PITUITARY CHROMOPHOBE ADENOMAS

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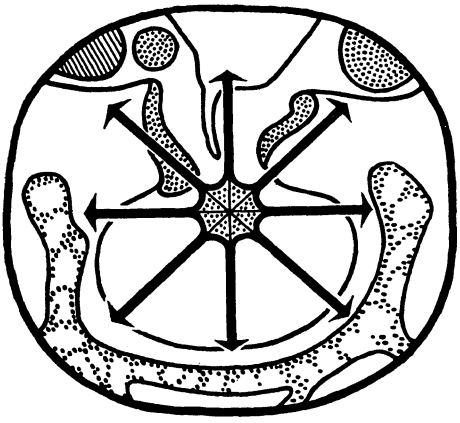
A CLINICAL STUDY OF THE SELLAR SYNDROME



PITUITARY CHROMOPHOBE ADENOMAS

NEUROLOGY
METABOLISM
THERAPY

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To

M. C. N.

and

D. B. K.

PREFACE

In the present study we have attempted to correlate information from several medical disciplines in order to portray the syndrome of chromophobe adenoma of the pituitary in its setting of pathologically modifield function. The book will serve a purpose if this segment of neurology is rejoined to the continuum of internal medicine and made readily available to the inquiring physician with general interests. Indeed this monograph has been written in awareness that some of the material included is beyond the range of the authors' immediate field of study. This investigation and resume is dedicated in all humility to the rapprochement of neurology to general medicine and to the reappearance of those compelling currents of medical thought which prevailed in American neurology under the influence of Cushing and Bailey.

It is idle to describe the vicissitudes involved in the publication of such a monograph: "the appeal is too limited," "the general practitioner won't be interested," etc. We are thankful to Mr. Bernhard Springer for publishing the work even in view of such opinions. We feel confident that if the material has been presented comprehensively, any physician will greet the work with interest; no more have the authors or the publisher a right to expect.

Our gratitude is extended to Dr. H. Houston Merritt whose aid and confidence in this study were sustaining factors to us. We also wish to thank Dr. Robert F. Loeb, who instructed us during the early stages of the work and gave us thoughtful guidance. Dr. Abner Wolf offered the pathologic material for review and conscientiously led us to a conservative estimate of the data obtained. Without the interest

and cooperation of the Drs. Henry A. Riley and the late Irving M. Pardee, the realization of comprehensive clinical investigations of endocrine problems in patients admitted to the Neurological Institute of New York would not have been possible. Dr. Ernest Wood critically reviewed the chapter on therapy and graciously supplied typical x-rays for incorporation into the text. Dr. Paul Hoefer supplied information and comment relative to the results of electroencephalography. Both Dr. Sidney Werner and Dr. Joseph Jailer furnished observations originating in their respective laboratories. We are indebted to Dr. J. R. Nickerson of the Department of Physiology, College of Physicians and Surgeons, for the facilities of his laboratory, where we did the plasma volume studies. Dr. G. B. Mudge performed flame photometric determinations of sodium and potassium on the patients and advised us as well. The attending physicians of Presbyterian Hospital have kindly allowed us to include in this series many patients studied under their personal supervision. Mr. Ivan Summers graciously lent his talents for the illustrations. For performing the arduous task of editing the manuscript we gratefully thank Dr. L. Rowland.

We gladly acknowledge the privilege extended to us by the many publishers who have graciously allowed us to include reproductions from their texts and journals. The following publishers contributed greatly to the present monograph: C. V. Mosby Company, St. Louis; Charles C Thomas, Springfield; The Williams and Wilkins Company, Baltimore; The Wistar Institute of Anatomy and Biology, Philadelphia; Paul B. Hoeber, Inc., New York; George Banta Publishing Co., Menasha; The Macmillan Company, New York; Longmans, Green and Co., New York; Archives of Ophthalmology, Chicago; Archives of Neurology and Psychiatry, Chicago.

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I

INTRODUCTION

During the years 1907 to 1912 pioneer studies of critical importance first stressed the relationship of hypopituitary states to chromophobe adenomas. It is not surprising, therefore, that descriptions of probable chromophobe adenomas prior to that period should have been devoted more to clinical abnormalities than to physiologic or pathologic mechanisms. Thus Mohr in 1840[cited in 37, 43] described a "sarcoma of the hypophysis" associated with unusual obesity, and Babinski and Onanoff in 1900[cited in 43, 296] reported an "epithelioma" of the pituitary which pressed on the tuber cinereum and was likewise associated with obesity. Fröhlich in 1901[181] published a detailed clinical study of a patient with a probable pituitary tumor associated with peculiarly disposed obesity and genital dystrophy. This case was not confirmed anatomically until 1907[296] and was then considered as a pituitary carcinoma or precancerous adenoma with cyst formation. Striking painful adiposity was a prominent finding in a patient studied both clinically and anatomically by Dercum and McCarthy in 1902.[124] Autopsy disclosed a large "eosinophilic" adenocarcinoma, ill-defined changes in the thyroid gland and fatty infiltration of the liver. The authors did not make clear the possible role played by the pituitary tumor but did suggest that the previous emphasis on thyroid disease as primary in such a disturbance might not be fully justified. In the light of present knowledge it is probable that all of these were examples of chromophobe adenomas.

By the end of 1912 the stage was set for an adequate presentation of chromophobe adenoma as an entity whose predominant clinical accompaniment was that of hypopituitarism. Erdheim and Stumme[145] had already published a classic article reviewing with clarity the various cytologic elements of the anterior pituitary. Dean Lewis had emphasized[304] the relative ease in differentiating lesions of the pituitary gland histologically, though interestingly enough he did not discuss chromophobe adenomas. Cushing had published his remarkable monograph[100] describing in a decisive and well documented manner not only hypo- and hyperfunctional pituitary states, but also their histopathologic correlates. He, as well as Geotsch shortly thereafter,[202] stressed the relative frequency of chromophobe adenomas in the pathogenesis of hypopituitarism. Yet the stage appears to have been set prematurely. Fully fifteen years passed during which only Cushing and those associated with him utilized this early knowledge to complete advantage.

In the interim from 1912 to 1930 chromophobe adenomas were accorded limited attention as a determinant of hypopituitary states. Despite Cushing's studies, the consistent lack of appreciation of their relative frequency made their consideration a remote and disinterested one in some clinical treatises of the period as, for example those of Gilford,[197] Engelbach,[141] and later those of Rowe and Lawrence[397] and Hartoch.[138] In some instances[154, 192, 339] chromophobe adenomas were considered worth mentioning only because they appeared to be unassociated with acromegaly or gigantism. An even greater number of workers was concerned with the possible role of such tumors in the production of pathologic obesity, with or without disturbance of genital structure and function.[45, 46, 216, 296, 356, 533] Careful endocrine and metabolic studies were exceptional.[46, 533] These clinical investigations nevertheless gave a necessary stimulus to the resultant intensive experimental study of the hypothalamus and its functions. In the late 1920s the possible relationship of such tumors to pituitary cachexia was discussed[390, 470] albeit general treatises of the period[43, 533] mention this problem summarily. Endocrine and metabolic investigations often lacked clearly defined clinical or pathologic criteria[2] though exceptions can be found.[182] Histopathologic differentiation of tumor type received little attention,[247, 356] in studies of juxta-hypophyseal pressure disturbances.

During the period just mentioned, which finds a faithful echo even in recent years,[441] a small group labored to categorize chromophobe adenomas, not only as a histopathologic entity but also as a unique determinant of metabolic dysfunctions. This labor has continued to the present. Cushing, as previously mentioned, laid the foundations for this work in 1912. Von Monakow,[348] Illig,[266] and Bailey and Cushing[24, 103] have advanced this approach; the latter authors have defined an entire subgroup of transitional or transitory hyperfunctional states as distinct from the condition of hypopituitarism characteristic of chromophobe tumors. More recently Schnitker and his co-workers,[416] Henderson,[239] Foley and co-workers,[167] Foster and McCarter,[170] Starr and Davis,[456] German,[193] Globus and his associates[200] and workers from the Lahey Clinic[294a, 531a] have considered the myriad problems associated with chromophobe adenomas. An increasingly mature and sophisticated interest in the dynamic metabolic disturbances associated with this tumor is manifest in these studies.

No attempt has been made to assign precedence to any worker or group in this introduction. Our purpose has been rather to stress the dominant trend in clinical studies of each period. Undoubtedly the struggles, distinctions and polemics of the so-called "syndrome" period served to direct attention to neurohypophyseal mechanisms later confirmed by controlled animal experimentation. It is hoped that the clinical analysis which comprises the bulk of the present study may serve, in some small measure, as a stimulus to continued experimental study. We have attempted to interpret signs and symptoms from the standpoint of the disturbed neurophysiology and metabolism concerned in their elaboration. Through this broader analysis an evaluation of the resources available to the patient with a chromophobe adenoma for enduring environmental exigencies can be made. The core of this report is the data obtained from patient records but the explanation of the observations involves discussion of neural and endocrine mechanisms of general significance.

II

ANATOMY OF THE PITUITARY

The pituitary gland arises from epithelial and neural elements in the usual tortuous manner of developing organs. The anlagen juxtapose but their constitutent cells do not intermingle. In the adult the main glandular mass occupies a secure position within a bony pit in the middle cranial fossa and by means of a dural investment is separated from the subarachnoid space. The vicinal neural organs are somewhat removed from the body of the pituitary but its relations to these structures become brutally apparent when neoplastic expansions of the gland disorganize their sensitive nervous tissue.[179] Blood reaches the pituitary through a portal system of vessels and directly from the internal carotids. Venous drainage is to the cavernous sinus and perisellar plexuses. The pituitary is innervated by autonomic nerves and by a definite bundle of fibers arising in the hypothalamus and ending in the neural lobe. The secretions of the gland probably enter the blood stream and to a lesser degree ascend toward the third ventricle of the brain.

EMBRYOLOGY

In the head end of the embryo there exists an area of adherence, (the neuro-ectodermal plate) between the inferior surface of the neural tube and the roof of the stomodeum.[196] In the course of the general

development of the head, mesenchymal tissue invades this region of contact and restricts the extent of the area of adherence to a median position, circumscribed by mesodermal elements (fig. 1). From the torsions produced on this region by the developmental flexions of the

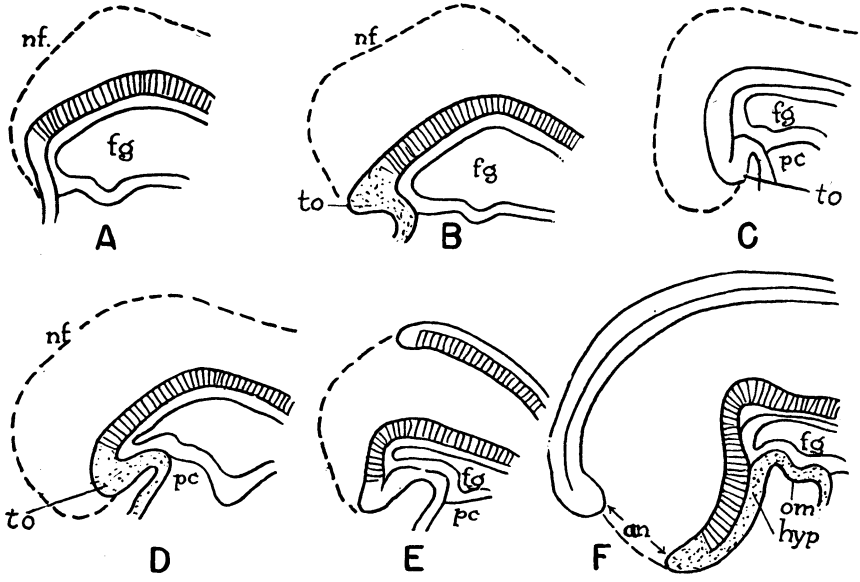

Fig. 1—Median sagittal sections of the anterior end of young human embryos: (A) 2 somite; (B) 7 somite; (C) 8 somite; (D) 10 somite; (E) 13 somite; (F) 16 somite.

These diagrams illustrate the fusion of the neural folds and surface ectoderm (thatched area) in the region of the torus opticus without the intervention of mesodermal elements. It it within this and the proximately caudal area, the region of neuroectodermal adherence, that the hypophysis develops.

Key: an, anterior neuropore; fg, foregut; hyp, hypophyseal area; om, oral membrane; pc, pericardial cavity; to, torus opticus.

From original of figure 2, Gilbert, M. S.: Some factors influencing the early development of the mammalian hypophysis. Anat. Rec. 1935, *62*: 347.

cephalon and by active local growth an outpouching of the roof of the stomodeum results. This is Rathke's pouch, which develops into the anterior lobe of the hypophysis. According to Gilbert,[196] in the early stages Rathke's pouch remains adherent to the neural tissue, which will later become the infundibulum of the diencephalon. The cells of the

infundibular region do not appear to be increasing in proportion to the configurational changes occurring at this time. This has led to the supposition that the outpocketing of the infundibulum is induced initially by the mechanical effects of rotation of the neuro-ectodermal plate from a dorso-ventral to a cephalo-caudal plane.

The concept expressed above states that the neural and stomodeal parts of adenohypophysis are in immediate connection with each other; the rearrangements of one element are reflected by its partner in development. Moreover, the development of both depends upon spatial changes occurring in the course of the general organization of the differentiating head.

The more usually accepted hypothesis of the dual origin of the adenohypophysis asserts that local evaginations proceed from the stomodeum and neural tube. Under the influence of "biotaxis," perhaps a synonym for a local organizer,[494] these outpouchings become associated with each other. Their interdependent orientation and configurations are the responsibility of local processes supposedly acting at each evagination. The later development of pituitary does not present similar controversy.[17, 481, 482]

The anterior lobe of the hypophysis is differentiated from Rathke's pouch (figs. 2, 3, 4). The tubular connection of this latter structure with the stomodeum elongates as the stomodeum becomes increasingly separated from the neural tube by ingrowing mesenchyme. The juxtaneural extremity of the tube expands into three evaginations. The central outpouching enlarges and becomes the pars distalis, the main component of the anterior lobe. The lateral projections elongate and fuse across the midline and, as the pars tuberalis, apply themselves to the median eminence. A thickening of the dorsal lip of the main midline evagination develops into another pair of pouches which also coalesce and envelope all but the dorsal aspect of the infundibular process and represent the pars infundibularis in the adult state. These latter protrusions contain the cavity of Rathke's pouch which is narrowed to an insignificant slit in the adult. A downward extension of the pars infundibularis separates the anterior lobe from the diencephalic posterior lobe. In the adult this downward extension is called the pars intermedia. The cleft-like residuum of the stomodeal cavity lies between the pars distalis and the pars intermedia.

During the early stages of pituitary development the tubular neck of Rathke's pouch disappears, terminating the connection of the mouth with the pituitary anlage. It is believed that embryologic rests from the dental ridges which have been incorporated into the walls of the oropituitary canal may persist and occasionally develop into craniopharyngiomas in the region adjacent to the stalk of the infundibulum.

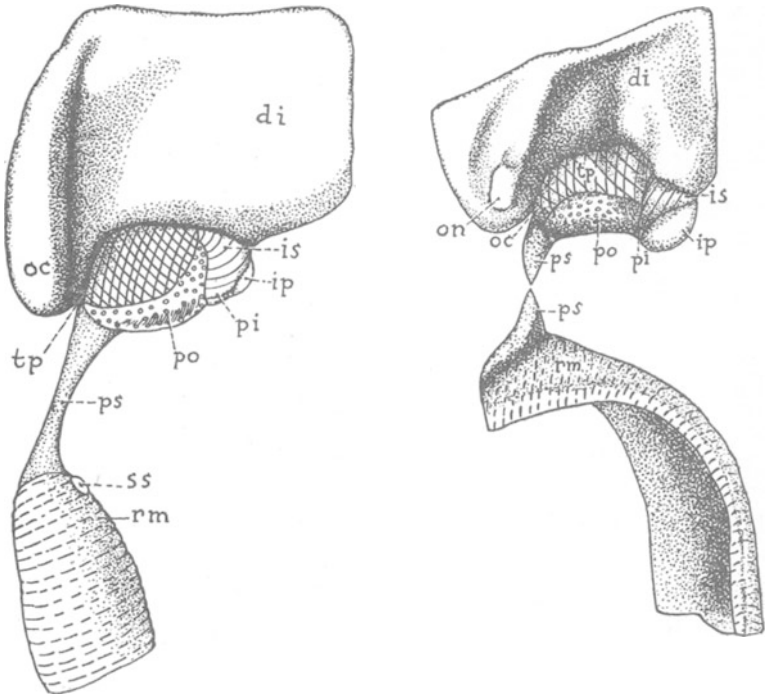

Fig. 2—(A) Left lateral view of reconstruction of pituitary region in 16 mm. human embryo. (B) Left lateral view of pituitary region in 24 mm. embryo.

The expansion of the juxta-neural end of the oropituitary tube comes into intimate relationship with the diencephalic region, enfolding the infundibular stem. The oropituitary canal becomes pinched off and the connection between the stomodeum and the future adenohypophysis is lost.

Key: di, diencephalon; ip, infundibular process; is, infundibular stem; oc, optic chiasm; on, optic nerve; pi, pars infundibularis; po, pituitary pouch; ps, pituitary stalk; rm, roof of mouth; ss, Sessel's pocket; tp, tuberal process.

From original of figures by Tilney, F.: The development and constituents of the human hypophysis. Bull. Neurol. Inst. New York 1936, *5*: 387.