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WHAT WE HAVE LEARNED FROM THE TOAD CONCERNING HYPOPHYSEAL FUNCTIONS*

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THERE are three reasons which justify the dedication of my first lecture to such a humble living creature as the toad: (1) because, more than twenty-five years ago, my first publication in *Physiology* was on the pituitary of amphibians; (2) because the toad is the species in which the largest number of functions related to the pituitary has been found and studied; and (3) because hormonal actions are not species specific, but have a fundamental similarity throughout the vertebrate series.

To these reasons others may be added which justify the use of this animal, as I can well appreciate after experimenting on more than 15,000 toads of the species *Bufo arenarum* Hensell.† Such are, its abundance and cheapness, its resistance to trauma, the facility of operative techniques, the great number and clarity of the symptoms of pituitary insufficiency, the rapidity and intensity of the reaction to implantation of any of the lobes of the pituitary, and the possibility of making experiments and obtaining proofs more easily and in larger numbers than with any other animal. For these reasons we have preferred to employ the toad rather than the frog, *Leptodactylus ocellatus* (L.) Gir, common to our country, which we studied in 1910-1916 and in 1924 but which is much less resistant.‡

Let us remember that the amphibian pituitary consists of four parts:[17, 18, 40, 75] (Figs. 1 and 2)

(1) The principal lobe (distal, chromophile or *pars glandularis*) which corresponds to the anterior lobe of the mammalian pituitary, but which lies posteriorly in amphibians.

(2) Intermediate part (proximal or chromophobe, *pars intermedia*).

(3) Neural part (nervous or neurohypophysis, *pars nervosa*).

(4) Tuberal part (*pars tuberalis*) which, however, we have not been able to identify in *Bufo arenarum* Hensell.

*Dunham Lecture delivered November 22, 1935 at the Harvard Medical School.

†In the first works we published we called this toad *Bufo marinus*, but since 1930 we have corrected this zoölogical error.

‡We have observed with only slight differences symptoms generally analogous in *Leptodactylus ocellatus* (L.) Gir (Houssay,[17 18] Houssay and Ungar,[51 52]), *Bufo marinus, Bufo paracnemis, Bufo D'Orbigny, Ceratophrys ornata, Hyla sp.*, etc.

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The intermediate and neural parts are closely united forming a lobe which is equivalent to the posterior lobe in mammals, although here it is anterior and may be called the *intermedioneural lobe*. The principal lobe can readily be extirpated whole; if afterwards the neuro-intermediate part is extirpated, the hypophysectomy is total. The pituitary is situated caudo-ventral to the infundibular lobe of the brain. The latter is a prolongation of the hypothalamus, behind the optic chiasm and may be designated as the *infundibulotuberal region.*

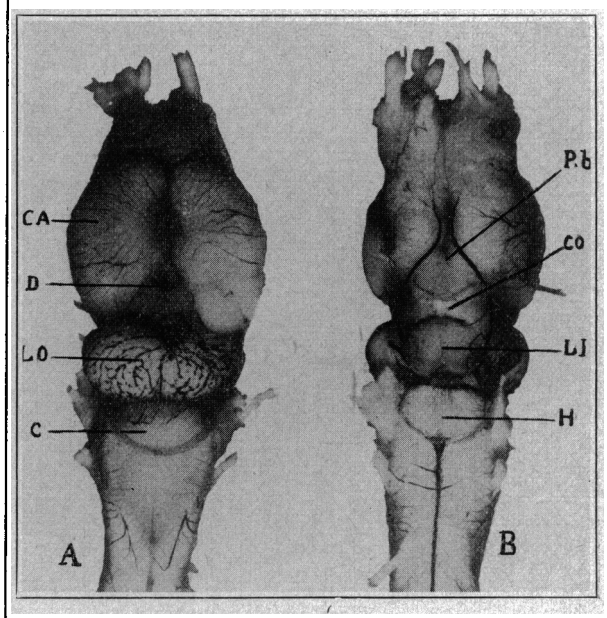


FIG. 1. Brain of *Bufo arenarum* (Hensell).

A.—Dorsal view: C.A. Anterior cerebrum (Hemispheres).
D. Diencephalon (thalamus opticus).
L. O. Optic lobes.
C. Cerebellum.

B.—Ventral view: P.b. Pars basalis of Lamina terminalis
C. O. Optic chiasm.
L. I. Lobus infundibularis.
H. Principal lobe of the Hypophysis.

The functions of the pituitary and of the tuberal region are studied by producing lesions or by implantations. The following techniques were systematically applied to the study of each function: (1) Trans-sphenoidal extirpation of the principal lobe only or of the entire pituitary.[16, 17, 18] (2) Puncture with a needle, or cauterization of the infundibulotuberal region,

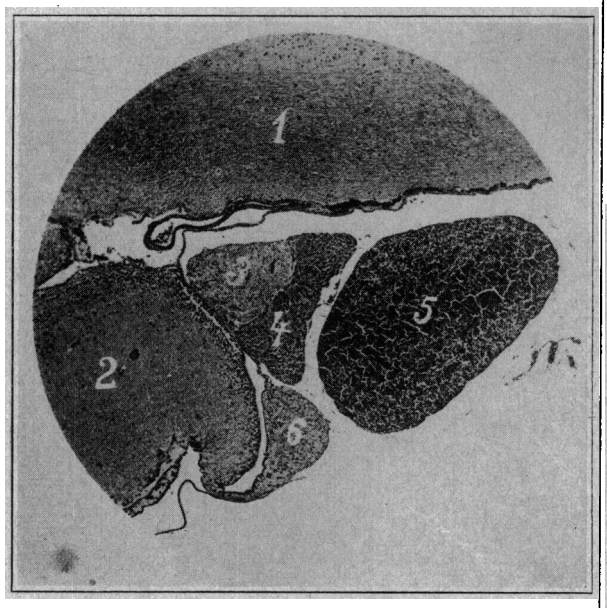
either posterior or anterior to the optic chiasm.* For cauterization a hot needle or the galvanocautery was used. (3) Subcutaneous implantation of the entire toad pituitary, or of the principal and neuro-intermediate lobes separately.

*The supra-optic nucleus is situated deeply in front of the chiasm; it is fairly large and sends fibres to the pituitary. (Greving, 1928; Scharrer, 1934; Carrillo, unpublished.)

(4) Injection, separately, of extracts of the same lobes or of extracts of the anterior, neural or intermediate parts of mammalian or other vertebrate pituitaries.

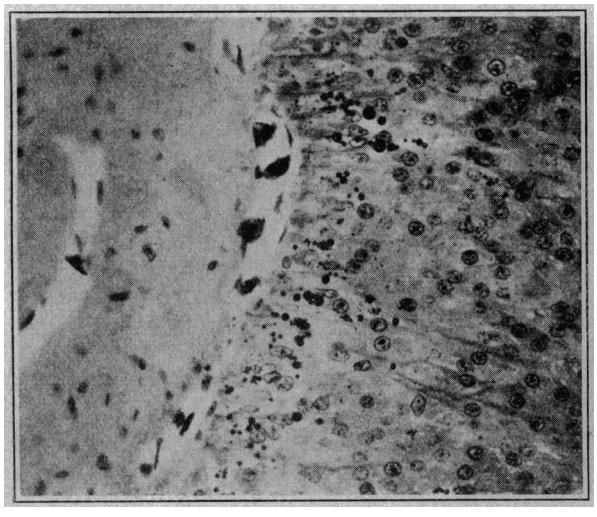
The symptoms which can be observed in the toad are referable to the following systems and processes: the skin; the genitalia; the circulatory system; the endocrine system; the neuromuscular system; gaseous exchange; nitrogen, carbohydrate and water metabolism; sensitivity to poisons; rate of mortality; etc. These have all been studied in our Institute and the results published in more than eighty papers.*

*For previously published summaries of this work see references 25, 35, 37.



A

B



C

D

FIG. 2. A. Microphotograph of the mid-sagittal section through the hypophysis of the frog. *Leptodactylus ocellatus* (L.) Gir. 1. Base of the brain. 2 and 6. Lobus infundibularis. 3. Pars nervosa. 4. Pars intermedia. 5. Pars principalis.

B. Microphotograph of a section through the pars neurointermedia of the hypophysis of a toad 70 days after extirpation of the principal lobe.

C. Microphotograph at high magnification of a section through the pars nervosa (left) and pars intermedia (right) of the hypophysis of a toad to show colloid droplets.

D. Microphotograph of a section showing the chromophile and chromophobe cells in the pars principalis of the hypophysis of the toad.

The syndromes which have so far been described may be classified in four large groups according to their etiology: (1) pituitary insufficiency, (2) pituitary hyperactivity, (3) infundibulotuberal syndromes, (4) infundibulohypophyseal syndromes.

PITUITARY INSUFFICIENCY

Insufficiency of the intermedioneural lobe.

These symptoms become manifest within a few minutes or hours after total hypophysectomy. They do not occur if only the principal lobe is extirpated or with lesions of the Lobus infundibularis of the brain. The implantation or injection of either lobe will correct the disorders, but the neuro-intermediate lobe is the most active. The symptoms are:

(a) *Cutaneous pallor*[16, 52, 83] due to contraction of the melanophores and expansion of the xantophores. (Fig. 3.) This pallor disappears on injection of extracts of the toad's intermedioneural lobe, or of extracts of the neural or of the intermediate parts of the mammalian pituitary. Of the last two, the second is the more active. Extracts of the anterior lobe of the mammal, or of the principal lobe of the toad, can produce darkening but are much less active and, in the case of the toad extract, seven times less potent than the neuro-intermediate lobe extract.*

(b) *Polyuria.*[38, 72] This is intense and persistent in 70 per cent of toads after total hypophysectomy. After removal of the principal lobe alone it is less frequent, occurring in only 33 per cent. It is rare and transient after tuberal lesions. It can be arrested by injection of toad neuro-intermediate lobe or mammalian posterior lobe. The polyuria is of renal origin as it is not observed in toads unless they are immersed in water. Absorption of water by the skin[77] is performed at the same rate in nephrectomized toads and in those with ureters tied, whether they be hypophysectomized or normal controls. The recent experiments of Pasqualini have induced the writer to abandon the belief that the polyuria is a tuberal symptom.

(c) *Fall in arterial pressure.*[69] If the whole gland is removed this is rapid, intense and progressive. The fall begins within a few hours after operation and continues progressively from 30 mm. of mercury to 24 mm. in a week and 17 mm. in a month. Extirpation of the principal lobe alone does not cause this hypotension, although a slight fall of blood pressure appears later on when asthenia develops. There is no fall of blood pressure with lesions limited to the infundibulotuberal region. The injection of neuro-intermediate or of glandular lobe causes the blood pressure to rise, the glandular lobe being less active.[17, 39, 69] Although the total amount of blood is almost the same in hypophysectomized toads as in the normal controls less can be obtained by bleeding the former, because it remains in the blood vessels. The circulating blood has fewer red blood corpuscles (Varela and Sellarés, 1934; Parodi, unpublished), and there is leucopenia with a decrease of the polymorphonuclear cells and of the monocytes. (Varela and Sellarés, 1934.)

(d) *Dilatation of the capillaries.*[3, 84] This can

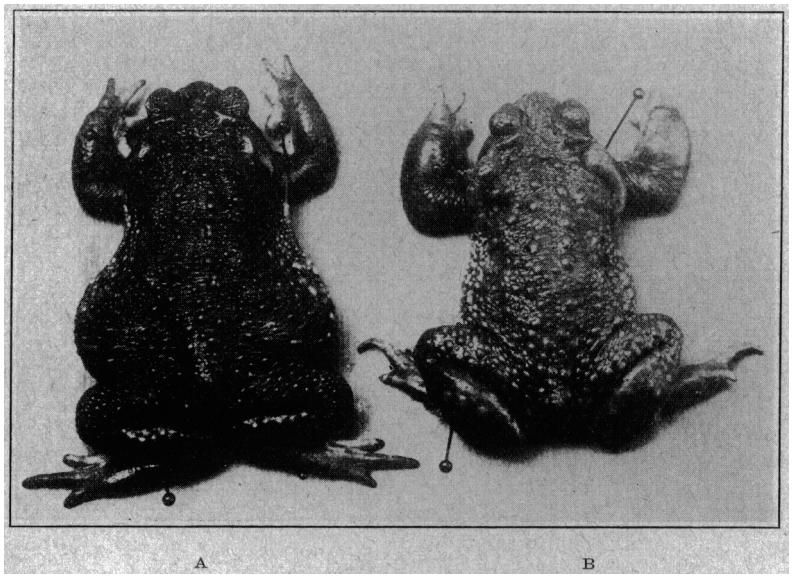


FIG. 3.
Unretouched photographs of toads. A. Injected with bovine posterior lobe, showing the dark color due to the expansion of melanophores. B. Hypophysectomized, showing the typical cutaneous pallor.

*Allen has shown that only the *pars intermedia* is active in other species of amphibia.

always be observed in the skin when the entire pituitary is extirpated but it is less constant and intense when the principal lobe alone is removed or the *Lobus infundibularis* of the brain injured.

Insufficiency of the principal lobe.

Following the extirpation of the principal lobe only (which corresponds to the anterior pituitary of mammals) characteristic symptoms slowly develop. These symptoms appear slightly more rapidly after removal of the whole pituitary, but they do not occur after simple lesions of the *Lobus infundibularis*. The morphogenetic and sexual symptoms are compensated only by administration of the principal lobe; the metabolic and general symptoms by both lobes, though the principal lobe is always more active.

I. *Morphogenetic and endocrine regulatory functions.*

(e) *Retardation and cessation of growth* have been described in other amphibians by Allen (1916), Smith and others, but we have not studied this point in *Bufo arenarum*.[cf 55]

(f) *The thyroid epithelium* shows signs of atrophy.[58, 59] It becomes flattened, the vesicles very large and the colloid homogeneous and readily stainable (see fig. 11).

(g) We have not been able to confirm with certainty the *atrophy of the adrenal cortex* seen by Smith (1920) in tadpoles; the medullary part is not altered and its adrenalin content is not lowered.[47]

II. *Sexual and reproductive functions.*

(h) *Testicular atrophy.*[15, 16, 36, 37, 40, 41] The testes weigh less than in the controls, and there is atrophy of the seminiferous epithelium and interstitial tissue. There is no compensatory hypertrophy after subtotal castration.[26]

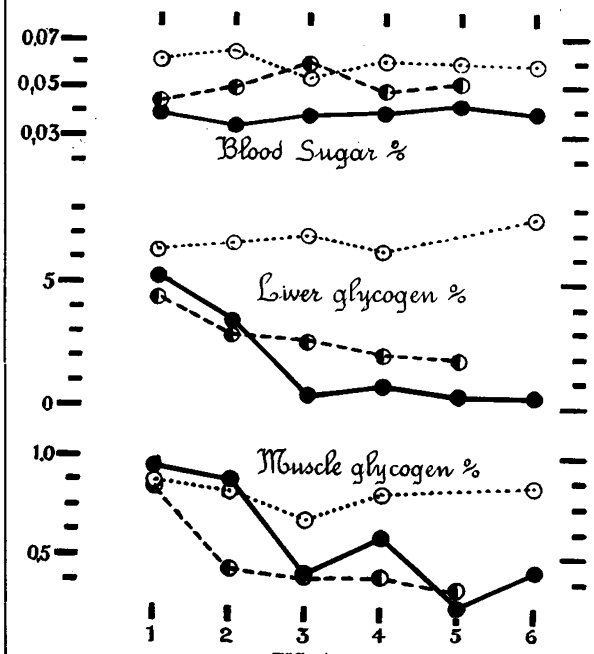


FIG. 4.

Chart showing the effects of removal of the principal lobe of the hypophysis (broken and solid lines) in the toad on the concentration of blood sugar, liver and muscle glycogen as compared with normal controls (dotted lines).

(i) *Atrophy of Bidder's organ*[41, 43], occurs both in castrated animals and in those with intact sex glands, and there is no compensatory hypertrophy in the castrates.

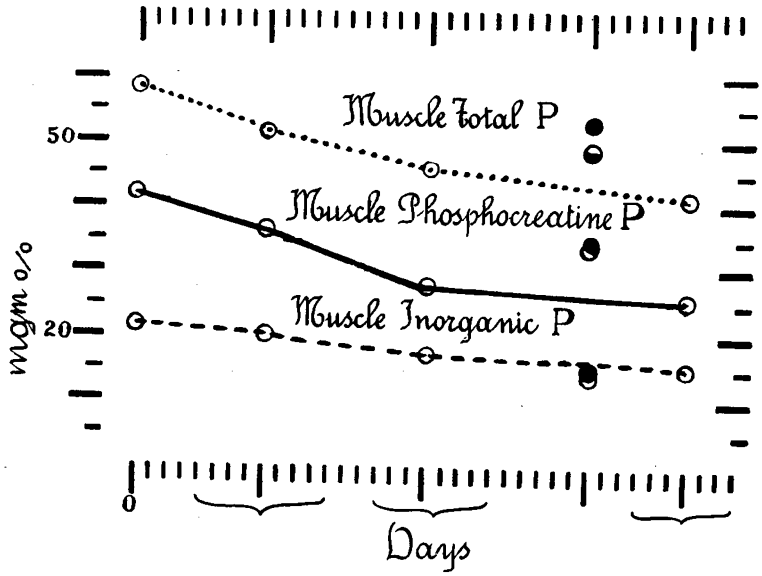


FIG. 5.

Chart showing decrease in the total phosphorus, phosphocreatine phosphorus and inorganic phosphorus in the muscles of the toad following removal of the principal lobe of the hypophysis.

(j) *Ovulation** fails to occur even in the mating season and with the normal sexual stimulation, namely the sexual embrace.

III. *Metabolic functions.*

(k) *The consumption of oxygen* does not diminish† until asthenia is marked.

(l) The concentration of *blood sugar* and the glycogen content of the liver[27, 34, 48] and heart[70] are progressively lowered. Later the muscle glycogen also decreases.[27, 34, 48] (Fig. 4.)

(m) *Phosphocreatine* and *glutathione* in muscle[60, 62] (figs. 5 and 6) and the glutathione of the liver are diminished. The basal *lactic acid*[61] is normal, but during muscular activity it increases less than in the controls.

(n) The *hyperglycemias following injection of adrenalin or morphine* are less marked than in the controls.[33]

(o) *Pancreatic diabetes*, which is intense in the controls, is less severe and may even fail to appear.[5, 7, 28, 29, 30, 32, 45 *]

(p) *Phlorhizin glycosuria* is less marked and may not occur.[11] However, hypoglycemia and convulsions develop and there is a high mortality.

(q) Sensitivity to the hypoglycemic and toxic actions of *insulin*[49,50] is marked, whereas sensitivity to other toxins is not changed.[17]

*Orias[68] has observed the same phenomenon in the fish, *Mustelus canis*, and Houssay and Biasotti[30] in other amphibia and reptiles.

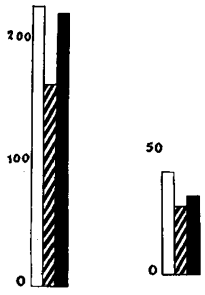


FIG. 6.

Chart showing the decrease in glutathione in the liver and muscle of the toad following removal of the principal lobe of the hypophysis and its restitution by injection of extract of bovine glandular (anterior) lobe.

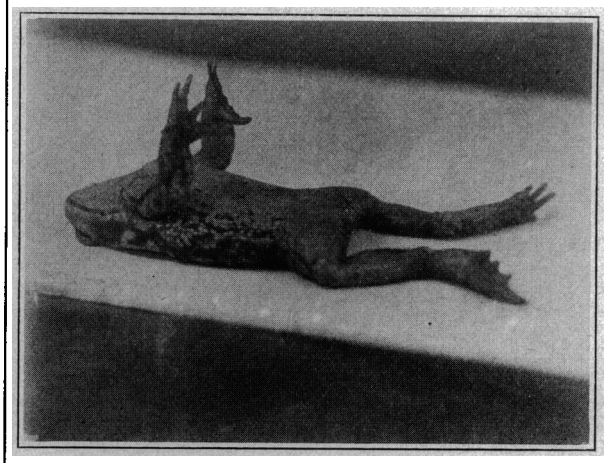
Normal

Hypophysectomized

Hypophysectomized and injected with glandular lobe extract of beef hypophysis.

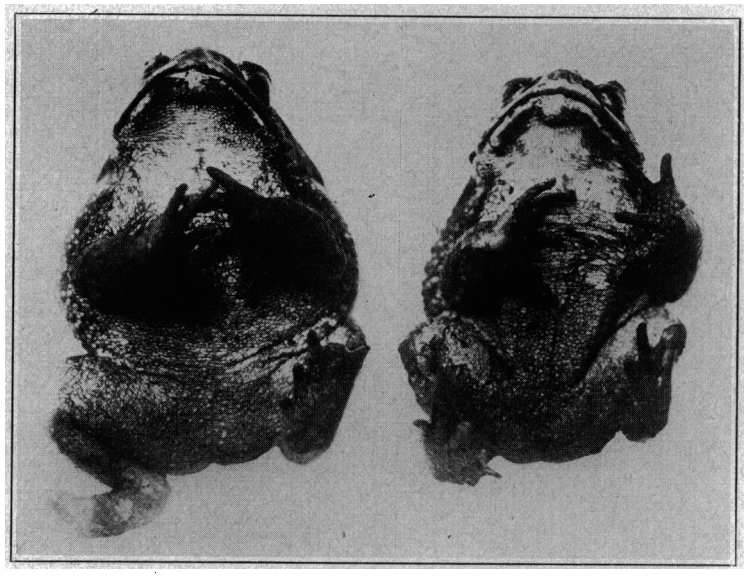
*See reference 25. Further proof of this, however, is necessary.

†Data obtained by Artundo, published by Houssay and Giusti.[35]



A

FIG. 7.



B

FIG. 7.

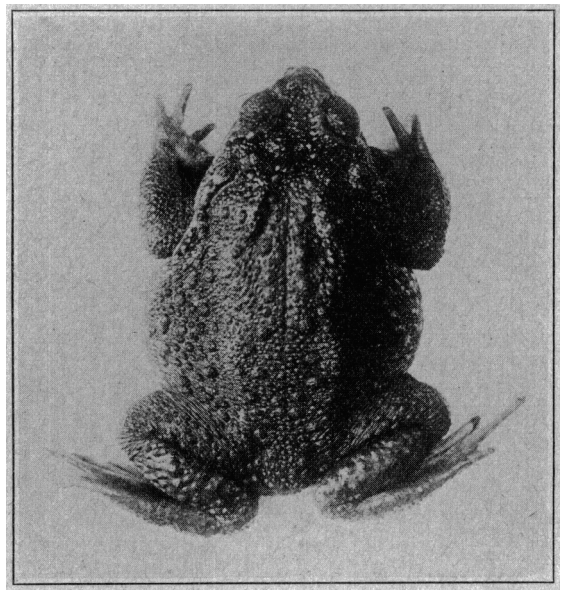
Figs. 7 A and B are unretouched photographs showing the state of *asthenia hypophysopriva* in the toad after removal of the principal lobe of the hypophysis. A. The earliest symptom, inability to regain the normal posture when laid upon its back. B. Typical posture at a later stage.

(r) Lowered elimination of *urinary nitrogen* during fasting has been observed. It may be 30 per cent less than in the controls.[6]

IV. *General symptoms, probably metabolic.*

(s) There is great sensitivity to slight *operations* and *traumata,* and the mortality rate is high.[2, 25, 26, 59, 72]

(t) Marked *neuromuscular asthenia* appears, which is progressive and finally fatal.[9, 14, 15, 16, 17, 18, 24, 25, 35, 36, 76] (Fig. 7.) This commences fifteen to twenty-five days after operation, the first symptom being the inability of the toad to turn over when placed on its back. Later there is slowness of movement and progressively increasing weakness. Convulsions occur in 5 to 10 per cent of the cases. The mortality is highest during the fourth to the seventh weeks, and very few animals live as long as three to five months. When the asthenia begins there is



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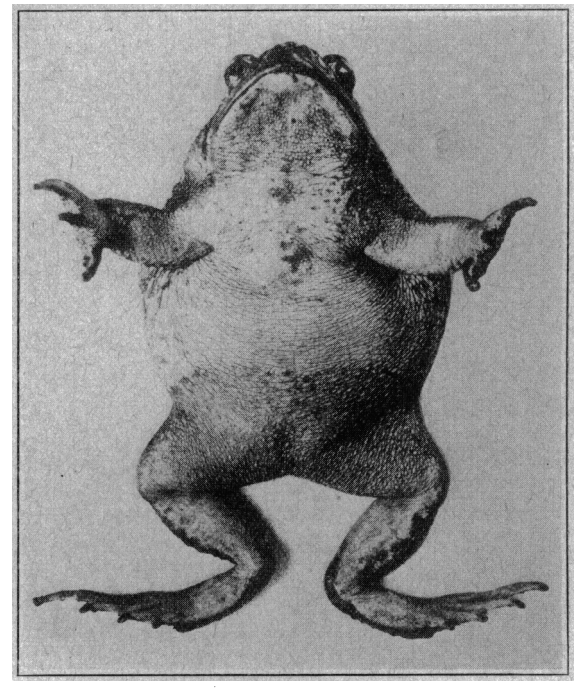

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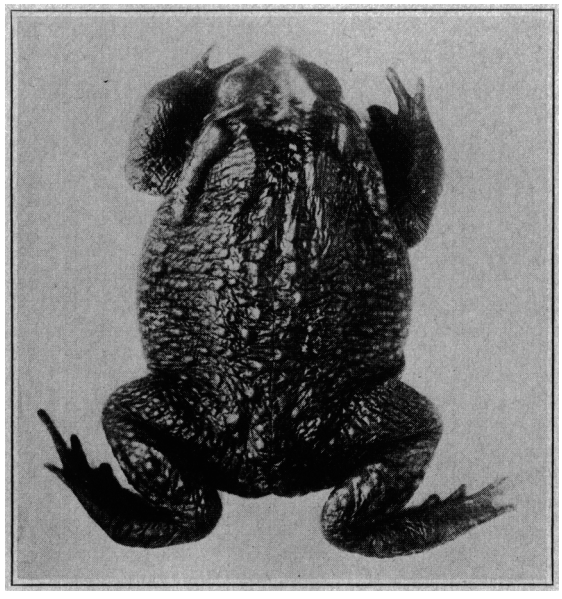

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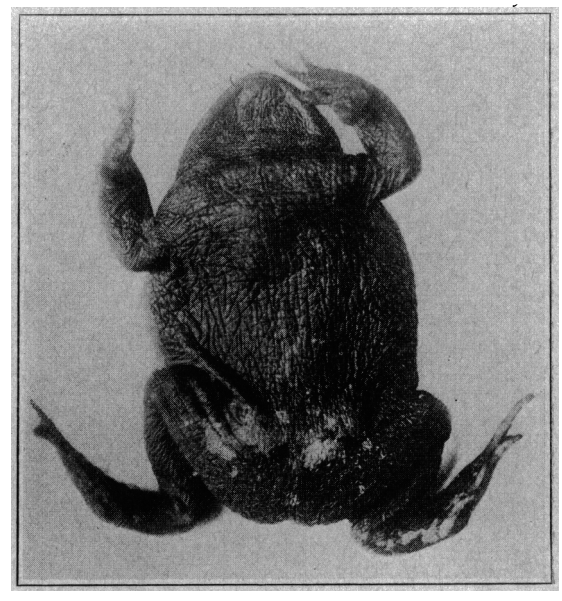


D

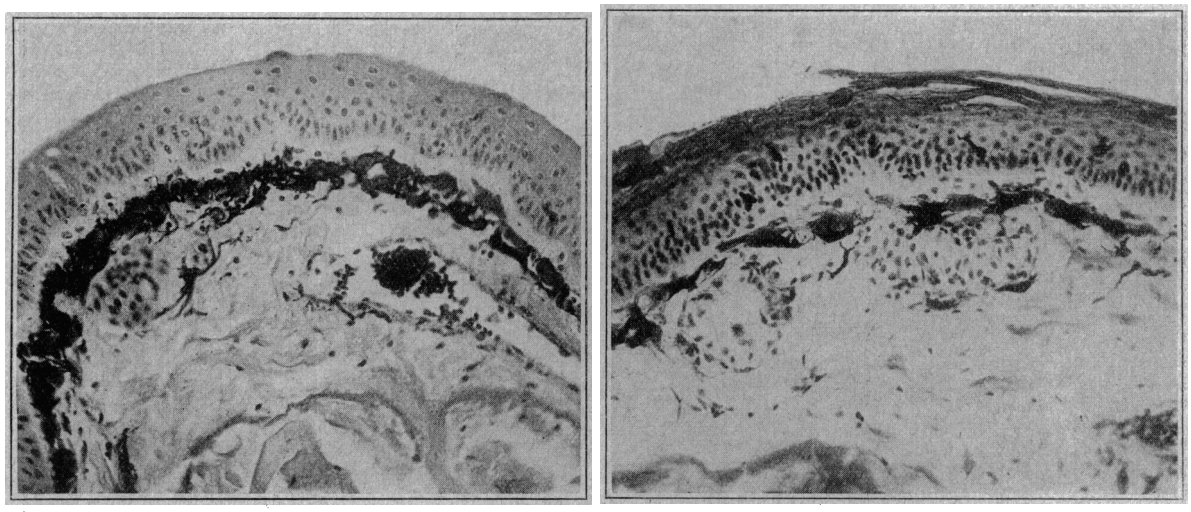
FIG. 8.

Unretouched photographs showing the hyperkeratinization in hypophysectomized toads. A and B. Dorsal and ventral views of normal toads (female). C and D. Dorsal and ventral views of hypophysectomized toads (female).

diminished excitability of the sensory reflexes, but the chronaxie of the nerve and muscle continues unaltered.[9*]

(u) *Cutaneous hyperkeratinization.* There is formation of a thick horny layer which is adherent to the skin.[2, 13, 14, 15, 16, 25, 35, 36, 37, 76] The skin becomes covered by a dark brown or bronze cuticle, due to an exaggerated production and a failure of normal desquamation of the horny layers.[1, 2] (Figs. 8 and 9.)

Symptoms j, m, n, p, q, appear immediately after operation, u in three to eight days and l, t, v and w in from fifteen to twenty-five days. All these symptoms, particularly the metabolic and general ones, can be prevented or corrected by the implantation of the principal lobe of the toad or of mammalian anterior lobe.* The sexual modifications are only influenced by the toad pituitary and to a lesser extent by that of other amphibians.†



A B

FIG. 9.

Microphotographs of the skin of a normal toad, A, as contrasted with that of a hypophysectomized toad, B. Note the thick cuticle of the latter, and the contracted state of the melanophores.

(v) The *cutaneous secretions* are greatly diminished.[1, 2]

(w) There is slowing of the *heart*, decrease of its glycogen content and rise in its chronaxie.[10, 70] After some time in a few of the toads the cardiomoderating action of the vagus is diminished, or may even be totally suppressed.[50, 56]

*Evidence for the central origin of the asthenia is furnished by the facts that the first indications of this symptom are alterations of the postural reflexes and reflex excitability, and also that there may be convulsions. Further, the motor nerve and muscle excitability is not affected until later, and then only slightly.[9] The peripheral factor is less important.[9 16 35]

PITUITARY HYPERACTIVITY

This is brought about by implantation of either lobe or by injection of toad pituitary extracts or extracts of mammalian pituitary. In general these symptoms are the opposite of those of pituitary insufficiency.

*The thyrotropic function of the latter is doubtful and the sexual is absent in this toad.

†Although other amphibia respond to the sexual activating principle of mammalian pituitary this toad is unaffected, a fact which up to now has remained without satisfactory explanation.

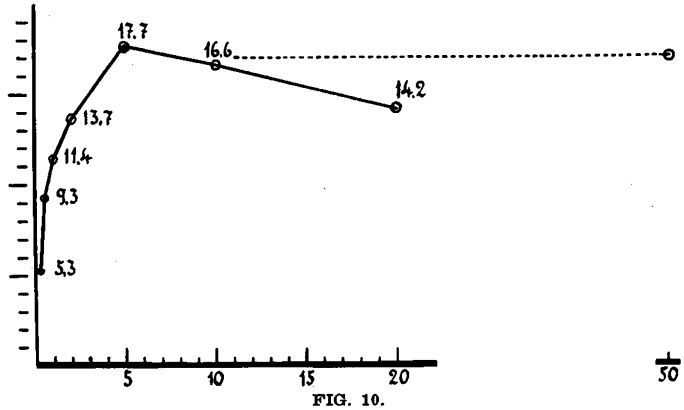


FIG. 10.

Graphic representation of the increase in weight of toads injected with graded doses of dry bovine posterior lobe.
Ordinates, percentage increase in weight.
Abscissae, milligrams of dry bovine posterior lobe injected.

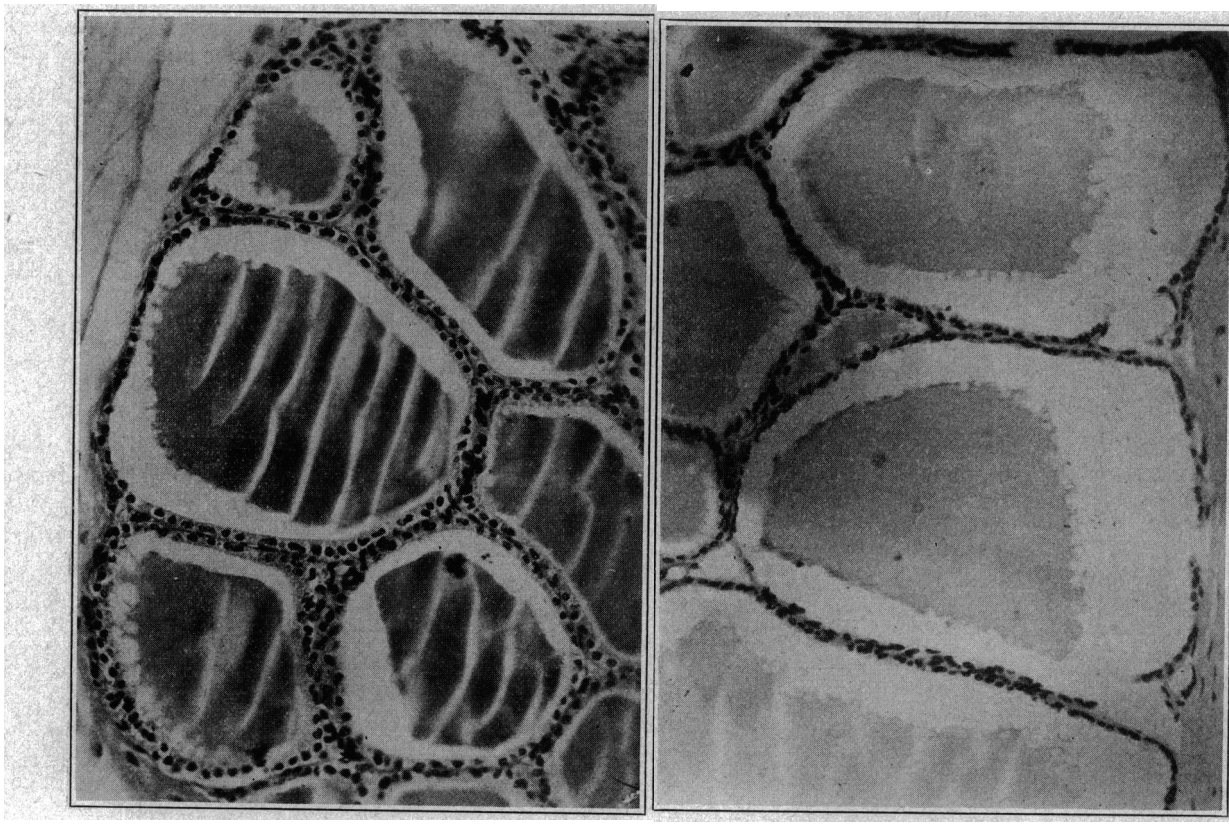


FIG. 11.

A. Microphotograph of a section through the thyroid of a normal toad.

B. Microphotograph of a section through the thyroid of a hypophysectomized toad.

C. Microphotograph of a section through the thyroid of a toad which had received implantation of the principal lobe of the hypophysis.

D. Graphic representation of the height of the thyroid epithelium in toads under different experimental conditions.

I. Normal. II. Craniotomized. III. Hypophysectomized. IV. Following cauterization of the tuber. V. Following implantation of principal lobe. VI. Following implantation of neuro-intermedial lobe. VII. Following implantation of other organs.

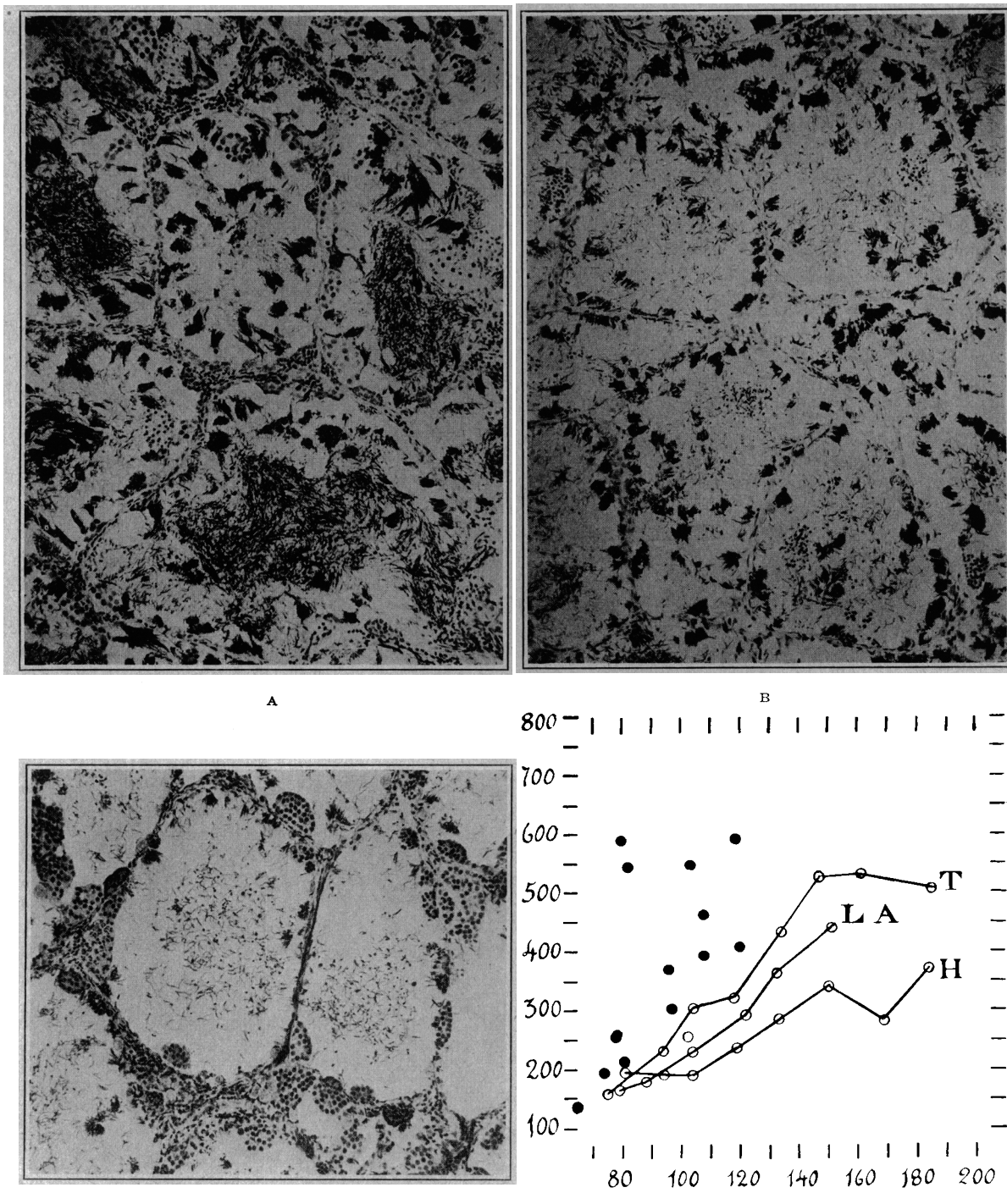


FIG. 12.

A. Microphotograph of a section through the testicle of a normal toad.

B. Microphotograph of a section through the testicle of a hypophysectomized toad.

C. Microphotograph of a section through the testicle of a toad which had received implantation of the principal lobe of the hypophysis.

D. Graphic representation of the weight, in mgm., of the testicles (ordinates) compared with the body weight, in Gm., of toads (abscissae) under different experimental conditions.

T. Normal.
L A. Without principal lobe.
H. Hypophysectomized.
Solid dots. Implanted with principal lobe.

Hyperactivity of the neuro-intermediate lobe.

This occurs with administration of the neuro-intermediate lobe of the toad or of the posterior mammalian lobe.

(a) There is *darkening of the skin*[4, 14, 15, 16, 20, 25, 35, 36, 37, 51, 52, 53, 54, 85] due to expansion of the melanophores; the principal lobe and the anterior mammalian lobe have a similar action which lasts a long time but is less intense.

(b) *Oliguria* with or without increase of weight.[50, 72] With small doses varying degrees of oliguria are produced, but with large doses there is complete anuria which lasts five to six hours. Increase in weight occurs in the latter cases and may be considerable (fig. 10), with interstitial, peritoneal and subcutaneous edema.[5, 35, 36, 37, 67, 72]

(c) The *rise in blood pressure* is marked in hypophysectomized animals with initial low blood pressure, but less so in normal animals. The neuro-intermediate (or mammalian posterior lobe) is more active than the principal lobe. The blood of the normal toad when injected into hypophysectomized toads causes a higher rise in blood pressure than the blood of hypophysectomized toads similarly injected. (Neubach, unpublished).

(d) *Contraction of the Capillaries*[11] of the skin may be produced by a large dose, if the vessels were previously dilated.

Hyperactivity of the principal lobe.

This can be produced by implantation of the glandular lobe, which is the only one that has morphogenetic effects and effects on other endocrine glands. The metabolic and a few other general symptoms can also be obtained to a certain extent, but in a less marked degree, by implantation of the neuro-intermediate lobe.

1. *Morphogenesis and regulation of endocrine glands.*

(e) *Acceleration of growth* has been observed in the larval form of other Anura by Allen, Smith, etc.; we have not studied it in *Bufo arenarum.*

(f) *Hyperplasia and hyperactivity of the thyroid*[58, 59] are revealed by the state of the epithelium. (Fig. 11.) The cells become high columnar in type and there is vacuolization and reabsorption of the colloid.

(g) *Stimulation of the adrenals* has been seen by Smith in tadpoles, but has not been confirmed in this toad.

2. *Sexual and reproductive functions.*

(h) *Hypertrophy of the testes*[25, 35, 36, 40, 41] occurs in normal and hypophysectomized animals. The testes increase in weight, the seminal canals are dilated by fluid containing free spermatozoa, there is hypertrophy of the seminiferous epithelium and of the interstitial tissue. (Fig. 12.) The sexual embrace reflex appears out of season, even when the tuber is destroyed, and in immature animals precocious puberty takes place.

(i) *Hypertrophy of Bidder's organ*[41, 43] occurs in normal and hypophysectomized animals, particularly in castrates. It can be definitely stated that Bidder's organ cannot be transformed into ovarian tissue unless the pituitary is present. (See II, i, Atrophy of Bidder's organ.)

(j) *Ovulation and expulsion of the ova*[32, 35, 36, 37, 40, 65, 66] occur in one to three days. Observations were made by us (loc. cit.) independently of those of Wolf. This phenomenon also takes place in the absence of various organs* and of the larger part of the brain. (See Infundibulohypophyseal symptoms.)

3. *Metabolic functions.*

The metabolic functions are only slightly affected in normal animals but much more so in the hypophysectomized.

(k) The *respiratory metabolism* does not change.

(l) There is *rise in blood sugar* and *hepatic glycogen,* also in *muscular*[27, 34, 48] and *cardiac*[10, 70] glycogen.

(m) The *hyperglycemia produced* by *morphin* and *adrenalin* is more pronounced.[33]

(n) There is a marked *increase in pancreatic diabetes*[5, 7, 28, 29, 30, 32, 45] particularly in the hypophysectomized toads and in those with infundibulotuberal lesions. In this reaction the liver plays an indispensable rôle (Campos and collaborators), but certain other viscera, namely the forebrain, the midbrain, the intermediate brain and the adrenals do not. In toads with intact pancreas no diabetogenic activity can be obtained, even when forty lobes are implanted.[31]

(o) *Phlorhizin glycosuria* is increased.[11]

(p) The *hypoglycemic* and the *toxic effects of insulin* are reduced both in normal and hypophysectomized animals.[49, 50]

(q) Increased *elimination of nitrogen* occurs in the hypophysectomized toads.[27]

4. *General symptoms* (probably metabolic).

These can only be produced to a slight degree in normal animals, but they are very marked in the hypophysectomized.

(r) *Operations are well tolerated*[2, 25, 26, 59, 72] by the hypophysectomized toads.

(s) *Asthenia* which follows hypophysectomy is prevented or cured.[2, 9, 24, 35, 76] The animals recover or, if treated early, maintain their agility and do not die. Sometimes it is possible to effect a cure even after convulsions have set in.

*The gonadotropic action of the principal lobe is not modified either in thyroidectomized or castrated animals.[65 66] There is also a gonadotropic action in fishes and reptiles.[23]

(t) The *formation of a horny cuticle*[76] by the hypophysectomized toads is prevented, or, if already formed, this cuticle is shed. Thus the principal lobe of the pituitary may be said to regulate the shedding of the skin.

(u) *Cutaneous secretion,* which is scarce in the hypophysectomized toads, is restored to normality or its diminution may be prevented.[2]

(v) It is possible to prevent or correct the bradycardia, the fall in cardiac glycogen, the decrease in cardiac chronaxie[70] as well as the ineffectiveness of the vagus which follows hypophysectomy.

INFUNDIBULOTUBERAL (DIENCEPHALIC) SYMPTOMS

There is only one symptom* referable to lesions which are limited to the diencephalon. This is the sexual embrace[36, 37] which occurs in a large number of male toads when the infundibulotuberal region is cauterized.

INFUNDIBULOHYPOPHYSEAL (DIENCEPHALO-HYPOPHYSEAL) SYMPTOMS

If the *Lobus infundibularis*† is injured secondary alterations occur in the pituitary. First, the circulation on its ventral surface stops and later a central infarct develops in the principal lobe. (Figs. 13 and 14.) This reaches its maximum in seven days, lasts some eleven to seventeen days and finally the lobe regenerates in twenty-five to thirty-five days, the chromophobe cells appearing earlier than the chromophile cells.[27, 28, 35, 57]

As a result there is an early stage of increased reabsorption of glandular products followed by a later stage of prolonged inhibition of the pituitary functions.‡

The initial increase in reabsorption is characterized by:

(a) *Transient darkening of the skin*[16, 38, 48, 49, 86] lasting one to three days, which does not occur if the neuro-intermediate lobe is absent.

*Originally we thought ovulation, polyuria and the formation of a thick horny layer were diencephalic symptoms (see infundibulohypophyseal symptoms).

†Anatomy and vascularization described by Houssay, Biasotti and Sammartino.[32]

‡The same is observed in the dog (Houssay, Davis, etc.).

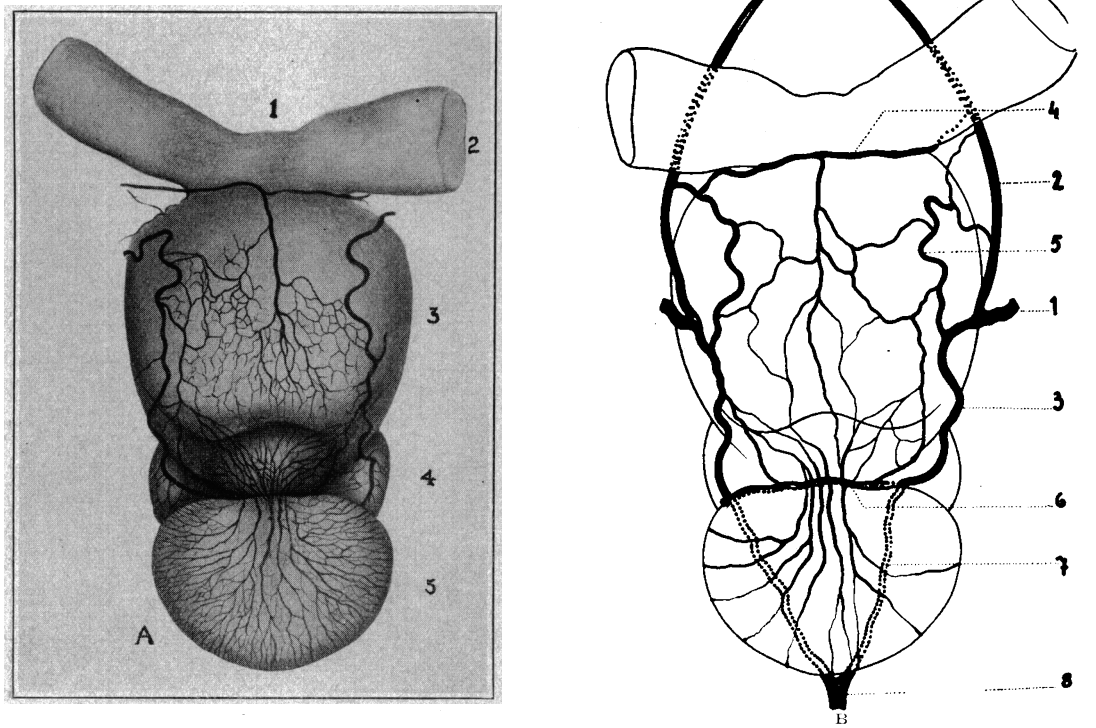


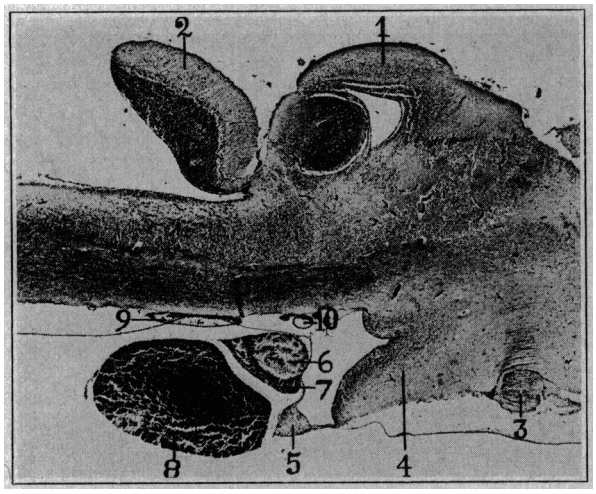
FIG. 13.

Drawing and diagram of the vascular supply of the hypophysis of the toad.

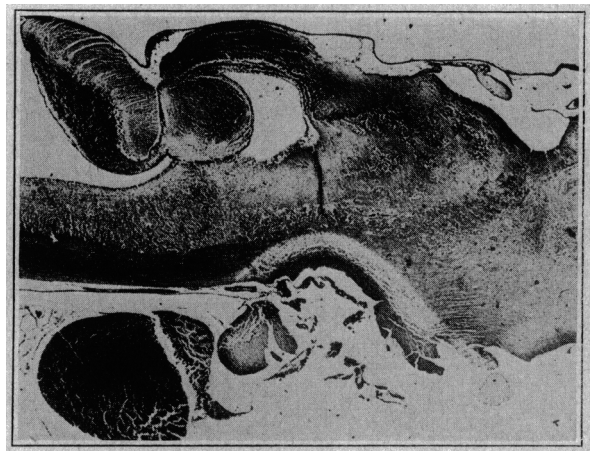
A.—(1) Pars basalis of the Pars terminalis.
(2) Chiasm n. optici (optic chiasm).
(3) Lobus infundibularis.
(4) Neuro-intermedial lobes of the Hypophysis.
(5) Principal lobe of the Hypophysis.

B.—(1) Cerebral carotid.
(2) Anterior branch.
(3) Posterior branch.
(4) Retrochiasmatic branch.
(5) Infundibular branches.
(6) Retroinfundibular communicating branch (anastomosis).
(7) Communicating branch to the vertebral artery.
(8) Vertebral artery.

(b) *Ovulation and expulsion of the ova,*[14, 15, 16] which is observed in 20 to 80 per cent of the females, but not if the principal lobe is absent.[36, 37]



A



B

FIG. 14.

Median section of the brain of *Bufo arenarum* (Hensell) (Magnification × 15).

A.—Normal.

(1) Optic lobes.
(2) Cerebellum.
(3) Optic chiasm.
(4) Infundibular lobes.
(5) Their posterior extension.
(6) Pars nervosa of Hypophysis.
(7) Pars intermedia.
(8) Pars glandularis (principal or chromophile lobe).
(9) Branch of the posterior cerebral artery that joins the basilar.
(10) Transverse retroinfundibular artery.

B.—Following cauterization of the infundibular lobes and tuber cinereum.
The lobus infundibularis, the base of the mesencephalon and the anterior part of the crura cerebri are involved.

(c) *Polyuria*[35, 36, 37, 38, 72] which is transient and inconstant and is due to neuro-intermediate insufficiency.

The functional inhibition of the principal lobe is characterized by:

(d) *Thickening and adherence of the horny layer of the skin*[1, 2, 14, 15, 16, 28, 32, 35, 37, 76] which is observed in 15 to 60 per cent of the cases and which may be corrected by administration of principal lobe extract.

(e) *Inhibition of pancreatic or phlorhizin diabetes,*[27, 28, 32] which is usually slightly less intense than in the hypophysectomized animals. When implanted these pituitaries have the usual diabetogenic activity, and their gonadotropic effect is only slightly diminished, but *in situ* they do not function normally.

Apart from these outstanding symptoms others which are less marked can be observed. Among these may be mentioned asthenia, which is rare, occurring only in 10 to 15 per cent of the cases;[24] a slight flattening of the thyroid epithelium;[58, 59] a slight but inconstant fall in blood sugar;[48, 49] and a slightly irregular arterial blood pressure which may be above or below normal.[17, 39, 69] The heart,[70] the testes,[41] the hemoglobin content of the blood,[71] and the liver glycogen[48, 49] are normal.

PITUITARY HORMONES

Although the actual hormones have not been isolated, nevertheless on the basis of an analysis of the symptoms of insufficiency and hyperactivity and the effects of restitution, it can be considered probable that hormones, with actions as listed below, exist.

The neuro-intermediate lobe possesses in larger proportion than does the principal lobe: melanophore dilator, arteriole and capillary constrictor,[50, 72] oliguric, water metabolic[50, 72] and oxytocic* actions; and in lesser degree than does the principal lobe a regulatory action on carbohydrate metabolism.[5, 7, 28, 29, 30, 32, 45]†

The principal lobe alone[2, 76] possesses gonadotropic,[2, 9, 24, 25, 35, 36, 40, 41, 43, 76] thyrotropic,[58, 59] growth stimulatory and cutaneous actions. In common with the other lobe, but to a much greater degree, it possesses a regulatory action on carbohydrate metabolism[5, 7, 28, 29, 30, 32, 45] † and to a lesser degree it acts on the melanophores, the small vessels, the excretion of urine and the metabolism of water.

SUMMARY

In the toad the pituitary is a most important organ, as it controls functions which are necessary for the maintenance of the life of the in-

*Houssay, Giusti and Lascano-Gonzalez[40, 41] found the activity of the principal lobe to be, on an average, 0.001 international units per mg. and 0.042 units per lobe; that of the neuro-intermediate 0.41 units per mg. and 0.95 units per lobe, which is the same as that found in bovine posterior pituitary lobe (Houssay, Giusti and Lahille[39]).

†Orias[68] has observed the same phenomenon in the fish, *Mustelus canis,* and Houssay and Biasotti[30] in other amphibia and reptiles.

dividual and also controls sexual and reproductive activities which are necessary for the maintenance of the species. It is the central organ in the endocrine constellation, as it is necessary for the development and maintenance of the anatomical and functional integrity of the other internal secretory glands.

The neuro-intermediate lobe governs various functions:

(1) It maintains the normal color of the skin (with its physiological and pharmacological changes) by preserving an adequate melanophore expansion. The secretion of this hormone is regulated reflexly, and is therefore under the control of the central nervous system.

(2) It preserves the tone of arterioles and capillaries, thus having an important influence in the maintenance of the arterial blood pressure.

(3) It regulates the water metabolism; first, by its action on the kidneys and, secondly, on the skin and other tissues.

The principal lobe governs the following functions:

(1) The development and maintenance of the thyroid and the gonads (including Bidder's organ). It also provides for their compensatory hypertrophy. An adrenotropic action has not been demonstrated in the adult toad.

(2) The occurrence of normal ovulation is due to a pituitary hypersecretion in the female which is reflexly stimulated by the sexual embrace.

(3) The development of the thyroid which permits the metamorphosis of the larva into the adult form.

(4) The regulation of the casting of the skin (with the formation and desquamation of the horny layer) and also the regulation of the cutaneous glandular secretions.

(5) The metabolic functions (carbohydrate metabolism, endogenous protein metabolism, etc.). These are so important, that the loss of pituitary control leads to a state of progressive asthenia, causing death in three to eight weeks. The central nervous system is affected and later the heart, muscles, etc.

Injury of the tuber cinereum produces secondary lesions in the pituitary with an initial glandular reabsorption and later a more or less marked state of pituitary insufficiency.

It is evident that many of these functions of the pituitary either cannot be seen in mammals or will have less importance than in the toad. I have found many functions in the latter which only later were seen in the mammal. For this reason I have studied each function primarily in the toad and simultaneously or subsequently in the more complex animals, and so have been able to understand its significance more readily. No student of the hypophysis can ignore the valuable results obtained by studying its functions in the toad, and all will feel grateful to this low species for the many secrets it has revealed on such an important organ.

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A STUDY OF THE USE OF CORAMINE IN DEALING WITH THE EFFECTS OF BARBITURIC ACID DERIVATIVES*

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THE drugs of the barbituric acid series, since their introduction to the medical profession, have been widely used in order to induce states of unconsciousness ranging from simple sleep from which it is easy to rouse an individual to what amounts to a barbituric acid coma from which no amount of urging, chemical or physical, will produce consciousness until the effect of the drug has worn off. It is only to be expected that with such wide use of these drugs, by both skilled and unskilled persons, a certain number of bad reactions will occur. But, unfortunately, some of these bad reactions become worse, and individuals die.

Furthermore, since it has been possible to buy these drugs for a small sum at any drug counter, the layman, becoming depressed or otherwise wishing to die, has by their use increased the number of near-deaths and deaths quite considerably. And there are sufficient reports in the existing literature relative to these fatalities to quiet any skeptic—to make him wish to have at hand a ready and safe counteracting drug should it fall to his lot to have to treat such a case of poisoning.

It is the belief of the writer that coramine is such a counteractant, such belief being the outcome of the work presented in this paper and the work which has been conducted for so many years by European workers and recently by a very few Americans, on the effect of coramine on hypnotics, narcotics and anesthetics.

One of the first pieces of work in this respect pointed to its possible value, for in 1892 Köppen[1] while studying the then relatively new drug, coramyrtin, reported that it was of value in the counteraction of narcosis. In 1924 Uhlmann[2] confirmed these findings, stating that coramine stimulated the centers of the medulla, respiration especially being affected, i.e., increased. In addition he found that this drug produced a rise in the blood pressure and increased the cardiac excursions. In 1925 Guth[3] demonstrated increased blood flow due to coramine in patients under the influence of general anesthesia. In 1926 Asher[4] at this time stated that coramine improved not only the circulation of animals under depressant drugs but also the

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