Recent Advances in the Diagnosis and Treatment of Pituitary Tumors

Edited by

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Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title:

Recent advances in the diagnosis and treatment of pituitary tumors.

Includes bibliographies and index.
1. Pituitary body–Tumors. I. Linfoot, John A.
[DNLM: 1. Pituitary neoplasms–Diagnosis. 2. Pituitary neoplasms–Therapy. WK585 R295]
RC280.P5R42 616.9'92'47 79-14948
ISBN 0-89004-365-5

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Preface

This volume reviews the current state of the art and science in the diagnosis and treatment of human pituitary tumors—difficult and frustrating problems for most clinicians. Neuroendocrine and neuroradiological advances in this rapidly growing area have decreased the wide variability in diagnostic evaluation and, in general, have lessened morbidity and mortality. However, no single treatment has been demonstrated to be uniformly effective, and local experience largely determines the treatment offered the patient.

The basic anatomical, histological, and biochemical features of the hypothalamohypophysial system are considered with respect to the pituitary tumors associated with acromegaly, Cushing's disease, and galactorrhea-amenorrhea syndrome. Chapters based on our own experience review neuroradiological and neuro-ophthalmological procedures. The clinical features and X-ray and laboratory evaluation of patients with pituitary tumors are presented at a clinical level. The indications, results, and complications of treatment with thermal, cryogenic, transcranial, subfrontal, and transsphenoidal microsurgical techniques; implantation hypophysectomy with ^{90}Y or ^{198}Au; and teletherapy with alpha particles, protons, and photons (gamma or X-rays) are presented. We also discuss recent drug therapy, especially agents with dopaminergic activity which have been demonstrated to alter hormone secretion by functioning pituitary tumors. These comprehensive and authoritative presentations provide a forum for critically evaluating treatment and defining areas for future investigation.

This volume will be of interest to neurosurgeons, clinical and basic endocrinologists, neuroradiologists, and neurologists.

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Raven Press, New York © 1979.

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History of Pituitary Therapy at the Donner Pavilion

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My interest in the pituitary goes back to the time when I wrote my first paper on the pituitary gland while working with Harvey Cushing (3,7,10). By coincidence, my first paper on the effect of irradiation with dense ionization or heavy particles was on the same program as Dr. Cushing who presented a paper on "pituitary basophilism," formerly called the pluriglandular syndrome. Finally, as an intern in surgery at the Peter Brigham Hospital, I evaluated the first patient in whom Dr. Cushing diagnosed "pituitary basophilism," now called Cushing's disease. This began a continuing interest in both the pituitary and heavy particle irradiation.

During these early years a series of studies using X-irradiation on animals and man was undertaken and later demonstrated the radioresistance of the hypophysis (8). Later, observations of a Wilson cloud chamber—which displayed dense ionization with protons compared to the weaker ionization of electrons, X-rays, and γ-rays—initiated dense ionization studies at the Lawrence Berkeley Laboratory. One could see the fine tracks in the background of the β-ray ionization and the very dense tracks from the ionization produced by protons as a result of collisions by neutrons. Studies were immediately begun on mice to see whether dose-for-dose dense ionization would produce a greater biological effect than ordinary X-ray ionization in tissue (4,9). Indeed this proved to be true (5), and safety standards were established for employees working with cyclotrons and reactors, allowing them only one-tenth of the then allowable X-ray dose exposure. Soon after the original studies on normal animals were concluded, studies were initiated on animals with tumors. It was found that there was a relatively greater increase in the biological effect of neutrons (dose for dose) than that produced by X-rays (6). This led to the early trial of neutrons in cancer therapy (12). Although we determined the greater effect of neutrons, the oxygen effect on ionizing irradiation was unknown. The tumors irradiated were relatively hypoxic *(in vitro),* which reduced the effectiveness of X-rays and had little effect on the neutrons. Many years later, Cornelius Tobias (Chapter 17) and Professor Luis Alvarez performed experimental work with positively charged heavy particles employing carbon-14 ions accelerated from the 60-inch cyclotron (13). Since those early days there has been tremendous activity at the Donner Laboratory and the Lawrence Berkeley Laboratory on the use of heavy charged particles in experimental biology, biophysics, and investigative medical therapy (1,11).

After World War II cellular experiments with relatively low energy heavy particles such as argon, krypton, etc. (energy not sufficient to penetrate animal tissues) were carried out (2). Although the Bragg peak was known from the early studies with alpha particles with radium, these studies with low-energy particles showed that the dense ionization at the Bragg peak had a greater radiobiological effect (RBE). With the greater density and high energy at the Bragg peak, accelerated particles from the Bevalac can produce tissue ionizations as high as 100 keV per micron at any depth in tissue. This density brings down the oxygen effect from approximately three to slightly over one. Utilizing the Bevalac and Bragg peak of particles such as carbon, neon, and other nuclei (300 to 400 meV per nucleon), it will be possible to deliver larger doses more accurately to the pituitary than currently employed.

Finally, because of the pioneering work at the Donner Laboratory, the Biology and Medicine Division of the Lawrence Berkeley Laboratory, a broad program of pituitary and cancer research is being carried out with heavy particles at many other centers in this country and abroad.

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Raven Press, New York © 1979.

2

Anatomy of the Pituitary and Hypothalamus

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The human pituitary gland was first described in 1524 by the great Italian anatomist Berengario da Carpi, who had described aspects of the ventricular system of the brain during the preceding year. The name was given to the rounded structure lying within the small bony fossa of the skull base, and derived from a notion of mucus or other secretory product coming from the brain, a prophetic concept for the time. Later, in 1672, Schneider dismissed the idea of a relationship of the pituitary gland to production of phlegm, and embryologic studies led to the recognition of a remarkable double developmental origin of the adult pituitary gland, culminating in the description of the origin of cells of the anterior pituitary from the stomodeum of the embryo. There was subsequently increasing reference to the relationship of the pituitary gland to hormonal function.

The extension of the primitive oral cavity, Rathke's pouch, comes into contact with an evagination of the ventricular floor, destined to become the posterior pituitary or neurohypophysis. Therefore the fully developed pituitary gland, which measures approximately 6 by 10 by 13 mm, consists of two embryologically and histologically distinct tissues. A third recognizable component, the pars tuberalis—in man a thin anterior cellular investment of the neural stalk—derives from portions of Rathke's pouch and is of uncertain physiological significance. In the human the adenohypophysis accounts for approximately three-fourths of the 0.5-g weight of the pituitary gland.

The pituitary gland is surrounded by a double layer of dura within the sella turcica of the sphenoid bone. The development of a more intimate investment continuous with intracranial pia matter was described by Ciric (Fig. 1). The neural stalk, or infundibulum, descending from the hypothalamic floor overlying the sella, penetrates a firm transverse dural roof of the sella, which takes its rostral origin from the anterior wall of the sella at a level approximately 3 mm inferior to the bony sellar margin, the tuberculum (Fig. 2). The size of the aperture through which the stalk passes varies greatly; when of a large diameter, it sometimes permits herniation of overlying arachnoid membrane

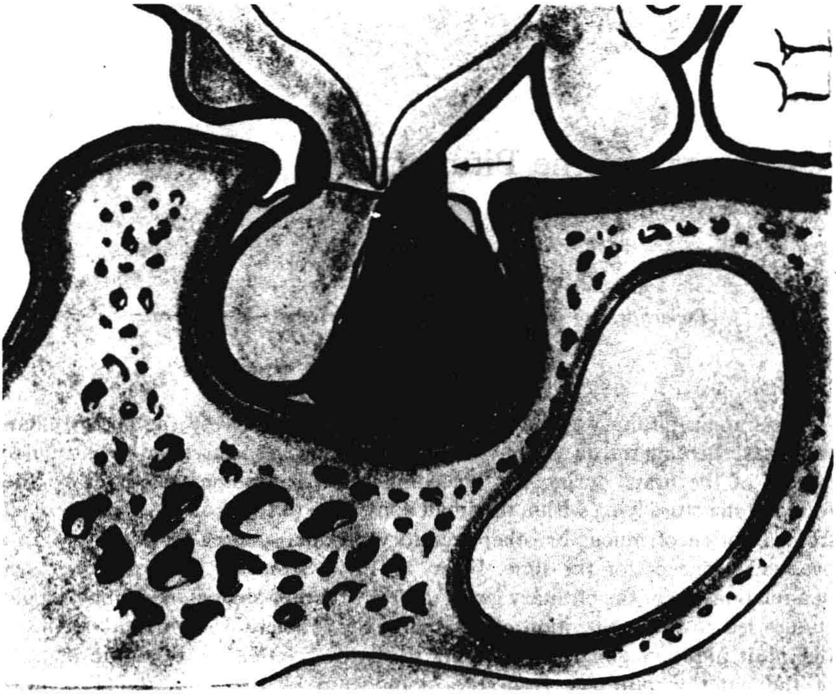

FIG. 1. Continuity of pituitary capsule and cerebral pia mater. (From ref. 4, with permission.)

into the sellar cavity. The anterior wall of sella separates its contents from the sphenoid sinus. It is of variable thickness, but in approximately 70% of cases is 1.0 mm thick or less. As a result, neoplasms arising within sella more frequently erode the anterior wall, with extension into the sphenoid sinus, than the thicker posterior bony barrier of the sella. The thin anterior wall similarly provides ready surgical access to sellar contents, a fact recognized by Cushing, who early developed an anterior approach to the pituitary gland.

Laterally the sella is bounded by the cavernous sinuses and their neural and vascular structures. The looping carotid arteries are in closest approximation at the sella level, and carotid tortuosity and ectasia may result in an arterial approach to the midline, which is of surgical importance in intrasellar manipulations (Fig. 3). Lateral extensions of pituitary tumors may produce clinical syndromes resulting from compromise or destruction of structures within the cavernous sinuses, as detailed by Jefferson in a classic contribution. Further, the cavernous sinuses are interconnected by venous channels of variable size