# GLANDULAR PHYSIOLOGY AND THERAPY

# Glandular Physiology and Therapy

A SYMPOSIUM

Prepared Under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association

1942

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET :: CHICAGO

# CONTRIBUTORS


FULLER ALBRIGHT, M.D.
Assistant Professor of Medicine, Harvard Medical School.

EDGAR ALLEN, PH.D., SC.D.
Professor of Anatomy, Yale University School of Medicine.

GEORGE W. BARTELMEZ, PH.D.
Professor of Anatomy, the University of Chicago.

CHARLES H. BEST, M.D., D.SC. (Lond.) (Chic.), F.R.S., F.R.C.P. (Can.)
Professor and Director, Dept. of Physiology and the Banting and Best Dept. of Medical Research, University of Toronto.

JAMES B. COLLIP, PH.D., D.SC., M.D., F.R.S.
Director, Research Institute of Endocrinology, McGill University.

CARL F. CORI, M.D.
Professor of Pharmacology, Washington University School of Medicine, St. Louis.

GEORGE W. CORNER, M.D.
Director, Dept. of Embryology, Carnegie Institution of Washington, Baltimore.

FRED E. D'AMOUR, PH.D.
Professor of Physiology, University of Denver.

EDWARD A. DOISY, PH.D., D.SC.
Professor of Biochemistry, St. Louis University School of Medicine.

EARL T. ENGLE, PH.D.
Professor of Anatomy, College of Physicians and Surgeons, Columbia University.

HERBERT M. EVANS, M.D.
Professor of Anatomy; Herzstein Professor of Biology; Director of the Institute of Experimental Biology, University of California.

MORRIS FISHBEIN, M.D.
Editor of The Journal of the American Medical Association.

C. FREDERIC FLUHMANN, M.D.
Associate Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco.

S. CHARLES FREED, M.D.
Headquarters Staff, Council on Pharmacy and Chemistry; Clinical Associate in Endocrine Gynecology, Loyola University School of Medicine; Adjunct in Medicine, Michael Reese Hospital.

E. M. K. GEILING, M.D., PH.D.
Frank P. Hixon Distinguished Service Professor and Chairman, Dept. of Pharmacology, The University of Chicago.

REUBEN G. GUSTAVSON, PH.D.
Professor of Chemistry, University of Colorado, Boulder.

JAMES B. HAMILTON, PH.D.
Assistant Professor of Anatomy, Yale University School of Medicine.

# *CONTRIBUTORS*


ANDREW C. IVY, PH.D., M.D.
Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago.

EDWARD C. KENDALL, PH.D.
Professor of Biochemistry, Mayo Foundation.

JACOB LERMAN, M.D.
Instructor in Medicine, Harvard Medical School; Assistant Physician, Massachusetts General Hospital.

LOUIS LEVIN, PH.D.
Research Associate in Anatomy, College of Physicians and Surgeons, Columbia University.

ROBERT F. LOEB, M.D.
Professor of Medicine, Columbia University; Associate Attending Physician, Presbyterian Hospital and Neurological Institute, New York.

FRANKLIN C. MCLEAN, PH.D., M.D.
Professor of Pathologic Physiology, The University of Chicago.

CARL R. MOORE, PH.D.
Professor of Zoology, The University of Chicago.

EMIL NOVAK, M.D.
Associate in Gynecology, Johns Hopkins University School of Medicine.

FRANCES K. OLDHAM, PH.D.
Research Assistant in Pharmacology, The University of Chicago.

OSCAR RIDDLE, PH.D., LL.D.
Research Staff, Carnegie Institution of Washington, Station for Experimental Evolution, Cold Spring Harbor.

HANS SELYE, M.D., PH.D., F.R.S. (C.)
Associate Professor of Histology, McGill University.

ELMER L. SEVRINGHAUS, M.D.
Professor of Medicine, University of Wisconsin.

PHILIP E. SMITH, PH.D.
Professor of Anatomy, College of Physicians and Surgeons, Columbia University.

WILLARD O. THOMPSON, M.D.
Associate Professor of Medicine, University of Illinois College of Medicine; Associate Attending Physician, Presbyterian Hospital, Chicago.

DAVID L. THOMSON, PH.D.
Professor of Biochemistry, McGill University.

E. T. WATERS, B.SC., PH.D. (Wales)
Associate Professor of Physiology, University of Toronto.

ARNOLD D. WELCH, PH.D., M.D.
Instructor of Pharmacology, Washington University School of Medicine, St. Louis.

RUSSELL M. WILDER, PH.D., M.D.
Member of Staff, Mayo Clinic; Professor and Chief, Dept. of Medicine, Mayo Foundation for Medical Education and Research, University of Minnesota.

OSKAR WINTERSTEINER, PH.D.
Associate Professor of Biochemistry, College of Physicians and Surgeons, Columbia University.

# CONTENTS


| Chapter | | Page |
|---|---|---|
| | Introduction. Morris Fishbein | 1 |
| I. | Relationship of Anterior Lobe of the Hypophysis to Other Endocrine Glands. Philip E. Smith | 3 |
| II. | Growth Hormone of the Anterior Lobe of the Pituitary. Herbert M. Evans | 19 |
| III. | Corticotropic (Adrenotropic), Thyrotropic and Parathyrotropic Factors. James B. Collip | 33 |
| IV. | The Anterior Lobe of the Hypophysis in Intermediary Metabolism.. David L. Thomson | 51 |
| V. | Lactogenic and Mammogenic Hormones. Oscar Riddle | 67 |
| VI. | Gonadotropins of the Anterior Lobe of the Pituitary and of Chorionic Tissue. Earl T. Engle and Louis Levin | 83 |
| VII. | The Antihormones. David L. Thomson, James B. Collip and Hans Selye | 101 |
| VIII. | Dysfunctions of the Anterior Lobe of the Pituitary and Their Treatment. Elmer L. Sevringhaus | 115 |
| IX. | The Neurohypophysis. E. M. K. Geiling and Frances K. Oldham | 127 |
| X. | Physiology of the Ovaries. Edgar Allen | 143 |
| XI. | The Estrogenic Substances. Edward A. Doisy | 169 |
| XII. | Corpus Luteum Hormone. George W. Corner | 185 |
| XIII. | Menstruation. George W. Bartelmez | 197 |
| XIV. | Ovarian Dysfunctions and Their Treatment. C. Frederic Fluhmann | 207 |
| XV. | Ovarian Tumors of Endocrine Nature. Emil Novak | 223 |

| Chapter | | Page |
|---|---|---|
| XVI. | Physiology of the Testis. Carl R. Moore | 233 |
| XVII. | Therapeutics of Testicular Dysfunction. James B. Hamilton | 253 |
| XVIII. | The Function of the Adrenal Cortex. Edward C. Kendall | 273 |
| XIX. | Adrenal Cortex Insufficiency. Robert F. Loeb | 287 |
| XX. | The Adrenal Medulla. Carl F. Cori and Arnold D. Welch | 307 |
| XXI. | The Adrenogenital Syndrome. Oskar Wintersteiner | 327 |
| XXII. | Clinical Significance of Hormone Assays. S. Charles Freed | 341 |
| XXIII. | The Assay of Gonadotropins and of Gonadal Hormones. Reuben G. Gustavson and Fred E. D'Amour | 365 |
| XXIV. | The Physiology of the Thyroid Gland. Jacob Lerman | 379 |
| XXV. | Thyroid Dysfunctions and Their Treatment. Willard O. Thompson | 413 |
| XXVI. | The Parathyroids—Physiology and Therapeutics. Fuller Albright | 443 |
| XXVII. | Activated Sterols in the Treatment of Parathyroid Insufficiency. Franklin C. McLean | 461 |
| XXVIII. | The Pancreas as an Organ of Internal Secretion. E. T. Waters and Charles H. Best | 495 |
| XXIX. | Therapy with Preparations of Pancreas. Russell M. Wilder | 515 |
| XXX. | Internal Secretions of the Gastrointestinal Tract. Andrew C. Ivy | 523 |
| XXXI. | Present Status of Commercial Endocrine Preparations. S. Charles Freed | 537 |
| | Index | 559 |

# INTRODUCTION *

MORRIS FISHBEIN, M.D.

CHICAGO

More than fifteen years have passed since there appeared the first collection of articles on "Glandular Physiology and Therapy," published under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Our knowledge has advanced more in these fifteen years than in all the previous centuries of the life of man. So rapid has been the advance that it was necessary to revise the first series in 1927 and the second in 1935. With the passing of the third five-year period, the Council on Pharmacy and Chemistry has considered it desirable again to survey the advancement of our knowledge.

Conspicuous among the reasons for publishing a summary of endocrinology in 1924 was the existence of a pseudoscientific therapy based on glandular materials promoted by pharmaceutical manufacturers with but slight evidence as to actual utility. Much of this empirical and unwarranted therapeusis has disappeared. With the establishment of a new Food and Drug Law and with the coming of the new powers given to the Federal Trade Commission under the Wheeler-Lea Bill, it is likely that still further improvement will occur. The sale of extracts of tonsil, kidney, spleen and heart and, indeed, of mixtures of these with innumerable other preparations, is likely to be better controlled in the future than it has been in the past. No doubt obvious charlatanism will be controlled. However, the difficulty of evaluating therapeutic results and the great psychologic factor involved in most glandular disturbances combine to confuse considerably many physicians who, witnessing the marvels of scientific glandular therapy, are ready to accept as established claims for much that is in no way proved.

The entire volume published in 1927 included only 98 pages. The series issued in 1935 included thirty-one contributions and made a book of 528 pages. In the

* This series of articles is published under the auspices of the Council on Pharmacy and Chemistry. The opinions expressed in these articles are those of the authors and do not necessarily represent the views of the Council.

present series the number of manuscripts is not greatly increased but the amount of material is considerably larger. Particularly important are the articles concerned with the endocrinology of the female reproductive mechanism. Interesting also are those articles which discuss new aspects of our knowledge of the adrenal and the pituitary. Extraordinary advances have been made with reference to the antihormones. Of special importance also are those articles which discuss the interrelationships of various portions of the glandular apparatus. The investigators who have contributed to this series of articles are all men of note in the fields about which they write. Appreciation is due the Council's special committee on this symposium, Drs. E. M. K. Geiling, chairman, W. W. Palmer, and Elmer L. Sevringhaus. Dr. S. C. Freed of the headquarters staff of the Council has had general supervision over the series, besides contributing two articles of his own. He has also assisted in editing the articles toward uniformity of expression and avoidance of excessive duplication.

During the process of publication of this series of articles in The Journal of the American Medical Association so many new contributions were made to our knowledge of glandular physiology and therapy that it became necessary to make extensive revision of the text before inclusion of the material in book form. This book may, therefore, be said to bring the accumulation of information up to the date when it was finally sent to the printer, namely, October, 1941.

CHAPTER I

# RELATIONSHIP OF ANTERIOR LOBE OF THE HYPOPHYSIS TO OTHER ENDOCRINE GLANDS

PHILIP E. SMITH, PH.D.
NEW YORK

The laboratory and clinical research which has been carried on since the last edition (1935) of Glandular Physiology and Therapy has not revealed any essentially new interrelationships between the hypophysis and the other glands of internal secretion. Nor have investigations revealed that any of the interrelationships of the hypophysis given in the last edition were erroneous. Important investigations have been reported, however, during this period. Those in the field of carbohydrate and fat metabolism have been especially fruitful. Contributions of preceding years, among which those from the laboratory of Houssay are especially noteworthy, laid the basis for this subsequent extensive work, which has revealed the importance of the interrelationship between the hypophysis and the adrenal cortex in the metabolism of fats and carbohydrates. The results from the work in this field have not yet sufficiently matured to enable one to determine what practical value they will have in clinical medicine, but they contribute greatly to an understanding of the physiology of the hypophysis.

Some advance has been made in the purification of preparations containing the pituitary hormones, though the advances, owing to the protein nature of these hormones, have not kept pace with those made in investigations on the chemically more simple hormones (steroids) of the adrenal gland and the gonads.

Aside from the so-called metabolic principles, five hormones or principles continue to be generally recognized as issuing from the anterior lobe of the hypophysis. These are: (1) the growth (somatotropic) principle; (2) the gonadotropic hormone(s) or complex; (3) the thyrotropic hormone; (4) the cortico-

tropic (adrenotropic) hormone, and (5) the lactogenic hormone.[1] The evidence for the secretion of these separate factors is based on data secured from (1) the effects of hypophysectomy and (2) the effects of the injection of hypophysial extracts in (*a*) animals in which an endocrine deficiency has been established by the ablation of one of the endocrine glands, usually the hypophysis, and (*b*) normal animals.

### EFFECTS OF HYPOPHYSECTOMY

The syndrome from a total deficiency of the anterior lobe of the hypophysis has been studied in all common laboratory animals, in monkeys and in man (Simmonds's disease). The studies are revealing in regard to the relationship of the hypophysis to the other glands of internal secretion and so merit a brief description.

The picture presented after hypophysectomy is quite uniform throughout all species of animals. The thyroid, the adrenal cortex and the gonads and accessory reproductive organs undergo profound involution, and their functional activity is greatly reduced. Parathyroid changes are less definite. Lactation ceases abruptly. The thymus involutes, although this may be an indirect effect. The capacity for muscular work is decreased, and activity is reduced. The appetite is diminished, hypoglycemia of varying degrees of severity develops, the circulation becomes sluggish, and the blood pressure is lowered. In young animals growth ceases abruptly, although very young rats may grow slightly. The viscera are small. Resistance to trauma and infection is greatly diminished, and the basal metabolism is lowered. The resultant effect, then, is atrophy or involution of most of the endocrine glands and polyglandular deficiency. Survival for extensive periods, however, is possible and is dependent to a considerable extent on maintaining the normal food intake and so preventing hypoglycemic coma or convulsions (especially in rabbits and monkeys) and on maintaining normal body temperature. Less care seems to be necessary with rats, ferrets and dogs in order to secure prolonged survival than with other species, including man. It is not probable that

1. Other hormones from the hypophysis have been described, but their existence and action are not as well established as the existence and action of the five listed. These other tropic hormones are a medullotropic (Collip) and a pancreatropic hormone (Anselmino, Harold and Hoffman).

even with the greatest care any animal with complete ablation of the anterior lobe of the hypophysis will survive for a normal life span.

A small fragment of functioning gland is able, however, to maintain an animal in an apparently normal condition, and even a fragment of microscopic size has some effect.[2] In rats as little as 10 per cent of the gland will prevent the development of the disabilities, and in monkeys certainly not more than one fourth of the gland is necessary. The hypophysis thus has a great margin of safety, as is true for the other endocrine glands. A fragment which remains appears to have little or no capacity to regenerate, although with regard to this data on monkeys and man are not available.

Experimental work has not sufficed to elucidate the condition of hypofunction in a gland of normal size, for such a condition has not been reported to occur in animals and therefore cannot be studied in them. It is essentially a clinical problem, arising in certain cases from a preponderance of nonsecretory (chromophobe) cells at the expense of secretory (chromophil, i. e., acidophil and basophil) cells.

Experimentally it has been found that a genetic deficiency of one of the two secretory cell types of the anterior lobe of the hypophysis may exist. In the particular strain of mice in which this defect appeared, the acidophils were totally absent, but the chromophobes and basophils were present.[3] The disabilities of hypophysectomy were all present except the atrophy of the genitals, thus supplying additional significant evidence that the basophils elaborate the gonadotropic hormone complex. That a similar condition may occasionally exist in the human subject is indicated in a case recently reported by Shorr and co-workers.[4] The opposite condition, overactivity of a cell type, has long been known from studies on acromegaly, in which there is a tumor of the acidophils.

Experimental and clinical work on the anterior lobe of the hypophysis thus shows that this gland influences,

2. The literature is reviewed by Smith, P. E., in Allen, Edgar; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, ed. 2, Baltimore, Williams & Wilkins, 1939, p. 391.

3. Smith, P. E., and MacDowell, E. C.: The Differential Effect of Hereditary Mouse Dwarfism on the Anterior Pituitary Hormones, Anat. Rec. **50**: 85 (July 25) 1931.

4. Reported at the Annual Meeting of the Association for the Study of Internal Secretions in June 1940.

and in most cases directly controls, all of the other glands of internal secretion. These interrelations were all established at the time that the last edition of this book was published, and much of the work since then has been directed toward determining the number of hormones elaborated by the hypophysis and their action and toward the purification of preparations of these hormones.

### ACTION OF PITUITARY HORMONES

*The Growth Principle.*—That the secretion of the hypophysis is essential for general body growth except in the earlier stages of development is unquestionable. The question of the existence of a specific growth-promoting principle would appear to have been raised largely for three reasons: 1. Preparations of the growth-promoting factor have not been free from substances affecting specific organs—thyroid glands, gonads and adrenal glands. 2. Growth is such a complex process, as has been especially pointed out by Stockard,[5] that it is difficult to conceive of its being due to a single hormone. Each of the pituitary tropic hormones is essential for the growth of the specific organ which it affects. 3. The injection of prolactin—a lactogenic factor—causes growth in pigeons and dwarf mice, as shown by Riddle and collaborators.[6] Moreover, in still lower forms (amphibian larvae) the hypophysis can be ablated without inhibiting growth to any great extent.

Specific endocrine stimuli, however, seem to be more necessary for the promotion of growth in mammals than in lower forms, and an interest in comparative physiology should not blind one to the fact that in medical practice the responses of mammals, especially those of man, are of predominant interest. In regard to the contamination of extracts of the growth factor with other anterior pituitary factors, it has been greatly reduced without impairing the growth-stimulating property of the extract.[7] It thus appears, as stated by Evans

5. Stockard, C. R.; in discussion on Evans.[7]

6. Bates, R. W.; Riddle, Oscar; Lahr, E. L., and Schooley, J. P.: Aspects of Splanchnomegaly Associated with the Action of Prolactin, Am. J. Physiol. **119:** 603 (July) 1937. Bates, R. W.; Laanes, Theophil, and Riddle, Oscar: Evidence Against the Individuality of the Growth Hormone, Proc. Soc. Exper. Biol. & Med. **33:** 446 (Dec.) 1935.

7. Evans, H. M.: The Hypophyseal Growth Hormone, A. Research Nerv. & Ment. Dis., Proc. (1936) **17:** 175, 1938. Meamber, D. L.; Fraenkel-Conrat, H. L.; Simpson, Miriam E., and Evans, H. M.: The Preparation of Pituitary Growth Hormone Free from Lactogenic and Thyrotropic Hormones, Science **90:** 19 (July 7) 1939.

nearly twenty years ago, that in mammals a specific principle is secreted by the hypophysis which is essential for general body growth. This principle appears to influence skeletal growth mainly by stimulating the epiphysial cartilages, although the effect extends to the soft tissues and the viscera, also.

*The Gonadotropic Complex.* — The investigations reported by Cushing and collaborators and by Aschner on dogs some thirty years ago revealed that the gonads atrophied after hypophysectomy. Work in 1927 in which atrophic gonads of hypophysectomized rats were repaired and immature ovaries were stimulated to precocious development by administration of pituitary extract gave conclusive proof that there was a factor (or factors) secreted by the hypophysis which was necessary for the structural and functional maintenance of the gonads and through them of the accessory reproductive organs. It was soon discovered, however, that the injection of extracts of hypophyses from different species did not give equal quantitative responses of the different types of tissue composing the gonads. In fact, Evans and Long showed in 1922 that crude extracts of beef hypophyses caused the formation of large amounts of lutein tissue in the ovaries of normal mature rats but had no follicle-stimulating effect. When it was found that the hypophyses of other species—rats, horses, sheep, man—gave pronounced follicle-stimulating effects, indirect evidence was thus supplied that more than one gonadotropic hormone had been encountered.

Fractionation and purification of gonadotropic extracts were undertaken by several investigators (Fevold, Hisaw and Leonard,[8] Wallen-Lawrence,[9] Evans and associates[10]). The present consensus from the labora-

8. Fevold, H. L.; Hisaw, F. L., and Leonard, S. L.: The Gonad-Stimulating and Luteinizing Hormones of the Anterior Lobe of the Hypophysis, Am. J. Physiol. **97**: 291 (May) 1931. Fevold, H. L.: The Follicle-Stimulating and Luteinizing Hormones of the Anterior Pituitary, in Allen, Edgar; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, Baltimore, Williams & Wilkins Company, 1939, p. 966.

9. Wallen-Lawrence, Zonja: Proof of the Existence of a Follicle-Stimulating and a Luteinizing Hormone in the Anterior Lobe of the Pituitary Body, J. Pharmacol. & Exper. Therap. **51**: 263 (July) 1934.

10. Evans, H. M.; Korpi, Karl; Simpson, Miriam E.; Pencharz, R. I., and Wonder, D. H.: On the Separation of the Interstitial Cell Stimulating, Luteinizing and Follicle Stimulating Fraction in the Anterior Pituitary Gonadotropic Complex, Univ. California Publ. Anat. **1**: 255, 1936.

tories in which these studies are being made is that two gonadotropic principles are elaborated by the anterior lobe of the hypophysis. The determination of the number of gonadotropic hormones is not easy to make, however, and in my opinion has not been definitely made. The length of treatment, the rate of absorption, the dosage and the site of injection (subcutaneous or intraperitoneal) all influence the response. That the solution of the problem is difficult is attested by the fact that within a six year period investigators in one prominent laboratory have stated that there was only one, that there were four and later that there were two pituitary gonadotropic hormones. The two postulated hormones are usually designated as the follicle-stimulating and the luteinizing hormone. The second hormone is sometimes designated as the interstitial cell–stimulating hormone instead of the luteinizer.

The hypophysial luteinizing hormone is not identical with the gonadotropic principle of human pregnancy urine, which is sometimes designated as the luteinizing hormone.[11] Little is known of the chemical composition of the gonadotropic factors, a statement which is also true of the other hypophysial principles.

*The Thyrotropic Hormone.*—It has been known since the classic work of Rogowitsch in 1889 that the hypophysis is influenced by the thyroid. The determination of an effect of the hypophysis on the thyroid is much more recent. This effect was first demonstrated by hypophysectomy and the injection of hypophysial extracts in amphibia[12] and later in mammals.[13] The threshold of the stimulus of structural response differs greatly in different species, the thyroids of rats being unchanged in structure by high doses of pituitary thyrotropic extract, whereas the thyroids of guinea pigs and rabbits undergo profound changes even with low doses. The injection of the thyrotropic extract in responsive species results in most of the thyroid changes

11. Some commercial descriptive advertisements are misleading in that it is indicated that the hormones from these two sources are identical. All the evidence indicates that the gonadotropic substance in human pregnancy urine is from chorionic tissue, not the hypophysis.

12. The literature is reviewed by P. E. Smith (Relations of the Activity of the Pituitary and Thyroid Glands, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1930, p. 129).

13. Loeb, L., and Bassett, R. B.: Effect of Hormones of Anterior Pituitary on Thyroid Gland in the Guinea-Pig, Proc. Soc. Exper. Biol. & Med. **26**: 860 (June) 1929. Aron, M.: L'hormone préhypophysaire excito-sécrétrice de la thyroïde, Rev. franç. d'endocrinol. **8**: 472 (Dec.) 1930.

characteristic of exophthalmic goiter, i. e., increase in size of the thyroid, depletion of iodine, loss of colloid, and hyperplasia and hypertrophy of the cells, with the characteristic irregular type of follicles. The infiltration by lymphocytes and the increase in connective tissue characteristically present in hyperplasia of human thyroids are not present in the hyperplasia experimentally induced. The absence of these changes may be due to the shortness of the period of treatment.

The injection of thyrotropic extract causes also a rapid and marked rise in basal metabolism, although a rise in metabolic rate from pituitary extract has also been reported in thyroidectomized animals.[14] The thyrotropic extract induces a hyperplastic response of thyroid tissue in vitro [15] and also of transplanted thyroids; [16] so it can act independently of any innervation. In man massive doses have been shown to be effective in cases in which hypothyroidism is due to underfunction of the pituitary and not to lack of responsiveness of the thyroid. The thyrotropic extract of pituitary may have a limited field of usefulness, in that its administration will give information as to whether or not hypothyroid states are due to lack of responsiveness of the thyroid to stimulation by the hypophysis. It seems improbable, however, that it can have any extensive clinical usefulness.

*The Corticotropic Hormone.*—A stimulating action of the anterior lobe of the hypophysis on the adrenal cortex was first shown in amphibia. Hypophysectomy caused profound atrophy of the cortical but not of the medullary component of the adrenal, an action which

14. This effect is stated to be due to a specific metabolic principle and not to a tropic hormone (Collip). This principle is remarkably thermostabile and is resistant to boiling in dilute acid and alkali and to peptic digestion. Its injection causes a sharp rise in the metabolic rate for only a few hours. Collip states that it probably has its origin in the pars intermedia but that it is not identical with the melanophore-expanding hormone.

15. Eitel, Hermann; Krebs, H. A., and Loeser, Arnold: Hypophysenvorderlappen und Schilddrüse: Die Wirkung der thyreotropen Substanz des Hypophysenvorderlappens auf die Schilddrüse in vitro, Klin. Wchnschr. **12**: 615 (April 22) 1933.

16. Houssay, B. A.; Biasotti, A., and Magdalena, A.: Hipófisis y tiroides; Acción del extracto del lóbulo anterior de la hipófisis sobre la histologiá de la tiroides del perro, Rev. Soc. argent. de biol. **8**: 130 (May-June) 1932. Marine, David, and Rosen, S. H.: The Effect of the Thyrotropic Hormone on Auto- and Homeotransplants of the Thyroid and Its Bearing on the Question of Secretory Nerves, Am. J. Physiol. **107**: 677 (March) 1934.

was confirmed in mammals some ten years later.[17] The atrophy could be prevented or the involuted glands restored to a normal condition by the administration of anterior lobe. There has been much question as to whether or not this cortex-stimulating action of the hypophysis was due to a distinct hormone, but the evidence supplied by Collip and co-workers,[18] Moon [19] and others shows that it is distinct from the thyrotropic, growth-promoting lactogenic and other hypophysial hormones. It appears to have no action other than that of stimulating the cortex of the adrenal.

The injection of a pituitary extract containing the corticotropic factor restores the adrenals after hypophysectomy. It partly restores the work capacity of hypophysectomized animals, although their work capacity still remains somewhat subnormal, as is the case also when cortical extracts are administered.[20]

The injection of cortical extract has been shown to repress the liberation of corticotropic hormone from the hypophysis.[21] It seems probable that the enlargement of the adrenals in normal animals under conditions of stress is due to liberation of unusual amounts of corticotropic hormone by the hypophysis.

As in the case of the thyrotropic extract, it is not probable that the corticotropic extract will prove of much clinical value.

*The Lactogenic Hormone.*—The pituitary lactogenic hormone (prolactin; galactin; mammotropin) is purely a secretogogue and does not cause development and growth of the mammary glands. It is the only pituitary hormone that has been secured in crystalline form,[22]

17. Smith, P. E.: The Pigmentary, Growth and Endocrine Disturbances Induced in the Anuran Tadpole by the Early Ablation of the Pars Buccalis of the Hypophysis, in American Anatomical Memoirs, Philadelphia, Wistar Institute of Anatomy and Biology, 1920, No. 11; Hypophysectomy and a Replacement Therapy in the Rat, Am. J. Anat. **45:** 205 (March) 1930.

18. Collip, J. B.; Anderson, E. M., and Thomson, D. L.: Adrenotropic Hormone of Anterior Pituitary Lobe, Lancet **2:** 347 (Aug. 12) 1933.

19. Moon, H. D.: Preparation and Biological Assay of Adrenocorticotropic Hormone, Proc. Soc. Exper. Biol. & Med. **35:** 649 (Jan.) 1937.

20. Ingle, D. J.; Moon, H. D., and Evans, H. M.: Work Performance of Hypophysectomized Rats Treated with Anterior Pituitary Extracts, Am. J. Physiol. **123:** 620 (Sept.) 1938.

21. Ingle, D. J.: The Effects of Administering Large Amounts of Cortin on the Adrenal Cortices of Normal and Hypophysectomized Rats, Am. J. Physiol. **124:** 369 (Nov.) 1938.

22. White, Abraham; Catchpole, H. R., and Long, C. N. H.: Crystalline Protein with High Lactogenic Activity, Science **86:** 82 (July 23) 1937. Shipley, R. A.; Stern, K. G., and White, Abraham: Electrophoresis of Anterior Pituitary Proteins, J. Exper. Med. **69:** 785 (June) 1939.

although the potency of the crystals does not exceed and even may not equal that of the amorphous powder.

The test used for determining lactogenic activity is the response of the crop gland of the pigeon. Riddle has shown that his special preparation, prolactin, has other effects in pigeons, stimulating general body growth and the gastrointestinal tract. These effects are not secured in mammals by the injection of prolactin. Prolactin also stimulates the basal metabolic rate of thyroidectomized pigeons.[23]

The injection of prolactin gives but a temporary increase in milk production in cows,[24] and clinical studies show little or no response following its injection in man.[25]

*Relations of the Anterior Lobe of the Hypophysis to Carbohydrate and Fat Metabolism.*—The interrelationships of the anterior lobe of the hypophysis and other internal secretory glands in carbohydrate and fat metabolism is a subject which is complex. The reported studies dealing with the injection of pituitary extracts concern themselves largely with "effects" produced by very crude extracts, for the principle or principles producing these effects are in most cases very labile and a degree of purification equal to that achieved with the other pituitary factors has not been obtained. These studies, particularly those of Long and Lukens, have shown an important interrelationship between the hypophysis and the adrenal cortex in carbohydrate metabolism.

Although this complex interrelationship will be discussed more fully in another section, it seems justifiable to discuss briefly some phases of it here. Certain important findings stand out in this work. These are: (1) the greatly increased sensitivity to insulin of hypophysectomized animals, first reported by Houssay and Magenta, in 1924, which was shown later to be due to the loss of the anterior lobe only (Houssay and

23. Riddle, Oscar; Smith, G. C.; Bates, R. W.; Moran, C. S., and Lahr, E. L.: Action of Anterior Pituitary Hormones on Basal Metabolism of Normal and Hypophysectomized Pigeons and on the Paradoxical Influence of Temperature, Endocrinology **20**: 1 (Jan.) 1936.

24. Folley, S. J., and Young, F. G.: The Effect of Continued Treatment with Anterior Pituitary Extracts on Milk Volume and Milk-Fat Production in the Lactating Cow, Biochem. J. **33**: 192 (Feb.) 1939.

25. Stewart, H. L., and Pratt, J. B.: Effect of Prolactin on Mammary Gland Secretion, Endocrinology **25**: 347 (Sept.) 1939.