following authors: Smith, and Smith and Engle (1927); Lipschütz and others (1928, 1931–32); Wallen-Lawrence and van Dyke (1931); Philipp 1931); Loeb and others (1932–33); Magistris (1932); Severinghaus (1932); D'Amour and van Dyke (1933); Hellbaum (1933); and Hill (1934). The reports of Magistris (1932) and of Hill (1934) deal particularly with this problem.

sensitive tests—ovarian changes in the immature mouse, and ovulation in the rabbit). Even in the hypophysectomized rat, Smith (1927, 1930) could produce no favorable effect on the ovary by injecting crude extracts of the anterior lobe of the ox, although growth was promoted by the treatment; in fact, crude or even refined extracts antagonized the gonadotropic effects of implants, pregnant mare's serum, and prolan (Smith; Evans and others, 1933; Leonard, 1934). In the female rat, receiving repeated injections either from an early age or after sexual maturity, extracts of the ox gland caused the extensive formation of corpora lutea atretica; the oestrous cycles either did not appear or appeared infrequently; the rats became sterile (Long and Evans, 1921–22, Evans, 1924; Brouha and Simmonet, 1928; Lépine, 1931; D'Amour and van Dyke, 1933; and McPhail, 1933). In the male mouse or rat, implants or extracts of the anterior lobe of the ox appear to affect the testes adversely. After the repeated injection of extracts, fertility may be preserved but the size of the testes (and tubules) may be reduced. Implants or extracts of the anterior lobe of the ox may inhibit the growth of the testes, spermatogenesis, and the activity of the interstitial cells (some interference with the growth of the secondary sexual organs).[13]

The effects of implants or extracts of the pars glandularis of the ox on the gonads of other animals are discussed in the sections which follow.

The pars glandularis of the sheep is of interest because it constitutes one of the best sources of gonad-stimulating extracts. Judged by different assay techniques, sheep glands are rich in the gonadotropic hormone(s). The anterior lobe of the pig—although less satisfactory than that of the sheep—appears to be a good source for obtaining the hormone.

[13] Crafts and Flower (1925); Evans and Simpson (1926); Brouha and Simmonet (1929); Lépine (1931); and Robson (1933). Brouha and Simmonet reported that small but not large doses of an extract of the ox gland might hasten the development (but not the growth) of the testes of the young mouse.

Wolfe (1931) investigated the potency of the pars glandularis of the pig in causing ovulation in the rabbit. If the anterior lobe was removed from pigs in pro-oestrus or just before the first oestrus, the dose of fresh gland required to produce ovulation was 1–2 mg. About 10 mg. was required if the pituitary was removed during oestrus. The largest doses (about 40 mg.) of anterior pituitary required were from pigs in the ovaries of which were found actively secreting corpora lutea. The effects of gonadotropic hormones (from the pituitary of the horse and the pig, and from the serum of pregnant mares) on the ovary of the immature pig 1–112 days old were investigated by Casida (1935). Different effects (follicle growth, hemorrhage into follicles, ovulation, and the formation of corpora lutea) were produced, but these depended upon the preparation used, the manner of administration, the age of the pig, the development of the ovaries, etc. The extracts had little or no effect on the ovaries of pigs younger than 5 weeks. In comparison with the effect on the ovary of the immature rat, luteinization was less easily produced in the ovary of the immature pig.

The pars glandularis of the horse contains a higher concentration of the gonadotropic hormone(s) than that of any other large animal (Hellbaum, 1933; Hill, 1934). This appears to be true particularly of the castrated horse. In immature rats, unrefined extracts of the anterior lobe of the (castrated) horse cause chiefly a follicle-growth, whereas those of the sheep cause luteinization as well. The experiments of Catchpole and Lyons (1934), who used material from pregnant mares, are referred to later.

2. *The mouse, rat, and guinea pig.*—The general effects of implants of the anterior pituitary on the gonads of immature mice and rats and of adult rats have already been described in the introductory part of this chapter. In this section some of the special effects of gonadotropic extracts will be considered.

Kraul (1931) treated various animals with corpus luteum extract, oestrin, etc., and then implanted the pituitary of the treated rabbits, guinea pigs, etc., into immature female mice. He concluded that the effect of the implant was related to the type of extract previously injected into the animal serving as donor. For example, if the donor-animal had received injections of corpus luteum extract, the predominant effect of its pituitary on the ovary of the immature mouse was luteinization. So far as the author is aware, there is some evidence against this view, but none other in favor of it.

In mice, as in rats, atretic corpora lutea may follow the use of implants, but they appear to be more frequently observed after the injection of extracts. The reverse is true of ovulation.

The effect of injections of a gonadotropic extract (sheep pituitary) for periods longer than that usually employed (4–5 days) has been investigated by Fluhmann (1933). The effect of a given dose of the extract on the weight of the ovary of the immature rat was greatest if the whole amount was given within 5 days. If the administration of the total dose was completed only after 10–20 days, the ovarian hypertrophy was less. Even if the daily dose was continued for 20 days (so that the total dose was much increased) the effect was not greater than after 5 days except when large doses were employed. Vogt (1931) found that the extirpation of the superior cervical ganglion and the interganglionic nerves prevented, in eight of thirteen adult female rats, pseudopregnancy due to the irritation of the cervix by means of a glass rod. The operation did not prevent pregnancy or pseudopregnancy due to mating between operated female rats and normal or vasectomized bucks. Her data, therefore, hardly support the conclusion that the liberation of gonadotropic hormone from the pituitary (pseudopregnancy following the irritation of the cervix by a glass rod) may be initiated by nervous stimuli passing by way of the cervical sympathetic.

The effects of a gonadotropic extract of the anterior pituitary on the metabolism of the isolated ovary, uterus, and testis removed at different intervals after the injection of the extract, was studied by Reiss (1932) in immature mice and rats. The effect on the testis was less pronounced, and appeared later. In the isolated ovary, increased oxygen consumption and increased glycolysis (both aerobic and anaerobic) were observed. Some of the changes, e.g., the increased oxygen consumption, were at a maximum before morphological changes were pronounced.[14]

In the normal immature male rat either homo-implants or extracts of the pituitary ordinarily have no effect on spermatogenesis, although testicular size may be increased and there may be stimulation of the internal secretion of the testis with or without a morphological change in the interstitial cells (Smith and Engle, 1927; Moore and Price, 1931; Engle, 1932).

The physiology of the gonadotropic hormone(s) of the pituitary in the guinea pig is peculiar in several respects. In the first place, implants or extracts of the guinea-pig pituitary are low in potency in comparison with those of the pituitary of the mouse, rat, and rabbit. Second, the prominent effect of implants of the guinea-pig pituitary in immature mice and rats is either oestrus (vaginal canalization with or without uterine hypertrophy) or oestrus and follicle growth. Third, the response of the ovary of the immature guinea pig is less easily elicited and perhaps qualitatively different in comparison with that of the immature mouse or rat.

The effects of implants of the pituitary of the guinea pig have been observed principally in immature mice, rats, and guinea pigs. In immature mice and rats, the implants may produce only the secretion of an increased amount of oestrin, shown by the completion of vaginal canalization, by the desquamation of nucleated epithelial or cornified cells in the

[14] Also see Szarka, Meyer, and Evans (1933).

vagina, and by oestral swelling of the uterus; such changes are not produced in immature mice or rats after ovariectomy. In addition, follicle growth in the ovary may be stimulated.[15] Lipschütz and his co-workers estimated that the amount of pars glandularis required to produce some luteinization of the ovary of the immature rat was about 10–15 times greater if the anterior lobe was obtained from guinea pigs instead of rats. To produce ovulation in the rabbit, 5 times as much anterior lobe from guinea pigs as from rats was needed. The amount of gonad-stimulating hormone in the pituitary of the immature rat is approximately the same as that in the adult rat (only the male?); the pituitary of the immature guinea pig, however, is said to contain less gonadotropic hormone than that of the adult. The qualitative effects of implants of the pars glandularis of the guinea pig are the same whether the pituitary is obtained from male, female, or gonadectomized guinea pigs. Lipschütz believed that the anterior lobe of this animal lacked a gonadotropic hormone necessary for the growth and/or sensitization of the graafian follicle; provided that follicular growth and/or sensitization was produced, the anterior pituitary of the guinea pig then caused luteinization (see the later discussion on the possible number of gonadotropic hormones).

Homoplastic implants of the pituitary into immature guinea pigs produce both growth and maturation of the graafian follicle. Generally, ovulation and subsequent formation of true corpora lutea can be produced by homo-implants, but not by implants or extracts of the pars glandularis of other animals (Watrin, 1929; Loeb, 1932; and Aff and Loeb, 1934). According to Loeb and others (1932–34), implants or extracts of the pituitary of the ox, sheep, and pig cause an atresia of the follicles with luteinization of the theca interna, whereas similar material from the rat, rabbit, and guinea pig bring about growth and maturation of the follicles followed

[15] Lipschütz and others (1928, 1931–35), and Severinghaus (1932).

by luteinization of both the granulosa and the theca interna. Other investigators also have observed the effects of implants or extracts on the ovaries of the immature guinea pig (ox pituitary: Brouha and Simmonet [1928]; Aron [1931]; and Guyénot and others [1933]; sheep pituitary: Guyénot and Ponse [1932]; and King [1933]).

In adult female guinea pigs, extracts of the anterior lobe of the ox bring about atresia of the follicles, proliferation of the theca interna, and the formation of interstitial gland tissue (Aron, 1931). Guyénot and others (1932–33) found that extracts of the ox gland not only produced theca-luteinization but also a hypertrophy of the clitoris. They stated that the latter effect could be observed in adult female guinea pigs even after ovariectomy.

Guyénot and his co-workers (1933) described a hypertrophy of the secondary sexual characters in immature male guinea pigs into which they had injected an alkaline extract of the anterior lobe of the ox. Moszkowska (1935) believed that atrophy of the penis took place more slowly or that some hypertrophy of the penis even occurred if an anterior-lobe extract was injected into mature or immature guinea pigs shortly after castration.

3. *The rabbit, cat, and ferret.*—The peculiarity in the physiology of the reproductive organs in these three mammals is the fact that ovulation ordinarily does not occur except after coitus. The most complete studies (and this is also true of gonadotropic hormones) have been made in rabbits. Rabbits normally ovulate about 10 hours after coitus; ferrets, about 30 hours; cats probably ovulate less than 25 hours after coitus (Greulich, 1934).

The effect of hypophysectomy on ovulation in the rabbit has already been discussed in chapter ii. It will be recalled that if the operation is performed less than 1 hour after copulation, ovulation does not occur. On the other hand, normal ovulation takes place in rabbits hypophysectomized later

than 1 hour after coitus. It therefore appears that the liberation of the hormone responsible for ovulation takes place with considerable rapidity. Dumont, D'Amour, and Gustavson (1932, 1934) injected serum or defibrinated blood, taken from adult female rabbits 1–2 hours after copulation, intraperitoneally or intravenously into young rabbits (12–18 weeks old). In only one case was ovulation produced; the other positive results were characterized by follicular growth or hemorrhagic corpora lutea (five of twelve immature rabbits receiving 60–100 cc. of blood; eleven of eighteen immature rabbits receiving 200–350 cc. of blood given by alternately bleeding and injecting the recipients). It is unfortunate that the investigators did not observe the production of ovulation in the more sensitive adult rabbit in oestrus. This was done by McPhail, Parkes, and White (1933) who performed cross-circulation experiments between adult female rabbits, one being in oestrus, the other having copulated shortly before. The blood was cross-circulated for 2–3 hours; the rabbits were then permitted to live about 20 hours longer. Ovulation was usually produced in the normal rabbit in oestrus provided that two of the animals' four ovaries had been removed before the cross-circulation was begun.

Not much is known as to how copulation gives rise to a liberation of the anterior pituitary hormone causing ovulation. Stimulation of the central nervous system, if powerful and diffuse (electrical), may cause ovulation (Marshall and Verney, 1935). However, the removal of the whole genital tract (except the lower portion of the vagina), as well as the anesthesia of the vulva and vagina locally, do not prevent ovulation after coitus (Friedman, 1929; Fee and Parkes, 1930). According to Haterius (1934), the electrical stimulation of the superior cervical ganglion is not followed by ovulation. In the author's experience, repeated intravenous injections of epinephrin or acetyl choline do not bring about ovulation. Foster, Haney, and Hisaw (1934) were unable to

produce ovulation by injecting salts of pilocarpine or physostigmine intravenously. However, the injection of atropine sulphate, if given at an appropriate time, seemed to prevent ovulation or pregnancy (if ovulation had already occurred).

A number of authors have confirmed Bellerby's observation (1929, 1934) that the intravenous injection of an extract of the pars glandularis (in this case, of the ox) is followed in about 11 hours by ovulation whether or not the hypophysis has been removed previously.[16] Most of the authors used extracts of the anterior pituitary of the ox or the sheep. However, it appears that the pars glandularis of all mammals is capable of causing ovulation in the rabbit provided that a suspension or extract of the gland is given intravenously. Subcutaneous or intraperitoneal injections usually cause follicular growth and—if the dose is large—atretic corpora lutea which may be hemorrhagic.[17] Hemorrhages are also frequently observed in large or growing follicles. Similar ovarian changes may follow the intravenous injection of anterior-lobe extracts. Once ovulation has been produced, either by the secretion of the rabbit's own pituitary or by the injection of an anterior-lobe extract, the growth and maintenance of the corpora lutea do not require the secretion of the animal's own pituitary until about 2 days later. By means of suitable doses of extract, ovulation can be produced in immature, pseudopregnant, or pregnant rabbits.

The dose of an anterior-lobe extract which will produce ovulation in an adult rabbit in oestrus may be less than one-fifth of the dose of the same extract required to cause an ovarian hypertrophy in the immature rat (Leonard, 1932). Hill (1934) has investigated the concentration of the ovulation-producing hormone in the pituitary of a number of mammals.

[16] Friedman (1930); Stricker and Grueter (1930); Hill and Parkes (1931); Kunischige (1931); Leonard (1931); Jares (1932); and others.

[17] But see Stricker and Grueter (1929).

Wolfe and Cleveland (1931) and Hill (1934) have estimated, under various conditions, the amount of gonadotropic hormone in the anterior pituitary of the rabbit. They used as their test the production of ovulation in adult rabbits. The anterior pituitary of rabbits 3 months old contained nearly as much hormone as that of the adult. The pituitaries of rabbits about 1 month old clearly contained less hormone than that of animals more than 3 months old. Hill found that the anterior pituitary of the adult female rabbit contained more gonadotropic hormone than did that of the adult male.[18] He also determined the concentration of the hormone in the pituitary of adult female rabbits under different conditions of sexual activity. The concentrations of hormone found were as follows:[19] during oestrus, 156; 30 minutes after mating, 122; 24 hours after mating, 21; pregnant, 15 days, 250; pseudopregnant, 10 days, 250. At other times of pregnancy and pseudopregnancy, lower concentrations of hormone were found (83–100 units). Immediately postpartum, the concentration was about 133 units. In general, the total amount of hormone in a single pituitary varied similarly.

Five to seven hours after the administration of an extract of the anterior pituitary of the ox, uterine movements of the unanesthetized rabbit are markedly reduced. This effect does not depend upon an ovarian change, for it occurs in ovariectomized does (Reynolds, 1932). Robson (1931–32) studied the uterine response to the oxytocic and pressor hormones of the pars neuralis in rabbits in which corpora lutea with subsequent pseudopregnancy had been produced by the administration of implants or extracts of the pars glandularis. The uterus of typical pseudopregnancy does not contract in the presence of the oxytocic hormone; the pressor hormone causes a reduction in uterine tone. In Robson's animals, in

[18] But see Table V.

[19] The concentrations are here expressed in arbitrary units $\frac{\text{(Units per gram)}}{10}$.

some instances, the pseudopregnant reaction of the uterus persisted longer than the corpora lutea. On the other hand, the repeated injection of an anterior-lobe extract might be accompanied by ovarian luteinization and pseudopregnant changes in the uterus; however, after a week, the oxytocic hormone often produced a uterine contraction even after the additional injection of a potent extract of the corpus luteum.

It is reasonably certain that the dose of an anterior pituitary extract required to produce ovulation is much greater in the cat than in the rabbit (Snyder and Wislocki, 1931; Goodman and Wislocki, 1933; unpublished experiments of the author). Courrier and Kehl (1929) injected (but not intravenously) extracts of the anterior lobe repeatedly into cats. Small doses of the extract produced cystic follicles; large doses produced corpora lutea atretica.

McPhail (1933) has produced ovulation in the ferret in oestrus. In earlier work, Hill and Parkes (1930) produced cystic follicles in the ovaries of ferrets into which they injected an anterior-lobe extract repeatedly. In hypophysectomized ferrets, extracts seem to bring about a luteinization of the theca interna of small follicles, but no follicular growth (McPhail, 1933).

4. *The dog, ground-squirrel, and whale.*—The gonads of the dog (like other mammals) are not affected by the feeding of the pars glandularis (Novak and Kun, 1931). Reichert (1928) administered fresh whole rabbit pituitary daily to a hypophysectomized dog (6 months after hypophysectomy which was performed when the puppy was about 6 weeks old). Swelling of the vulva appeared within 48 hours, and was marked after 72 hours. There was considerable secretion in the vagina 2 weeks after the hetero-implants were started; after that, a pronounced vaginal secretion was observed as long as the implants were continued. In normal dogs, the administration of an extract of the anterior lobe of the ox has caused hypertrophy of the ovary, uterus, and vagina (Benedict, Putnam,

and Teel, 1930), or external signs of oestrus in the female (Barnes and Bueno, 1933).[20]

Johnson and his colleagues (1934) administered implants of the pars glandularis of the rat to adult, male ground-squirrels (*Citellus tridecemlineatus arenicola*) during the period of sexual inactivity. This treatment produced an increase in the volume of the testis and in the diameter of the tubules. In the animals receiving more prolonged treatment, the seminal vesicles, Cowper's glands, and the prostate were enlarged; spermatogenesis was also stimulated.

Valsö (1934) investigated the amount of gonad-stimulating hormone(s) in the acetone-desiccated anterior lobe of the whale. From assays in immature mice, he estimated that about 4 mg. were required to produce follicle growth, and 9 mg., to produce corpora lutea. He concluded that the concentration of hormone in the whale gland was comparable to that in the anterior lobe of the ox.

5. *The monkey and man.*—In the immature female monkey (most of the experiments have been performed in *Macaca mulatta*, also known as *Macacus rhesus*) the usual effect of homo-implants, hetero-implants, or extracts of the pars glandularis, is a stimulation of follicular growth. Secondary to this effect there occurs an edema and reddening of the sexual skin as well as changes in the uterus characteristic of the follicular (proliferative) phase of the adult menstrual cycle. Growth of the mammary glands may also occur. Similar changes in the secondary sexual organs are produced by the injection of oestrin into spayed monkeys. If the implants or injections of the anterior lobe are stopped, uterine bleeding from an "interval" mucous membrane sets in after 4–9 days.

[20] Thompson and Cushing (1934) administered a gonadotropic pituitary extract (sheep) to a female puppy for which a littermate female control was available. The injected dog was given the extract for 3 months (3–5 months old). The authors concluded that the extract produced some of the changes (adiposity, delayed growth, etc.) characteristic of "pituitary basophilism" in man.

Such a uterine bleeding resembles that following the injection of oestrin or that of non-ovulatory menstruation.[21]

The growth of the follicles, which usually takes place after the administration of anterior-pituitary implants or extracts, is not ordinarily accompanied by follicular maturation. On the contrary, the prominent changes are cyst formation and follicular atresia.[22] It appears that no investigator has succeeded in causing ovulation in the immature monkey by administering the anterior lobe either as implants or in the form of an extract. After follicle growth has been stimulated, however, the partial or complete luteinization of follicles can be accomplished by the intravenous injection of an anterior-pituitary extract or by the intravenous injection of extracts both of the anterior pituitary and of pregnancy-urine (Hisaw and others, 1932; Engle, 1934). Lutein cells are then formed both from the granulosa and the theca interna. Engle believed that luteinization of the granulosa was caused by the anterior-pituitary extract, whereas that of the theca was due to the pregnancy-urine extract. However, Hisaw and his colleagues used only an extract of the anterior pituitary, yet they produced luteinization of both the granulosa and the theca interna.

According to Hartman, Firor, and Geiling (1930), the bleeding from the uterine mucosa following the cessation of oestrin treatment in spayed monkeys does not occur if hypophysectomy as well as ovariectomy have been performed, unless anterior pituitary implants or extracts are also administered. They concluded that a hormone of the anterior pituitary is the direct cause of bleeding from the uterine mucosa (e.g., in menstruation). This hypothesis requires support—

[21] Allen (1928); Courrier, Kehl, and Raynaud (1929) (they performed an experiment in an immature magot [*Macacus inuus seu ecaudatus*]); Ehrhardt, Wiesbader, and Focsaneanu (1929); Hartman (1930); Hartman and Squier (1931); Hisaw, Fevold, and Leonard (1931); and Saiki (1932).

[22] The injection of the urine of spayed women may stimulate follicle growth without causing cystic degeneration (Smith and Engle, 1934).

so far lacking—both from the confirmation of their experiments and from other data.

Engle (1932) found that the injection of an extract of the anterior pituitary into immature male monkeys brought about both a descent and a hypertrophy of the testes. The treatment, although causing an increase in the diameter of the tubules, did not hasten spermatogenesis.

There exist comparatively few observations in man. The discussion of the gonadotropic hormones found in human body-fluids and tissues in pregnancy, in individuals with malignant tumors, in spayed women, or in old age, etc., will be found in chapter v.[23] Zondek (1931), and Schockaert and Siebke (1933), as well as others, have investigated the amount of gonadotropic hormone in the human pars glandularis. Schockaert and Siebke concluded that the amount of hormone in the human pituitary[24] is far greater than formerly had been supposed. They estimated that the adult gland contains 3,000–4,000 units of follicle-stimulating hormone (1 mouse-unit is about 0.1 mg. of tissue) and 1,000–1,500 units of luteinizing hormone (1 mouse-unit is about 0.3 mg. of tissue). Their data—if correct—indicate that the human anterior pituitary is one of the richest sources of gonadotropic hormone(s).

The urine of children, and of pubescent or adolescent boys and girls, appears to contain gonadotropic hormone more often than does that of adult men and women with physiologically active gonads (Soeken, 1932).[25] Is this due to the excretion of anterior-pituitary gonadotropic hormone until the time it is utilized by the mature gonads when there is less

[23] Watts (1932) could detect no gonad-stimulating hormone in the urine (as much as 24 cc.) or serum (as much as 7.5 cc.) of patients in whom chromophobe or oxyphil (acromegaly) adenoma of the pituitary was diagnosed. Also see Candela (1931); Hirsch-Hoffmann (1932); and Trancu-Rainer and Vladutiu (1933).

[24] Of males and non-pregnant females.

[25] This observation was not confirmed in the smaller series of observations by Katzman and Doisy (1934).

of an excess to be excreted, or is it due to an increased secretion and renal excretion of gonadotropic hormone in the absence of the antagonizing gonadal activity characteristic of adults? Failure in utilization and/or absence of gonadal activity may also explain the increased urinary excretion of gonadotropic hormone by women past the menopause or after ovariectomy.

Little is known of the effect of the anterior-pituitary gonadotropic hormone(s) on the human ovary.[26] In one case of amenorrhea in a young woman who came under the author's observation, several intramuscular and one intravenous injection of an extract of the pituitary of the sheep caused the formation of a great number of cystic follicles. Wagner (1928) found numerous lutein cysts in the ovaries of a woman with a tumor of the pars glandularis; the uterine mucosa was progravid in appearance—as is the case if the ovary contains an actively secreting corpus luteum. Kraus (1933) stated that cystic degeneration of the ovary was found in about three-fourths of female patients with increased intracranial pressure. The urine of such patients often contained an increased amount of gonadotropic hormone. Kraus's results suggested that an excessive amount of gonadotropic hormone was secreted by the pars glandularis which was found to be hypertrophied.

THE SECRETION OF GONADOTROPIC HORMONE(S) BY THE PARS GLANDULARIS OF THE PITUITARY IN RELATION TO THE GONADS AND THEIR INTERNAL SECRETIONS

The gonadotropic potency of the pituitary in relation to sex.—No general statement as to the relationship between the gonadotropic effects of the pituitary and the sex of the animal serving as donor can be made; in some animals, the male pituitary is the more potent, in others, the female. The results of different authors are summarized in Table V.

[26] The paper of Laroche and Simmonet (1932) contains no useful data.

There is some evidence that the greater potency of the pituitary of the female rat, less than 20 days old, may depend upon the lack of activity of the ovaries. If very young rats

TABLE V

THE GONADOTROPIC POTENCY OF THE ANTERIOR PITUITARY IN RELATION TO SEX

Animal Serving as Donor	Assay Method	Result	Authority
Rat:			
To age of 20 days	Ovarian changes in immature mice	Female > male	Clark (1935)
At puberty	Ovarian changes in immature mice	Male ≷ female	Clark (1935)
4–6 months old	Ovarian changes in immature mice	Male = female	Clark (1935)
Adult	Ovarian changes in immature mice	Male > female	Clark (1935)
Adult	Ovarian changes in immature mice	Male ≷ female	Magistris (1932)
Adult	Ovarian changes in immature rats	Male > female	Evans and Simpson (1929)
Adult	Ovulation in rabbit	Male > female*	Hill (1934)
Adult guinea pig	Ovarian changes in immature mice	Male = female	Severinghaus (1932)
Adult guinea pig	Ovulation in rabbit	Female > male	Hill (1934)
Adult rabbit	Ovarian changes in immature mice	Male > female	Smith, Severinghaus, and Leonard (1933)
Adult rabbit	Ovarian changes in immature mice	Male ≷ female	Magistris (1932)
Adult rabbit	Ovulation in rabbit	Female > male*	Hill (1934)
Adult cat	Ovarian changes in immature mice	Female > male	Magistris (1932)
Adult cat	Ovulation in rabbit	Male > female	Hill (1934)
Adult dog	Ovulation in rabbit	Female > male	Hill (1934)

* The difference is not great (about 25 per cent).

are castrated or spayed, there is interference with the early development of the male accessory organs but not with that of the female (Wiesner, 1935). If gonadectomy is performed

in rats on the first day of life, and the pituitary is removed on the sixteenth to eighteenth day, the pituitary of the castrated rat is about as potent as that of the spayed rat. However, if the gonads are intact, the female pituitary is the more potent. Moreover, castration changes in the pituitary can be found in the male rat as early as the sixth day of life (castration on the first day of life). These observations were made by Clark (1935). It therefore appears that the internal secretion of the testis is elaborated and liberated into the blood early in life; the testis hormone lessens the secretion (or storage) of gonadotropic hormone in the pituitary (see the sections following this). On the other hand, the hormone of the ovary[27] is not secreted in appreciable amounts until the age of the rat is greater than about 3 weeks. Therefore, the pituitary of the very young female rat secretes (or stores) more gonadotropic hormone and, in fact, is similar in this respect to the pituitary of the castrated male.

Lipschütz (1933–34) believed that the pituitary of the adult female rat lacked a principle causing follicle growth or sensitization. He suggested that the pituitary of the immature male or female rat as well as that of the adult male rat contained this principle without which luteinization could not occur. On the other hand, if this hypothetical substance was supplied by also administering the urine of spayed women, implants of the adult female rat pituitary then caused marked luteinization.

Experiments in animals living parabiotically; the bearing of such experiments on the interrelationship of the gonads and the anterior pituitary.[28]—The experiments were performed in rats

[27] Reference here is made only to a hormone of the "oestrin" type.

[28] For the discussion of experiments in this field, reference in this section is made to the following authors: (1) Matsuyama (1921); (2) Yatsu (1921); (3) Goto (1924); (4) Zacherl (1928); (5) Fels (1929); (6) Kallas (1929); (7) Martins (1930); (8) Martins and Rocha (1930); (9) Hill (1932); (10) Lower and Hicken (1932); (11) Witschi, Levine, and Hill (1932); (12) Hill (1933); (13) Levine and Witschi (1933); (14) Møller-Christensen (1933); and (15) Witschi and Levine (1934).

in many of which a free communication between the peritoneal cavities was established usually by the method of Sauerbruch and Heyde. However, there is evidence that the effects discussed here largely depend upon the transfer of blood from one animal to the other rather than upon a transfer of the fluid of the peritoneal cavity. Hill (1932) has particularly studied this aspect of the problem; he preferred not to join the peritoneal cavities.

The principal experiments can be summarized as follows:[29]

1. ♂♂. This type of parabiosis is accompanied by no change in either rat (5).

2. ♀♀. The oestrous cycles of the two animals occur independently and are unaffected or only slightly affected (4, 5, 9).

3. ♂♀. No changes occur in the testis and prostate (2) or degenerative changes are later observed (1, 5).

Various opinions on the changes in the female genital tract have been expressed (1, 4, 9, 15). The oestrous cycles may recur normally for a long period or may be succeeded, a few days after parabiotic union, by a prolonged dioestrous stage. Cystic follicles may be found in the ovaries or the early ovarian changes may be described as a combination of luteinization and follicle growth.

4. ♂♂̸. The genital organs of the normal male are increased in size. The castration changes in the secondary sexual organs of the castrated male are not affected (1, 5, 10).

5. ♂♀̸. Hypertrophy of the male genitalia may follow (5). Yatsu (2), however, could find no change in the testes or prostate.

6. ♀♀̸. The changes usually occur only in the normal female (occasionally oestrus may appear in the spayed rat).

[29] The experiments here summarized were nearly all performed in rats after puberty. ♂ and ♀ refer to normal male and female rats; ♂̸ refers to a castrated rat, ♀̸, to a spayed rat. ♂ ♀ refers to parabiosis between a normal male and a normal female rat; ♂ ♀̸ refers to parabiosis between a normal male and a spayed female, and so on.

The oestrous cycles of the rat with intact ovaries may recur normally. More often they become lengthened or disappear; in the latter event, a period of prolonged dioestrus is later succeeded by a period of prolonged oestrus. The following are some of the ovarian changes which have been described: growth of follicles, atresia of follicles, and formation of corpora lutea or of corpus luteum cysts (4, 5, 7, 9, 10, 12, 14).

7. ♀ ♂. In this type of experiment is found the best agreement among different investigators as to the effects on the female genital tract (1, 2, 3, 5, 7, 12, 15). Shortly after the animals have been united (or after the castration of the male if the rats were made parabiotic before gonadectomy) oestrus appears in the female rat and persists, except for an occasional short dioestrous stage, for weeks or months.[30] The important change in the ovaries is a marked growth of follicles with the formation of follicular cysts. Atresia of follicles and corpora lutea atretica have also been found in the ovaries of the female parabiont.

Experiments still more complex have also been undertaken. In the experiments ♀ ♂, observations have been made either after making the testes cryptorchid or after irradiating (X-rays) the testes (Martins, 1930; Witschi, Levine, and Hill, 1932). Either treatment of the testes caused degeneration of the germinal epithelium without appearing to impair the secretory activity of the interstitial cells. The genital tract of the female responded as in Experiment 7 (♀ ♂); the response, however, was less pronounced. In the experiment ♀ ♀, one of the parabionts was subjected to X-ray irradiation of the ovaries so that the oestrus cycles, if present, were abnormal; the germ cells were destroyed by the irradiation. In the normal parabiont, prolonged oestrus and the formation of cystic follicles in the ovary were observed—resembling the effects

[30] In the early period preceding oestrus, the ovaries may contain numerous corporea lutea; the rat is then in dioestrus.

in the normal female rat in Experiments 6 (♀ ⚲) and 7 (♀ ♂) (Levine and Witschi, 1933).

If testicular tissue is administered to the castrated male rat of the experiment ♀ ♂, the changes in the ovaries of the normal female rat are less pronounced (Martins and Rocha, 1930).

In Experiments 6 (♀ ⚲) and 7 (♀ ♂), the changes in the genital tract of the normal female were compared by Hill (1933). In Experiment 7 (♀ ♂) the more or less continuous oestrus and the formation of cystic follicles in the ovary appeared earlier (e.g., if corpora lutea were present in the ovary at the time the rats were united) and were more pronounced. These observations suggested that the pars glandularis of the castrated rat secretes more gonadotropic hormone than that of the spayed rat.

In the experiments ♀ ♀ and ♀ ♂, impregnation of a female may be accomplished. Pregnancy in one female in the experiment ♀ ♀ seems to prevent oestrus in the other normal rat (Hill, 1932; however, Zacherl, 1928, found no disturbance of the oestrous cycles). Some growth of the mammary gland may occur in the normal rat. If the female rat of the experiment ♀ ♂ becomes pregnant, the course of pregnancy is normal; the mammary glands, however, develop poorly, and the mother does not nurse the young.

Precocious sexual maturity can be produced in immature female rats as in the experiment ♀ ⚲, in which both animals are immature. No changes in the secondary sexual organs of the spayed female are observed (Kallas, 1929). In other experiments in young (but perhaps not sexually immature) male rats, Kallas found that at first the testes and seminal vesicles of the normal rat were enlarged in the experiments ♂ ♂ and ♂ ⚲.

The interpretation of the results of the parabiosis experiments.—If a gonadectomized and a normal rat are united surgically so that an interchange of their blood and lymph occurs, there

generally follows a "stimulation" of the testes or ovaries of the normal rat with appropriate secondary changes in the accessory sexual organs. The experiment demonstrating this fact most clearly is that in which a castrated male rat and a normal female rat are made parabiotic (♀ ♂). Yatsu (1921) correctly inferred that the changes in the female genital tract were due to the transfer of hormone or hormones from the castrated male; only more recently, however, has it been possible to demonstrate that the pars glandularis of the pituitary of the castrated male is the probable source of the hormone. As will be shown later, the internal secretions of the testis and the ovary (at least "oestrin") lessen the secretion (or storage) of gonadotropic hormone by the pituitary. If this inhibiting influence is removed, as by gonadectomy, an excess of gonadotropic hormone is produced by the gonadectomized animal (which presumably also no longer utilizes the hormone). It is then carried to the parabiont with intact gonads and adds its effect to the hormone secreted by the normal animal's pituitary so that an unusual development of the ovary (or testis) follows.

Ordinarily the internal secretion of the ovaries or testes, liberated in increased amounts because of the gonad-stimulation (as in the experiments ♀ ♀ and ♂ ♂) affects the accessory sexual organs only of the normal rat. This may be due to such factors as inadequate supply for both animals, too slow a transfer of the hormone, etc. According to Møller-Christensen (1933), however, oestrus is more frequently observed in the spayed rat of the experiment ♀ ♀ if the rat with intact ovaries has been hypophysectomized before parabiotic union.

According to Witschi and Levine (1934), the establishment of marked follicular growth and oestrus in the experiment ♀ ♂ may be delayed as long as several months. They stated that during the first few weeks after such a parabiotic union, anoestrus and the formation of corpora lutea in unusual num-

bers occur in the female rat. They attributed this to the secretion of a luteinizing hormone by the pituitary of the normal female. In their crucial experiment they first united normal males and females (♀ ♂); they later hypophysectomized the female. After the hypophysectomy, only an occasional vaginal smear characteristic of oestrus was found in the female (this never occurred if hypophysectomy was performed in both animals of the pair, ♀ ♂). Five to fifteen weeks after the hypophysectomy of the female, the male was castrated—the pairs now being ♀h ♂.[31] Oestrus, instead of being delayed several weeks as in the pair ♀ ♂, appeared within 4–5 days. The stimulation of follicular growth in the female of the pair ♀h ♂, was even greater than in the pair ♀ ♂. From these as well as other experiments, Witschi and Levine drew the following conclusions: (1) the pituitary of the castrated male rat chiefly secretes a follicle-stimulating hormone, and (2) the follicle-stimulating hormone inhibits the secretion of the luteinizing hormone.[32] Only some weeks after the parabiotic union, ♀ ♂, is the secretion of luteinizing hormone by the pituitary of the normal female finally suppressed. Witschi and Levine, however, do not attempt to explain why (in their experiments, at least) anoestrus and abnormally large numbers of corpora lutea were frequently observed in the normal female in the first few weeks after the establishment of parabiosis between a normal female and a castrated male.

The gonad-stimulating effects of the anterior pituitary after gonadectomy.—In chapter i it was pointed out that gonadectomy may be followed by anatomical changes in the pars glandularis; this is strikingly illustrated in the rat. Engle

[31] ♀h indicates a hypophysectomized normal female, ♀h, a hypophysectomized spayed rat, and so on.

[32] Martins and Rocha (1930) transplanted the ovary to the kidney of castrated and spayed rats. In the ovarian transplants in castrated males, only follicular growth was observed, whereas in the transplants in spayed females there occurred both follicular growth and the formation of corpora lutea.

(1929) was the first to demonstrate that the gonadotropic potency of the pituitary of the adult castrated or spayed rat was increased, as shown by the effects of implants on the ovaries of immature mice and rats. His work was extended in the same year by Evans and Simpson (1929),[33] who concluded that the increase in the potency of the pituitary of the donors was greater the longer the period elapsing between gonadectomy and the assay of the pituitary. A similar but less pronounced increase in potency was observed in cryptorchid male rats. They concluded, moreover, that the increase in potency of the female pituitary was greater than that of the male. Gonadectomy was also followed by an increase in the weight of the pars glandularis; but this change, unlike the change in potency, was greater in males than in females.[34] According to Lipschütz (1933), who used immature female rats for assay, a much greater degree of luteinization is caused by the pituitary of the spayed rat than by that of the adult normal female rat. The experiments of Clark (1935) and Wiesner (1935) in very young rats have already been discussed (see the first section of this division).

So far, changes in the gonadotropic potency of the anterior lobe as a result of gonadectomy have been demonstrated only in mammals.[35] The gonadotropic effects of the pituitary of the guinea pig, assayed in mice, are increased after gonadectomy (Smith and Engle, 1929); the change is about the same in both male and female guinea pigs (Severinghaus, 1932). Wolfe (1932) performed his assays by producing ovulation in rabbits. He found that the pituitary of the spayed female rat

[33] Also see Emanuel (1931); Higuchi (1931); Emery (1932); and Siegert (1932).

[34] The pituitary of the normal adult female rat—although heavier—contains less gonadotropic hormone(s) than the normal male.

[35] Novelli (1932) reported that the castration of the toad (*B. arenarum*) did not alter the amount of the pituitary hormone causing ovulation in the female of the same species. Domm (1931) had the impression that the degree of stimulation of the gonads of the immature fowl differed, according to the source of the homoimplants used, as follows: capon>cock>hen.

was more potent than the normal. The potency of the female rabbit's pituitary appeared not to be altered as a result of ovariectomy. However, Hill (1934), who also performed his assays by producing ovulation in rabbits, concluded that gonadectomy caused a reduction in the gonadotropic potency not only of the pituitary of the female and male rabbit, but also of the pituitary of the male cat. Still other results were obtained by Smith, Severinghaus, and Leonard (1933), who investigated the gonadotropic potency of the pituitary of normal and gonadectomized rabbits. By the ovulation test, the pituitary of the spayed female was more potent than the normal female pituitary.[36] In terms of its effects on the ovary of the immature mouse, the pituitary of castrated or spayed rabbits was more potent than the pituitary of normal males or females. The change in potency was more pronounced in the female rabbits.

It is well known that spayed women excrete considerable amounts of gonadotropic hormone (usually described as follicle-stimulating).[37] Probably this is a secretion of the anterior lobe (see chap. v).

Therefore, in the rat, guinea pig, rabbit, and man, there is evidence that gonadectomy is followed by an increased secretion (and storage?) of gonadotropic hormone(s) by the anterior lobe of the pituitary.[38] This fact suggests that the internal secretions of the gonads inhibit the secretion of gonadotropic hormone by the anterior lobe. Also in favor of this view are numerous experiments in which hormones of the ovaries or testes (either extracts of the gonads or hormones obtained elsewhere [e.g., urine] but having effects on the secondary organs like the true internal secretions) have been used. It will be pointed out later that all these data may be

[36] Similar experiments were not performed with male rabbits.

[37] The pars glandularis of the male horse appears to produce a stimulation of follicle growth, particularly if it is obtained from a castrated male (Hellbaum, 1933).

[38] Different results were obtained by Hill (1934). See the preceding discussion.

used to explain some of the cyclic sexual phenomena (e.g., oestrus) which are observed in normal sexually mature animals.

The gonadotropic effects of the anterior pituitary after the injection of oestrin and allied substances.[39]—Although Fluhmann and Kulchar (1931) were unable to demonstrate that the administration of oestrin[40] affected either the appearance or the number of the "castration-cells" in the pars glandularis of the spayed female rat, Hohlweg and Dohrn (1931–32) concluded that appropriate doses of oestrone ("Progynon") prevented both castration changes in the pituitary and an increase in gonadotropic potency. To produce such effects they estimated that the following doses of oestrone were required: $\frac{1}{30}$ rat-unit per day to the spayed immature rat, and 5–6 rat-units per day to the spayed adult rat.[41] Haterius and Nelson (1932) prevented castration changes in the pituitary by successfully transplanting ovarian tissue into adult castrated rats.[42]

In normal rats—especially in females—the repeated injection of oestrone (and probably oestriol) causes a hypertrophy of the pituitary. This effect is also observed in spayed rats. The hypertrophy probably is due to the enlargement of the pars glandularis (Leiby, 1931; Halpern and D'Amour, 1934;

[39] Oestrin, as the term is used here, usually refers to preparations causing oestrus in ovariectomized mice or rats. Whenever it appears that a pure preparation—as oestrone or oestriol—has been used, it has been so designated.

[40] Total doses of 135–225 rat-units of oestrin were injected over periods of 77–90 days.

[41] The castrated immature rat required about $\frac{2}{3}$ rat-unit per day. The dose of oestrone for the adult spayed rat could be reduced to 1 rat-unit if $\frac{1}{5}$ rabbit-unit of progesterone (corpus luteum hormone) was also given.

[42] For other descriptions of the effects of oestrin on the pituitary of spayed or castrated rats, see Montpellier and Chiapponi (1930); Friedl (1933); Halpern and D'Amour (1934); and Nelson (1934). It appears that oestrin is much less effective in abolishing castration changes in the castrated male's pituitary.

Hohlweg, 1934; Lipschütz, 1934; Nelson, 1934; Clauberg and Breipohl, 1935; and Wolfe, 1935).[43]

Meyer, Leonard, Hisaw, and Martin (1930, 1932) were the first to show that the administration of oestrin over a long period (they injected 2–10 rat-units per day for 30–70 days) lessened the gonadotropic potency of pituitary implants in immature rats. The donors, which received oestrin, were either young normal female rats or adult castrated and spayed rats. The clearest evidence of a diminished gonadotropic potency was obtained by weighing the ovaries of the rats used for assay. Those of animals receiving the pituitary of oestrin-treated rats weighed 40–47 per cent less than the ovaries of animals receiving pituitary tissue from non-injected rats. Similar results were obtained by Bialet-Laprida (1933) and Lipschütz (1934). The latter author emphasized the absence of a luteinizing effect by the pituitary of the normal male rats to which he had administered oestrin.

As a result of the closer study of the effects of oestrin on the pituitary, some investigators have concluded that it increases the secretion (and storage?) of a luteinizing hormone (Hohlweg, 1934; Lane, 1935; and Wolfe, 1935; Hohlweg and Wolfe used large doses of "Progynon" or the benzoate [oestradiol] of this preparation). In adult normal rats there appeared an ovarian luteinization which, following shorter periods of treatment (200 rat-units daily for 8–15 days), was demonstrated by an increase in the size of the corpora lutea, without any change in the number. The injection of oestrone also brought about the formation of corpora lutea in immature rats. In Hohlweg's experiments, implants of the pituitary from oestrone-treated donors produced few or no corpora lutea in the ovaries of immature rats. Lane, using "oestrin,"[44]

[43] The repeated injection of oestrin into the female dog causes a reduction in the size of the pituitary—especially of the pars glandularis (Kunde and others, 1931).

[44] 6.25 rat-units daily for 5–39 days. His rats were 22 days old when the injection of oestrin was begun.

concluded from a study of the ovaries of the injected rats and from implantation experiments that the effects of oestrin on the production of gonadotropic hormone(s) by the pituitary occurred in two stages. The early effect was an increased liberation of gonadotropic hormone(s). This was soon followed by a stage of diminished liberation and secretion of the follicle-stimulating hormone. In this later stage there was an increased secretion and liberation of luteinizing hormone shown by the production of numerous "vesicular follicles."

Kuschinsky (1931) reported that the injection of 25 rat-units of prolan daily for 10 days to adult female rats caused a reduction in the amount of gonadotropic hormone in the pituitary. This appeared to be due to the inhibitory effect of ovarian hormone(s) liberated in increased amounts, for the effect was not observed in spayed rats. Goodman (1934), by injecting oestrin, caused a partial or complete atrophy of successful transplants of the ovary in the anterior chamber of the eye of rats. Presumably the oestrin inhibited the secretion of gonadotropic hormone essential for the maintenance of the transplant.

A curious observation was made by Emery (1933). He reported that immature rats were abnormally refractory to oestrone for several weeks after precocious sexual maturity had been produced either by implants or by extracts of the anterior pituitary. As much as 100 rat-units of oestrone ("Theelin") did not produce oestrus. Neither ovariectomy nor hysterectomy made the rats less refractory.

The internal secretion of the corpus luteum in relation to the secretion of gonadotropic hormone(s) by the anterior pituitary.—There is not much direct evidence that the administration of corpus luteum hormone (progesterone) affects the secretion of gonadotropic hormone. According to Hohlweg and Dohrn (1931), the anatomical changes in the pituitary characteristic of castration in the adult spayed female rat can be prevented by the daily injection of 1 rat-unit of oestrin and $\frac{1}{5}$ rabbit-unit

of progesterone, but not by the injection of such a dose of oestrin alone. Clauberg and Breipohl (1935) were able to prevent the castration changes in the anterior lobe, also in adult spayed female rats, by administering progesterone alone (7.5 rabbit-units in a period of 35 days).

In so far as oestrus can be prevented or altered by the injection of corpus luteum hormone, this effect may at least partly depend upon an alteration in the pars glandularis. According to Mahnert (1930), copulation is not followed by ovulation in the rabbit if corpus luteum extract has been administered previously.

Wolfe (p. 130) concluded that the pars glandularis of the sexually mature pig contained the least amount of the hormone causing ovulation in the rabbit, if the pituitary was removed from pigs, the ovaries of which contained actively secreting corpora lutea.

The internal secretion of the testis[45] *in relation to the secretion of gonadotropic hormone(s) by the anterior pituitary.*—There is some direct as well as considerable indirect evidence indicating that the internal secretion of the testis lessens the secretion (and storage) of gonadotropic hormone by the anterior pituitary. For example, the administration of testicular tissue or hormone may prevent or "cure" castration changes in the pituitary of immature or adult castrated rats (Martins and Rocha, 1931; Migliavacca, 1935). Some of the indirect evidence has already been considered. The sexual difference in the gonadotropic potency of the pituitary of very young rats (the female pituitary is the more potent) appears to depend upon the fact that the internal secretion of the testis is liberated at an earlier age than is that of the ovary. In parabiosis experiments the genital organs of the female of the experiment ♀ ♂ are strikingly affected, whereas those of the female of the experiment ♀ ♂ are not. Apparently the removal of the testis also removes an organ inhibiting the lib-

[45] No distinction between extracts of urine and extracts of testis is made here.

eration of gonadotropic hormone.[46] There is some evidence that castration changes in the male pituitary are more readily abolished by testicular hormone than are those in the pituitary of the spayed female (Martins and Rocha, 1931).[47] As has already been shown, the pituitary of castrated rats contains more gonadotropic hormone than that of normal males.

From all the reported observations, which are too numerous to cite, it appears that internal secretions of both the tubules and the interstitial cells affect the pars glandularis.

What is the significance of the data on the interrelationship between the pituitary and the gonads?—The experiments considered so far in this section clearly suggest that the interactions of the gonadotropic hormone(s) and the internal secretions of the gonads are important in the physiology of all these structures in the normal animal. The rhythm of oestrous cycles, especially if repeated throughout the year, probably depends at least in part upon a pituitary-gonadal interrelationship. Smith and Engle (1927) stated that the periodic liberation of gonadotropic hormone seemed best to account for cyclic changes in the ovaries. Siegmund (1928) suggested, on the basis of his experiments in mice, that the oestrous rhythm might depend upon an antagonism between the follicular hormone and the gonadotropic hormone(s). By implanting the pituitary of adult female guinea pigs into mice, Smith and Engle (1929) demonstrated that the pituitary of the guinea pig in oestrus contained less gonadotropic hormone than when the guinea pig was in dioestrus (fifth to fourteenth day of cycle). In similar experiments, Siegert used adult female rats, the pituitaries of which were implanted into immature rats; he too found that the pituitary of dioestrus contained more gonadotropic hormone than that of oestrus. A recent explanation of the oestrous cycle in the rat, in terms of

[46] The utilization of hormone by the testes is, of course, also abolished.

[47] Similarly, oestrin appears to abolish the castration changes in the pituitary more readily in spayed female rats than in castrated males.

follicle-stimulating hormone, oestrin, luteinizing hormone, and progesterone, is given by Hisaw and others (1934).

It is worthy of note that the gonadotropic potency of the pars glandularis in pregnancy is reduced only in those animals (man and horse) the body fluids of which also contain large amounts of "oestrin" during pregnancy.

All explanations of feminization of male animals and masculinization of female animals—as by testicular grafts or the injection of testicular hormone into females, or by ovarian grafts or the injection of ovarian hormones into males—must take into account the part played by the anterior pituitary. Moore and Price (1932) have studied this question particularly from the standpoint of the alleged antagonism between the internal secretion of the testis and that (or those) of the ovary. On the basis of numerous experiments, they concluded that the testicular and ovarian hormones are not directly antagonistic toward each other. On the contrary, it appears that they are alike, if present in the body fluids in too high a concentration, in inhibiting the secretion of gonadotropic hormone(s) by the anterior pituitary. Either testicular or ovarian (oestrin) hormone may therefore damage either the testis or the ovary, not by direct effects, but by interfering with the secretion of gonadotropic hormone by the pituitary. As work subsequent to that of Moore and Price has shown, the effects of oestrin (and probably of testicular hormone) on the pars glandularis include changes more complex than is implied in the statement simply that oestrin and testicular hormone inhibit the secretion of gonadotropic hormone.[48]

SPECIAL CONSIDERATIONS

The secretion of gonadotropic hormone and the response of the gonads in relation to age and development.—Gonadotropic hor-

[48] Also see Golding and Ramirez (1928); Borchardt and others (1929); Leonard, Meyer, and Hisaw (1931); Schoeller and Gehrke (1933); Halpern and D'Amour (1934); and Wade and Doisy (1935).

mone has been detected in the pituitary of the fetuses of man, the ox, and the pig. For detecting gonadotropic hormone in the pituitary of the human fetus, the immature mouse usually has been employed. The hormone (or hormones) is said to be present after the fifth lunar month of gestation but not before (Siegmund and Mahnert, 1928; Schultze-Rhonhof and Niedenthal 1929; Philipp, 1930; and Wirz, 1933). Schultze-Rhonhof and Niedenthal stated that the pituitary of the ox fetus contains the hormone. In the pig fetus, growth-promoting hormone is detected first (crown–rump length: 9–11 cm.); later, just before testicular growth becomes rapid (crown–rump length: 17–18 cm.), gonadotropic hormone can be detected (Smith and Dortzbach, 1929). According to Catchpole and Lyons (1934) the pituitary of horse fetuses (crown–rump length: 50–90 cm.) only infrequently contains gonadotropic hormone(s).

Corey (1928) was unsuccessful in his attempts to alter the gonads of rats (after the fifteenth day of prenatal life) by injecting a suspension of the rat pituitary into the peritoneal cavity of the fetuses.[49] However, Aron (1933) stated that the injection of an anterior-lobe extract into guinea pig fetuses longer than 40 mm. caused a development of interstitial cells in the testis (sometimes with secondary effects on the epididymides and seminal vesicles in fetuses longer than 80 mm.); in the female fetus, he observed a hypertrophy of the interstitial cells in the medulla and at the hilum of the ovary.

According to Swezy (1933–34) the pituitary of the rat 1–13 days old has no gonadotropic effect on the testes and secondary organs of the hypophysectomized rat but does have such an effect on the sexual organs of normal immature male rats. She therefore postulated that the implantation of the pituitary of very young rats stimulates the secretion of gonadotropic hormone by the pituitary of the normal imma-

[49] The equivalent of only 2–5 per cent of a whole pituitary was injected on alternate days.

ture rat used for assay; such an explanation, however, is not the only one which might be given. Swezy also found that the pituitary of the rat 21 days old contained more gonadotropic hormone, per unit weight, than the adult pituitary (assayed in hypophysectomized adult rats and immature normal rats). The experiments of Clark (1935), who estimated the gonadotropic effects of the pituitary of very young male and female rats, have been discussed previously. Lipschütz (1933–34) concluded that, whereas the implantation of the pituitary of adult male or immature male or female rats causes the formation of considerable luteal tissue, the pituitary of the adult female lacks this effect because it contains little or none of the hormone responsible for follicle growth and/or sensitization. If a follicular change is first produced, then the pituitary of the adult female rat causes luteinization.

In their first report, Smith and Engle (1927) pointed out that the effects of implants were greater in rats receiving the pituitary tissue after weaning (22 days old) rather than before.[50] From a study of the gonadotropic effects of pituitary extracts, Selye, Collip, and Thomson (1935) concluded that the ovary of the immature rat is incapable of responding to the gonadotropic hormone of the pituitary (they specifically mentioned the follicle-stimulating hormone) until after an age of about 18 days.[51] If pituitary extract was administered daily from an age of 12 days, neither oestrus nor significant ovarian changes were observed after 8–11 days' treatment (ages, 20–23 days)—in marked contrast to the effects produced when injections were begun later or prolonged a few days more. The similar injection of prolan, however, produced oestrus and a luteinization of the theca cells.

The pituitary of the immature or young guinea pig con-

[50] In mice 10 days old, daily implants for 5 days were required to produce precocious sexual maturity; in mice 17 days old initially, daily implants were needed for only 2–3 days.

[51] Also see Swezy and Evans (1931).

tains less gonadotropic hormone than the adult. However, age seems to make no difference in the qualitative effects (Siegmund and Mahnert, 1928; Lipschütz and Kallas, 1929).

The concentration of gonadotropic hormone in the pars glandularis of rabbits about 1 month old is less than that in rabbits more than 3 months old (assayed by the ovulation test; Wolfe and Cleveland, 1931). The response of the ovary of the rabbit in relation to age and weight is discussed in the papers of Brindeau and others (1932), and Hertz and Hisaw (1934).

The sterility of male mice with hereditary dwarfism due to changes in the pituitary can be corrected by the administration of implants of rat pituitary (Smith and MacDowell, 1930). In similar female mice after the same treatment, irregular oestrous cycles as well as follicular growth and corpus luteum formation in the ovary were observed. In the hairless strain of rats studied by Emery (1935), the gonadotropic potency of the pituitary seemed to be greater than that of normal albino rats provided that the same sexes were compared. After spaying, however, the increase in the gonadotropic potency of the pituitary of the albino female was greater than that of the hairless female. (The oestrous cycles of the unoperated hairless female were usually abnormal and often absent.)

The gonadotropic hormone(s) and ovogenesis.—According to Swezy and Evans (1931) and Swezy (1933), ovogenesis does not depend upon an internal secretion of the pars glandularis of the pituitary. Gonadotropic extracts of the pituitary may, however, play a part in regulating ovogenesis.

The relation of the gonadotropic hormone(s) to compensatory ovarian hypertrophy and to the successful transplantation of the ovary.—Engle (1928) administered homo-implants to nulliparous mice and rats (3–4 months old) from some of which he had removed one ovary. As a result of this treatment, the compensatory hypertrophy of the ovary was so great that, in

some cases, the single ovary of the operated animals weighed twice as much as both ovaries of the normal animals which also received implants. From this and other experiments it may be concluded that compensatory ovarian hypertrophy depends upon the secretion of gonadotropic hormone(s) by the anterior pituitary.[52] However, the gonadotropic potency of the pituitary (stored gonadotropic hormone?) is not altered by the unilateral removal of the testis or ovary (Emery, Bash, and Lewis, 1931).

Engle (1927) found that the implantation of the pituitary prevented degenerative changes and the resorption of ovarian grafts placed in the abdominal muscles or the testis. In the abdominal-muscle transplants (in castrated males), large mature follicles could be found; in the transplants in the testis, an ovariotestis was formed. The success of ovarian transplants in castrated male rats, not treated otherwise, probably depends upon the increased amount of gonadotropic hormone available (for the testes, if present, both utilize gonadotropic hormone and lessen its secretion by the anterior lobe).

The gonadotropic hormone(s) and pseudopregnancy.—Although in the rat corpora lutea may persist anatomically for abnormally long periods after hypophysectomy, physiologically active corpora lutea cannot be maintained in the absence of the pars glandularis. This is clearly shown in the rabbit. If hypophysectomy is performed long enough after copulation so that ovulation and corpus luteum formation occur subsequently, the corpora lutea begin to regress after about the second day.[53] Other observations on (1) pseudopregnancy in rabbits following the injection of gonadotropic hormone and (2) the amount of gonadotropic hormone in the pituitary of the pseudopregnant rabbit are discussed in the

[52] Also see chap. ii.

[53] See chap. ii.

section dealing with the comparative physiology of the gonadotropic hormone(s).

In the rat, spontaneous deciduomata,[54] unrelated to any known injury, have been found after the single injection of an anterior-pituitary (ox?) extract (Innes and Bellerby, 1929). Teel (1926), as well as Brouha (1928) and Shelesnyak (1931, 1933) have caused the formation of typical deciduomata in the rat's uterus by producing the irritative lesion (threading of the uterus) 5–9 days after the administration of an extract of the ox pituitary (adult rats) or after the administration of homoplastic implants and ox pituitary extract or of oestrin and ox pituitary extract (immature rats). In both cases, luteinization of the ovaries and the liberation of corpus luteum hormone, essential for the reaction, occurred.

The gonadotropic hormone(s) and pregnancy.—The gonadotropic potency of the anterior lobe of pregnant women and mares (Catchpole and Lyons, 1934) is reduced in comparison with the normal; there perhaps is a causal relation between this finding and the fact that the body-fluids of pregnant women and mares—unlike other animals—may also contain large amounts of "oestrin." Although the literature contains discrepancies, there probably is no reduction in the concentration or total amount of gonadotropic hormone in the pars glandularis of the pregnant cow, pig, rabbit, and rat; reports that the pituitary of these animals, if pregnant, contains a decreased amount of gonadotropic hormone are about balanced by reports to the contrary.[55]

Changes in the pregnant mouse, rat, guinea pig, and rabbit, due to the administration of gonadotropic hormone, have likewise been studied. Ovulation can be produced in the pregnant mouse; the corpora lutea subsequently formed are

[54] The formation of this tumor-like growth requires the internal secretions of both the follicle and the corpus luteum.

[55] Evans and Simpson (1929); Bacon (1930); Ehrhardt and Mayes (1930); Zondek (1931); Magistris (1932); and Siegert (1933).

smaller than those of pregnancy (Zondek and Aschheim, 1928).[56] Teel (1926) injected a crude extract of the anterior lobe of the ox into rats from the day of impregnation until delivery. He concluded that this treatment, which may cause the excessive formation of lutein tissue in adult females, resulted in a prolonged gestation period (25–29 days instead of 23) probably because implantation was delayed. Furthermore, the fetuses were usually still-born; if they were removed at about the time of normal term, they could be nursed by the mothers. Similar but less pronounced effects were observed by Sontag and Munson (1934), who used a more refined extract of the anterior pituitary of the ox. The new-born fetuses from the injected mothers were heavier than the fetuses of normal mothers (14 per cent in Teel's series, and 7 per cent in the series of Sontag and Munson); in both sets of experiments the gestation period was prolonged.

Different results were obtained by Engle and Mermod (1928), who administered homoplastic or heteroplastic pituitary implants (mouse, rat, rabbit) to pregnant mice and rats. This treatment, in the first part of pregnancy, either prevented implantation or caused the resorption of the fetuses. In the middle third of pregnancy either abortion or fetal resorption followed the administration of implants; a similar effect was much less frequently observed in the last third of pregnancy, at the end of which normal litters were usually born. The authors were inclined to attribute the effects to the increased liberation of follicular hormone resulting from follicular stimulation.[57]

According to Kelly (1933), the fluid which can be expressed from the anterior lobe, if administered to pregnant guinea pigs, does not prevent implantation but does cause abortion (twenty-seventh to fifty-second day of pregnancy). He made

[56] Also see Siegmund (1929).

[57] The injection of oestrin into pregnant rats either prevents implantation, or, if given later, terminates the pregnancy (see D'Amour and Gustavson, 1934).

one or two injections of the tissue-fluid of 3–12 anterior lobes of the ox.

A number of authors have found no difficulty in producing ovulation in pregnant rabbits by injecting (subcutaneously, intramuscularly, or intravenously) extracts of the pars glandularis (Loeser, 1930; Wolfe, 1930; Snyder and Wislocki, 1931; and others). Wislocki and Goodman (1934) produced unusual numbers of hemorrhagic follicles and corpora lutea by intravenous injections of anterior-lobe extract (ox) into rabbits after copulation and ovulation. Despite this treatment, implantation was not delayed and pregnancy was not interrupted.

The gonadotropic hormone(s) in relation to other glands of internal secretion, vitamins, etc.—Several authors have suggested that the growth-promoting hormone antagonizes the effects of the gonadotropic hormone(s) (e.g., Evans and Simpson, 1928). However, Targow concluded that growth-promoting hormone did not lessen the secretion of gonadotropic hormone by the pituitary of young castrated rats. Leonard (1934) found that the gonad-stimulating effect of prolan could be inhibited by the intraperitoneal injection of extracts of the pars glandularis of the ox but that this effect probably was not related to the growth-promoting properties of the extracts.

There is clinical evidence of an interrelationship between the adrenal cortex and the gonads. Also, there is some experimental evidence that the pars glandularis—by means of its gonadotropic hormone(s)—may participate in such a possible interrelationship. According to Shumacker and Firor (1934) a moderate atrophy of the gonads is observed in adrenalectomized rats. This atrophy can be repaired by the administration of pituitary implants. Moreover, the pituitary of adrenalectomized rats appears to contain less gonadotropic hormone than the normal, but not in rats in which accessory cortical tissue grows quickly (Del Castillo, 1934). Adrenal

cortical hormone has no effect on the gonads of hypophysectomized rats.

The repeated injection of a gonadotropic extract of the anterior lobe of the sheep has no significant effect on either the basal metabolic rate or the respiratory quotient of rats (Lee and Gagnon, 1930).

Vitamin deficiency (vitamin E), manifested by changes in the physiology of the sexual glands, may depend upon a change in the secretion of gonadotropic hormone(s) (see Verzár, 1931; Verzár, v. Árvay, and v. Kokas, 1931; Evans and Simpson, 1931; and Agnoli, 1932). In rats subsisting on a diet deficient in vitamin B, anoestrus and loss of weight appear at about the same time. A comparable loss of weight due to starvation is also accompanied by anoestrus. However, the pituitary of the rat which has lost weight and is in anoestrus because of a vitamin-B-deficient diet contains about the usual amount of gonadotropic hormone (Marrian and Parkes, 1929). Manganese deficiency (Orent and McCollum, 1931) and poisoning by sodium fluoride or thallium salts possibly likewise affect the gonads indirectly by injuring the pars glandularis.

The metabolism of the gonadotropic hormone(s).—The presence of gonadotropic hormone(s) in the blood and their excretion in the urine are discussed elsewhere in this chapter and in the chapter following it. In human beings, at least, it appears that the urine contains the least amount of gonadotropic hormone during active sexual life. Probably the urine of children contains greater amounts (concentration) than that of normal adults. The greatest amounts are found after gonadectomy in adults and, to a less extent, after the normal menopause or after X-ray sterilization.[58]

Little is known about the behavior of gonadotropic hormone secreted by the animal's own anterior lobe. The most

[58] Reference here is made only to gonadotropic hormone presumably secreted by the pituitary and does not include the prolan group.

extensive experiments are those with rats living in parabiosis; in such animals the hormone(s) apparently are carried in the blood. In rabbits, Brambell and Parkes (1932) found that the anterior pituitary hormone, liberated as a result of copulation, could still cause ovulation after the removal of 30 per cent of the blood; if 40 per cent was removed, ovulation did not occur unless the mass of ovarian tissue (follicles) was first reduced. Later experiments (McPhail, Parkes, and White, 1933) showed that 50 and even 60 per cent of the blood could be removed without preventing ovulation. In most of these later experiments the ovaries were left intact.

If anterior pituitary extract is administered by way of the gastrointestinal tract, gonadotropic effects are not observed unless the dose is 15–30 (rabbit; Lépine, 1931) to 100 (rat; Janssen and Loeser, 1931) times as great as the parenteral dose. Goodman and Wislocki (1933) administered anterior-lobe extract intravenously to pregnant rabbits and cats; subsequently, they could find no gonadotropic hormone (ovulation test in the rabbit) in either the amniotic or the allantoic fluids.

If gonadotropic extract obtained from the anterior lobe of other (different) animals is repeatedly injected into immature rats, rabbits, etc., the gonadotropic effects tend to recede and may finally disappear. Collip and his colleagues have suggested that the hormone effects are antagonized by antibodies ("antihormones") produced by the animal receiving the injections. In favor of this view there is considerable evidence which cannot be evaluated until pure gonadotropic hormone (or hormones) is available for study.[59] That "antihormones" are of physiological significance is doubtful. It is true that the effects of homoplastic implants may be slight if daily administration is continued for 2–3 months; however, the administration of gonadotropic hormone in this way, suitable as

[59] See Bachman, Collip, and Selye (1934); and Selye, Collip, and Thomson (1934). There is further discussion in chap. v.

it appears to be, is not comparable to the liberation of the secretion from the gland *in situ*. Probably the least objectionable example of "hyperhormonization" may be taken from experiments with animals living parabiotically. In the experiment ♀ ♂ (parabiosis between a normal female and a castrated male), the excess gonadotropic hormone secreted by the castrated male's pituitary, added to that of the female's pituitary, finally produces marked follicular growth and cystic follicles with continuous oestrus.[60] These changes, once they appear, may persist for months. No "antihormone" is produced to antagonize the effects of the hormone secreted far in excess of the female rat's needs.

The preparation of gonadotropic extracts of the pars glandularis.—The gonadotropic hormones so far extracted from the pars glandularis usually appear not to have been purified even to the extent of separating them from each other (if we adhere to the belief that there are perhaps several gonadotropic hormones). Therefore, the most that will be attempted here is (1) to refer to authors who have prepared extracts,[61] sometimes in an effort to separate gonadotropic hormones,[62] and (2) to discuss some of the apparent chemical properties of gonadotropic hormones.

The initial extraction is most conveniently performed by using acetone-desiccated and defatted pituitary in the form of a powder. If whole glands are used, extracts may contain considerable amounts of the pressor and oxytocic hormones of the pars neuralis. Methods for removing these have been

[60] Similar or greater changes are observed after the removal of the female rat's pituitary.

[61] Evans and Long (1921–22); Biedl, Evans and Simpson (1928); Hewitt, Reiss and Haurowitz (1929); Wiesner and Crew (1930); Loeser (1930–31); Wallen-Lawrence and van Dyke, Wiesner and Marshall (1931); Guyénot and others, Marshall, Robson (1932); Aschheim, Evans and others, van Dyke and Wallen-Lawrence (1933); Hill, Meyer and Fevold (1934); Selye and others (1935).

[62] Fevold and others (1931, 1933); Evans and others, van Dyke and Wallen-Lawrence (1933); Bates and others, Dingemanse, Guyénot and others, Wallen-Lawrence (1934).

described. A great number of solvents have been used, such as aqueous solutions of acids (e.g., acetic acid) and alkalis (e.g., 1 per cent NH_4OH, 50 per cent pyridine), aqueous solutions of higher alcohols (6 per cent butyl alcohol, 3 per cent amyl alcohol), aqueous solutions of ethyl alcohol or acetone (50–60 per cent) containing ammonia (2–4 per cent), and glycerine. For subsequent purification, methods too numerous to describe in any detail have been used. The reader is referred to the authors listed above.

The cruder the preparation, the greater is its stability either in solution or in the form of a solid. The hormone (or hormones) is destroyed or inactivated by boiling in aqueous solution (if perfectly dry, however, it is not affected by a temperature of 100° C. for hours). Inactivation or destruction of the hormone is also said to occur in the presence of a polypeptidase or of trypsin. The preparations so far made do not dialyze through parchment or collodion; some have thought that the hormone(s) is a polypeptide with a molecular weight of 800–900. The hormone(s) is ordinarily rendered insoluble by the addition of a sufficient amount of a protein precipitant.

The assay of the gonadotropic hormone(s) of the anterior pituitary.—In an earlier section of this chapter reference was made to difficulties in the performance and interpretation of accurate assays of gonadotropic hormones. Here an effort will be made to discuss briefly the different methods by means of which various authors have attempted to express quantitatively the gonadotropic potency of implants or extracts. The following methods have been suggested:

1. The production of ovulation in the toad.
2. The stimulation of the growth of the immature pigeon's testis.
3. The production of ovulation in the adult rabbit in oestrus.
4. The stimulation of the growth of follicles and/or the formation of corpora lutea in the ovaries of immature or adult mice and rats.

To what extent is the amount of the same hormone (or hormones) measured by these various methods? This question

cannot be answered until pure gonadotropic hormones are available for assay by the various methods. It is safer to assume that results obtained by one method cannot be compared with those secured by another; qualitative or quantitative differences which may be found—especially if the animals used belong to different classes or if different methods of administration are employed—may or may not be of importance in establishing the production of identical or different effects. Some of the factors which may affect assays in the mouse and rat are probably also of importance in the performance of assays with other animals; these factors are discussed in section 4 below.

1. *The production of ovulation in the toad.*—Bellerby (1933) studied some of the conditions affecting the assay of gonadotropic hormone by the production of ovulation in the toad (*Xenopus laevis*). Temperature appeared chiefly to affect the rapidity of the response. He recommended that quantitative assay, by the administration of the same dose of extract to a large enough group of toads, each of about the same weight (35 g.), be based upon the percentage of toads in which ovulation occurred. If ovulation was produced in 50 per cent of a group of toads, a "unit" was the dose administered to each toad. The method appears to be sensitive (1 kg. of fresh pars glandularis of the ox was found to contain 750 "toad-units").

2. *The stimulation of the growth of the immature pigeon's testis.*—Following Riddle's report (1931), Evans and Simpson (1934) estimated the approximate amount of gonadotropic hormone by its stimulating effect on the growth of the immature pigeon's testis. According to Evans and Simpson this testicular response is useful not only because of its sensitivity (greater than that of the ovary of the immature rat) but also because of its specificity. Unlike the other three methods by which effects are observed by gonadotropic extracts not obtained from the pars glandularis (e.g., prolan), precocious growth of the immature pigeon's testis is caused only infre-

quently by gonadotropic extracts other than those of the anterior lobe. No accurate quantitative studies by this method have been made.

3. *The production of ovulation in the adult rabbit in oestrus.*—A sensitive and accurate[63] method of determining the amount of a gonadotropic hormone is by the production of

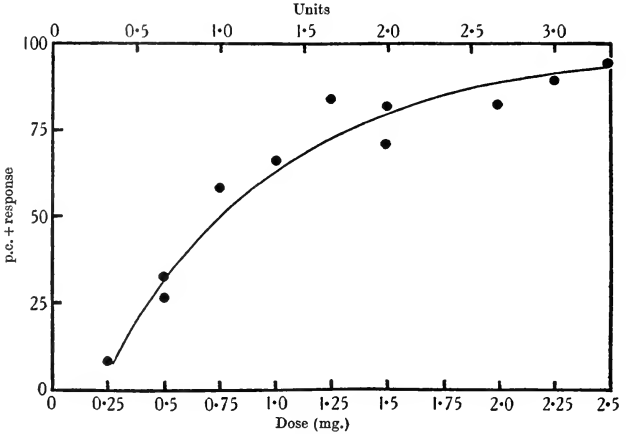


FIG. 33.—The relationship between the dose of an extract of the pars glandularis and ovulation in the rabbit. Each point represents a group of twenty or more rabbits. The percentage of animals in which ovulation was observed is indicated along the ordinate. From Hill, Parkes, and White (1934).

ovulation in the adult rabbit in oestrus. The presence of oestrus is important because the ovaries then contain large or ripe follicles. The only adequate quantitative study of the relationship between the dose and the response is that of Hill, Parkes, and White (1934). They concluded that there is a satisfactory relationship between the dose of gonadotropic hormone and the percentage of rabbits ovulating (see Fig. 33). In other studies in which prolan was used, they pointed

[63] Provided that a large enough group of rabbits (20–30) is given each dose.

out that the response is less if the rabbits have already been used three times (at intervals of 3 weeks). They define their "unit" as the amount of extract (given intravenously to each rabbit) causing ovulation in 50 per cent of a group of at least 10 rabbits. If a standardization curve is to be employed it probably should be first determined by the use of larger groups (20–30).

4. *The stimulation of the growth of follicles and/or the formation of corpora lutea in immature or adult mice and rats.*— Both the qualitative and the quantitative assay of gonadotropic hormones in immature mice and rats have been undertaken by many investigators. For qualitative effects, oestrus (including uterine changes), follicular growth, follicular maturation, ovulation, and corpus luteum formation have been studied. Quantitative studies have been concerned mainly with the changes in the weight of the ovaries. For the assay of most gonadotropic extracts, the determination only of the change in the weight of the ovaries must be considered unsatisfactory if one is to bear in mind the possibility or probability of the existence of several anterior-lobe gonadotropic hormones. Such a quantitative change (increase in ovarian weight) may not be related to the qualitative change. The qualitative changes probably are interrelated in a complex way not only among themselves but also with the administered extract. The difficulty of analysis is further increased by the presence of the test animal's own pituitary[64]—usually an unknown factor in the response. Nearly all the data from which conclusions are drawn as to the presence of several gonadotropic hormones in the pituitary were obtained in animals with the pituitary intact.

Other factors in the response of the ovary of immature mice and rats to gonadotropic hormone(s) are diet, age, and weight. Ordinary assays probably should not be started in

[64] For example, see Swezy (1933–34); Hohlweg (1934); and Selye and others (1935).

rats before weaning (21–22 days) and in mice before an age of 18–20 days. The response is probably greater in animals a few days older; one must avoid, however, any possible complication due to normal "sexual maturity," which has been known to occur in the rat at an age of 34 days, and in the mouse at an age of 28 days. Animals may be of the same age but differ markedly in development, which can be roughly gauged by their body-weights. Under such circumstances, although the same dose may be used, the ovaries of the heavier and better-developed animals usually respond much better.

The technique of injection is one of the most important factors determining the ovarian response. Using an extract of sheep pituitary, Maxwell (1934) gave the same dose divided into four single injections daily, or into six injections daily for 4 days. In the group of immature rats receiving the latter series of injections, the average weight of the paired ovaries was 55 mg.; the paired ovaries of animals receiving single daily injections weighed 25 mg.[65] By adding to the dissolved extract, before injection, zinc sulphate equivalent to a dose of 3 mg. per day, Maxwell produced as great a change in ovarian weight (weight of paired ovaries, 52 mg.) by administering less than one-tenth of the dose used in the other experiments. He considered that the zinc sulphate, altering the solubility of the proteins present, caused a retardation in the absorption of the hormone (which may be protein or protein-like). Fevold and others (1933) have used tannic acid to alter extracts so as to retard their absorption.

Probably the optimum time over which injections should be distributed is 4–5 days. The ovaries should be removed 24–48 hours after the last injection.[66] If moderate doses of gonadotropic hormone (pituitary) are used, the ovarian hypertrophy is no greater, although injections are continued

[65] In some strains of rats such an ovarian weight may be found in normal (uninjected) rats less than 30 days old.

[66] Variations in a standardized technique of administering extracts must not be introduced, although it is desired only to compare qualitative effects.

10–20 days and total doses are doubled or quadrupled (Fluhmann, 1933). Not much success has attended efforts to refine the quantitative assay of gonadotropic hormone by using the hypertrophy of the immature rat's ovary as a criterion. Doses differing in amount by more than 50 per cent possibly can be distinguished if twenty rats are used in a group and conditions are rigidly standardized (van Dyke and Wallen-Lawrence, 1933).[67] Using doses, in part large enough to produce ovaries weighing more than 100 mg., Hill, Parkes, and White (1934) also were not able to demonstrate a satisfactory relationship between the dose of an anterior-pituitary extract and the ovarian weight. In experiments in adult mice, however, they obtained more consistent results.

In adult rats the injection of an anterior-pituitary extract may cause considerable or even marked luteinization of the ovary in which corpora lutea atretica are formed; the oestrous cycles consequently become irregular and lengthened, or disappear (Evans and Long). The luteinizing potency of an extract can be determined roughly by its effect on the length of the oestrous cycle of a group of rats; there is a fairly satisfactory relationship between the dose of a preparation and the consequent lengthening of the oestrous cycle (D'Amour and van Dyke, 1933). Lipschütz estimated the amount of luteal tissue by determining the weight of the ovary and the percentage volume of luteal tissue in serial microscopic sections of the ovary. He recommended that the luteinizing effect of an extract or implants on the ovary of the immature rat be stated as the quotient

$$\frac{\text{mg. lutein tissue}}{\text{mg. anterior-lobe implant (or extract)}}.$$

The weight of a "unit" of anterior-pituitary gonadotropic extract assayed in the immature or adult mouse appears to be $\frac{1}{4}$–$\frac{1}{3}$ of the weight of a unit assayed in the immature rat.

[67] In the experiments of van Dyke and Wallen-Lawrence another preparation, the dose of which was not varied, had to be given for comparison.

This statement is based on the investigation of only a few preparations (Hill and others, 1934; Nelson and Overholser, 1935). Neither mouse- nor rat-units can be stated in terms of rabbit-units.

How many gonadotropic hormones are there?—Together with the papers of the authors listed below,[68] many other reports have been used as a basis for postulating the secretion of different gonadotropic hormones by the pars glandularis.[69]

As many as five different hormones have been suggested:

1. An oestrogenic hormone which, by acting on the ovary, causes a liberation of "oestrin" accompanied by anatomical changes in the uterus and vagina but not in the ovary.
2. A hormone causing follicular growth. This hormone may even be divided into two hypothetical substances with respect to the effects on the granulosa and may or may not be regarded as identical with
3. A hormone causing follicular maturation. This hypothetical hormone may or may not be considered the same as another hypothetical hormone, that causing sensitization of the follicle and permitting luteinization by the luteinizing hormone. Hormones 2 and/or 3 may be described as that (or those) responsible for potentiating the gonadotropic effects of prolan in immature rats.
4. A hormone producing ovulation.
5. A hormone producing luteinization—even occasionally subdivided with respect to lutein-cell transformation of the granulosa or the theca interna.

How these various "hormones" are related to the gonadotropic hormone(s) responsible for the growth and maintenance of the testis is not known. Some observations suggest that the follicle-stimulating hormone stimulates the testis; other observations speak equally in favor of the luteinizing hormone. There is evidence that spermatogenesis chiefly depends upon a follicle-stimulating principle [Smith and Engle, 1934].

[68] Loeb (1930); Aron, Fevold and others, Hill and Parkes, Lépine (1931); Lipschütz and others, Schockaert (1932); Aschheim, Collip and others, Evans and others, Fevold and others, Lipschütz, Loeb and Friedman, van Dyke and Wallen-Lawrence (1933); Bates and others, Dingemanse, Fevold and others, Hertz and Hisaw, Hisaw and others, Hohlweg, Lane and Hisaw, Lipschütz, Wallen-Lawrence, Witschi and Levine (1934); Lipschütz, Pfeiffer, Selye and others (1935). The following authors discuss the potentiation of the gonadotropic effects of prolan by the administration of anterior-pituitary extract: Evans and others (1932–34); Leonard (1932); Collip and others, Fevold and others (1933); Engle, Leonard (1934).

[69] Prolan (etc.) is discussed in chap. v.

Obviously the question of the number of hormones which can be *extracted* from the pars glandularis cannot be answered until these have been separated as pure substances. Even after this question will have been settled it will not be known how many hormones extracted from the anterior lobe are separately *secreted* by the normal gland.

In the preceding section dealing with the assay of gonadotropic hormone(s) in the mouse and rat, some of the difficulties of assay there discussed are especially significant in the attempted identification of separate gonadotropic hormones. Qualitative and quantitative assays are simultaneously attempted in the presence of the following variables: (1) the hormone administered acts upon a structure (the ovary) which is complex both anatomically and physiologically. Many investigators believe that each change, or, more often, physiologically similar groups of changes, depend upon specific gonadotropic hormones. However, about the only ovarian change which can be reasonably isolated for study is ovulation from fully ripened follicles. (2) In most studies the pituitary of the animal used for assay has been disregarded; and (3) the manner in which the hormone is metabolized after injection appears to be of great importance. A single preparation, depending upon dose, frequency of injections, and altered solubility characteristics (as by the addition of a small amount of zinc sulphate to the dissolved extract) may cause only oestrus, or oestrus and follicle growth, or follicle growth and corpus luteum formation (Maxwell, 1934).

The most clear-cut experiments suggest that two gonadotropic hormones—one stimulating follicle growth, the other causing luteinization—can be extracted from the pars glandularis. Fevold and Hisaw interpret all the cyclic changes in the adult ovary of the rat, in so far as these changes depend upon the pars glandularis, in terms of follicle-stimulating and luteinizing gonadotropic hormones.

CHAPTER V

THE GONADOTROPIC SUBSTANCES OCCURRING IN URINE, BLOOD, AND TISSUES, PARTICULARLY DURING PREGNANCY

THAT the urine of pregnant women contains "anterior pituitary hormone" was first reported by Aschheim and Zondek in 1927. Apparently Polano made a similar observation in 1923 without realizing its significance. Since 1927 there has accumulated an enormous number of reports on the gonadotropic properties of urine, body-fluids, and tissues. Gonadotropic substances which are not directly obtained from the anterior pituitary will be discussed in this chapter although it is realized that at least some may originate in the gland. The important sources of these gonadotropic substances are briefly summarized in Table VI. For detailed discussion they will be classified as follows: I, prolan (groups 1, 2, 3, 4, and 5); II, gonadotropic hormones in cases of malignant tumors of the genitalia (groups 6, 7, 8, and 9); III, gonadotropic hormones in cases of diminished gonadal secretion or absence of the gonads (group 10); and IV, gonadotropic hormones in the pregnant horse (group 11).

I. PROLAN[1]

The distribution of prolan.—The discovery of prolan has raised many questions of great scientific interest, among the more important of which is the question of its origin. Its *raison d'être*, like that of the associated oestrin, has not been plausibly explained. From a practical standpoint, however, its discovery has been important in offering a reliable method for the early diagnosis of pregnancy. For some months, at

[1] Although the term "prolan" is also used to identify a commercial extract (made from pregnancy-urine) it is employed here because of its general use (by Zondek and others), its brevity, and its vagueness as to the site of formation of the substance.

least, it is invariably present in the urine and blood of pregnant women, especially in the first half of pregnancy. As a commercial source of the hormone, the urine of pregnant women is still the best. According to Aschheim (1930), prolan

TABLE VI

GONADOTROPIC HORMONES FROM TISSUES OTHER THAN THE ANTERIOR PITUITARY AND FROM BODY-FLUIDS AND SECRETIONS

Group	Mammal	Condition	Source
1.....	Man	Pregnancy	Urine; blood; pregnant uterus and contents: placenta (chorion), uterine and tubal mucosa, amnion, amniotic fluid, umbilical cord blood, and fetal urine; corpus luteum graviditatis; sweat; saliva; cerebrospinal fluid (?); edema and blister fluid; skin; vaginal fluid; colostrum
2.....	Man	Newborn	Urine and blood
3.....	Orang-utan	Pregnancy	Urine
4.....	Chimpanzee	Pregnancy	Urine
5.....	Macaque?	Pregnancy	Urine; placenta(?)
6.....	Man	Hydatidiform mole	Urine; blood; colostrum; cerebrospinal fluid; placenta; uterine mucosa; tumor and fluid from tumor
7.....	Man	Chorionepithelioma	Urine; blood; tumor
8.....	Man	Malignant tumors of testis	Urine; tumor; hydrocoele fluid
9.....	Man	Malignant tumors of female genitalia	Urine
10.....	Man	After menopause, spaying, or castration	Urine and blood
11.....	Horse (deer, donkey)	Pregnancy	Blood; chorion; endometrium, (urine)

may be detected in the urine as early as the sixteenth day following fertile coitus. Large amounts of hormone are excreted in the urine during the first few months of pregnancy (Aschheim and Zondek, 1927–28). It is generally agreed that much less prolan, determined by assay in the rabbit and the

immature mouse or rat, is excreted in the last third than in the first two-thirds of pregnancy. Hamburger (1933), for example, found that the maximum excretion occurred during the second and third months. Oestrin, on the contrary, is excreted in greater amount as the pregnancy advances. In toxaemias occurring late in pregnancy, however, abnormally large amounts of prolan were found in the urine which often contained less than the normal amount of oestrin (Smith and Smith, 1934). Murphy (1933) believed that the excretion of the hormone could be accurately determined only in 24-hour specimens of urine. Following placental death, abortion, or normal delivery, the amount of prolan in the urine diminishes rapidly and may disappear in less than a week after the termination of pregnancy.

During pregnancy (see Table VI, group 1) prolan has been detected in many tissues and body-fluids of the mother, including at least part of the contents of the pregnant uterus.[2] The tissues, particularly of the young fetus, fetal urine, as well as the blood and urine of the newborn child, have all been found to contain prolan. The relative concentrations of prolan in the blood and urine throughout pregnancy are of interest because of their bearing on the behavior of the substance in the body. However, there is no report of any quantitative value available comparing urinary concentration or total excretion with concentration in blood, because an acceptable technique for the quantitative biological assay of prolan has rarely been used. As will be pointed out later, "units" which are mentioned are difficult to evaluate qualitatively and are usually of little quantitative significance. The most careful

[2] For reports on the distribution of prolan, chiefly of qualitative value, see the following: Aschheim (1926, 1930), Aschheim and Zondek (1927, 1928); Zondek and Aschheim (1927, 1928); Brühl (1929); Ehrhardt (1929, 1933); Philipp (1930); Siegert and Schmidt-Neumann (1930); Zondek (1930, 1931); Huddleston and Whitehead, Macchiarulo, Trancu-Rainer, in 1931; Cozzi, Heim, Loeser, Vozza, Winter, in 1932; Castagna, Maroudis, Smith and Smith, in 1933; von Árvay, Fukushima, Garofalo, Geist and Spielman, Kaneko, Smith and Smith, in 1934; Gutman and Dalsace, Zuckerman, in 1935.

investigations reported suggest that the quantity of prolan in the blood may remain high in the later months of pregnancy although the urinary excretion of prolan falls. Kennedy (1933) found that there was a progressive increase in the concentration of prolan in the plasma of pregnant women and that the maximum (about 10,000 "mouse-units" per liter) was reached in the twenty-fourth week of pregnancy and persisted up to the thirty-sixth week. Thereafter, and until term, variable amounts (5,000–10,000 mouse-units per liter) were found. Even 1 week after delivery as much as 4,500 mouse-units per liter could be detected. Kennedy did not estimate the amount of prolan in the urine. It is commonly believed that the "rat-unit" of prolan is considerably smaller than the "mouse-unit"; yet Smith and Smith (1934) mentioned 500 rat-units per liter as the concentration of prolan in the serum of normal women in the latter months of pregnancy. They believed that five to ten times as great a concentration was present in the serum of patients suffering from toxaemia of pregnancy or eclampsia.

The injection of the cerebrospinal fluid (ventricular, cisternal, or lumbar) of pregnant women has usually been reported to be without effect on the ovary of the immature rodent (Ehrhardt, 1929; Zondek, 1930; Colombi and Porta, 1934; and Kjellin and Kylin, 1934). Aronowitsch (1930) and Soule and Brown (1932) (normal cases?) believed that stimulation of the graafian follicle *without* subsequent luteinization could be produced by the administration of cerebrospinal fluid. Similar effects were produced by Ehrhardt, and Kjellin and Kylin, by injecting the cerebrospinal fluid of pregnant patients with eclampsia or renal disease—an observation in harmony with the findings of Smith and Smith referred to in the preceding paragraph.

In 1926 Aschheim reported that prolan could be detected in the placenta both at full term and in very early tubal pregnancy from which decidual cells were absent. All other re-

ports, such as those of Aschheim and Zondek (1927, 1928), Murata and Adachi (1927), Zondek and Aschheim (1928), and Klein (1929) confirmed Aschheim's finding.[3] From implantation experiments with placentae of early pregnancy (Aschheim, Maroudis, and others), it may be concluded that prolan is obtainable from the chorionic cells. According to Philipp (1930) and others the placentae of early pregnancies (less than six months) are the richest in prolan. Philipp was among the first to maintain that the prolan so obtained represented an internal secretion of the placenta. He furthermore postulated that the prolan of human pregnancy was entirely secreted by the placenta and not by the cells of the anterior pituitary. The evidence for and against this hypothesis will be considered later.

Prolan is said not to occur in the gastric juice during pregnancy (Zondek, 1930).

In only a few mammals other than man can gonadotropic substances be found in the blood or urine during pregnancy. During a rather sharply defined period high concentrations of gonadotropic hormone can be found in the blood of the pregnant horse (and possibly closely related animals such as the pregnant deer and donkey).[4] The effects of this gonadotropic substance (or substances) are different from those of prolan, and will be considered separately. In the urine of the pregnant anthropoid ape (e.g., orang-utan and chimpanzee) a prolan-like substance can be found. Allen, Maddux, and Kennedy (1931), as well as Snyder and Wislocki (1931), could detect no prolan in the urine of the pregnant monkey (*Macaca mulatta*). On the other hand, using the same species, Aschheim and Zondek (1928) reported that prolan could be found in the urine; subsequently Philipp (1930) produced a partial

[3] Also see the reports of Bourg, Collip, Fels, Motta, Philipp, Siegert, Wiesner in 1930. Among subsequent reports may be mentioned those of Seitz (1931), and Maroudis (1933).

[4] Unterberger, Vozza (1932).

prolan reaction by implanting placental tissue. No gonadotropic hormone has been found in the blood, tissues, or secretions of any other mammals which have been investigated during pregnancy.[5] In these attempts to demonstrate the presence of prolan, the following tissues and body-fluids have been unsuccessfully studied: blood, urine, amniotic fluid, fetal membranes, milk, saliva, and feces in the cow; urine, amniotic fluid, and fetal membranes in the guinea pig, sheep, and pig; urine and placenta in the rat, rabbit, and cat; urine in the mouse, ferret, goat, dog, lion, tiger, and elephant.

Changes in the genital tract of female animals following the administration of prolan.—Particularly in the earlier reports on the effects of gonadotropic hormones, little or no distinction was made among preparations of varied origin which caused about the same biological effects. In this section, consideration will be limited, as far as possible, to the gonadotropic effects of placenta, urine, and blood (or extracts of these) obtained from pregnant women.

At the outset it is necessary to point out that Zondek and many others consider prolan to be a mixture of two gonadotropic hormones, "prolan A" and "prolan B." "Prolan A" is thought chiefly to stimulate the growth of the graafian follicle. "Prolan B" is thought to produce "luteinization" of the granulosa and theca cells of growing or mature follicles; some consider that only theca luteinization will occur if "prolan B" acts on very immature follicles. The relationship of these hypothetical substances to ovulation has not been adequately explained. What is the evidence in favor of this hypothesis? In the first place, "prolan A," more or less free from "prolan B," has been secured only from the urine or blood of nonpregnant individuals. When present it probably has originated in the anterior pituitary. Although the origin of pro-

[5] Other reports are by the following: Aschheim and Zondek (1927); Gutman (1930); Hill and Parkes (1931); Kraul (1931); Bruhn (1933); Ehrhardt and Ruhl (1933), Küst (1934); and Maurer (1934).

lan in the pregnant individual is still undecided, it more likely is secreted by the placenta than by the pituitary. (The crucial experiment of hypophysectomizing a pregnant woman and subsequently determining the distribution and excretion of prolan is not likely to be performed.) Therefore, although the gonadotropic substance secured from urine of spayed or other non-pregnant individuals may be called "prolan A," it is not necessarily identical with or related to the prolan of pregnancy. Second, a prolan causing "B," but no other effects, has been secured only by Brindeau, Hinglais, and Hinglais (1934). They give no worth-while description of their method of preparation. Moreover, they postulate a third "preluteinizing" hormone which must be present before "prolan B" can bring about luteinization.[6]

The presumed separation of follicle-maturing and luteinizing fractions from gonadotropic extracts of the anterior pituitary (see chap. iv) provides an analogy but no direct support for the belief that prolan is composed of at least two gonadotropic substances.[7] Small doses of prolan tend to cause only follicular growth; larger doses tend to cause hemorrhage into follicles and the formation of corpora lutea with or without preceding ovulation. Some interpret this rough relationship between dose and effect as indicating the presence of only one hormone. However, it might with equal justice be interpreted as indicating a different and steeper "curve of response" to "prolan A" than to "prolan B" (see Fig. 40). Again, different samples of prolan differ in the relative doses required to cause follicular maturation (or oestrus) and luteinization. For example, the dose causing oestrus in immature rats may vary from 9 to 55 per cent of the dose causing luteinization if different samples of prolan are examined (Coester,

[6] Also see Lipschütz (1933, 1935), and chap. iv.

[7] Prolan from pregnancy-urine or placenta could not be separated into "A" and "B" fractions by methods which were used in separating the follicle-maturing and luteinizing fractions of anterior pituitary extracts (Fevold, Hisaw, Hellbaum and Hertz, 1933).

1932). This would be expected if prolan actually is a mixture of prolans "A" and "B." Most of the reported effects of prolan can be interpreted as the effects of two or possibly more combined prolans; some effects appear to be related to only one of two or more prolans. However, proof of their existence awaits chemical separation. That the most potent preparations yet made produced both follicular maturation and luteinization may have depended (1) on the method of assay which did not permit the recognition of prolan "B" alone, or (2) on the difficulty of separating substances of similar properties. Considered as a whole, the evidence suggests but does not prove that there is more than one prolan.

As Aschheim and Zondek emphasized in their first reports, prolan resembles anterior pituitary implants or extracts in its effects on the genital tract of the immature mammal: as a result of its administration, internal secretions peculiar to the ovary or testis are secreted at a faster rate or in greater amount so that secondary "stimulating" effects are produced in the uterus, vagina, seminal vesicles, prostate, etc. On the other hand, the genital tracts of animals deprived of their ovaries or testes are not altered following the administration of prolan. Although most experiments have been performed in mammals, the gonads of animals of other classes are known to respond to prolan. Calvet (1932) found that considerable development of the ovaries could be produced in lampreys (*Petromyzon planeri*) simply by placing them in a bath containing pregnancy-urine. According to Ogilvie (1933) prolan caused ovulation in both the Mexican axolotl and the Japanese newt (*Triturus pyrrhogaster*). In the toad, *Xenopus laevis*, Bellerby (1934) as well as Shapiro and Zwarenstein (1934) produced ovulation by injecting pregnancy-urine. Similar results were obtained by injecting an extract of pregnancy-urine into the bull frog (*Rana catesbiana*) and into Fowler's toad (Rugh, 1935). However, in the American toad (*Bufo americanus*) and in some frogs (*R. clamitans*, *R. pipiens*, and

R. palustris), the injection of prolan was not followed by ovulation (Kuyper, Pfeiffer, and Wills, 1933; Rugh, 1935).

All reports agree that the injection of prolan has no stimulating effect on the gonads of birds (pigeon, fowl, and duck). These observations are discussed on pages 200, 209.

The effects of prolan administration on the female genital tract of mammals have been observed in the bat, hedgehog, mouse, rat, guinea pig, rabbit, ferret, cow, cat, dog, monkey, and man. The most numerous observations have been made in mice, rats, and rabbits. Zondek (1933) administered prolan to hibernating female bats. The hormone caused ovulation and the ova were fertilized by sperms already present in the uterine cavity. Usually the ovaries contained only one or two large follicles; large doses of prolan, however, also caused luteinization of other follicles. Similarly, Caffier (1934) used prolan to cause ovulation in the hibernating bat (*Myotis*). As in Zondek's experiments, the ova were fertilized without disturbing hibernation. Herlant (1931) injected prolan into hibernating hedgehogs. In immature animals there occurred ovarian hypertrophy with follicular growth and atresia, and hypertrophy of the theca cells. In adult animals he found similar changes in the ovaries as well as ovulation in two instances; there were also secondary changes in the uterus and vagina.

The effects of prolan on the genital tract of the female mouse.— The changes in the genital tract of the female mouse following the injection of prolan have been investigated in detail by Aschheim and Zondek. As is well known, they have described three changes which may occur in the ovary of the immature mouse after the injection of prolan: (1) follicle growth,[8] (2) hemorrhage into follicles which may be partially luteinized, and (3) corpus luteum formation commonly without ovulation (corpora lutea atretica). The response of individu-

[8] Moricard (1933) has particularly studied the ovum.

al animals to the same dose of prolan may be extraordinarily variable. Doses approaching the liminal tend to produce chiefly follicle growth; larger doses also cause hemorrhage into follicles and the formation of corpora lutea atretica. Ovulation[9] may be produced under appropriate conditions, but usually does not follow the injection of prolan as it is ordinarily given. The cells of the theca interna, and to a lesser extent of the membrana granulosa, enlarge, proliferate, and take on the appearance of lutein cells in the later stages of the ripening of the follicle (or, under some conditions, without follicular growth). At this time blood may be extravasated into the follicular cavity.[10] Finally, corpora lutea well supplied with blood vessels are formed. Such corpora lutea are usually atretic.

The striking changes here described may be observed in immature mice after the administration of prolan for only a few days. However, the character and degree of the alterations produced vary with the size of the total dose and the manner in which it is distributed. Zondek and Aschheim (1928, 1930) ordinarily injected prolan six times within 48 hours and examined the genital tract about 100 hours after the first injection. Brouha and Simmonet (1930) have given an account of the effects of doses distributed differently.

Associated changes occur in the fallopian tubes, uterus, and vagina. During follicular growth, or later, all the phenomena of oestrus such as hypertrophy of the uterus, distension of the uterus with fluid, opening of the vaginal orifice, and cornification of the vaginal mucous membrane may appear. Later, when progesterone may be the chief ovarian secretion, both the uterus and the vagina may assume the appearance of dioestrus in the adult.

[9] See the reports of Hill (1932) and Zondek (1932).

[10] Hemorrhagic follicles are not found in the ovaries of normal mice or rats. However, they have been observed in the ovaries of other adult animals, e.g., the rabbit. Also see the reports of Emanuel (1930), and Zondek (1931).

The regression of the ovarian changes following prolan administration to immature mice has been studied by Zondek (1933) and Kennedy (1934). Hemorrhagic follicles persisted as long as 5 weeks after injection. Even after a period of 2 months, the ovaries of injected mice differed histologically from those of normal mice, and appeared more infantile.

Zondek and Aschheim (1928) were able to bring about an enormous hypertrophy of the adult mouse ovary by repeatedly administering prolan, thus provoking an excessive formation of corpora lutea. Zondek (1929) also interrupted pregnancy in mice apparently because of ovarian changes following the administration of prolan. Later Hirsch-Hoffmann (1932) administered prolan to adult normal and pregnant mice. He observed an incipient luteinzation of the walls of follicles as soon as 36 hours after injection. Both Mandelstamm and Tschaikowsky (1931) and Kennedy (1934) found that the repeated injection of prolan into adult mice might cause a temporary sterility (also see Marshall, 1933). This appeared to be due to an abnormal luteinization of ovarian follicles. The atrophic ovaries of senile mice also responded to prolan in the experiments of Zondek and Aschheim (1928) and Zondek (1929). Follicle-ripening and oestrus, previously absent, again appeared. According to Wirz and Goecke (1931) auto-transplants of ovaries, if adequately vascularized, exhibited the expected changes after the injection of prolan.

Reiss, Druckrey, and Fischl (1932) studied the oxygen consumption and glycolysis of isolated ovaries and uteri of mice and rats which had received prolan. Anaerobic and especially aerobic glycolysis as well as oxygen consumption (maximum after 48 hours) were all increased in the tissues of the injected animals. The changes in the metabolism of the uteri appeared later and also occurred after oestrin administration (also see Büngeler and Ehrhardt, 1931).

The effect of prolan on the genital tract of the female rat.—Until there is available a more complete comparison of differ-

ent preparations of prolan assayed by accepted techniques in different laboratories, it will be difficult to decide what is the quantitative relationship of prolan effects in the rat as compared with the mouse. Zondek (1929), Hamburger (1933), White and Leonard (1933), Reiprich (1934), Rowe, Simond, and Nelson (1934), and Nelson and Overholser (1935) believed that the rat was the more sensitive (1 mouse-unit equivalent to 2 or more—usually about 4—rat-units). However, Katzman and Doisy (1932) estimated that an immature rat required about four times as much hormone as an immature mouse. Inasmuch as Katzman and Doisy based their assays on indirect effects (opening of vaginal orifice and oestrus), their results cannot be compared with those of others. On the other hand, the same preparations were assayed only in rats by Katzman and Doisy and by Rowe and his co-workers, and were found to have about the same potency. Other results of Rowe, Simond, and Nelson indicated that assays by the technique of Katzman and Doisy cannot be done accurately in mice. Less has been written about qualitative or other quantitative differences. Bourg (1930) believed that follicular hemorrhage occurred less frequently in rats; Brouha and Simmonet (1930) concluded that follicular maturation and corpus luteum formation were more pronounced in rats. Some of the effects of prolan on the ovaries and uteri of immature rats are illustrated in Figures 34 and 35.

If prolan be administered for several days to immature rats about 3 weeks old, and a well-marked development of corpora lutea appears, the ovarian changes are not markedly increased by increasing the dose ten- to fifty-fold (Evans, Meyer, and Simpson, 1931; Fluhmann, 1932; and Collip, Selye, Anderson, and Thomson, 1933). However, morphological changes in the ovaries and uterus can probably be detected earlier (e.g., 24–30 hours) after the administration of large doses (Reiprich, 1934). Moreover, moderate doses of prolan

can produce increased secretion of oestrin by the ovary without associated morphological changes. Fels (1930) excised the ovaries of immature rats about 30 hours after the first injection of prolan; although the ovaries histologically appeared unchanged, oestrus was observed later. Transplanted

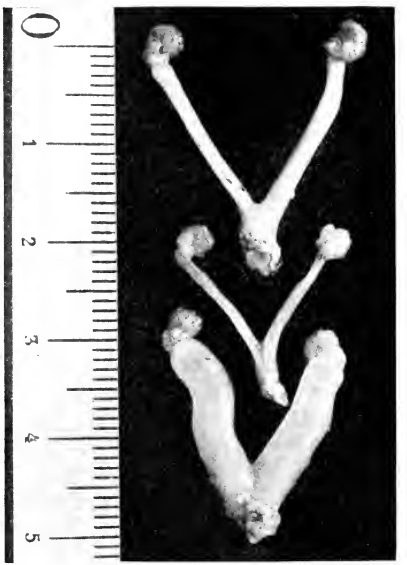


FIG. 34.—The effect of prolan on the uterus and ovaries of the immature rat. The dose was distributed over 4 days. Specimens from littermate rats 26 days old at death. Body-weights: control (middle), 54 g.; bottom and top receiving same dose of prolan, 55 and 51 g. Scale in cm. See Figure 35.

ovaries also respond to the injection of prolan. Goodman (1934) transplanted the ovaries of immature rats into the anterior chamber of the eyes of adult male and female rats. In both, corpus luteum formation occurred following the injection of prolan. Without prolan administration there oc-

curred complete cyclic changes including corpus luteum development in the ovaries transplanted into the eyes of adult

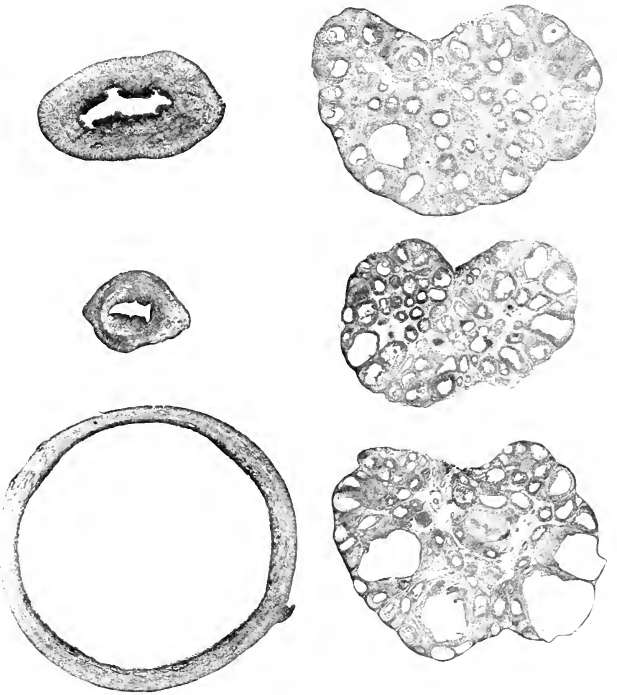


FIG. 35.—Photomicrographs of uteri and ovaries of specimens of Figure 34, ×13.5, arranged in same order: control, middle; injected with same dose of prolan, bottom and top. Predominant changes in bottom specimens: oestrin effect on uterus; follicle growth with some corpus luteum formation and some lutein-cell formation within ripening follicles in ovary. Predominant changes in top specimens: condition of uterus corresponds more to adult dioestrous (corpus luteum) stage; corpus luteum formation with hemorrhage into cavity of one corpus luteum and probably some follicle-ripening in ovary.

females, but only follicular maturation in those transplanted into the eyes of adult males. In the past, some have ques-

tioned whether or not the corpora lutea appearing after prolan injection were truly functional corpora lutea. In the rat, as well as in other animals, there is good evidence that the corpora lutea so produced really do secrete progesterone. For example, Shelesnyak (1933) showed that deciduomata could be produced in immature rats, particularly if the uterine irritation (threading) was begun about the fifth day of the injection period.

Boeters (1931) and Zondek (1932), but not Mahnert (1930), have observed pregnancy in immature rats mated after the injection of prolan.

The type of ovarian response also depends upon the age of the rat. Wiesner (1932) administered prolan to very young rats (newborn to 2 days of age) and could produce no ovarian response. According to Dorfmüller and De Fremery (1932) the injection of prolan into rats 10 days old caused ovarian and uterine growth; in the ovaries the interstitial tissue was particularly prominent, but there were no follicle-ripening and corpus luteum formation. Collip, Selye, and Thomson have also investigated the effects of prolan administered to young rats.[11] If injections of prolan were begun during the sixth to the sixteenth day of life, oestrus was present almost continuously; but the only prominent ovarian change was a luteinization of theca cells. The ovarian response remained unchanged if injections were continued to the twenty-sixth day; whereas if injections were not begun until the twenty-first day, typical follicular development and formation of corpora lutea atretica occurred. Luteinization of theca cells is the prominent change produced in the ovaries of hypophysectomized rats which have received prolan. Collip and his coworkers believed that an anterior pituitary secretion (particularly that causing ripening of follicles) necessary for facilitating the usual ovarian response of older animals is not avail-

[11] Collip, Selye, and Thomson (1933); Selye, Collip, and Thomson (1933, 1935); and Selye and Collip (1933).

able to very young animals. They also remarked that prolan causes theca luteinization in guinea pigs and rabbits unless ripe follicles are present in the ovaries. The effects of prolan on the ovaries of hypophysectomized rats are also discussed on pages 210–11.

If prolan is repeatedly administered to adult rats, continuous oestrus appears for about a week and is followed by a longer period of partial or complete anoestrus apparently because of persistent progesterone secretion (Katzman and Doisy, 1931; McPhail, 1933). Thus a "hormonal sterilization" may be produced. After injections have been stopped, however, normal oestrous cycles reappear shortly (Siegmund, 1934; but Reiprich, 1934, believed recovery to be slower). Evans and Simpson (1929), Zondek (1929), Levin, Katzman, and Doisy (1931), D'Amour and others (1933), and Hoopes (1934) have administered prolan to pregnant rats. Delayed parturition, increased fetal growth, and, commonly, fetal death were found to be associated with marked luteinization of the ovaries. Selye and others (1934) injected prolan into normal and hypophysectomized pregnant rats. Provided that the pituitary was intact, the injection of prolan was followed by a greater ovarian hypertrophy (due to luteinization of the theca and the formation of cystic corpora lutea) in the pregnant rat than in the non-pregnant adult; in lactating rats, chiefly theca luteinization was produced. According to von Árvay (1934), prolan diminished or inhibited the movements of the isolated uterus of the pregnant rat.

The effect of prolan on the genital tract of the female rabbit.— Ovulation characteristically occurs after the intravenous injection of prolan into the adult rabbit, especially if the ovaries contain large follicles.[12] If the hormone is administered subcutaneously or intraperitoneally, the ovarian changes resemble those produced in immature mice and rats. Friedman

[12] Normally ovulation in adult rabbits (cats and ferrets) occurs only after coitus, provided that the anterior pituitary is intact.

(1929), who first produced ovulation by injecting pregnancy-urine intravenously, later concluded that the dose required was equivalent to about 1 "rat-unit" per kilogram body-weight—a belief shared by others.[13]

If prolan is given by repeated doses subcutaneously or intraperitoneally, ovulation frequently does not occur. In the ovaries of very young rabbits necrosis not only of primordial follicles but also of the membrana granulosa and the ova of hemorrhagic follicles has been observed. In older animals there may occur only a ripening of some follicles. More often, particularly in adults, there are produced hemorrhages into follicles which may or may not be enlarged, depending upon the rabbit's age. Luteinization, particularly of the theca, occurs and is associated with the phenomena of pseudopregnancy.[14]

The intravenous dose required to produce ovulation may be less than one-tenth of the subcutaneous or intraperitoneal dose provoking an ovarian response (Snyder and Wislocki, 1931). These authors concluded that only in animals more than 3 months old were ovarian changes such as hemorrhage into follicles readily produced by intravenous injection. Typical ovulation was produced in rabbits more than 7 months old. Ovulation cannot be produced earlier than 10 hours after injection, even with increased doses (Jares, 1932). Following ovulation, typical corpora lutea develop and the rabbit becomes pseudopregnant (Hill and Parkes, 1930). If repeated doses of prolan, individually too small to cause ovulation, be given intravenously, there may follow follicular enlargement, occasional hemorrhages into follicles, some luteinization but no ovulation (Wolfe and Ellison, Friedman, 1932). Friedman (1932) produced corpora lutea by injecting pregnancy-urine directly into follicles; such corpora lutea,

[13] Such a relationship is not true of anterior pituitary extracts.

[14] Reiss and Langendorf, Watrin, Watrin and Brabant, Zondek (1929); Friedman, Mahnert (1930); Wolfe and Ellison (1932).

however, regressed rapidly and did not secrete progesterone. In ovarian transplants in the anterior chamber of the eye, the injection of prolan produced follicular hemorrhage as well as follicular growth (Allen and Priest, 1932; also see Spirito, 1933).

There is good evidence that the corpora lutea formed after the injection of prolan secrete progesterone like normal corpora lutea whether or not ovulation has also occurred. Pseudopregnancy may either be initiated or prolonged with the development of breast changes and the characteristic progravid uterus. McPhail (1933) injected 5 cc. of pregnancy-urine intravenously into rabbits every 10 days. After each injection ovulation followed and the animals remained pseudopregnant during the period of observation (5 weeks). The progestational changes in the uterus, however, seemed more pronounced after 4 weeks than after 5 weeks. Siegmund (1930), Winter (1931), and Robson (1932) have shown that posterior pituitary extract either has no effect or inhibits the movements of the isolated uterus of the doe rendered pseudopregnant by the injection of prolan. Knaus had previously shown that "pituitrin-insensitivity" of the uterus could be demonstrated in pregnant does during the period of active corpus luteum secretion (see chap. xi). The uterus *in situ* was found by Reynolds (1932) to become quiescent after the injection of prolan. This change, unlike that just described, appeared not to depend on indirect effects due to the internal secretion of the corpus luteum—for it appeared (1) if only follicular growth was produced, and (2) in ovariectomized animals in which uterine motility had been increased by the injection of oestrone. "Hormonal sterilization" was produced in rabbits by Reiprich (1934), who found that the period of sterility was roughly 3 weeks after the administration of 2,000 rat-units of prolan, and might be prolonged to a year, particularly after larger doses. Reiprich attributed the sterility to a persistence of corpora lutea. Rosenblatt, Hal-

ber, and Pruszczynski (1932), however, considered that repeated large doses of prolan caused ovarian damage similar to that caused by X-ray treatment. Rosahn, Greene, and Hu (1934) injected prolan into female rabbits of low fertility 2 hours before to 24 hours after mating. Fertility was increased. In the authors' opinion this was because ovulation occurred more frequently; however, the effect might have been equally well attributed to increased corpus luteum secretion and consequent facilitation of implantation.

Padoutcheva and others (1934) produced pregnancy in rabbits by artificial insemination (vagina or uterus) at about the time of ovulation induced by prolan.

Martins and Fabiao (1930), Snyder and Wislocki (1931), Hill and Parkes (1932), Jares (1932), and Wislocki and Goodman (1934) have all produced ovulation in the pregnant doe. The course of pregnancy usually was not altered as a result of the formation of new corpora lutea; however, Hill and Parkes believed that the latter sometimes adversely affected the corpora lutea of pregnancy. Jares was of the opinion that the ovulatory dose had to be increased if functioning corpora lutea were present, but did not offer convincing evidence in favor of this view.

Prolan will still cause ovulation after injection into rabbits hypophysectomized only a short time before, as was shown by Hill and Parkes (1931) and White and Leonard (1933). The latter were of the opinion that the dose had to be increased about 50 per cent. Hinsey and Markee (1933) injected large doses of pregnancy-urine intravenously into rabbits after the removal of the cerebral hemispheres, diencephalon, and hypophysis. They found that the size of the rabbits and the interval between operation and injection affected the ovarian response. In large does, ovulation occurred less frequently if more than 3 hours elapsed between operation and injection. No ovulation was observed in smaller does (2.0–2.3 kg.) which received prolan 5–40 minutes after

the operation. Whether or not ovulation can be produced in the complete absence of anterior pituitary secretion cannot be definitely decided from these data. They suggest, however, that some pituitary secretion must be present in the body-fluids if the intravenous injection of prolan is to cause ovulation.

The effect of prolan on the genital tract of the female guinea pig, ferret, cat, and dog.[15]—It appears that the ovaries of the immature guinea pig are much less readily altered by the injection of prolan than are those of the mouse, rat, and rabbit. Follicular development or follicular atresia, hypertrophy or luteinization of the interstitial cells, and luteinization of the theca and membrana granulosa can be produced by large doses of prolan repeatedly administered (Watrin, 1929; De Fremery and Dorfmüller, 1932; Loeb, 1932; and King, 1933). The intravenous injection of many times the rabbit-ovulating dose of prolan causes neither ovulation nor any alteration of the normal oestrous cycle (Jares, 1931). Cordaro (1934) could not affect the fertility or course of pregnancy by injecting large doses of prolan into adult guinea pigs. Guyénot, Ponse, and Trolliet (1934) as well as Papanicolaou and Falk (1934) reported that the clitoris became hypertrophied after the injection of prolan into immature female guinea pigs only if the ovaries were intact.

Hill and Parkes (1930) obtained precipitates from pregnancy-urine by adding alcohol to various concentrations. By administering one of these subcutaneously to anoestrous ferrets, they were able to bring about ovulation associated with oestrus-like changes in the uterus, vagina, and vulva. Corpora lutea were not formed unless injections were continued. The subcutaneous injection of other fractions produced cystic ovaries or corpora lutea atretica. Like the ferret and rabbit, the cat does not ovulate spontaneously but only after cop-

[15] For a report of experiments with cows, horses, pigs, and sheep, see Hupka and Majert (1932).

ulation. Snyder and Wislocki (1931) found that ovulation could not be produced in cats by intravenous doses causing ovulation in rabbits. Bourg (1930–33) has studied the anatomical changes in the genital tract of cats receiving repeated injections of pregnancy-urine. Ovarian changes could be produced in kittens only 15 days old. In cats of all ages there were observed, following the administration of pregnancy-urine, cystic development of ripe or growing follicles, degeneration of the ova, luteinization of the membrana granulosa and theca, and pseudopregnancy. Young corpora lutea tended to be cystic; older corpora lutea were solid. Similar ovarian changes were produced in pregnant cats without apparently affecting the course of pregnancy. Gustavson and van Dyke (1931) found that the uteri of cats which had received injections of pregnancy-urine contracted in response to sympathetic stimulation thus behaving like the pregnant uterus or the uterus of the spayed cat treated with oestrin and progesterone. Sympathetic stimulation caused relaxation of the uterus (as in the normal non-pregnant cat) if chiefly follicle growth occurred or if the pregnancy-urine was injected into spayed cats.

Reiss and Langendorf (1929), Mathieu (1933), and Gaebler (1935) have described oestrus and anatomical changes in the genital tract of the dog as a result of the administration of prolan.

The effect of prolan on the genital tract of female primates.—Novak and Kun (1931), Engle (1932–34), Marshall (1933), and Hartman (1934) have investigated the condition of the genital tract of the female macaque (*Macaca mulatta*, *Macacus rhesus*) after the administration of prolan. The observations of Engle were the most complete and the best controlled (see Fig. 36). Like other investigators, he found that prolan did not "stimulate" the ovaries of the immature macaque. In older monkeys it appeared to produce a lessening of ovarian secretion—for the sexual skin lost its intense red

color, and there appeared uterine bleeding from a "resting" ("interval") mucous membrane, which might persist for days if injections of prolan were continued. The most striking ovarian changes in immature monkeys consisted of atresia of larger follicles with luteinization of the theca interna; corpora lutea atretica were thus formed. As a result of changes in smaller follicles a different type of atretic corpus luteum was produced. Extensive hyalinization of smaller follicles was frequently observed. No follicular growth or effect

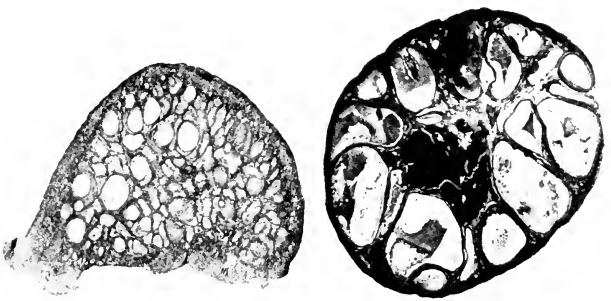


FIG. 36.—The effect of prolan and of anterior-pituitary extract on the ovary of the immature monkey (*Macaca mulatta*). From Engle (1933). Left: Ovary of a monkey receiving prolan; there is extensive hyalinization of small follicles. Right: Ovary of a monkey receiving anterior pituitary extract; there is marked stimulation of follicle growth.

on the sexual skin appeared. Bleeding from an "interval" mucosa might also set in and persist during the period of injection. Similar changes were produced in older monkeys. Engle also was unable to cause ovulation in immature monkeys by injecting prolan intravenously (3,000–9,900 rat-units in 4 days). The changes observed depended upon the age of the monkey, but were essentially similar to those already described. However, he brought about a more extensive formation of corpora lutea atretica by first injecting anterior-lobe extract subcutaneously to produce a growth of follicles; he then

injected prolan intravenously to produce theca luteinization. The injection of as much as 1,500 rat-units of prolan did not disturb the menstrual rhythm of adult monkeys (Hartman). Similarly, Johnson (1935) could detect no histological evidences of luteinization in the ovaries of adult macaques which had received 2,400 to 5,400 rat-units of prolan (200–450 rat-units daily).

Courrier and Gros (1934) injected prolan into immature Algerian baboons (magot, *M. inuus?*). The ovarian and uterine changes differed strikingly from those observed in the immature macaque. There occurred follicle-ripening with or without subsequent formation of corpora lutea atretica. They also observed swelling of the sexual skin and menstruation from the progravid uterine mucosa. In this species, therefore, prolan appeared to cause a true ovarian stimulation without, however, inducing ovulation.

Prolan has been experimentally administered to women either for therapeutic purposes or solely to observe the effects on the genital tract.[16] There is little scientific evidence that prolan has much therapeutic value in gynecology except as a means of controlling severe "functional hemorrhage" of the uterus in young women (Novak and Hurd, 1931; Reiprich, 1934). The results of Johnstone, Wiesner, and Marshall (1932) suggested that "habitual" abortion was less frequent in women treated by injections of prolan over a long period. There is no unequivocal evidence that prolan is of use in treating primary or secondary amenorrhea. Geist (1933)[17] made the best observations on the effects of prolan (600–2,200 rat-units) injected subcutaneously into women $1\frac{1}{2}$–4 days before laparotomy. Changes were produced in the ovaries of two-thirds (thirty-three) of the women. Geist believed that

[16] Zondek (1929); Campbell and Collip, Ehrhardt, Falta and Högler (1930); Collip and others (1931); Campbell (1932); Čertok and Pen'kov (1934).

[17] Also see the well-controlled experiments of Hamblen (1935), who injected larger doses of prolan over a period of 4–9 days.

the injection of prolan halted the normal development of the follicle. Other abnormalities of the ovary attributed to the treatment were the formation of cystic follicles, which often contained blood, and luteinization of the theca interna. The atretic corpora lutea were occasionally hemorrhagic. Pratt believed that the most characteristic sequel of prolan-administration was the formation of an increased number of atretic follicles.

The effect of prolan on the mammary gland.—In animals in which typical pseudopregnancy can be produced by the injection of prolan, concomitant hypertrophy of the nipples and breasts also occurs (e.g., rabbit and cat) and is said sometimes to be accompanied by the secretion of milk (Reiss and Langendorf, 1929). Selye, Collip, and Thomson (1933) produced marked development of the mammary glands of rats by injecting 200 rat-units of prolan daily for 26–53 days. No secretion of milk occurred. However, large amounts of milk were secreted if the ovaries of the injected animals were removed. The release of the secreting mechanism by ovariectomy did not occur in injected animals which were simultaneously hypophysectomized. Enzmann and Pincus (1933) reported that the injection of small doses of prolan into nursing mice affected milk-secretion unfavorably. Prolan was observed to have a similar effect on lactation in ovariectomized mice (De Jongh, 1933). On the other hand, Majert (1932) believed that more milk was secreted by pigs, in which there was a deficiency of secretion, if prolan was administered. Koch (1934) administered prolan to sheep and cows but observed no effect on the mammary glands before or during lactation.

Changes in the genital tract of male animals following the administration of prolan.—The primary and only important effect of prolan in male animals is on the testis. As in female animals, castration prevents the secondary changes in the accessory sexual organs. Prolan has no stimulating effect on spermatogenesis in immature male mammals but does stimu-

late markedly the activity of the interstitial cells so that more of the internal secretion characteristic of the testis is liberated. In adult hypophysectomized male animals, however, prolan will maintain both the gametogenetic and internal secretory functions of the testis; this is not the case in hypophysectomized female animals. There is evidence that the hypothetical "B" (luteinizing) fraction of prolan is responsible for the stimulation of the interstitial cells. Brindeau, Hinglais, and Hinglais (1934) stated that they isolated a purely luteinizing fraction from pregnancy-urine which caused the testicular changes characteristic of prolan in immature mice. Frequently, also, stimulation of the interstitial cells can best be obtained from those samples of prolan causing the most pronounced luteinization.

Apparently in some fish prolan may cause stimulation of spermatogenesis. Boucher, Boucher, and Fontaine (1934) injected a total dose of 6–15 cc. of pregnancy-urine over a period of 2 weeks or more into immature male silver eels. So marked was the stimulation of spermatogenesis that the testes had the appearance of approximately normal sexual maturity. Rugh (1935) caused the clasping reflex to appear in male amphibia (*R. catesbiana* and *Bufo fowleri*) by injecting prolan. All investigators agree that prolan has no effect on the gonads of the male bird.

The effect of prolan on the genital tract of the male mouse and rat.—Qualitatively there appears to be no difference in the gonadotropic effects of prolan in immature mice and rats. Some believe, however, that the rat responds more readily than the mouse. In the first reports (1929) by Brouha and Simmonet, and Engle, who injected pregnancy-urine into immature mice and rats, there appeared discrepancies in results and interpretation. Engle found that the chief effect was a stimulation of interstitial tissue with secondary effects on the accessory sexual organs; the injections also appeared to cause some destructive changes in the seminal epithelium

and did not stimulate spermatogenesis. Brouha and Simmonet believed that premature spermatogenesis also occurred. Numerous subsequent reports support the observations of Engle.[18] Some investigators like Borst, Borst and Gostimirović (1930), Boeters (1931), and Gostimirović (1932) believed that particularly the spermatogonia or spermatocytes developed more rapidly or were sensitized to more rapid development in immature mice and rats receiving prolan. They did not observe true premature spermatogenesis. Practically all other investigators are not convinced that prolan has any effect on the germinal epithelium of the immature mouse and rat.[19]

All reports agree that the amount of interstitial tissue in the testis is increased after the injection of prolan into immature animals (see Fig. 37). Depending upon the animals' age, the dose, and the duration of treatment, the weight of the testes may be unaltered (or even lighter) or increased. However, testicular hypertrophy is not ordinarily observed in experiments of short duration. The most striking effects are secondary to the stimulation of the interstitial cells. All the accessory sexual organs (seminal vesicles, prostate, bulbourethral glands, etc.) undergo a hypertrophy which is most clearly and easily observed in the seminal vesicles. The injection of prolan into castrated animals is followed by no changes in the accessory organs. For a description of the effects of prolan on the testes of hypophysectomized rats, see page 211.

Large doses of pregnancy-urine or extracts of pregnancy-urine, particularly if administered over a considerable period, appear to damage or cause degenerative changes in the

[18] For references not mentioned in the text, see: Colombi, De Jongh and Dingemanse, Laurent (1930); De Jongh, De Jongh and Laqueur, Kunischige (1931); Molien, D'Amour, and Gustavson, Robson and Taylor (1933); Geiger (1934).

[19] Hertwig (1933) studied spermatogenesis in older rats to which prolan had been administered. Abnormally small spermatids, incapable of transformation into spermatozoa, were formed.

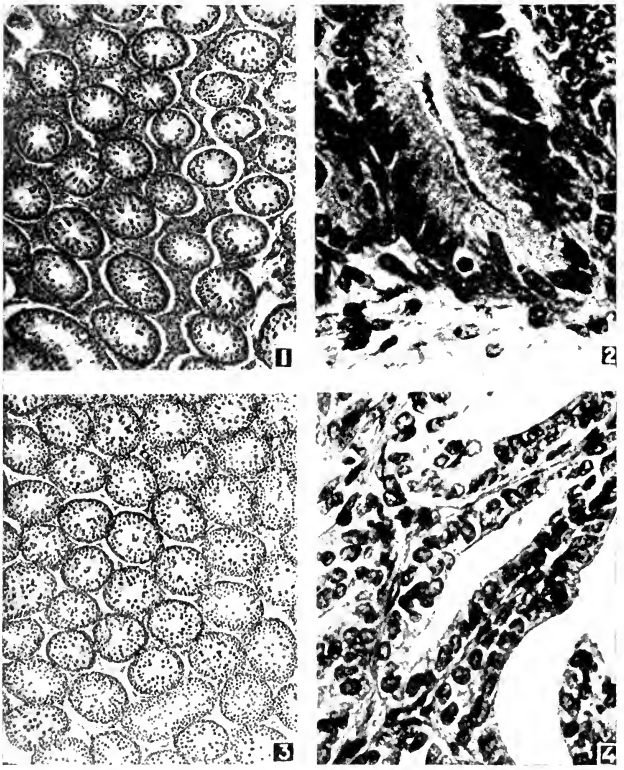


FIG. 37.—The effect of prolan on the testis and seminal vesicle of the immature rat. From Moore and Price (1931). Nos. 1 and 2: Photomicrographs of testis and seminal vesicle of an injected rat. Note the marked hypertrophy of the interstitial tissue and the enlargement of the epithelium of the seminal vesicle. Nos. 3 and 4: Photomicrographs of similar tissues from an uninjected rat.

seminal epithelium (Engle, 1929; Kraus, 1930; Neumann and Péter, 1931; and Gostimirović, 1932).

Dorfmüller and De Fremery (1932) reported that typical effects could be produced in rats only 10 days old. The injection of prolan into adult mice and rats may cause a considerable hypertrophy of the accessory sexual organs without, however, altering the histological appearance of the testis (Brouha and Simmonet, 1929, 1930; Boeters, 1931; and Moore and Price, 1931). De Jongh and Laqueur (1931) injected 5 mouse-units of prolan daily for 2 weeks into "senile" male rats (most of these weighed less than 200 g.); as a result there occurred stimulation of interstitial cell activity with hypertrophy of the testis but without an effect on spermatogenesis. The seminal vesicles were often found to be enormously hypertrophied. Spermatogenesis did not appear in the cryptorchid testes of adult rats which were given prolan (Nelson, 1934).

Bourg (1930, 1931) irradiated (X-rays) the testes of young rats and thus produced degenerative changes in the germinal epithelium. He believed that the administration of prolan hastened the repair of the damaged germinal epithelium perhaps because of some developmental interdependence between Leydig's cells and the germinal epithelium. The metabolism of isolated testis of rats after the administration of prolan was investigated by Reiss, Druckrey, and Fischl (1932). The most marked effect—an increase in aerobic glycolysis—was observed after the injection of prolan into immature rats for 3 or 4 days. There were also moderate increases in anaerobic glycolysis and oxygen consumption. No convincing change in metabolism was observed in the testes of injected adult rats.

The effect of prolan on the genital tract of the male guinea pig, rabbit, hedgehog, and ferret.—Both Brouha and Simmonet (1930) and Papanicolaou and Falk (1934) have commented on the striking hypertrophy of the penis observed in imma-

ture guinea pigs which had received prolan. In other respects the response of the genitalia is similar to that observed in mice and rats (Foncin, 1931, and Colombi, 1931). The hypertrophy of the seminal vesicles of adult guinea pigs, occurring as an effect secondary to the injection of prolan, was found by Bacq and Brouha (1932) to be increased after excision of the hypogastric ganglion. Such an operation did not alter the hypertrophy observed in immature guinea pigs. Kraus (1931) observed stimulation of the interstitial cells but no premature spermatogenesis in one immature male rabbit. Herlant (1931) injected pregnancy-urine into immature and adult hibernating hedgehogs. There occurred no effect on the germinal epithelium; however, hypertrophy or increased secretory activity was observed in the accessory male organs as a result of hypertrophy and hyperplasia of Leydig's cells. The injection of prolan into the anoestrous male ferret apparently increased the activity of the interstitial cells (Hill and Parkes, 1930), because only the injected animals copulated. (Ferrets have no seminal vesicles or prostate.) The prolan had no effect on spermatogenesis.

The effect of prolan on the genital tract of male primates.—Although Novak and Kun (1931) believed that spermatogenesis was hastened by the injection of prolan into a male macaque (one monkey of unknown age), their report was not substantiated by the studies of Engle (1932). As the important effects of prolan administration to immature male macaques, Engle mentioned descent of the testes, hypertrophy of the testes, and growth of the scrotum. In no case was spermatogenesis accelerated. The hypertrophy of the testis appeared to be due to (1) an increase in the size of the tubules, and (2) an increase in the size and number of the interstitial cells. Aberle and Jenkins (1934) confirmed the work of Engle, but observed incomplete descent of the testis more frequently. Similar changes were reported by Courrier and Gros (1934) who injected 500 rabbit-units daily for

about 3 weeks into immature male magots (*M. inuus?*). Testicular descent was incomplete; but marked changes ("spongiocyte" formation) occurred in the interstitial cells together with hypertrophy of the seminal vesicles and prostate. They observed no effect on spermatogenesis.

Schapiro (1930) was the first to administer prolan to boys or men; he injected as much as 600 rat-units daily. In cases of cryptorchidism or partial descent of the testis he caused complete descent in 14 cases and partial descent in others. More recently Aberle and Jenkins (1934) injected prolan into four boys with undescended testicles. Partial descent in one case and complete descent in another (both in the inguinal canal at the beginning of treatment) followed the administration of total doses of 1,700 to 4,500 rat-units. Rubinstein (1934) reported that descent of the testes from the abdomen into the inguinal canal followed the injection of prolan into a boy suffering from dystrophia adiposogenitalis.

THE ORIGIN OF PROLAN

By what organ is prolan secreted?—In the discussion of the tissues and body-fluids from which prolan can be obtained during pregnancy the question of its origin was postponed for later consideration. Zondek particularly has maintained that prolan is secreted by the anterior pituitary; others, among the first of whom was Philipp, believed that the placenta secreted prolan. The evidence for and against these views will be considered in this section and may conveniently be classified as follows:

1. The gonadotropic effects of the anterior pituitary, placenta, and other tissues during pregnancy.
2. Analogous or different effects following the administration of prolan or anterior pituitary extract to normal or hypophysectomized animals.

The distribution of gonadotropic substances in tissues of pregnant women.—In their first reports, Aschheim and Zondek (1926, 1927) recognized that considerable amounts of

prolan could be demonstrated in the placenta particularly in the early months when the urinary excretion was highest. Confirmatory studies were made by Murata and Adachi (1927), Klein (1929), and Bourg, Collip, Motta, Philipp, and Wiesner in 1930. No accurate quantitative studies of the amount of prolan in the placenta as compared with other tissues during pregnancy have been made. However, there appears to be no other tissue in pregnant women, including the anterior pituitary, as rich in gonad-stimulating principle(s). Moreover, prolan is no longer excreted after the removal of all the placenta, but it may still be excreted if living remnants of the placenta, as in cases of abortion, are not completely removed (von Árvay, 1934). As will be shown in discussion later, women with tumors of placental origin (hydatidiform mole, chorionepithelioma) often excrete tremendous amounts of "prolan" in the urine. Such tumor tissue, including metastases, contains "prolan." Finally, an argument by analogy may be offered: the placenta secretes oestrin during pregnancy and may therefore secrete prolan.

The other most probable origin of the prolan of pregnancy appears to be the anterior pituitary, because prolan seems to produce gonad-stimulating effects like those of implants or extracts of the anterior pituitary. However, the more the two are compared, the less alike they appear. A strong argument against the pituitary origin of prolan was furnished by Philipp (1930), who found that little or no gonad-stimulation could be produced by implants of the anterior pituitary of pregnant women in comparison with similar implants of men, non-pregnant women, and women after delivery.[20] This observation was confirmed by Zondek and others. However, Zondek still maintained that prolan is of pituitary origin and simply is stored in the placenta. He believed that hyper-

[20] Evans and Simpson (1929); Bacon (1930); Ehrhardt and Mayes (1930); Zondek (1931); Magistris (1932); and Siegert (1933) have studied the gonadotropic potency of the anterior pituitary of pregnant animals.

thyroidism, in which the concentration of iodine in the thyroid may be low, is an analogous case of hypersecretion in which the gland concerned contains an abnormally small amount of its characteristic hormone. The analogy, however, is by no means a satisfactory one. Moreover, the richest source of hormone in all normal glands of internal secretion is the gland secreting the hormone. Zondek's latest view (1935) is that prolan is a secretion of the anterior pituitary lacking a "synergic factor" (see the later section on the potentiation of prolan effects). The complete anterior pituitary gonadotropic secretion(s) he describes as "prosylan," the "synergic factor" as "synprolan"; prolan, therefore, would be "prosylan" without "synprolan."

Analogous or different effects following the administration of prolan to normal animals.—Although at first it appeared that prolan and anterior pituitary implants or extracts produced about the same gonadotropic effects after administration to immature rodents, much of the later work has disclosed important differences. If prolan is administered to immature female rats for 4 or 5 days, the ovarian hypertrophy is not much increased by markedly increasing the dose; whereas a potent anterior pituitary extract produces hypertrophy more nearly proportional to the dose. For example, Evans and Simpson (1929) reported that the ovarian weights of immature animals receiving prolan were trebled by increasing the dose one hundred and sixty fold; on the other hand, a fourfold increase of the dose of anterior pituitary extract, similarly injected into other animals, approximately quadrupled the ovarian weights. A similar "quantitative" difference has been reported by others (Evans, Meyer, and Simpson, 1931, 1932; Fluhmann, 1933–34; Leonard, 1933; and Hamburger, 1934). According to Fluhmann, the greater uterine hypertrophy may be caused by prolan. Both Evans and Simpson, and Hamburger believed that prolan brought about less follicular growth and maturation than

did anterior pituitary extract when their effects were compared in immature rats; precocious ovulation, however, could occur after the administration of either. A comparison of the effects of prolan and anterior-lobe extract after injections continued up to 20 days was also made by Fluhmann; the results were different from those obtained by himself and others in immature female rats injected only 5 days. For example, the same total dose of prolan produced a greater ovarian hypertrophy if distributed over 10 days instead of 5, whereas the reverse was true of anterior pituitary extracts. Collip, Selye, and Thomson (1935) found that prolan, but not anterior pituitary extract, produced theca luteinization and oestrus in female rats less than 18 days old.

These investigators (1934) also offered another type of evidence against the belief that prolan is secreted by the anterior pituitary. They injected prolan repeatedly into female rats until its effects progressively diminished and finally disappeared. They then administered anterior pituitary extract and produced typical ovarian hypertrophy with luteinization. They also performed experiments in which the order of administration was reversed and obtained the same results. On the other hand, Fluhmann (1935) produced an "anti-serum" by repeatedly injecting an extract of *human* pituitary. This "anti-serum" prevented the gonadotropic effects of both human pituitary extract and prolan but not those of sheep pituitary extract. Unfortunately, Fluhmann did not attempt to produce "anti-serum" by extracts of other human tissues.

Wallen-Lawrence and van Dyke (1931) found that about the same dose of prolan was required to produce ovarian hypertrophy in female immature rats and seminal vesicle hypertrophy in males; anterior pituitary extract, however, caused ovarian hypertrophy in much smaller doses than those required to cause seminal vesicle hypertrophy. Similarly, Engle (1932) and Schockaert (1933) found that prolan

stimulated Leydig's cells much more effectively than did anterior pituitary extract. According to Leonard (1932) the dose, in rat-units, of anterior pituitary extract causing ovulation in the rabbit is much less than the dose of prolan also evaluated in rat-units. Mahnert (1933) found prolan relatively less effective, but he injected what appear to be excessive doses of both prolan and anterior-lobe extract. Hill, Parkes, and White (1934) obtained perhaps different curves of response (see Figs. 33 and 41) when they produced ovulation by injecting prolan or anterior pituitary extract.

The effects of prolan and of anterior pituitary extract have been compared in male and female immature monkeys (*M. mulatta*) by Engle (1932, 1933). In males, prolan more effectively stimulated the interstitial cells of the testis. In females, anterior pituitary extract, unlike prolan, brought about follicular growth in the ovaries, and reddening and edema of the sexual skin; prolan caused atresia of the graafian follicles and luteinization of the theca (see Fig. 36).

All investigators agree that prolan causes no hypertrophy of the gonads of immature (or mature) male and female birds; it may, indeed, have the opposite effect. On the other hand, anterior pituitary extracts do "stimulate" or otherwise affect the gonads of the fowl, the duck, and the pigeon.[21]

Analogous or different effects following the administration of prolan to hypophysectomized animals.—The administration of prolan to hypophysectomized animals has been found not to bring about functional and anatomical repair of the degenerated or degenerating gonads except in one instance—the hypophysectomized adult male rat. The administration of anterior pituitary implants or extract, on the contrary, may restore the gonads to an apparently normal condition. These

[21] See the articles by Noether (1930); Riddle, and Riddle and Polhemus (1931); Calvet (1932); Dingemanse and Kober, Leonard, Pompen and others, Reiss and others, and Schockaert (1933); Evans and Simpson, Hamburger, and Martins (1934); Bates, Lahr, and Riddle (1935).

results show that if prolan is still to be considered a secretion of the anterior pituitary, it must be an unusual part of the normal secretion.

The comparative effects of prolan and anterior pituitary implants or extract have been observed in hypophysecto-

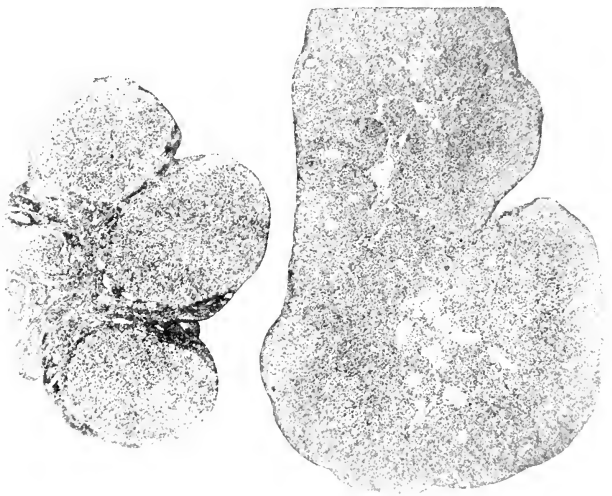


FIG. 38.—The effect of prolan on the ovary of a hypophysectomized mature rat. From Leonard and Smith (1934). Left: Persistent corpora lutea in the left ovary removed 78 days after hypophysectomy. Right: The right ovary of the same rat after the injection of 10 rat-units of prolan daily for 10 days. The marked proliferation of interstitial tissue makes difficult the recognition of corpora lutea.

mized female rats by a number of investigators. All agree that prolan, unlike anterior pituitary extract, does not stimulate follicular growth. Moreover, the effects of prolan depend upon the age at which the rat is hypophysectomized, the duration and course of treatment, etc. One of the best reports is that of Leonard and Smith (1934). They administered prolan to immature or older female rats 16–78 days

after hypophysectomy. The important direct and indirect results of prolan injection were hypertrophy of the theca cells and interstitial cells and persistent oestrus (see Fig. 38). Oestrus did not necessarily occur if a long period elapsed between hypophysectomy and prolan treatment. Anterior-lobe implants caused ovarian hypertrophy due to follicular growth (the follicles might be cystic and contain blood) and corpus luteum formation. The corpora lutea were larger than those formed after luteinization of the theca due to prolan. Apparently Noguchi (1932) was the first to describe theca luteinization as a result of prolan administration to hypophysectomized rats. Selye, Collip, and Thomson (1933) confirmed and extended the observation of Noguchi.

Collip, Selye, and Thomson (1933) believed that prolan, as in the normal immature male rat, stimulated Leydig's cells but had no effect on spermatogenesis in hypophysectomized rats after degeneration of the tubules had appeared. Smith and Leonard (1934), however, were able to maintain spermatogenesis (including fertility) by prolan administration to adult rats soon after hypophysectomy (see Fig. 39). Despite continued administration, regression of the effects on both spermatogenesis and Leydig's cells took place. The important effect in immature hypophysectomized male rats was a stimulation of the interstitial cells. Particularly in immature rats did implants restore the testes to a more nearly normal condition (e.g., spermatogenesis).[22]

The production of ovulation in hypophysectomized rabbits has already been discussed (pp. 194–95). McPhail (1933) compared the effects of anterior pituitary extract and prolan in hypophysectomized female ferrets; in these animals prolan produced some follicular growth (and atresia) whereas anterior-lobe extract caused chiefly a theca luteinization.

[22] For other reports on the effect of prolan in hypophysectomized male and female rats see: Reichert and others, Wallen-Lawrence and van Dyke (1931); Freud, Kraul (1932); Freud, Wade, Wade and others (1933).

Reichert and his co-workers (1931, 1932) reported that prolan (unlike heteroplastic pituitary implants, etc.) was without effect on the ovaries of the hypophysectomized dog.

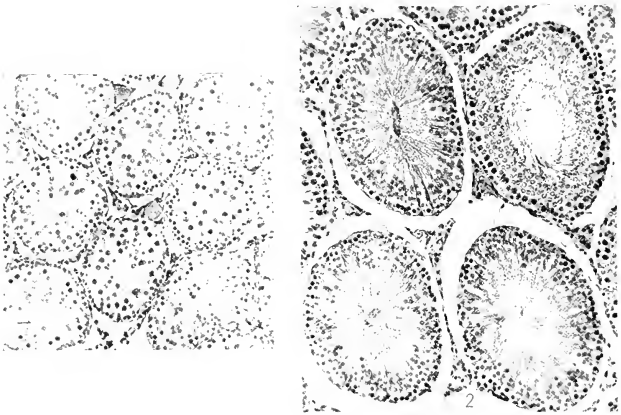


FIG. 39.—The effect of prolan on the testis of the hypophysectomized mature rat. From Smith and Leonard (1934). Left: Photomicrograph of testis of uninjected rat 20 days after hypophysectomy. Right: Photomicrograph of testis of injected rat 20 days after hypophysectomy. This rat received 25 rat-units of prolan daily throughout the period following operation. Replacement therapy during this period was complete inasmuch as mating between this male rat and two females was fertile.

THE POTENTIATION AND ANTAGONISM OF PROLAN EFFECTS

The potentiation of prolan effects.—If an extract of the anterior pituitary and prolan are simultaneously administered to mice or rats, the ovarian hypertrophy is much greater than would be expected from a mere addition of effects. The explanation of this potentiation of the effect of prolan is still a matter of controversy. Evans and his co-workers[23] at first believed that the growth-promoting hormone of the anterior

[23] Evans, Meyer, and Simpson (1932), and Evans, Simpson, and Austin (1933).

pituitary was the responsible factor; later they found that potentiation could be caused by pituitary extracts causing gonad stimulation but no increased growth; recently they have expressed the view that a new hormone, different from any so far described, is responsible for potentiation. Others[24] believed that potentiation depends on a gonad-stimulating fraction in anterior pituitary extracts and that in this respect prolan behaves more like a "luteinizing" hormone. In hypophysectomized male and female rats gonad stimulation by prolan is increased if even apparently ineffective doses of anterior pituitary extract are simultaneously administered (Collip, Selye, and Thomson, 1933; Evans, Pencharz, and Simpson, Leonard and Smith, 1934).

The antagonism of prolan effects.—De Jongh and Laqueur (1931) described signs of lessened activity of Leydig's cells in male rats receiving oestrone. These effects could be abolished or prevented by the administration of prolan except when relatively large doses of oestrone were used. Later (1934) they were of the opinion that the previous administration of oestrone facilitated interstitial cell stimulation by prolan. Spencer, D'Amour, and Gustavson (1932) showed that atrophy of the ovaries and testes of rats after oestrin administration was less if prolan was also given; the testes, however, still weighed less than those of uninjected males. In castrated or spayed animals prolan is said to lessen the effects of testis hormone (Funk and Zefirow, 1932) and oestrone (Baum and Pincus, 1932). Korenchevsky and others (1933), however, reported that prolan administration did not alter the response of the accessory organs of castrated male rats to testis hormone.

According to Evans, Simpson, and Austin (1933) and Leonard (1934), some anterior pituitary extracts, adminis-

[24] Leonard (1932, 1934); Fevold and others (1933); and Fevold and Hisaw (1934). Anselmino and Hoffmann (1934) discussed the potentiation of prolan effects by an extract of urine of women after the menopause or spaying.

tered intraperitoneally, seem to prevent or lessen the ovarian changes caused by injecting prolan into immature rats.

If prolan is repeatedly administered over a period of weeks or months, the ovarian changes in injected rats gradually disappear until no hypertrophy or even some atrophy is found (Selye, Collip, and Thomson, 1934). Similarly, prolan causes ovulation in rabbits less frequently if it has already been injected thrice previously (Hill, Parkes, and White, 1934). Again, Wade (1933) was able to cause the transformation of "wheel" cells into lutein-like cells in the ovaries of hypophysectomized rats by injecting prolan, but not if the rats had received prolan 2 or 3 weeks previously. To explain facts like these, Selye, Bachman, Thomson, and Collip (1934) have postulated the production of an "antihormone" which they detected biologically in the blood of animals given a long course of injections of prolan. Even 70 days after injections had been stopped, sera still prevented gonad stimulation by prolan in immature rats; the serum of gonadectomized rats which had received a series of prolan injections also contained "antihormone" (Bachman, Collip, and Selye, 1934).

PROLAN AND OTHER GLANDS OF INTERNAL SECRETION

Prolan and the pituitary body.—In studies of the effect of prolan on the anterior pituitary in rats, the usual findings are as follows: (1) hypertrophy of the anterior pituitary occurs in female animals but not in males; (2) this hypertrophy does not occur in spayed or very young females; and (3) the gonadotropic potency of the pituitary is reduced in both male and female animals which have received prolan. Some of these facts are interpreted by Collip, Selye, and Thomson (1933), and Bergmann (1934) as indicating that gonad stimulation by prolan in the female requires the participation of the anterior pituitary, whereas in the male, Leydig's cells are directly stimulated. The anatomical changes, also re-

ported by Zondek and Berblinger (1931), and Collip and others (1933), have been studied in detail by Baniecki (1932), Desclin (1933), Nelson (1934), Severinghaus (1934), and Wolfe and his co-workers (1934).[25] Microscopically they appeared to resemble the changes occurring in the course of normal pregnancy (particularly loss of granules from basophilic cells and hypertrophy of basophilic cells according to some authors). Similar changes were not observed in spayed rats. The anatomical changes in the pituitary following castration were not prevented by the administration of prolan (Zondek and Berblinger, 1931; Baniecki, 1934) unless they were the result of cryptorchidism (Nelson, 1934). The reduced gonadotropic potency of pituitaries of rats which had received prolan (Kuschinsky, 1931; Leonard, 1933) is best interpreted as an effect of the increased secretion of oestrin or testicular hormone.

Severinghaus reported hypertrophy of the pars intermedia as a result of prolan administration. There is no evidence that prolan has any effect on the pars neuralis.

Prolan and the thyroid, parathyroids, adrenals, epiphysis, and thymus.—Prolan seems to have no significant effect on the thyroid (see chap. vii) although Collip and others (1933) reported that it might become hypertrophied in female but not male rats following the administration of the hormone.[26] In thyro-parathyroidectomized female dogs, prolan caused severe tetany if the ovaries were intact and oestrus appeared (Mathieu, 1933). Histologic changes in the adrenal cortex have been attributed to the administration of prolan by

[25] Karp (1933) has studied the pituitary of the rabbit after prolan injection; Desclin (1932, 1934) has made a similar study in the guinea pig after the injection of pregnancy-urine. Goodman (1935) declared that the gonad-stimulating potency of the pituitary of the adult male or female rabbit was *increased* after the administration of prolan. His series of rats used for assay was small; although the rats were nearly 4 weeks old at death, the weights of their paired ovaries were often very low (e.g., 4.4–12.0 mg. after "stimulation").

[26] Fluhmann (1934) investigated the changes in the ovaries brought about by the administration of both prolan and desiccated thyroid.

Nürnberger, Madruzza (1932), Inchara, Schenck (1933), and Geyer (1934). On the other hand, the administration of cortical extract or adrenalectomy 12 hours prior to the first injection did not alter the luteinizing effect of prolan in immature rats (Hicks and Matters, 1935). Engel (1934, 1935) reported that alkaline extracts of dried epiphysis, if administered with prolan, prevented such characteristic effects as corpus luteum formation and stimulation of Leydig's cells. According to Richter (1934), gonadectomized rats which drank water containing pregnancy-urine were more active; the size of the thymus of such animals was similar to that of normal animals but much smaller than that of gonadectomized rats which had drunk water not containing pregnancy-urine.

OTHER EFFECTS OF PROLAN

There is no convincing evidence that prolan alters the basal metabolic rate. Crude preparations of prolan cause hyperglycemia (Böhm, Eidelsberg, 1932); purer preparations tend to cause hypoglycemia (Dingemanse and Kober, 1933).[27] Cannavó and Indovina (1932, 1933) believed that the concentration of magnesium in the serum was elevated following the injection of prolan. In rats and mice rendered anoestrous by thallium-poisoning, prolan caused the reappearance of oestrus at least once (Bickel and Buschke, 1933). Vitamin deficiency (C and E) was not lessened by the administration of prolan (Agnoli, 1932; Diakov and Krizenecky, 1933), nor did vitamin E cause precocious sexual maturity.

Zondek, Zondek, and Hartoch (1932) as well as Möller (1933) found that the injection of large amounts of prolan into mice into which Ehrlich's adenocarcinoma had been transplanted markedly inhibited the growth of the tumor

[27] Also see Houssay and Biasotti (1933); Davis, Hinsey, and Markee (1934); and Hrubetz (1935).

and rendered its transplantation very difficult.[28] Exactly opposite results with a different tumor were obtained by Wiesner and Haddow (1933), who reported that the Jensen sarcoma grew more rapidly in rats receiving prolan.

THE DETECTION AND ASSAY OF PROLAN

In relatively few reports in the literature on prolan has any attempt been made to refine the assay technique. The ordinary tests for prolan are of little use other than as qualitative tests for its presence and hardly deserve to be designated as "mouse-units" or "rat-units." Even less trustworthy are some of the statements as to the relative quantities of "prolan A" and "prolan B" in pregnancy-urine or samples or prolan. Only a few of the more important of fifty-odd papers dealing partly or entirely with the assay of prolan will be considered in this section.

In their first papers on the assay of prolan, Aschheim and Zondek (1927, 1928) injected the material into immature female mice. They ascribed three effects, or combinations of these, to the injection of prolan: (1) follicular growth and maturation; (2) hemorrhage into follicles; and (3) formation of corpora lutea. They maintained that the conclusive demonstration of the presence of prolan demanded the production of reactions (2) and/or (3). Subsequently, numerous other techniques, such as those using the following criteria, have been recommended:

1. Indirect effects (opening of vaginal orifice and oestrus, thickness of uterine wall) in immature female mice and rats.
2. Effects on the ovaries of immature female rats.
3. Indirect effects (particularly, hypertrophy of the seminal vesicles) in immature male mice and rats.
4. Ovulation in the rabbit.
5. Ovulation in the toad. (Bellerby, and Shapiro and Zwarenstein, 1934).

[28] According to Engel (1934), the inhibition of the growth of this tumor by the injection of prolan is greater if an extract of the epiphysis is also administered. Also see Krehbiel and others (1934).

It is important to emphasize that "units" assayed by these various techniques are not necessarily interchangeable or related to each other. In every case the assay is based on a "gonad-stimulating" effect.[29] Too frequently in assays, important factors influencing the type or degree of response elicited are neglected. Among these may be mentioned age, race, and nutritional condition of the animals, season or other factors (as in the use of rabbits), route of administration, distribution and frequency of doses, and the use of a sufficiently large group of animals (twenty or more) receiving an amount of hormone producing changes in only part of the group.

Particularly in immature female mice and rats does assay by indirect methods appear to be undesirable and incomplete. When these have been compared with the direct effects—e.g., luteinization—the relationship has appeared to be the same to some or variable to others. A priori it would seem to add an unnecessary and complicating variable. On the other hand, the assay of prolan in male immature mice and rats by noting indirect effects appears to be a more sensitive and exact method because only a relatively small part (interstitial cells) of the total testicular tissue is affected by prolan. Variable changes in testicular weight are produced only by large doses of prolan.

The assay of prolan in immature female mice and rats.—The relative sensitivity of mice and rats has already been discussed (see pp. 186–87). The use of rats in preference to mice appears to have the following advantages: rats produce larger litters, are better standardized, are more sensitive to the hormone, but are less easily poisoned by substances accidentally present. In rats, assay may be based either on the frequency of qualitative changes such as follicular growth

[29] Some authors assert that melanophore changes (dispersion of melanosomes) in fish scales and frog skin can be used for the assay of prolan (Binet, Verne, and Luxembourg, 1934, Konsuloff, 1934).

and luteinization or more simply and perhaps less adequately on the total weight-change in the paired ovaries. In the case of prolan in which the weight-change is much less closely related to dose than is the case if anterior pituitary extract is used, a better criterion would be the frequency of significantly increased ovarian weight in a group of animals. There are available no adequate data on the relationship between weight-change or frequency of weight-change of ovaries and

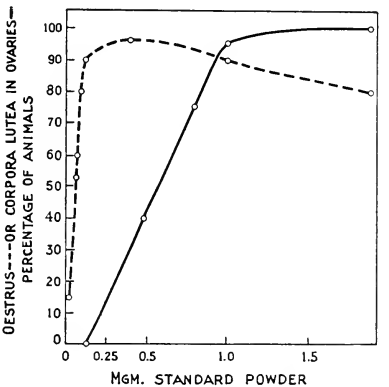


FIG. 40.—The appearance of oestrus and or corpora lutea in immature rats receiving different doses of one preparation of prolan. Ten animals were used for each dose. From Coester, *Arch. exp. Path. Pharm.*, CLXVIII (1932), 745–52.

dose. On the other hand, Coester (1932) has determined the frequency of oestrus and luteinization produced by several preparations of prolan given to groups of ten rats. The curves he obtained with one preparation are reproduced in Figure 40. Two facts emerge from his studies: (1) oestrus may be produced by a fraction of the dose required to produce luteinization, and (2) different preparations of prolan vary in the relationship between oestrus-producing and luteinizing doses. From the latter fact it may be argued that there exist

separate "A" and "B" principles; oestrus, however, does not necessarily signify follicular growth and maturation.[30]

The assay of prolan in immature male mice and rats.—The use of male animals for the assay of prolan was proposed by Borst and Gostimirović, and Brouha and Simmonet in 1930. As was explained above, this is best accomplished by de-

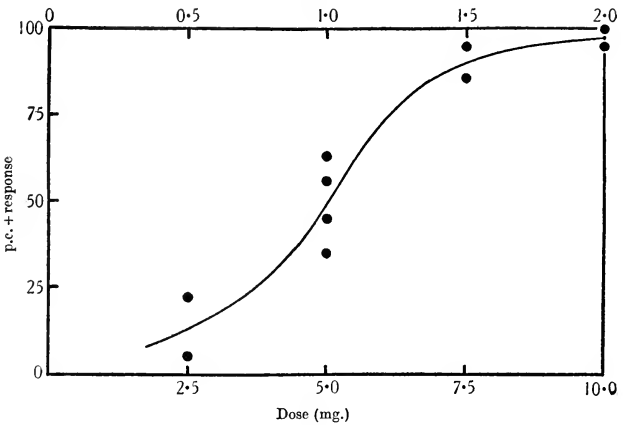


FIG. 41.—The relationship between the intravenous dose of one preparation of prolan and ovulation in the rabbit. Each point (except two) represents a group of more than twenty rabbits. The percentage of animals in which ovulation was observed is indicated along the ordinate. From Hill, Parkes, and White (1934).

termining the indirect effects on the accessory organs (e.g., seminal vesicles) following the stimulation of the interstitial cells. However, no one has seriously investigated the relationship between response and dose.

The assay of prolan in female rabbits.—The female rabbit, like the female mouse and rat, has been extensively used for

[30] Also see Aschheim, Ehrhardt, Zondek (1929); Brouha and Simmonet (1930); Wallen-Lawrence and van Dyke (1931); De Jongh and Kober, Katzman and Doisy (1933); Reiprich, Rowe and others (1934); Nelson and Overholser (1935).

the detection of prolan (Schneider, 1930; Friedman and Lapham, Wilson and Corner, 1931). Although it has been said that approximately 1 "rat-unit" of prolan per kilogram rabbit is the ovulation dose when administered intravenously, there is no evidence that the effects produced in these different animals are due to the same substance. Hill, Parkes, and White (1934) studied the factors which might influence ovulation in groups of rabbits receiving different doses of prolan. The "curve of response" found by them is reproduced in Figure 41; its shape differs from that found in similar experiments with anterior pituitary extract (Fig. 33). They observed that the response of animals diminished after three tests (at intervals of 3 weeks) had been made.

The diagnosis of pregnancy.—The detection of prolan in the urine or blood of pregnant women is unquestionably the best means of diagnosing early pregnancy. In experienced hands the test probably indicates pregnancy in 98 or 99 per cent of cases. The numerous reports since the first given by Aschheim and Zondek do not require consideration.

THE PREPARATION OF PROLAN; THE PROPERTIES OF PROLAN

The preparation of prolan.—By the earlier methods,[31] prolan was prepared from raw or concentrated urine, which often was first acidified, by the addition of various concentrations of alcohol or acetone or of ammonium sulphate to saturation. Most of the prolan was carried down with the precipitate. Separation of the prolan from some of the inert substances could be effected by repeated alcoholic precipitation, by the addition of colloidal iron or tannic acid, or by dialysis. Subsequent work has also shown that crude prolan often behaves like a protein, or as if it can be adsorbed on proteins

[31] Zondek and Aschheim, Biedl (1928); Dickens, Zondek (1930); Wiesner and Marshall (1931); and Evans, Meyer, and Simpson (1933). "Emmenin" which Collip prepared from the placenta is no longer considered to be a gonad-stimulating substance but rather a compound of oestriol (see Collip and others, 1930, 1931, 1933, 1934, and Butenandt and Browne, 1933).

or protein-like substances. Generally, protein precipitants, such as tungstic acid, phosphotungstic acid, or phosphomolybdic acid (but not sulphosalicylic acid) free urine or a solution of prolan more or less completely from the hormone, particularly if protein is present or has been added. For methods primarily based upon this behavior of prolan, see the descriptions of Katzman and Doisy (1933, 1934), Marshall (1933), and Zondek, Scheibler, and Krabbe (1933). Katzman and Doisy were able almost completely to remove prolan from very dilute solutions.

Other methods of both initial preparation and subsequent purification are more clearly dependent on the adsorption of prolan to other substances. Among the adsorbents used may be mentioned aluminum hydroxide (Reiss and Haurowitz, 1929), Lloyd's reagent (Davy, 1934), activated carbon of vegetable or animal origin (Schmidt and Derankowa, 1931; Katzman and Doisy, 1932; Elden, 1933), kaolin (Fischer and Ertel, 1931), permutit (Lejwa, 1932), and benzoic acid (Katzman and Doisy, 1932, 1933). Funk and Zefirow (1932) used either benzoic acid or quinine. Marshall (1933) believed that benzoic acid was an efficient adsorbent only in the presence of protein. Apparently the most potent preparations of prolan yet made, 3,000–30,000 "mouse-units" per mg. (one "mouse-unit" = 0.3–0.03 γ), were at least partly purified by adsorption on benzoic acid (Katzman and Doisy, 1932; Haurowitz, Reiss, and Balint, 1933 [but also see Haurowitz and others, 1934]).

Marshall (1932) used filters of various porosities to free prolan from part of the associated impurities.

The chemical properties of prolan.—Properties which prolan does not possess can be given with some assurance. Until it has been isolated as a pure substance, however, less that will ultimately be recognized as accurate can be said about its chemical nature. Prolan in aqueous solution is rather rapidly inactivated by heating (above 60° C.) especially if the solu-

tion is boiled. Askew and Parkes (1933) considered this to be due to hydrolysis inasmuch as dry prolan readily withstood an hour's heating at 100° in the presence of oxygen. According to von Euler and Zondek (1934), prolan resembled enzymes as to the conditions (temperature and pH) under which it was inactivated. It was also inactivated by ultraviolet rays[32] and by hydrogen peroxide, but not by a dipeptidase. Fairly pure preparations of prolan do not contain protein but they have usually been considered to resemble a derived protein (e.g., a polypeptide). Prolan is said to be inactivated by trypsin but not by pepsin (Reiss and Haurowitz, 1929; Wiesner and Marshall, 1931; and others). Good preparations of prolan contain no amines, tyrosine (negative Millon reaction), tryptophane (negative Adamkiewicz reaction), adenine, phloroglucinol, halogen, sulphur, or phosphorus. The most potent preparations are said to contain 1–2 per cent histidine, 6 per cent arginine, and carbohydrate equivalent to about 7 per cent glucose (C, 43 per cent, H, 6 per cent, O, 39 per cent, and N, 12 per cent).[33]

THE FATE OF PROLAN IN THE ANIMAL BODY

A few observations have been made on the fate of prolan after its administration by various routes (also see pp. 178–79). It is not surprising that prolan has little effect when administered by way of the gastrointestinal tract. To produce ovarian changes in mice 20–150 "units" had to be given by stomach tube (Reiss and Haurowitz, 1929; Dickens, 1930). According to Zondek (1929), and Huddleston and Whitehead (1931), prolan *per os* also stimulated the gonads of immature rats. They gave no data on dosage.

After the intravenous administration of pregnancy-blood to men or non-pregnant women (Ehrhardt, 1930; Ehrhardt

[32] Also see Trettenero (1934).

[33] Fischer and Ertel (1931); Marshall (1932); Haurowitz, Reiss, and Balint (1933).

and Ruhl, 1933), the urine contained prolan as soon as 10 minutes after injection. The hormone often could not be detected in the urine 24 hours later. Owing apparently to variations in the individual recipients and the dose, prolan could still be detected in the blood 2–20 hours after transfusion.

Prolan has been injected intravenously into normal rabbits and its excretion in the urine or its disappearance from the blood has been subsequently followed. Parkes and White (1933) found that about one-third of the intravenous dose was excreted in about 9 hours. They believed that female rabbits, like women, can excrete about 10 rabbit-units of prolan per kg. per 24 hours. Lipschütz and Vivaldi (1934) investigated the disappearance of prolan from the blood of rabbits each receiving 100 "rabbit-units" intravenously. They calculated that 80 per cent of the dose had disappeared after 6–8 hours, and nearly all after 10 hours. In later experiments, Lipschütz and others (1935) followed more closely the rate of disappearance of prolan, and believed that it depended upon the renal excretion of the hormone.

The placentae of normal or acutely hypophysectomized rabbits were found to contain prolan after the intravenous injection of pregnancy-urine (Hill and Parkes, 1931).

11. GONADOTROPIC HORMONES IN CASES OF MALIGNANT TUMORS OF THE GENITALIA

The distribution of gonadotropic hormones in human beings with neoplasms of the genital tract is given in Table VI (groups 6, 7, 8, and 9). The gonadotropic hormone found in cases of hydatidiform mole and chorionepithelioma appears to be identical with prolan (or a fraction ["B"] of prolan). A similar but not always identical hormone is excreted by men with malignant neoplasms of the testis. The gonadotropic hormone found in the urine of women with malignant tumors, such as carcinoma of the cervix uteri, is different from prolan but may resemble the hypothetical "A" fraction.

Hydatidiform mole and chorionepithelioma.—The close relationship between hydatidiform mole and chorionepithelioma, heretofore demonstrated anatomically, is equally well shown by the apparent secretion of large amounts of gonadotropic hormone resembling prolan by both tissues. The abnormal chorionic cells, like the normal chorionic cells of pregnancy, secrete prolan. According to Brindeau, Hinglais, and Hinglais (1934) the gonadotropic effects of serum of one patient with hydatidiform mole differed from prolan in seeming to possess only "luteinizing" properties. The serum had no effect on the ovaries of immature mice but did cause hemorrhage into follicles and luteinization of the ovary of the rabbit and stimulation of the interstitial cells in immature male mice. Usually, however, the effects of urine or blood of patients of this group are not distinguishable from those of the prolan of pregnancy.

Gonadotropic hormone is probably as generally distributed in body-fluids and tissues in patients with neoplasms of the chorion as in normal pregnancy. The concentration of the hormone in urine or serum is variable, but may be 5 to 10 times as great as that found in normal pregnancy. Shortly after the complete removal of the tumor, prolan can no longer be detected; it may reappear, however, if the tumor recurs or because of the production of the hormone by metastases. Obviously the assay of prolan in urine or blood of patients with such neoplasms is of great value in diagnosis and in prognosis after treatment.[34]

It has long been known that lutein-cell cystomata are frequently found in the ovaries of patients with hydatidiform mole or chorionepithelioma. Apparently similar but less pronounced changes may be found in the ovaries of pregnant women. Aschheim (1928) and Fels (1929) pointed out that these ovarian changes were probably due to the large

[34] See the following: Aschheim (1928); Rössler, Zondek (1929); Ehrhardt, Fels, Meyer, Philipp (1930); Heim, Zondek (1932); Hamburger (1933); Fluhmann and Hoffmann (1934).

amounts of gonadotropic hormone secreted by the abnormal chorionic cells. Similarly, Novak and Koff (1930) described hyperluteinization of the granulosa and theca which they also ascribed to the prolan.

Malignant tumors of the testis.—A prolan-like gonadotropic hormone may be excreted in small or very large amounts (e.g., 10,000 mouse-units per liter) in the urine of patients with malignant tumors of the testis (Heidrich, Fels, and Mathias, 1930; Zondek, 1932; Ferguson, Gerber, Hamburger, 1933; Fluhmann and Hoffmann, 1934; and others). The testicular neoplasms in these patients have been described by a variety of terms such as teratoma, chorionepithelioma (teratoma?), carcinoma, epithelioma, and seminoma. It is of interest to note that direct and indirect effects of gonadotropic hormone may be manifested in the patient himself by changes in the interstitial cells, hypertrophy of the prostate and seminal vesicles, and histological and biological changes (gonadotropic potency of implants) in the anterior pituitary resembling pregnancy.

In the opinion of Evans and others,[35] the gonadotropic hormone obtained from the urine of a case of embryonal carcinoma of the testis differed from prolan in its biological effects (pronounced ovarian and testicular growth including an effect on spermatogenesis in immature rats, hypertrophy of the pigeon testis, etc.). Main and Leonard (1934) reported that an extract of urine from a man with teratoma testis produced, like prolan, a limited degree of ovarian hypertrophy; however, this hypertrophy, unlike that due to prolan, was chiefly the result of follicular growth. On the other hand, Twombly and Ferguson (1934) produced "antihormone" by the prolonged injection into rabbits of prolan or gonadotropic hormone from the urine of cases of teratoma testis. Assays in mice showed that the injection of the "anti-serum" of prolan prevented gonadotropic effects by either prolan or the

[35] Evans, Simpson, Austin, and Ferguson (1933), and Evans and Simpson (1934).

other gonadotropic hormone; similarly, the "anti-serum" of the gonadotropic hormone excreted in men with teratoma testis prevented the ovarian effects either of that hormone or of prolan. Others have reported that the effects of extracts of urine from patients with teratoma testis were indistinguishable from those of prolan in immature and hypophysectomized female rats.

Malignant tumors of the female genital tract other than chorionepithelioma.—Aschheim and Zondek reported in 1928 that the urine of about one-fifth of the cases of genital carcinoma contained prolan.[36] Zondek subsequently (1930) stated that urine from patients with benign or malignant tumors (particularly carcinoma of the cervix and malignant ovarian tumors) contained chiefly follicle-stimulating hormone ("prolan A"). The amount of the hormone found was of the order of 200 rat-units per liter of urine. It was without effect on the interstitial cells of the testis of immature male rodents but seemed to stimulate some of the initial stages of spermatogenesis (Borst and Gostimirović, Neumann and Péter, 1931; Gostimirović, 1932). Similar reports have been made by others (e.g., Brühl, 1932; Hamburger, 1933; Saphir, 1934), although in many but not all cases the functional condition of the ovaries was not carefully investigated. In cases complicated by hypofunction of the ovaries, the excretion of follicle-stimulating hormone might be the result of ovarian hypofunction (as after the menopause or ovariectomy) rather than the result of the growth of a neoplasm.

III. THE GONADOTROPIC HORMONES FOUND IN BLOOD AND URINE OF CASES OF DIMINISHED GONAD SECRETION OR ABSENCE OF THE GONADS

In 1929 Fluhmann reported that follicle maturation and ovulation could be produced in immature white mice by the

[36] Apparently Polano's case (1923) of myxosarcoma of the ovary belonged to this group.

injection of serum of spayed women (operative or after X-ray treatment) or of women with symptoms of ovarian hypofunction (irregular menstruation, functional amenorrhea). The hormone might appear in the blood as early as 8 days after bilateral ovariectomy, and could be recognized in patients who had undergone operation 13 years previously. Other investigators have obtained the hormone from the urine of women not only in cases similar to Fluhmann's, but also at or after the menopause and in cases of migraine. Like Zondek, they have considered it to be identical with the prolan "A" excreted in cases of cancer of the female genitalia (Zondek, 1930; Brühl, 1932; Hamburger, Österreicher, Saethre, 1933; and others). The amount excreted may be several hundred rat-units per liter urine. In old men an increased urinary excretion of a gonadotropic hormone is less frequent or less pronounced (Kukos, 1934). This is probably due to the fact that testicular secretion may continue to an advanced age; a sharply defined climacteric does not occur in men (Saethre, 1935).

Unquestionably its effects differ from those of prolan.[37] The hormone does not stimulate the interstitial cells of the immature mouse testis (Gostimirović, Neumann and Péter, 1931), but does, unlike prolan after similar administration, cause follicle growth and uterine hypertrophy in immature guinea pigs (Leonard, 1934).[38] The "mouse-unit" of the hormone is smaller than the "rat-unit," whereas the reverse is true of prolan (Hamburger, 1933; Leonard and Smith, 1934). In senile mice several irregular oestrous cycles may follow the administration of the hormone, but only one follows the similar administration of prolan (Bickel and Buschke, 1933). In immature rats and monkeys the gonadotropic

[37] But its effects on the anterior pituitary resemble those of prolan (Severinghaus, 1934).

[38] For observations on the combined effects of this hormone and prolan or anterior pituitary also see Anselmino and Hoffmann (1934), and Lipschütz (1935).

hormone of "castrate urine" causes marked stimulation of follicle growth without the cystic degeneration of the follicles frequently observed after anterior pituitary extracts (Smith and Engle, 1934). Leonard and Smith (1933, 1934) compared the effects of prolan, follicle-stimulating hormone (from urine of cases of menopause and migraine), and anterior pituitary implants. In normal immature rats, ovarian hypertrophy was greatly increased (potentiation effect) if follicle-stimulating hormone and prolan were given together. In hypophysectomized rats follicle-stimulating hormone brought about maturation of the follicles but neither ovulation nor luteinization unless anterior pituitary implants or prolan were also administered. Their results suggested that the hormone with which they worked might be the true follicle-stimulating hormone of the anterior pituitary. Smith and Engle (1934) reported that extracts of urine from spayed women stimulated spermatogenesis in hypophysectomized male rats much more effectively than prolan. On the other hand, the hormone caused no hypertrophy of the interstitial tissue so that the accessory organs underwent atrophy. Under appropriate conditions, however, prolan could stimulate both spermatogenesis and hyperplasia of the interstitial cells.

Katzman and Doisy (1934) determined the amount of gonadotropic hormone in the urine of normal male and female human beings of different ages, and compared their results with those obtained by other investigators.

IV. THE GONADOTROPIC HORMONE FOUND IN THE BLOOD AND TISSUES OF THE PREGNANT MARE

In 1930 Cole and Hart, as well as Zondek, reported that a prolan-like substance could be detected in the blood of the pregnant mare. Subsequent investigations have shown that this gonadotropic hormone (for purposes of discussion it will

be assumed that there is only one) produces effects different from those characteristic of prolan but resembling those of the anterior pituitary. Like the pregnant woman, the pregnant mare also excretes oestrin-like hormones, but in much larger quantities, particularly in the latter part of pregnancy.

The gonadotropic hormone peculiar to the blood and tissues of the pregnant mare appears not to be as readily excreted by the kidneys as prolan. Ordinarily, but not invariably, the concentration of prolan in the urine of pregnant women resembles that in the blood; the gonadotropic hormone of pregnant mares, however, is found in a much higher concentration in the blood than in the urine. Moreover, when it is injected into other animals for assay, a single dose in comparison with repeated doses is about as effective or even more effective (Cole, Guilbert, and Goss, 1932; Catchpole and Lyons, 1934). Cole and Hart pointed out that the hormone did not appear in the blood until about the time of nidation (about the thirty-seventh day). The maximum concentrations were found between the forty-third and eightieth days. "Oestrin," on the other hand, appeared in the blood later, and unlike the gonadotropic hormone persisted throughout the remainder of pregnancy.[39] The period between the fortieth and one hundred and fiftieth days, when gonadotropic hormone could be found in the blood, was also the only period in which new corpora lutea (presumably following ovulation) were formed in the ovaries of pregnant horses (Cole, Howell, and Hart, 1931). Catchpole and Lyons (1934) determined the presence or the approximate amounts of the hormone in blood, chorion, and endometrium at different stages of pregnancy (different fetal lengths). The endometrium of the fertile horn was found, at appropriate stages, to contain the most hormone (in fact it appeared to be richer in gonadotropic hormone than any other tissue so far investi-

[39] Also see Cole and Saunders (1935).

gated). Catchpole and Lyons favored the belief that the hormone is secreted by the chorionic epithelium.[40]

The effects of this gonadotropic hormone resemble those of the anterior pituitary rather than those of prolan.[41] Its administration to immature female rats produces, initially at least, a hypertrophy of the ovaries roughly proportional to the dose (see Fig. 42). It causes follicular growth and

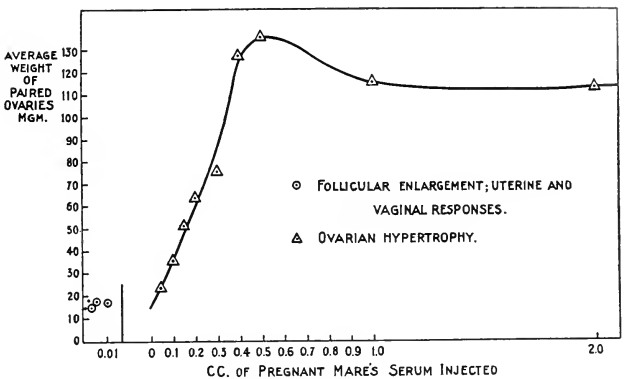


FIG. 42.—The relationship between the dose of pregnant mare's serum and ovarian weight in immature rats. Each point represents the average weight of the paired ovaries of four rats. Adapted from Figure 2 of Cole and Hart (1930).

maturation far exceeding that observed after the injection of prolan. Administered in small doses, it may cause ovulation; large doses, however, bring about luteinization without ovulation. In comparison with (prolan or) normal horse

[40] Evans, Meyer, and Simpson (1933) stated that the anterior pituitary of the pregnant mare contains much gonadotropic hormone even late in pregnancy, when none can be detected in the blood. Catchpole and Lyons, however, later showed that a marked reduction in the gonadotropic potency of the anterior lobe occurs in the latter part of pregnancy.

[41] Cole and Hart (1930); Cole, Guilbert, and Goss (1932); Evans and others (1933); Evans and Simpson, Hamburger (1934).

serum, its effects are not much increased if an anterior pituitary extract is also given (Cole and Hart, 1934). In immature male rats the hormone stimulates Leydig's cells, thus indirectly causing hypertrophy of the accessory sexual organs. The testis itself increases in size in part because of the growth of the tubules which contain an increased number of spermatocytes. Cole and others (1932, 1933) have caused ovulation in the anoestrous ewe and oestrus in the young sow by administering the gonadotropic hormone of the pregnant mare.

In contrast to prolan, but like anterior pituitary extract, the hormone stimulates the gonads of immature birds (Evans and Simpson, Hamburger, Martins, 1934). Particularly in the case of the testis of the immature pigeon, however, Evans and Simpson found that the stimulation-dose in terms of rat-units was considerably higher for pregnant-mare gonadotropic hormone than for anterior pituitary extract. Meyer and Gustus (1935) injected a gonadotropic extract of pregnant-mare serum into immature rhesus monkeys. There occurred marked stimulation of follicular growth without ovulation or luteinization. With the regression of the ovarian effects specific "antihormone" (not antagonizing prolan or gonadotropic extracts of sheep or human pituitary) was found in the monkeys' blood. Engle and Hamburger (1935) found that proliferation of the granulosa of the larger follicles was the characteristic effect of the hormone on the monkey's ovary. In the monkey, therefore, it produced an effect like that of the gonadotropic hormone excreted by spayed women.

The gonadotropic effects of the hormone have also been observed in hypophysectomized rats by Evans, Pencharz, Simpson, and Meyer (1933). In females the ovarian hypertrophy produced was greater than that following the administration of anterior pituitary extract and far greater than that following prolan. In males, apparently complete substitution

therapy could be attained by administering an extract of pregnant-mare serum. Spermatogenesis reappeared and the accessory organs grew to normal size. The testes of injected animals appeared normal histologically.

According to Evans and Simpson (1934), atrophy of the thymus of mature or immature rats followed the injection of an extract of placenta or endometrium of pregnant mares. This effect did not appear after spaying or castration. Evans, Simpson, and McQueen-Williams (1934) studied the effects of the hormone on the pituitary of young and mature rats. It produced changes like those of prolan (see pp. 214–15). However, the hypertrophy of the female pituitary was perhaps greater than that caused by prolan; in the authors' opinion this fact disposes of the theory that the hypertrophy is the result of the increased secretion of a "synergic factor" which potentiates the effects of prolan. The "synergic factor" does not potentiate the effects of the gonadotropic hormone of pregnant-mare's serum.

By determining the gonadotropic effect of serum (especially in the second to fourth months) or the effects of the "oestrin" in serum or urine, pregnancy in the mare can be diagnosed with a high degree of accuracy (Zondek, 1930; Ehrhardt and Ruhl, Glud and others, 1933; Greenwood and Blyth, Küst, Magnuson, Miller, 1934).

Methods of preparing the hormone from serum or tissues as well as some of the properties of the impure hormone are given by Goss and Cole (1931), Cole, Guilbert, and Goss (1932), Evans, Gustus, and Simpson; Evans, Meyer, and Simpson (1933), and Catchpole and Lyons (1934).

CHAPTER VI

THE EFFECTS OF HORMONES OF THE PITUITARY BODY ON THE SECRETION OF MILK[1]

THE first hint that a hormone of the pituitary body might affect the secretion of milk came from the experiments of Ott and Scott (1910). They found that an increased amount of milk could be withdrawn from the udder of the lactating goat immediately after the intravenous injection of an extract of the pars neuralis. Extracts of the pars neuralis, however, are probably not truly lactogenic; rather, they seem to cause an emptying of the milk-distended alveoli and ducts without furthering the secretion of milk. More important was the report of Stricker and Grueter (1928) that lactation could be produced in the pseudopregnant rabbit, before or after spaying, by the injection of an extract of the pars glandularis. Moreover, by means of similar treatment, they caused a resumption of lactation in a doe and a bitch, both of which had secreted no milk for 10 days or more. The work of Stricker and Grueter has been confirmed and extended by a number of investigators.

Lactation cannot occur in the hypophysectomized animal.[2] Beyond this statement, it is difficult to make generalizations either because various mammals differ in the mechanism of lactation or because our knowledge of the controlling factors is deficient. At least the later stages of the growth and differentiation of the breasts appear to depend upon the

[1] Also see p. 199, chap. v.

[2] Except in animals (e.g., rats) hypophysectomized during pregnancy. After parturition, lactation of only a few hours' duration sets in.

internal secretion(s) of the ovaries. Inasmuch as normal ovarian function requires the gonadotropic hormone(s) of the pars glandularis, the latter indirectly controls the development of the breasts. To what extent an internal secretion of the pars glandularis, in the absence of the ovaries, can bring about a development of the parenchyma of the breasts is a matter of controversy. The clear-cut direct effect of extracts of the pars glandularis—and with these, chiefly, this chapter deals—is on the fully developed alveolar cells prepared to secrete milk but unable to do so. Lactogenic extracts of the pars glandularis seem to release the secreting mechanism so that an abundant flow of milk follows the parenteral administration of the hormone. In the normal lactating animal, however, there appear to be more complex interrelationships involving the uterus, the ovary, and the lactogenic hormone[3] (and perhaps other hormones) of the pars glandularis.

An interesting homologous effect of the lactogenic hormone on the crop glands of the pigeon was discovered by Riddle and Braucher (1931). Normally, the crop glands (two circumscribed portions of the dorsal part of the crop mucosa, several square centimeters in area) undergo a marked development during the last few days of the brooding period. This occurs in both sexes. After hatching, the young are fed for a short time by a mixture of food, and secretion and cells of the crop mucosa—the "crop milk." In feeding the young, either parent may regurgitate this mixture. At times other than at the end of the brooding period (and also, of course, before sexual maturity) the crop glands remain undeveloped. Riddle and Braucher were able to show that marked development of the crop glands could be produced by injecting extracts of the pars glandularis into pigeons about 75 days after

[3] There is evidence that extracts of the pars glandularis may produce lactogenic effects unrelated to effects on growth, the gonads, and the thyroid. To designate the lactogenic hormone, the names "galactin" (Turner) and "prolactin" (Riddle) have been suggested.

hatching. Subsequent work, principally by Riddle and his collaborators, has also shown that this effect is probably due to the hormone causing lactation in mammals. At least there is evidence in favor of this view and none against it.

THE EFFECTS OF THE LACTOGENIC HORMONE IN BIRDS

The effects of the lactogenic hormone on the crop glands of the pigeon.—Extracts of the pars glandularis appear to stimulate the growth of the crop glands independently of their effects, if any, on growth, on the gonads, and on the thyroid. Similar extracts of other tissues have no effect on the crop glands (Riddle, Bates, and Dykshorn, 1933). The hormone which stimulates the development of the crop glands appears to be identical with that causing lactation in suitable mammals (De Fremery, Spanhoff, and Tausk, 1933; Riddle and others, 1933; Anselmino and Hoffmann, 1934).

Riddle and Braucher (1931) found that a macroscopic growth of the crop glands could be observed about 3 days after the injection of an anterior-lobe extract. One or 2 days later, typical "crop milk" was present. The same effects were produced on the denervated crop gland. Riddle and his colleagues stated that they produced crop-gland growth by injecting the hormone into a hypophysectomized pigeon. The crop glands of mature birds can be stimulated by $\frac{1}{4}$–$\frac{1}{3}$ the dose of lactogenic hormone required for immature birds.

Provided that the pure lactogenic hormone—when or if it is isolated—produces, like extracts, lactation in mammals paralleling the growth of the crop glands, it appears that the latter effect is the more suitable basis for assay. In the first place, assay in the pigeon requires the exercise of only a few simple precautions, whereas in the mammal, assay can be performed only after the animal has been suitably prepared. Second, no attention need be given to the sex of the pigeon; to use the male mammal, however, preparation for assay

may be more complex than in the female mammal. Third, assay results in the pigeon can be expressed quantitatively (weight of the crop glands), whereas, in the mammal, the quantitative statement of the results of an assay is difficult both because the results are more variable (the mechanism of action is more complex) and because the measurement of the results (e.g., the amount of milk secreted) is not feasible except in large animals. If hypophysectomy has not been performed, the pituitary of the mammal (probably more than that of the pigeon) may also affect lactation. It is therefore not surprising that the only satisfactory attempts to assay the lactogenic hormone quantitatively have been made in pigeons. A study of some of the factors affecting quantitative assay in the pigeon will be found in the paper of Riddle, Bates, and Dykshorn (1933).

The effects of the lactogenic hormone on the gonads of birds.[4]—The administration of the lactogenic hormone to the mature male pigeon is followed by a rapid diminution in the size of the testes. No such effect, however, is produced in the mature male mammal (rat). In the mature female fowl (hen), the parenchyma of the ovary, active or resting, is reduced as a result of the injection of a lactogenic extract. Secondary effects indicating a diminished ovarian secretion are also observed (reduced size of oviduct and comb, diminished space between pubic bones). These changes in the hen may be associated with the appearance of broodiness (see chap. iv).

THE EFFECTS OF HYPOPHYSECTOMY ON LACTATION[5]

Lactation cannot continue in the absence of the hypophysis. If the lactating mouse, rat, or ferret is hypophysectomized, the secretion of milk ceases within approximately 24 hours. If the pituitary is removed from the pregnant mouse, rat, or guinea pig, lactation of a few hours' duration

[4] Riddle and others (1933–35); Bates and others (1933, 1935).

[5] Also see chap. ii.

may occur after parturition. Less frequently this may also be observed in the ferret. In the pregnant rat, but not in the pregnant ferret, growth of the mammary glands continues after hypophysectomy.[6] In the sections following this, it will be pointed out that lactation may follow procedures such as the removal of luteinized ovaries from rats, cesarean section in rats, etc. In several instances it has been shown that hypophysectomy prevents the lactation ordinarily appearing under such conditions.

By the injection of extracts of the pars glandularis, lactation has been produced in the hypophysectomized rat, dog, and ferret (Riddle and others, 1933; Lyons and others, 1933; McPhail, 1935).

THE EFFECTS OF THE LACTOGENIC HORMONE IN MAMMALS

The conditions suitable, in various mammals, for inducing lactation either by the secretion of the lactogenic hormone or by the injection of anterior-lobe extracts: 1. *The gonads and their internal secretions.*—In their studies of the production of lactation by the injection of an anterior-lobe extract into rabbits, Stricker and Grueter concluded that no effect could be produced in the adult female rabbit unless its ovaries had at some time secreted corpus luteum hormone. In their first experiments, pseudopregnant rabbits were used. Later they produced lactation in spayed rabbits even months after ovariectomy, but declared that this was possible only in case such rabbits had previously been either pregnant or pseudopregnant. From their results it would appear that the development of the breasts, great enough so that an anterior-lobe extract could stimulate the secretion of milk, depended partly upon the secretion of progesterone (corpus luteum hormone). However, Corner (1930) was able to produce

[6] Collip, Selye, and Thomson (1933); Selye, Collip, and Thomson (1933-34); Jeffers (1935); and McPhail (1935).

growth of the mammary glands and lactation, comparable to that following normal pregnancy, by injecting an extract of the whole pituitary body of the sheep into adult, virgin, spayed rabbits. Inasmuch as the rabbit does not ordinarily ovulate except after copulation, it was reasonable for Corner to conclude that the lactogenic hormone can cause the secretion of milk in the absence of any previous conditioning of the mammary gland by corpus luteum hormone. Similar results in the rabbit were obtained by Lyons and Catchpole (1933).

Instead of favoring the action of the lactogenic hormone, once growth of the breasts has occurred, the ovary and its internal secretions seem rather to antagonize it. Lyons and Catchpole (1933) reported that merely the removal of the ovaries from the adult, virgin rabbit may be followed by lactation for as long as a month (apparently maintained by the lactogenic hormone of the animal's own pituitary). Nelson (1935) transplanted the ovary into the male guinea pig; if the ovarian graft was removed, lactation set in and was often pronounced. He also found that ovariectomy alone might be followed by lactation in the guinea pig. According to Selye and his colleagues (1933), lactation promptly appears in the mature or immature rat after the removal of the ovaries if pronounced luteinization has been produced in the latter by injections of prolan.[7] Likewise, the removal of the ovaries of the pregnant rat is followed by lactation within 24 hours (Collip, Selye, and Thomson, 1933). From studies in the mouse, Bradbury (1932) concluded that ovariectomy (and/or hysterectomy) was followed by lactation provided that an anterior-lobe extract had been administered to cause a development of the alveoli of the mammary gland. The anterior-lobe extract caused considerable luteinization of the ovaries.

[7] Lactation does not appear if the pituitary has been removed before ovariectomy.

The experiments discussed in the preceding paragraph suggest that either corpus luteum hormone or oestrin may antagonize the lactogenic effect of anterior-pituitary secretion. Several investigators have reported that the injection of "oestrin" or oestrone inhibits lactation (mouse, rat, and guinea pig).[8] How this effect is produced is not clear; it seems likely that oestrin interferes both with the secretion of the lactogenic hormone and with the effect of this hormone on the mammary gland.[9] If, after the repeated administration of oestrone to guinea pigs or rats, the dose is reduced or no more oestrone is given, lactation is frequently observed within a few days (De Jongh and Laqueur, 1930; De Jongh, 1934). De Jongh concluded that hysterectomy after the period of oestrone-treatment facilitated the appearance of lactation in rats at least.

What ovarian secretion (or secretions) prepares the mammary gland so that the lactogenic hormone can act? In the rabbit it appears that only the development due to "oestrin" secretion is necessary. Evidence supplementing the observations of Corner and others was furnished by Frazier and Mu (1935), who observed, in male rabbits, lactation which appeared after injections of oestrin[10] had been given about 3 months. Injections of oestrin were then continued; lactation was present for 90–200 days. (Such findings are clearly not similar to those of others in mice, rats, and guinea pigs in which oestrin has been observed to interfere with lactation.)[11] In the guinea pig, also, the mammary gland will secrete milk in response to the lactogenic hormone provided that the

[8] De Jongh (1933); Nelson (1934–35); and others.

[9] Nelson (1935) reported that the administration of a sufficiently large dose of oestrone prevented lactation which otherwise followed the administration of an anterior-lobe extract. Also see the discussion, below, of the experiments of Frazier and Mu.

[10] A butyl-alcohol extract of pregnancy-urine.

[11] Kunde, D'Amour, Carlson, and Gustavson (1930) injected oestrin repeatedly into dogs. In one female dog lactation appeared and persisted (with suckling) throughout the period of injection.

growth of the breasts has been stimulated solely by the administration of oestrone (experiments in males by Nelson, 1935). Lactation occurs in the male rat several days after a long course of oestrin treatment has been discontinued (Halpern and D'Amour, 1934).

It therefore appears that the development of the breasts due to "oestrin" alone is preparation sufficient to permit the lactogenic hormone to cause lactation in three different animals: the rabbit, the guinea pig, and the rat. According to Bradbury (1932), this is not the case in the mouse. Oestrone and oestriol ("Theelin" and "Theelol") caused development only of the galactophores. The development of the secondary ducts and the alveoli seemed to require the secretion of the corpus luteum hormone as well as (a secretion of?) the uterus. If hysterectomy was performed before luteinization of the ovaries was produced (anterior-lobe extract or prolan), the secondary ducts did not develop. However, an extract of the sheep pituitary (but not prolan) caused a development of the alveoli even after ovariectomy and hysterectomy, provided that some growth of the secondary ducts was already present.

2. *The uterus.*—A puzzling but perhaps important factor in the physiology of the lactogenic hormone is the uterus.[12] Bradbury (1932) reported that lactation followed hysterectomy in the mouse after anterior-lobe extract had been injected to bring about a development of the mammary-gland alveoli. In pregnant mice (eleventh day of gestation), hysterectomy was followed by lactation. De Jongh (1934) administered 50 rat-units of oestrone daily to female rats. After 2 weeks the treatment was stopped; lactation then usually appeared if the uterus was removed also. According to Selye, Collip, and Thomson (1934), cesarean section late in pregnancy (rat) is followed by lactation; lactation is prevented,

[12] Usually the authors do not indicate whether or not experimental hysterectomy may have interfered with the ovarian circulation.

however, by distending the emptied uterus with an inert substance like paraffin. The observations of Nelson (1933–35) were made in guinea pigs. He found that the removal of the ovaries of a pregnant guinea pig was not followed by lactation unless the uterus was also removed or until abortion or parturition had occurred. The removal of the pregnant uterus of the guinea pig was not followed by lactation (unlike the mouse). Cesarean section—of the fetuses only—was not followed by lactation until after the later expulsion of the placentae. Nelson also found that a purified galactogenic extract of the anterior lobe did not cause lactation in the pregnant guinea pig. The foregoing experiments in pregnant and non-pregnant mice and rats suggest that the uterus may influence (inhibit) the secretion of the lactogenic hormone of the pars glandularis, although an effect on the breasts cannot be excluded. In the pregnant guinea pig, the ovaries and the uterus may both be interrelated in exerting such an inhibitory control.

3. *Suckling as a factor.*—Selye, Collip, and Thomson (1934) concluded that the act of suckling influences the secretion of the lactogenic hormone. In lactating rats, they tied all the main galactophores of the breasts on one side, and excised the nipples on the other. Suckling at the breasts from which no milk could escape maintained lactation in all the breasts beyond the time when lactation ceases in normal rats due to weaning. Suckling may initiate lactation in the pseudopregnant rat.[13]

4. *Observations in parabiotic animals.*[14]—In the experiment ♀ ♀p, the hypertrophy of the breasts of the normal female rat may be nearly as great as that of pregnancy.[15] Such a de-

[13] Also see Selye and McKeown (1934); and Jeffers (1935).

[14] ♀ or ♀̸ indicates a normal or a spayed female; ♀p, indicates a pregnant female; ♂ or ♂̸, indicates a normal or a castrated male. ♀ ♀p, indicates parabiosis between a normal female and a pregnant female, and so on. Also see chap. iv.

[15] The oestrous cycles of the normal female may be almost completely suppressed.

velopment of the breasts is not observed in the spayed female of the experiment ♀ ♀ p (Ernst, 1927; Zacherl, 1928; and Hill, 1932). Zacherl cites the cases of the pygopagous sisters, Blaček, one of whom became pregnant; after parturition, lactation also occurred in the non-pregnant twin.

Kallas (1929) produced parabiosis between rats weighing 50–100 g. according to the schemata ♂ ♀ and ♂ ♂. He then transplanted ovarian tissue into the normal male in which the breasts subsequently developed, forming alveoli but not lactating. In three pairs of rats, living in parabiosis according to the plan ♂ ♀ p, Hill (1932) found that there was little development of the breasts in the female and no lactation after parturition.

Other experiments in which lactation has been produced by the injection of anterior-lobe extracts into mammals.[16]—The extent to which anterior-lobe extracts can cause development of the breasts is still a debated question. It appears that growth of the breasts, roughly comparable to that of puberty, must have occurred before an anterior pituitary extract will cause either further growth or lactation. In the rabbit and mouse, an anterior-lobe extract may cause a further development of the breasts after ovariectomy.[17] In the female rat, breast development seems to depend almost entirely upon the internal secretions of the ovary; the breasts rapidly undergo involution in ovariectomized pregnant rats despite the administration of homo-implants or anterior-lobe extract (Evans and Simpson, 1931).

The injection of extracts of the pars glandularis has produced or altered lactation in the following animals: guinea pig (6, 17, 18); rabbit (1, 2, 3, 7, 14, 15); dog (1, 2, 12, 16);

[16] Riddle, Lahr, and Bates (1935) concluded that the lactogenic hormone may cause maternal behavior in rats (virgin rats 67–81 days old which had first received injections of prolan or anterior-pituitary gonadotropic hormone).

[17] Corner (1930), Bradbury (1932); and Lyons and Catchpole (1933).

pig (2); goat (4, 8, 9, 11); cow (4, 10); monkey (5, 13).[18] Not much is to be gained from a detailed discussion of the various experiments. The conditions under which an anterior pituitary extract will cause lactation in the mouse, rat, and monkey particularly require further study (see Turner and Schultze, 1931; and Gardner and Turner, 1933). The milk secreted in response to the lactogenic hormone contains more ash which, however, is less alkaline (goat, 9), or more ash and less fat and solids (cow, 4), or normal fat, more chloride, less lactose with a normal pH and coagulation-time (cow, 10).

THE ASSAY OF THE LACTOGENIC HORMONE OF THE PARS GLANDULARIS

The assay of the lactogenic hormone by determining its effect on the crop glands of the pigeon was discussed earlier in this chapter. Provided that the development of the crop glands is stimulated by the same hormone causing lactation in mammals—and this so far seems to be true—this method of assay appears to be best. For discussions of the best method of assaying the lactogenic hormone in mammals (a matter of controversy), the reader is referred to the papers of Gardner and Turner (1933), Lyons and Catchpole (1933), and Nelson (1934).

THE PREPARATION AND PROPERTIES OF LACTOGENIC EXTRACTS OF THE PARS GLANDULARIS

In the paper of Riddle, Bates, and Dykshorn (1933) will be found the evidence from which they concluded that the lactogenic hormone is different from the gonad-stimulating

[18] The numbers in parentheses refer to the following authors: (1) Stricker and Grueter (1928–29); (2) Grüter and Stricker (1929); (3) Corner (1930); (4) Grüter (1931); (5) Hisaw and others (1931); (6) Nelson and Pfiffner (1931); (7) Turner and Gardner (1931); (8) Asdell (1932); (9) von Fellenberg and Grüter (1932); (10) Catchpole and others (1933); (11) Evans (1933); (12) Gaebler (1933); (13) Hartman, quoted by Riddle and others (1933); (14) Gardner and Turner (1933); (15) Lyons and Catchpole (1933); (16) Lyons and others (1933); (17) Nelson and Smelser (1933); and (18) Nelson (1935).

and growth-promoting hormones of the pars glandularis and from prolan. They concluded that the lactogenic hormone could be found only in the pars glandularis of the pituitary. Methods of preparing lactogenic extracts have been described by Gardner and Turner (1933), Lyons and Catchpole (1933), and by Riddle and his colleagues (1933).

According to Gardner and Turner (1933) and Anselmino and Hoffmann (1934), the lactogenic hormone is heat-labile, being readily inactivated in solution at temperatures of 60°–70° C. within 5–15 minutes. On the other hand, Riddle and others (1933) reported that the potency of a lactogenic extract in aqueous solution at pH 7.5–8.5 was only slightly reduced after the solution had been boiled for 1 hour. At other hydrogen-ion concentrations, higher or lower, partial or complete destruction was caused by this treatment. Bates, Riddle, and Lahr (1934) found that tryptic digestion destroyed the lactogenic properties of an extract.

THE PARS NEURALIS AND LACTATION

Nothing significant has been added to our knowledge of the relationship between the hormone(s) of the pars neuralis and the secretion of milk.[19] Probably extracts of the pars neuralis do not affect the activity of the secretory cells but simply cause the contraction of smooth muscle, or of cells resembling those of smooth muscle, so that nearly all the milk already secreted can be removed from the alveoli, secondary ducts, and galactophores.[20] There is no evidence that the hormones of the pars neuralis are of any physiological importance in lactation.

[19] See Geiling (1926); Sharpey-Schafer (1926); and Trendelenburg (1929) for reviews of the literature.

[20] For recent experiments in the milch cow and in lactating women, see Turner and Slaughter (1930), and Kulka (1933).

CHAPTER VII

THE INTERRELATIONSHIP BETWEEN THE PITUITARY AND THE THYROID

SINCE 1888, when Rogowitsch (or Rogowitch) reported that thyroidectomy in the rabbit was followed by definite changes in the anterior-lobe cells and possibly by hypertrophy of the pars glandularis (1889), the functional relationship between the thyroid and the pituitary has been intermittently investigated. Up to a decade ago the most convincing experiments had been performed in cold-blooded animals. Among the earliest of such experiments were those reported by Adler in 1914. Only more recently has the unquestionable importance of the anterior pituitary as a regulator of thyroid activity been demonstrated in birds and mammals.

The thyroid-pituitary interrelationship in amphibia.—The discovery of Gudernatsch (1912) that the metamorphosis of the tadpole could be markedly accelerated by the administration of thyroid gland provided a new method for the study not only of metamorphosis but also of the physiology of the thyroid. Two years later Adler was able to prevent metamorphosis and to cause thyroid atrophy by destroying the hypophysis in tadpoles. All subsequent experiments with the larvae of urodele and anuran amphibia[1] (salamander, newt,

[1] Black (1934) found that, as a result of the injection of a pituitary extract with thyrotropic effects, the oxygen consumption, carbon dioxide production, and nitrogen excretion were all increased in catfish. He concluded that these effects were due to a substance secreted or excreted into the water inasmuch as (1) the effects were not observed in fish kept in flowing water, and (2) the effects were also observed in non-injected fish placed in water in which injected fish had been kept.

Snakes (*Thamnophis sistalis*, *T. radix*) shed repeatedly after hypophysectomy. This effect is prevented by feeding thyroid (Schaefer, 1933). Either hypophysectomy or thyroidectomy lengthens the molting cycle in another reptile, *Hemidactylus brookii* (Noble and Bradley, 1933). However, the cycle can be shortened to normal by thyroid treatment.

frog, and toad) have confirmed Adler's work and justify the conclusion that normal metamorphosis depends as much upon the anterior pituitary as upon the thyroid. The peren-

FIG. 43.—The effect of the destruction of the pars glandularis on the metamorphosis of the tadpole. Operated animals above, control animals below. From Adler, *Arch. Entw.-mech. Organ.*, XXXIX (1914), 21–45.

nibranchiate mud puppy (*Necturus* and *Proteus*) does not "metamorphose" even after thyroid treatment (Jensen, 1916; Spaul, 1925; Allen, 1929).

Adler (1914) attempted to destroy the anterior pituitary of

rather large (22–23 mm.) larvae of *Rana temporaria* by means of a galvanocautery. Among 1,200 operated animals, 10 of of the survivors failed to undergo metamorphosis. Three of the operated tadpoles in which subsequently no anterior-lobe cells could be demonstrated histologically, and 3 control tadpoles, are shown in Figure 43. The striking associated atrophy of an operated tadpole's thyroid in comparison with that of a control tadpole is illustrated by the photomicrographs of Figure 44. Adler also mentions an atrophy of the

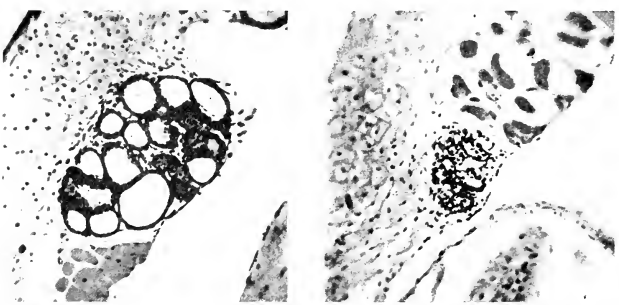


FIG. 44.—Photomicrographs of the thyroid glands of a normal control tadpole (left) and a hypophysectomized tadpole (right). From Adler, *Arch. Entw.-mech. Organ.*, XXXIX (1914), 21–45.

gonads of the operated animals. Two years later Smith and Allen independently performed successful excision of the anlage of the anterior pituitary in tadpoles about 4 mm. long, and thus avoided serious injury of the mouth and brain so common in Adler's series. All investigators agree that hypophysectomy in the tadpole prevents metamorphosis because of the subsequent atrophy of the thyroid (Smith, 1916, 1920; Allen, 1917–18, 1922, 1924–25; Smith and Smith, 1922; and Magdalena, 1933). Smith and Smith found that the size of the thyroid gland of the hypophysectomized tadpole was only 7–20 per cent of the normal. They also found clear-cut mi-

croscopic evidence of hypofunction. Smith's monograph (1920) gives a detailed account of all the anatomical changes resulting from hypophysectomy in the tadpole. In Figure 45 the albinism and persistence of the larval form in the hypophysectomized as compared with the normal tadpole are illustrated.

Similar findings in urodele amphibia were reported by Schotté in 1926 (*Triturus cristatus*, *T. alpestris*, and *Salaman-*

FIG. 45.—Albinism and lack of metamorphosis as a result of hypophysectomy. Control animal above; operated animal below. From Smith (1920).

dra maculosa) who could prevent metamorphosis if he performed hypophysectomy sufficiently early. Adams and her co-workers (1930, 1933) showed that hypophysectomy in *T. viridescens* and *T. cristatus* prevented molting and that this effect was the result of an inactivity of the thyroid. Extracts of the mammalian pituitary stimulate the thyroid and cause molting (which is excessive in normal animals) in either the normal or the hypophysectomized salamander, *T. viridescens* (Adams, 1934). Implants of the fowl pituitary also cause histological signs of stimulation of the thyroid (Stein, 1934). For a discussion of numerous observations on the ef-

fects of implantation or removal of the pituitary or its parts in larvae of *T. taeniatus*, *carnifex*, and *alpestris*, the reader is referred to the articles of Klatt (1931, 1933). Successful transplantation of the adult pituitary into larvae of *Amblystoma tigrinum* (age about that of sexual differentiation) is followed by a marked stimulation of the testis but not by an effect on metamorphosis (Burns, 1934). Uhlenhuth and others (1934) produced precocious metamorphosis in larvae of this same salamander by repeatedly injecting anterior pituitary extract; they believed that metamorphosis occurred earlier if either pilocarpine or epinephrin was also administered. By itself, neither drug had any effect.

Magdalena (1935) found that hypophysectomy prevented compensatory hypertrophy of the thyroid in the toad (species?). Larson (1918), Rogers (1918), and Hoskins and Hoskins (1920) all reported that hyperplasia of the anterior lobe appeared after thyroidectomy in frogs, toads, and tadpoles.

During normal metamorphosis the pituitary is richer in "thyrotropic" hormone, as shown by the experiments of Allen (1932) who could produce metamorphosis by homotransplants of the pituitaries of metamorphosing tadpoles (*Bufo halophilus*) but not by transplants taken from nonmetamorphosing larvae. The weight of the experimental evidence overwhelmingly favors the view that functioning thyroid tissue must be present if extracts or implants of the anterior pituitary are to produce metamorphosis. Hoskins and Hoskins (1920) and Hogben (1923), who used a commercial anterior pituitary preparation which apparently contained thyroid gland (Smith and Cheney, 1921), alone reported that thyroidectomy did not prevent metamorphosis following the administration of anterior pituitary. All investigators except Hoskins and Hoskins have found that the feeding of anterior pituitary is ineffective and that the parenteral administration of tissue or extracts is necessary. Many investigators have produced metamorphosis in normal or hypophysectomized

amphibian larvae by administering implants or extracts of anterior pituitary (Allen, 1920; Smith and Smith, 1922, 1923; Swingle, 1922; Spaul, 1924; Uhlenhuth and Schwartzbach, 1928; Magdalena, 1933; and Schreiber, 1933). Spaul (1928) was of the opinion that metamorphosis induced by anterior pituitary differed in some respects from that induced by thyroid treatment. Witschi (1931), using *T. torosus*, produced parabiosis between normal and hypophysectomized larvae. Delayed metamorphosis occurred in both individuals; but the hypophysectomized members always remained a lighter color. According to Smith and Smith (1922) and Smith (1926) the response of the Colorado axolotl is exceptional (among axolotls) in that anterior-lobe extract antagonizes metamorphosis occurring normally or induced by small doses of thyroid extract.

The metabolism of the axolotl, measured by oxygen consumption, is increased following the injection of anterior-lobe extract (Schwartzbach and Uhlenhuth, 1929). This effect is prevented by thyroidectomy and can therefore be attributed to thyroid stimulation. Winton and Hogben (1923) found that hypophysectomy or removal of only the anterior lobe lowered the rate of carbon-dioxide production of adult frogs. Hypophysectomy or removal of the anterior lobe likewise markedly reduced the oxygen consumption of *Xenopus laevis* (Charles, 1931).

The thyroid-stimulating hormone appears to be specifically elaborated in the anterior pituitary. The injection of extracts or suspensions of muscle, pars intermedia, or pars neuralis caused neither metamorphosis nor thyroid stimulation in the tadpole (Smith and Smith, 1922; and Spaul, 1925). Smith and Smith (1923) found that the central part of the beef anterior pituitary, often distinguishable grossly as a darker area and composed chiefly of basophil and reserve cells, was more effective in causing thyroid stimulation (and metamorphosis) than the outer lighter portion made up of

oxyphil and reserve cells. Their results therefore suggested that the thyrotropic hormone is secreted by the basophil cells.[2] Allen (1932) later studied the anterior pituitary of tadpoles before and during metamorphosis. During metamorphosis the basophil cells were more numerous and stained more deeply than before metamorphosis. By a different type of evidence Allen also supported the view that the basophil cells secrete the thyroid-stimulating principle.

Coincident with metamorphosis induced by anterior pituitary there occur histologic changes in the thyroid indicating increased activity characteristic of normal metamorphosis. The colloid tends to disappear or stain poorly and the acinous cells appear cuboidal or columnar rather than flat; hyperplasia and cytologic changes have also been described (Uhlenhuth and Schwartzbach, 1927, 1928; Ingram, 1929; Grant, 1931; and Clements, 1932).

The suggestion that lack of pituitary development is responsible for neoteny (appearance of sexual maturity during the larval stage) in some amphibia was made by Goldschmidt in 1912 (see Adler, 1914). Ingram (1929) was of the opinion that neoteny is the result of a hyposecretion of the thyrotropic hormone. The existence of neotenic species suggests that stimulation of the thyroid by the pituitary is due to a principle differing from that stimulating the gonads.

In most of the work on thyroid stimulation in amphibia, suspensions or crude extracts of the anterior pituitary have been administered. Apparently the principle withstands boiling in dilute aqueous solutions of acid (Spaul, 1930; and Crew and Wiesner, 1930) or alkali (Krichesky, 1934). The usefulness of dilute acetic acid solutions as extracting media was discussed by Spaul. Metamorphosis induced by iodine or iodine-containing compounds will not be discussed inasmuch as this type of metamorphosis is said to occur after thyroidec-

[2] Also see the report of Spaul and Howes (1930) who concluded that the thyrotropic (metamorphic) hormone is elaborated by the oxyphils.

tomy or after both thyroidectomy and hypophysectomy (Hoskins and Hoskins, 1920; and Allen, 1920, 1929).[3]

The thyroid-pituitary interrelationship in birds.—The observations which have so far been made in birds (duck: Schockaert, 1931, 1932; pigeon: Larionov and co-workers, 1931, Riddle, Bates, and Dykshorn, 1933, Thurston, 1933; fowl: Domm and van Dyke, Noether, 1932, Domm, and Foster, Gutman, and Gutman, 1933) indicate that the administration of implants or the injection of crude suspensions or extracts of the anterior pituitary cause hypertrophy and signs of hypersecretion of the thyroid similar to that produced in the mammal.

Although Schockaert (1930) at first denied that the effects on the duck-thyroid and thymus were specific, his later experiments led to the opposite conclusion. After ducks had been treated several weeks, exophthalmos and emaciation often appeared. At necropsy the heart was found to be enlarged. The lobes of the thyroid were hypertrophied and weighed three to eight times as much as those of control ducks. The anatomical changes in the thyroid were those usually considered as accompanying an increased rate of thyroid secretion (enlargement and proliferation of acinous cells, disappearance of colloid, etc.). The retrogression of the thymus in the immature duck was caused only by the administration of anterior pituitary. Schockaert and Foster (1932) particularly studied the iodine content of the duck's thyroid after the administration of anterior pituitary. They concluded that 1 week's treatment reduced the total iodine to its lowest level, but that with further treatment the concentration of iodine diminished because the thyroid continued to undergo hypertrophy.

Noether (1932) observed that the administration of an extract of the anterior lobe to hens caused a proliferation of the cells of the thyroid as well as a loss of colloid. The presum-

[3] Also see Uhlenhuth (1923).

ably purified thyrotropic hormone, which he used in large doses, interrupted ovulation for as long as a month. All investigators agree that the gonad-stimulating principle of pregnancy-urine has no effect on the bird's thyroid (Schockaert and Noether). This finding is similar to that in the mammal. Ohnishi (1931) reported that anterior-lobe extract caused an accumulation of colloid in the thyroid when administered to chick embryos; but this observation, if confirmed, must be considered exceptional.

The thyroid-pituitary interrelationship in mammals.—The recognition of the fact that in mammals, as in amphibia and birds, the thyroid is controlled by a thyroid-stimulating (thyrotropic) hormone secreted by the anterior lobe of the pituitary is of great importance for the understanding of both normal and pathological secretion by the thyroid. Graves's disease and other disorders of thyroid secretion must be reconsidered from this new position.[4] The experimental data reviewed below demonstrate that an internal secretion of the anterior lobe is essential for the normal functioning of the thyroid and that the administration of this anterior-lobe secretion (as crude gland or extract) causes a marked increase in the rate of thyroid secretion so that the condition of an injected animal may, for a time at least, resemble Graves's disease. Among the mammals from which experimental data have been obtained are man, the dog, cat, sheep, guinea pig, rabbit, rat, and mouse.

The effects of thyroidectomy.—Rogowitsch (1888, 1889) was the first to observe the effects of thyroidectomy on the pituitary of the dog and rabbit. He believed that he had obtained histologic evidence of the vicarious formation of the thyroid hormone (colloid) in the anterior pituitary, especially of the rabbit, and explained the longer survival of the thyroidectomized rabbit by the fact that the pituitary is relatively larger in the rabbit than in the dog. In reality his dogs were

[4] For one interpretation, see Drouet (1934).

thyroparathyroidectomized and probably died as a result of parathyroid deficiency. All the evidence in favor of the view that the anterior pituitary vicariously secretes a thyroid-like hormone after thyroidectomy or in the presence of a thyroid deficiency is anatomical and lacks the support of physiological or biochemical evidence. Although Wells (1897), for example, could detect about 0.004 per cent iodine in dried human pituitary, Simpson and Hunter (1910, 1911) found only traces of iodine in beef and sheep pituitary bodies. Sheep pituitary bodies, removed 5–6 months after thyroidectomy, contained no iodine even after iodides had been fed.[5]

Anatomical studies of the pituitary after thyroidectomy have also been made by Stieda (1890), Hofmeister (1894), Leonhardt (1897), Katzenstein (1899), Herring (1908), Tatum (1913), Livingston (1914), Kojima (1917), Izumi (1922), Hammett (1923, 1926), Dott (1923), Satwornitzkaja (1926), Poos (1927), Bryant (1930), and Pugliese (1931). Usually hypertrophy of the anterior pituitary follows thyroidectomy and is often more marked in the male than in the female. The longer the period of thyroid deficiency, the greater is the hypertrophy. Histologically the important changes (in the anterior pituitary) consist of a marked reduction in the number of oxyphil cells and a hypertrophy of the reserve cells in which there appear to be signs of degeneration (vacuolization, karyolysis, etc.).[6] Apparently the anatomical findings can be interpreted better as indicating degenerative changes in the anterior pituitary than as suggesting increased secretory activity. In man and the dog similar changes have been described in cretins or goitrous individuals. Berblinger (1921), for example, considered that an increase in the num-

[5] Also see the reports of Seaman (1920); Frey (1934); Koppenhöfer (1934); and Sturm (1934).

[6] Severinghaus, Smelser, and Clark (1934) stated that in the thyroidectomized male rat the basophils resembled those following castration. Herring believed that at least the early changes were limited to the pars intermedia and the pars neuralis.

ber of reserve cells was pathognomonic of hypothyroidism in man. For a recent study of the pituitary of goitrous individuals, see the report of Scalabrino (1934).

In the rat, guinea pig, and dog, thyroidectomy is followed by no alteration in the amount of thyrotropic hormone in the pituitary (Houssay, Novelli, and Sammartino, 1932; Kuschinsky, 1933; and Hohlweg and Junkmann, 1933).[7] In the rabbit, Chen and van Dyke (1934) did not find a striking change after thyroidectomy. These findings are contrary to what one might anticipate from the fact that gonadectomy gives rise to an increase in the amount of gonad-stimulating principle in the pituitary. The amount of gonad-stimulating principle in the rat pituitary was considered by Smith and Engle (1930) to be unaltered by thyroidectomy; on the other hand, Evans and Simpson (1930) concluded that thyroidectomy reduced the amount of gonad-stimulating hormone. Both sets of experiments were performed in female rats and do not aid in the interpretation of Schockaert's (1931) statement that thyroidectomy improves the response of male rats to gonad-stimulating extracts.[8] Van Dyke and Chen (1933, 1935) found that thyroidectomy in the rabbit reduced the concentration of the ovulation-producing hormone in the pituitary; despite the pituitary hypertrophy, the total amount of the hormone causing ovulation also appeared to be reduced. The data so far gathered indicate that thyroidectomy has no important effect on the total amounts of either thyrotropic or gonadotropic hormones in the anterior pituitary. The amount of growth-promoting hormone in the pitui-

[7] However, the pituitary of the young ovariectomized guinea pig is said to contain more thyrotropic hormone than that of the normal young female (Loeser, 1934). The thyroid of the ovariectomized guinea pig appears, histologically, to be secreting more actively. In respect to this change, Benazzi (1933) came to exactly the opposite conclusion from his study of the thyroids of normal and ovariectomized mice.

[8] Thyroidectomy does not alter the response of the ovary to gonad-stimulating extracts (Bourg, 1930; and Loeser, 1932).

tary of the thyroidectomized animal has not been determined.

According to Kuschinsky (1933) and Hohlweg and Junkmann (1933), treatment of the rat with thyroxin reduces the amount of thyroid-stimulating hormone in the pituitary.[9] Livingston (1914) prevented pituitary hypertrophy in thyroidectomized male rabbits by administering thyroid gland. These findings are in harmony with the view that thyroxin lessens the formation of thyroid-stimulating hormone. The absence of the thyroid, however, does not facilitate the formation of an increased amount of thyroid-stimulating hormone.

The effects of hypophysectomy.—Following hypophysectomy or the removal of the pars glandularis the thyroid becomes inactive and even atrophic (Aschner, 1912; Ascoli and Legnani, 1912; Houssay, 1916; Dott, 1923; Smith, 1926, 1930; Koster, 1929; Houssay, Biasotti, and Mazzocco, 1931; and McPhail, 1935). Histologically this is indicated by the flattened appearance of the epithelium and the persistence of deeply stained colloid. The diameter of the alveoli may be increased or diminished. Grossly the thyroid of the hypophysectomized animal is much smaller and appears less vascular than that of the control animal. These changes are illustrated in Figure 46, showing the gross appearance of the thyroids of the littermate normal and hypophysectomized rats of Figure 11. Photomicrographs of the thyroids of Figure 46 are reproduced in Figure 47. As will be pointed out below, the administration of anterior pituitary as tissue or extract restores the thyroid of the hypophysectomized animal to a

[9] Severinghaus and others (1934) studied the effects of thyroid-feeding or thyroxin-injection on the histologic appearance of the male rat's pituitary. A similar study was made by Thomson and others (1934), who administered a thyrotropic extract repeatedly to female rats. In both sets of experiments the basophils appeared like "castration"-cells; in addition, changes in the oxyphils and the reserve cells or degenerative changes were described. A marked atrophy of the ovaries was observed in the rats used by Thomson and his colleagues (also see Campbell and others, 1934).

normal anatomical condition and raises the metabolic rate, which is low chiefly because of a thyroid deficiency subsequent to hypophysectomy.

The effects of administration of anterior pituitary tissue or extracts.—Smith (1926, 1930) clearly demonstrated that the atrophic thyroid of the hypophysectomized rat could be restored to normal both grossly and microscopically by the administration of fresh homoplastic implants. Similar results

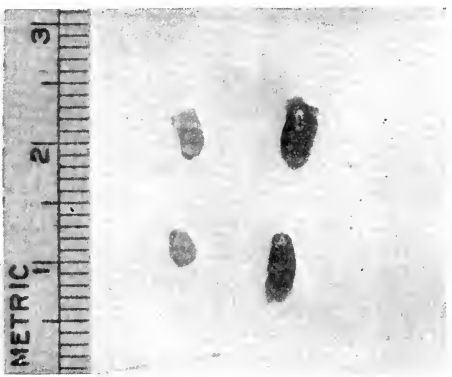


FIG. 46.—Gross appearance of the lobes of the thyroid of a hypophysectomized rat and of a normal littermate control rat. The thyroid lobes of the operated animal are to the left.

following the use of extracts in other species such as the dog have been reported (Houssay, Biasotti, and Magdalena, 1932).

The response of young normal mammals differs enormously among different species. There is some evidence that thyroid sensitivity to anterior pituitary extracts is inversely proportional to the amount of thyrotropic hormone in the animal's own pituitary (see the results of Loeb, 1932; and Loeb and Friedman, 1933). None more sensitive than the young guinea pig has so far been found; the young rat, on the other

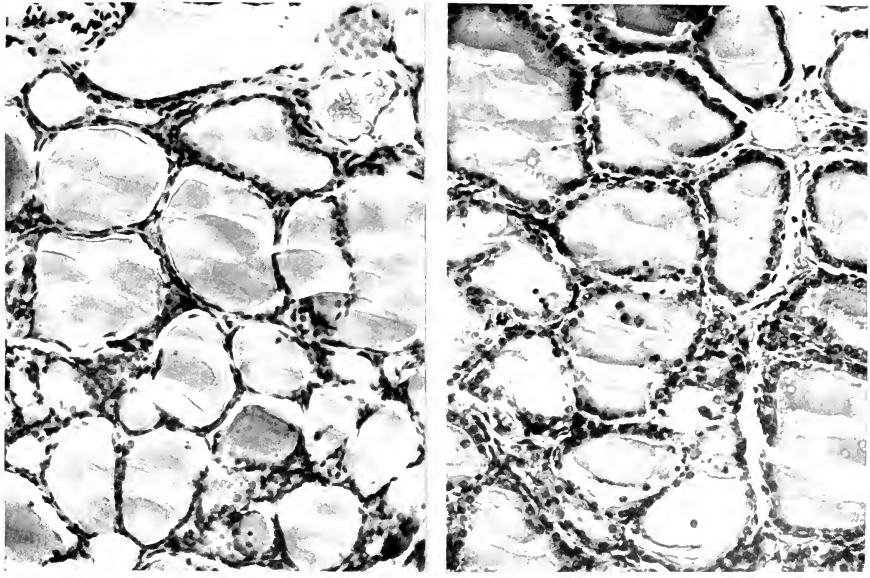


FIG. 47.—Photomicrographs of the upper pair of thyroid lobes shown in Figure 46. Left: a section of the thyroid of the operated rat; right: a section of the thyroid of the littermate control rat. ×234.

hand, is among the most resistant. This fact helps to explain the success of Evans and Long (1921–22) in demonstrating the growth-promoting properties of crude anterior pituitary extracts in the rat; if they had attempted this in the guinea pig their extract would have caused, at least initially, a loss of weight due to hypersecretion by the thyroid. Thurston (1933) has given the most complete account of species differences in the response to thyroid-stimulating hormone. The mouse and rat are the least sensitive; the guinea pig is the most sensitive; intermediate in the order of increasing sensitivity are the rabbit, cat (and pigeon). The typical anatomical effects of extract administration in the guinea pig, described in the paragraph below, are modified in the cat in which the chief change consists in a diminution in the amount of colloid. Aron (1932), Houssay, Novelli, and Sammartino (1932), Houssay (1932), Kleine (1932), and Loeser (1934) reported in less detail on similar differences in response among different animals.

Like Aron (1929) most investigators have found the response of the guinea pig is most marked in the young animal (weight, 150–200 g.) and that older animals are relatively insensitive. According to Friedgood (1935) the response of the female guinea pig is more intense and persists longer than that of the male. The extract is ineffective by mouth and must be given parenterally (Janssen and Loeser, 1931; Anderson and Collip, 1934). As soon as 2 hours after injection changes can already be observed in the thyroid according to Eitel and Loeser (1932). It has usually been the practice to inject the anterior-lobe extract for several days and to sacrifice the animals about 24 hours after the last injection. The anatomical changes, which depend to a considerable extent on the amount of material injected, were first described by Aron (1929) and Loeb[10] and Bassett (1929), whose findings

[10] The experiments of Loeb and his co-workers with Armour's pituitary tablets are not considered because these tablets appear to contain thyroid as shown in

have since been repeatedly confirmed. There is usually only a moderate hypertrophy of the thyroid such as a 50 per cent increase in weight; Loeb and Friedman (1931), however, have reported that the thyroid lobes of treated animals may weigh nearly three times as much as those of control animals.[11] Microscopically the colloid-containing vesicles are reduced in size presumably because of colloid absorption and discharge through the acinous cells. The remaining colloid is more vacuolated and stains less well than that of control thyroid tissue. The acinous cells hypertrophy and assume a cuboidal or columnar appearance in contrast to the flatter normal cells. Granules appear in the acinous cells, particularly in the lumen poles. Proliferative activity in the acinous cells is apparently great inasmuch as the number of mitoses is markedly increased. Indeed, Watrin and Florentin (1932) regarded the increase in the number of mitoses as the best criterion of thyroid stimulation. Heyl (1933) believed that the other effects could be graded in six stages. The histologic appearance of the thyroids of littermate guinea pigs, one of which had received anterior pituitary, is shown in Figure 48.

If injections of anterior-lobe extract are continued, the microscopic appearance of the thyroid indicates that different parts of the gland are in stages of activity ranging from rest to active secretion (Aron, 1930). Loeb and Friedman (1931) secured the maximum effects from six or seven injections, given once daily, into young guinea pigs. They found that if injections were continued 2 months or longer the microscopic evidences of stimulation of the thyroid disappeared except

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Loeb's laboratory (effective by mouth even after thyroidectomy, contain 10–50 times as much organic iodine as ordinary anterior-lobe powder, prevent compensatory hypertrophy, etc.).

[11] According to Heyl (1934), thyroid hypertrophy is due to a separate anterior-lobe principle which produces this effect only by acting synergistically with the principle causing histologic signs of thyroid stimulation.

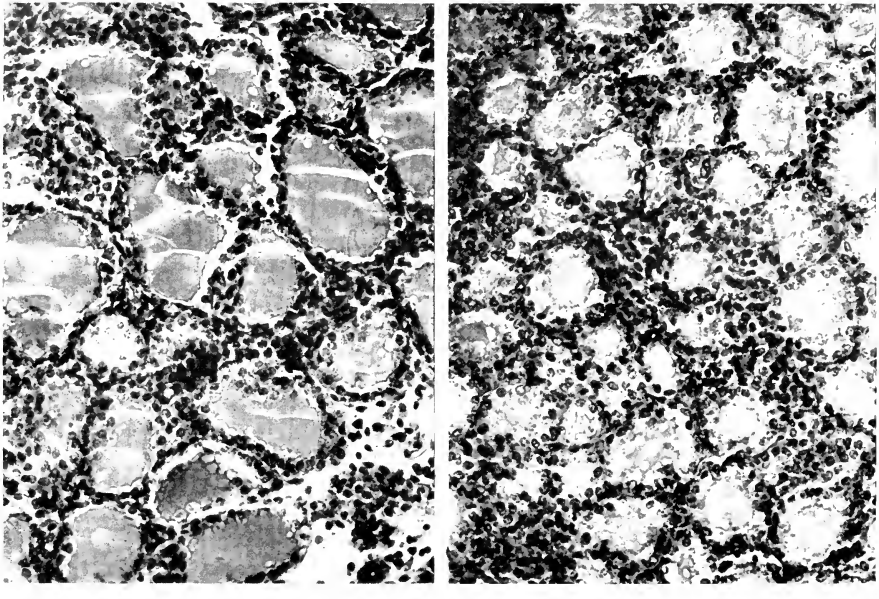


FIG. 48.—Histologic changes in the thyroid of the immature guinea pig following the administration of a total dose of 8 mg. of fresh rabbit anterior pituitary. Thyroid of normal littermate control on the left; that of treated animal on the right. ×234.

after small doses.[12] This fact, confirmed by the observations of others, may be related to the endogenous formation of an "antithyrotropic" hormone postulated by Collip and Anderson.[13] A fraction from the serum of horses previously treated with large doses of thyrotropic hormone not only lowered the basal metabolism of normal rats but also prevented any increase of basal metabolism if administered simultaneously with thyrotropic hormone. In the latter case, however, there were anatomical indications of stimulation of the thyroid. Animals rendered resistant by prolonged treatment with thyrotropic hormone or by treatment with "antithyrotropic" principle still reacted promptly to thyroxin; so the effect was considered not to be "antithyroid." Confirmatory observations have been made by others (e.g., Scowen and Spence, 1934; and Eitel and Loeser, 1935).

"Antithyrotropic hormone" can be produced by the hypophysectomized rat (Collip and Anderson). When it is presumably present in the blood of rats or guinea pigs, the pituitary contains little or no thyrotropic hormone (Anderson and Collip, Eitel and Loeser). This "antihormone," however, does not prevent the increased excretion of creatine attributed to the thyrotropic hormone (Pugsley and others, 1934). Eitel and Loeser injected large doses of thyrotropic hormone repeatedly into the wether. They found that the maximum amount of "antihormone" in the blood was present in the fourth to fifth week, and that very little was present in the twelfth to thirteenth week; later, when even less "antihormone" was present, there was also little histologic evidence of stimulation of the animal's thyroid.

Inasmuch as thyroxin produced as prompt and intense an effect in rats in which the "antihormone" prevented thyrotropic effects, Collip and Anderson concluded that the action

[12] For a description of similar experiments in the rabbit, see Hertz and Kranes (1934).

[13] Collip and Anderson (1934–35), and Anderson and Collip (1934).

of the "antihormone" could not be described as antithyroid. Such a conclusion, however, leaves out of account the fact that the true thyroid secretion is not necessarily thyroxin. The report of Collip and Anderson that "antithyrotropic" hormone causes a reduction of the basal metabolic rate of the rat speaks against the possibility that the internal secretion of the thyroid is the "antihormone" (thyroid extract, among other substances, may lessen or prevent thyrotropic effects). According to the observations of Eitel and Loeser, the thyroidectomized wether is unable to produce "antihormone" in response to the injection of thyrotropic hormone.[14]

The compensatory hypertrophy of thyroid tissue remaining after partial thyroidectomy in the dog has been prevented by hypophysectomy (Houssay, Biasotti, and Magdalena, 1932; and Kahler, 1934); on the other hand, Houssay, Biasotti, and Mazzocco (1932) could restore the compensatory hypertrophy of the thyroid in the hypophysectomized dog as well as greatly increase it in the normal animal by the administration of anterior pituitary extract. Silberberg (1933) and Moore (1933) studied the effects of anterior pituitary extracts on compensatory hypertrophy in otherwise normal guinea pigs. Transplants of thyroid tissue were found to be stimulated and to survive better if the recipient guinea pigs received injections of anterior pituitary extract (Silberberg, 1934).

Krayer (1933) bilaterally extirpated the cervical sympathetic of guinea pigs and rabbits; he then administered a potent thyrotropic extract days to months after operation. Both the anatomical changes and the rise in basal metabolism were nevertheless unchanged. Pieper (1934) unilaterally denervated the thyroid of the rabbit. He also concluded that denervation had only a slight effect on the response (histologic) of the thyroid to thyrotropic hormone. According

[14] Magistris (1935) believed that an "antithyroid" substance can be extracted from the pars glandularis.

to Aron (1933) and Döderlein (1933), large doses of the hormone, administered to the mother or fetus, stimulate the fetal thyroid.

Physiological evidence of thyroid stimulation by anterior-lobe extract has been obtained by recognizing effects presumably produced more or less specifically by the thyroid hormone. The body-weight falls or tends to fall in the young guinea pig although injections are made during a period of rapid growth. Hageman and McCordock (1932) reported that anterior-lobe extract caused an increase in the heart-rate and in the reflex response to an acoustic stimulus; furthermore, in thyroidectomized guinea pigs the extract did not produce these effects. Loeb and Friedman (1932) stated that exophthalmos[15] could be observed in guinea pigs after the injection of anterior-lobe extract. Grab (1932) injected anterior-lobe extract into both dogs and cats; as a result, the blood and serum of the treated animals contained an increased amount of thyroid hormone demonstrated by the protection of mice against acetonitril and by the acceleration of tadpole metamorphosis. Pighini (1933) found that the serum of treated dogs (but not of normal dogs) accelerated the metamorphosis of tadpoles, but he could detect no differences in the amount of thyroid hormone in the thyroid. Grab believed that the treated animal's thyroid might contain less thyroid hormone but that this change could be obscured by the new formation of thyroid hormone. If the experiments of Oehme, Paal, and Kleine (1932) were sufficiently accurate quantitatively, they seemed to indicate that the mouse thyroid can only discharge the equivalent of less than 1.5 γ of thyroxin.

[15] Exophthalmos can be produced in the thyroidectomized guinea pig by either acetonitril or anterior-lobe extract (of Armour's powder) according to Marine and Rosen (1933). They believed that exophthalmos is produced by a secretion of the anterior pituitary, particularly if there is a thyroid deficiency. They performed no experiments with hypophysectomized guinea pigs to support their theory that the exophthalmos following the administration of acetonitril is the result of a direct or indirect stimulation of the pituitary.

Such a dose of thyroxin protected mice against a larger dose of acetonitril than did anterior-lobe extract. Symptoms resembling those of Graves's disease have been produced in man by doses of 600–1,000 guinea pig-units of thyrotropic hormone (Eitel and Loeser, 1932; Schittenhelm and Eisler, 1932; and others). Following a latent period of several days, there appeared an increased basal metabolic rate, an increased body temperature, an increased pulse rate, a tremor of the fingers, and a bruit over the thyroid.

The metabolism of isolated thyroid tissue of the puppy was increased by the addition of thyrotropic hormone as reported by Eitel, Krebs, and Loeser (1933). Reiss, Hochwald, and Druckrey (1933) injected an anterior-lobe extract into rats with sarcoma (Jensen); they stated that the oxygen consumption of isolated liver and kidney were raised as soon as 2 hours after injection, but that there was no effect on isolated sarcoma. These latter experiments, however, have little meaning until other control observations have been made.

No correlation between the amount of thyroid-stimulating hormone in the pituitary of the ox and the known seasonal variations in the ox thyroid could be demonstrated (Byars and others, 1932).

Studies of the concentration of iodine or thyroxin in the blood and the thyroid, as well as the distribution of iodine in the blood after the administration of anterior-lobe extract, have been made by Loeser (1931), Houssay and his coworkers (1931, 1932), Closs, Loeb, and MacKay (1932), Grab (1932), Schittenhelm and Eisler (1932), Foster, Gutman, and Gutman (1933), and Holmquist (1934) in the guinea pig, sheep, dog, and man. The total amount of iodine in the thyroid is not much changed by hypophysectomy; the operation, however, reduces the concentration of iodine in the blood (Loeser). Thyroidectomy, of course, prevents the increase in blood iodine following the injection of anterior-

lobe extract. The administration of an anterior-lobe extract to a susceptible animal like the young guinea pig produced the striking results given diagrammatically in Figure 49 (data of Closs, Loeb, and MacKay). It is evident that the anterior-lobe extract caused a hypertrophy of the thyroid with a reduction in both the concentration and total amount of iodine present. The marked increase in blood iodine was practically entirely due to an increase in the alcohol-insoluble

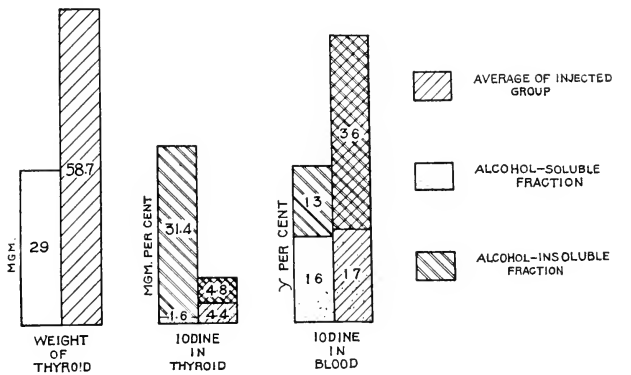


FIG. 49.—The effect of anterior-pituitary extract on the weight of the thyroid and on the amount and distribution of iodine in the thyroid and blood of the guinea pig. Adapted from Experiment 2 of Closs, Loeb, and MacKay (1932).

(thyroid hormone) fraction. Foster, Gutman, and Gutman showed that the reduction in the total iodine of the thyroids of sheep treated with anterior pituitary extract was due to a reduction of thyroxin and organic iodine, whereas the inorganic iodine was scarcely affected.

Any increase in basal metabolism as a result of the administration of anterior pituitary implants or extracts appears to depend upon the stimulation of the thyroid. Benedict and Homans (four dogs, only one reported as completely hypo-

physectomized; obesity in all) and Aschner and Porges (one dog) reported in 1912 that hypophysectomy lowered the basal metabolic rate. According to Houssay (1934), the basal metabolism of the dog is reduced to about 15 per cent below normal as a result of hypophysectomy. This is due to a reduced thyroid function. Hypophysectomy, in one series of dogs, was followed by a lowered basal metabolic rate (−12 per cent); subsequent thyroidectomy caused a further reduction (to −22 per cent) similar to that following thyroidectomy alone (−24 per cent). Hypophysectomy after thyroidectomy was found not to alter the basal metabolic rate. Foster and Smith (1926) were the first to observe that replacement therapy by pituitary homo-implants raised the basal metabolic rate of the hypophysectomized animal (rat) to normal. In the hypophysectomized dog, Houssay and Artundo (1933) and Strieck (1933) showed further that anterior pituitary extracts usually caused no increase in the basal metabolic rate unless the thyroid was intact.

Numerous experiments have been performed with non-hypophysectomized animals. Siebert and Smith (1930) were the first to demonstrate that a crude extract of the anterior pituitary markedly raised the metabolic rate only if the thyroid was intact. Treatment of young normal guinea pigs for a period of 10 days raised the metabolism as much as 60 per cent. When the injections were continued for a period of 4 weeks, the metabolism progressively fell to a normal level just as the thyroid's microscopic appearance again resembled that of an untreated animal. Verzár and Wahl (1931) reported that thyroid stimulation by an anterior-lobe extract could be demonstrated by an increased oxygen consumption in guinea pigs 20–36 hours after the injection of the extract. Guinea pigs and rats which had received injections of anterior-lobe extract were markedly more sensitive to atmospheres low in oxygen tension than similarly treated animals which had previously been thyroidectomized (Houssay and

co-workers, 1932). Observations in the dog (Bueno and Barnes, 1933; Houssay and Artundo, 1933; and Zajic, 1935) with the exception of those of Gaebler (1933, 1935) agreed that there was no effect following treatment by anterior pituitary extract if the thyroid had been removed. On the other hand, Gaebler observed a marked calorigenic response after the subcutaneous injection of an anterior-lobe (ox) extract into dogs which had been thyroparathyroidectomized (very little accessory tissue was found at necropsy). The effect, which was comparable to that following the intravenous injection of thyroxin, was thought not to be due to the foreign protein in the extract. Schoedel (1933) compared the effects of thyrotropic hormone and of thyroid on the basal metabolism of the guinea pig. In the rat, apparently, extracts may cause a considerable rise in the basal metabolism without accompanying microscopic indications of increased thyroid activity except in the hypophysectomized rat or in the normal rat receiving other treatment (Anderson and Collip, 1933–34; Fluhmann, 1933; and Szarka,[16] 1933).

The older clinical literature dealing with the pituitary and basal metabolism contains many observations which cannot be classified because the results were equivocal or the data were insufficient. For example, the clinical diagnosis may have been uncertain or the potency and specificity of the preparation used may not have been convincingly determined. Recently, however, purified thyrotropic hormone or anterior-lobe extract has been administered to man; as a result, the basal metabolic rate was elevated as much as 59 per cent (Eitel and Loeser, 1932; Feuling, 1933; Strieck, 1933; Jonáš, 1934; Sylla, 1934; and Thompson and others, 1935).

Verzár and Wahl (1931), Péter (1934), and Schoedel (1934) concluded that anterior pituitary extracts lowered the basal metabolic rate of thyroidectomized guinea pigs and rats. Gonadectomy did not prevent this effect.

[16] Also see p. 99.

Another metabolic effect of thyrotropic hormone,[17] which also is indirect and is the result of an increased liberation of thyroid hormone, is the reduction of the concentration of hepatic glycogen following adequate treatment. In the guinea pig the maximum effect was not seen until after about 1 week's treatment, but the effect might disappear a few days later despite the continuation of treatment (Eitel and Loeser, 1932; Holden, 1934). To produce a similar fall in the concentration of hepatic glycogen in the rat, Eitel, Löhr, and Loeser (1933) had to administer enormous doses of thyrotropic hormone (400 guinea pig-units daily) and yet they produced no significant histologic changes in the rat thyroid. Thyroidectomy, however, prevented the effect of the extract on the hepatic glycogen. According to Jonáš (1934) the glucose-tolerance is reduced in man (normal or with Graves's disease) after the injection of an extract with thyrotropic effects. This change is not related to the alteration in basal metabolic rate. The blood sugar remains unaltered unless the liver has been damaged, when there may occur a hypoglycemia (Lucke, Heydemann, and Duensing, 1933; and Horsters, 1933). However, in the dog under chloralose anesthesia, the intravenous injection of a large dose of thyrotropic hormone causes a reduction in the concentration of blood-glucose amounting to 11–18 mg. per cent (Zunz and La Barre, 1934–35). This change is not observed in thyroidectomized dogs and apparently is due to an increased liberation or secretion of insulin. The thyrotropic hormone is said not to cause a loss of the hepatic glycogen of animals receiving levulose and insulin (Loeser, 1934).

Some elevation of the concentration of ketone-bodies in the blood was produced by the administration of large doses of a purified thyrotropic hormone to normal but not thyroidectomized rats (Eitel, Löhr, and Loeser, 1933). Feuling (1933)

[17] Also see the hypothesis of Barnes (1934).

did not observe any change in the dog or man. Anselmino and Hoffmann (1934) believed that a "ketogenic hormone" could be separated from the thyrotropic hormone by suitable extraction of the anterior pituitary.

Pugsley and Anderson (1934) found that a thyrotropic extract caused an increase in the fecal excretion of calcium by the rat at about the time the basal metabolic rate was raised. Creatine excretion in the rat and dog was also elevated following the administration of thyrotropic extract (Pugsley and others, 1934). According to Houssay (1934) the specific dynamic reaction to proteins is normal in hypophysectomized dogs unless the thyroid has also been removed (in which case it is lowered). Therefore, the thyrotropic hormone appears to play no part in this metabolic response.

Substances which prevent thyroid stimulation by the anterior pituitary.—The administration of potassium iodide, Lugol's solution, or di-iodotyrosine is said to lessen or even to prevent the thyroid-stimulating effect of anterior-lobe extract (Silberberg, 1929, 1930; Okkels and Krogh, 1932, 1933; and Elmer, 1933). Siebert and Thurston (1932) as well as Okkels and Krogh, and Friedgood (1935) concluded that the increase in basal metabolism characteristically following the injection of a potent anterior-lobe extract could be prevented or converted into a decrease below the normal level by the administration of iodine or iodides. According to Loeser and Thompson (1934), potassium iodide has no effect on the thyroid of the hypophysectomized rat whether or not thyrotropic hormone is also administered. They concluded that potassium iodide, depending upon the dose, diminishes or increases the secretory activity of the pars glandularis thus indirectly affecting the thyroid.[18] Most of such experimental evidence

[18] Marine, Rosen, and Spark (1935) studied the effects of potassium iodide or desiccated thyroid on the pituitary of goitrous or thyroidectomized rabbits. They observed that the anatomical abnormalities in the pars glandularis after thyroidectomy could be corrected by desiccated thyroid but not by potassium iodide.

supports the use of iodine and iodides as part of the modern treatment of Graves's disease if one assumes that stimulation of the thyroid by a pituitary hormone is an etiological factor in the disease. The administration of thyroid gland, thyroxin, or substances related to thyroxin also lessens or prevents thyroid stimulation by anterior-lobe extracts as shown by Aron (1930), Loeb, Bassett, and Friedman (1930), Houssay, Biasotti, and Magdalena (1932), and Loeser (1934). The effects of the "antithyrotropic hormone" of Collip and Anderson have already been discussed (pp. 261–64).

Agnoli (1934) concluded that the thyrotropic effects of anterior-lobe extract were antagonized by bromide (but not fluoride) and by salts of the following metals: copper, arsenic, zinc, and manganese (slightly by salts of cobalt and nickel).

Thyroid-stimulating extracts from the anterior pituitary, other tissues, and body-fluids.[19]—For making thyroid-stimulating extracts, beef anterior lobes, fresh or desiccated and defatted, have generally been used. Investigators who have mentioned the most potent preparations (0.01–0.3 mg. per "guinea pig-unit") have not adequately described their method of preparation. Descriptions of methods, some detailed and some vague, have been given by Loeb and Bassett (1930), Janssen and Loeser (1931), Oehme, Paal, and Kleine (1932), Guyénot and others (1932), Junkmann and Schoeller (1932), Loeser (1932, 1934), Anderson and Collip (1933–34), Andreis (1933), Krogh and Okkels (1933), Müller (1934), Rowlands and Parkes (1934), and Greep (1935). The first extraction may be carried out with water or dilute solutions of acid (CH_3COOH) or alkali (NaOH, HN_4OH). Such extracts are apparently still potent after deproteinization by ultra-filtration or by treatment with sulfosalicylic or trichloracetic acids. Loeser has then effected further purification by precipitation of the hormone by acetone and later methyl alcohol. The hormone is soluble in aqueous solutions of ethyl alcohol, ace-

[19] Also see Spaul (1931); Heyl (1934); and Schittenhelm and Eisler (1935).

tone, and pyridine. Purified preparations of the hormone are readily adsorbed. Aqueous solutions of the hormone stimulating the mammalian thyroid are said to lose their activity after boiling, whereas those stimulating the amphibian thyroid are said to be little affected; the difference may depend upon differences in experimental conditions (pH of solution, purity of extract, dosage, etc.). There is more or less satisfactory evidence that the thyrotropic hormone can be separated from the growth-promoting, gonad-stimulating, and lactogenic hormones of the anterior pituitary (also see Riddle, Bates, and Dykshorn, 1933; Greep, 1933, 1935; Guyénot and others, 1934; and Wallace, 1934).

In the normal animal, the thyroid-stimulating hormone appears to be specifically elaborated by the anterior pituitary. Extracts of kidney, testis, placenta, and muscle cause no thyroid stimulation (Aron, 1930). Aron stated that one milligram of anterior pituitary was more effective than the equivalent of 10 g. of any of the control tissues mentioned above. Extracts or suspensions of placenta were found to cause no thyroid stimulation (Geyer, 1933; and Greep, 1933) or "stimulation" only in the female (Collip, Thomson, and Selye, 1933). According to Geyer, urine from a case of hydatidiform mole as well as a suspension of the tumor tissue caused marked thyroid stimulation. Heyl (1934) found that ascorbic acid stimulated the thyroid but believed that ascorbic acid was more readily oxidizable than the true hormone. Nearly all investigators agree that the gonad-stimulating principle of pregnancy-urine (prolan) does not stimulate the thyroid (Aron, 1931; Janssen and Loeser, 1931; Paal, 1931; Verzár and Wahl, 1931; Loeb, 1932; Döderlein, 1933; Greep, 1933; and Junkmann, 1934). All who have investigated the effect of prolan on the basal metabolism of man or animals have found that it does not elevate the basal metabolism; some workers, indeed, reported that prolan depresses the metabolism.

Although Aron (1930, 1931, 1933–34) has produced thyroid stimulation by extracts of normal urine and serum, others have failed to confirm this finding, particularly in cases of Graves's disease (Del Castillo and Magdalena, 1931; Krogh and Okkels, 1933–34; and Smith and Moore, 1933). According to one of the latest reports, that of Loeser (1934), injected thyrotropic hormone is excreted in a potent form by the kidneys (rabbit). Loeser as well as Schittenhelm and Eisler (1935) have also studied other aspects of the metabolism of the thyrotropic hormone.

The assay of the thyroid-stimulating hormone.—For convenience and specificity, probably the response of the young guinea pig's thyroid is best as a means of assaying the thyrotropic hormone. The histologic changes may be determined after administering minimally effective doses, distributed over several days, to littermate animals kept under exactly similar conditions. The control member of a littermate pair may be given nothing or a standard preparation. Assay by means of weight-changes in the thyroid certainly requires larger doses and is said to be less reliable. Aron (1932), Del Castillo (1932), and Kleine (1932) have described the technique of the test and the precautions which they believe to be necessary. The acetonitril test of Reid Hunt, the effect on metabolism, and the effect on metamorphosis in amphibia have also been employed. These three methods are indirect (i.e., indicate an increased rate of thyroid secretion or the presence of thyroid hormone in the material tested) and appear a priori to be less specific and more variable than the determination of the effect on the guinea pig's thyroid. According to Oehme, Paal, and Kleine (1932), however, some indirect methods are the most sensitive. (See also Grab, 1932; Kleine and Paal, 1933; Oehme, Paal, and Kleine, 1933; Schoedel, 1933; Anderson and Collip, 1934; and Atwell, 1934.)

In several recent reports more attention has been given to

the quantitative assay of the thyrotropic hormone. Rowlands and Parkes (1934) based their assay on the change in weight of the thyroid lobes of female[20] guinea pigs weighing 200 g. initially. They define as a "unit" the daily dose, administered once daily for 5 days, which causes sufficient hypertrophy of the thyroid lobes so that the latter weigh 60 mg. (this is about twice the normal weight). They estimated that the fresh pars glandularis of the ox contained six units. Rowlands and Parkes also studied the relationship between dose and response (weight-change of thyroid). In another report, Heyl and Laqueur (1935) recommended that the quantitative assay of the thyrotropic hormone be based upon the histologic change in the immature guinea pig's thyroid. They were of the opinion that weight-change is an unsatisfactory criterion because it is due to a second substance, acting synergistically with that producing histologic signs of thyroid stimulation.

Other interrelationships or effects of the thyrotropic hormone.—Although Aron and Benoit (1932) reported that large doses of oestrin antagonized the thyrotropic effect of an anterior pituitary extract, this has been denied by other investigators. It is agreed that the injection of oestrin into mice or rats may be followed by histologic signs of lessened secretory activity on the part of the thyroid without markedly interfering with the thyrotropic effect of the pituitary. Therefore, it has been suggested that oestrin interferes with the liberation of thyrotropic hormone from the pars glandularis. (See Benazzi, 1933; Bialet-Laprida, 1933–34; Calatroni, Heyl, Repetti, 1934.) Parabiosis between a normal and a thyroidectomized rat or between a normal and a spayed rat is accompanied by no changes in the thyroid (Naiko and Ikonen, 1934). On the other hand, experimental hyperthyroidism may markedly prolong the oestrous cycle (Reiss and Perény, 1928; Suzue and

[20] Some authors consider that the thyroid response is greater in female than in male guinea pigs.

Murohara, 1929; and others). Some investigators have reported that large doses of a relatively pure thyrotropic preparation or pituitary implants cause hypertrophy of the adrenal cortex of guinea pigs or rats provided that the thyroid is intact (Loeser, 1933–34; also see Eitel, Krebs, and Loeser, 1933; Emery and Winter, Holmquist, McQueen-Williams, 1934); Del Castillo (1934) found that adrenalectomy in the rat did not affect the amount of thyrotropic hormone in the pituitary. According to Elmer and his colleagues (1935), the injection of adrenal cortical extract does not interfere with the effect of the thyrotropic hormone on the guinea pig's thyroid. The injection of thyrotropic hormone does not affect the amount of epinephrin in the adrenal gland of the guinea pig (Loeser, 1934). Aron (1933) stated that the development of pancreatic islet tissue of the guinea-pig embryo was hastened by the administration of either thyrotropic hormone or thyroxin. The diuretic effects of anterior pituitary extract, first observed by Teel, were found not to occur after thyroidectomy (Barnes, Regan and Bueno, 1933; and Biasotti, 1934).[21] According to a later report (Dix, Rogoff, and Barnes, 1935), pancreatectomy also prevents the diuresis which follows the injection of an anterior-lobe extract.

Thaddea and Waly (1934) stated that a thyrotropic extract facilitated erythropoiesis and leukopoiesis in the rabbit (e.g., anemia due to phenylhydrazine) and in man (e.g., anemia). The effects of a similar extract on the spleen and leukocytes of the guinea pig were investigated by Kleine and Paal (1934).

The interrelationship of the pars neuralis and the thyroid.—That there is no interrelationship, physiologically significant, between the internal secretions of the posterior lobe and that of the thyroid is the best interpretation of the experimental

[21] Gaebler (1935) reported that the anterior-lobe (ox) extract which he used caused a storage of water later followed by a diuresis. These effects were both present after thyroparathyroidectomy.

data. Thyroidectomy and thyroid feeding were found not to alter the amounts of pressor and oxytocic principles in the posterior lobe (Herring, 1921). Thyroid feeding may increase the systemic effects of the pressor principle (Clark, 1929; and Appel, 1932) or the action of posterior-lobe extract on the isolated duodenum (Tada, 1929). In Graves's disease, posterior-lobe extract has been said to be less effective in delaying diuresis (Hoff and Wermer, 1927) but more effective in eliciting a pressor response (Herzum and Pogány, 1927). None of these data, however, supports the hypothesis that there is an important functional relationship between the thyroid and the pars neuralis of the pituitary.

CHAPTER VIII

THE INTERRELATIONSHIPS BETWEEN THE PARS GLANDULARIS AND THE ADRENALS, PANCREAS, PARATHYROIDS, AND THYMUS; EXPERIMENTAL EVIDENCE THAT THE METABOLISM OF FOODSTUFFS DEPENDS PARTLY UPON INTERNAL SECRETIONS OF THE PARS GLANDULARIS[1]

TO COMPLETE the discussion of the physiology of the pars glandularis, interrelationships between the anterior lobe and other glands of internal secretion will be considered in this chapter. The experimental evidence for and against the belief that the pars glandularis affects the metabolism of various foodstuffs will also be reviewed.

THE INTERRELATIONSHIP BETWEEN THE ANTERIOR PITUITARY AND THE PARATHYROID GLANDS, THE THYMUS, AND THE ADRENAL GLANDS

The interrelationship between the anterior pituitary and the parathyroid glands.—The effect of hypophysectomy on the parathyroid glands has been studied by only a few investigators. As a result of the removal of the hypophysis (pars buccalis) from tadpoles, the epithelial bodies, which are homologous with the mammalian parathyroid glands, undergo atrophy (Smith).[2] Dogs were used in the experiments of Houssay and Sammartino (1933). They concluded that atro-

[1] Other references to nearly all the topics discussed in this chapter will be found in the Index.

[2] Charles (1931) found that there was a reduction in the concentration of calcium in the serum of female toads (*Xenopus laevis*) amounting to 20–37 per cent after the removal of the anterior lobe or of both the anterior and the posterior lobes of the pituitary.

phic changes in the parathyroids occurred in about two-thirds of a group of hypophysectomized dogs. However, if thyroidectomy or pancreatectomy had also been performed, atrophy of the parathyroids was present in all the animals. At least in dogs there appears to be no unequivocal change (diminution) in the concentration of calcium in the blood after hypophysectomy.

Anselmino, Hoffmann, and Herold (1933–34) concluded that a "parathyrotropic" hormone can be extracted from the pars glandularis. They stated that a suitable extract caused hyperplasia of the chief cells as well as hypertrophy of the parathyroids (200–300 per cent) in male rats weighing about 150 g. According to Hertz and Kranes (1934), the parathyroid glands of the rabbit may be grossly larger and more vascular after the administration of anterior-lobe extract. Hypertrophy and hyperplasia of the cells of the parathyroids were often observed microscopically. These effects, however, were also produced by pregnancy-urine or oestrone. Anterior pituitary extracts have been said to cause an increase, or a diminution, or no change in the concentration of calcium in the blood.[3] It is not possible to conclude, on the basis of the available evidence, that there exists an anterior pituitary "parathyrotropic" hormone. At least, some data from hypophysectomized animals should be secured.

The interrelationship between the anterior pituitary and the

[3] According to Hogben and Charles (1932), the concentration of calcium in the blood is reduced after the injection of a suspension of fresh anterior lobe (ox) into female rabbits (before injection, 14.5 mg. per cent; after injection, 11.5 mg. per cent in normal rabbits, and 12.8 mg. per cent in ovariectomized rabbits). Dixon (1933) could detect no change in the concentration of the blood calcium in female rats after they had received an anterior pituitary extract which caused luteinization of the ovaries. Hoffmann and Anselmino (1934) found an increased concentration of calcium in the blood after the injection of an anterior-lobe extract (Rat: before injection, 10.6 mg. per cent; after injection, 12.0 mg. per cent. Parathyroidectomized rat: before injection, 9.2 mg. per cent; after injection, 9.6 mg. per cent. Normal dog: before injection, 10.8 mg. per cent; after injection, 12.5 mg. per cent). Teel and Cushing (1930) injected anterior pituitary extract into the dog every day; several days after treatment was begun, an increased amount of calcium was excreted in the urine.

thymus.[4]—If the young mammal (rat or dog) is hypophysectomized, the thymus undergoes a more rapid involution than is normally the case (Smith, 1930, and Houssay and Lascano-Gonzalez, 1934). However, hypertrophy of the thymus has been observed in rats hypophysectomized when adult (Richter and Wislocki, 1930). References to other observations in hypophysectomized dogs will be found on pages 64–65.

The administration of anterior-lobe extracts or implants usually has been found to hasten the involution of the thymus—a change which has also been observed after the administration of oestrin (fowl—Wulzen, 1914, fed fresh anterior lobe; duck, Schockaert, 1930–31; rat, Golding and Ramirez, 1928, Tsunoda, 1934; guinea pig, Watrin and Florentin, 1932). An exceptional case is that of mice with hereditary dwarfism. The administration of a growth-promoting extract of the anterior pituitary to such mice causes a marked proliferation of the parenchyma of the thymus (Kemp, 1934).

The interrelationship between the anterior pituitary and the adrenal glands.—The effect of hypophysectomy on the adrenal glands of the rat is illustrated by the data and photomicrographs of Figures 50–51. Striking changes occur in the cortex in which the atrophic change appears to be due to a cellular atrophy; fat is distributed in a narrow zone rather than throughout the cortex (Smith).[5] Although there may also occur some atrophy of the medulla, the microscopic appearance of the latter is not appreciably altered. Descriptions of the effect of hypophysectomy on the adrenals of other animals will be found in chapter ii. Direct or indirect interrelationships between the pituitary and the adrenals are suggested by other experiments in which hypophysectomized rats were used. Smith, Greenwood, and Foster (1927) found

[4] For other references see the Index.

[5] Smith (1930) concluded that the atrophy of the adrenal was greater than could occur merely as a result of a thyroid deficiency.

that the administration of thyroid caused adrenal growth in thyroidectomized rats but not in hypophysectomized rats.

FIG. 50.—Photomicrographs of adrenal glands of the male rats shown in Figure 11. ×24. Top, an adrenal gland of the hypophysectomized rat; weight of both adrenals, 9.1 mg.; note that the atrophic changes are almost entirely confined to the cortex. Bottom, an adrenal gland of the normal rat; weight of both adrenals, 48.5 mg. Also see Figure 51.

The hypophysectomized rat does not survive adrenalectomy as well as the normal rat (Shumacker and Firor, 1934). Compensatory adrenal hypertrophy does not occur after the re-

FIG. 51.—Photomicrographs of the cortex of the adrenal glands shown in Figure 50. ×99. Top, the adrenal cortex of the hypophysectomized rat. Bottom, the adrenal cortex of the normal rat.

moval of one adrenal gland from the hypophysectomized rat (Collip and others, 1933; Shumacker and Firor, 1934).

Some of the symptoms of hypophysial deficiency may be due to the insufficient secretion of adrenal cortical hormone. Although Atwell (1932) considered that adrenal cortical hormone "somewhat restored," histologically, the "cortical" tissue of hypophysectomized tadpoles, he found (1932) no change in the adrenal cortex in similar experiments in the hypophysectomized rat. Evans and others (1933) concluded that cortical hormone affected neither the growth nor the cachexia of hypophysectomized rats; however, Atwell stated that such rats were more active if they had received the cortical hormone. According to Perla (1935), the lethal dose of histamine in hypophysectomized rats is much lower (200–400 mg.[6] per kg. body-weight) than in normal rats. On the other hand, after the administration of adrenal cortical hormone, the lethal dose of histamine is raised to a level (700–800 mg.[6] per kg. body-weight) closely approaching that which kills the normal rat. Kalk's patient (1934) with hypophysial deficiency (Simmonds' disease) was apparently benefited by the administration of an adrenal cortical extract, but not by an anterior-lobe extract.

The adrenal cortex of the hypophysectomized rat can be restored to a normal size and appearance by the administration of homoplastic pituitary implants (Smith, 1930); but the restoration is not as easily effected as in the case of the gonads. According to Evans and others (1932–33), prolan (as well as the serum of pregnant mares) has no effect on the adrenal cortex of the hypophysectomized rat. They found that growth-promoting extracts of the anterior pituitary caused cellular hypertrophy especially in the zona fasciculata, as well as an increase in the amount of lipoid in the cortex. They believed that these changes were related to the bene-

[6] Apparently the author refers to the base rather than to the salt (acid phosphate) which he used.

ficial effect of the pituitary extract on the cachexia following hypophysectomy. Growth-promoting extracts had no effect on the cachexia or survival of adrenalectomized rats.

Homoplastic or heteroplastic pituitary implants do not readily cause hypertrophy of the adrenal glands of the rat (Emery, 1933). According to Emery and Winter (1934), moderate adrenal hypertrophy (14–48 per cent) follows the administration of eight implants (donor: rat or guinea pig). Implants of pituitaries of female animals appeared to be more effective than those of males (castration seemed to have little effect). Adrenal hypertrophy was observed only in rats more than 30 days old and could be prevented by thyroparathyroidectomy. A number of authors have reported that pituitary extracts—usually of the anterior lobe—cause hypertrophy of the adrenal glands. Emery and Atwell (1933) studied the effects of an extract of the whole pituitary body of the sheep on the adrenal glands of castrated and normal male rats weighing 125–200 g. As a result of the injections, hypertrophy of both the medulla (13–52 per cent) and the cortex (67–127 per cent) was observed. (The absolute change in weight was far greater in the cortex than in the medulla inasmuch as the cortex was found to constitute about 90 per cent of the gland.) In the cortex the principal microscopic changes were an increased amount of cytoplasm and an increased amount of lipoid in the cells of the fasciculate and reticulate zones—effects which are the opposite of those due to hypophysectomy.[7]

Other studies of the effects of extracts of the pars glandularis on the adrenals of mice, rats, guinea pigs, rabbits, and dogs have been made by Anselmino, Hoffmann, and Herold (1933–34), Collip, Anderson, and Thomson (1933), and Houssay and others (1933). Some of the observations were made in hypophysectomized animals (rat: Collip and others;

[7] Emery and Atwell reported that large doses of prolan caused no change in the adrenal glands of spayed or castrated rats. Also see Lopez (1934) and pp. 215–16.

dog: Houssay and others) or after thyroidectomy or gonadectomy or splanchnotomy (dog: Houssay and others). According to Anselmino, Hoffmann, and Herold, the important changes in the cortex consist of hypertrophy and hyperplasia of the cells of the zona fasciculata and the zona glomerulosa; they stated that the gonad-stimulating hormone(s) affects the zona reticularis. They concluded that they had separated a "hormone" different from all known "hormones" of the pars glandularis. Collip, Anderson, and Thomson believed that the hormone stimulating the adrenal cortex differed from the thyrotropic hormone and from that promoting growth.

Anselmino, Herold, and Hoffmann (1934) also concluded that they had secured an extract of the pars glandularis which, only 2 hours after injection, caused changes in the microscopic appearance of the cells of the medulla of the adrenal of male mice and rats (loss of chromaffin property, vacuolization, and alteration in the cells' shape). To account for the changes they postulated an "adrenotropic" hormone different from a cortex-stimulating or "corticotropic" hormone. Houssay and his co-workers (1933) found that an anterior-lobe extract, causing adrenal hypertrophy in the dog, at first brought about a reduction, both relative and absolute, in the amount of epinephrin present. Later, the concentration but not the total amount of epinephrin was reduced in comparison with that of normal dogs.

The anatomy of the pituitary body in adrenalectomized rats has been studied by Lehmann (1929) and Shumacker and Firor (1934). In the pars glandularis the important change is described as a reduction in the number of basophils. In black and piebald rats, pigment in the cells of the pars intermedia is either absent or diminished in amount. The pars neuralis is said to be edematous.

The interrelationship of the pars glandularis, the adrenals

(apparently the medullary tissue), and the metabolism of carbohydrates is discussed in the next section.

THE METABOLISM OF CARBOHYDRATES. EXPERIMENTAL EVIDENCE THAT THE PARS GLANDULARIS, THE PANCREAS, AND THE ADRENAL GLANDS MAY BE INTERRELATED IN CONTROLLING THE METABOLISM OF CARBOHYDRATES[8]

The effects of the extirpation of the gland(s). 1. *Hypophysectomy.*[9]—Different phases of the metabolism of carbohydrates have been investigated in hypophysectomized fish, amphibia, birds, and mammals (rat, rabbit, cat, and dog). Most of these data have been considered already; however, the conclusions which can be reached will be reviewed here.

After hypophysectomy the concentration of sugar in the blood may be normal or reduced—sometimes markedly. Usually starvation promptly causes hypoglycemia, which may be so severe that convulsions appear. There is general agreement that the hypophysectomized animal is abnormally sensitive toward insulin. Not only do small doses of insulin provoke a marked hypoglycemia, but there is also an abnormal delay in the return of the blood-sugar concentration to its former level. Epinephrin (or the pressor hormone of the pars neuralis) is then much less effective in increasing the concentration of the blood sugar. (Also, without insulin treatment these substances cause only a slight hyperglycemia in the hypophysectomized animal in comparison with the normal.)

There is some evidence that the blood of the hypophysectomized dog contains an increased concentration of insulin

[8] See also the following pages in chap. ii: 35–36, 39, 42–43, 57, 61–64, 69, 71, and 75–76. For clinical observations or recent references to the clinical literature, see Colwell (1927); Davidoff and Cushing (1927); Atkinson (1932); Cushing (1933); and Houssay (1933).

[9] Besides the references of chap. ii, see Houssay and others (1925); Gaebler (1929); Di Benedetto (1931); Houssay and others (1933); Corkill, Marks, and White (1934); Képinov and Guillaumie (1934); and Fluch, Greiner, and Loewi (1935).

due to a more rapid rate of secretion on the part of the pancreas. The blood of the starved hypophysectomized dog has been found to cause a greater lowering of the blood-sugar concentration of the rabbit than is caused by the blood of the starved normal dog (Cowley, 1931; these observations were not confirmed by Di Benedetto, 1934). Képinov and Guillaumie (1934) anastomosed the pancreatic vein of normal or hypophysectomized dogs to the jugular vein of normal dogs in which the adrenal veins had been tied. They observed a considerable depression of the glucose-concentration in the blood of the recipient dog when it received pancreatic-vein blood from a hypophysectomized dog. For example, 1 hour after transfusion had been completed (duration of transfusion, 30 minutes), the blood-sugar concentration of the recipient dog was 65 mg. per cent if the donor had been hypophysectomized, and 90–100 mg. per cent if the donor was normal.

Although in the toad and rabbit the tolerance toward glucose has been found to be increased as a result of hypophysectomy, the opposite appears often to be true of the dog. In nearly all the more recent reports[10] the authors stated that after the administration of glucose, whether by stomach-tube or by injection, the concentration of blood sugar rose to higher levels and returned to a normal level more slowly in hypophysectomized dogs than in normal dogs. However, the respiratory quotient rises after the administration of glucose to the hypophysectomized dog (Biasotti, 1934). Moreover, Gaebler (1929) found no change in the basal respiratory quotient of the dog after hypophysectomy. All these observations indicate that sugar-tolerance studies in the dog do not support the view that hypophysectomy causes hyperinsulinemia. The diminished tolerance apparently is not due to interference with the oxidation of sugar.

[10] Mahoney (1934) concluded that the sugar tolerance of the hypophysectomized puppy is high.

To some, as to Corkill, Marks, and White (1934), it has seemed that the chief effect of hypophysectomy on the carbohydrate metabolism is a derangement of the normal mechanisms for the deposition and liberation (in and from deposits like the hepatic glycogen) of carbohydrate. Their work (in the hypophysectomized rabbit) as well as that of others supports this belief. The increased insulin-sensitivity and the diminished effect of epinephrin on the blood-sugar concentration (and on the excretion of glucose in the urine) are consistent with this view, which is also supported by the reports of a diminished sugar tolerance in the hypophysectomized dog (but not by reports to the contrary in hypophysectomized toads and rabbits). Usually hypophysectomy is not followed by a striking change in the concentration of hepatic glycogen; however, the change is in the direction of a reduction. According to Corkill, Marks, and White, insulin causes a deposition of glycogen in the liver of the young normal rabbit, but not if hypophysectomy has been performed. Phillips and Robb (1934) concluded that the storage of glycogen in both the liver and the striated muscle took place at a slower rate in hypophysectomized than in normal rats. In the experiments of Fluch, Greiner, and Loewi (1935) the livers of normal frogs and of frogs from which the pars glandularis had been removed were perfused with Ringer's solution sometimes containing a low concentration of epinephrin. Extirpation of the pars glandularis had no effect on the amount of the hepatic glycogen. As a result of perfusion, however, more glucose was liberated from the normal livers than from those of the frogs lacking the pars glandularis. The differences observed were more striking when the perfusion was performed with Ringer's solution containing epinephrin.

From their observations on the effects of phlorhizin in hypophysectomized dogs Houssay and his collaborators concluded that hypophysectomy interferes with the formation of carbohydrate from protein (see pp. 62–63).

2. *Pancreatectomy.*—Kraus (1920–21, 1923) investigated the gross and microscopic appearance of the pituitary in human beings and cats with diabetes. He concluded that the typical changes (diabetes in youth or experimental diabetes) were a reduction in the weight of the pituitary and, in the pars glandularis, a reduction in the number and size of the oxyphils, hydropic degeneration of the basophils, and the proliferation of a "fetal" type of cell. Others do not agree with these findings (Verron, 1921; Schwab, 1923). Binet, Verne, and Messimy (1934) found that the pars glandularis of the pancreatectomized dog was largely made up of oxyphils and that the pars intermedia and pars neuralis contained an increased amount of colloid.[11]

In the dog and monkey the injection of oestrin or oestrone ("Theelin") has been found to reduce or prevent the glycosuria following pancreatectomy. The injections also prolonged life or improved the condition of the animals. These effects were attributed to an interference with the secretory activity of the pars glandularis (Barnes, Regan, and Nelson, 1933; Nelson and Overholser, 1934).

3. *Hypophysectomy and pancreatectomy.*—Houssay and Biasotti (1930) studied the course of diabetes in the toad (*Bufo arenarum*) and the dog after both pancreatectomy and hypophysectomy. Their important conclusion, which has since been confirmed both in their laboratory and elsewhere,[12] was that the diabetes of pancreatectomy was either ameliorated or prevented by hypophysectomy performed before or after the removal of the pancreas. Confirmatory observa-

[11] The effects of insulin on the pituitary are a matter of dispute. Eaves (1926), Igura (1927), and Maeda (1932) all believed that insulin caused pituitary hypertrophy accompanied by an increase in the number of oxyphils (rat and rabbit); Collin and others (1932) described effects on the formation of colloid (rabbit). Muthmann (1932) denied that the repeated injection of insulin into the rabbit altered the structure of the pituitary.

[12] Houssay and Biasotti (1930–31, 1933); Orias (1932); Barnes and Regan, Regan and Barnes (1933); Biasotti (1934); Lucke, Heydemann, and Berger (1934); and Long and Lukens (1935).

tions have been made in fish, a reptile, other amphibia, the cat, and the dog.

The glycosuria of hypophysectomized-pancreatectomized dogs may be moderate or slight, but usually disappears during fasting. The D:N ratio is low (0.9–1.9). Similarly, the concentration of sugar in the blood is much lower (e.g., 210–280 mg. per cent) than in pancreatectomized dogs (e.g., 420 mg. per cent). If the doubly operated dog is starved, the amount of sugar in the blood may fall precipitously so that symptoms of a hypoglycemia appear. The animal can live in a fair state of health for months without insulin. On the other hand, the insulin-sensitivity, characteristic of hypophysectomy, persists after the removal of the pancreas. This fact throws doubt on the attempt to explain insulin-sensitivity in the hypophysectomized animal as due to an increased secretion of insulin, perhaps following the removal of an inhibitory or antagonistic pituitary secretion.

If glucose is administered to hypophysectomized-pancreatectomized dogs, a variable amount—roughly 50 per cent—is recovered in the urine. After the intravenous injection of glucose the respiratory quotient rises (but later than in hypophysectomized dogs). The glycemic curve is similar to that of hypophysectomized dogs except that the return to the pre-injection level is slower. After the double operation, therefore, the metabolism of carbohydrates is unstable, extreme changes occurring after the administration of insulin or epinephrin, or in the presence of a deficiency or an excess of available carbohydrate (Lucke and others). On the basis of the amelioration of the symptoms of pancreatic diabetes, Houssay and Biasotti postulated the secretion of a "diabetogenic" hormone by the pars glandularis. The effects of anterior-lobe extracts on the metabolism of carbohydrates in hypophysectomized or hypophysectomized-pancreatectomized animals will be considered later (pp. 292–93).

4. *Adrenalectomy and pancreatectomy.*—Long and Lukens

(1935) removed the pancreas and the adrenals from cats which were given adrenal cortical hormone to replace the extirpated adrenal cortex. As in hypophysectomized-pancreatectomized cats, the diabetes was strikingly ameliorated (there being a reduction in blood-sugar concentration, less glycosuria, and a marked reduction in ketosis; the excretion of nitrogen was also reduced).

The effects of extracts of the pars glandularis on the metabolism of carbohydrates.—Borchardt (1908) was impressed by the frequent occurrence of glycosuria in patients suffering from acromegaly (60 of 156 cases). Therefore, he investigated the effect of a pituitary extract on the excretion of sugar by the rabbit and dog. He concluded that he could regularly produce glycosuria (as well as hyperglycemia) in rabbits but that the effects were uncertain in dogs. Unfortunately it appears that he used an extract of the pars neuralis which is now known also to have an effect on the carbohydrate metabolism. Keeton and Becht (1915) concluded that in the dog the stimulation of the pituitary body (tetanizing current for 20–30 minutes) caused an increase in the concentration of sugar-like substances in the blood, but that this effect could be prevented by bilateral splanchnotomy. Because of the difficulty they experienced in attempting to produce a pronounced hypoglycemia by the injection of insulin into decerebrate cats, Olmsted and Logan (1923) made observations in cats after both decerebration and hypophysectomy. In the latter case the concentration of blood sugar tended to fall spontaneously; typical insulin-convulsions could be readily produced.[13] Whether or not the adrenals were intact made little difference. In 1927, Johns, O'Mulvenny, Potts, and Laughton produced hyperglycemia, glycosuria, and polyuria in dogs by injecting extracts of the pars glandularis of the ox. They concluded that these effects

[13] The effect of insulin could be antagonized to some extent by the intravenous injection of an extract of the pars neuralis.

were due to an increase in glycogenolysis (liver). The latest period began with the observations of Houssay and Potick (1929) and Houssay and Biasotti (1930) who showed, by means of experiments in toads and dogs, that the pars glandularis contains a substance (or substances) antagonizing the effect of insulin in hypophysectomized animals and causing a recurrence of diabetic symptoms in animals which were both pancreatectomized and hypophysectomized.

A number of investigators have confirmed the earlier report of Johns and his colleagues (1927) that the injection of anterior pituitary extract may cause, in normal animals, symptoms resembling those of diabetes mellitus.[14] The important changes, which may occur 2–6 days after injections have been started, are a hyperglycemia (as high as 475 mg. per cent), a glycosuria (the rabbit may excrete as much as 10–35 g. of glucose per day), and a reduced glucose tolerance. Lipemia, ketonuria, polyuria, polydipsia, polyphagia, and emaciation may also be present. Although injections are continued, the symptoms may persist for only a week, the blood-sugar concentration then falling to a normal or slightly subnormal level (Evans). Houssay, Biasotti, and Rietti observed that the ease with which hyperglycemia and glycosuria could be produced in different animals was as follows: cat > dog > guinea pig > rabbit. They also produced similar changes in the pigeon, rat, and mouse but not in the toad and snake. A diet rich in carbohydrate facilitated the effect, particularly in the dog. Similar changes were not produced by extracts of other tissues (pars neuralis, thyroid, liver, spleen, kidney, and skeletal muscle).

Differing from other investigators whose work is discussed later, Houssay, Biasotti, and Rietti concluded that extracts were still diabetogenic in the absence of the adrenal medulla

[14] Houssay and Biasotti (1931); Baumann and Marine (1932); Evans and others (1932–33); Houssay, Biasotti, and Rietti (1932, 1934); Gaebler, 1933 (observed no change in carbohydrate metabolism; he mentions some of the negative results of others); Houssay (1933); and Biasotti (1934).

or after splanchnotomy. Hyperglycemia and glycosuria could be produced by the injection of an anterior pituitary extract into dogs after pancreatectomy and/or hypophysectomy, gonadectomy, or thyroidectomy.[15] In dogs which had received anterior pituitary extract, the blood-sugar concentration was high (e.g., 183 mg. per cent compared with 110 mg. per cent in normal dogs); however, epinephrin or morphine caused a greater elevation of the blood-sugar level than in normal animals. Similar results were obtained in hypophysectomized toads in which the hyperglycemic response was increased if implants had been administered (Houssay and Di Benedetto, 1932–33).

According to Marenzi (1934), an increase in the concentration of lactic acid in the blood coincides with the hyperglycemia and glycosuria due to the administration of anterior pituitary extract

Implants or extracts of the pars glandularis produce an increased concentration of sugar in the blood of hypophysectomized-pancreatectomized toads (Houssay and Biasotti, 1930–31; Braier, 1933) or dogs (Houssay, Biasotti, and Rietti, 1931; Képinov, 1934; and others). Using toads subjected to both operations, Houssay and his colleagues detected the diabetogenic hormone not only in the pituitaries of fish, amphibia, birds, and mammals, but also in the urine of normal or diabetic human beings.

On the basis of their numerous experiments Houssay and his collaborators concluded that the liver is the only gland of internal secretion necessary for the production of diabetogenic effects by extracts of the pars glandularis. However, other investigators[16] have found that anterior pituitary ex-

[15] Houssay and his co-workers cordinarily injected, in the form of an alkaline extract, the equivalent of 1.4 g. of fresh anterior lobe (ox) per kg. body-weight, intraperitoneally each day.

[16] Lucke (1933–34); Lucke and Hahndel (1933); Lucke, Heydemann, and Berger (1933); Lucke, Heydemann, and Hahndel (1933); Lucke, Heydemann, and Hechler (1933); Cattaneo (1934); Shpiner and Soskin (1934); and Steppuhn (1934).

tracts may produce hyperglycemia only if the splanchnic nerves and the adrenal glands are intact. Their observations clearly indicate that anterior-lobe extracts, by an effect on the central nervous system, may cause an increased liberation of epinephrin which in turn causes a glycogenolysis (in the liver) and a hyperglycemia. Besides adrenalectomy or splanchnotomy, the following procedures—with which are employed the technique and extracts of the authors cited—prevent hyperglycemia otherwise occurring after the administration of anterior-lobe extract: the injection of ergotamine (to paralyze sympathetic nerve endings); high spinal anesthesia; and anesthesia by "Somnifen" (considered to narcotize the brain stem). The extracts used were found to produce more marked effects in pancreatectomized dogs and to be more potent if introduced intrathecally. Lucke has named the substance causing these effects the "contra-insular hormone." According to his description (1934), some of which is not justified by his experimental data, its mechanism of action is complex.[17]

So far, in this section, the anterior-lobe extracts used appear to affect carbohydrate metabolism in a direction opposite to that following insulin. However, several investigators[18] have concluded that suitable anterior-lobe extracts are "pancreatropic"—i.e., they cause hyperemia and hypertrophy of the islet tissue of the pancreas, the formation of new islet tissue, and changes in the concentration of blood sugar or hepatic glycogen interpreted by the authors (Hoffmann and Anselmino) as indicating a hyperinsulinemia.

THE EFFECTS OF EXTRACTS OF THE PARS GLANDULARIS ON THE METABOLISM OF FATS

The effects of anterior-lobe extracts on the metabolism of fats probably cannot be adequately interpreted until more

[17] See also Fasold's observations in a case of *Glykogenose*.

[18] Anselmino, Herold, and Hoffmann (1933); Anselmino and Hoffmann (1933); Hoffmann and Anselmino (1933); and Bierring (1934). Also see Aron (1933) and p. 270.

extensive data have been gathered. The experimental evidence at hand does not justify the belief that the anterior lobe secretes a separate hormone which increases the rate at which fat is metabolized. In fact, the data have also been interpreted as indicating the opposite effect—an interference with the metabolism of fats.

A lipemia, which may be very marked, has been observed in the rabbit and dog after the administration of anterior-lobe extracts (which cause hyperglycemia and glycosuria as well). Simultaneously, there also occurs a ketonuria (Baumann and Marine, 1933; Evans, 1933; Houssay and others, 1933). Munoz (1933) stated that, although the injection of an alkaline anterior-lobe extract into the dog for 5 days might cause an increase in the concentration of fatty acids, cholesterol, or phospholipin in the blood,[19] hypophysectomy was followed by little change, if any. Rietti (1934) found that hypophysectomy in the dog was followed by a slight fall in the amount of acetone bodies excreted in the urine.

In 1930 Burn and Ling (also 1933) injected an extract of the pars glandularis (ox) into rats (body-weight, 120–180 g.) on a diet of butter. Chiefly in the 24 hours following an injection, there occurred an increase in the urinary excretion of acetone bodies by female rats (seven of twelve animals) but not by males (five animals). One year later, Anselmino and Hoffmann (1931) described a "fat-metabolism hormone" which caused an increase in the amount of acetone bodies in the blood of the rat.[20] At the time of the maximum change—about 2 hours after injection—the concentration of the acetone bodies had risen from an initial value of about 4 mg. per cent to about 12 mg. per cent. Most of the change was attributed to an increase in the concentration of β

[19] In no case was the concentration increased more than 76 per cent. Considerable changes were caused by extracts of the kidney.

[20] The effect was obtained by injecting the equivalent of 3 mg. of anterior pituitary "acetone-powder." A similar change was produced by the injection of 5 rat-units of prolan.

hydroxy butyric acid and was interpreted as indicating an increase in the rate of the metabolism of fats. The observations of Burn and Ling as well as those of Anselmino and Hoffmann have been confirmed not only in the rat, but also in man, the rabbit, and the dog.[21] However, the experimental conditions under which the later experiments were performed were sometimes different. Butts, Cutler, and Deuel administered an alkaline extract of the anterior lobe of the ox to rats also receiving diacetic acid; the extract caused a marked increase in the excretion of acetone bodies in the urine. Also, in fasting rats receiving a solution of sodium chloride (10 per cent) the injection of the extract elevated the excretion of acetone bodies from 1 mg. to 30–65 mg. These effects were not related to sex (male, female, and gonadectomized rats were used). Similar results were obtained in the later experiments of Deuel.

Hoffmann and Anselmino also found that the concentration of acetone bodies in the blood of the rat was increased following the injection of serum from dogs to which fat had been fed. This finding was interpreted as indicating that the fat-metabolism hormone is secreted by the pituitary at an increased rate in response to the body's need to metabolize an increased amount of fat. This phenomenon was employed by Goldzieher, Sherman, and Alperstein (1934) as a clinical test to determine whether or not the secretion of the hormone was normal. According to Funk (1933), extracts which cause a marked increase in the rate of excretion of acetone bodies in the urine of rats (about 2 hours after injection) can be obtained from the urine of man or animals.

[21] Hoffmann and Anselmino (1931); Boenheim and Heimann (1932); Magistris (1932–33); Butts, Cutler, and Deuel (1933); Anselmino and Hoffmann (1934); Deuel (1934); Rietti (1934); Schultze (1934); and Steppuhn (1934). See also Leiner (1934).

Magistris called the fat-metabolism hormone "orophysin." He believed that small amounts of the substance could be detected in the spleen, liver, cerebrospinal fluid, etc. The fat-metabolism hormone of Raab ("lipoitrin") is said also to occur in the pars neuralis and will be considered later.

How the substance affecting fat-metabolism is related to the substances affecting the metabolism of carbohydrates (either by increasing the liberation of epinephrin[22] or by some more direct mechanism) is not known; however, it seems probable that the effects are closely related. Rietti (1934) produced the most striking change in the excretion of ketone bodies in pancreatectomized dogs; after both thyroidectomy and pancreatectomy his extract still caused an increase in the hyperglycemia but no increase in the ketonuria. On the other hand, the substance obtained by Funk from the urine was equally effective in normal or thyroidectomized rats. Extracts may cause a fall in the concentration of hepatic glycogen without any change (Deuel), or with an increase (Steppuhn), or with a diminution (Schultze, 8–12 per cent change) in the concentration of liver-fat. As Deuel pointed out, the fat-metabolism hormone seems to oppose rather than to aid the metabolism of fat perhaps by interfering with the metabolism of carbohydrates. He found that, under appropriate conditions, the ketonuria produced by the injection of anterior-lobe extract into rats could be prevented by the administration of glucose.[23]

THE EFFECTS OF EXTRACTS OF THE PARS GLANDULARIS ON THE METABOLISM OF PROTEINS[24]

The effects of hypophysectomy on the metabolism of proteins has been considered already (chap. ii). Hypophysectomized animals, such as the dog, may excrete less nitrogen

[22] Epinephrin, e.g., causes a ketosis probably by interfering with the combustion of carbohydrate.

[23] Funk's extract (obtained from urine) produced, after a single injection, a greater ketonuria in rats on a low-fat diet than in those on a high-fat diet. Gaebler (1935) observed an increase in the rate of fat-oxidation in thyroparathyroidectomized dogs which had received two injections of anterior-lobe extract provided that the diet contained an appropriate amount—but not too much—carbohydrate.

[24] Including creatine-creatinine metabolism.

in the urine (e.g., one-third less) than normal dogs, especially if fasted. On a diet of meat, the hypophysectomized dog excretes about one-fourth less creatinine than the normal dog (Braier, 1931; Houssay, 1932). The concentration of amino-acids in the blood is about the same in hypophysectomized or normal dogs; likewise the rate of disappearance of glycocoll, injected intravenously, is about the same (Re, 1932).[25]

The important effect of anterior pituitary extracts on the protein metabolism is to alter the nitrogen balance in a positive direction. This is largely due to a diminished excretion of urea; also, there is a simultaneous fall in the concentration of the various substances making up the non-protein nitrogen of the blood (Teel and Cushing, 1930; Gaebler, 1933; and others). The same effects are observed in thyroparathyroidectomized dogs (Gaebler, 1935). Gaebler observed no notable change in the creatinine excretion of dogs which had received anterior pituitary extract. In the male or female rabbit, however, the excretion of creatinine in the urine may be increased about 25 per cent following the injection of anterior-lobe extract (Schrire and Zwarenstein, 1933–34). In gonadectomized rabbits, in which the rate of creatinine excretion is much higher than in normal animals, the extract has no appreciable effect. (Schittenhelm and Bühler [1935] believed that in man the anterior pituitary may be responsible for increases in the excretion of creatinine which normally is low because of the inhibiting effect of the internal secretions of the gonads.)

According to many clinical reports, the specific dynamic response to proteins may be reduced or disappear in disease (hypofunction) of the pituitary.[26] Fulton and Cushing

[25] According to Agnoli (1928-29), a lipoidal extract of the pars glandularis hastens the rate of catabolism of glycocoll injected intravenously into normal dogs.

[26] Examples of such reports are those of Plaut (1922); Liebesny (1925); Kestner, Liebeschütz-Plaut, and Schadow (1926); Peters (1930); and Sylla (1934).

(1932) and Johnston (1932), however, could detect no abnormality in the specific dynamic response to protein in patients with disease of the pituitary (both hypo- and hyperfunction). In reports such as that of Kestner and others, the administration of three tablets of "Präphyson" daily for 2 weeks was thought to have been followed by an increase in the specific dynamic response.

In the hypophysectomized dog the specific dynamic response is not lost but, because of a lowered basal metabolic rate, may be relatively increased (Gaebler, 1929; Artundo, 1931; and Mazzocco, 1933; see also Knipping, 1923). Some investigators have found that thyroidectomy lessens or prevents the specific dynamic response to protein (dog and rat). On the other hand, thyrotropic hormone is also said to lessen the response in man and in the dog (Schittenhelm and Eisler, 1932; Feuling, 1933).[27] The only experimental report indicating that the specific dynamic response is abolished by hypophysectomy is that of Foster and Smith (1926) who performed their experiments in rats. They concluded that the intraperitoneal injection of glycocoll produced a calorigenic effect only if both the pars glandularis and the pars neuralis were intact.

OTHER CONSIDERATIONS

Bromine in the pituitary.—The pituitary (particularly the pars glandularis) of the normal individual is said to contain a higher concentration of bromine than any other tissue (5–30 mg. per cent). The belief that this finding has a bearing on sleep or other forms of unconsciousness (e.g., narcosis) lacks sufficient experimental support (see Uhlmann, 1931–32; and Zondek and Bier, 1932).

Miscellaneous interrelationships or effects.—Anatomical studies of the pituitary of the rat and the pigeon, which had

[27] Sylla (1934) concluded that the specific dynamic response was normal in "thyrogenic obesity" in man and that it was low but could be raised by the injection of thyrotropic hormone in cases of "pituitary obesity."

received a vitamin-deficient diet, were made by Satwornitzkaja and Simnitzky (1928) and by Ueno (1934).

Studies of the effects of different anterior pituitary extracts on some of the constituents of the liver of the rabbit (water, glycogen, phosphorus, cholesterol, fatty acids, enzymes, and urea) were made by Chamberlain (1927) and Cruz-Coke and Altamirano (1930). Baltacéano, Vasiliu, and Paraschiv (1934) investigated the effect of an anterior-lobe extract on the secretion and composition of bile in dogs.

According to Sincke (1928) and Sawade (1929), the capillary endothelium of the pituitary (man, rat, and rabbit) is not part of the reticulo-endothelial system.

CHAPTER IX

THE PARS INTERMEDIA AND THE PARS TUBERALIS; THE HORMONAL REGULATION OF CHROMATOPHORES

NEARLY all the experiments in amphibia lead to the conclusion that the pars intermedia elaborates an internal secretion which causes a dispersion of the black pigment granules in the epidermal melanophores. As a result, the cell outlines can then be identified more or less completely, so that the change has often been called an "expansion."[1] This internal secretion of the pars intermedia can be identified not only in the pituitary of fish,[2] amphibia, reptiles, and birds but also in the pituitary of mammals, including man. The function of the hormone, except in amphibia and some fish, is not clear. It is thought by some to be concerned in visual adaptation in forms like the mammal. Certainly there is no experimental evidence supporting Biedl's belief (1922) that the pars intermedia is a "metabolism-gland." Therefore, except for the brief mention of a few experiments dealing with possible functions of the pars tuberalis, this chapter will be almost entirely concerned with the behavior of chromatophores in relation to internal secretion(s) of the pituitary body.[3]

The following are the chief chromatophores which may be found in fish, amphibia, and reptiles: melanophores, leuco-

[1] See Sumner (1933) and Mast (1933). Part of the terminology proposed by Sumner is used in this chapter.

[2] Hogben and Winton (1922) were unable to detect the hormone in the "pituitary" (subneural gland) of a tunicate (*Ascidiella*).

[3] An elaborate review of observations on the distribution and characteristics of chromatophores can be found in Fuchs's article published in 1914.

phores, xanthophores (or xantholeucophores), erythrophores, and guanophores (iridocytes). Xanthophores and erythrophores are sometimes classified together as lipophores. The most consistent effects of the hormone of the pars intermedia are on the chromatophores of amphibia. In animals of this class the hormone causes a dispersion ("expansion") of the melanin-granules (melanosomes) and an aggregation or concentration ("contraction") of the pigment granules of the xantholeucophores. In fish the effects vary in different species. In reptiles changes in the chromatophores have not been shown to be related to any internal secretion of the pituitary body.

The effects of hypophysectomy or of extracts of the pituitary on the chromatophores of fish. 1. *Hypophysectomy.*—After the removal of the neuro-intermediate lobe from the elasmobranch fish, *Mustelis canis*, there occurs a pallor of the skin due to the concentration of the melanosomes in the central part of the melanophores (Lundstrom and Bard, 1932). This effect is not produced by the removal of the pars glandularis or by injury of the hypothalamus. The reverse effect, darkening of the skin, is caused by the injection of extracts of the posterior lobe including an extract with pressor effects ("Pitressin") but not one containing chiefly the oxytocic principle ("Pitocin"). Lundstrom and Bard concluded that the control of the melanophores in this fish was a function of the neuro-intermediate lobe and that (the sympathetic nervous system as well as) tissue secreting epinephrin[4] probably played no important part as a supplementary controlling agency.

Matthews (1933) hypophysectomized a teleost fish, *Fundulus heteroclitus*, without affecting the chromatophore response to various backgrounds and to darkness. He concluded that, perhaps in teleosts generally, the control of the chromato-

[4] In both fish and amphibia epinephrin generally causes a pallor of the skin due to a concentration of the melanosomes.

phores was chiefly nervous rather than humoral.[5] However, as will be shown, the chromatophores of other teleost fishes may change in response to pituitary extracts.

2. *The effects of extracts.*—In several teleost fishes changes in the chromatophores may follow the injection of extracts of the pars intermedia or of the posterior lobe of the pituitary. To what extent the formation of pigment and the control of the chromatophores depend on the pituitary is not known except in *Fundulus* in which the pituitary appears to be of little importance in regulating chromatophores. In other teleost fishes the effects of hypophysectomy have not been observed except, perhaps, in the experiments of Giersberg (1932).

If isolated scales of the killifish, *F. heteroclitus*, are placed in a solution containing an extract of the posterior lobe, the melanosomes become concentrated in the central part of the melanophores (Spaeth, 1918; Wyman, 1924; and Matthews, 1933). (Previous treatment of the scales in order to cause melanosome dispersion may be necessary to demonstrate clearly this effect.) Odiorne (1933) could detect no change in the melanophores of *Fundulus* either after the injection of posterior-lobe extract into the intact fish or by placing scales in a diluted posterior-lobe extract. He also injected a posterior-lobe extract into catfish (*Amiurus nebulosus*) without subsequently observing any change in the melanophores. In the pope (a member of the perch family, *Acerina cernua*) and in *Gobio fluviatilis* the injection of a posterior-lobe extract is said to be followed by a dispersion of the melanosomes (Blanchard, Prudhomme, and Simmonet, 1932). Hewer (1926) concluded from his studies in the minnow that posterior-lobe extract causes a concentration of the melanosomes (melanophores) but dispersion of the erythrosomes (erythrophores) and xanthosomes (xanthophores). Recently

[5] See also the reports of Parker and that of Fries (1931).

the effect of pituitary extracts particularly on the erythrophores of other fishes has been studied.

At the time of spawning there occur changes in the pigmentation of fishes such as the stickleback (*Gastrosteus aculeatus*), the Bitterling (*Rhodeus amarus*), and the small carplike *Phoxinus laevis*. The most prominent alteration consists of the development of a brilliant red color in the ventral part of the body, especially about the fins. This "wedding dress" is much more prominent in the male and may persist for more than 2 months. According to Osterhage (1932), the pigmentary change is due principally to the formation of new pigment-containing cells as well as to the deposition of new pigment in old cells. Most of the studies on the dispersion of the erythrosomes ("expansion" of erythrophores) have been made in *P. laevis* in which the response appears to be more delicate than in other fishes. However, it appears that extracts of the posterior lobe or pars intermedia do not cause changes in the pigmentation so that the appearance is like that of a typical "wedding dress." The development of the latter also probably depends in part upon the gonads.

The first experiments in *P. laevis* were performed by Abolin (1925). He found that the injection of a posterior-lobe extract caused a dispersion of the pigment granules in all the important chromatophores (melanophores, xanthophores, and erythrophores). However, the melanophores did not behave like the other chromatophores. The response of the melanophores to posterior-lobe extract appeared earlier and was of shorter duration. Also, the melanophores, unlike the other chromatophores, seemed to be controlled partly by the sympathetic nervous system (see also Giersberg, 1931, and Smith, 1931). Others have observed that posterior-lobe or pars intermedia extract causes a dispersion of the melanosomes in *Phoxinus* (Osterhage, 1932, and Zondek and Krohn, 1932; on the other hand, Collin and Drouet, 1933, using "Pitressin" observed the opposite effect). Generally, how-

ever, changes in the erythrophores are regarded as being due to the secretion or extract of the pars intermedia. Indeed, some investigators limit their observations to the erythrophores.

In Giersberg's experiments (1932) the effects of the application of pressure to the pituitary *in situ* as well as those of pituitary destruction were investigated in *Phoxinus*. He concluded that the distribution of pigment granules in erythrophores and xanthophores was probably under the control of the pituitary whereas that in the melanophores was regulated by the nervous system. Pressure on the pituitary was followed by a dispersion of the xanthosomes and erythrosomes. Analogous experiments were undertaken by Collin and Drouet (1933) who used fish in full "wedding dress"; unlike Giersberg they found that pressure on the pituitary caused a concentration of the erythrosomes. Zondek and Krohn (1932) studied the effect of pituitary extracts on the appearance of the erythrophores. They concluded that the hormone[6] is specifically elaborated in the pars intermedia and described a technique for assaying the hormone in fish about 7 cm. long.[7] Peczenik (1933), unlike most observers who believe that the hormone acts directly on the erythrophores, concluded that part of the hormone's effect is on spinal autonomic centers. According to Zondek and Krohn, the injection of an extract of the pars intermedia (ox) may cause an increased formation of red pigment in the skin of *Phoxinus*.

Collin and Drouet (1934) as well as Stutinsky (1934) concluded that extracts of other tissues (e.g., thyroid, ovary, thymus, spleen, etc.) may also cause a dispersion of erythrosomes similar to that produced by extracts of the pars intermedia. They also believed that only the male is suitable for

[6] They proposed the name "intermedin."

[7] The maximum adult length is 14 cm.

assay inasmuch as the female *Phoxinus*, although only 6 cm. long, may or may not respond depending upon the condition of the ovaries. According to Wunder (1931) a typical "wedding dress" can be produced in the Bitterling by the injection of a testicular extract but not by the injection of oestrin. Abolin was impressed by the variable response of the chromatophores of *Phoxinus*.

The effects of hypophysectomy or of extracts of the pituitary on the chromatophores of amphibia. 1. *Anura.*—The effects of hypophysectomy on the chromatophores of tadpoles were first observed by Allen (1916) and Smith (1916). (See chap. ii, pp. 39–40.) The appearance of the hypophysectomized in comparison with the normal frog tadpole is shown in Figure 45.[8] The most striking changes consist of a concentration of the melanosomes, particularly in the melanophores of the epidermis, and a dispersion of the pigment granules in the xantholeucophores. Both of these changes are responsible for the silvery (albino) appearance of hypophysectomized tadpoles. It is also agreed that the amount of free melanin in the epidermis is reduced. According to Smith (1916, 1919–20) hypophysectomy in the tadpole is also followed by a reduction both in the amount of intracellular melanin and in the number of the epidermal melanophores. This has been questioned both by Allen (1917) and by Atwell. According to Atwell (1919, 1921), the melanosomes are also concentrated in the deep-lying melanophores; however, Smith observed no change either in these cells or in the retinal pigment cells. Smith found that the transplantation of the skin from a hypophysectomized to a normal tadpole was promptly followed by a return of the pigment granules of the xantholeucophores from the dispersed to the concentrated state.

Hypophysectomy in frogs or toads is likewise followed by a concentration of the melanosomes and a dispersion of the

[8] It appears that not all the pars buccalis was destroyed in Adler's tadpoles (Fig. 43).

xanthosomes (or xantholeucosomes).[9] Removal of the pars glandularis alone is not followed by such changes whereas they occur in a typical fashion after the removal of the neurointermediate lobe. Other experiments are in accord with the view that the hormone causing dispersion of the melanosomes is secreted by the pars intermedia. Among such observations is that of Bayer (1930) who investigated the pituitary of a frog which, among a large shipment, alone had a pallor of the skin. He found a pronounced atrophy of the pars intermedia due, he believed, to the invasion of a trematode, which had died subsequently. The transplantation of the pars intermedia (adult frogs) into normal or hypophysectomized tadpoles causes a marked dispersion of the melanosomes persisting as long as the graft remains alive (Allen 1920, 1925, 1928–30, and Swingle, 1921). If suspensions of the various parts of the ox-pituitary are injected into tadpoles, the most marked immediate effects are caused by extracts of the pars intermedia; suspensions of the pars glandularis were found to be more potent than those of the pars neuralis (Smith and Smith, 1923). (Other data on the distribution of this hormone in the pituitary and elsewhere are discussed later.)

Although in some amphibia light may directly affect the chromatophores, the melanophores of the frog (and probably toad) are altered chiefly because of optic stimuli. Adaptive coloration in these Anura, so far as the melanophores are concerned, appears to depend upon the nervous regulation of secretory activity in the pars intermedia. In support of this statement several types of experiments may be described. The removal of the eyes, but not spinal transection, abolishes the changes in the chromatophores adapting animals to light or dark backgrounds (Hogben and Slome, 1931, and others). Schürmeyer (1926) found that an injury of the floor of the

[9] Hogben (1923–24); Hogben and Winton (1923); Giusti and Houssay (1924); Houssay and Ungar (1924); Hogben and Slome (1931); and Zieske (1932).

third ventricle of the frog was soon followed by a dispersion of the melanosomes. This change was not prevented by transection of the spinal cord in the cervical region. From his experiments Zieske (1932) concluded that secretory fibers probably pass down the "stalk" and, after entering the neuro-intermediate lobe, terminate in the lateral portions of the pars intermedia. He found that, after the division of the neuro-intermediate lobe in the mid-line, the frogs (*Hyla arborea*) remained dark or black, whereas if similar incisions were made on either side of the mid-line, the coloration of the frogs changed from black to green.

If frogs are kept in complete darkness for about 20 minutes, the melanosomes become concentrated and the hormone causing their dispersion is said almost to disappear. On the other hand, exposure to light for as short a time as 15 seconds causes the reappearance of the hormone because of optic stimuli. The effective stimuli arise from the blue end of the spectrum; red or yellow light is much less effective (Koller and Rodewald, 1933). Rodewald (1935) later made a further study of these and related phenomena; however, unlike Jores (1934), she did not find that alkaline extraction of the pituitary of frogs kept in darkness "reactivated" the pituitary.

According to Dietel (1933), the melanosome-dispersing hormone causes a capillary dilatation in the frog.

The effects of an extract of the pars intermedia (ox) on the appearance of a normal frog is illustrated in Figure 52. Photomicrographs showing the cutaneous melanophores before and after the injection of the extract are reproduced in Figure 53. Hogben and Winton (1922 and later) as well as numerous other investigators have studied the effect of extracts on the melanophores of intact and hypophysectomized frogs and toads as well as on the isolated skin of the frog. Most of these reports are referred to later. However, ex-

tracts of the pars neuralis, which have been frequently employed, cause dispersion of the melanosomes or effects on

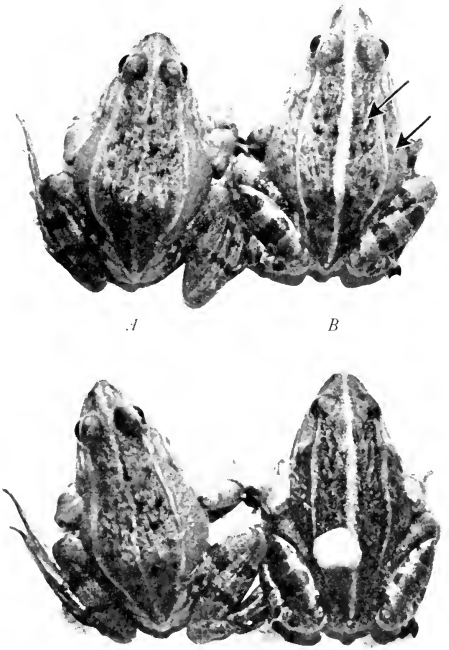


FIG. 52.—The effect of an injection of an extract of the pars intermedia (ox) on the dispersion of the melanosomes in the skin of the frog (*Rana nigromaculata*). Frog *A* received no injection; frog *B* received the extract. Top: before injection. Bottom: after the injection of the extract into frog *B*. Particularly note the blackening of the skin of the back and flanks (indicated by the arrows, frog *B*, top).

other chromatophores because of the presence of some substance other than the oxytocic or the vasopressor hormone.

2. *Urodela.*—With the exception of the newt, *Diemyctylus*, in which posterior-lobe extract was found to cause a concen-

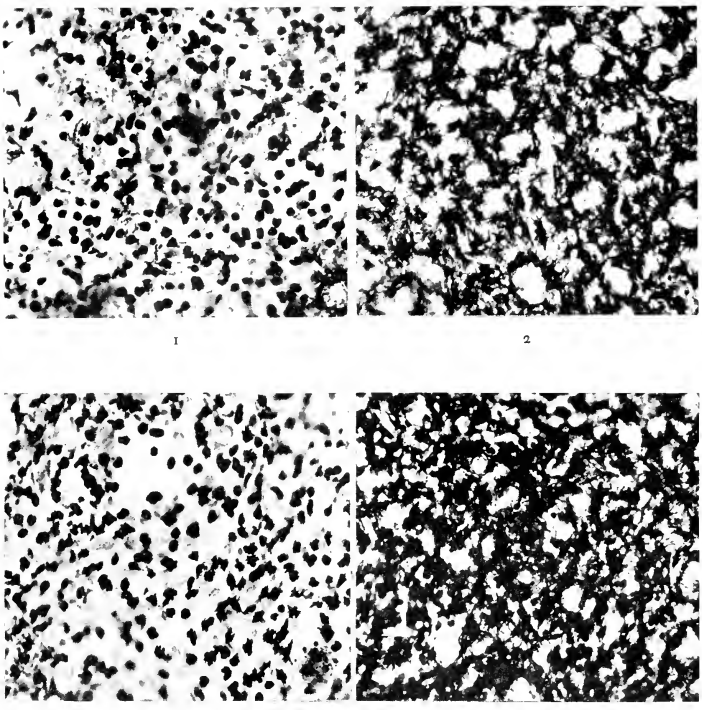


FIG. 53.—Photomicrographs of the cutaneous melanophores of the frogs of Figure 52. ×99. 1. Skin of back of frog *B*, top (before injection). 2. Similar area of skin of back of frog *B*, bottom (after injection). 3. Skin of flank of frog *A*, bottom (no injection). 4. Skin of flank of frog *B*, bottom (after injection).

tration of the melanosomes (Collins and Adolph, 1926),[10] the changes in the chromatophores of *Urodela* after hypophysectomy or after the administration of pituitary tissue or extract are similar to those already described in *Anura*. However, the observations are fewer and not so complete. The effects of hypophysectomy on the chromatophores of *Urodela* have been described by Blacher (1927), Marx (1929), Klatt (1931), and Dubowik (1933).[11] The effects of pituitary transplants or extracts have been investigated by Smith and Smith (1922), Burns (1930), and Noble and Richards (1932). (See also chap. vii.)

Witschi (1931) performed parabiosis experiments in newts (*Triturus torosus*) and frogs. If a larval normal newt and a larval hypophysectomized newt were united parabiotically, metamorphosis, although delayed, occurred in both. However, the cutaneous melanosomes were always more concentrated (lighter hue) in the hypophysectomized newt. Witschi also produced parabiotic union between normal and hypophysectomized frogs; after about 2 weeks, there was no difference in the melanophores of a pair of such animals.

The effects of drugs on chromatophores.—It is necessary to mention only a few of the many reports describing the effects or lack of effects of drugs on the chromatophores. Nearly all the experiments have been performed in intact frogs. Epinephrin causes a concentration of the melanosomes (Lieben, 1906, and others);[12] Kobayashi (1928) found that the effect of acetyl chlorine was similar. Hogben and Winton (1922) tested some of the commonly used alkaloids, glucosides, and amines (including barium chloride). Only nicotine or apocodeine caused dispersion of the melanosomes provided that

[10] According to Hogben and Slome (1931), light has important direct effects on the melanophores of *Necturus*.

[11] Other cutaneous changes, such as an interference with molting, may also occur.

[12] Dietel (1933) believed that epinephrin is not a hormonal antagonist of the melanosome-dispersing hormone under normal conditions.

paralytic doses had been administered. After death as well as under general anesthesia (ether, chloroform), the melanosomes are said to be dispersed, but not completely. Oxygen causes a concentration of the melanosomes; carbon dioxide (in concentrations described as "toxic") causes a dispersion (Hewer, 1922; Uyeno, 1922). For experiments with other drugs (guanidines, diuretics), see the reports of Ochoa (1928) and Zieske (1932).

The distribution in the pituitary body and in tissues and body fluids of the hormone(s) causing dispersion of the melanosomes or the erythrosomes. 1. *In the pituitary body.*—The melanosome-dispersing hormone can be detected in the hypophysis of the ox-fetus and of the fetus of the sheep (both at a fetal age of 3 months—Hogben and Crew, 1923); in the hypophysis of the embryonic pig (crown-rump length of 30 mm.—Snyder, 1928); and in the hypophysis of the human fetus (Ehrhardt, 1932).

There is fairly complete evidence, which has been reviewed already, that the pars intermedia of the amphibian pituitary secretes the melanosome-dispersing hormone. The distribution of the hormone in the mammalian pituitary has chiefly been studied in glands obtained from the ox and man. In considering the experimental data the reader should bear in mind that Spaul (1927) found that the amount of the hormone in the pars glandularis of the ox rapidly increased during the first few hours after the removal of the pituitary. This change was probably due to a rapid diffusion of the hormone from the posterior lobe (pars intermedia). Hogben and Winton (1922) performed their assays in the intact frog. They concluded that the pars intermedia contained the most (concentration) melanosome-dispersing hormone. The pars glandularis contained the least amount. That present in the pars neuralis was considered to have diffused from the pars intermedia. Van Dyke (1926) controlled histologically the dissected tissues (ox-pituitary) from which his extracts were

made. Using the isolated frog skin as a test object, he found that the pars intermedia contained the highest concentration of the hormone. The colloid of the ox-pituitary also contains the hormone(s) affecting the chromatophores (Smith and Smith, 1923; Zondek and Krohn, 1932).

Zondek and Krohn (1932) as well as Jores and Will (1934) agreed that the highest concentration of the erythrosome-dispersing hormone (*Phoxinus*) is found in the pars intermedia (ox). However, Jores and Will believed that the melanosome-dispersing hormone (isolated frog skin) is present in the basophil area (Smith) of the pars glandularis in slightly greater concentration than in the pars intermedia.[13] Their other results dealing with the distribution of the erythrosome-dispersing hormone do not agree with those of Zondek and Krohn.

The pituitary of the pregnant woman contains the melanosome-dispersing hormone, but little or no gonadotropic hormone (Ehrhardt, 1932; Zondek and Krohn, 1932). The pars intermedia of the human adult is at most a rudimentary structure. According to Roth (1932), the human pars glandularis is richer in melanosome-dispersing hormone than the "intermedia-zone" or the pars neuralis. He concluded that the basophil cells of the pars glandularis secrete the hormone. Jores and Glogner (1933) found that the concentration of the hormone was especially high in the basophil adenoma (pars glandularis) and low in the reserve-cell adenoma.

In the pituitary of the whale the erythrosome-dispersing principle is found in the pars glandularis but not in the pars neuralis (Valsö, 1934).

2. *The distribution in tissues and body fluids of substances causing erythrosome dispersion in Phoxinus or melanosome dispersion in the skin of the frog.*—According to Zondek and

[13] Jores is of the opinion that melanosome-dispersion (frog skin) is due to a hormone different from that causing erythrosome-dispersion (*Phoxinus*). See the later discussion.

Krohn (1932), extracts of the stalk and of the wall of the third ventricle may cause dispersion of the erythrosomes in *Phoxinus*. Lumbar or cisternal cerebrospinal fluid has no effect.

The effect of extracts of tissues or body fluids on the state of the melanosomes in frog skin has been determined by several methods such as by administration to the intact frog, perfusion of the hind limbs, or immersion of the isolated skin in the extract or body fluid. To what extent the effects observed really depend upon the presence of the pituitary hormone is not known. Melanosome dispersion has been caused by the following tissues or fluids or extracts of these: hypothalamus, cerebrospinal fluid (lumbar fluid is often reported not to have an effect), eye (and aqueous humor), blood, urine, and colostrum.[14]

Effects in mammals attributed to the hormone(s) causing chromatosome dispersion.—According to Holmquist (1934) and Jores and Beck (1934), the "melanophore-hormone" causes, after repeated administration, a hypertrophy of the adrenal cortex (rat, guinea pig, rabbit) without affecting the amount of either ascorbic acid or epinephrin. Jores (1933) and Jores and Hotop (1934) reported that the instillation of an extract containing the hormone shortened the time required for adapting the eye to darkness. They believed that the pituitary of animals with nocturnal habits contained a higher concentration of the hormone than that of animals with diurnal habits. Jores also reported that the pituitary of the rabbit kept in darkness contained more melanosome-dispersing hormone than the pituitary of the rabbit kept in well-lighted surroundings.

There is no satisfactory evidence that the secretion of the

[14] Houssay and Ungar (1924); Krogh (1926); Trendelenburg (1926); Ehrhardt (1927); McLean (1928); Karplus and Peczenik (1930); Candela (1932); Dietel (1932); Collin and Drouet (1933); Jores (1933); Jores and Velde (1933); and Konsuloff (1934).

chromatosome-dispersing hormone is related to pigmentation in mammals.

Zondek (1935) reviews the clinical evidence in favor of the view that extracts of the pars intermedia may cause antidiuresis in cases of diabetes insipidus.

The assay of hormone(s) causing dispersion of chromatosomes.—The assay of the hormone affecting the melanophores of the frog has been carried out by means of injections into intact frogs or toads (Hogben and Winton, 1922–23; Hogben and Gordon, 1930), by perfusing the hind limbs or a greater portion of the body (Fenn, 1925; Krogh, McLean), and by immersing isolated frog skin in a solution of the material to be tested (Trendelenburg). If reliability is taken into account, the last-named method appears to be the most sensitive and, according to Jores, can be employed with a maximum error of 25 per cent.

Zondek and Krohn have described a method of determining the presence of the erythrosome-dispersing hormone by observing the effects of solutions injected into *P. laevis*.

From all the preceding discussion it is apparent that changes in the melanophores of fish or frogs cannot be used as a means of assaying the active principles of the pars neuralis as was proposed by Spaeth (1918), Loewe and Ilison (1925), and Treuter (1925).

Does the pituitary secrete more than one hormone affecting the chromatophores?—This question has been raised by Jores[15] who has concluded that the substance causing melanosome dispersion (frog) is different from that producing erythrosome dispersion (*Phoxinus*). The distribution of the "hormones" in the pituitary of the ox is said to differ. However, differences which are not great are difficult to evaluate because of possible postmortem diffusion and because of the errors of assay. Jores and Will concluded that "activation" of the erythrosome-dispersing hormone is accomplished by

[15] Jores and Lenssen (1933); Jores (1934); and Jores and Will (1934).

means of "acid" whereas "activation" of the melanosome-dispersing hormone is effected by means of "alkali." They also observed that, if solutions at an alkaline pH were boiled, the potency of a melanosome-dispersing hormone was increased whereas that of an erythrosome-dispersing hormone was diminished. The "erythrophore-hormone," but not the "melanophore-hormone," is readily soluble in absolute ethyl alcohol (however others, including Jores, have reported that the "melanophore-hormone" is soluble in absolute alcohol). They believed that the erythrosome-dispersing hormone is secreted by the pars intermedia and that the melanosome-dispersing hormone is secreted by the basophils of the pars glandularis.

Rodewald's observation (1935) should also be mentioned. She found that the pituitary of frogs kept in the dark caused practically no melanosome dispersion in the frog, but still caused erythrosome dispersion in *Phoxinus*.

The preparation of extracts producing changes in the chromatophores; the chemical properties of such extracts.—Prior to 1930, the extraction of the melanosome-dispersing hormone had commonly been accomplished by boiling the tissue (e.g., acetone-desiccated posterior lobe) for a few minutes in a dilute (0.25 per cent) solution of acetic acid. In 1930, however, Hogben and Gordon showed that the addition of NaOH (final concentration 1.35 N) to an extract of the pars neuralis abolished the pressor effect of the extract but increased the extract's melanosome-dispersing effect. Hogben and Gordon believed that, by its local vasoconstricting action, the vasopressor hormone had lessened the melanosome-dispersing effect of the extract. Recent work of others, however, has led to the conclusion that extraction in an alkaline medium "activates" or liberates more of the hormone affecting the melanophores. Methods employing an alkaline extraction-medium initially have been described by Dietel (1933–34) who used a saturated solution of $Ba(OH)_2$ and by Jores and

Glogner (1933) who used N/10 NaOH. Dietel (1934) purified his extract further by precipitation with acetone and by dissolving the active principle, precipitated by acetone, in boiling absolute alcohol. The alcoholic extract, after the removal of the solvent, was dissolved in water. The potency of the extract was high (1 "*Phoxinus*-unit," 0.2 $\gamma = 0.0002$ mg.; 1 "frog-unit," 0.0003 γ). Zondek and Krohn (1932) recommended that 0.25 per cent acetic acid be used for the initial extraction of the erythrosome-dispersing substance.

It has been reported that blood may "activate" the chromatophore-affecting principle contained in a pituitary extract (Popa and Fielding, 1933; Jores and Will, 1934).

Solutions of the chromatophore-dispersing principle(s) can be prepared free from protein; the Pauli reaction is negative. The hormone readily withstands boiling even in a solution containing N/10 NaOH (see pp. 315–16). The hormone is quite soluble in various concentrations of ethyl alcohol including hot absolute alcohol; it is insoluble in ether and acetone, and only slightly soluble in butyl alcohol and chloroform. Dietel (1933) considered that it was not an easily adsorbed substance (see also Houssay and Ungar, 1924, and Jores and Velde, 1933).

Several investigators have confirmed the observation of Hogben and Winton (1922) that the chromatosome-dispersing hormone(s) is destroyed by tryptic but not by peptic digestion. Light and particularly ultraviolet radiation are said to inactivate the hormone especially if it is exposed when in an acid solution (Dietel, 1932; Jores, 1932; Zondek and Krohn, 1932). Although the chromatosome-dispersing hormone(s) has sometimes been identified with the pressor principle (but less frequently with the oxytocic principle) of the pars neuralis, its distribution, its physico-chemical characteristics (solubility, ultrafiltration, etc.), and its survival in alkaline solution even after boiling have all served to demonstrate that it is not identical with either the vaso-

pressor or the oxytocic principle (Hogben and Winton, 1922–23; Dreyer and Clark, 1924; Houssay and Ungar, 1924; Knaus, Dreyer, and Clark, 1925; Gaddum, 1928; Rowe, 1928; Hogben and Gordon, 1930; and Stehle, 1934).

THE PARS TUBERALIS

The pars tuberalis of the pituitary of the ox appears to have no significant effect on either the uterus (contraction of isolated uterus) or on the blood pressure (Atwell and Marinus, 1918). Later (1927) Atwell found that the intravenous administration of an extract of the pars tuberalis to the anesthetized rabbit caused a diuresis which, unlike that due to the vasopressor principle, was preceded by no short period of anuria and was accompanied by no change in the blood pressure.

Hogben and Slome (1931) concluded from extirpation-experiments that the white-background response of *Xenopus laevis* depends upon a secretion of the pars tuberalis. Further, they inferred that in the hypophysectomized frog (which is hypophysectomized except for the pars tuberalis), the secretion of the pars tuberalis antagonizes the melanosome-dispersing effect of pituitary extract.

CHAPTER X

THE ACTIVE PRINCIPLES OF THE PARS NEURALIS; IS THERE CONVINCING EVIDENCE THAT THE PARS NEURALIS IS A GLAND OF INTERNAL SECRETION?

NEARLY all the extracts of the pars neuralis which have been used commercially or for scientific investigation have been obtained from the most convenient source—the posterior lobe of the ox-pituitary.[1] The simpler extracts or the fractions with predominantly vasopressor effects usually contain the hormone causing a diffusion of the melanosomes. Inasmuch as there is satisfactory evidence that this hormone is derived from the pars intermedia, its presence in posterior-lobe extracts will require no further discussion (see chap. ix). From the pars neuralis itself, two extracts with different effects have been separated: (1) the oxytocic or uterine-stimulating principle, and (2) the vasopressor principle (elevating the blood pressure, stimulating the bowel [particularly the colon], and, depending upon conditions, causing a moderate diuresis or inhibiting a diuresis which would occur otherwise).[2]

THE DISTRIBUTION OF THE ACTIVE PRINCIPLES

The initial extraction of the active substances of the pars neuralis is a simple procedure. Posterior-lobe tissue, preferably in the form of a powder made by dehydrating and defatting the fresh tissue by acetone, is thoroughly mixed with

[1] The posterior lobe includes both the pars neuralis and the pars intermedia.

[2] On the basis of comparative assays of simple, commercial extracts of the posterior lobe Bijlsma, Burn, and Gaddum (1928) concluded that neither the oxytocic nor the pressor principle is responsible for diuresis inhibition. In all subsequent work the vasopressor fraction has been found to cause diuresis inhibition.

a dilute (0.25–0.50 per cent) solution of acetic acid; the mixture is quickly brought to boiling and filtered. The water-clear extract can then be stored in ampoules and sterilized by a fractional method. Usually, but not always, such extracts contain about the same proportions of oxytocic and vasopressor principles. This and other evidence have convinced some investigators like Abel that only one hormone existed originally and that the oxytocic and vasopressor principles are derived from a single substance. However, until this single complete substance has been isolated in pure form, it is simpler to conclude that separate oxytocic and pressor principles exist in the pars neuralis.

According to Herring (1913), the pituitary of the cyclostome (*Petromyzon fluviatilis*) contains little or no vasopressor principle. This is also true of the pituitary of an elasmobranch fish (*Raja batis*, or skate); the pituitary of this fish, however, was found to cause a "secretion" of milk in the lactating cat as well as a contraction of the isolated rat's uterus (Herring, 1915). In the teleost fish (*Gadus morrhua*, cod) the pituitary but not the saccus vasculosus contains the pressor principle (Herring, 1908). The active principles characteristic of the mammalian pars neuralis are found in the pituitary body of amphibia, reptiles, and birds.

Nearly all the pressor and oxytocic substances in the pituitary of the fowl are found in the pars neuralis (De Lawder, Tarr, and Geiling, 1934). In the ox-pituitary the different anatomical divisions can be rather easily separated. The pars neuralis contains the highest concentration of oxytocic and pressor (including antidiuretic) principles; all the other divisions, except the pars intermedia, contain only very low concentrations of the hormones (Herring, 1915; Hogben and De Beer, 1925; van Dyke, 1926; and Kurose, 1929). Herring as well as Hogben and De Beer concluded that the pars intermedia contained relatively more oxytocic than pressor principle. However, Herring's estimate of the

concentration of pressor hormone in the pars intermedia in terms of that in the pars neuralis was undoubtedly too low. The pars intermedia probably contains one-fourth (and often less) the concentration of oxytocic hormone found in the pars neuralis; the concentration of pressor hormone in the pars intermedia is probably less than one-sixth that in the pars neuralis.

"Units" of pressor or oxytocic hormone will be referred to frequently in this chapter and in those succeeding it. The international standard powder, which is almost everywhere accepted as a standard, is arbitrarily considered to contain 2 units of whatever active principle is under investigation in each milligram of powder.[3] According to Simon (1934), the rat-pituitary contains about 0.8 unit of pressor or oxytocic principle. Like others he found that the amount present was not related to body-weight (100–300 g.). Activity, fasting, adrenalectomy, etc., did not alter the total amount of the hormones; however, a reduction in the amount of both principles occurred if the supply of water in the diet was deficient. Pak (1926) found that the amount of oxytocic hormone in the rat's pituitary was not affected by thyroidectomy, thyroid-feeding, or poisoning by "arsenic" or carbon monoxide; the amount of the hormone was often reduced in animals poisoned by mercuric chloride or diphtheria toxin. In four of five animals faradic stimulation of the cervical sympathetic appeared to cause an increase in the total amount of the oxytocic principle. Simon and Kardos (1934) estimated that the amounts of pressor principle in the pituitary of the guinea pig, rabbit, and cat were 0.5–1.3 units, 1.3–2.5 units, and 5.6–13.1 units, respectively; the amounts of oxytocic principle appeared to be 0.4–1.0 unit, 0.6–1.5

[3] The international standard powder was prepared by Smith and McClosky (1923–24). In the German literature the international unit is frequently called a *Voegtlin-Einheit.*

One mg. of international standard powder represents about 7 mg. of fresh posterior lobe (ox).

units, and 5.0–8.1 units, respectively. The concentration of hormone (pressor) was about the same in the posterior lobe of the ox and the rabbit, but was considerably higher in the posterior lobe of other animals.

In the cat as in the rat thyroid-feeding or thyroidectomy does not affect the amount of posterior-lobe principles (Herring, 1921). Castration (of the toad) or ovariectomy (guinea pig) probably does not affect the amount of the oxytocic hormone in the pituitary (Siegert, 1929; Novelli, 1932). According to Jores and von Wittern (1934), a marked increase in the amount of oxytocic principle is found late in pregnancy in the rabbit. Their conclusions are based on studies in only a few animals; moreover, their estimate of the total amount of oxytocic principle in the pituitary of the non-pregnant rabbit (0.05–0.25 unit) is inexplicably lower than that of Simon and Kardos (0.6–1.5 units). Smith and McClosky (1923) concluded that the concentration of oxytocic principle in the posterior lobe of the ox is the same in both male and female animals as well as after gonadectomy; similarly, the concentration of the hormone is not different at different times of the year. The potency of the human pars neuralis has been investigated by Lampe (1926), Jores and Zschimmer (1934), and Simon and Nagy (1934). Differences related to sex were not observed. The concentration of hormone may be highest in the infant; the total amount (maximum, 30 units) appeared to be greatest in the age-period 18–50 years (Simon and Nagy; Jores and Zschimmer believed the maximum occurred in the seventh decade). The conditions necessarily were not uniform (5.5–82 hours post-mortem); the total amounts of hormone found varied greatly.

THE ASSAY OF THE ACTIVE PRINCIPLES

The oxytocic principle.—Following the discovery of Dale, Bell and Hicks, and others (1909) that extracts of the pars neuralis cause a powerful contraction of the smooth muscu-

lature of the uterus, this phenomenon was soon employed as a means of assaying posterior-lobe extracts. However, no generally satisfactory method of quantitative assay was possible until the international standard powder became available. A salt of histamine, which was first recommended by Roth (1914), is unsatisfactory not only because its pharmacological behavior is different (e.g., it causes a relaxation of the rat's uterus) but also because the oxytocic effects of extracts are quantitatively different if a histamine salt and a posterior-lobe extract are compared as standards.

Today the isolated uterus of the immature guinea pig immersed in some modification of Locke's solution is most generally employed for the biological assay of the oxytocic principle. An effort is made to cause equal and reproducible (in the sense of equality of contractions) submaximal contractions of the uterus both by the standard and by the unknown extract. The details of technique vary considerably; an example of a method widely followed is that of Burn and Dale (1922).[4] With good technique an assay may be performed with an accuracy of ± 20 per cent.

A study of the effects of changes in the ionic environment on the contraction of the isolated guinea pig's uterus in response to posterior-lobe extract was made by van Dyke and Hastings (1927). (See also Martinescu and Popoviciu [1925] and Salzberg [1931].)

According to Trendelenburg (1928) and Pénau, Prudhomme, and Simmonet (1931), the isolated uterus of the young sheep, although less sensitive than the guinea-pig uterus, can be satisfactorily used for the assay of the oxytocic principle. Schübel and Gehlen (1928, 1933) recommended that quantitative assay be performed in the puerperal cat (2–4 days postpartum) by distending the uterus with fluid

[4] For other reports on the technique of assay, see Trendelenburg and Borgmann (1920); Trendelenburg (1922 and later); Kochmann (1921); Stern and Peyrot (1921); Smith and McClosky (1924); Sawasaki (1925); Pénau and Simmonet (1925–26); Fromherz (1926); and Gulland (1933).

under a pressure of 1–4 cm. of water and determining whether or not the intra-uterine pressure is raised by the administration of extract. They declared that the quantitative assay can be expressed in absolute "cat-units" (intravenous dose about 0.01 unit per kilogram cat). The same cat can be used for several assays.

The pressor principle (or its associated principles). 1. *The pressor principle.*—The assay of the pressor principle is often difficult because doses after the first may bring about progressively smaller increases in the blood pressure (tachyphylaxis). The extract should, of course, be free of depressor substances. To avoid tachyphylaxis the animal used for assay should be carefully chosen; doses should be moderate or small and must not be administered too frequently. The anesthetic, if any, is also of importance. Hogben, Schlapp, and Macdonald (1924) used the "spinal" cat into which they gave an intravenous injection at intervals of 1 hour. They recommended that the dose be about one-half that which produces a maximal response. Swanson (1929) has used this method or has used cats anesthetized by means of "Amytal"; he made injections every 30 minutes. In the author's experience the method used by Kamm and his co-workers (1928) is satisfactory. By this method the pressor response to intravenous injections of small doses of posterior-lobe extract is determined every 15 minutes in dogs deeply anesthetized by "Chloretone."

The determination of a vasoconstrictor effect by perfusing an isolated structure such as the rabbit's ear cannot be made quantitatively with posterior-lobe extracts. Moreover, such a test object is relatively insensitive. Heymans (1925) has performed assays by determining the vasoconstrictor effect of posterior-lobe extracts on the vessels of the perfused head of the rabbit.

2. *The principle stimulating the musculature of the bowel.*—According to Simon (1933), this principle (which is often

considered to be identical with the pressor principle) can be assayed accurately by using the isolated ileum of the guinea pig. As little as the equivalent of 1 unit in a liter of Tyrode's solution can be detected.

3. *The principle inhibiting water diuresis (at present considered to be identical with the pressor principle).*—The inhibition of water diuresis in unanesthetized animals has been used as a means of assaying posterior-lobe extracts in man, the dog, the rabbit, the rat, and the mouse. The adult human being is exceedingly sensitive; the effects of a total subcutaneous dose as small as 0.2 unit can be detected (Burn). The dog is more sensitive than the rabbit (Bijlsma, 1925; Kestranek, Molitor, and Pick, 1925).

The suitability of the dog with a fistula of the bladder for the assay of the diuresis-inhibiting principle also has been studied by Molitor (1926), Bijlsma, Burn, and Gaddum (1928), Glaubach and Molitor (1932), and Pénau and Simmonet (1934). Apparently the response of dogs varies considerably; therefore, if the extracts are to be given subcutaneously, small animals which can be used in larger numbers should be employed. Stehle (1934) found that, by the intravenous injection of the extract into dogs with bladder fistulae, 0.001 unit of the diuresis-inhibiting extract could be detected. Bentz, Marx, and Schneider (1934) also performed assays in the dog by administering extracts intravenously.

Accurate assay of the diuresis-inhibiting hormone probably can be performed most conveniently by using the mouse or the rat. Large enough groups of animals can then be used so that the assay will take into account the naturally occurring variations in response. Gibbs (1930) was the first to perform assays in mice. He administered tap water intraperitoneally and injected the posterior-lobe extract subcutaneously. He then compared the rate of secretion of the urine by control mice (water only) with that by mice receiving both water and the extract. This method has been extended and refined

by Nelson and Nelson (1931), and Nelson and Woods (1934). One of the most convenient methods appears to be that of Burn (1931) who used rats to which he administered by stomach-tube 5 cc. of water per 100 grams body-weight as well as a posterior-lobe extract subcutaneously (dosage range: *ca.* 0.002–0.012 unit per 100 grams body-weight). The assay is based upon the time elapsing between the administration of water and the maximum secretion of urine during periods of 15 minutes. The elapsed time is naturally greater, the larger the dose of extract. By using at least sixteen rats and by referring to a previously constructed curve in which was shown the relationship between dose and time elapsing until maximum urinary secretion occurred, Burn could estimate the potency of an extract with a maximum error of less than ±20 per cent. Marx (1933) also has used the rat in assaying the diuresis-inhibiting hormone.

In the urine secreted during the inhibition of water diuresis by posterior-lobe extracts or the vasopressor fraction the concentration of chloride is increased—sometimes markedly (see Fig. 55). This "chloride-concentrating" effect of an extract may be investigated to strengthen the belief that the effect of an extract is similar to the effect of the vasopressor hormone. However, the phenomenon appears to be of little value for purposes of quantitative assay.

The toxicity of the active principles.—The toxicity of the active principles of the pars neuralis has been approximately determined in only a few animals. In mice it is said that the "lethal dose" is 1,700 pressor units per kilogram body-weight (total dose divided over 12 hours; Hill, Long, and Bischoff, 1932) or 6,000–8,000 units per kilogram body-weight intraperitoneally (Haferkorn and Lendle, 1933). According to Voegtlin and Dyer (1924), the subcutaneous lethal dose in the rat is about 2,200 units (1,080 mg.) per kilogram body-weight; they considered the intravenous lethal dose to be about 160 units per kilogram body-weight. Bischoff and

Long (1931) stated that the lethal dose of the vasopressor fraction administered to rabbits intravenously is 25 units per kilogram body-weight; 3–15 units intravenously per kilogram per hour killed some rabbits within 2–3 hours.

THE PREPARATION AND THE CHEMICAL PROPERTIES OF THE ACTIVE PRINCIPLES OF THE PARS NEURALIS

How many active principles can be extracted from the pars neuralis?—Although Abel and his collaborators have maintained that the pars neuralis contains only one active principle from which are derived the oxytocic and the vasopressor fractions, this single, complete hormone has never been secured in pure form. Until this has been accomplished, it is just as reasonable and more convenient to consider that the two fractions represent two different substances not previously combined in one molecule. None of the active principles has been prepared in pure form. Histamine certainly is not the oxytocic principle (Guggenheim, 1912; Dudley, 1919; Hanke and Koessler, 1920; and Dale and Dudley, 1921). Thus far only two fractions have been secured: the oxytocic fraction (oxytocin, α hypophamine, "Pitocin," "Orasthin") and the vasopressor fraction (vasopressin, β hypophamine, "Pitressin," "Tonephin"). Although it has been suggested that the substance inhibiting water diuresis is not identical with the oxytocic or the vasopressor substance (Bijlsma, Burn, and Gaddum, 1928), and although Kamm, Grote, and Rowe (1931) stated that they had obtained a "derived hormone" with powerful antidiuretic effects but without any pressor action, most investigators believe that the most potent preparations with vasopressor effects are similarly the most potent preparations with antidiuretic effects.

Dudley (1919, 1923), followed by Schlapp (1925) and Draper (1927) who confirmed and extended Dudley's observations, was clearly able partly to separate the oxytocic and

the vasopressor substances. Kamm and his collaborators (1928) went much further. Not only were they able to effect a much more complete separation of the oxytocic and the pressor principles, but they also could account quantitatively for the oxytocic and pressor "potency" in the crude material with which they started. On the basis of their own work and that of others they concluded that these two active principles were amines. In terms of international standard power their oxytocic substance had been concentrated one-hundred-and-fifty fold, and their vasopressor substance, eighty fold. Both substances appear to have a molecular weight of about 600 (Kamm, 1928). Du Vigneaud and his collaborators (1933) investigated some of the chemical differences between purified oxytocic principle (500 units per mg.) and vasopressor principle (200 units per mg.). The oxytocic principle appeared to contain about 9 per cent cystine (Sullivan-reaction), whereas the pressor principle contained scarcely any; however, both principles contained about 3 per cent sulphur. More tyrosine (?) in terms of phenolic groups was found in the oxytocic fraction (14.3 per cent) than in the pressor fraction (10.5 per cent).

Stehle (1933–34) has also described a method of separating in potent form the oxytocic and the pressor fractions. Stehle's method is simpler than that of Kamm and others. Some chemical properties of the oxytocic principle as well as attempts to purify it are described in the papers of Gulland and Newton (1932), Gulland (1933), Guha and Chakravorty (1933), and Das and Guha (1933–34).

As a rule the oxytocic and the pressor principles occur in about the same proportion in the pars neuralis of the ox. They dialyze through collodion membranes at about the same rate (Smith and McClosky, 1924, and Kamm, 1928). They are destroyed at about the same rate by acid (e.g., by boiling in 0.5 per cent HCl) or by alkali (e.g., 1 or 2 N NaOH at room temperature). Fractionally sterilized and sealed in

ampoules, solutions of the active principles at pH 3–4, if kept in the icebox, retain their activity without loss for at least a year (Smith and McClosky, 1924). The heat stability of aqueous extracts at one or different pH's has been studied by Smith and McClosky (1924), Gerlough (1930), Gerlough and Bates (1930), and Guha and Chakravorty (1933). The effects of digestion by different enzymes have been studied by Dale and Dudley (1921), Rees and Whitehead (1923), Thorpe (1926), and Gulland and Macrae (three papers, 1933).

IS THERE CONVINCING EVIDENCE THAT THE PARS NEURALIS IS A GLAND OF INTERNAL SECRETION?[5]

Evidence bearing on this question has been briefly discussed already (chap. ii). It is proposed here to consider in greater detail the numerous data which support or deny the belief that the pars neuralis (perhaps in association with the pars intermedia) is an internally secreting gland of some importance. The simplest argument in favor of an affirmative answer to the question proposed above is deductive: substances having powerful effects on the movements of the uterus, on the blood pressure, and on the secretion of the urine can be extracted from the pars neuralis; therefore, in life these substances are secreted and produce, in a less exaggerated fashion, their characteristic effects. This argument, however, does not attempt to explain why the posterior lobe of the male animal contains just as much oxytocic principle as the female posterior lobe; it also leaves out of account the function of the oxytocic hormone in female animals of lower classes which possess no uterus.

The evidence furnished by studies of hypophysectomized animals.—Hypophysectomy is probably never complete; the most important tissue remaining is a large part of the pars

[5] For a discussion of the possible origin and paths of secretion of the active principles of the pars neuralis, see chap. i.

tuberalis. Extracts of the pars tuberalis may have some pharmacological effects resembling those of the pars neuralis. Quantitatively, however, these effects are much weaker than those of the pars neuralis or the pars intermedia. Also, it is not known to what extent the effects are due to the post-mortem diffusion of the active principles of the pars neuralis. On the other hand, some effects resembling those of posterior-lobe extracts have been obtained by administering extracts of the pars tuberalis and overlying tuber cinereum after hypophysectomy. It must be admitted, therefore, that observations in hypophysectomized animals do not exclude the possibility that active principles resembling those extracted from the pars neuralis are vicariously secreted by the tissues of the pars tuberalis and/or tuber cinereum. In animals hypophysectomized by an adequate technique, however, we can obtain information on the importance of the pars neuralis and the pars intermedia.

Krogh and Rehberg (1922) concluded that the vasomotor system in the frog is unstable after hypophysectomy. Dilatation of the capillaries often followed by rapid transient constriction or dilatation was observed. They were inclined to believe that the effects were partly due to an absence of the hormone maintaining the tone of the capillaries. (See also the later work of Krogh [1929].) According to Orias (1934), the blood pressure of toads (*Bufo arenarum*) 1 month after operation is lower after total hypophysectomy than after extirpation of the pars glandularis (control: 38 mm. Hg; extirpation of the pars glandularis: 29 mm. Hg; hypophysectomy: 17 mm. Hg). This difference can hardly be attributed to the loss of the pars neuralis inasmuch as Orias found that the blood pressure of hypophysectomized toads was elevated to about equal levels by implants of either the pars neuralis (50 mm. Hg) or the pars glandularis (46 mm. Hg).

The blood pressure of the mammal (dog) may be lower after the removal of the pars glandularis but not after the

removal of the pars neuralis (Braun-Menendez, 1932). Hypophysectomized dogs may metabolize water like normal dogs (Houssay and Hug, 1921, and others).

Despite all that has been written on the presumed importance of the oxytocic hormone in parturition, there is good experimental evidence that normal parturition can occur in the dog, cat, and rabbit after hypophysectomy or after the removal of the posterior lobe (Aschner, 1912; Dott, 1923; Allan and Wiles, 1932; Firor, 1933) and in the mouse and rat after the removal of the posterior lobe or the whole pituitary (Smith, 1930; Selye, Collip, and Thomson, 1933–34). In Smith's carefully controlled experiments the whole of the pars neuralis and the pars intermedia was removed. Subsequently, pregnancy, parturition, and lactation occurred exactly as in normal animals. Whether or not, as some believe, hormones identical with or similar to those of the pars neuralis are produced vicariously by the pars tuberalis and the tuber cinereum cannot be decided from the available data. Earlier reports (e.g., Trendelenburg, 1924; Miura, 1925) indicated that the oxytocic substance of cerebrospinal fluid disappeared after hypophysectomy. Later work, however, seemed to show that hypophysectomy merely lowered the concentration of the substance and then only temporarily (Geesink and Koster, 1928; Sato, 1928; Trendelenburg, 1928; Trendelenburg and Sato, 1928).[6] Trendelenburg and Sato concluded that vicarious production of the active principles of the pars neuralis took place in the tuber cinereum. After hypophysectomy the tuber cinereum was found to contain increased amounts of oxytocic and antidiuretic (including "chloride-concentrating") substances. (See also the comments in chap. ii.)

Verney's acute experiments (1926) have been discussed already (pp. 74–75). According to Verney, blood which has

[6] See also McLean's account (1928) of changes or lack of changes in the concentration of oxytocic substance in the blood of hypophysectomized dogs.

circulated through the head and is then circulated through the isolated kidney may not only inhibit the secretion of the urine but also bring about an increase in the concentration of chloride in the urine. However, if the pituitary body has been removed, the blood causes no similar change in the secretion of the urine. Experiments confirming those of Verney have been performed by Compère (1932–33).[7] The conclusion reached by means of such experiments has appeared to Fee (1929) and to Newton and Smirk (1934) not to be justified. Indeed, Newton and Smirk believed that neither the pituitary body nor the hypothalamus are essential for the control of water diuresis.

In Dixon's acute experiments (1923), various procedures caused marked changes in the apparent concentration of oxytocic hormone in the cerebrospinal fluid of dogs. However, he was unable to explain his observation that no diminution occurred after hypophysectomy.

Can the active principles of the pars neuralis be recognized in the cerebrospinal fluid and blood of normal or diseased animals? 1. *The oxytocic principle.*—The concentrations of the "hormones" of the pars neuralis in the cerebrospinal fluid (in most experiments, the oxytocic principle has been investigated) vary remarkedly in the different reports. A "normal" variation of 300–2,000 per cent has been found by several authors who investigated cerebrospinal fluid or blood. In normal mammals estimates of the concentration of oxytocic substance in cerebrospinal fluid have differed by as much as five thousand times (500,000 per cent)! If the true active principles were really being determined, it would be a remarkable biological fact that the concentration of such powerful substances could vary so greatly. One is, therefore, driven to accept one (or more) of the following conclusions: (*a*) the assays are not specific for the true active principles so that the true concentration, if any, is not known; or (*b*) only a few

[7] See also Klisiecki, Pickford, Rothschild, and Verney (1933).

of the many investigators are capable of performing even a crude biological assay; or (*c*) enormous variations in the concentration of the oxytocic hormone occur.

The author believes that most of the results can be explained by the first of the three conclusions just mentioned. Van Dyke, Bailey, and Bucy (1929) found that ventricular or lumbar cerebrospinal fluid had no effect on the isolated guinea-pig uterus provided that the ionic composition of the "physiological" fluid in which the uterus was suspended before assay was exactly the same as that of the cerebrospinal fluid. If the only variation introduced was an increase in the calcium-ion concentration, a uterine contraction resembling that produced by a posterior-lobe extract followed. Therefore, it appeared probable that ionic differences between the cerebrospinal fluid tested and the "physiological" solution in which the uterus was first immersed could account for many of the positive results of other authors. All adequately controlled experiments in which the detection of the oxytocic principle in cerebrospinal fluid has been attempted have failed (Whitehead and Huddleston, 1931; Friedman and Friedman, 1933; and Simon, 1933).[8]

Experiments in which the oxytocic effect of blood, blood serum, or extracts of these has been demonstrated likewise appear to have little significance.[9]

[8] Samples of cerebrospinal fluid of man and animals under various experimental conditions have caused the contraction of the isolated uterus. In none of the following reports, however, is there satisfactory evidence that the oxytocic effect was due to the oxytocic principle of the pars neuralis: Cow (1915); Dixon (1923); Dixon and Marshall (1924); Trendelenburg (1924); Jánossy and Horváth (1925); Miura (1925); Blau and Hancher (1926—most of their experiments were negative); Dixon and Wadia (1926); Mestrezat and van Caulaert (1926–27); van Dyke and Kraft (1927); Geesink and Koster (1928–29); Hoff and Wermer (1928); McLean (1928); Sato (1928); Trendelenburg (1928); Trendelenburg and Sato (1928); Jánossy and Magoss (1930); Karplus and Peczenik (1930–33); Barbour and Hambourger (1933); and Colombi and Porta (1934).

[9] McLean (1928); Fontes (1929–31); Da Cunha (1931); Figueroa (1933); Bell and Morris (1934—in preparing extracts, these authors added HCl to plasma and brought the mixture to boiling; after these steps the concentration of HCl was still 3.6 per cent); Donnet (1934); and Caroca and Koref (1935).

Cockrill, Miller, and Kurzrock (1934) detected an oxytocic substance in the urine of women in labor but not in the urine of men or a non-pregnant woman. Without other control experiments it is difficult to accept the suggestion that this oxytocic substance resembles that of the pars neuralis.

2. *The vasopressor principle.*—The vasopressor principle has been thought to have been detected in cerebrospinal fluid (Cushing and Goetsch, Karplus and Peczenik, and others). However, Carlson and Martin as well as Jacobson (1920) and Hoyle (1933) have failed to confirm part of these observations. Likewise, Simon (1933), using the isolated ileum of the guinea pig, could detect no vasopressor principle in cerebrospinal fluid under various conditions.

Anselmino and Hoffmann (1931) reported a number of experiments supporting their conclusion that the important symptoms of renal disease of pregnancy or of eclampsia are due to a marked hypersecretion or intoxication by the vasopressor principle of the pars neuralis.[10] They believed that a liter of the ultra-filtrate of the blood plasma from a patient with either of these diseases contained 2–15 units of the principle. Their observations were not confirmed by Byrom and Wilson (1934) or by Hurwitz and Bullock (1935) who investigated the antidiuretic effects of ultra-filtrates. On the other hand, Marx (1935) concluded that the blood of the eclamptic contains about 2 units of antidiuretic hormone in each liter (four times that of the normal adult or about three times that of the normal pregnant woman). The statement of Anselmino and Hoffmann that ultra-filtrates of the plasma of patients with a hypertension greater than 180 mm. Hg produces a pressor effect resembling in most respects that of posterior-lobe extracts was not confirmed (Hurwitz and Bullock).

Conclusions.—Despite the apparent wealth of evidence in favor of the importance of the pars neuralis as a gland of

[10] See also Bickenbach and Rupp (1934) and Rupp and Bickenbach (1934).

internal secretion, closer examination of the experimental data reveals that the evidence is unsatisfactory and still inconclusive. The most numerous experiments—those in which oxytocic effects have been studied—are the least satisfactory. The demonstration of vasopressor or antidiuretic effects by blood or cerebrospinal fluid or by extracts of these is, by itself, suggestive, but does not prove that the effects demonstrated are due to the active principles of the pars neuralis. Vasopressor substance(s) which are pharmacologically different from that of the pars neuralis can be extracted from both the blood and the cerebrospinal fluid (Page, 1935). Finally, even an antidiuretic substance, differing from that of the pars neuralis (destroyed by boiling), has been extracted from the liver (Theobald and White, 1933).

CHAPTER XI

THE EFFECTS OF EXTRACTS OF THE PARS NEURALIS ON THE CIRCULATORY SYSTEM AND ON THE SMOOTH MUSCLE OF STRUCTURES SUCH AS THE UTERUS AND THE BOWEL; OTHER EFFECTS OF EXTRACTS[1]

FOLLOWING the announcement of Oliver and Schäfer in 1894 that the intravenous injection of extracts of the pituitary body causes a rise in the blood pressure, Howell (1898) pointed out that the active substance is in the posterior lobe. A more detailed analysis of the effects of posterior-lobe extract on the circulation has been made during the forty years following the discovery of Oliver and Schäfer—particularly since 1928 when the vasopressor and oxytocic principles, as substances fairly completely separated from each other, were made available for investigation.

The effects of extracts of the pars neuralis on the circulatory system.—The vasopressor principle causes an elevation of the blood pressure by a direct effect probably on the smooth musculature of the small arteries and the arterioles. There also may occur, depending upon conditions, a constriction of the capillaries and venules. The pressor effect can be produced in the absence of the adrenal glands or after the destruction of the central nervous system. It is not prevented by substances which paralyze the peripheral terminations of the sympathetic (ergotoxine, ergotamine) or parasympathetic (atropine) nervous systems. Intramuscular or subcutaneous injections sometimes have no effect or cause a slow rise in blood pressure. If repeated doses are administered intra-

[1] Detailed references to the earlier literature bearing on the subjects discussed in chaps. xi and xii will be found in the review of Geiling (1926) and in Sharpey-Schafer's *The Endocrine Organs* (1926).

venously—especially if the doses are large or if they are given too frequently—a "tolerance" appears so that successive doses cause less pronounced effects and finally almost no change (tachyphylaxis). However, some extracts, if injected repeatedly, may later cause a depressor effect. This "inversion" phenomenon appears to be due not to the vasopressor principle but to depressor substances included in the extracts.[2]

A typical tracing of the effects of the vasopressor principle on the circulatory system varies considerably depending upon the experimental conditions. The one selected for reproduction here (Fig. 54) illustrates the effect of an intravenous injection of the vasopressor principle on the blood pressure, heart-rate, and respiratory movements of an unanesthetized dog.[3] A preliminary rise in the blood pressure is followed by a marked fall which lasts approximately 30 seconds; the secondary rise which then appears (225 mm. Hg in comparison with 170 mm. Hg in the control period) persists throughout the remainder of the tracing (longer than 8 minutes). The primary fall in blood pressure is probably due to a marked diminution in the volume of blood pumped by the heart in each unit of time. As the minute-volume output increases in the face of a peripheral vasoconstriction, the blood pressure rises to a maximum of 225 mm. Hg.

Both the early and all the later investigations of the effects of posterior-lobe extract or of the vasopressor hormone on the heart indicate that the marked transient impairment of the heart's efficiency is due to a constriction of the coronary arteries producing cardiac dilatation and even signs of asphyxia of the cardiac musculature. Anesthetics like "Chlore-

[2] References to only a few reports dealing with this controversy need be given: Hogben and Schlapp (1924); Geiling and Campbell (1926); Vincent and Curtis (1926); and Stehle (1929).

[3] For experiments in man see Rosenow (1920); Sacks (1924); Csépai and Weiss (1926); Pógany and Pintér-Kováts (1927); Hartl (1933); Moffat (1933); and Gönczy and Kiss (1934).

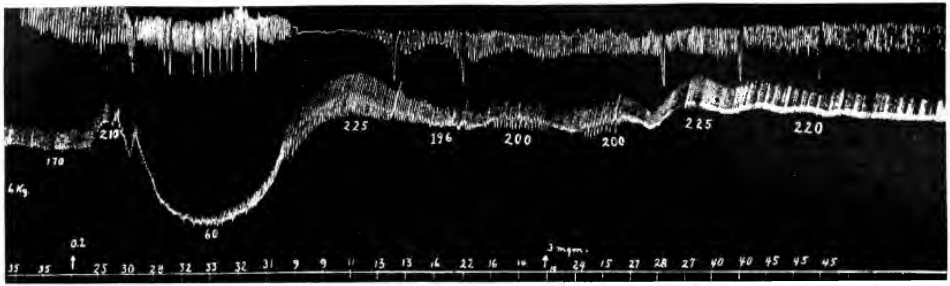


FIG. 54.—The effect of the vasopressor principle ("Pitressin") on the circulatory system and on the respiratory movements of the dog. Local anesthesia only. Top record: respiratory movements (pneumograph and tambour); middle record: blood pressure (membrane-manometer; figures indicate blood pressure in mm. Hg); bottom record: time in 15-second intervals (figures indicate number of heart-beats in each 15-second period). At ↑0.2, 0.2 cc. "Pitressin" given intravenously ($\frac{2}{3}$ unit per kg. body-weight?). At ↑3 mgm., 3 mg. atropine sulphate given intravenously. From Gruber and Kountz (1930).

tone" may prevent the cardiac effects (presumably due to coronary constriction); phenobarbital ("Luminal"), on the other hand, may have the opposite effect. Depending upon experimental conditions, the injection of epinephrin may favor or oppose the vasoconstricting effect of the vasopressor principle on the coronary arteries (Melville, 1933; Antopol and Rössler, 1934). Under appropriate conditions ephedrine, histamine, morphine, nitrites, and papaverine have all been found to lessen or prevent the adverse effects of the vasopressor principle on the heart of normal or anesthetized animals; in every case the investigator has considered that the drug caused a dilatation of the coronary arteries, thus opposing the constrictor effect of the posterior-lobe extract. The phenomenon of tachyphylaxis can be observed in the coronary arteries as in other arteries.[4]

The feeding of thyroid extract has been found markedly to increase the toxic effect of posterior-lobe extract on the heart (Clark, 1929; Appel, 1932).

Apparently carotid-sinus reflexes play no important part in the circulatory effects of the vasopressor principle. Changes in the respiratory movements are usually attributed to local circulatory changes in the respiratory center (Sharpey-Schafer and Macdonald, 1926; Gruber and Kountz, 1930).

An account of some of the effects of posterior-lobe extracts on the pulmonary circulation will be found in the reports of Sharpey-Schafer and Macdonald (1926) and Holtz (1932).

The blood flow in the carotid artery and jugular vein and

[4] The heart has been investigated in the cat, dog, and rabbit. In some experiments the isolated heart (terrapin, rat, rabbit, and cat) has been used: Smith, Miller, and Graber (1925); Gruber (1926); Häusler (1929); Mautner and Pick (1929); Raginsky, Ross, and Stehle (1930); Ross, Dreyer, and Stehle (1930); Goldenberg and Rothberger (1931); Melville and Stehle (1931); and Raginsky and Stehle (1932).

The minute-volume output of the human heart before and after the injection of posterior-lobe extract has been studied by Grollman and Geiling (1932) and Hartl (1933).

in the femoral artery and vein is diminished for about 90 minutes after the injection of the vasopressor principle into the normal dog. The injection of the oxytocic principle is followed by no change (Geiling, Herrick, and Essex, 1934). It is agreed that the pressure within the portal vein falls after the injection of posterior-lobe extract; however, the interpretation of this effect varies (Clark, 1928; Holtz, 1932; and McMichael, 1932).

According to Meyenburg and Schürch (1923), arteriosclerotic changes may appear in the aorta of rabbits into which a posterior-lobe extract has been repeatedly injected intravenously. Moehlig (1930) believed that such changes occur oftener if the animals receive a high-fat diet.

The intravenous injection of a posterior-lobe extract into the bird produces a fall in the blood pressure (Paton and Watson). In the fowl and duck it has been shown that this change is due to the oxytocic principle and not to the vasopressor principle or to substances like choline, acetylcholine or histamine (Gaddum, 1928; Morash and Gibbs, 1929; and Dietel, 1934). According to Gruber and Kountz (1930), the oxytocic principle causes a dilatation of the coronary vessels of the isolated rabbit's heart.

The effects of posterior-lobe extracts on the capillaries of the frog have been described by Krogh and Rehberg (1922), Killian (1925), and Krogh (1929). Hogben and Schlapp (1924) found that enormous doses of posterior-lobe extract were required to produce a rise in blood pressure in the frog. The prominent effect on the blood pressure of the tortoise was found to be depressor. The vasopressor hormone has no clear-cut effect on the branchial vessels of the eel, *Anguilla vulgaris* (Keys and Bateman, 1932).

In the intact animal the vasoconstrictor effects of a posterior-lobe extract are not the same in different tissues. In the cat, for example, the effects on the vessels of the intestines are more marked than those on the vessels of

striated muscle; the effects on the cutaneous vessels are constrictor whereas those on the vessels of the pia-arachnoid are, perhaps, dilator (Clark, 1930; Forbes, Finley, and Nason, 1933). To cause vasoconstriction in isolated organs like the ear or kidney of the rabbit, high concentrations of extract are required; moreover, the effects on the same preparation are not reproducible with any regularity (see Solntzew, 1928, and Ssentjurin, 1928). Portman and Macdonald (1928) found that even high concentrations of posterior-lobe extract were without effect on the isolated carotid, femoral, or renal arteries or veins.

The effect of posterior-lobe extract on the formation of lymph and edema fluid and on absorption.—The intravenous injection of a posterior-lobe extract into a dog from whose thoracic duct the lymph is being collected is followed by a prompt reduction in the flow of lymph. Chemical changes in the lymph before and after injection have also been investigated (Meyer and Meyer-Bisch, 1921; Bayley and others, 1922; Petersen and Hughes, 1925). The subconjunctival injection of a posterior-lobe extract into the rabbit brings about a fall in the intra-ocular pressure which may persist for several hours; the instillation of the extract into the conjunctival sac is followed by scarcely any change (Samojloff, 1927). Edema of the conjunctiva caused by mustard oil, or by dionine, and inflammation of the skin caused by mustard oil may be inhibited by the subcutaneous injection of a posterior-lobe extract (Saxl and Donath, 1925; Poulsson, 1927; and Tainter, 1928). Poulsson attributed the inhibition or delay in chemosis to an effect on the capillaries. He also reported that the subcutaneous injection of a posterior-lobe extract prevented paraphenylenediamine-edema; this report could not be confirmed by Tainter. Blalock and others (1933) found that the intravenous injection of a posterior-lobe extract into the dog did not prevent the loss

of plasma or of plasma proteins due to the administration of histamine, incompatible blood, etc.

According to Thienes and Hockett (1930–31), the subcutaneous injection of posterior-lobe extract lessens the rate of absorption of a number of substances from the gastrointestinal tract: glucose (rat), iodides (rabbit, rat, man), morphine or an extract of cannabis (dog), and strychnine (rabbit). Gellhorn (1933) concluded that the glucose permeability of the intestine of the frog is not affected by perfusing the vessels of the gut with a solution containing posterior-lobe extract provided that the perfusion-rate is kept constant.

The effect of extracts of the pars neuralis on the smooth muscle of other structures. 1. *The uterus.*—No accurate comparative studies of the sensitivity of the isolated uterus toward the oxytocic principle have been made. The isolated uterus of the immature guinea pig appears to be one of the most sensitive.[5] The oxytocic principle is usually considered to cause changes in the uterus (increased rate of rhythmic contractions if present, increased tone, contraction) by "acting" directly on the smooth musculature. The effect of the principle on the uterus may be sensitized by substances like serum albumin, $BaCl_2$, or quinine (Fröhlich and Paschkis, 1926; Schübel, 1928).[6] Probably the oxytocic substance and histamine act differently on the contractile mechanism of the uterine musculature.

The injection of the oxytocic principle into the unanesthetized rabbit with a fistula of the uterus, by means of which tracings of the movements can be secured, causes a sustained contraction of the uterus followed by the normal rhythmical movements present before the injection. However, after the injection of a posterior-lobe extract, the phase

[5] The fallopian tube (man, rabbit, cow) is very insensitive (Kammerhuber, 1932).

[6] Extracts of the urine of both pregnant and non-pregnant women may cause sensitization (Illingworth, Marshall, and Robson, 1932).

of contraction is followed by a phase of inhibition of the normal movements. This inhibitory phase is due to the vasopressor hormone. The vasopressor hormone alone causes inhibition and may antagonize small doses of the oxytocic hormone. Tachyphylaxis (of the inhibitory effect) appears after repeated doses of the vasopressor principle (Reynolds, 1930, 1933; Weinstein and Friedman, 1935). Similarly, the isolated uterus (of the rabbit), not responding to the oxytocic principle because it has been obtained from an animal in which there are actively secreting corpora lutea in the ovary, may relax if posterior-lobe extract or the vasopressor principle is added to the bath (Robson).

The effect of ovarian secretion of hormones or of pregnancy on the response of the isolated or intact uterus of man, the cat, the guinea pig, the rabbit, the rat, and the mouse has been studied by a number of investigators. Sahako (1925–26) reported that the response of the isolated or intact uterus of the rabbit is related to the condition of the ovaries. He found that the uterine response to a posterior-lobe extract was diminished or was inhibitory if actively secreting corpora lutea were present in the ovary as in pregnancy. However, late in pregnancy the uterine response was found to be increased. Sahako's findings have been extended and confirmed by Knaus, Okazaki, Robson, and others.

The most numerous experiments have been performed in rabbits. Pregnancy can be limited to one horn, so that the other horn is left free for testing its response to posterior-lobe extract *in vitro* (Knaus, 1927–28). The response of the uterus to the oxytoxic principle becomes markedly reduced about 48 hours after coitus. If coitus is infertile and pseudopregnancy appears, the oxytocin response is absent or diminished for about 2 weeks. In the case of pregnancy this is true for a period of 3 weeks. Thereafter, the uterine response to the oxytocic principle increases, especially during the last few days of pregnancy; the sensitivity of the uterus

is greatest just before parturition. If the corpora lutea are removed during the first part of pregnancy, the uterus becomes oxytocin-sensitive after about 10 hours (Knaus, 1927–28, 1930; Robson, 1933).

If pseudopregnant proliferation of the rabbit's uterus has been provoked by the injection of anterior-lobe extract (so that corpora lutea are formed in the ovaries) or by corpus luteum extract, oxytocin-insensitivity may also be observed (Robson, 1932; and others). Not infrequently, however, a pseudopregnant uterus may be oxytocin-sensitive. Therefore, it has been suggested that the loss of the uterine response to the oxytocic principle is due to some substance other than progesterone (Hartmann and Störring, 1931; Robson and Illingworth, 1931; and Robson, 1932; see also Siegmund, 1930).

Assuming that the human uterus exhibits similar changes in response in relation to secretory activity by the corpus luteum, Knaus (1929–30) made records of the intra-uterine pressure of women to whom he also gave 0.1 cc. of a posterior-lobe extract intravenously. He concluded that the effect of the extract disappeared about the ninth day before menstruation and was slight or absent thereafter. This change he attributed to the secretion of the corpus luteum of ovulation; he estimated that ovulation occurred on the fourteenth to sixteenth day. Wittenbeck's general results (1930) confirmed those of Knaus although in one patient a positive oxytocin response was obtained despite the presence of a corpus luteum. Quite the opposite results were obtained by Schultze (1931) and Tachezy (1934). These authors concluded that the uterine response to the oxytocic principle is greatest after the sixteenth day of the menstrual cycle. The intact pregnant human uterus (2–5 months) responded to the oxytocic principle in seven of eight patients (Wittenbeck, 1930; Tachezy, 1934). Robson (1933) studied the response of

the isolated pregnant human uterus; he concluded that the changes in the oxytocin response throughout pregnancy resembled those in the uterus of the pregnant rabbit. Similar variations in the uterine response to ergotoxine occurred.

The response of the uterus of the rat and the guinea pig at different times of the oestrous cycle or during pregnancy has been investigated by Harne (1932) and Guidetti (1934).

Bourne and Burn (1928), who could use only impure preparations of oestrin, found that these sensitized the isolated guinea-pig uterus toward the oxytocic principle. Apparently this effect was due to an impurity; for all subsequent work (isolated uterus of rat, guinea pig, or rabbit) has shown that oestrone, or oestriol, either antagonizes the effect of the oxytocic principle or is without action (Siegert, 1931; Heller and Holtz, 1932; Jeffcoate, 1932; Pompen and Gompaerts, 1932; Marrian and Newton, 1933; and Fomina, 1935).

Klein and Klein (1933) used pregnant or pseudopregnant rabbits. The injection of 2,500 rat-units of oestrin each day did not abolish the oxytocin-insensitivity. Parkes (1930) found that abortion followed a few hours after the injection, into pregnant mice, of doses of both oestrin and oxytocin which by themselves were without effect. According to Møller-Christensen (1934), the sensitivity of the uterus of the immature guinea pig is increased 24–48 hours after the administration of an enormous dose of oestrone (3,000 international units).

2. *The stomach and bowel.*—Posterior-lobe extracts may cause a diminution in the tone and movements of the stomach in man (Schoendube and Kalk, 1925–26) and in the dog (Quigley and Barnes, 1930). A description of the effects of the oxytocic and pressor principles on isolated strips of the stomach of the cat and rabbit is given by Robson (1931).

The effects—if any—of posterior-lobe extracts on the movements of the intestines appear to be due chiefly to the

vasopressor principle. In man the striking change produced by 3–10 units is the appearance of large peristaltic waves in the colon ("mass-peristalsis") culminating in defecation (Isaac and Siegel, 1929; Rondelli, 1929; Oppenheimer, 1931). The effects, of course, may be greatly modified depending upon the tone and contents of the colon. Carlson (1930), who studied patients after colostomy or ileostomy, concluded that the injection of posterior-lobe extracts caused an increase in the peristaltic movements both in the colon and in the small intestine.

The effects of the oxytocic and vasopressor principles on the intestinal movements of dogs (usually unanesthetized) are irregular and inconsistent. The activity of the small intestine has often been found to be inhibited as the result of the injection of an extract. In some experiments, however, the bowl activity appeared to be increased (e.g., Melville and Stehle, 1934).[7]

The intestine of the rabbit appears to be more sensitive than that of other animals (e.g., dog and cat). There is fair agreement among different investigators that the important effects are an increase in tone and a stimulation of peristalsis especially in the distal part of the colon. There is evidence that these changes are chiefly due to the vasopressor principle.[8] Among the divisions of the small intestine the ileum appears to be more sensitive than either the duodenum or the jejunum.[9]

[7] Dixon, 1923; McIntosh and Owings (1928); Gruber and Robinson (1929); Carlson (1930); Gruber and others (1931); Puestow (1933); and Quigley, Highstone, and Ivy (1934).

[8] Kaufmann (1927) concluded that a substance different from the oxytocic or the vasopressor principle stimulated the isolated small intestine of the rabbit and cat.

[9] Zondek (1920); Gruber (1926); Gaddum (1928); Elmer and Ptaszek (1930); Melville and Stehle (1934). For experiments in which the isolated intestine of the rat and cat has been used, see Voegtlin and Dyer (1924); McDonald (1925); and Gaddum (1928).

According to Simon (1933), the isolated ileum of the guinea pig can be used as a sensitive means of assaying the vasopressor principle.

3. *The gall bladder, spleen, and ureters.*—According to Schoendube and Kalk and Schoendube (1925–26—man), Adlersberg and van Goor (1928—rabbit), and Shi (1933—dog), the subcutaneous or intravenous injection of a posterior-lobe extract often causes a contraction of the gall bladder. Nissen (1932—man, isolated guinea-pig gall bladder) believed that this effect is not due to either the oxytocic or the pressor principle.

De Boer and Carroll (1924) concluded that any reduction in the splenic volume occurring as the result of the injection of a posterior-lobe extract is due to a vasoconstriction.

Gruber (1928) found that the addition of a posterior-lobe extract to the fluid bathing the isolated ureter (pig) caused an increase in the amplitude and rate of the rhythmical movements.

4. *The heart and smooth muscle of invertebrates.*—Hogben and Hobson (1924) performed their experiments on the isolated heart of a crab, *Maia*, on the perfused heart of a bivalve, *Pecten*, on the isolated crop of a mollusk, *Aplysia*, and on the isolated pharynx of an annelid, *Aphrodite*. In no case did posterior-lobe extract produce any effect (concentration equivalent to about 10 units in 40 cc. of fluid).

OTHER EFFECTS OF EXTRACTS OF THE PARS NEURALIS

The effects of the injection of extracts into the lumbar subarachnoid space, the cisterna magna, or the lateral ventricles.—The injection of a posterior-lobe extract into the lumbar subarachnoid space of the cat or rabbit is followed by a greater rise in blood pressure than that following the injection of a similar dose intravenously. The effect is prevented by ligation or section of the cervical cord (Leimdorfer, 1926; Ozu, 1928).

Although Inaba (1928), who used cats and rabbits, was unable to observe any vasopressor effect as a result of the injection of a posterior-lobe extract into the cisterna magna, Heller and Kusunoki (1933) and Bouckaert (1934) found that the suboccipital injection of an extract into the dog caused a stimulation of the vasomotor center. A pressor response appeared as early as after an intravenous injection but, unlike that following the latter, was accompanied by no preliminary fall in blood pressure (coronary constriction) or tachyphylaxis.

The effects of injections of posterior-lobe extracts into the lateral ventricles have been studied in the rabbit, cat, and dog (Spiegel and Sato, 1924; Inaba, 1928; Henstell,[10] 1933), in the primate (Light and Bysshe, 1933), and in man (Cushing, 1931). The important vasomotor effect is depressor and apparently is due to the vasopressor principle which has usually been given in large doses.[11] From his experiments in man Cushing concluded that the symptoms (vasodilation, sweating, marked lowering of body temperature, lowering of basal metabolism) were in part due to a stimulation of diencephalic parasympathetic nuclei. His data leave undecided the question of the specificity of the effects.[12]

The effects of posterior-lobe extracts on the stomach.—The injection of posterior-lobe extract may inhibit the secretion of gastric juice, particularly the secretion of hydrochloric acid; the experimental data do not indicate that this is an important effect (dog: Hess and Gundlach, 1920; Alpern,

[10] Henstell injected the vasopressor principle into the third ventricle of anesthetized cats. The blood pressure was not affected.

[11] In their experiments in the "sooty mangabey" (*Cercocebus aethrops*), Light and Bysshe injected 20 vasopressor units into the lateral ventricle of animals weighing 2.5–4.5 kg. Dilute acetic acid (equivalent to that used in the extract), the oxytocic principle, histamine, or acetylcholine were without effect.

[12] Little is known concerning the pharmacology of the parasympathetic centers (e.g., responses to drugs affecting the peripheral parasympathetic nervous system). Cushing could not exclude peripheral effects by other drugs (pilocarpine, atropine) which he used.

1923; Elkeles, 1926; man: Hoffmann, 1921; Schoendube and Kalk, 1925–26; Cascao de Anciaes, 1926).[13]

Dodds, Noble, and Smith (1934) reported that large doses of posterior-lobe extract or of the vasopressor principle (200–800 units subcutaneously; 600 units by mouth), administered to rabbits, cause hemorrhagic necrosis and ulceration of the mucous membrane of the stomach. In addition, there may occur a marked anemia which cannot be accounted for solely by the gastric hemorrhages (Dodds and Noble, Dodds and others, 1935). Bergami (1935) found that posterior-lobe extracts or the vasopressor principle may cause, in the rat and rabbit, hemorrhagic lesions in the mucous membrane of both the stomach and the lungs.

Miscellaneous effects.—Nikolaeff (1929) reported that posterior-lobe extract caused an increased liberation of epinephrin from the perfused adrenal gland of the ox.

There is disagreement as to the effects of the oxytocic and the vasopressor principles on the coagulation of the blood (Curtis and Pickering, 1928; La Barre and Patalano, 1930; and Nitzescu, 1930).

Rogers (1921, 1926) found that the injection of a posterior-lobe extract into pigeons in which the optic thalamus had been destroyed after the removal of the hemispheres caused a considerable rise in the body temperature. After the injection he also could readily cause a fatal reflex cardiac inhibition by stimulating the cloaca, oviduct, etc.

Observations on the metabolism of the active principles.—The oxytocic principle may be absorbed from the stomach or duodenum (Rees and Whitehead, 1923; Hansen and Burnett, 1930). The intravenous injection of the pressor principle into sheep during the second half of pregnancy may cause some elevation of the fetal blood pressure (Cattaneo, 1933).

Knaus (1925) found that the pressor effect in comparison with the oxytocic effect of a posterior-lobe extract was much

[13] See also Namba-Kiichi (1928).

less after an intra-arterial injection (1/60 and 2/5 respectively) than after an intravenous injection. These results seemed to indicate that the pressor principle, by passage through the tissues, is destroyed to a greater extent than the oxytocic principle. However, Hartmann (1930) did not observe such a striking reduction in the pressor effect of an extract after injection into the femoral artery (also used in Knaus's experiments) or the splenic vein. He did not investigate the oxytocic effect. Both authors used cats.

CHAPTER XII

THE EFFECTS OF EXTRACTS OF THE PARS NEURALIS ON THE METABOLISM OF WATER, MINERALS, CARBOHYDRATES, AND FATS

THE direct effects of a subcutaneous dose of a posterior-lobe extract (including those of separated oxytocic and vasopressor principles) on the general metabolism (oxygen consumption) probably are unimportant. There is very little agreement among different investigators as to the nature of the effects (rat: Chahovitch, 1930; Himwich and Haynes, 1930–31; Uyldert, 1933; man: Nitzescu and Gavrilla, 1929; Schill and Fernbach, 1929; Castex and Schteingart, 1930; Hartl, 1933). After the intramuscular injection of a posterior-lobe extract or the vasopressor principle into man, the oxygen consumption at first falls; the "oxygen debt" is repaid by an increased consumption which persists over a longer period (Grollman and Geiling, 1932). A similar change occurs in the dog after the intravenous administration of 5–10 units of vasopressor principle or posterior-lobe extract to dogs weighing 15–20 kg. (Geiling and De Lawder, 1932). An increase in the oxygen consumption, rather than a decrease, was found to be the first effect of the oxytocic principle.

Geiling and De Lawder (1932–33) have studied the tension of oxygen and carbon dioxide as well as the concentration of glucose, lactic acid, and inorganic phosphate in the blood of the femoral artery and vein of unanesthetized dogs after the intravenous administration of various posterior-lobe extracts. The initial effect of the vasopressor principle was apparently to alter tissue respiration (as if anaërobic metabolism was

increased). The venous blood resembled the arterial blood in color and in its tension of oxygen[1] and carbon dioxide. The concentration of glucose, inorganic phosphate, and lactic acid was increased. During the subsequent recovery period the venous blood had a lower oxygen tension and a higher carbon-dioxide tension than normal venous blood; the concentration of lactic acid continued to increase for some time. The changes in the blood of the external jugular vein during the first stage were different (the oxygen tension was decreased; there was little change in the carbon-dioxide tension).

The first change in the blood of the femoral vein following the intravenous injection of the oxytocic principle was a reduction of the oxygen tension below that of the normal venous blood without much alteration of the carbon-dioxide tension or the concentration of lactic acid.[2]

The effects of the oxytocic or vasopressor principle on the metabolism of isolated tissues are variable; the consumption of oxygen often is lowered (Himwich, Finkelstein, and Humphreys, 1931; Pincus, 1933).

The effect of extracts of the pars neuralis on the metabolism of water and minerals.—It is impossible to describe typical effects of a posterior-lobe extract on the metabolism of water and minerals without defining clearly the experimental conditions. The effects are modified by anesthetics, the amount of salt in the diet and/or the salt stored in the tissues, the presence or absence of diuresis, the cause of the diuresis if present, the method by which the extract is administered, etc.

The first observations of Magnus and Schäfer were made in anesthetized animals. Under such conditions the intravenous injection of a posterior-lobe extract causes a transient

[1] There was no interference with the dissociation of oxygen (Geiling, Eastman, and De Lawder, 1933).

[2] See also Gollwitzer-Meier (1926), and Draper and Hill (1929).

reduction (due to a vascular change or a ureteral spasm[3] or both?) followed by a considerable increase in the rate at which the urine flows from the ureters; a phase of lessened urinary secretion may then appear. It appears that this effect is almost always accompanied by changes (usually an increase) in the flow of blood through the kidneys. Probably this diuretic effect has little in common with the diuresis-inhibiting effect so easily observed in unanesthetized mammals. However, both changes are due to the vasopressor principle.

The view held by most investigators is that the transient diuresis induced by the intravenous injection of a posterior-lobe extract or the vasopressor principle into anesthetized animals is due to local renal circulatory changes, chiefly in the glomeruli. An increased rate of urine formation may be associated with an increased blood flow (Cushny and Lambie, 1921) or may occur in spite of a diminished blood flow (Richards and Plant, 1922). In the latter case it is postulated that an increased constriction of the glomerular efferent vessels has occurred so that the blood pressure within the glomeruli has been raised with a consequent increase in the rate of filtration of the urine. It is also possible that the blood is circulating through a greater number of glomeruli.[4]

During the diuresis caused by a posterior-lobe extract the oxygen consumption of the kidney is not increased (Knowlton and Silverman, 1918). The urine of posterior-lobe diuresis contains an increased amount of chloride—both relative (percentage) and absolute (Lomikowskaja, 1929; Nelson, 1934). Diuresis induced by the injection of solutions of NaCl (hypertonic) or urea (5–10 per cent) is increased by the additional intravenous administration of a posterior-lobe ex-

[3] Mackersie (1924) and McFarlane (1926). Under some conditions the immediate cessation of urinary secretion is not due to a spasm of the ureters (Ross and Stehle, 1930).

[4] See also Frey (1926); McFarlane (1926); Macdonald (1933); and Nelson (1934).

tract (Knowlton, Curtis, and Silverman, 1927). Precisely how the effects of posterior-lobe extract or the vasopressor principle are modified by anesthetics is a matter of debate.

In 1913 von den Velden reported that the subcutaneous injection of a posterior-lobe extract inhibited water diuresis in man. During the antidiuretic period the urine contained an increased amount of chloride, phosphate, and total nitrogen. Von den Velden's general findings have everywhere been confirmed and extended in both man and other mammals. This diuresis-inhibiting effect in unanesthetized mammals appears to be due to the vasopressor principle and is one of its most characteristic actions.[5] A large part of the effect is unquestionably of renal origin. It is not yet clear what is the significance of extra-renal effects (on the central nervous system and on other tissues); these extra-renal effects, however, appear to be of secondary importance and will be discussed briefly later.

The results which might be obtained from an experiment in a dog are illustrated diagrammatically in Figure 55. A single dose of posterior-lobe extract merely delays diuresis; moreover, the delayed diuresis may be greater than that following the administration of water alone. If repeated injections of both water and posterior-lobe extract are administered, severe symptoms including prostration may appear ("water-intoxication"—Weir, Larson, and Rowntree, 1922).

The diuresis inhibition undoubtedly is not due to an interference with the absorption of water from the intestines. The typical antidiuretic effect can be produced on the isolated kidney (Starling and Verney, 1924). Denervation of the kidney *in situ* does not prevent the effects. If the kidneys have been injured by the administration of cantharides or of a salt of uranium, the polyuria is not reduced by the injection

[5] If no water has been administered, the subcutaneous injection of posterior-lobe extract usually causes a transient diuresis followed by a period of lessened urine formation (McFarlane, 1926; and others).

of a posterior-lobe extract (Molitor and Pick, 1924). Similarly, in man water diuresis is not inhibited in certain types of renal disease. From these data and from other evidence it may be concluded that the antidiuretic effect of posterior-lobe extract (or the vasopressor principle) is primarily on the kidneys.

The most striking therapeutic use for the diuresis-inhibiting principle is in the treatment of diabetes insipidus. Five

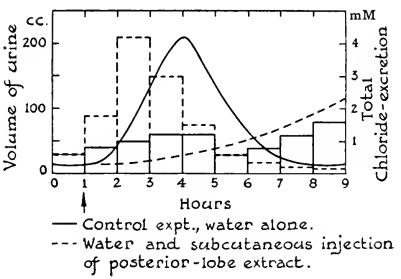


FIG. 55.—The effect of posterior-lobe extract on the secretion of urine and of chlorides in the urine (unanesthetized dog weighing about 10 kg.) (The diagram is not based on an actual experiment.) First hour: control period. At the arrow a large dose of water (e.g., 75 cc. per kg. body-weight), with or without a dose of posterior-lobe extract subcutaneously, is given by stomach tube. Curves: volume of urine. Each 0.29 sq.cm. represents 50 cc. of urine per hour. Rectangles: total chloride-excretion (millimols per hour).

to 10 units of the vasopressor principle subcutaneously may be a dose effective in an adult for 5–6 hours (Isaac and Siegel, 1929). No loss of sensitivity occurs in spite of the long continued use of the extract. A number of workers also have used posterior-lobe extract for diagnostic purposes in patients with primary or secondary renal disease.[6]

There is concordant evidence, which, however, sometimes

[6] Gutmann (1928); Lebermann (1928, 1930–31); Minder (1928); Hitzenberger and Merkler (1929); Seelig and Voigt (1932); and others. It is usually recommended that posterior-lobe extracts containing the vasopressor principle be not administered to patients with a toxemia of pregnancy.

is not good evidence, that the diuresis inhibition in mammals is due to an increased reabsorption of water. Likewise, in mammals glomerular filtration appears not to be affected. Burgess, Harvey, and Marshall (1933) determined the rate of glomerular filtration and water reabsorption in different classes of animals by injecting non-metabolized sugars like xylose and sucrose. They found that posterior-lobe extract did not affect glomerular filtration but did markedly increase the rate of reabsorption of water in the dog and in man. In the fowl two effects occurred: increased reabsorption of water and diminished glomerular filtration. In the reptile (*Alligator mississippiensis*) the only effect of the extract was a diminished glomerular filtration. No diuresis inhibition was observed in the amphibian[7] (*Rana catesbiana*) and in the fish (*Ameriurus nebulosus*). Correlating these observations with the anatomy of the kidney in the different classes of animals used, Burgess, Harvey, and Marshall concluded that posterior-lobe extract causes an increased rate of water reabsorption because of its effect on Henle's loop which is found in the kidney of the mammal and bird but not in that of animals of other classes. Their conclusion is in good agreement with the physiological-anatomical studies of Gersh (1934).[8]

The reabsorption of water by the kidney under the influence of posterior-lobe extract does not proceed beyond—and usually does not reach—the kidney's maximum concentrating power (e.g., urine containing *ca.* 0.3 M or 1 per cent chloride). Conversely, diuresis provoked by the administration of solutions of salt or urea may be little affected by the coincident administration of posterior-lobe extract (Brunn,

[7] See also Noguchi (1926); Tangl and Hazay (1927); and Namba (1932).

[8] Other studies, principally in man, indicate that increased reabsorption of water without much change in the rate of glomerular filtration is the chief cause of the diuresis-inhibiting effect (Poulsson, 1930). Iversen and others (1933–34) believed that filtration also was diminished. It is difficult to evaluate the experiments of Hauptfeld (1934).

1920; Fromherz, 1923; Molitor and Pick, 1924; McFarlane, 1926; Adolph and Ericson, 1927; Haldane, 1928; Daniloff, 1934; and Nelson and Woods, 1934).

Various phases of the metabolism of water (usually of excess water) have been studied.[9] Water-intoxication has been mentioned already. McQuarrie and Peeler (1931) found that *grand mal* seizures could be provoked in children with latent or mild epilepsy by the repeated administration of water and sufficient posterior-lobe extract to cause diuresis inhibition. Usually the administration of water and posterior-lobe extract is followed by evidence of hydremia. Even with clear-cut diuresis inhibition, however, the change may be slight. The relative increase in the amount of water is slighter in the tissues but has been observed in the skin and striated muscle.[10]

Diuresis inhibition and its associated phenomena following the injection of posterior-lobe extract appear to be best explained as the results of renal effects. Evidence that extra-renal factors are important is so far inconclusive. It is thought, on the one hand, that direct tissue effects may occur. On the other hand, Molitor and Pick (1925–26, 1930), believed that in the presence of excess water, a water center in the diencephalon is stimulated with resulting diuresis; if, however, posterior-lobe extract is administered, diuresis is inhibited because of the extract's effect on the water center. In favor of a direct tissue effect it has been reported that the injection of posterior-lobe extract causes an increase (10–15 per cent) in the concentration of chloride in the blood of the nephrectomized rabbit (Miura, 1925; Buschke, 1928). The

[9] See also the experiments of Ballinari (1929); Klein (1930); Kiss (1931); Manchester (1932); Adlersberg and Paul (1933); and Czika (1933).

[10] See Bayley and others (1922); Weir and others (1922); Lamson and others (1923); Weir (1923); Hines and others (1927–28); Kucharski (1927); Leese and others (1927); Raab (1928); Brednow (1931); Friedrich (1931); Roboz (1931); Heller and Smirk (1932); Robert (1932); Smirk (1933); and Wada (1933).

change reported is not great[11] and was not observed in the nephrectomized dog (McIntyre and van Dyke, 1931). Morris (1933) believed that 12–17 per cent of the blood chloride (goat) is organic chloride and that posterior-lobe extract caused a disappearance of the organic chloride perhaps with the conversion of the latter into inorganic chloride. The validity of the hypothesis of Molitor and Pick has been both supported (Jánossy, 1926; Mehes and Molitor, 1926; Hoff and Wermer, 1927; Buschke, 1928; Molitor and Nikoloff, 1929; Silbermann, 1932) and denied (Janssen, 1928; Theobald, 1934). From an experimental standpoint the importance of the central nervous system as a factor in posterior-lobe diuresis inhibition remains to be proved.

After the injection of posterior-lobe extract into man or the dog the urine is more alkaline, perhaps because of an increase in the total amount of fixed base in relation to sodium (Poulsson, 1930; McIntyre, 1933). McIntyre also observed this change after the injection of the oxytocic principle.

From their mineral-balance experiments in man Engel, McQuarrie, and Ziegler (1933) concluded that posterior-lobe extract causes a loss of K, Na, and Cl without influencing the balance of Ca, Mg, P, S, and N.[12] In experiments in man and animals lasting only a few hours, increases in the concentration in the urine of Na, K, Ca, Mg, Cl, PO_4, total nitrogen, urea, and creatinine have been observed (Fromherz, 1923; Stehle and Bourne, 1925; Stehle, 1927; Gollwitzer-Meier and Bröcker, 1928; Manchester, 1932; McIntyre and Sievers, 1933; and others). The most generally observed change, however, is an increase in the concentration and total amount of Na and Cl. Urechia, Groze, and Retzeanu (1930) concluded that the intravenous injection of the vasopressor principle in-

[11] Errors of chloride estimation, animal variability, and lack of completely controlled experiments must be taken into account.

[12] See also Nakazawa (1928).

to man is followed by a diminution in the concentration of calcium in the blood. The concentration of calcium in the blood of the toad, *Xenopus laevis*, is lower 3 hours after the injection of 0.5–1.0 cc. of posterior-lobe extract into the dorsal lymph sac (Shapiro and Zwarenstein, 1934). In the thyroparathyroidectomized dog the administration of a posterior-lobe extract is not followed by any change in the concentration of the blood-calcium (Larson and Fisher, 1928). Toxopéus (1930) believed that in dogs, to which bromide had been administered, the striated muscle contained more bromide and the skin contained less promide after the administration of a posterior-lobe extract; the reverse was thought to occur in thyroidectomized or thyroid-fed animals which received no posterior-lobe extract. According to McIntyre and van Dyke (1931), the distribution ratio of chloride and/or bromide between erythrocytes and serum (dog) is not affected by the administration of posterior-lobe extract.[13]

The injection of posterior-lobe extract into a lymph sac of the frog or toad kept in water causes an increase in the body-weight (e.g., a gain of 20 per cent in weight 5–10 hours after the injection of 5–10 units of extract). Brunn (1921), who first studied this effect, concluded that the increased water content of the frog's body is not due to a renal effect analogous to diuresis inhibition in mammals. The effect was also observed after nephrectomy. From the studies of Brunn and others (Biasotti, 1923; Jungmann and Bernhardt, 1923; Heller, 1930; Steggerda, 1931; Novelli, 1933; Steggerda and Freedman, 1933; Steggerda and Essex, 1934),[14] it may be concluded that: (1) the effect appears to be due to a change in the physiology of the skin and (2) the oxytocic principle has a considerably greater effect than the vasopressor principle. The increase in the body-weight due to the extract is greater in summer than in winter; also it is less in the de-

[13] See also Daniloff (1934), and Dietel and Ditsch (1934).

[14] Collin and Drouet (1932) doubted that the effect could be produced.

cerebrated or decapitated frog. The transplantation of the pars neuralis into tadpoles is followed by a reduction (shrinkage, emaciation) in body size (Swingle, 1922; Allen, 1929). Bělehrádek and Huxley (1927) found that the injection of posterior-lobe extract into *Amblystoma* (larval and adult) was followed by an increase in weight during the fifth to tenth hour after injection; repeated injections, however, caused a marked loss of weight.

The effects of extracts of the pars neuralis on the metabolism of carbohydrates.—Borchardt (1908) discovered that the injection of an extract of the posterior lobe into rabbits produced a glycosuria. He also found that hyperglycemia was present. The effects were most marked 2–6 hours after injection. As a result of the refinement and the more extensive use of methods of investigating carbohydrate metabolism, some knowledge of the mechanism of posterior-lobe hyperglycemia has been gained. However, the physiological importance of these studies appears doubtful. The subcutaneous injection of a posterior-lobe extract into a normal mammal produces, after about an hour, a moderate hyperglycemia (e.g., blood-sugar concentration of 150 mg. per cent). The effect depends upon the liberation of glucose from the liver and appears not to be mediated through the sympathetic nervous system. After the hyperglycemia has subsided, there often appears a moderate or slight hypoglycemia which seems to be the result of an increased liberation of insulin. In its more pronounced first stage of action posterior-lobe extract antagonizes both the hypoglycemic and the phosphate-lowering (blood) effects of insulin.

Although either the vasopressor or the oxytocic principle has been found to cause a typical hyperglycemia, the results perhaps depend partly on the use of incompletely separated principles. The vasopressor principle appears to be more powerful in its effects both in causing hyperglycemia and in antagonizing insulin. Whether the effects are due to the

true vasopressor principle or to an unidentified principle is not known.[15] Houssay and Di Benedetto (1933) reported on the relationship between the dose of a posterior-lobe extract and the hyperglycemic effect. They made intravenous injections of the diluted extract into dogs.

In antagonizing the hypoglycemic effect of insulin posterior-lobe extract has a moderate but well-sustained effect. The antagonism is greater than would be expected from the moderate hyperglycemia which follows the injection of the extract into normal animals (Burn, 1923; Voegtlin, Thompson, and Dyer, 1925; Heymans and Pupco, 1926; and others). Under conditions in which severe symptoms of hypoglycemia appear, the injection of posterior-lobe extract may abolish a part or all the symptoms without altering significantly the concentration of sugar in the blood (venous?) (Cassidy, Dworkin, and Finney, 1926; Geiling, Britton, and Calvery, 1929). Perhaps in such experiments the blood-sugar concentration is increased only in the arterial blood.[16] Also, in opposition to the effect of insulin, posterior-lobe extract or the vasopressor principle causes an elevation in the concentration of inorganic phosphate in the blood (Niitsu, 1930; Geiling and others, 1931). Lambie and Redhead (1929) observed this effect in the rabbit but not in man.[17]

An increase in the concentration of lactic acid in the blood is said characteristically to occur after the injection of large

[15] Burn (1928); Geiling and Eddy (1928); Himwich and others (1928, 1932); Elmer and Scheps (1930); Gavrila and Mihaileanu (1930); Nitzescu and Benetato (1930); Geiling and others (1931); Hynd and Rotter (1932); Schroeder (1933); Thaddea (1933); Thaddea and Waly (1933); and McIntyre (1934).

Houssay and Magenta (1929) as well as Holman and Ellsworth (1935) believed that the oxytocic principle is the more effective.

[16] Geiling, De Lawder, and Rosenfeld (1931) found that the hyperglycemia due to posterior-lobe extract initially was much greater in arterial in comparison with venous blood.

[17] Insulin has been found to antagonize the diuresis-inhibiting effect of posterior-lobe extract (Klissiunis, 1925; Serebrijski and Vollmer, 1925; and Koref and Mautner, 1926).

doses of posterior-lobe extract into mammals (e.g., from control concentrations of 13–20 mg. per cent to concentrations of 30–40 mg. per cent). The change does not parallel that in the blood-sugar concentration (Himwich and Fazikas, 1930; Bischoff and others, 1931; Nitzescu and Munteanu, 1931; Marenzi, 1934). Collazo, Puyal, and Torres (1933) concluded that moderate doses of extract cause a diminution in the lactic acid of the blood and that only toxic doses cause an increase. Certainly the doses used by other investigators were large.

If both glucose and posterior-lobe extract are continuously injected intravenously into dogs, the hyperglycemia and glycosuria are greater and the amount of glucose retained is less than after the injection of glucose alone (Hines, Leese, and Boyd, 1927). The usual hyperglycemia after the injection of extract alone does not appear if the liver contains no glycogen or if the liver has been excluded from the circulation (Lambie, 1926; Imrie, 1929; and others). Depending upon experimental conditions (dose, diet, period of starvation, animal, etc.) the concentration of glycogen in the liver may be diminished (Burn and Ling, 1929; Gömöri and Marsovszky, 1932; Gömöri and Csomay, 1934) or remain unchanged (Fukui, 1927; Bischoff and others, 1931; Lawrence and McCance, 1931; Murao, 1931) after single or repeated injections of posterior-lobe extract.[18]

The hypoglycemia which often follows posterior-lobe hyperglycemia usually is thought to be due to an increased secretion of insulin (Blotner and Fitz, 1927; Velhagen, 1929; Thaddea, 1933). From cross-circulation experiments in dogs La Barre (1927–28, 1930) concluded that posterior-lobe extract causes a liberation of insulin by stimulating the pancreas directly. Epinephrin hyperglycemia may be reduced considerably by the injection of posterior-lobe extract (Stenström, 1913; Partos and Katz-Klein, 1921; Burn, 1923;

[18] See also Nitzescu and Benetato (1931).

Fujino, 1931; and Silver and Mislowitzer, 1931).[19] Blotner and Fitz suggested that this perhaps is due to insulin liberation.

Ergotamine does not prevent posterior-lobe hyperglycemia but may prevent epinephrin hyperglycemia (Clark, 1926; Nitzescu, 1928; Thaddea, 1933).[20] Although it is stated in some reports that the adrenal glands reinforce or are necessary for the production of posterior-lobe hyperglycemia (Fritz, 1928; Yamamoto, 1929; La Barre, 1930; Houssay and Di Benedetto, 1933), this seems unlikely and is denied by Clark (1926) and Thaddea and Waly (1933).

The effects of extracts of the pars neuralis on the metabolism of fats.—Coope and Chamberlain (1925) reported that the subcutaneous injection of a large dose of posterior-lobe extract into rabbits or rats was followed in 10–15 hours by an increase in the concentration of fat (determined as fatty acids) in the liver. Histologically the change was found to be a fatty infiltration. Coope (1925) later reported that the change could be prevented by the injection of insulin (40 units of insulin antagonized the effects of 4 cc. of posterior-lobe extract in the rabbit). This increase in the concentration of liver-fat due to the injection of posterior-lobe extract often is neither as striking nor as easily elicited as the first results of Coope and Chamberlain suggested. The finding was not confirmed in the small group of experiments of van Dyke (1926). Oshima (1929) confirmed the observations of Coope and Chamberlain; he found that the injection of oestrone or thyroxin into rabbits causes a similar but perhaps less pronounced change. In the experiments of Hynd and Rotter (1932) rats were used. Many of their results were irregular.

[19] Under different conditions (intravenous injection) posterior-lobe extract with epinephrin may cause a greater hyperglycemia than that following epinephrin alone (Houssay and Di Benedetto, 1933).

[20] Posterior-lobe hyperglycemia is prevented in the cat and in man by the administration of ethyl alcohol (blood concentration of alcohol greater than 100 mg. per cent) (Murray, 1933). Is this due to an effect of alcohol on the liver?

Also, they appear to have drawn conclusions from too few data. They believed that the increase in liver-fat is produced by the vasopressor principle and that the oxytocic principle actually opposes this effect of the vasopressor principle. White (1933) showed that the vasopressor principle causes a much greater increase in the concentration of ether-soluble material in the rabbit's liver than is caused by the oxytocic principle.

Best and his co-workers have demonstrated that the marked increase in the liver-fat of rats receiving a fat- or cholesterol-rich diet can be prevented by feeding choline chloride. However, the feeding of choline chloride was found not to prevent the acute increase in the concentration of fatty acids in the liver of rabbits receiving large doses of the vasopressor principle (Mukerji and van Dyke, 1935).

All the other experiments on the effects of posterior-lobe extracts on the metabolism of fats are concerned with the behavior of the fat and lipins of blood after the administration of extracts. The injection of posterior-lobe extract probably does not affect significantly the concentration of either cholesterol or phosphatide in the blood of the normal mammal.[21]

Raab (1926, 1928, 1930, 1933–34) has published numerous reports on the effect of posterior-lobe extract on the neutral fat of the blood of the dog and man. He postulates the presence in the pituitary body of a hormone, "lipoitrin," which has not been identified otherwise. The subcutaneous injection of this hormone (usually Raab employed posterior-lobe extracts) is thought to cause a reduction in the concentration of the neutral fat of the blood by affecting a fat-metabolism center in the tuber cinereum whence nervous impulses, passing to the liver by way of the cervical cord and

[21] Blix and Ohlin (1927); Moehlig and Ainslee (1927); Reiss and Langendorf (1929); George (1930); Nitzescu and Benetato (1930); Raab (1930); Long, Hill, and Bischoff (1932); and Recht and Flesch (1934).

sympathetic, cause a deposition of fat in the liver. Before other aspects of Raab's hypothesis require examination, it is necessary to inquire how generally and how consistently others have observed a fall in the blood-fat concentration after the injection of a posterior-lobe extract. The injection of posterior-lobe extract into the dog was followed by a decrease in the concentration of neutral fat or fatty acids in the blood (experiments of Blix and Ohlin, 1927, and of Nitzescu and Benetato, 1930). In the experiments of Himwich, Haynes, and Spiers (1928) who injected posterior-lobe extract, the oxytocic principle, or the vasopressor principle into dogs, the results were irregular; posterior-lobe extract usually caused a reduction in the concentration of the blood fat. All investigators agree that posterior-lobe extract has no effect on the blood fat of the rabbit (Blix and Ohlin, 1927; George, 1930; and Long, Hill, and Bischoff, 1932).

Rabb also concluded that the fat-metabolism center of obese human beings is unresponsive to posterior-lobe extract. Furthermore, he believed that posterior-lobe extract causes a reduction in the concentration of blood-fat in alimentary lipemia. However, no effect was observed by Rony and Ching (1930), who administered to fasting dogs 4.4 cc. of olive oil per kilogram body-weight with or without an injection of posterior-lobe extract.

APPENDIX

SCIENTIFIC AND COMMERCIAL NAMES OF HORMONES AND HORMONE PREPARATIONS[1]

Adrenalin, 17
Adrenin, 17
Agomensin, 7
α Folliculin, 2B
Amniotin, 2B
Androfort, 6
Androkinin, 6
Androl, 6
Andronin, 6
Androsterone, 4
Androstin, 5
Anteglandol, 9
Antephysan, 9
Anteron, 9, 10
Antex, 12
Antophysin, 10
Antuitrin "G," 9
Antuitrin "S," 10
A.P.L., 11

Benzo-gynoestryl, 1

Coluitrin, 13
Cortidyn, 18
Cortin, 18
Cortisupren, 18

Dehydroandrosterone, 4
Dihydrofolliculin, 1
Dihydrotheelin, 1
Dimenformon, 1

Elityran, 16
Emmenin, 2A
Enarmon, 6
Epinephrin, 17
Equilene, 2C
Equilenin, 2D
Erugon, 5
Eschatin, 18
Exophysin, 13

Folliculin, α, 2B
Folliculin hydrate, 2A
Folliculin-menformon, 2B
Follutein, 10

Galactin, 8
Glanduantin, 9
Glanduitrin, 13
Gonan, 10
Gravidine, 10
Gynantrin, 9
Gynoestryl, 1
Gynophysin, 14

Hebin, urinary, 10
Hogival, 2B
Hombreol, 6
Homhormon, 9, 10
Hormovar, 2B
Hormovarine, 2B
Horpan, 9, 10
Hypolantin, 9
Hypophen, 13
Hypophysin, 13
Hypototal, 9

[1] The numbers of the groups are given in Arabic numerals; those of the formulas are given in Roman numerals. The list of commercial names of hormone preparations was compiled from reports of authors or manufacturers solely to aid readers in determining the presumed nature of commercial products mentioned in the literature.

Iliren, 18
Infundin, 13

Ketohydroxyoestrin, 2B

Luteogan, 7
Luteosterone, 7
Lutin, 7
Lutren, 7

Mammatropin, 8
Menformon, 2B
Myo-pituigan, 14

Oestradiol, 1
Oestrin, 2
Oestriol, 2A
Oestroform, 2B
Oestroglandol, 2B
Oestrone, 2B
Orasthin, 14
Oxytocin, 14

Pancortex, 18
Paranephrin, 17
Perlatan, 2B
Phyone, 9
Physormon, 13
Pitocin, 14
Piton, 13
Pitowop, 13
Pitraphorin, 13
Pitressin, 15
Pituglandol, 13
Pituigan, 13
Pituilobine, 13
Pituisan, 13
Pituitrin, 13
Porofan, 6
Posthypin, 13
Prähormon, 10
Prähypophen, 9
Prälobin, 10
Präphyson, 9
Präpitan, 9, 10
Pregnon, 10
Pregnyl, 10
Preloban, 9
Prephysin, 9
Progesterone, 7
Progestin, 7
Progynon, 2B
Progynon "B," 1
Prolactin, 8
Prolan, 10
Proluton, 7
Proviron, 6

Sistomensin, 7
Suprarenalin, 17
Suprarenin, 17
Synhormon, 6

Testinon, 6
Testosterone, 3
Theelin, 2B
Theelol, 2A
Thyractin, 16
Thyroidin, 16
Thyroxin, 16
Tonephin, 15
Trihydroxyoestrin, 2A
Trophoblast hormone, 10

Unden, 1, 23

Vasophysin, 15
Vaso-pituigan, 15
Vasopressin, 15

GROUP CLASSIFICATIONS

Oestrus-producing hormones:

1. From the follicular fluid of the ovary and the urine of the pregnant mare:
   Oestradiol I
   Dihydrofolliculin

Dihydrotheelin
Gynoestryl
Oestradiol benzoate:
Benzo-gynoestryl
Dimenformon
Progynon "B"
Unden (with oestrone)

2. From the urine of pregnant women and/or mares:
   A. Oestriol II
      Emmenin (as part of the extract)
      Folliculin hydrate
      Theelol
      Trihydroxyoestrin
   B. Oestrone III
      α Folliculin
      Amniotin (composition uncertain)
      Folliculin-menformon
      Hogival (from follicular fluid?)
      Hormovar
      Hormovarine
      Ketohydroxyoestrin
      Menformon
      Oestroform
      Oestroglandol
      Perlatan
      Progynon
      Theelin
      Unden (sometimes with oestradiol benzoate)
   C. Equilene IV
   D. Equilenin V

It has been suggested that the term "oestrin" include both oestrone and oestriol. In the spayed adult rodent, oestradiol is more potent than oestrone; oestriol is by far the least potent.

Hormones obtained from the testes or male urine (sometimes prepared synthetically):

3. From the testes:
   Testosterone VI
4. From male urine:
   Androsterone VII
   Dehydroandrosterone VIII

(In the capon, testosterone is by far the most potent preparation; androsterone is more potent than dehydroandrosterone.)

5. Commercial preparations obtained from the testes:
   Androstin
   Erugon

6. Commercial preparations obtained from male urine:

Androfort	Hombreol
Androkinin	Porofan[2]
Androl	Proviron
Andronin	Synhormon[2]
Enarmon	Testinon

Corpus luteum hormone or extracts:

7. Progesterone IX. (Two crystalline forms have been prepared—the one melting at the higher temperature has been called "A" progesterone, the other melting at the lower temperature, "B" progesterone.)

Agomensin (?)	Lutren
Luteogan	Progestin
Luteosterone	Proluton
Lutin	Sistomensin (?)

The lactogenic hormone:

8. Suggested names:

Galactin
Mammatropin
Prolactin

Extracts of the pars glandularis:

9. Names in commercial use:

Anteglandol	Hypolantin
Antephysan	Hypototal
Anteron	Phyone
Antuitrin "G"	Prähypophen
Glanduantin	Präphyson
Gynantrin	(Präpitan)
(Homhormon)	Preloban
(Horpan)	Prephysin

Gonadotropic preparations obtained from pregnancy-urine:

10. Names used scientifically or commercially:

Anteron	(Horpan)
Antophysin	Prähormon
Antuitrin "S"	Prälobin
Follutein	(Präpitan)
Gonan	Pregnon
Gravidine	Pregnyl
Hebin, urinary	Prolan
(Homhormon)	Trophoblast hormone

[2] Prepared synthetically.

Gonadotropic preparation obtained from the placenta:

11. A.P.L.

Gonadotropic preparation obtained from the serum of the pregnant mare:

12. Antex

Extracts of the posterior lobe of the pituiary body:

13. Those presumably with the usual effects of posterior-lobe extracts:

Coluitrin	Pitowop
Exophysin	Pitraphorin
Glanduitrin	Pituglandol
Hypophen	Pituigan
Hypophysin	Pituilobine
Infundin	Pituisan
Physormon	Pituitrin
Piton	Posthypin

14. Those causing chiefly a contraction of the uterus:

Gynophysin	Oxytocin
Myo-pituigan	Pitocin
Orasthin	

15. Those causing chiefly an elevation of the blood pressure (including effects on the secretion of urine):

Pitressin	Vaso-pituigan
Tonephin	Vasopressin
Vasophysin	

The essential fraction of the thyroid hormone:

16. Thyroxin X
(Desiccated thyroid, or commercial preparations such as Elityran, Thyractin, or Thyroidin perhaps contain the true hormone.)

Extracts of the adrenal glands:

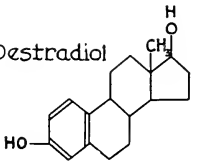
17. Of the medulla:

Adrenalin	Paranephrin
Adrenin	Suprarenalin
Epinephrin XI	Suprarenin

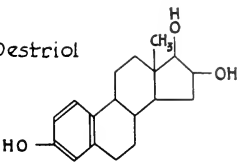
18. Of the cortex:

Cortidyn	Eschatin
Cortin	Iliren
Cortisupren	Pancortex

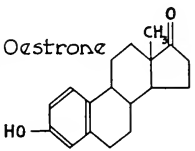
I. Oestradiol



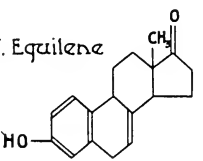
II. Oestriol



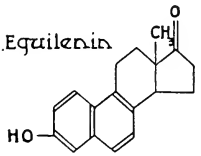
III. Oestrone



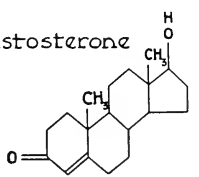
IV. Equilene



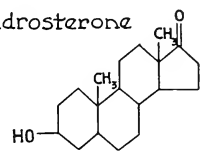
V. Equilenin



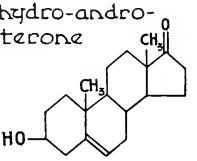
VI. Testosterone



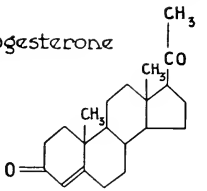
VII. Androsterone



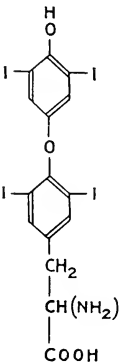
VIII. Dehydro-androsterone



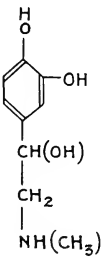
IX. Progesterone



X. Thyroxin



XI. Epinephrin



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