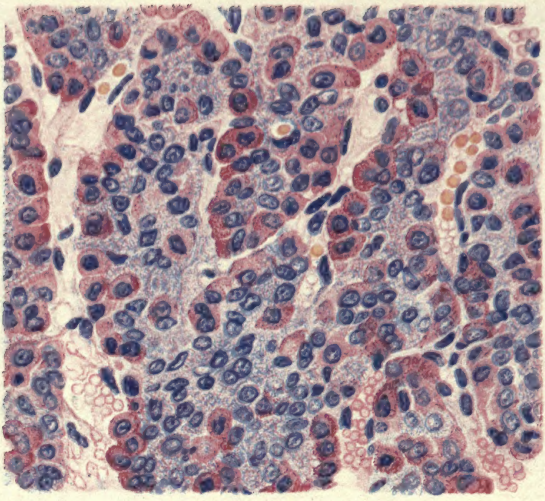
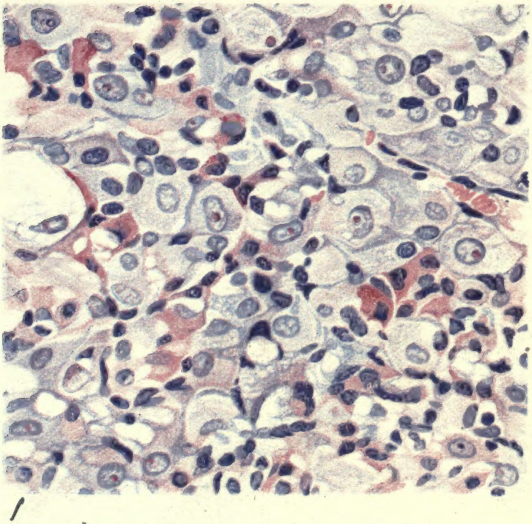


Field from the center of a normal canine (puppy) pars anterior. Note the excess of eosinophiles lining the sinuses. No basophiles in the field, as they are more in evidence in the glandular periphery. The central elements in the cell columns are neutrophilic (Hauptzellen).



Showing pars anterior transformation under functional hyperplasia. In this animal a fragment of the gland had been removed some days before at operation. Pilocarpine was administered just before death. Note the predominance of large neutrophilic elements with a few acid cells (eosinophilic) crowded to the center of the columns as in the gland of pregnancy.

THE PITUITARY BODY AND ITS DISORDERS

CLINICAL STATES PRODUCED BY DISORDERS OF THE HYPOPHYSIS CEREBRI

BY

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AN AMPLIFICATION OF THE HARVEY LECTURE
FOR DECEMBER, 1910

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PREFACE

THE results of some clinical studies made upon a series of 20 patients with hypophyseal disease observed before December of 1910 were at that time used as the basis of an address in the Harvey Lecture series before the New York Academy of Medicine.

About an equal number of cases have come under observation during the succeeding nine months, so that it has become possible to fill in some obvious gaps in the original series with certain clinical types of which we then had no satisfactory examples. Consequently these additional case reports—recognizable by the fact that the dates of admission to the hospital read subsequent to the time of the address—have been used in this amplification of the original manuscript. Unfortunately, while acquiring its adolescence the manuscript has so far outgrown its clothes as to preclude the possibility of its incorporation in the annual volume containing the year's lectures, where a fragment only of the text will have appeared.

During the present year, moreover, studies in conjunction with Drs. Goetsch and Jacobson on the carbohydrate metabolism of patients with hypophyseal disease have reached a point at which they can be used as a further aid in the recognition of certain of the more obscure constitutional states consequent upon glandular insufficiency. The results of these studies, which have also been incorporated, serve to support the views advanced at the time of the lecture regarding hypopituitarism and its relative frequency in many intracranial diseases.

We are unquestionably approaching a stage in our knowledge when the classification or grouping of the cases, here employed as a provisional basis for clinical use, will no longer be necessary. However, it may temporarily serve others, as it has served us, and some one, it is to be hoped, will provide a more useful subdivision, if any subdivision at all is necessary.

The rapid increase in the number of individuals suffering from grades of dyspituitarism which are observed and correctly diagnosed by physicians throughout the country convinces me more strongly than ever of the truth of the statement made some years ago, that there is every reason to believe that cases of clinically recognizable pituitary disease are at least as common as are cases of clinically recognizable thyroid disease. And despite the wide publicity among the profession of matters relating to dysthyroidism, it is unquestionable that in only a small proportion of the individuals afflicted with low grade functional disorders of the thyroid is the nature of the malady appreciated. How much more this is true of pituitary body disorders needs no comment.

There are few subjects in medicine which promise a wider overlap upon the fields of many special workers than this one of hypophyseal disease. From the frequent direct implication of the optic nerves by the glandular enlargement the ophthalmologist has often been the first to recognize these maladies. The neurologist's interest was early aroused through the

pressure disturbances on the part of the encephalon, and will be reawakened in view of the possible relation of epilepsy to glandular insufficiency. The gynæcological and genito-urinary clinics have long been frequented by the fat amenorrhœics and impotent males with hypophyseal disease; and the studies of Erdheim and Stumme will give the scientific obstetrician reason for hypophyseal study for years to come. The experimental and morbid anatomist has been aroused to renewed interest in the ductless glands, particularly from the standpoint of their interrelational activity. The importance of forcing a knowledge of these states upon the internist, and especially upon the pediatrician, is evident when we realize that except for the adult acromegalic conditions the manifestations of hypophyseal disease have been almost entirely overlooked; and now that organotherapy promises much for all cases of glandular insufficiency whether adult or infantile it will need no prodding to bring this about. Specialists whose activities are as divergent as are those of the actinographer and the physiological chemist are now called upon, not only to aid in matters of diagnosis, but it lies in their province to add materially to our further knowledge of the subject. To the general surgeon duties now fall which a few years ago were entirely unanticipated—duties similar to those he has assumed in the case of such thyroid enlargements as are productive of pressure disturbances. And needless to say, to the operating specialist in maladies of the nose and throat the subject is of prime importance, not only because the hypophysis itself abuts upon his preserves, but for the special reason that there exists a pharyngeal organ which may possibly be a not infrequent seat of disease and which may possess some physiological properties of importance to the organism.

In presenting the original lecture at the invitation of the Harvey Society under my own name, I felt that I was acting merely as the spokesman for my several assistants and co-workers in the Johns Hopkins Hospital and Hunterian Laboratory, especially Drs. S. J. Crowe, John Homans, Emil Goetsch, Walter E. Dandy and Conrad Jacobson. Such investigations as have been undertaken require the mutual industry of a group of workers. The task is not for an individual, and without coöperative devotion to the problems concerned it would have been impossible to have made even our little progress toward a better understanding of the function of the hypophysis in health and disease.

I wish to express my deep obligation to Professor Halsted, in whose Surgical Service at the Johns Hopkins Hospital the clinical studies have been made; to Professor Welch and his associates of the Pathological Department for their generosity in giving my assistants and myself the privilege of making our own first-hand studies of the fatal cases; to Dr. F. H. Baetjer, the Actinographer of the hospital, and his assistants, Dr. Boardman and Dr. Waters, for their cordial collaboration. I am indebted to Mr. Louis S. Brown of the Massachusetts General Hospital for a number of the microphotographs which accompany the text. To Miss Mary Brinkley, my secretary, I wish likewise to add here my acknowledgment of gratitude.

Baltimore, September 15, 1911.

THE PITUITARY BODY
AND ITS DISORDERS

PART I

INTRODUCTION

From various sources in recent years new facts have been unearthed both in clinic and laboratory which have thrown light on many heretofore obscure activities of the pituitary gland. As the archæologist is enabled to construct an historical background through the fortunate discovery of a few telling fragments, so may the physiologist venture to build up at least a provisional working hypothesis on the basis of a few suggestive findings.

Needless to say, in either case such a background can at first be but roughly indicated. As is true of the painter's canvas, preliminary studies must be made, patiently worked over, and altered from time to time, possibly even in their fundamental arrangement, if the superimposed details are ultimately to furnish a satisfying sense of proportion.

Certain indelible lines which determine the final disposition of the background for our present subject were long since drawn in. Thus the existence of what we now speak of as an internal secretion was perhaps first experimentally demonstrated by Berthold's studies in 1849 on transplantation of the cock's testis. The idea was given a further impulse by Bernard's classical investigations on hepatic function showing the existence of a *secretion interne* (glycogen) in addition to the known *secretion externe* (bile). In the same year (1855) appeared Addison's immortal monograph attributing a definite clinical syndrome to a destructive process of disease of the suprarenal capsules.* The relation of glands of internal secretion to disease being proven, Brown-Séquard's inestimable service (1869) in introducing the idea of organotherapy came in its natural sequence. The way was thus prepared for the concerted action of experimentalists, pathologists and clinicians, whose brilliant series of studies in the later years of the century resulted in placing our knowledge of the disorders of the thyroid gland and their effective treatment almost on its present plane.

The other glands have notably lagged behind, with the pituitary body at the tail of the procession. For though this structure was added to the group of so-called ductless glands by Liegeois some fifty years ago, its inaccessibility has been sufficient to discourage investigation even were there no other

* To be sure, Graves and Basedow had preceded Addison in describing a malady which we now attribute to a functional disturbance of one of the glands of internal secretion, but it was not until long afterward that the full significance of the rôle played by the enlarged thyroid in the symptom-complex of exophthalmic goitre was fully appreciated.

difficulties to be confronted. One important principle, however, underlying the whole subject of ductless gland disorders, namely that lesions of one gland affect the structure and function of others, was the outcome of studies made by Rogowitsch[217] on alterations in the hypophysis due to thyroid extirpation.

To this we shall return in the attempt which will be made to sketch in certain faint outlines which may serve temporarily to piece together a number of clinical states which on the basis of experimental investigations are seemingly due to disorders of hypophyseal functions. Let us first of all briefly see what are the more important facts that have been acquired in the laboratory.*

ANATOMY OF THE HYPOPHYSIS

Morphology.—The gland, varying somewhat in its configuration, is present in all vertebrates (Fig. 1). As shown first by Rathke (1838)[212] and elucidated by Mihalkowics (1875)[188] it arises from an epithelial (ectodermic

Specimen furnished by Dr. Wilfred Grenfell.

FIG. 1.—Pituitary gland (natural size) of man compared with that of the common "humpbacked" whale (megaptera boöpes).

rather than entodermic) pouch which buds off from the roof of the buccopharyngeal cavity (stomodæum). This pouch meets and partly envelops a corresponding prolongation (infundibular) from the adjoining base of the anterior cerebral vesicle, the tip of which becomes thickened into the infundibular body (neurohypophysis, or pars nervosa). By the subsequent formation of the sphenoidal bone the lumen of practically all of Rathke's diverticulum except its tip becomes obliterated. This unobliterated tip of the pouch comes to enfold the infundibular body as a ball is held in a catcher's mitten.

* As this lecture was primarily intended for those more especially interested in clinical problems and who supposedly were less familiar with the anatomical and physiological data upon which its conceptions were based, it seemed advisable to assemble certain facts, the rehearsal of which may be tiresomely unnecessary for the laboratory workers who have more closely followed the progress of their acquirement.

The external epithelial surface of this mitten thickens so that it resembles more the proportions of a boxing-glove, the palmar surface of which adheres to the infundibular ball. Hence, when by surgical manipulations the infundibular ball is dislocated from its bed, the line of cleavage occurs at the situation of the cavity or cleft which represents the lumen of the original pouch and which serves to separate the purely epithelial anterior lobe from the posterior lobe, consisting of the infundibular body and its adherent epithelial investment, or pars intermedia. In the canine gland the two lobes can be readily separated by operative manipulations.

The neurohypophysis itself is connected with the tuber cinereum by a stalk which varies in length in different species and which contains the infundibular recess of the third ventricle. In some species this recess projects far into the pars nervosa itself and there bifurcates widely. Hence in some of the lower vertebrates the posterior or infundibular lobe appears to be a true glandular organ—a "brain gland"—retaining its connection with the ventricular cavity. The ventricle, as we shall see, apparently represents the outlet for the posterior lobe secretion.

This combined neuro-epithelial structure becomes enveloped in an adherent dural capsule and occupies the sella turcica. The dural capsule in man has an upper diaphragm which stretches from the four clinoid processes and is perforated for the passage of the infundibular stalk. It is capable of distention upward under the diaphragm and laterally toward the cavernous sinuses; but any considerable enlargement antero-posteriorly can take place only with deformation of the bony sella itself.

Histology.*—The anterior lobe (pars anterior: pituitary gland proper) is made up of columns of cells surrounded by large sinusoidal spaces into which the numerous arterioles entering the gland promptly break up. The cells themselves, as first shown by Flesch and Lothringer, are of two fundamentally different types, styled, depending upon their staining affinities, chromophiles and chromophobes (neutrophilic cells). The chromophilic cells (subdivided by Schönemann into (1) eosinophilic or acidophilic and (2) cyanophilic or basophilic cells) contain granules which appear more abundant (Studnicka) on the side of the cells adjoining the blood sinuses, giving the characteristic appearance of a gland of internal secretion. Edinger,[66] however, has recently claimed that there is actually an interposed lymph space between the cells and the sinusoid space.

The three types of cells vary greatly in different parts of the gland in their relative number and disposition. The acidophiles are as a rule more abundant in the centre of the gland, where they tend to line the sinuses; the basophiles occupy the periphery. Hence the centre of the "normal" stained anterior lobe is more strongly eosinophilic than the outer portions. So many changes occur, however, in different physiological (not to mention pathological) states that it is often difficult to say whether the deviations shown by a given pars anterior are actually abnormal. Striking and characteristic rearrangements of the cells occur normally in certain states—in pregnancy, for example—and in conditions of supposed compensatory hyper-

*An excellent presentation of the results of a thorough study of the comparative histology of the gland has recently been made by Frederick Tilney.[250]

plasia induced by partial extirpations equally characteristic changes in the histological picture (cf. frontispiece) may be brought about.

It is a much-mooted question whether these cells with different staining affinities actually represent different types (Scaffidi, Gemelli, Erdheim, *et al.*) or merely different stages of activity of the same type of cell (Saint-Rémy, Pirrone, Thaon, Guerrini, Launois, Joris, *et al.*). Arguments might be advanced for both sides. Benda in particular is inclined to the view of functional unicellularity. He regards the granular eosinophilic cells as those charged with secretion, and claims that they are numerically increased in acromegaly. Erdheim presents a strong case for the opposing side. He has pointed out[73] that adenoma-like formations or clusters of cells of each of the three cellular types are often seen in the pars anterior, an adenoma of eosinophile elements being characteristic of acromegaly.

The posterior lobe comprises the pars nervosa (infundibular body: neurohypophysis) and its epithelial investment (pars intermedia of Herring). The investing epithelium, composed largely of neu-

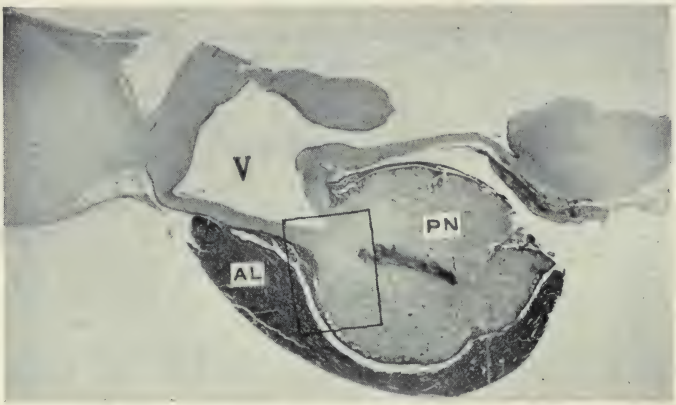

FIG. 2.—Mesial sagittal section of canine gland after injection (cf. central streak) into pars nervosa (PN) of a drop of India ink. Note layer of colloid globules arising from epithelial investment of PN. Anterior lobe (AL) separated from posterior lobe by cleft. Third ventricle (V).

trophilic elements, covers the greater part of the pars nervosa with a thin epithelial veneer (Fig. 2), which thickens into a mass of cells at the anterior part of the stalk. Here a fusion takes place between pars intermedia and pars anterior, the cells being of a transition type, the cleft no longer serving to separate them. Under certain conditions of activity the pars intermedia cells multiply and tend to form acini (Figs. 3 and 4) containing a faintly acid-staining colloidal substance, which under certain conditions appears (Cushing and Goetsch)[59] to discharge into the pars nervosa. At other times, notably in conditions of stasis, this "colloid" accumulates into cystic acini of varying size, and, becoming inspissated, acquires basic-staining properties. There have been many differences of opinion concerning the nature of this substance. It has been regarded as a product of cellular degeneration (Benda, Gemelli) and as a phylogenetic trace of a former external secretion (Erdheim).

The pars nervosa consists of a meshwork of loosely placed neuroglia (cf. Fig. 255) whose fibres radiate toward the infundibulum. In view of

the recognized physiological activity of extracts of this portion of the gland, its indifferent histological appearance has been the source of comment by many. However, between the fibres there appear to be spaces which under special circumstances contain faintly acid-staining, hyalin-like bodies which seem to arise either as a form of secretion from the cells of the pars intermedia or as an actual metamorphosis of migrating epithelial cells (Fig. 4).

Methods of Secretion.—As stated, the histological appearances of the vascular pars anterior suggest a typical gland of internal secretion discharging a stainable colloidal substance (Thaon)[248] directly into the blood stream. It is otherwise with the posterior lobe, which is comparatively non-vascular and in the neurogliar meshes of which exceedingly soluble colloidal or hyaline bodies are readily seen under suitable methods of fixation.

These bodies were first thoroughly described by Herring (1908),[120] who expressed the opinion, based on histological studies, that they represented the products of secretory activity. In the normal animal they give an appearance of assembling near the tip of the infundibular cavity, into which they seem to discharge (Figs. 3 and 5). Herring's views have been sustained and amplified by some experimental studies by Cushing and Goetsch,[59] who have claimed that the cerebrospinal fluid actually contains a substance with the properties of extracts of the posterior lobe itself.

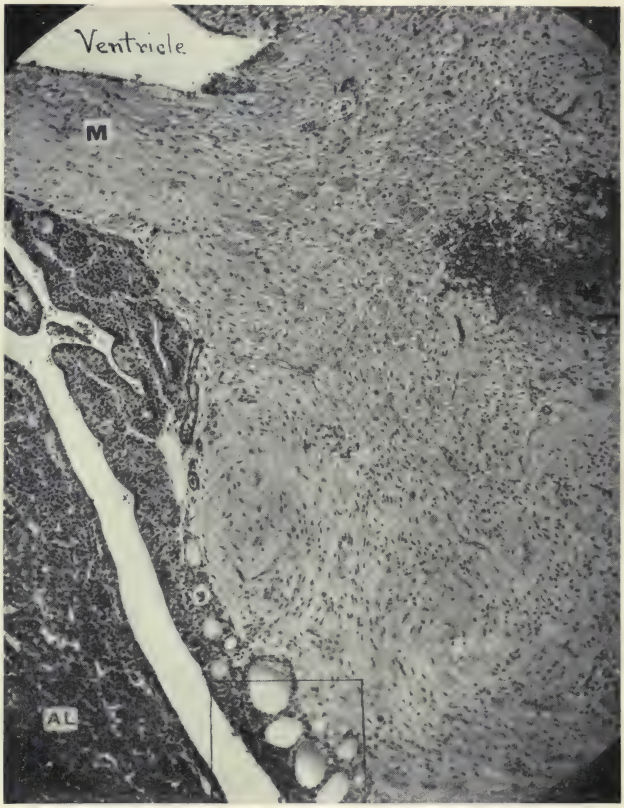

FIG. 3.—Enlargement of squared area in Fig. 2. Showing upper end of injection streak and many hyaline bodies streaming toward ventricle: a mass of them at point M. Pars anterior (AL) separated by cleft from investment of pars nervosa containing colloid masses.

This possibility that the posterior lobe discharges into the cerebrospinal fluid—an external secretion, therefore, in a certain sense—is a matter of such importance that much will be made of it in topics to be considered later on. Upon this view, some unexplained matters concerning the nature of the colloid follicles of pars intermedia are more easily understood. The pars

intermedia cells are capable of forming acini (Fig. 4) which discharge a semi-fluid, soluble product into the spaces of the pars nervosa, many pars intermedia cells actually wandering into the tissue spaces. Under certain conditions of stasis, or glandular involution, this secretory product becomes encysted, inspissated and insoluble, just as in the case of the involutional colloid transformation which Marine has described for the thyroid acini.

Accessory Glandules.—As might be anticipated from the method of development of the pituitary body, cell inclusions may persist anywhere between the infundibulum and the pharynx, owing to an incomplete involution of Rathke's pouch. Indeed, an intact strand of tissue representing the original pharyngeal diverticulum—the so-called *canalis craniopharyngeus*

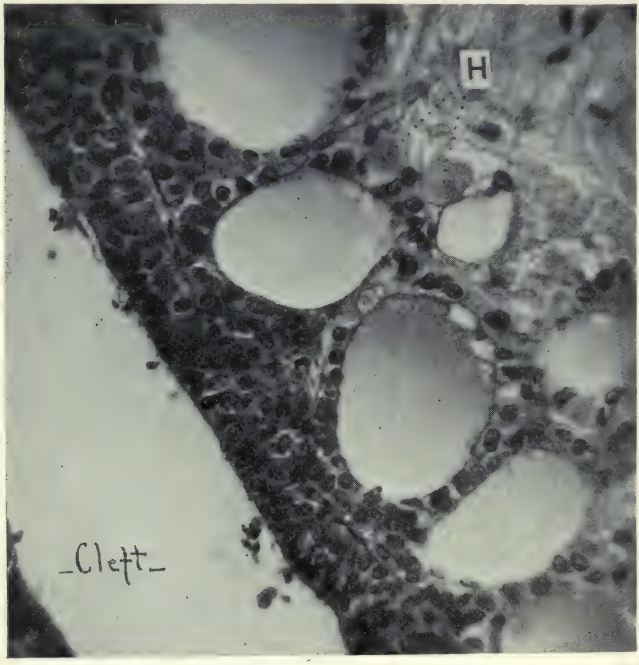

FIG. 4.—Further enlargement of area squared in Fig. 3. Showing formation of colloid by cluster of pars intermedia cells, making temporary vesicles which discharge their contents into tissue spaces of pars nervosa as hyaline bodies (H).

—is normal for some of the lower vertebrates, and more or less complete traces of such a structure, with a central perforation in the sphenoidal floor, sometimes persist even in adult man.

In the tract of this canal and situated in the pharyngeal mucosa, a small epithelial body was found by Erdheim[71] (1904) and called the *Rachendach-hypophyse*. Later studies by Arai[1a] (1907), by Civalleri[42] (1908), and more particularly by Haberfeld[106] (1909), have confirmed Erdheim's discovery. In a systematic study of a series of 51 human subjects of all ages Haberfeld found with regularity a small glandular strand, varying from 1 to 7 mm. in length, situated in the mucous membrane just behind the alæ of the vomer. This he designated the "Hypophysis pharyngea."

We observed as a more or less constant anatomical feature of the canine and feline sellar floor a small centrally placed pit, and between the layers of the hypophyseal envelope of dura which fits into this depression Dandy and Goetsch[62] (1911) found another epithelial rest, called by them the parahypophysis. This vestigial structure, composed of a cluster of chromophobe cells, can almost always be demonstrated by serial sections, at least in the dog. Arai had previously noted the presence of the same or a similar body in a single case.

There exists, therefore, in some animals a cell inclusion which is a relic of the upper end of the obliterated pouch (Rathke), just as in man the "Rachendachhypophyse" is a relic of its pharyngeal end. Both structures possibly possess some physiological significance. Naturally, as Erdheim[71] has pointed out, a neoplasm may be expected, according to the theory of Cohnheim, to occasionally take its origin from such an anlage.

Circulation.—The hypophysis is so placed as to have a most liberal blood supply—the very hub of the *rete mirabile* of the early anatomists. Curiously enough, the anterior lobe of buccal origin receives its supply from a number of small arterioles which pass down the infundibular stalk, whereas the posterior or infundibular lobe is nourished by a single artery which enters from below and behind. On developmental grounds one would expect the reverse arrangement. A certain portion of the pars intermedia alone receives a collateral circulation from both sources. The parahypophysis has its individual blood supply (Dandy and Goetsch[62]).

Sympathetic nerve fibres have been demonstrated (Dandy) passing along these vessels to the gland—an important matter, as we shall see. Indeed, its extraordinarily well protected position, its presence in all vertebrates and persistence throughout life, its remarkably disposed and abundant blood supply, would of themselves be enough to stamp the hypophysis as an organ of vital importance.

HYPOPHYSEAL PHYSIOLOGY

The ancient view that the gland elaborated a secretion for the lubrication of the nasal cavities was superseded in the past century, under the influence of comparative embryology and the doctrines of evolution, by the still more erroneous conception that it was merely a vestigial relic, certainly of no great importance to the economy at least of the higher animals.* After

* It is no more than just to recall the opinions of earlier physiologists, some of which prove to be near truths. It was the Galenic and Vesalian view that the gland secreted a mucous substance (pituita) which entered the nose—this it may actually do under certain conditions of disease.

Vieussens, Sylvius and others considered that it was concerned in forming the cerebrospinal fluid—it at least adds something to this fluid.

Richard Lower in a remarkable tract (Dissertatio de Origine Catarrhi, 1672) was the first to experimentally disprove the Galenic doctrine. "For whatever Serum is separated into the ventricles of the brain and tissues out of them through the Infundibulum to the Glandula pituitaria distills not upon the Palate but is poured again into the blood and mixed with it."

Magendie regarded it as akin to a lymph gland which collected the cerebral lymph and passed it into the circulation—its pars anterior does discharge its elaborated products into the circulation, and the pars nervosa apparently contains certain interneurogliar spaces resembling lymph channels

the publication of Marie's later papers (1888–89) in which the anomalies of growth characterizing acromegaly were shown to be associated with a pituitary tumor or hypertrophy, there was a widespread awakening of interest in the gland, leading to the discoveries to be enumerated.

I. **By Injection of Extracts.**—(a) *Acute Effects.* It was shown that intravenous injections of extracts of the whole gland even when boiled causes a long-continued rise in blood pressure due to the combined action of peripheral vascular constriction and augmentation in the force of the heartbeat (Oliver and Schäfer,[200] 1895); that this property is confined to extracts of the infundibular lobe, primary injections of which slow and strengthen the pulse (Howell,[131] 1898); that there may be a slight inaugural primary fall, probably due to a double substance, pressor and depressor, the latter being soluble in alcohol (Schäfer and Vincent,[225] 1899). With large doses the depressor effect may be so marked as to mask the usual subsequent rise, which some (Silvestrini[236]) have failed to obtain.* The renal vessels appear to be exempt from the peripheral vascular constriction which causes the pressor response. On the contrary, the renal arteries dilate, and after a latent period of constriction (Hallion and Carrion,[112] 1907) marked diuresis occurs (Magnus and Schäfer[174], 1901), due to a specific stimulation of the renal epithelium (Schäfer and Herring,[226] 1906). The peripheral vascular constriction which causes the pressor response depends more upon a direct action on the vessel walls than upon an excitation through the vasomotor centres (Salvioli and Carraro,[221] 1907).

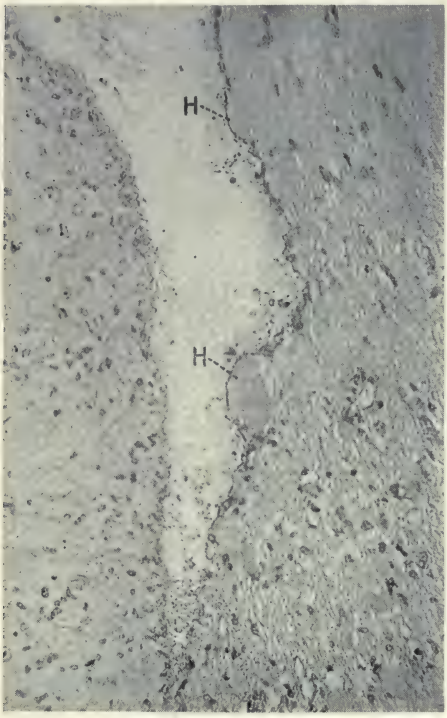

FIG. 5.—Tip of infundibular cavity in the dog. Showing hyalin masses (HH) about to burst through the bulging ependyma into the ventricle. Note globules of hyalin in posterior lobe (right) streaming toward infundibular cavity. (Mag. 190 diams.)

As a natural outcome of the knowledge of the action of the extract on the muscle coats of the arteries, it was observed that it produced uterine (Dale,[60] 1906) as well as vesical and intestinal contractions (Bell and Hick,[17] 1909; Dale,[60] 1909; Frankl-Hochwart and Fröhlich,[89] 1910) and that it would

* There is unquestionably great individual variation in these blood pressure responses to an equal dosage of extract for different animals of the same species. Furthermore, as was shown by Howell,the responses become less and less pronounced with each repeated injection. Hamburger[115] (1910) and Lewis, Miller and Matthews[165] (1911) have shown, contrary to the experience of earlier investigators, that the pars anterior and pars intermedia also contain a pressor and depressor substance giving responses similar to, though less pronounced, except for the depressor effect, than those in the pars nervosa.

dilate the pupils of the isolated frog's eye (Cramer,[50] 1908); also that the serum of animals which have received intravenous injections possesses slight mydriatic properties (Franchini,[86] 1910). Furthermore, injections of the extract lower the assimilation limit for carbohydrates and cause glycogenolysis (Borchardt[21], 1908; Goetsch, Cushing and Jacobson,[100] 1911).

Hence the reactions of posterior lobe extract (infundibulin) bear a close resemblance to those of extracts of the adrenal medulla,* differing from them in the primary depressor and longer pressor response of the general circulation; in the slowing of the pulse after atropin or section of the vagi; in the constriction of the coronary and dilatation of the renal vessels, adrenalin having an opposite effect (Pal,[202] 1909); in the production of diuresis from a specific action on the renal epithelium; and in their direct action on the involuntary muscles rather than on the sympathetic nerve endings (Dale,[60] 1909). The direct effects of "pituitin" (Parke, Davis and Co.) on the isolated intestine have been studied by Bayer and Peter[13] (1911). They call attention to a primary inhibition and subsequent augmentation of peristalsis with increase in tonus which they attribute to an excitation of the plexus of Auerbach.

It has recently been shown (Ott,[201a] 1910; Schäfer and Mackenzie,[227] 1911) that posterior lobe extracts contain a powerful galactogogue substance —more powerful than that possessed by corpus luteum extracts.

The presence of the active principle in the cerebrospinal fluid has been claimed (Cushing and Goetsch,[59] 1910) on the basis that corresponding physiological reactions may be obtained by the injection of slightly concentrated fluids of both man and animals. The anterior lobe is, relatively speaking, inactive, such reactions as occur with its extracts being attributable to traces of pars intermedia in the preparations.

The view advanced by de Cyon,[59a] that the hypophysis, serving as an auto-regulator of the intracranial circulation, is called into activity by mechanical stimuli, has not been supported by others. As we shall see, however, it is quite probable that mechanical influences, such as cerebrospinal fluid stasis, may serve to activate the gland, either by direct pressure or by excitation of its nerve supply, so that with this interpretation some of de Cyon's hypotheses may become more generally accepted.

(b) *Chronic Effects.*—Repeated subcutaneous injections of sterile extracts or emulsions of the whole gland or of the posterior lobe alone given subcutaneously are apt to lead to emaciation (Fodera and Pittau,[85] 1909); (Crowe, Cushing and Homans,[53] 1910), indicating a stimulus to metabolic processes—a condition, as we shall see, the reverse of that effected by partial extirpation leading to states of insufficiency (Fig. 6). Extreme hepatic degenerations with cellular necrosis are often seen in animals subjected to oft-

* The similarity of the reactions of adrenalin and posterior lobe extract and the fact that they are both presumably present in the blood stream should make pause those who are accustomed to attribute to adrenalin alone the presence in the blood of a substance which has pressor qualities and which acts on unstripped muscle fibre. It is of interest that J. M. O'Connor (Ueber Adrenalinbestimmung im Blutes. *Munchen. med. Wchnschr.*, 1911, lviii, p. 1433) has noted that the action of blood serum is greater on the rabbit's uterus than is the action of an epinephrin solution of the same concentration: and further, that while epinephrin inhibits the intestine, blood serum containing an equal amount of this substance stimulates it. He suggests that some other substance with similar properties must be present. In all likelihood it may prove to be infundibulin.

repeated injections of posterior lobe extract (Carraro,[34] 1908). In our experience corresponding injections of pars anterior extracts lead to no especial changes—an argument which indirectly favors the view that acromegaly, for example, is due to some perversion of secretion rather than merely to an excess of the normal secretion.

Caselli[35] (1900) noted no effect on growth after long continued injections of whole gland glycerine extracts. Others (Cerletti,[37] 1907; Sandri,[222] 1909; Etienne and Parisot,[75] 1908) have noted retardation of skeletal growth with epiphyseal changes. In all likelihood these are posterior lobe effects. Atheromatous changes in the aorta similar to those ascribed to frequent injections of adrenalin have been described (Baduel,[6] 1908). Certain changes take place, furthermore, in all of the ductless glands, one of the most notable, observed by Rénon and Delille in rabbits, being similar apparently to the cellular desquamation and hyperplasia which we have observed in the canine thyroid after total extirpation of the hypophysis (Fig. 7).

FIG. 6.—Extreme emaciation after repeated posterior lobe injections.

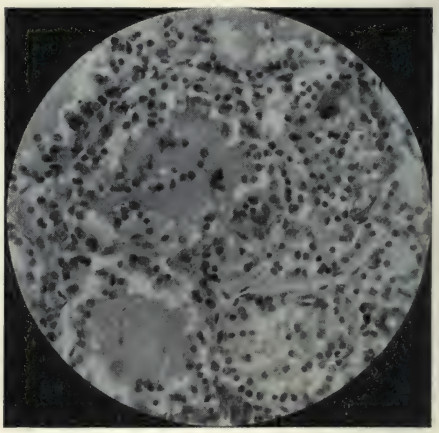

FIG. 7.—Showing extreme proliferation of thyroid epithelium with solution of colloid. Acute hyperplasia 48 hours after total hypophysectomy.

II. **By Ingestion of Extracts.**—Feeding the gland over long periods of time is a laborious and uncertain performance. It has been supposed not to influence growth in any positive manner, though in some cases it has seemed to retard it (Caselli,[35] 1900.) Naturally, to simulate in any striking way the effects of hyperpituitarism, the experiment must be carried out in young animals, with controls preferably from the same litter. Sandri's experiments[222] (1909) in this direction, on feeding young rats with bovine anterior lobe, were quite negative, whereas posterior lobe feeding arrested development—an effect attributed to the toxicity of the active principle. In Schäfer's similar experiments,[224] on the other hand, the average measurements of the animals in whose food powdered whole gland was mixed exceeded those of the controls

Our results (Goetsch and Cushing, unpublished) with the canine have been largely negative. Of a litter of three puppies a few weeks old, one, the largest, was partially hypophysectomized, one was fed daily over a period of nearly nine months with powdered extract of the whole gland in 3-grain doses; the third and smallest was kept as a control. The control finally exceeded the fed animal in height, the latter showing no changes which could be ascribed to the opotherapy. The hypophysectomized animal remained undersized but outweighed the others, owing to an early acquired obesity.

It is possible that the administration of anterior lobe alone may be essential to the success of such an experiment, inasmuch as posterior lobe extracts appear so definitely to break down rather than to build up tissue.

III. **By Glandular Transplantations.**—As in the case of the thyroid so with the hypophysis, futile attempts have been made to simulate the chronic clinical states due to increased functional activity by glandular implantation. When one of the ductless glands is sufficiently active for the animal's needs, it is probable that another gland of the same sort from another animal of the same species will undergo absorption after implantation and will appear to remain functionally active only for so long a time as may be required for the tissues of the host to absorb the products of secretion which it may previously have contained. The effects, therefore, of such an implantation are merely comparable to the slow subcutaneous administration of an equal amount of glandular extract.

On the principle formulated by W. S. Halsted[114] and based on his parathyroid studies, an existing "physiological deficit" is one of the essentials for a successful organo-transplantation. Thus, Crowe, Cushing and Homans observed[54] that the life of animals after a total hypophysectomy could be prolonged by the immediate reimplantation into the cerebral cortex of the excised gland, the transplant showing histological evidences of viability for at least a month.

Apparently in the absence of such a previously established deficit, glandular transplants will not remain viable. Clairmont and Ehrlich,[43] for example, found that isotransplants into the spleen became completely absorbed. Schäfer[224] likewise was unsuccessful in establishing permanent grafts, though the hosts showed a temporary diuresis "due to absorption of the diuretic substance which the transplanted pituitary contained, or perhaps to a temporary functioning of the implanted organ preceding this degeneration." In Exner's[77] experiments on rats transplantations were made of several glands taken from young animals, and the hosts appeared to show for a short period an increase in growth and weight, compared with control animals. Here, also, this was probably the result of slow absorption of the secretory products which the implanted glands already contained. However, the results of these various transplantation experiments suggest some therapeutic possibilities for this method, inasmuch as the slow absorption of the secretion which the transplanted organs contain may be an effective means of administering the active principle, and at least will be comparable with the subcutaneous injection of the crushed gland; and in case the host is actually suffering from a physiological deficiency it is not impossible that fragments of glandular tissue may survive and remain permanently active (cf. p. 320).

Thus the clinical manifestations of overgrowth presumably due either to an oversecretion or to a perversion of glandular activity have not been conclu-

sively reproduced either by repeated injections of extracts, by the continued ingestion of glandular substance, or by isotransplantations.

IV. **By Extirpation Methods.**—Inasmuch as Marie and Marienesco had been led to believe that the syndrome acromegaly was due to hypophyseal insufficiency, attempts to reproduce conditions of skeletal overgrowth by glandular extirpation were made at many hands by various operative methods of approach (intra- and extracranial) on various species (dog, cat, frog, chicken, rabbit, tortoise) and by diverse methods of mutilating the gland (curette, cautery, acids).* We now understand why these attempts signally failed. However, during the progress of the experiments it was observed by some (Vassale and Sacchi: Paulesco) that complete removal or destruction of the gland led, in the course of a few days, to a peculiar train of symptoms (*cachexia hypophyseopriva*) with tremors, fibrillary twitching, arching of the back, insensitiveness, slow pulse and respiration, a terminal abrupt fall in body temperature, and apathy passing into coma and death.

Though there have been many opponents to the view suggested by these findings, that at least a viable fragment of the gland is essential to the long maintenance of life, the studies of Paulesco[203a] (1906) of a long series of animals operated upon by a perfected method, corroborated by postmortem serial sections of the infundibular region, would seem to establish the fact beyond peradventure. The onset of the acute symptoms was shown to depend on the loss of the anterior rather than on the loss of the posterior lobe.

Paulesco's main contentions were fully supported by subsequent studies in the Hunterian Laboratory by Reford, Crowe, Cushing, Homans and Goetsch†. In the course of their experiments, which have comprised more than 200 hypophysectomies, it was observed[53] that puppies survived a total extirpation longer than did adults (adults 3 to 5 days, puppies 10 to 30 days), possibly due to the greater functional adaptability in early life of some accessory glandule such as the *Rachendachhypophyse* of Erdheim or the dural parahypophysis of Goetsch and Dandy. It was found[54] that life could be prolonged (spared?) by an immediate transplantation of the removed gland; that in all recovered cases, in agreement with Paulesco, a viable fragment of anterior lobe was invariably present, though not always visible to the naked eye; that animals with a remaining fragment of pars anterior temporarily insufficient to support life could be tided over a period of threatened cachexia hypophyseopriva by subcutaneous injections or by the ingestion of anterior lobe extract; and that removal of the posterior lobe alone led to no definitely recognizable symptoms, it being fully realized that a fragment of pars intermedia was inevitably left adherent to the stalk even in the most complete total extirpations.

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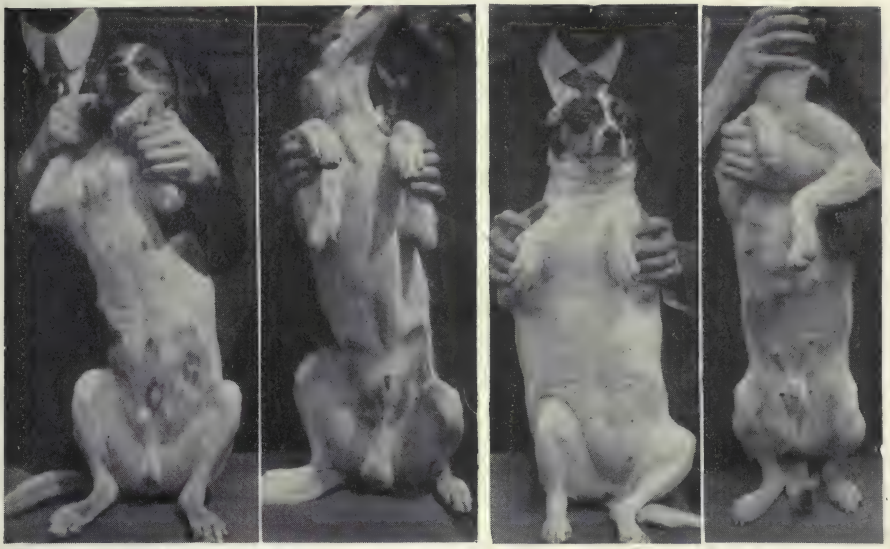
*These researches have been fully reviewed by Paulesco[203a] and by Crowe, Cushing and Homans.[53]

†Aschner,[3] it must be confessed, has opposed the view of essentiality of the gland to life. He is inclined to attribute the fatalities to some injury of hypothetical nerve centres of the infundibular region. As Biedl points out, the operative method Aschner employed is open to criticism, and the same objection may be raised in the case of Gemelli's experiments.[96]

This criticism also holds for the experiments recently reported by Handelsmann and Horsley.[116] The early fatalities in practically all of their total extirpations they attribute to shock, hæmorrhage, infection or œdema cerebri—complications from which our canine series has been almost exempt and which could easily obscure symptoms of apituitarism.

Contrary to Paulesco, mere separation of the hypophyseal stalk, disconnecting the gland from the infundibular attachment, was not found to be necessarily fatal, for under these circumstances, though the circulation of the pars anterior is largely cut off, sufficient circulation may persist to keep viable enough of the structure to maintain life, and fragments of functionating pars intermedia necessarily remain. These animals behave like those experimentally deprived of the posterior and a part of the anterior lobe.

Experimental Hypopituitarism.—Of more interest and importance than the acute conditions mentioned above were the constitutional disturbances observed in animals which had recovered after partial hypophysectomies—disturbances which simulate some of the clinical syndromes observed in man,* those which deserve chief note being a widespread adiposity, nutritional changes in the skin and its appendages, disturbance of carbohydrate metabolism, of body temperature, of growth and of renal secretion. Sexual inactivity



From the Johns Hopkins Hospital Bulletin

FIGS. 8 and 9.—Example of adult hypopituitarism in the male (*a*), showing beginning adiposity and testicular atrophy: control (*b*). Adult hypopituitarism in the female (*c*), showing marked adiposity after extirpation: control (*d*).

or actual atrophy of the reproductive glands was observed; and indeed modifications in most of the other ductless glands proved to be histologically demonstrable.

Some of these experimentally acquired manifestations of hypopituitarism may justify a more detailed discussion, for many of them, as will be seen, occur in the clinical states to be described; and it was these findings that gave the first experimental proof that certain heretofore recognized clinical syndromes are a

*In our earlier paper (Crowe, Cushing and Homans, May 1910) too great stress, we fear, was laid upon the anterior lobe deficiency as the chief agent in producing all of these manifestations. The later studies (Goetsch, Cushing and Jacobson, June 1911) on carbohydrate tolerance have brought the effects of posterior lobe deficiency into greater prominence.

consequence of lessened glandular activity. Both Biedl and Aschner have since noted corresponding post-operative constitutional disturbances.

Cutaneous Changes and Adiposity.—A number of animals in our first series (1908–1909),[54] having recovered after partial extirpations, were observed to grow very obese. In one instance an adult bitch, after fragmentary anterior lobe removal combined with stalk division, nearly doubled her weight, and similar tendencies were shown by other individuals of the series, the majority of whom were adults (Figs. 8 and 9). Correspondingly striking examples, however, occurred in the second series (1909–1910)[100] in which puppies were the usual subjects (Figs. 10, 11 and 12).

The deposition of fat proves to be widely distributed, not only in the subcutaneous tissues but in many of the organs of the body, there being a special tendency toward a fatty change in the liver and in many of the ductless glands (*adipositas universalis*). The fat does not seem to be tender and no isolated lipomata have been observed.

Fig. 10.—Fat, undersized animal, *a*, on the left, compared with the control, his brother, *c*.

In a number of animals, particularly of the second series, peculiar boggy, recurring œdemas were observed—in the paws, over the face, in the submental region. There is often a definite change in the skin, which seems dense, dry and less movable than is usual. The hair becomes bristly and tends to fall out in patches — changes not unlike those seen in experimental myxœdema (hypothyroidism).

Disturbances of Body Temperature.—With any considerable degree of hypophyseal deficiency a subnormal temperature is the rule. In states of cachexia hypophyseopriva the temperature becomes greatly lowered, and in fatal cases may fall abruptly during the last twenty-four hours, often nearly to room temperature—as low as 18° or 20° C. in some cases.[53] Under these circumstances it is possible to approximately restore the normal body temperature by applying external heat, but this has an unfavorable effect and appears to hasten the end.

In the experimental states of chronic hypopituitarism the temperature ranges a degree or so below normal. In some animals in this state in whom symptoms of cachexia were threatened it was observed that the lowered temperature would be raised either by the ingestion or subcutaneous injection of hypophyseal whole gland extract. Injections of extracts of other

ductless glands did not have a corresponding effect, nor did the hypophyseal extract in equal dosage elevate the temperature of a normal control animal. It was further found that a thermic reaction occurred only upon the injection of pars anterior preparations in cases of anterior lobe deficiency. This thermic response to injections of boiled anterior lobe extracts has been used, as we shall see, as a clinical test when states of anterior lobe deficiency are suspected (cf. Cases XII, XVII and XXXVI).

With the lowering of temperature, the pulse rate and respiration are apt to be slowed and the blood pressure is often considerably lowered.

Disturbances of Growth.—A suggestive retardation of development after an hypophysectomy was noted by Caselli[35] (1900), denied by Friedmann[90] (1902) and observed again by Fichera[82] (1905) after his operations on chickens. In addition to the tendency to adiposity, a number of the puppies in our earlier (1908–1909) series failed to attain their expected stature after a partial hypophysectomy.

Fig. 11.—Experimental hypopituitarism in a 6 months old puppy — dull, fat, undersized, mangy and sexually infantile.

In the fall of 1909 further studies directed toward this particular problem were undertaken in the Hunterian Laboratory by Emil Goetsch. For example, three terrier puppies from the same litter were selected for a growth test. A, the largest of the three, was hypophysectomized, all but a fragment of the pars anterior being removed; B was fed daily upon whole gland extract; C, the smallest of the three, was intentionally selected as the control. The hypophysectomized animal (A) outstripped the others in weight, and, though lively, became very fat and pudgy (Figs. 10 and 11). The skull and paws were noticeably small. Both B and C, however, rapidly outstripped A in length of limb and body; C, as stated above, finally exceeding B (the animal subjected to organotherapy) in all dimensions.

Though the X-rays of the long bones of these animals showed, in the case of A, a certain amount of epiphyseal thickening and a tendency to delayed ossification, the changes were not particularly striking and the bones did not exhibit any such definite abnormalities as Klose and Vogt[144] have described after thymectomy in the puppy—changes which suggest experimental rachitis. Aschner[3] observed similar growth retardations in the partially hypophysectomized puppies in his series.

Mental Changes.—We have observed a degree of mental dullness, often with irritability, in a number of these animals. In the experiment

mentioned above, it was soon apparent that A, though inclined to play with his fellows, was handicapped not only on account of his ponderous size but also through deficient mentality. Several times in the excitement of a rough and tumble play he had epileptic fits. Similar occurrences were observed in animals of other series. One partially hypophysectomized puppy was simple and foolish. These animals are often strikingly insensitive to pain stimuli.

It seems quite probable that some of the psychic disturbances to be described in clinical hypopituitarism may be due in many cases to the glandular deficiency rather than to the possible pressure effects of a growth on the cerebrum itself.

FIG. 12.—Experimental hypopituitarism in an 8 months old puppy, four months after operation, the animal, though adipose, remaining undersized and infantile.

ALTERATIONS IN CARBOHYDRATE TOLERANCE.—There has been much confusion not only in regard to the glycosurias related to ductless gland disorders in general, but more particularly in regard to those of encephalic, and possibly of hypophyseal, origin. In our earlier experiments, though the presence of sugar was occasionally observed in the urine after the canine hypophysectomies, not until the studies with Goetsch and Jacobson[100] were directed specifically toward this matter was it found that a transient mellituria almost invariably followed any procedure which led to contusions of the hypophyseal stalk. This led us to believe at first that a condition of relative carbohydrate intolerance would be demonstrable after partial extirpations, and a long series of tests were made, disclosing, however, quite the opposite condition.

After the hypophysectomy a temporary spontaneous glycosuria would usually ensue, followed by a short period during which the assimilation limit was below normal. Subsequently the animals would gradually acquire such a tolerance for sugars that it often proved difficult to produce alimentary glycosuria with such amounts of glucose or cane sugar as could be retained when administered with a stomach tube. From these results it was natural to suppose that the operative manipulations had dislodged some glycogenolytic substance into the circulation, occasioning the temporary glycosuria, and at the same time had checked the further elaboration of this substance, with the ultimate production of a state of over-tolerance for sugars.

Having come to believe in the truth of Herring's suggestion that the posterior lobe discharges its secretion *via* the pars nervosa into the ventri-

cles, it was conjectured that the acquired carbohydrate tolerance in these animals bore some relation to the operative removal of this lobe. This was confirmed by Goetsch, who found that a subcutaneous or intravenous injection of posterior lobe extract coincident with the administration of amounts of sugar below the established assimilation limit would cause a glycosuria. It was shown to be possible, after determining the post-operative assimilation limit, to give enough posterior lobe extract to produce mellituria with the same quantity of carbohydrate which had been established before the operation as the measure of the animal's normal tolerance.

It had been observed by Borchardt (1908)[21] that injections of whole gland extract in rabbits would usually cause glycosuria, and though Franchini (1910)[86] could not substantiate his findings, we can most emphatically do so with regard to infundibulin. Intravenous injections in the rabbit of posterior lobe extracts in .05 gram doses or of 2 cc. of a 20 to 1 concentration of cerebrospinal fluid will almost without exception occasion hyperglycæmia and abundant glycosuria.

During the course of our experiments it was noted that the animals deprived of the posterior lobe rapidly put on weight during the consecutive days of sugar feeding when the assimilation limit was being determined; and the same thing, it may be said, has been observed in the clinical cases, in the study of which we have made wide application of these findings. It may be added that later (unpublished) studies with Jacobson have shown that concentrated cerebrospinal fluid possesses the same sugar-tolerance lowering properties as posterior lobe extracts themselves.

The following interpretations seem permissible: Normal posterior lobe activity is essential to effective carbohydrate metabolism. An intravenous injection of posterior lobe extract produces glycogenolysis, and its continued administration in excessive amounts leads to emaciation. A diminution of posterior lobe secretion occurring in certain conditions of hypopituitarism (whether experimentally produced or the result of disease) leads to an acquired high tolerance for sugars, with the resultant accumulation of fat.

We shall see that the acquired degree or tolerance for sugars is not only of possible value from a diagnostic point of view as a measure of posterior lobe activity, but that it also offers a suggestive therapeutic lead for rational opotherapy.

Urinary Secretion.—In view of the known diuretic effect of posterior lobe extracts, it might be anticipated that the removal of this part of the gland would diminish the urinary output. This, however, has not been observed in our experiments. A transient polyuria occurs in nearly all of the animals,[54] particularly after operations which have necessitated stalk manipulations, due presumably to the same influences which occasion the temporary glycosuria—in other words, to the liberation of an excess of posterior lobe secretion. The polyuria and glycosuria, however, do not seemingly go hand in hand, for in many instances the former persists even when the tolerance for sugar has become abnormally high. Animals which, under pre-operative conditions, pass an average of 200 cc. often excrete from three to five times that

amount—a veritable diabetes insipidus. A corresponding condition occurs, furthermore, in many of the clinical cases, as will be pointed out.

Secondary Changes in Other Ductless Glands.—Experimental hypophyseal deficiency leads to polyglandular lesions—indeed, to a polyglandular syndrome, if one wishes to so designate it. In states of canine hypopituitarism, however, the physical examination of the other ductless glands during life is restricted largely to the evidences of testicular or ovarian activity or inactivity. Certain of the males in our 1908–1909 series, after partial posterior lobe extirpations showed manifestations of persistent sexual excitation—an observation which we as yet are unable to satisfactorily account for.

On the other hand, the majority of the animals with more complete extirpation, particularly those which evidenced a tendency toward obesity, showed the reverse condition. Of the adults, the females—some of them kept under observation for nine months—never came in heat; the males were quite anaphrodisiac, a number of them ultimately acquiring a definite testicular atrophy (Fig. 8). The puppies, both male and female, usually remained sexually infantile.* This has been confirmed by Biedl and by Aschner.

Histological Studies of the organs in these states of experimental hypopituitarism served to show, what we have found to be true of primary hypophyseal disease in man, that in addition to the fatty changes which are particularly noticeable in the liver, more or less definite alterations occur throughout the whole ductless gland series. After some of his hypophysectomies an hypertrophy of the thyroid was observed by Caselli, and in our experience the gland in the acute stage of the experimental lesion is often the seat of active hyperplasia (Fig. 7) and in the later stages is somewhat enlarged and colloidal. A persistent thymus is often demonstrable. The adrenal medulla is frequently hypertrophic, and the cells of the zona fasciculata often show an extreme fatty degeneration. The genital organs of the female puppies remain infantile and the ovaries show but few forming Graafian vesicles; the testes of the male puppies likewise show the persistence of a preadolescent type of tubule and the Leydig cells appear to have undergone a lipoid metamorphosis. Special studies by Goetsch have demonstrated the existence of alterations in the pancreatic islets and in the secretory cells immediately adjoining them.

It appears, therefore, that in consequence of experimentally induced hypophyseal deficiency marked changes occur in the histological picture of many if not of all of the other ductless glands. It is, of course, well known that alterations occur in the reverse direction; for example, in the hypophysis after castration (Fichera,[81] Tandler,[244] *et al.*) or thyroidectomy (Rogowitsch,[217] Herring,[123] *et al.*), especially in young animals; and we have observed definite changes in the posterior lobe after pancreatectomy. However, it may be said that the secondary alterations occurring in the ductless gland series seem to be more pronounced when induced by a primary

*It is interesting that the male puppies who do not acquire their secondary sexual characteristics usually continue the infantile habit characteristic of both sexes of squatting during micturition. "Leg lifting," according to breeders, is an expression of male adolescence.

hypophyseal lesion than after corresponding lesions of any other member of the series.

Our first experiences, therefore, with hypophysectomized adult canines deprived of all but a fragment of the pars anterior disclosed a clinical syndrome with adiposity, increased sugar tolerance, lowered body temperature and reversive sexual changes as its chief features. Later experiences, with the production of corresponding hypophyseal defects in puppies, disclosed a similar syndrome, with a persistence of sexual infantilism and the additional factors of skeletal undergrowth and evident psychic disorders. The latter condition, as corroborated by Aschner and Biedl, corresponds, as we shall see, with the human *typus Fröhlich:* the former is the experimental counterpart of what will be recognized in man as an adult form of this syndrome—hypopituitarism originating before adolescence *versus* hypopituitarism originating subsequently.

PATHOLOGY OF THE HYPOPHYSIS

Aside from the recognition of an occasional gross lesion—gumma, tuberculoma or neoplasm—postmortem studies have notoriously failed in the past to furnish any satisfactory interpretations of the diverse histological changes which the pituitary body obviously undergoes. The reasons are not far to seek. In the first place, the inaccessibility of the gland has so discouraged investigation that it has rarely been studied in a long series of autopsies with the motive of correlating its given cellular alterations with a specific group of maladies. It is necessarily altered by most of the conditions in themselves the cause of death—by infection, by trauma—and certainly in almost all diseases of the nervous system. Its appearance changes markedly at different ages and during critical physiological periods—in adolescence, during pregnancy, at the climacteric, and probably in other states. As has been suggested, too, diseases primary in any other member of the ductless gland series lead to confusing secondary changes in the hypophysis itself; and the obvious need of investigating the various accessory glandules still further complicates the matter.

Then again, there has been no uniformly established method of sectioning the gland so as to include its various anatomical subdivisions together with the infundibular stalk. This important structure is usually broken when the brain is removed, leaving the pituitary body proper to be dug out as an isolated organ. Sections taken at random encourage misinterpretations. Thus in the usual gland a section through the centre of the pars anterior may show a seeming increase of eosinophiles while others nearer the periphery show a preponderance of basophilic elements. Particularly in the case of the posterior lobe, an estimate of conditions can be obtained only by a median sagittal section including the stalk, and, owing to the extreme solubility of the hyaline bodies, the greatest care must be exercised in handling, fixing and staining the tissues, with possible recourse to the study of frozen sections.

The average histologist quickly recognizes what is designated a "normal" thyroid gland, though actual hyperplasias or colloidal resting stages may really represent the physiological normal for the conditions existing at the time. However, in the case of the hypophysis the variations, particularly of pars anterior, are so kaleidoscopic that there seems to be no fixed adult type of "normal" gland—at least no type which can be pointed out as representing the hypophysis of perfect adult health and past freedom from the many diseases which are capable of modifying its appearance.

Many of the so-called tumors of the gland itself are in all probability mere hyperplasias, and again, many neoplasms considered to be of hypophyseal origin actually arise from a neighboring anlage (sphenoidal or infundibular) but have so compressed or flattened the gland that it easily escapes detection.

Confusion reigns in what appears to be the simplest of all problems, that of anterior lobe hyperplasia, the state of activity supposedly responsible for the skeletal overgrowth of acromegaly and gigantism. The condition obviously may exist without a great enlargement of the gland, just as Graves' disease may exist without great thyroid enlargement. Arnold[2] and Ponfick[208] have reported cases of acromegaly with glands "normal" in all respects. Certainly no tumor with consequent enlargement of the sella is necessary. There is no unanimity of opinion as to the corresponding histological picture, though Benda and Dean Lewis have made a strong plea in favor of a multiplicity of eosinophilic elements, which Erdheim believes to be commonly gathered in adenomatous clusters. Unfortunately for this determination it has not been possible, as in the case of the functional hyperplasias of the thyroid, to study the changes in the making, and the findings after the natural death of an acromegalic or giant may actually represent a condition of late inactivity rather than the presupposed hyperplasia of the gland.*

A better knowledge of the alterations which occur under the influence of various physiological states, such as Erdheim's[74] important investigations have given us for the gland in pregnancy (p. 234), will doubtless be required before we can attempt to interpret the changes occurring in disease. Aid will come, too, from the study of such alterations in the nature of compensatory hyperplasias as follow partial extirpations. Our studies of the changes which occur in the posterior lobe after the experimental obstruction of the stalk or after inducing an experimental hydrocephalus, lie in this direction and have enabled us to appreciate better than we otherwise could have done the histological alterations in pars intermedia and nervosa which occur in many conditions of intracranial disease in man, particularly in those relating to the invasion of pars nervosa by the investing cells.

As will be pointed out later, in every case of increased intracranial tension, from whatever source, there probably occur secondary changes in the hypophysis, often with gross deformations and resultant functional disturbances which frequently elicit recognizable clinical manifestations.

* What we have come in the Hunterian Laboratory to regard as a compensatory anterior lobe hyperplasia is indicated in the frontispiece, but we do not wish as yet to commit ourselves definitely in this matter.

Chemical studies, likewise, have as yet taught us little, though doubtless from them most is to be expected. It is thought that the gland contains phosphorus and calcium in relatively considerable amounts. Traces of choline have been demonstrated as in other organs (Gautrelet).[95]

In view of a fancied histological resemblance between the pituitary and thyroid glands, iodine has been looked for and has been thought to be present by Schnitzler and Ewald.[232] Halliburton, Candler and Sikes,[111] however, failed to substantiate their findings, and in a series of 22 human glands Wells[256] found traces of iodine in only three instances, in which iodine had been administered therapeutically. Even in the glands of thyroidectomized sheep Simpson and Hunter[237] found no iodine, its absence being used as an argument against the view of an hypophyseal compensatory hypertrophy under these conditions.

The active principle of the posterior lobe is unaffected by boiling and is soluble in water and salt solution (*vide* the cerebrospinal fluid). It has been shown (Schäfer and Vincent)[225] that the depressor substance is soluble in alcohol and ether as well as in watery solutions, whereas the pressor substance is soluble only in the last. It is claimed, too, that the active principle has a chemical kinship with adrenalin. However, it has been shown (Schäfer and Herring)[226] to be dialyzable through parchment paper, and the gland does not yield a crystallizable body when subjected to processes similar to those used for obtaining the active principle of the adrenal medulla. Schäfer and Herring showed, furthermore, that it is not destroyed by a 24-hour immersion in gastric juice nor by an 18-hour treatment with trypsin. It is not affected by reducing agents, such as the addition of ammonium sulphide, with the evaporation and extraction of the residuum in water. The same is true after treatment with zinc and hydrochloric acid.

The substance, therefore, is not protein, as it withstands boiling temperatures; it is not adrenalin, as it has different reactions; not thyreoidin, as it contains no iodine. Only when the active principles of anterior and posterior lobe have been isolated * and synthetized may we expect further great strides in our knowledge of this gland, and the same is true, indeed, of other members of the ductless gland series. As Halliburton says: "It is probably but a matter of time before biochemists make themselves acquainted with the hormone (or hormones) it contains."

There is no established therapeutic dosage either for the fresh glands or their prepared extract, given by mouth or subcutaneously. Experiments to establish the toxicity of extracts have shown that different individuals vary

* Extracts of the whole or of large parts of the gland have been variously termed *pituitin, hypophysin* and *infundibulin*. It would possibly be best to reserve the term pituitin for extracts of the pars anterior or anterior lobe proper, and infundibulin for extracts of the pars nervosa or infundibular lobe proper. The term hypophysin might be reserved to indicate extracts of the whole gland.

T. B. Aldrich (*Proc. Am. Physiol. Soc.*, 1907–8, xxiii) has succeeded in separating a base from the organ, from which a crystalline picrate and sulphate was prepared, having a pressor effect. Allers (*Munchen. med. Wchnschr.*, 1909, lvi, p. 1474) attributes the pressor action to a substance which contains alkalated ameno-nitrogen.

More recently Houssay[130] has obtained a crystalline substance from the posterior lobe which he believes to be its active principle, as it gives the characteristic reactions of glandular extract. The crystals are insoluble in alcohol, ether and chloroform but soluble in water, and are obtained by precipitating a boiled watery extract of fresh glands with acetate of lead, by filtration, by treatment with sulphuric acid and by evaporation.

exceedingly in their degree of tolerance. We have attempted to establish a rational dosage for individuals suffering from posterior lobe deficiency on the basis of the production of an alimentary glycosuria (cf. p. 261).

Studies of Metabolism.—Malcolm (1904)[174a] investigated the effect of administration of pituitary substance on the excretion of inorganic substances. Feeding the fresh gland caused an increase in the output of nitrogen; feeding of pars anterior caused a retention of phosphorus, while the posterior lobe produced first a loss and then a retention. An increased output of calcium followed an administration of both anterior and posterior lobe. Thompson and Johnston (1905)[249a] found that injection of whole gland substance stimulated metabolism, increasing the output of nitrogen, urea and phosphorus.

The metabolism of animals in states of experimental hypopituitarism has been studied by Narbut (1909) in von Bechterew's laboratory.[15a] The excretion of phosphorus and nitrogen was increased both absolutely and relatively, that of the phosphates being increased threefold. The oxygen consumption and the CO_2 exhalation were decreased.

Narbut in agreement with Erdheim is inclined to attribute the disturbances (the fall in temperature, etc.) following hypophysectomy to an injury of an hypothetical centre in the tuber cinereum rather than to deficiency of the hypophysis itself. Our studies have shown the important relation of the posterior lobe at least to the excretion of carbohydrates; and before reliance can be placed on any past metabolism observations in these states, it must be known in just what condition of physiological competence or incompetence the gland actually was at the time the observations were made. Similarly in the case of studies upon man, particularly individuals with acromegaly (Levy, Parhon, Franchini, Miller, Edsall, *et al.*) confusions have arisen from the failure to fully appreciate that early functional overactivity of the gland is replaced by subsequent secretory insufficiency. Doubtless in the latter states, just as after experimental hypophysectomy, there is a lowering of the metabolizing capacity of the organism.

PART II

CLINICAL MANIFESTATIONS OF DISORDERED PITUITARY FUNCTION

Dyspituitarism.—Bearing in mind the various facts, which, acquired largely through anatomical and experimental researches upon animals, have been enumerated in the foregoing section, let us turn to the clinical and pathological aspects of the question in man.

Our slowly acquired comprehension of the disorders of the thyroid and parathyroid glands resembles, in the deviousness of its progress, the steps which have been taken in the approach toward a better understanding of disorders of the pituitary body. In both instances surgery has played an important rôle, in laboratory as well as in clinic, more especially in throwing light on the consequences of diminished function due to glandular extirpation—a negative method, to be sure, of studying glandular activity.

Owing to the more obvious complicity of the thyroid in certain clinical syndromes as well as to its greater surgical accessibility, it was made the object of operative attack long before this was ventured in the case of the hypophysis; but in both instances, as may be recalled, it was the coincident enlargement or tumor of the gland which first suggested its active and possibly causal participation in the newly recognized constitutional maladies.

Had it not been for the neighborhood pressure symptoms, especially those of tracheal distortion, the early operations for goitre (1883–1886) by Kocher and Reverdin would not, in all probability, have been undertaken, and the experimental explanation of Gall's myxœdema (1873) might have been much longer delayed. Had it not been for the obvious tumor of the pituitary body, which likewise causes its own characteristic neighborhood symptoms, Marie and Marienesco (1889) probably would not have come to associate acromegaly with, and Babinski (1900) and Fröhlich (1901) certainly would not have attributed adiposity and sexual infantilism to, a lesion of this supposedly unimportant and vestigial structure.

In the investigations concerning the functions of the hypophysis, which were largely instigated by Marie's later writings (1888–89)* many lessons have been drawn from the earlier experiences with the thyroid, and, difficult as the problem is, many confusions have been avoided by bearing in mind the pit-falls into which the earlier thyroid investigators stumbled. This applies particularly to the fact that there was a long overlooked double glandular representation—thyroid and parathyroids—for advantage was not taken

* Eduard Melchoir has pointed out that Marie was possibly not the first to demonstrate a causal relationship between the hypophysis and acromegaly. He gives the credit of this to Minkowski, of Naunyn's clinic, who first clearly stated (Ueber einen Fall von Akromegalie, *Berl. klin. Wchnschr.*, 1887, p. 371) that an enlargement of the gland had been observed in all carefully examined cases.

of Sandström's discovery until Gley's experimental demonstration of the functional significance of these lesser bodies led to the unravelling of many obscurities regarding supposed states of athyroidism as experimentally induced in animals. This should have warned us at the outset of the possible confusion incidental to the study of the function of the pituitary body as a whole: nevertheless even now insufficient attention is paid to the chief subdivisions of the gland, which in all certainty have such diverse physiological properties.

Now, in the case of the thyroid gland, separate from its accessory glandules, a fairly satisfactory working basis was established through a combination of laboratory and clinical experiences, with a symptomatology attributed to conditions of overaction of the gland—h y p e r t h y r o i d i s m, with Graves' disease as its clinical prototype—and another due to glandular loss or inactivity— h y p o t h y r o i d i s m, with Gall's myxœdema as its typical adult, and cretinism as its typical childhood manifestation.

This basis proved satisfactory enough for a time, and extreme grades of these opposed states are now unmistakable. However, further experience has shown that the symptomatology of the two types may merge to a surprising degree, certain clinical manifestations of exophthalmic goitre often being overlapped by those supposedly characterizing myxœdema. Surgical misjudgments, more than any other factor, have made this clear, many patients, for the simple reason that nervousness, tachycardia and exophthalmos persisted or returned after earlier operations, having been again subjected to arterial ligation or partial thyroidectomy, despite the fact that a dry and puffy skin, a subnormal temperature, and what not, indicated the early signs of glandular insufficiency. Indeed, as Marie has so clearly pointed out, oft repeated stages of pathological overactivity tend toward a final stage of pathological glandular sluggishness. Hence the transition symptoms may be neither one thing nor the other, neither hyper- nor hypothyroidism, but rather d y s t h y r o i d i s m. Now, these same principles, as we shall see, are equally applicable to disorders of the pituitary gland.

In an earlier paper,[56] the contents of which were founded more upon experimental than upon clinical experiences, the two usual subdivisions, which had long served a useful purpose in the case of the thyroid, were taken as a temporary working basis: namely, states of overactivity (h y p e r - p i t u i t a r i s m) and states of underactivity (h y p o p i t u i t a r i s m). These simple subdivisions, however, often prove clinically misleading, particularly in the presence of such syndromes as have at the outset been called into being by presumed conditions of primary overactivity. For these become blended later on with symptoms equally characteristic of known* stages of functional insufficiency, so that although, disregarding for the moment the separate lobes, states of hyper- and of hypopituitarism may be distinguishable, evidences of the latter state are commonly superimposed on evidences of the former, and it may be difficult to tell which predominate. Hence the term d y s p i t u i t a r i s m becomes in the majority of cases more appropriate.

* Tamburini, as far back as 1894, has expressed a similar view of a two-stage process in acromegaly; a glandular hypertrophy with hyperactivity characterizing the first phase, while in the second or terminal phase there occur degenerative changes with diminished activity and resultant cachexia.

But even accepting dyspituitarism as a sufficient mantle for all states due to a perverted function of the hypophysis, we nevertheless are still so far from a complete knowledge of the various clinical syndromes which may be elicited by disturbances primary in one or the other lobe that, for a time at least, we shall do well to adhere to the more cumbersome, though temporarily useful, clinical subdivisions. For if not carried to the point of confusion through excessive subdivision, the separation, on the basis of certain striking clinical features, of the various types of disease attributable to lesions of a given organ may serve as a temporary convenience, even though such symptomatic pigeon-holing does not prove to be of enduring value. This, of course, harks back to Morgagni's "De sedibus et causis morborum." Unquestionably the day is rapidly dawning which will disclose the chemical or other influences at work behind the gross alterations in a given organ which has long been styled "the seat of disease" by the morbid anatomist.

Classification of States of Dyspituitarism.—In an analysis of our cases of obvious hypophyseal implication a tentative grouping was first made into (1) those in which the gland was seemingly the primary seat of disease, and (2) those in which it was secondarily involved, usually by the direct compression of an adjoining, or the more remote effects of a distant, cerebral lesion. However, on clinical grounds it often proved impossible to tell, in the first place, whether or not many of the interpeduncular tumors were actually glandular in origin; and secondly, recognizable hypophyseal symptoms brought about by distant lesions—cerebral tumors for example—proved to be so uniformly present that this simple subdivision was abandoned in favor of one comprising a larger number of clinical groups—five as a matter of fact. These groups are as follows:

Group I.—*Cases of dyspituitarism in which not only the signs indicating distortion of neighboring structures but also the symptoms betraying the effects of altered glandular activity are outspoken.*

Group II.—*Cases in which the neighborhood manifestations are pronounced but the glandular symptoms are absent or inconspicuous.*

Group III.—*Cases in which neighborhood manifestations are absent or inconspicuous though glandular symptoms are pronounced and unmistakable.*

Group IV.—*Cases in which obvious distant cerebral lesions are accompanied by symptomatic indications of secondary pituitary involvement.*

Group V.—*Cases with a polyglandular syndrome in which the functional disturbances on the part of the hypophysis are merely one, and not a predominant feature of a general involvement of the ductless glands.*

Under each of the first four groups there will naturally occur three subdivisions: namely (1) the cases in which the clinical manifestations of past or of existing h y p e r p i t u i t a r i s m p r e d o m i n a t e (more particularly overgrowth, resulting in gigantism when the process antedates ossification of the epiphyses—*typus Launois*; resulting in acromegaly when it is of later occurrence—*typus Marie*); (2) those in which the clinical manifestations of h y p o p i t u i t a r i s m p r e d o m i n a t e (adiposity, with a persistence of both skeletal and sexual infantilism when the process originates in childhood—*typus Fröhlich*); adiposity with sexual infantilism of the reversive form when it originates in the adult—the type we have explained on

experimental grounds and of which clinical illustrations are to be given); and (3) the mixed or transition cases exhibiting some features of both states —in other words, with evident d y s p i t u i t a r i s m.

It will be possible for us to give examples, from our series of some fifty-odd cases, of the majority of these types, and though gaps will occur, these can be easily supplied from the great number of individual cases, reports of which begin to crowd the literature of the subject.

The subdivision of cases in the first three main groups according to the presence or absence of neighborhood disturbances attributable to the local pressure effects of a tumor or glandular enlargement seems advisable, not only in view of the important rôle which from the first an existing tumor has played in calling attention to the actual seat of disease, but also for the reason that we must still depend largely on its presence in many cases to certify the existence of hypophyseal implication, whether the gland is actually the primary seat of the growth or whether its disturbed function is merely a secondary consequence of a neighboring lesion.

That there are obvious crudities in this provisional method of grouping these patients is freely acknowledged. One striking fault lies in the fact that it does not take into consideration the dualistic character of the gland; for we may doubtless have either an over- or underactivity of both the anterior and the posterior lobe or of either one alone. The pars anterior, so far as we can tell, not only seems to be more closely correlated with the other ductless glands, but presides more intimately over skeletal growth; whereas the posterior lobe has been shown to be more closely allied to the processes of tissue metabolism—an insufficiency causing a marked deposition of fat—and to the activity of the renal and vascular systems.

Hence there occur in our series individuals whose overgrowth suggests a former state of glandular overactivity of one or possibly of both lobes but who in time have acquired evidences of insufficiency of both lobes (Case XXXII) or of the posterior lobe alone (Case XXX). Other individuals suggest, by their undergrowth and adiposity as well as by their high sugar tolerance, that there has been an early functional interference with both lobes (Case III). Still others, from the outset, have shown evidences of posterior lobe deficiency alone and one individual (Case XXXVIII) shows a composite of anterior lobe hyperplasia with the coincident obstructive effects of posterior lobe secretion due to a distant lesion in the cerebellum. And so instances might be multiplied.

We therefore may have combinations of inactivity of the posterior lobe with overactivity of the anterior lobe; a combination of overactivity of the posterior lobe with anterior lobe deficiency; and finally a combination showing either overactivity of both lobes or deficiency of both lobes. All of these possible states, furthermore, may occur either before or after adolescence, leading, as might be conjectured, to very different clinical pictures, which in time may come to be sufficiently well unravelled to justify a classification on a new basis. But in the present state of our knowledge of the different rôles played by the two lobes in disease it would be unsafe in many instances to draw conclusions as to their individual participation in the given syndrome.

The Element of the Tumor.—Without the coexistence of a growth which is capable during life of elbowing itself into clinical prominence by crowding

aside important adjoining structures, it is doubtful, as already suggested, whether either the syndrome of Marie and that of Fröhlich would ever have been suspected of its long-secret alliance with an hypophyseal lesion.

It is important to recall that Marie and Marienesco interpreted their post-mortem findings of an hypophyseal tumor in a case of acromegaly as an evidence of glandular insufficiency, so that for years experimentalists attempted without success to reproduce acromegaly by glandular extirpation. It has always surprised us that no one hit upon the illuminating fact, until the studies of 1908–1909 in the Hunterian Laboratory,[53] that animals who survived for long periods after partial extirpations exhibited an unmistakable symptom-complex of lessened glandular activity—a picture the reverse of acromegaly.

It will be recalled that cases of acromegaly have been recorded in which not only was there no tumor present but in which, as was claimed, the gland showed no recognizable histological change. Such experiences as these (and illustrative cases will be given in our Group III) were boldly advanced as a total refutation of Marie's view that the pituitary lesion was the cause of acromegaly, for on this basis, inasmuch as the disease could exist without demonstrable (by the existing methods) alterations of the gland, the presence of an hypophyseal growth in some cases must necessarily have been a mere coincidence.

To still further complicate the matter, case reports began to appear describing individuals with actual tumors of the hypophysis who showed, nevertheless, no signs of acromegaly whatsoever, the direction of the recorder's thoughts being clearly indicated by the usual title of "A Case of Pituitary Tumor without Acromegaly"—an indirect argument, as it were, against Marie's doctrine. Thus it was pointed out by Fröhlich that a preadolescent tumor of this sort was often accompanied by a definite symptom-complex of another order characterized by adiposity and imperfect acquirement of the secondary sexual characteristics.

Fortunately, as has been made clear, experimental investigations have served to reproduce this condition in so far as to make it apparent that this so-called state of dystrophia adiposo-genitalis (Bartels) is due in all probability to a condition of glandular insufficiency. The experiments, furthermore, disclosed the fact that glandular deficiency produced symptoms in adult as well as in preadolescent animals, for the latter remained undersized as well as fat and sexually infantile, whereas the adults became fat and showed a tendency for the sexual organs to revert to the preadolescent state. We shall see that there are parallel conditions in man, namely, an adult as well as an infantile type of the syndrome described by Fröhlich, just as there are adult and infantile types of the syndrome produced by thyroid insufficiency.

It becomes at once apparent that an enlargement or other extreme change in the configuration of the involved gland is no more essential to states of dyspituitarism than it is essential to Basedow's syndrome or to myxœdema in the case of the thyroid. Nevertheless we are unquestionably under deep obligation to these not infrequent glandular enlargements for their aid in having called attention to this stowaway gland, which has been dragged to the light and by "third degree" methods is being questioned as to its motives. And furthermore in the larger number of cases heretofore recog-

nized the tumor has actually been such a conspicuous element that for the time being it deserves recognition in the grouping of these conditions.

Clinical states of increased functional activity—states, unfortunately, which as yet are beyond experimental reproduction—have with but few exceptions been shown to be associated with an enlargement of the gland caused by a hyperplastic or adenomatous process. The reported exceptions have been too few to weigh heavily against this view, even were it not possible to otherwise explain them. For once an acromegalic always an acromegalic. Even though the formerly hyperplastic gland may have undergone complete involution and show no gross or microscopic alteration, the bony changes, if the hyperplasia sufficed to call them into being, necessarily remain as a permanent telltale of the process.

On the other hand, clinical states of diminished functional activity when associated with tumor may be due either to an actual loss of glandular tissue from partial destruction by an infectious or malignant growth, by vascular disease, hæmorrhage, cyst formation or what not, or, on the other hand, and what is perhaps more common, to the mere "blocking" of the secretory activities from a superimposed interpeduncular growth.

It must be borne in mind, furthermore, that an hypophyseal struma, which at one time has represented a condition of functional hyperplasia, may, in the end, actually block or destroy the secretory possibilities of the gland. As a matter of fact it may be expected (1) that in all cases of original hyperpituitarism associated with tumor, the functional end result will be hypopituitarism and (2) that in many of the cases in which existing hypopituitarism is the striking feature traces at least of an early tendency to hyperpituitarism can be detected.

GROUP I. CASES IN WHICH BOTH NEIGHBORHOOD AND GLANDULAR SYMPTOMS ARE OUTSPOKEN.

Only thirteen of the patients in our series are included under this heading, though the group would naturally embrace a far larger proportion of the examples of hypophyseal disease which have been recorded in the literature; for unquestionably when there is no tumor to loudly call attention to the seat of disease, the glandular symptom-complex receives at the present day but scant attention.

The neighborhood manifestations indicative of an interpeduncular growth, whether or not it is primarily of hypophyseal origin, comprise such unmistakable local pressure disturbances as primary optic atrophy, characteristic constriction of the fields of vision, oculomotor palsies, grades of anosmia, indications even of pressure on crura cerebri and uncinate region, epistaxis, pharyngeal protrusions and so on. And to these signs sellar deformation forms an all important adjunct. Varying in their number and intensity alone, they are practically identical for all of the individual cases in this and in the succeeding group.

The glandular symptoms, on the other hand, vary in type as well as in intensity, for we shall find (a) cases in which the effects of

hyperactivity are the more striking; (b) those in which the consequences of hypo-activity are more in evidence; and (c) those in which there is an obvious mixture or blending of these symptoms.

A. **Neighborhood Tumors with the Consequences of Hyperpituitarism the Most Striking Feature.** No illustrations of this symptom-complex originating in infancy occur in our series, though the literature contains a number of instances. Had the two giants (Cases XXXI and XXXII of Group III) been observed at a preadolescent age they would possibly have fallen in this category. They both at one time showed definite neighborhood symptoms, due probably to a temporary glandular hyperplasia, the ultimate involution of which left merely a "struma" which, far from compromising adjoining structures, no longer served even to fill the enlarged sella turcica.

Through the kindness of Dr. G. W. Crile I am permitted to cite an unreported instance of overgrowth which was observed by him in 1904 and which is of interest, though the record, from our present viewpoint, is rather incomplete.

Malignant hypophyseal tumor in a child, leading to gigantism and adiposity.

A female infant, aged 3, notably backward in mental and physical attributes, began abruptly at two and a half years of age to grow with extreme rapidity (Fig. 13). She became drowsy and excessively fat. The obesity was ultimately associated with a general tenderness (adiposis dolorosa?) and with polydipsia and polyphagia. Five weeks before coming under observation an area of pressure atrophy from a subjacent tumor appeared over the left frontal region.

Examination.—The child was overgrown and exceedingly adipose—twice as large as the usual child of three. Her waist measured 57 cm., her hips 60 cm. Her height was 90 cm. The hair was luxuriant and the skin coarse, giving her a peculiar gross appearance. The facies were suggestive of "cretinism or myxœdema." The thyroid was not palpable. The temperature was slightly elevated. Thyroid extract was tentatively given, without improvement. Operative intervention was unthinkable. She died three weeks later.

A *postmortem examination* (limited to the head) disclosed a large "mixed-cell sarcoma." The pituitary fossa was "subjected to sufficient direct pressure to flatten it out." The tissues unfortunately have not been preserved, so that a comparison with the histological picture of other tumors has been impossible.

FIG. 13.—Gigantism and adiposity with hypophyseal tumor. Age 3; height, 90 cm.

This is presumably an instance of rapid transition from an over- to an underactive glandular condition as the tumor or hyperplasia took on its excessively rapid increase. Similar cases of marked invasion of the cranial chamber by the tumor occur in our own series. In this baby the local conditions must have been very similar to those which preceded death in the Giant Wilkins as described by Bassoe.[11] In this giant signs of excessive overgrowth were not apparent until the age of four, and he was twenty-eight before an aggravation of pressure symptoms, through secondary malignancy in the hypophyseal tumor, caused death.

The following case is an illustration of supposedly early hyperpituitarism producing a "normal giant," or well-proportioned overgrown person. A later accession of growth led to pronounced acromegalic changes. Still later, in association with marked tumor manifestations, the unmistakable ultimate symptoms of hypopituitarism appeared.

CASE I. (Surgical No. 27045.) **An hypophyseal tumor causing pronounced neighborhood systems with almost total blindness. Former glandular overactivity, shown by tendency to excessive overgrowth, traceable to the adolescent period, and by subsequent addition of acromegalic changes of unusual degree. Present indications of glandular insufficiency shown by adiposity and high sugar tolerance (dyspituitarism). Operation: sellar decompression. Glandular therapy. Improvement.**

December 8, 1910. M. Van W., a farmer, single, aged 35, of Dutch extraction and excellent family history. Referred by Dr. H. G. Marxmiller of Los Angeles. *Complaint:* Acromegaly with threatened total loss of vision.

Patient is the oldest of six children. Mother is not large but has massive features: father is 6 feet tall and weighs 190 pounds. Patient was a large, healthy, 10-pound baby. Aside from the customary infantile infections nothing unusual was noted until he was 13 years of age, when he began to grow with extreme rapidity, and at 19 measured about 6 feet 4 inches, having developed into a powerful man of unusual strength, weighing 200 pounds. He was noted for feats of physical prowess, such as lifting a 900-pound rail onto a truck. He was intelligent, a good student, and aside from an uncontrolled libido sexualis had good habits.

FIG. 14.—Case I. Patient at 25, apparently free from acromegalic changes.

At 23 (1898) he had a severe illness, accompanied by marked polyuria, and followed by a persistent furunculosis (diabetic?). He was said to be "threatened with consumption." At 25 (Fig. 14) there seem to have been no traces of acromegaly. He and his father are positive that a second period of growth began eight years ago (aet. 27), antecedent to the:

Present Malady.—About 1903 he began having violent, bursting frontal *headaches:* also pains in the extremities. These attacks would be followed by the discharge from the nose of quantities of "slimy mucus," occasionally tinged with blood, and relief would ensue for some days or weeks. He was told at this time that he had acromegaly.

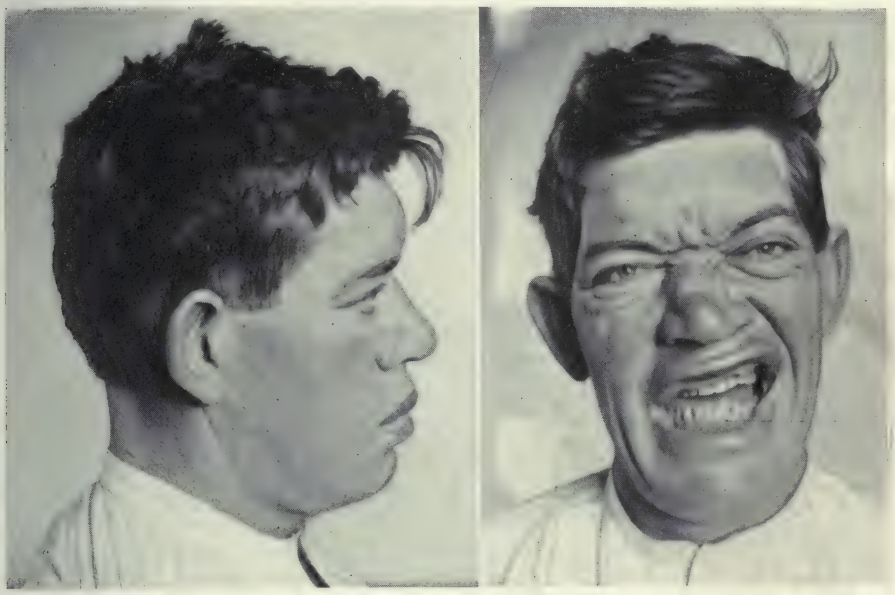
Two years later (1905) difficulty in sighting his rifle first called attention to a *failure in vision.* Subsequently there was diplopia, and possibly hemianopsia.

In 1907 his parents realized that his "features were changing" and that he "was getting large all over" (cf. Fig. 14 and Figs. 15 and 16) and was losing his strength—his so-called "second period of growth." *Polyuria* was observed at this time, but there is no knowledge of glycosuria (cf. the furunculosis). He has become very weak and drowsy, and tires easily. There has been a complete loss of libido et potentio sexualis. Reading vision was lost a year ago. The left eye is now blind and the right nearly so. There has

been no change in disposition, though he is rather over-placid and amiable. His appetite is large and he always has a box of sweets at hand. He has become very constipated.

Physical Examination.—The patient's *height* is 6 feet 6 inches; *weight* 269 pounds. Neither these measurements nor the photographs (Figs. 17–19) give more than a scant indication of his extraordinary size and the disproportions of the acral parts—head, hands and feet. He is a veritable Gargantua. *Visceral examination* (abdominal and thoracic) negative. *Cardiovascular:* "Moderate arteriosclerosis with slight hypertrophy of left ventricle" (Dr. Futcher). *Blood pressure* exceedingly low (75 to 100 mm. Hg.). *Urine* negative. *Blood* negative.

Analysis of Hypophyseal Manifestations.—(a) *Neighborhood Symptoms:* The X-ray shows a greatly enlarged sella (Fig. 20), measuring 3.5 cm. in its antero-posterior diameter and 2.8 cm. in depth. The anterior and posterior clinoids are separated 2.5 cm. and the



FIGS. 15, 16.—Case I. Left, showing marked frontal protrusion, thick lips, etc., in profile. Right, patient in the act of showing teeth while jaws which meet only on the right are held closed. Note the deep furrows of the thickened cutaneous tissues.

thin dorsum sellæ is tilted back, indicating an extension of the glandular struma into the cranial chamber.

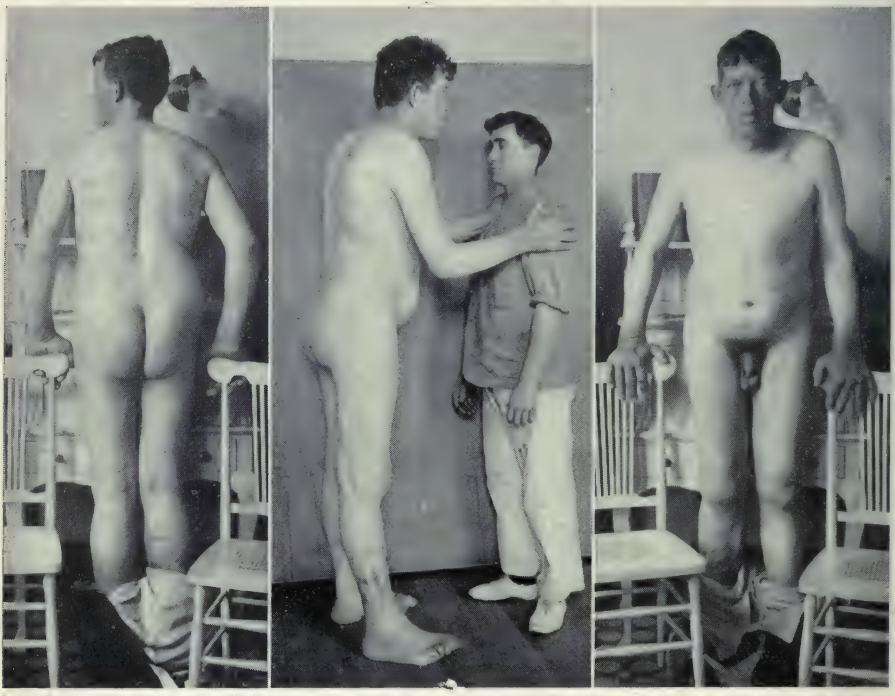
The *eyes* are large, protruding, widely separated, and show a divergent squint. There is a bilateral primary optic *atrophy*, and only two small remaining patches of vision can be plotted for the right eye with 4 cm. discs (Fig. 22)—a superior hemianopsia.

Pharyngeal examination shows greatly enlarged tonsils and a protrusion in the pharyngeal vault resembling adenoid tissue. Formerly there occurred a periodic discharge of mucus from the sphenoidal cells (?). No history of epistaxis.

(b) *General Pressure Symptoms.*—The former severe paroxysmal headaches, apparently due to the sellar distention, have subsided and are replaced by merely a dull bitemporal discomfort. He has never had any nausea or vomiting. There is bilateral exophthalmos, perhaps due more to change in the form of the orbits than to venous stasis. He is at times very dull: drops to sleep during a conversation. There are, however, no mental changes (frontal) to be made out. When awake he is intelligent and responsive. There is no present, or evidence of former, choked disc.

(c) *Glandular Symptoms.—Skeletal:* Within the past six years he has become very round-shouldered, but the height has nevertheless increased two inches, to 6 feet 6 inches. He has had "growing pains" in the extremities. The huge chest measures 112 cm. in circumference; clavicles and sternum are enlarged. Arms and legs are long, but are dwarfed by the huge hands and feet. Circumference at knee 46 cm.; at elbow 31 cm. Xiphoid large and prominent.

Head: The circumference of the cranium is 64 cm. Frontal bones are very prominent; sinuses enormous (Fig. 15). Lips are huge; tongue also, though it hardly fills the cavernous mouth. Ears measure 8 cm. in vertical diameter. Nose 5.5 cm. in breadth at nostrils: a deflected septum. Teeth in fair condition but meet only at one quadrant, owing to widen-



FIGS. 17, 18, 19.—Case I. To show patient's great stature; enlargement of acral parts and adiposity.

ing, protrusion and tilting of mandible (Fig. 16). Some spacing of lower teeth. Neck measures 42.5 cm. over larynx, which is enlarged.

Hands: Always large, have become huge; extraordinarily supple joints: fingers can be bent back far on to dorsum: not especially spadelike, but X-ray shows characteristic tufts and thickenings (Fig. 21). Circumference of wrist 21.5 cm.; of middle finger 10 cm.; glove measurement 30.5 cm. The radius and humerus are about the length of his father's, but his hand is 3 cm. longer.

Feet: Colossal: could formerly wear a number eleven shoe, but now must have them specially made. Great thickening of subcutaneous tissues of the soles, so that the large and much facetted toes do not touch the floor (Fig. 18). Circumference over metatarsophalangeal juncture 36 cm. The big toe itself is 13 cm. in circumference.

Skeletal Coverings.—Cutaneous: The skin is moist and remarkably smooth and velvety. It is exceedingly elastic and wrinkles in deep folds (Fig. 16). There is considerable boggy œdema, especially of the lower extremities and eyelids: this fluctuates in degree. The lower legs are pigmented in patches where boils occurred after his illness. There are vari-

FIG. 20.

FIG. 21.

FIG. 20.—Case I. X-ray of sella (nat. size) showing almost complete obliteration of sphenoidal cells. Note extreme widening of frontal sinuses.

FIG. 21.—Case I. X-ray of middle finger (nat. size) showing characteristic tufts. exostoses, and widened phalangeal shafts. No epiphyseal lines.

cosities. *Hair:* He has practically no beard and except for a scant pubic growth of feminine distribution (Fig. 19) the skin of the trunk and extremities is practically hairless. On the scalp the hair is abundant and coarse. *Subcutaneous:* Panniculus overabundant: a single discrete fatty tumor under the left scapula. Recent increase in *weight* (partly skeletal?) from 225 to 269 pounds.

Carbohydrate Tolerance.—Estimated at something over 300 grams of glucose: larger amounts not retained. Tolerance for lævulose not established: 200 grams vomited. He has a distinct craving for sweets. The *temperature* ranges below normal (97° to 98°); the *pulse* is usually below 70; the *blood pressure* below 100.

Polyuria has existed in the past: not in evidence now.

No *thermic reaction* followed the injection (December 14th) of 0.4 gram anterior lobe extract, though it produced a profuse sweat.

No definite mental changes, though the extreme *drowsiness* is a notable feature.

Other Ductless Glands.—Genitals small; the testes definitely soft and atrophied. *Thyroid* small, soft, scarcely palpable. Possible increase of substernal dullness. *Adrenals(?):* some faint yellowish areas of skin pigmentation; marked asthenia; low blood pressure.

December 17, 1910.—**Operation:** *Sellar Decompression.*—Usual sublabial approach with submucous resection of vomer. A difficult case, owing to depth of nares and hypertrophy of turbinates. Greatly thinned sellar base presented on first entering the sphenoidal cells. Base removed and dura incised. Glandular tumor protruded under tension. Two fragments of tissue removed for section. Uneventful convalescence.

A *histological study* of the glandular fragments shows (Fig. 25) masses of chromophobe cells separated by greatly dilated sinusoidal spaces, giving an appearance which would suggest a telangiectatic round-celled sarcoma, did one not know the source of the tissue. There are large non-cellular areas which bear the faintly acid-staining properties of hyalin (hyalin degeneration or secretion?): a few small acini containing colloid. No eosinophiles seen. The nuclei of the cells stain deeply and are of a small type. There is possibly some increase in interstitial tissue.

December 23.—Subjective improvement in vision. By *December 29* the field, for a 3 cm. disc, had widened, and on *January 6, 1911*, the two islands had coalesced (Figs. 22–24) and there was some color recognition for large sheets. A remarkable form of superior hemianopsia.

Glandular therapy instituted at 30 grains of whole gland extract per diem.

January 28.—Some subjective improvement. Patient feels stronger; less nervous. *Discharged.*

Subsequent Reports.—Letter *February 27:* Further improvement in vision. Temperature normal. Constipation has been relieved.

May 4: An increase in weight to 281 pounds.

June 27: Patient seen in Los Angeles. Vision in right eye further improved; recognizes colors; field has widened out on to superior areas. Less nervous and drowsy than before.

INTERPRETATION.—Though there are many exceptions, it is commonly recognized that the victim of acromegaly is apt to have been an individual above the average height.

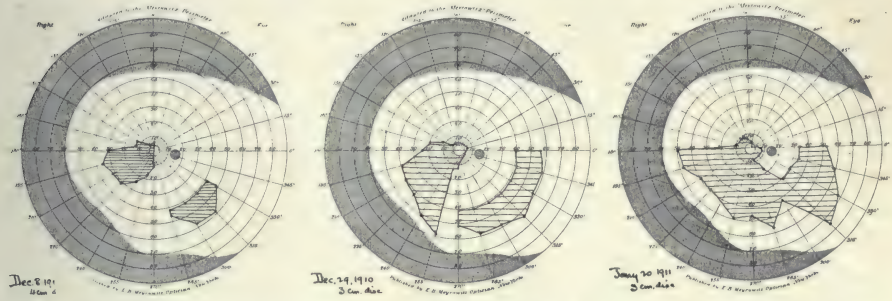
Comment will be made in a later section (page 233) upon the possible relationship of an hypophyseal hyperplasia to the rapid growth which normally occurs at puberty. It is not inconceivable that an exaggeration of the normal physiological hyperplasia of this period occurred in this patient, accounting for the unusual skeletal growth and vigor which were acquired during his early adolescence—a condition which possibly indicated some functional instability of the gland in his particular case. However, during the decade from nineteen to twenty-nine he would have passed merely as a "normal giant" according to Sternberg's interpretation of these states of skeletal overgrowth: in other words, he would have been

regarded as a normally proportioned, sexually intact individual of unusual stature, possessed, as is not uncommon, of exceptional physical strength.

It is improbable that a röntgenogram taken at this time would have shown an enlarged sella, for it is not likely that a pathological enlargement of the gland occurred until the second period of growth which was accompanied by acromegalic manifestations; and of course the complete destruction of the sella did not occur until the recent "adenomatous" transformation of the hypertrophic gland.

The presumption that he had an abnormally active and unstable hypophysis would seem to receive support from the subsequent superimposition of acromegalic symptoms after a resting period of ten years, during which time, doubtless, ossification of the epiphyses occurred. This, according to Launois and Roy's doctrine, would have been necessary to the production of the special enlargement of the acral parts (cf. Case XXXI of Group III). Had the period of active glandular hyperplasia continued without the intermission, he would have been a pure pathological giant without essential acromegalic manifestations (cf. Case XXXII of Group III).

Just what led to the second unaccountable flare-up in the gland's activity, with actual invasion of the cranial chamber by the adenomatous growth or hyperplasia, is not clear. Possibly his acute illness may have been an element in this, for it is well known (Delille *et al.*) that with infectious diseases demon-



FIGS. 22, 23, 24.—Case I. (1) Form field taken on admission with 3 cm. disc: (2) taken 12 days after operation with 3 cm. disc: (3) taken with 3 cm. disc 34 days after operation.

strable changes occur in the gland. Possibly a gland which in the past has shown signs of instability may become reactivated by what ordinarily would hardly seem a sufficient cause. It will be seen later on that many of the acromegalics in our series give a history of an illness antecedent to the onset of the hypophyseal symptoms.

Whatever may have been the influences at work in eliciting the glandular hyperplasia, the patient has passed through this period and now exhibits the characteristic signs of superimposed dyspituitarism indicating the terminal stage of glandular insufficiency. This is shown by his adiposity, high sugar tolerance, subnormal temperature, impotence, low blood pressure and great physical weakness. The asthenia is the more notable in view of his former muscular prowess. The tradition of bodily feebleness ascribed to giants applies only to the true pathological giant and largely to the terminal stage. Another example of great physical strength still possessed by an acromegalic giant in a quiescent stage and in whom no signs of glandular insufficiency have appeared will be found in a subsequent group (Case XXXI).

Indeed, were it not for the marked neighborhood symptoms exhibited by this patient, he would naturally have been grouped alongside of the three other individuals of the series exhibiting more or less outspoken signs of gigantism; namely with Case XXXII, a typical pathological giant without acromegaly, Case XXXI, an individual showing a moderate degree of gigantism with acromegalic tendencies and Case XXX, showing the predominance of acromegaly though increase of stature has also occurred.

There is, of course, no basis for a presumption that hyperpituitarism is a persistent condition. Indeed there is every reason to suppose that remissions, and possibly spontaneous cures, occur, if one may draw a parallel with hyperthyroidism; and it is quite likely that in such a quiescent period epiphyseal ossification may take place and that with a recrudescence of glandular activity under some unknown stimulus the acromegalic features of the disease occur. On this basis one can at least harmonize the views of Sternberg and Launois with the various types of acromegalic gigantism.

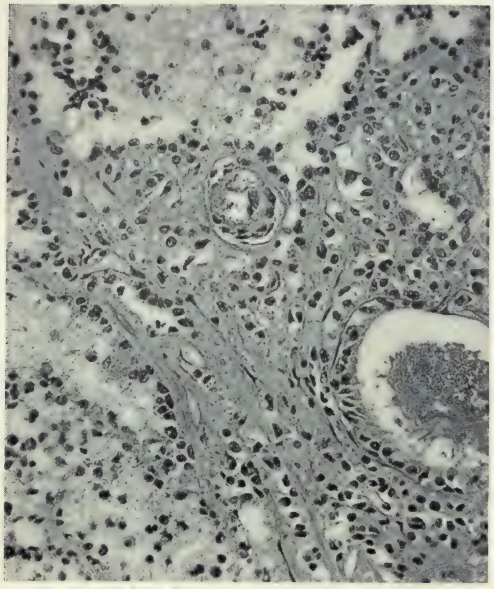


FIG. 25.—Struma from Case I with chromophobe elements; colloid cyst and increase in connective tissue (mag. × 190).

In the case under discussion there exist no definite clinical polyglandular manifestations aside from the testicular atrophy and resultant impotence, though possibly the extreme weakness, slight pigmentation and low blood pressure might be regarded as an indication of secondary adrenal insufficiency. The thyroid was disproportionately small considering the patient's size.

The neighborhood symptoms were particularly outspoken, and it was for their relief alone that surgical measures were indicated. The operation unfortunately was not particularly successful. With the optic nerves so seriously implicated, the mere sellar decompression which was performed was probably insufficient, and doubtless a larger amount of the struma should have been scooped out (cf. Case XIX) and radiotherapy used in addition.

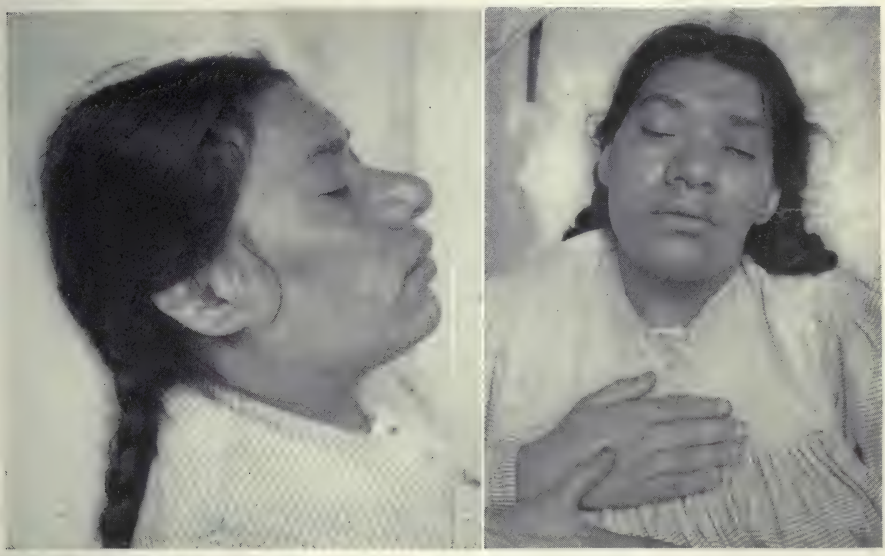
The patient's sugar assimilation limit never having been established, his glandular dosage rests merely on a haphazard basis, but in spite of a possibly insufficient amount he has shown considerable subjective improvement. The probable invasion of the cranial chamber by the adenomatous hyperplasia speaks ill for the ultimate prognosis.

Such an invasion by the tumor mass was an unexpected postmortem finding in the following case, which will serve, furthermore, as an instance of the effects of hyperpituitarism originating in adult life.

CASE II.—(Surgical No. 25971). Typical recent hyperpituitarism of adult life (acromegaly), with an actively-growing chromophobe struma, producing both pronounced neighborhood and general pressure symptoms. Operation. Death. Autopsy.

May 9, 1910. Mrs. S. S., a Russian Jewess, 26 years of age, a seamstress, was admitted through her physician, Dr. H. G. Beck, to Prof. Barker's service. *Complaint:* Amenorrhœa, to which she attributes her malady.

She is one of a healthy family of twelve. She has always been well, with the exception of a single illness in Russia seven years ago, when she was in a hospital for several



FIGS. 26, 27.—Case II. Profile shows absence of mandibular prognathism. Acromegalic changes chiefly involve soft parts. Note somnolence.

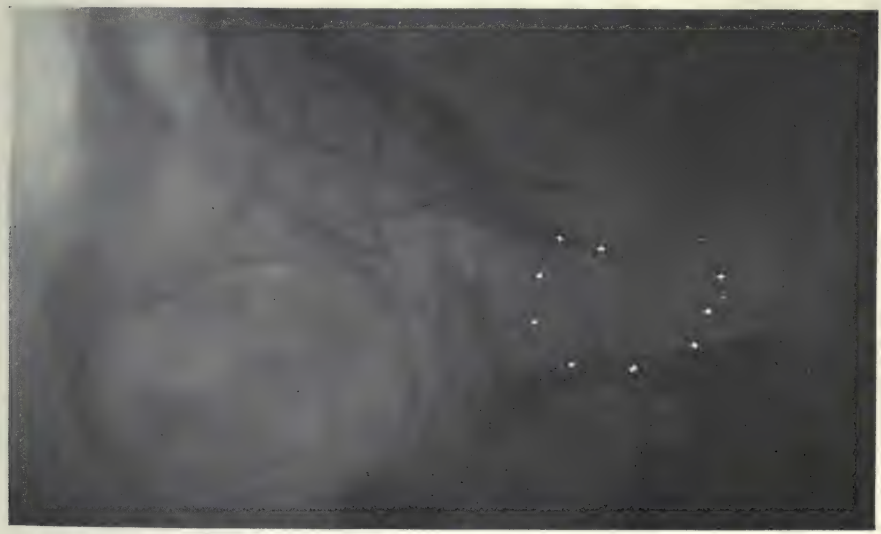


FIG. 28.—Case II. X-ray of sella (nat. size). Outlines dotted. Frontal sinus not greatly enlarged.

weeks with "headache, fever and blindness." During this illness "leeches were applied behind her ear." She regained her vision after a few weeks.

Her menses began at 15 and are said to have been regular until her marriage three years ago.

The Existing Malady.—This she dates from her marriage, soon after which the catamenia ceased and she was said to be pregnant. She became temporarily blind in the right eye at this time. Eleven months after her marriage the menses reappeared for four months, but since then amenorrhœa has been complete.

An *enlargement* of the nose, hands and feet was first observed two years ago, as she could not get on her rings or shoes. *Headaches*, present from the onset, have recently become severe. They occur in paroxysmal attacks several times a day, accompanied by burning flushes and occasionally by nausea, projectile vomiting, temporary amaurosis and relaxation of the sphincters. No loss of consciousness occurs. There have been periods of diplopia and her *vision* has been rapidly failing. *Sweating* has been profuse for two months particularly at night, with itching and burning of the extremities. She feels drowsy; yawns frequently; sleeps most of the time. She has had attacks of palpitation and of polyuria. She is habitually constipated.

Physical Examination.—A short (5 feet 5 inches) overnourished woman, weighing 143 pounds—a manifest acromegalic (Figs. 26, 27). Her expression is dull and stolid and drowsiness is pronounced. The thoracic and abdominal viscera are negative. The

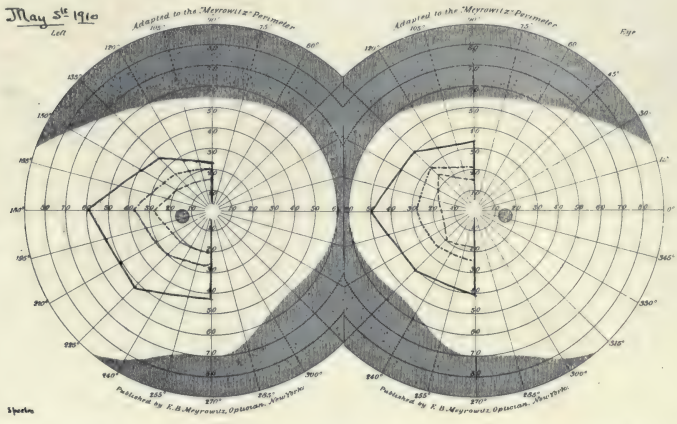


FIG. 29.—Case II. Fields showing typical homonymous hemianopsia—not an infrequent manifestation of primary hypophyseal struma.

heart and peripheral vessels are normal: the *blood pressure* low, 90 to 100. *Blood*, negative (eosinophiles 0.3 per cent.). No arteriosclerotic changes.

Analysis of Hypophyseal Manifestations.—(a) *Neighborhood Symptoms:*—The *sella* (Fig. 28) is enlarged (2.2 cm. antero-posteriorly by 1.5 cm. in depth). *Eyes:* Slight exophthalmos; bilateral ptosis; left oculomotor palsy with diplopia; a bilateral (apparently primary) *optic atrophy* with superimposed choked disc. Right homonymous hemianopsia (Fig. 29) with positive hemianopic reaction (Wernicke); left pupil larger than right. No anosmia: no history of epistaxis. Pharyngeal examination not made.

(b) *General Pressure Symptoms.*—Profound headaches; nausea and vomiting; a low grade of œdema superimposed on discs showing an atrophic pallor.

(c) *Glandular Symptoms.—Skeletal:* The skull itself is not particularly modified, though the malars and zygomatic arches are enlarged. The jaw is not undershot nor are the teeth spaced (Fig. 30). There is no dorsal kyphosis. The hands and feet are characteristically modified, and the X-ray shows the typical bony changes (Fig. 31). *Cutaneous:* The enlargement of the soft parts is more characteristic, especially of the nose, lips, tongue and extremities. Width of the nose is 4.5 cm.; breadth of the hand at knuckles is 9.5 cm. The usual deep creasing of forehead, palms and knuckles due to thickening of the tissues

is apparent. The *hair* is thick and luxuriant; the skin moist and much pigmented, especially on the exposed parts, but also in the axillæ and about the waistline. Dermatographia is marked. The patient is well nourished, but adiposity is not a striking feature.

The *temperature* persists slightly above normal (99° to 99.6°); no slowing of the pulse. There is a tendency to *polyuria* (2000 cc. not infrequent—3310 on one occasion). *Torpor* and *drowsiness* are marked features.

The *sugar assimilation limit* was not definitely established: it was not high. On one occasion (May 14) a glycosuria occurred after 250 grams of glucose. At times the urine gave spontaneously an atypical reduction with Fehling's solution. On May 16, 100 grams lævulose led to this atypical reduction, but there was no fermentation and no rotation with the polariscope. On May 29th an *anterior lobe injection* (2 cc. of 5 per cent. solution) into the deltoid caused a slight atypical thermic reaction to 100°.

FIG. 30.—Case II. Showing the regular unspaced teeth with no protrusion of lower jaw.

Ductless Gland Series. The *thyroid* is palpable; possibly enlarged. Pelvic examination shows an undersized uterus: only one small ovary palpable. *Adrenal* (?): Marked pigmentation of the skin.

June 4, 1910.—**Operation.** *Hypophyseal decompression by the sublabial route with submucous resection of vomer. Terminal pressure phenomena of unsuspected intracranial extension of struma. Medullary failure on the following day.*

Owing to the lingual hypertrophy unusual difficulty in anæsthetization. Owing also to an enormous hypertrophy of the turbinates it was difficult to secure the usual generous exposure. The sphenoidal cells were small. The sellar base, however, was easily identified and its floor removed, exposing the glandular capsule, which was split. The gland bulged greatly through the opening: no tissue removed.

June 5th.—Though restless during the night the patient was conscious and rational and in good condition, desiring nourishment. The following morning she had one of her typical seizures with sudden severe headache and projectile vomiting. Another attack followed at noon, accompanied by slow, irregular and feeble pulse, cyanosis and Cheyne-Stokes respiration (evidently a medullary phenomenon), lasting for half an hour. At two p. m. a third attack occurred, with sudden onset; pulse 60; Cheyne-Stokes respiration, severe headache and vomiting, with unconsciousness lasting fifteen minutes. During a fourth attack at six p. m. there was complete respiratory cessation. Artificial respiration was kept up until eight-thirty p. m., when cardiac action ceased, with no resumption of spontaneous breathing.

Postmortem Examination. — The *brain* after hardening in situ was removed in its meningeal coverings, with the sphenoidal bone and adjacent operative field attached. A median longitudinal section (Figs. 32, 33) shows an encapsulated, reddish, friable, soft tumor mass occupying the situation of the third ventricle. This mass overlies a glandular struma filling the enlarged sella and is separated from it at this mid-level by the intact dural diaphragm of the pituitary fossa. The distended fossa measures 2.2 by 1.5 cm.

The adenomatous tumor arising in the gland proper has burst through between the clinoid processes on the left side of the fossa where it envelopes and partly obliterates the internal carotid and deeply indents the uncinate region of the temporal lobe. Here it is continuous with the superimposed oval-shaped mass which occupies the mid-region as described above. This mass has pushed its way upward to the outer side of the left optic

tract, for on scooping out the portion of tumor indenting the right hemisphere (Fig. 33) the entire chiasm is found to be dislocated far to the right, the left tract being thinned to a mere web of tissue. The brain stem, furthermore, is dislocated backward by this mass, and the foramina of Monro are occluded, causing an obstructive hydrops of the lateral ventricles.

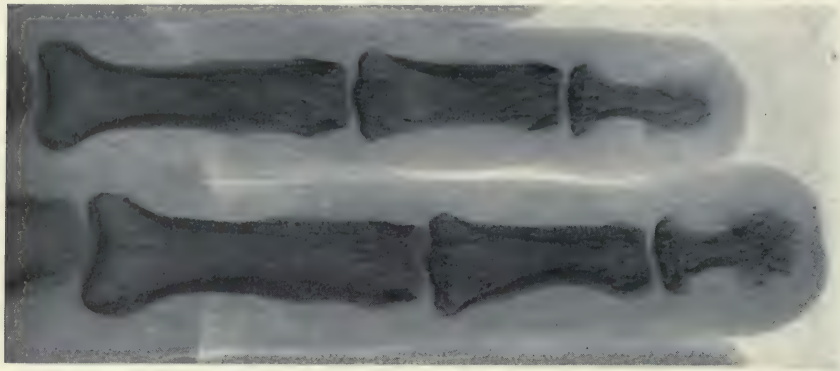
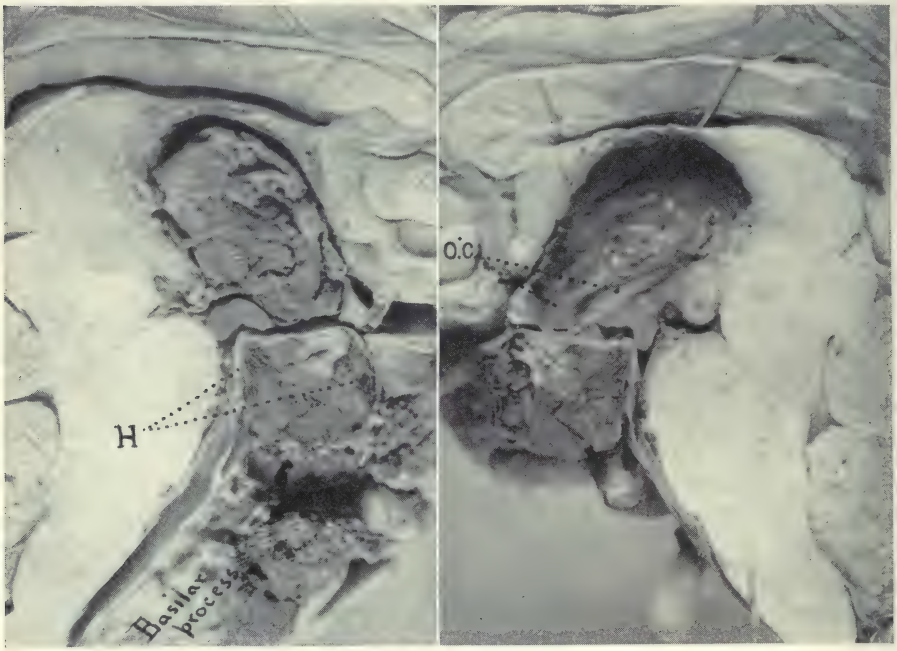


FIG. 31.—Case II. X-ray of middle and ring fingers (nat. size) showing characteristic acromegalic changes. No epiphyseal lines.



FIGS. 32, 33.—Case II. Left. Median section (slightly reduced) shows distended sellar pocket (H) and the mid-brain extension of the growth. Floor of sella removed at operation. Pars basilaris and sphenoid removed with brain.

Right. Hemisphere after removal of sphenoid and pars basilaris, and enucleation of struma, which protruded into the third ventricle. Note smooth lining of the cavity, with optic commissure (OC) pushed to right. Probe enters distorted foramina of Monro.

The median floor of the sella has been completely removed by the operation. The field of operation is clean and the procedure itself has accomplished its primary object of sellar decompression.

Histologically, the tissue occupying the enlarged sella is made up chiefly of a mass of hyaline material, taking a faint acid stain, in the centre of which is an area, visible to the naked eye, measuring 3 by 8 mm. This area is calcareous and takes a heavy hæmatoxylin stain. It is surrounded by a dense fibrous capsule. In the fresh, this area had a boiled-yolk-of-egg color and its translucent connective tissue capsule was visible to the naked eye.

Around this central area are many cell masses containing for the most part chromophobe elements, though some eosinophilic cells are present. Many cells are multinuclear, others have eccentric and deeply staining nuclei. No mitotic figures are observed. There is considerable pigment. In the extrasellar portions of the struma the cells are loosely placed and practically without visible supporting substance. There are no acidophiles. Many of the cells have bizarre nuclei with increase of chromatin. Many multinuclear cells.

In résumé, the picture is that of an anterior lobe (chromophile) hyperplasia largely undergoing degenerative changes, with a superimposed actively invading struma (Fig. 34) of chromophobe elements, possibly originating in pars intermedia.

In the pharyngeal mucosa are two epithelial lined pockets (relics of Rathke's pouch?).

The Other Ductless Glands.—The *thyroid* is somewhat enlarged and shows histologically a colloid goitre. The *ovaries* are large, cystic and degenerated. The *pancreatic islets* are

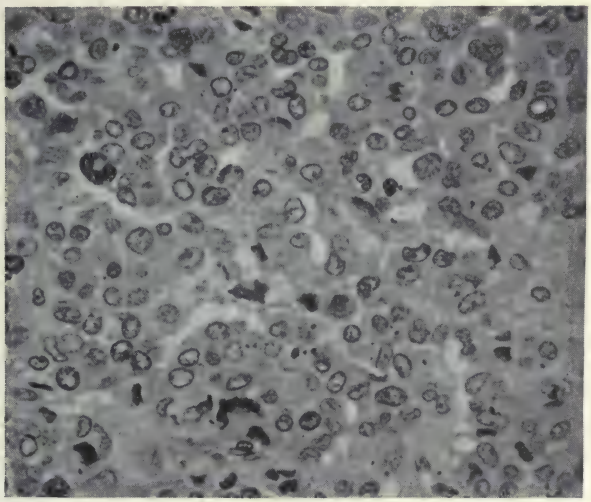


Fig. 34.—Case II. Microphotograph (mag. × 375) of chromophobe struma, showing bizarre types of nuclei often seen in these rapidly progressing hyperplasias.

numerous and large and the gland shows a fatty infiltration. There is considerable persistent *thymic tissue.* The *adrenals* are large; the medulla apparently hypertrophic, and the cells of the zona fasciculata have undergone marked fatty change.

The *liver* on section shows a pale yellow zone about the portal spaces; histologically there is a marked fatty change throughout, though more evident in the centre of the lobules.

The *uterus* is small; 6 cm. in length, 3 cm. in breadth.

No arteriosclerosis; some slight yellow opacities on the intima of the aorta.

Interpretation and Discussion.—The condition represents an acute or subacute stage of hyperpituitarism originating in an adult after epiphyseal ossification had occurred, with consequent enlargement only of the acral parts. It is possible that the hypophyseal instability may actually have dated from the illness contracted shortly before her marriage and that no attention was paid to the latent malady until the onset of the neighborhood symptoms and amenorrhœa.

No outspoken evidences of dyspituitarism were present, though she was small and somewhat obese. Her luxuriant hair, moist skin, elevated temperature, normal sugar tolerance and the insignificant thermic reaction to an injection of anterior lobe extract all pointed to a state of hypophyseal hyperactivity. However, in view of the postmortem findings there can be but little doubt that a state of insufficiency was near at hand, for the enlarged anterior lobe was undergoing degenerative changes.

The degree of neighborhood distortion brought about by the adenomatous hyperplasia was extreme. Notable is the fact that the growth had burst through the dural capsule toward the left side rather than by way of the stalk. Consequently the primary implication of the chiasm was such as to produce an homonymous rather than the supposedly more typical bitemporal hemianopsia. It had also deeply indented the left temporal lobe, and possibly some of her peculiar attacks may have been of uncinate origin.

The severe paroxysmal headaches with vomiting, together with the somewhat unusual local signs, should have made us suspicious of this intracranial invasion by the growth, and consequently more wary of a primary operative attack from below on the distended sella. The conditions found at autopsy make it clear that the suprasellar extension of the tumor was doing the chief damage. This obviously could have been approached only by a left subtemporal operation, such as Horsley practises.

Doubtless, in view of the postmortem findings, a preliminary subtemporal decompression would have been advisable at least before the sellar operation was attempted. However, the intracranial conditions were entirely unsuspected, though the somewhat bizarre local signs should have put us on our guard even in this, our first experience with a lesion of this type. The internal hydrocephalus had produced a medullary dislocation into the foramen magnum, to which the terminal symptoms of respiratory failure were due.

B. **Neighborhood Tumors with the Consequences of Hypopituitarism the Most Striking Feature.**—We now come to a consideration of the group of cases in which evidences of glandular deficiency dominate the clinical picture from the outset. There occur a number of clinical types, though the main line of division will be drawn between forms which have originated before and those which have originated subsequent to full adolescence.

Further subdivisions, however, of both of these types might well be made on a pathological basis, with a differentiation between cases in which the lesion is actually hypophyseal in origin and those in which the direct pressure of an extraglandular growth interferes with the normal hypophyseal function.

Such tumors as arise from a congenital anlage in sphenoidal or infundibular regions serve as illustrations of the latter, and owing to their existence from birth they are apt to compromise the hypophysis and give signs of their presence in the earlier decades of life. True glandular strumas which are productive of functional insufficiency are, on the other hand, more often associated with the third or fourth decades. This, however, is not an invariable occurrence, for a tumor arising from a congenital rest may not actively enlarge until relatively late in life (cf. Cases VII and XVII), and a true hypophyseal struma may occur in time to modify adolescence (cf. Case V).

The Preadolescent Types.—Of these, doubtless the most striking is the type to which the widespread attention of clinicians was first drawn

by Fröhlich's[91] paper (1901), though Babinski the year before under a similar title[4] had described the same condition in a young woman. Fröhlich's patient was a 14-year-old boy, with an hypophyseal tumor, who not only showed no signs of acromegaly but on the contrary symptoms of quite a different nature. These on the basis of our subsequent experimental studies can be safely ascribed to a state of glandular insufficiency. Fröhlich was able to collect a sufficient number of cases from the earlier literature to justify the assumption that a new clinical syndrome was before us.

In addition to the neighborhood manifestations of tumor the main clinical features of the *typus Fröhlich,* to which Frankl-Hochwart[87] has since drawn especial attention, are the peculiar adiposity, with a feminine type of distribution when it occurs in males, aplasia of the genitals, hypotrichosis, subnormal temperature, psychoses of varying nature and an undersized stature. To these symptoms we may add the important factor of a high carbohydrate tolerance. Barring the tumor, the clinical syndrome is the counterpart of the experimental states following partial hypophysectomy in puppies.

Though this particular type is now a well recognized one, there seem to be other preadolescent forms associated with tumor, in which adiposity is a less striking feature, though the combination of tumor with obvious signs of genital dystrophy and undergrowth are manifest (cf. Cases III and IV). And we must not forget at this stage of the discussion, not only that there are adult forms as well, but, and what is more important, that both pre- and post-adolescent forms are recognizable (cf. Group III) in the absence of the tumor on which Fröhlich and Frankl-Hochwart have laid so great stress.

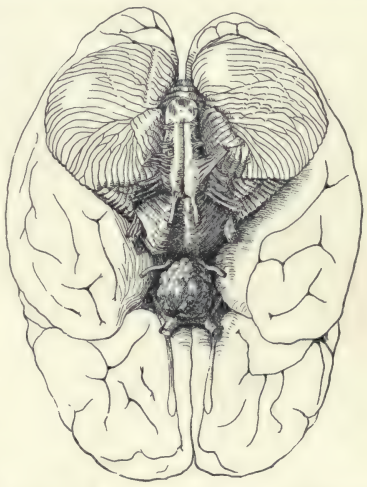


FIG. 35.—Case III. Infundibular teratoma causing hypopituitarism.

The following case, already recorded in some detail,[55] is the most typical example of the *typus Fröhlich* occurring in this series, though Case V belongs in the same category. Unfortunately at the time the patient was seen (1901) insufficient attention was paid to most of the points which now interest us.

CASE III. (Surgical No. 13054.) **An interpeduncular mixed tumor causing neighborhood symptoms and hypophyseal insufficiency (hypopituitarism of the type Fröhlich) by glandular obstruction.**

December 12, 1901. Mary D., a seamstress, aged 16, entered Dr. Osler's service with the complaint of dizziness and headaches.

She has suffered for some years with headaches and has always been small and delicate. She has never menstruated. For a month there has been failing vision, pain in the back, drowsiness, nausea and vomiting, constipation and "swelling of the extremities."

Physical Examination shows a well-nourished though undersized (height 4 feet 8 inches) and undeveloped girl. Mucous membranes of good color: gums soft and spongy (pyorrhœa alveolaris). The skin is smooth and presents a waxy appearance. Axillary and pubic hair is very scant. The subcutaneous tissues appear œdematous, probably due to

the glossy appearance of the skin stretched over the abundant panniculus. There is no "pitting" on pressure. The breasts are undeveloped: pelvic organs are infantile. Hands and feet are particularly small; the fingers delicate and tapering.

Visceral examination (thoracic and abdominal) negative. The *urine* is of low specific gravity and is increased in amount.

The only positive neurological findings are a suggestive pallor of the optic nerves with superimposed œdema (choked disc of low degree); shrinkage of the visual fields for form without hemianopsia, and exaggeration of the deep reflexes. Her mentality is of a childish order.

Two months later the choked disc had become pronounced, and three futile *exploratory operations* were performed (Feb. 21, March 8 and March 17, 1902), disclosing only an internal hydrocephalus. In April she became stuporous, and extreme rigidity of the four extremities developed. She died May 1, 1902, from an inhalation pneumonia.

Postmortem Examination. The thoracic and abdominal viscera were normal; pelvic organs infantile. (The ductless glands were not especially observed.)

On removing the brain (not hardened in situ) a nodular tumor mass the size of a golf ball was found occupying the infundibular space (Fig. 35) and extending up as far as the corpus callosum. It greatly distorted the mid-brain and obstructed the foramina of Monro, producing a hydrops of both lateral ventricles. It also pressed upon and moulded the crura cerebri.

Histologically the growth was a mixed tumor containing cartilage, bone cells, myxomatous tissue and so on. It was pronounced a teratoma by Dr. Welch. No histological study was made of the pituitary body and the gland has since been lost.

INTERPRETATION.—This, a typical instance of Bartels' syndrome "dystrophia adiposo-genitalis" of the type Fröhlich, was my earliest certified case of hypophyseal disease and first aroused my interest in the subject. At the time the patient was under observation (1901), though an intracranial growth was surmised, the absence of bitemporal hemianopsia, without which one hardly ventured to make a diagnosis of a pituitary tumor, together with the overshadowing general pressure disturbances due to the internal hydrocephalus, completely threw us off the track. No X-ray studies were made and the interpeduncular tumor proved a postmortem surprise. A case of close similarity occurring in a young woman of 17 had been described the year before by Babinski. Fröhlich's report had just appeared. Neither paper, unfortunately, had been seen.

The process in this patient, due to the slow-growing, mesially placed tumor from a congenital anlage in the infundibular region, gave as its chief symptoms the retardation of sexual development and skeletal growth, certain obscure nutritional disturbances and general headaches. The acute onset of general pressure symptoms, with the formation of a choked disc, was doubtless due to the internal hydrocephalus. A review of the medical history of this case (Dec. 12, 1901—Feb. 20, 1902) is interesting, in view of the discussion which arose in regard to the peculiar adiposity which the patient exhibited, many observers ascribing it to a nephritic œdema because of the polyuria though the usual evidences of nephritis were absent.

In an article dealing with tumors of the hypophysis Pechkranz[204] (1899) attributed to these growths the undeveloped genital organs, the femininity of the skeleton and the œdema of the face and extremities. Inasmuch as genital hypoplasia and optic atrophy are prominent features of these conditions, gynæcologists and ophthalmologists were naturally among the

first to see and record them,[3a] and solely with emphasis on this combination of symptoms my early report of this and one other patient (Case XIV) was made.

Another case of infantilism of a somewhat different type, associated with an hypophyseal tumor, is as follows:

CASE IV. (Surgical No. 26920.) **An interpeduncular tumor (uncertified) causing neighborhood symptoms and hypophyseal deficiency with infantilism (type Lorain) but no adiposity. Operation: subtemporal decompression. Encouraging experience with glandular therapy. Subsequent death. No autopsy.**

November 6, 1910. Miss E. D., single, 18 years of age, entered Prof. Barker's service and was subsequently transferred for operation. *Complaint:* Headache; vomiting; delayed adolescence.

Her parents and seven brothers and sisters are healthy and of usual stature. She has had no past illness, but has been undersized and delicate, shy, nervous and retiring. Highest recorded weight 94 pounds. Never adipose. She has never menstruated.

Present Symptoms. Bitemporal headaches of increasing severity for past two years; frequent vomiting; transient attacks of diplopia with strabismus; progressive weakness; recurring "numb spells" (uncinate?) with gustatory impressions, increase of headache,

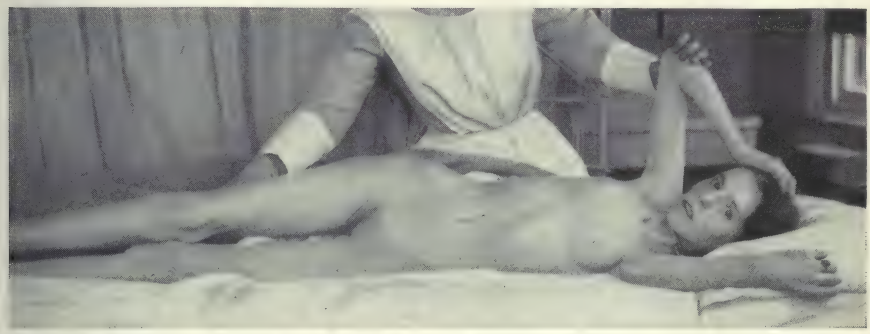


FIG. 36.—Case IV. Photograph to show patient's emaciation and infantilism.

rigidities, and occasional loss of consciousness. Some mental hebetude; irritable and lachrymose at times. Extreme polyphagia and polyuria for a period of three months (4000 cc. one day's measured amount).

Physical Examination. A pale, emaciated young woman of infantile appearance: dull and stuporous most of the time, with sluggish response to questions. She has acquired practically no secondary sexual characteristics (Fig. 36).

Viscera (abdominal and thoracic) negative. *Pelvic organs* infantile. Neurological tests show, in addition to the local signs to be given, a marked *tremor* with exaggeration of the deep reflexes. Cardiovascular examination negative. *Blood pressure* often too low to be registered; averages 50 mm. Hg. *Blood:* Hæmoglobin 56 per cent. (eosinophiles 1.4 to 2.6 per cent.). *Urine* negative except for the polyuria. Stools negative.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood:* The X-ray shows sellar enlargement with obscuration of outlines. *Eyes:* No optic atrophy. A left internal strabismus; slight nystagmus. Pupils dilated; no light reactions. Fields not taken—patient cannot sit up. No gross hemianopsia. Acuity low.

Examination of the pharyngeal vault shows a median slit-like opening in the mucous membrane just posterior to the edge of the vomer (persistent Rathke's pouch?). No adenoids. No epistaxis. Suggestive *uncinate gyrus* symptoms; also rigidities suggesting pressure against crura cerebri.

(b) *General Pressure Symptoms.* Severe headaches; vomiting; low grade of choked disc; excessive drowsiness and yawning.

(c) *Glandular Symptoms.* *Skeletal* growth infantile: height about 140 cm.; weight 58 pounds. *Hands:* Fingers very delicate and tapering (Fig. 37). Incomplete ossification of epiphyses (Fig. 38).

Cutaneous. Skin rough, dry, shiny; no perspiration whatsoever. Numerous pigmented freckles. Hypotrichosis. The hair of the scalp is dry and thin: practically no pubic or axillary hair. Nails thin and small; no crescents visible.

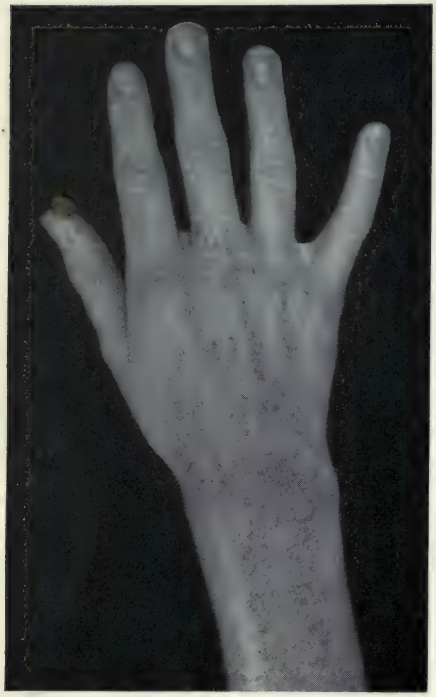


FIG. 37.—Case IV. Delicate, infantile, much pigmented hand.

Secondary sexual characteristics in abeyance.

Sugar tolerance not tested owing to vomiting. Positive *thermic response* to injection of anterior lobe extract. Marked *polyuria* and *polydipsia.* *Temperature* (per rectum) ranges slightly subnormal.

Other Ductless Glands. *Thyroid* somewhat enlarged. *Ovaries* not palpable; uterus infantile. *Adrenal(?)*: pigmentation: exceedingly low blood pressure: asthenia.

While in her stuporous condition organotherapy (hypophysin, 9 grains daily) was begun on *November 16.* Under this she brightened considerably; took more nourishment; blood pressure was higher. In view of this improvement it was thought that an operation might be undertaken, though the feeble pulse, anæmia and stupor made the risk considerable.

November 26. **Operation.** *Right subtemporal decompression.* Practically no anæsthesia necessary, as there seemed to be a general hypæsthesia of the body. The subtemporal bone was thin, brittle and without diploë; cerebral tension was high. No post-operative complications. Continuance of glandular feeding.

Subsequent Notes. *Nov. 27–Dec. 20.* Her headaches ceased; vomiting became infrequent; she gained in weight; the blood pressure rose, occasionally exceeding 100; she became bright and wakeful. After a month of this improvement the opotheraphy was discontinued, and within two days she relapsed into her former stuporous condition.

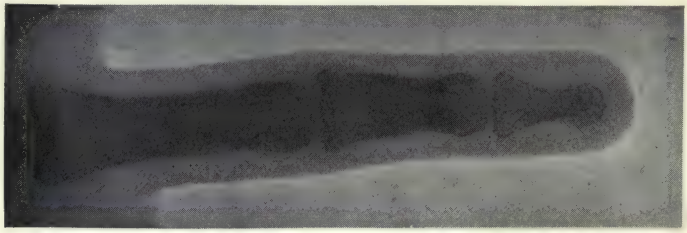


FIG. 38.—Case IV. X-ray showing delicate finger with tardy epiphyseal union (aet. 18).

While in this state a *lumbar puncture* was performed and 30 cc. of fluid withdrawn. This fluid had but a slight pressor effect on a test rabbit. The puncture caused an abrupt thermic response from 98° to 101°, enduring about ten hours, possibly (?) from liberation of anterior lobe secretion. Four days later (*Dec. 24*) a positive *thermic response* was ob-

tained by the subcutaneous injection of 0.2 grams of boiled anterior lobe extract, with a rise of nearly three degrees. The skin became moist; there was a marked lessening of the urinary secretion for the day (a diminution from 2130 to 425 cc.). The improvement on the following day in her general condition was striking: her mind was clear; she was cheerful and hungry.

Opotherapy by mouth was then resumed, with continued improvement. It was again interrupted after two weeks, and thyroid and lutein extracts given instead. Under this treatment she lapsed into her former stuporous condition, with subnormal temperature and so on. On resuming the hypophyseal feeding she again improved greatly.

A few weeks later (*Jan. 20*) she was removed by her relatives to a distant city, and the glandular feeding was discontinued, against advice. She died *March 18*. No postmortem examination was permitted.

Fig. 39.—A typical case of infantilism of type Lorain, with an enlarged 2 cm. sella. Patient aged 20 years 6 months: height 4 ft. 4 in. (133 cm.) (Ettore Levi).

Interpretation.—A review of the question of infantilism of various types, upon which the French in particular have written widely, will be reserved for a later section (page 253). Suffice it to say here that the condition of this patient corresponds with the *type Lorain*—a weak, delicate, undersized individual with the bodily proportions of an adult (in the absence of secondary sexual characteristics) rather than those of infancy. The whole discussion of nanism unfortunately overemphasizes the external appearance rather than the possible underlying morbid processes which may prove important ætiological factors in these conditions.

Ettore Levi[158] has contributed greatly to our understanding of this type of infantilism by radiographic studies of a typical case (Fig. 39). Not only had the epiphyses failed to ossify, but the cranial X-ray showed an enlarged and deformed sella, doubtless due to a pituitary tumor. The skeletal conditions therefore closely resemble those of this Case IV, though the pressure phenomena were less advanced.

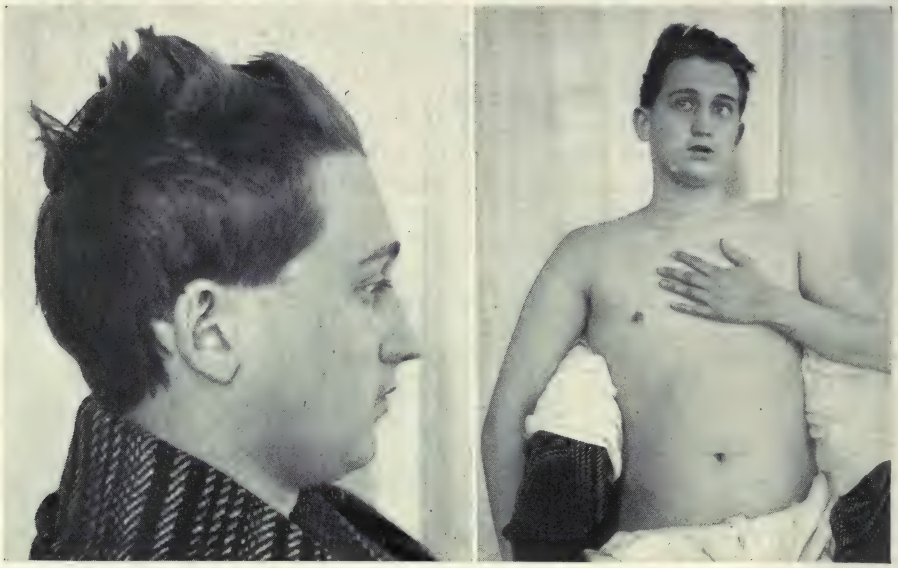
Cases of hypophyseal infantilism of this type show, in their freedom from adiposity, a striking contrast to the adiposo-genital dystrophy of the cases to which attention was called by Fröhlich. A good example has been recorded by Lemann and Van Wart[157]. Probably in the end all of these instances of hypophyseal infantilism (due to preadolescent hypopituitarism) will come to be grouped together, whether they exhibit adiposity or not.

Here certainly there was an early functional deficiency of the pars anterior which resulted in the persisting infantilism (sexual and corporeal). The positive thermic reaction to anterior lobe extract supports this view. It is barely possible that there may not have been a comparable degree of posterior lobe implication. Unfortunately no tests of the carbohydrate tolerance were admissible. Both lobes of the gland are doubtless affected in the *typus Fröhlich*.

The local pressure manifestations had become marked, leading to a spasticity resembling the terminal conditions of Case III. They were so pronounced, indeed, that a primary direct surgical attack on the gland was inadmissible, and in view of the patient's considerable improvement subsequent to the decompression and glandular feeding, it was opposed by her relatives.

In the following case, infantilism akin to the *typus Fröhlich* is a marked feature, though the growth in this instance is a primary struma of the gland itself, not a superimposed lesion which obstructs the gland, as in the preceding case.

CASE V. (Surgical No. 27100.) **Huge hypophyseal struma distorting the brain. Primary hypopituitarism, with neighborhood, general pressure and glandular symptoms all pronounced. Sella destroyed: hemianopsia; choked disc on primary atrophy; adiposity, feminism, genital dystrophy. Subtemporal decompression. Death. "Status lymphaticus."**



FIGS. 40, 41.—Case V. Showing the characteristic facial contour (maxillary prognathism) associated with interpeduncular tumor and hypopituitarism. Note, on right, the abundant panniculus, small hand and tapering fingers.

December 21, 1910. H. G. W., aged 22, single, referred by Dr. K. F. Junor of Brooklyn, through Dr. M. Allen Starr. *Complaint:* Headaches, vomiting, loss of vision, epileptiform attacks.

A negative family history. He was exempt from the usual children's maladies. At the age of 5 he had a severe fall, striking his forehead: he has been subject to headaches ever since. It is obvious that his adolescence was imperfect, and childlike tendencies have persisted; he has never shown any sexual instincts.

He has undertaken some business tasks of late, but they proved too much for him; he "broke down" five weeks ago and since then has been confined to his bed. He has suffered for years with insomnia.

Present Aggravation of Symptoms. Increasing headaches led to an ophthalmological examination, when, seven months ago, Dr. Scott Wood found a nasal *hemianopsia* of the left eye; right normal; no choked disc. Vision is now completely lost in the left eye and is rapidly failing in the right.

The *headaches*, which are accentuated by recumbency, have gradually become much more severe; they are "bursting" in character, so that his head has to be held, and are accompanied by hallucinations of a "horn growing from his forehead." There has been projectile *vomiting* of late and much nausea. For three or four weeks he has had many

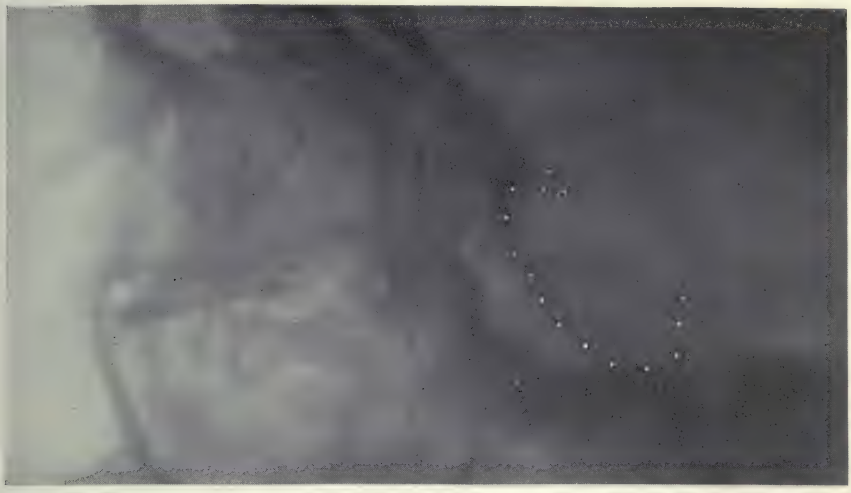


FIG. 42.—Case V. X-ray of cranial base (nat. size), showing much distended sella (dotted).

Jacksonian attacks, accompanied by an indescribable olfactory and gustatory sensation, and several seizures with unconsciousness, one lasting twenty-four hours. There has been marked loss of memory; also periods of dysarthria or actual aphasia.

Absence of cutaneous perspiration has been noted for years. Polydipsia and polyuria have also been present in the past.

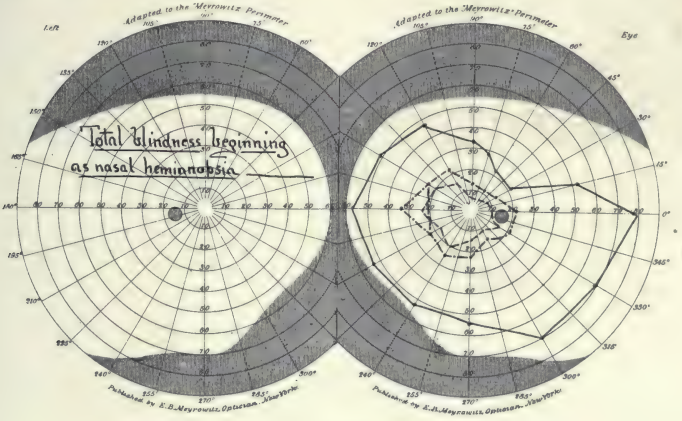


FIG. 43.—Case V. Visual fields Dec. 21st.

Physical Examination. An overnourished, delicate, boyish-looking young man (Fig. 41), suffering intensely with symptoms of cerebral pressure. The localizing signs obviously point to a large interpeduncular tumor. *Blood* and *urine* negative.

Analysis of Hypophyseal Disturbances. (a) *Neighborhood Symptoms:* Stereoscopic X-ray plates show the sella to be practically destroyed (Fig. 42). *Eyes:* Bilateral exoph-

thalmos. Left primary optic atrophy; right, a low grade of choked disc. No photophobia. *Fields:* Amaurosis total on the left; right, upper temporal defect (the lesion therefore has produced a right homonymous hemianopsia). Complete anosmia. Uncinate attacks. Exaggerated deep reflexes, which possibly indicate pressure on crura. Retropharyngeal examination shows a median crypt, regarded as a relic of Rathke's pouch (cf. Case IV).

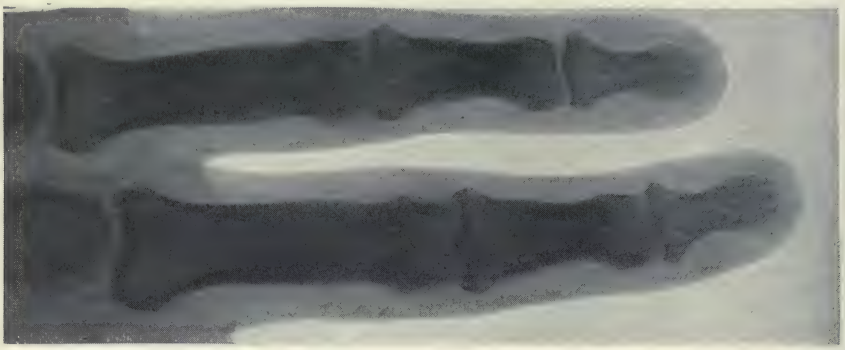


FIG. 44.—Case V. X-ray of fingers (nat. size): united epiphyses.

No nose-bleeds; but there has been a mucous discharge, occasionally blood-tinged, from the pharynx for years.

(b) *General Pressure Symptoms.* Extreme headaches; marked dilatation of extra-

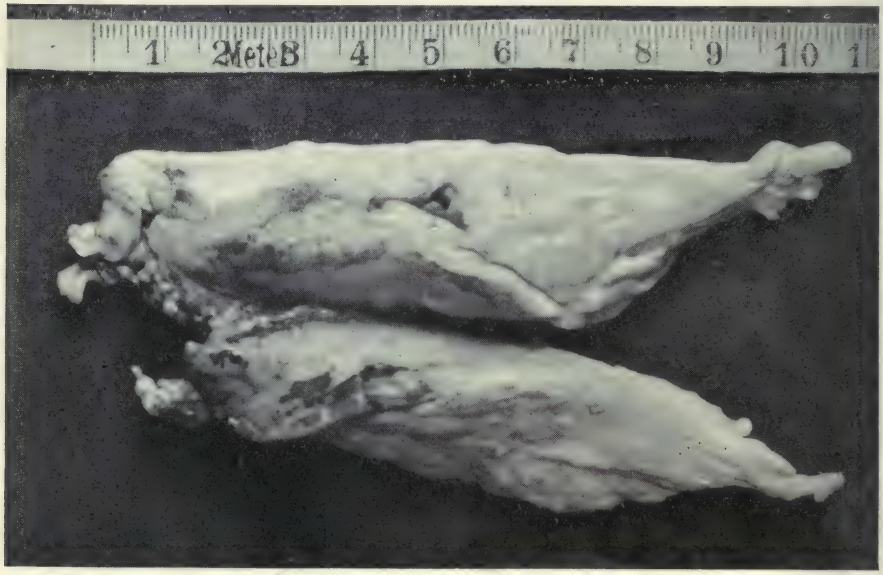


FIG. 45.—Case V. Persistent thymus (slightly reduced).

cranial vessels, vomiting, dizziness, choked disc, evidences of foraminal (*F. magnum*) herniation with medullary symptoms.

(c) *Hypophyseal Symptoms. Skeletal:* Small stature and delicate bony framework; feminine outlines; tapering extremities. *Height* 5 feet 6 inches; *weight* 147 pounds. Configuration of head and features typical of a long-standing interpeduncular tumor (Fig. 40)

(cf. profiles shown in Figs. 71, 101, 114*a*, etc.). Hands delicate, covered with a dry, wrinkled skin; fingers tapering (Fig. 44). Epiphyseal lines (radial) still present.

Cutaneous. *Skin* smooth and delicate as an infant's; practically hairless, excluding the scalp; almost no beard, axillary or pubic hair: skin dry; rarely perspires. *Adiposity* definite; of feminine distribution; especial depositions of fat over pectorals, hips and pubes.

Carbohydrate tolerance high: 350 grams dextrose negative; larger amounts vomited.

No *thermic reaction* to 0.2 gram boiled pars anterior extract, but some sweating with rise in pulse-rate and blood pressure resulted. Slight *polyuria* (1500–2000 cc.); amount of urine often exceeding amount of liquids ingested. The *temperature* ranges subnormal (96° to 98°); the *pulse* also (60 to 70). The *blood pressure* is very low (85 to 90 mm.).

Polyglandular. *Thyroid* not palpable. *Thymus:* substernal dullness increased. *Testes* somewhat small; no noticeable hypoplasia of the genitalia.

Though mental disturbances are marked, it is difficult to distinguish between those the consequence of glandular deficiency and those due to local pressure (uncinate) and general pressure effects. There is definite enfeeblement of memory, occasional aphasia, convulsive seizures, etc. (not a matter of wonder in view of the postmortem findings).

Patient's condition regarded as very critical. While under observation there were a number of attacks with unconsciousness and rigidity without convulsions, in which symptoms indicative of medullary implication occurred. Decompression for the general pressure symptoms seemed urgently indicated.

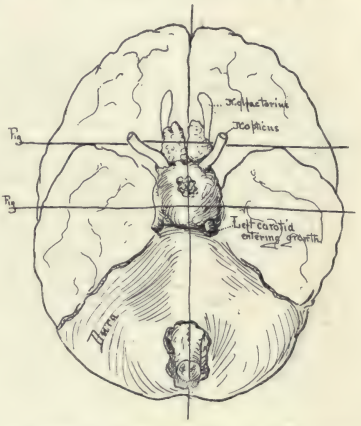
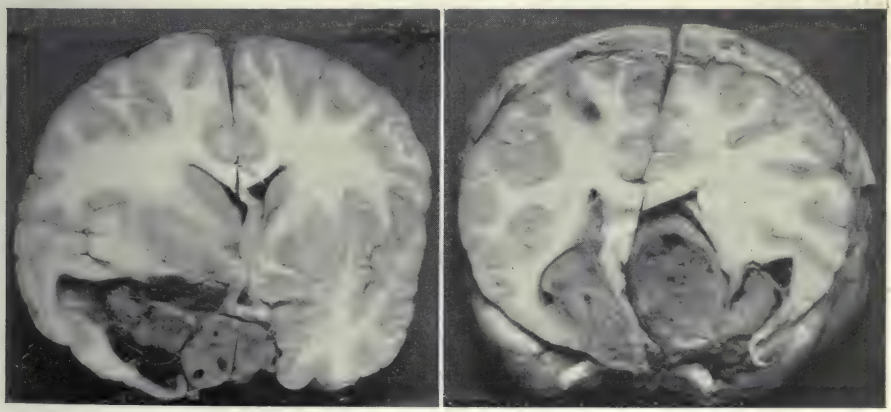


FIG. 46.—Case V. Sketch of cerebra base after removal of sphenoidal cells. Showing tumor covered by mucous membrane and greatly thinned dura, through the centre of which some of the tumor protrudes. Note envelopment of carotid, optic and olfactory nerves. Lines indicate coronal sections in Figs. 47 and 48.

Operation. *December 27. Left subtemporal decompression. Right ventricular puncture.* A most difficult and trying operation. Exceedingly tense dura; unusual vascularity of bone. To lower tension before opening the dura a ventricular puncture was made, with



FIGS. 47, 48.—Case V. Left: coronal section through centre of sella turcica (looking forward). Note left carotid surrounded by tumor; also extension of tumor into left temporal lobe, where it is encysted by a gelatinous material.

On right, coronal section (looking backward) at tip of temporal lobes and anterior to chiasm, showing the three main lobes of the struma.

the withdrawal of 25 cc. of clear fluid. Operation concluded; prompt recovery from the anæsthetic. Patient thought to be doing well, when a sudden respiratory cessation (medullary?) occurred six hours later.

Postmortem Examination. *Anatomical Diagnosis.*—Status lymphaticus: hypophyseal tumor.

The body has a strikingly feminine configuration. The panniculus is unusually thick, measuring 5 cm. over the abdomen. Mesenteric and retroperitoneal fat particularly abundant. There are a few small lipomatous masses free in the peritoneal cavity.

Such abnormalities as were shown by the thoracic and abdominal organs are as follows:

Intestines. A most extraordinary mottling with solitary lymphoid follicles, which in the large bowel are as large as peas and closely packed. Mesenteric glands very numerous, though not particularly large. The cut surface of the *spleen* shows closely-placed, yellowish dots, presumably lymph hyperplasia. The *adrenals* are very large, particularly on the left. Cortical zone sharply marked, but central grayish streak of medulla barely visible and presumably deficient. The *liver* is extremely fatty. The *thymus* is very large, bilobular, weighing 30 grms. and measuring 10 by 5 by 2.5 cm. (cf. Fig. 45). The *thyroid* is extremely small; of normal appearance on section. Two possible parathyroids identified. The *aorta* is small, thin, elastic, infantile. The subintimal coat shows a yellowish discoloration from fat. The *testes* are small, soft, but appear normal on section.

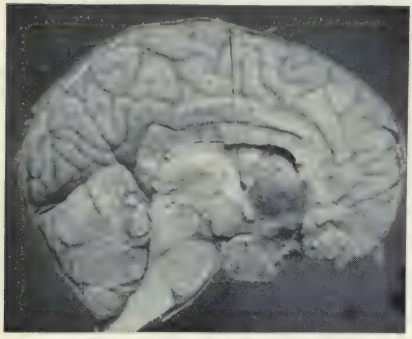


FIG. 49.—Case V. Longitudinal section showing how median protrusion of tumor bulges into region of third ventricle from left side.

Histological Appearances. Adrenal: Extreme fatty degeneration of the reticular layer. Medulla exceedingly small; cells appear normal. *Pancreas:* Islets inconspicuous, small, apparently normal. *Thyroid.*—Excess of colloid in the distended acini. *Testes:* Absence of interstitial cells; tubules appear normal. Sertoli cells present; also some spermatozoa (cf. Case VIII). *Thymus.*—Extreme hyperplasia.

Examination of Brain. Removed in its dural envelope, after formalin fixation *in situ*, together with the sphenoidal bone. The dura shows many large pacchionian granulations and many arachnoidal herniæ (Wolbach). Marked cerebellar herniation through foramen magnum. Convolutions much flattened.

On dissecting away the sphenoidal bone from below it is found that the intrasellar portion of the tumor has distended and absorbed the pituitary fossa and partly herniated into the sphenoidal cells (Fig. 46). Practically nothing but mucous membrane covers this portion of the gland, the dura having completely disappeared. The growth has spread forward under each frontal lobe (Figs. 46, 50) and surrounds the olfactory nerves; it completely envelops the left carotid artery, just as in Case II, and both optic nerves are also surrounded by extensions of the tumor mass.

Sections (coronal) of the brain show (Figs. 47 and 48) that the struma has burst through the left side of the pituitary dural envelope. Thence it has spread upward and greatly deformed the brain, by indentation rather than by invasion of the nervous structures. The tumor extends upward in tripartite fashion. A central protrusion fills the third ventricle (Fig. 49) obstructing both foramina of Monro and distorting the anterior end of the corpus callosum. Each lateral protrusion extends into the adjoining temporal lobe, deforming the uncinate region and projecting apparently into the lateral ventricles. The growth actually lies within the subdural space and has merely pushed aside intact pia-arachnoid.

The tumor tissue on section has a grayish, succulent, translucent appearance, with a few discolored, brownish spots. *Histological examination* shows it to be composed entirely of solid masses of chromophobe cells with a non-granular protoplasm and large sharply-cut vesicular nuclei—the type of neutrophilic cell comprising pars intermedia.

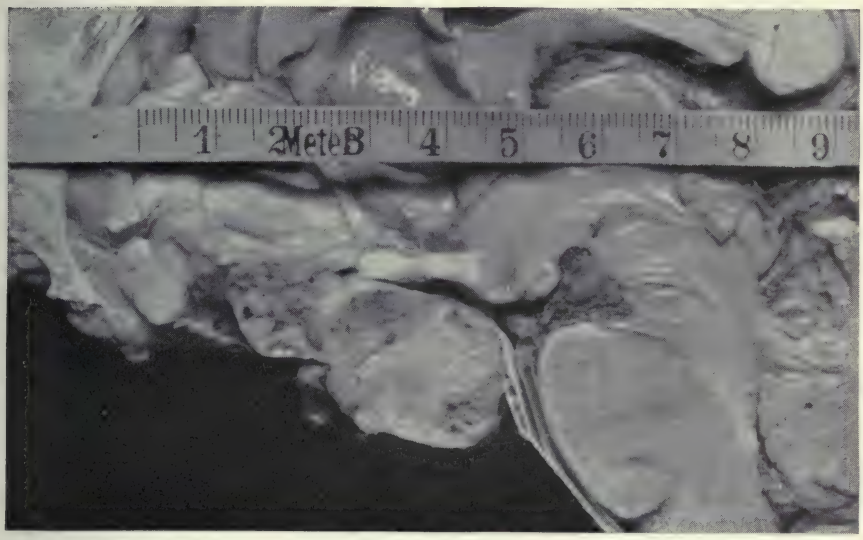
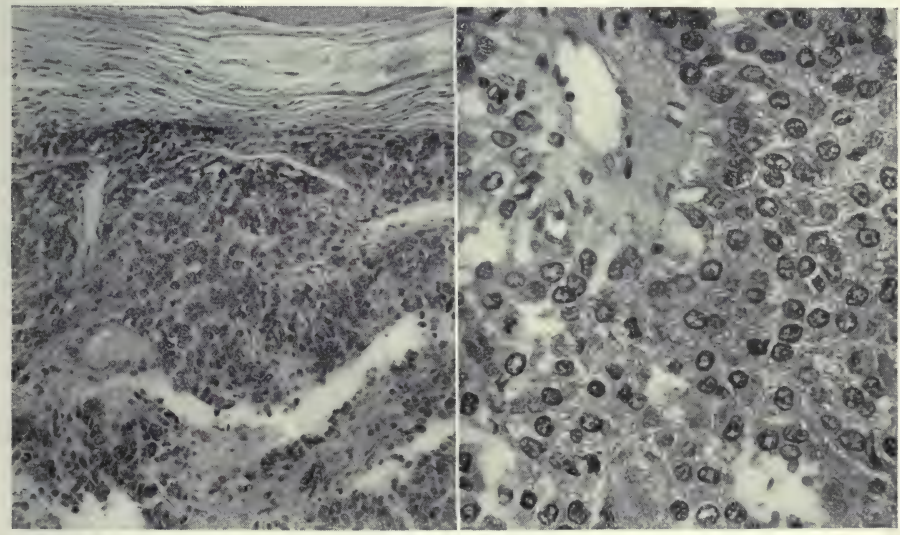


FIG. 50.—Case V. Longitudinal section showing primary pituitary struma and frontal extension. Superior dural envelope intact. (Nat. size.)



FIGS. 51, 52.—Chromophobe struma of Case V, showing (left) mass adjoining internal carotid, which it envelops (mag. × 190): (right) higher magnification (375 diams.)

INTERPRETATION.—A state of hypopituitarism dating from a preadolescent age and possibly related to the cranial injury of early life. There was unquestionably an imperfect acquirement of the secondary sexual characteristics, though without the striking hypoplasia of the genitalia seen in the more typical cases of the Fröhlich type in the male. It is particularly noteworthy that the spermatogenous epithelium was shown histologically to be active, though no Leydig cells could be identified in the interstitial spaces (cf. p. 276).

His sexual indifference, though recognized, had not been a source of anxiety to his intelligent parents, on whom he showered his affections with childlike exclusiveness. Despite his rather small stature, one would perhaps have commented rather on his outward appearance of femininity than upon the persistence of any physical characteristics of the preadolescent age.

Even more than in Case II, the examination of the brain showed what an extraordinary deformation and distortion of the adjoining parts of the encephalon may be brought about by this type of chromophobe hyperplasia, adenomatous struma, or whatever it is to be called. Here again, as in Case II, the growth burst through the side of the pituitary capsule and spread up to the left of the chiasm (producing a type of right homonymous hemianopsia), enveloping the carotid, the olfactory and optic nerves in its progress. None of these growths in our series—so-called malignant adenomas—have caused metastases, though in view of the fact that the cells seem to thrive with such a scant blood supply and to be supported by practically no intercellular substance, there seems no reason to believe that they could not survive and multiply if transplanted.

The polyglandular syndrome is notable in this case particularly in its thymic relations. Had the patient died a few years before under an anæsthetic given for some minor operation, and had the postmortem examination been confined to the body alone, the condition would have been regarded as an instance of "*mors thymica*," associated with extreme status lymphaticus. There can be, however, little doubt but that the hypophyseal disorder was the primary element in the undoubted pluriglandular syndrome.

It was particularly difficult in this case to know what were the proper steps to take in an attempt to furnish some measure of relief. These strumas are unquestionably slowly growing affairs, capable of degenerative metamorphoses, and in view of this, it is essential that time be gained if possible. Here the general pressure symptoms were such as to demand urgent attention. Hence it was deemed best to perform a subtemporal decompression, with the idea of subsequently decompressing the sella or partly emptying it of its contents in the hope of preserving the optic nerves from further implication. The anæsthetic was well taken, and death was attributable, I think, to a post-operative increase in the medullary herniation rather than to the existent status lymphaticus. Possibly, however, both conditions may have played a part. Certainly a primary attack on the tumor in an individual in this critical condition, whether by a subtemporal or by a transphenoidal route, is unthinkable.

Taken as a whole, the case represents the more advanced or terminal stage of conditions which prove to characterize some of the adult types of hypopituitarism with tumor, to be described. The critical feature of the

excessive enlargement of an hypophyseal struma lies in the secondary intracranial complications rather than in the effects of glandular insufficiency. The reverse is true of the large cervical struma, the frequent accompaniment of cretinism or myxœdema, for in these states the pressure manifestations are less apt to be a source of distress than the constitutional effects of the disease.

In the following case there were no corporeal manifestations of infantilism, and the evidences of glandular insufficiency were somewhat less marked and were seemingly delayed until adolescence was established—a transition case, in a measure, between the foregoing and the subsequent cases in this group.

Case VI. (Surgical No. 25715.) **Chronic (stationary) hypopituitarism in an adolescent with deficient mentality and epilepsy. Definite neighborhood symptoms of interpeduncular tumor (uncertified). Sellar decompression. Glandular therapy.**

April 14, 1910. Linda T., a Jewess, 15 years of age, was admitted with the complaint of headaches, failing vision, amenorrhœa, increase in weight and attacks of unconsciousness.

Fig. 53.—Case VI. X-ray of sella (nat. size).

Her family history is without note. She was regarded as a normal child until her fourth year, when there occurred a series of convulsive seizures with loss of consciousness, followed by some mental impairment and a notable increase in weight. Three years ago, after a period of severe headache accompanied by vomiting, strabismus was observed. During the two succeeding years frontal headaches and vomiting were of frequent occurrence, and she complained much of orbital pain.

Her *menses* began a year ago with two scanty periods, but she has not menstruated since. She has gained almost 40 pounds in weight in the last eight months. Polyphagia and polydipsia have been excessive. There is a constant itching of the skin, which is always dry; "she never perspires, even in the summer months."

Physical Examination. An overnourished girl, rather oversized for her age. Weight 136 pounds. There are no objective motor or sensory disturbances. There is definite muscular weakness, tenderness of the tissues, and she complains of paræsthesias in the limbs and body.

During her hospital residence she had two or three attacks of unconsciousness without convulsion but with marked retraction of the neck and subsequent stupor. The extremities during the attacks were flaccid.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The X-ray shows a slightly enlarged sella (Fig. 53) of normal configuration. There is a bilateral primary optic atrophy with almost complete loss of vision on the right; acuity, left, 15/30

FIG. 54.—Case VI. Note expression; also the abducens palsy.

FIG. 55.—Case VI. Delicate, long-fingered hand.

(perimetric fields cannot be taken); also an abducens palsy on the right (Fig. 54). Impairment of olfactory sense. Attacks have possibly an uncinate origin.

(b) *General Pressure Symptoms.* Headaches, vomiting, a low grade of œdema superimposed on a primary atrophy.

(c) *Glandular Manifestations. Skeletal:* Patient is rather overgrown than otherwise; certainly there is nothing infantile in her stature. The epiphyses are ununited, the radial

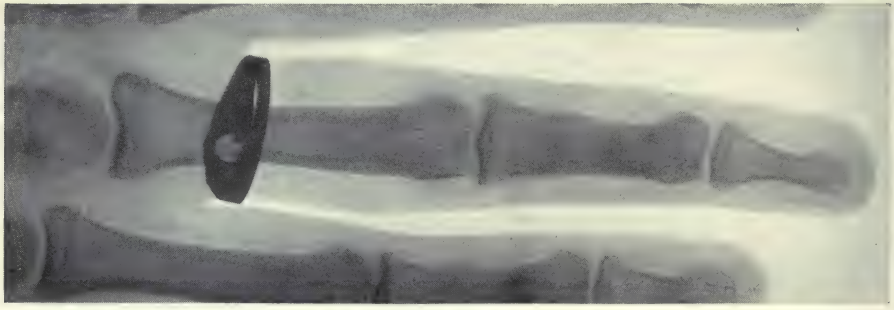


FIG. 56.—Case VI. Middle finger (nat. size). Note persistence of epiphyses, with possible overgrowth. Marie's *type en long.*

line showing intercartilaginous discs of bone. There are no acromegalic changes. The hands are large and the fingers peculiarly long and tapering (Fig. 55) with epiphyseal lines still traceable (Fig. 56). She is very round-shouldered.

Cutaneous. The skin is smooth and without perspiration. There is very little axillary and pubic hair, though the hair of the head is abundant. The nails show no crescents. Teeth are normal; upper incisors prominent.

There is a noticeable excess of panniculus. Pelvic organs are infantile. *Amenorrhœa* has been present for eight months.

Her *carbohydrate tolerance* was not fully established, amounts of glucose exceeding 200 grams being rejected. Though 175 grams could be retained, this amount gave no glycosuria. However, 175 grams with a coincident injection of .1 grain of posterior lobe extract gave an abundant reduction. She gained several pounds in weight under the carbohydrate tests.

She has slight *polyuria* (2000–3000 cc.), a slowed *pulse* and subnormal *temperature* (97.6°–98° F.). A subcutaneous injection of 1 cc. of 5 per cent. solution of anterior lobe on April 10th caused a positive *thermic response* from 97.6° to 100° F.

April 21. **Operation.** *Sellar decompression by the sublabial approach after primary tracheotomy.* No difficulty was experienced in exposing and removing the floor of the sella and incising the dural envelope of the gland. The gland seemed unusually tense—rubbery—and resisted such efforts to remove a portion for examination as were thought justifiable. The cervical and sublabial wounds were closed without drainage. Urotropin. A comfortable convalescence without complication. There was a marked post-operative increase in polyuria.

April 25. Patient has a free menstrual discharge—the first in eight months. Her mental condition seems much improved, and it appears that she can see better (her mother is confident of this). Discharged *May 29th,* improved: free from headaches: taking whole gland extract.

Subsequent Notes. *June 16, 1910.* There has been a gain in weight of 10 pounds, to 146. She remains free from headache and is said to be much less dull and sleepy. Her mental condition, however, is practically unchanged. She has had a second menstrual period.

September 1, 1911. Returns for observation. No organotherapy for several months. Has just recovered from a severe typhoid. Has menstruated regularly since the operation. Her weight has increased to 165 pounds. Her mother says "she eats equal to five men." She is still sleepy and drowsy. No headaches. Right pupil much larger than left. Vision: normal left: indistinct right. Not possible to take fields.

Interpretation.—In view of the positive neighborhood symptoms in the absence of deformation of the sella, the condition suggests a superimposed, possibly infundibular, tumor which has caused glandular insufficiency by pressure obstruction. The symptoms of hypopituitarism are shown as usual by the adiposity, the infantile pelvic organs with an interruption of full adolescence, the dry skin, hypotrichosis, polyuria, subnormal temperature, febrile response to anterior lobe injection, and increased carbohydrate tolerance.

The glandular disease has apparently not affected the patient's growth and indeed may have been preceded by a period of slight overactivity of pars anterior. She showed, furthermore, the four cardinal symptoms of "adiposis dolorosa" (cf. Case XXXVII, Group III) according to Vitaut's classification —namely, adiposity, spontaneous pains with tenderness, muscular weakness and psychic manifestations. Further consideration of types of adiposity and psychic disturbances, especially in so far as they border on epileptic conditions, must be reserved for a later section.

The therapeutic indications were chiefly on the side of glandular administration, but a sellar decompression was performed in the hope of giving the supposedly obstructed gland a better opportunity of resuming its functions. In consequence of one or the other measure—or of the two combined—there was an abeyance of the headaches, a re-establishment of the menses, restoration of the normal temperature and possibly a somewhat improved mental condition.

The Post-adolescent Types.—We come now to a group of patients with the combination of tumor and hypopituitarism, in whom, however, more or less complete sexual adolescence occurred before symptoms manifested themselves. The cases are merely adult types of hypophyseal insufficiency and represent states comparable to the experimental conditions brought about by partial extirpation in adult animals—male or female. The physical condition is a common one, and though unquestionably in the past it has rarely been recognized, when once seen and appreciated it is as unmistakable as are manifestations of hypothyroidism.

Had it not been for the onset of distressing neighborhood symptoms from an enlargement of the struma or tumor, most of these individuals would have continued to pass merely as stout, nervous persons with amenorrhœa or anaphrodisia, for whom rest and restricted diet is usually prescribed. In

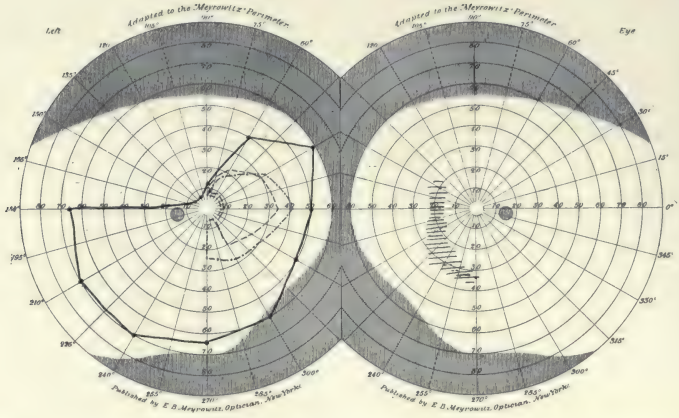


Fig. 57.—Case VII. Fields on admission, showing presumable bitemporal defect. Note hemiachromatopsia on left. The faint vision for large objects in the shaded area of right eye was lost after a few days.

Group II will be found cases (p. 94 *et seq.*) in which the evidences of hypopituitarism are less manifest, though the consequences of the local lesion are equally marked; whereas in Group III examples of the same constitutional syndrome will be given, (p. 132 *et seq.*) in the absence of characteristic neighborhood signs.

The following three histories are fairly typical ones. In the first patient (Case VII) the lesion, though uncertified, is presumably an infundibular growth which interferes with the functional action of the gland—an adult type, in other words, of the preceding Case III (certified) and Case VI (uncertified).

Case VII. (Surgical No. 27156.) **Infundibular tumor (uncertified) with primary optic atrophy and a stage of bitemporal hemianopsia. Adiposity. Amenorrhœa. High sugar tolerance. Sellar decompression: unavailing. Subtemporal decompression and glandular therapy. Improvement.**

January 2, 1911. Mrs. R. K., a Jewess, 40 years of age, was referred by a former patient in this series, who recognized the similarity of their symptoms. *Complaint:* Headache, failing vision, amenorrhœa and asthenia.

FIGS. 58, 59.—Case VII. Facies. Note relative width and prominence of median zone of face: "maxillary prognathism."

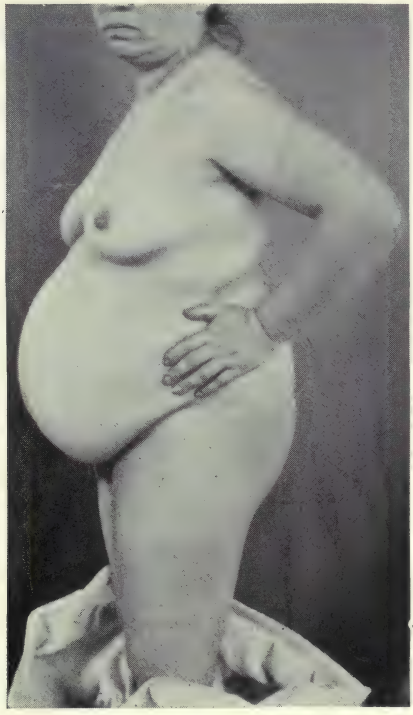


FIG. 60.—Case VII. Note stubby hand and marked adiposity.

She has several healthy brothers and sisters; all slender. Her adolesence appears to have been normal. She had typhoid at 17, but has otherwise been well. She was married at 22, and has had eight children. All but one died at or near the time of birth.

Present Malady. Eighteen months ago she noticed on closing her left eye that she could see but very little out of the other. At about this time her frontal *headaches* com-

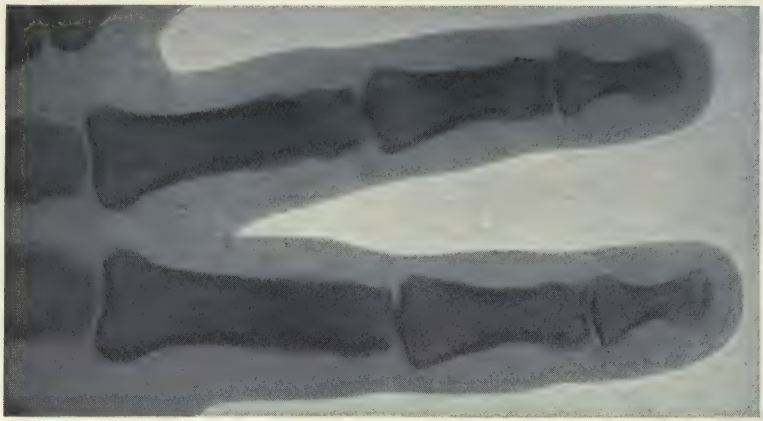


FIG. 61.—Case VII. Middle and ring fingers (nat. size), showing tendency to exostoses of first, and to tufting of terminal phalanges. *Epiphyseal* lines obliterated.

menced. Vision gradually failed, until she became practically *blind* in the right eye and the sight began to leave the left. Her *menses* ceased at this time and she began to grow stout. The breasts are said to have enlarged and to have secreted milk! She thought herself pregnant. Excessive thirst and *polyuria* have been present for some months. She

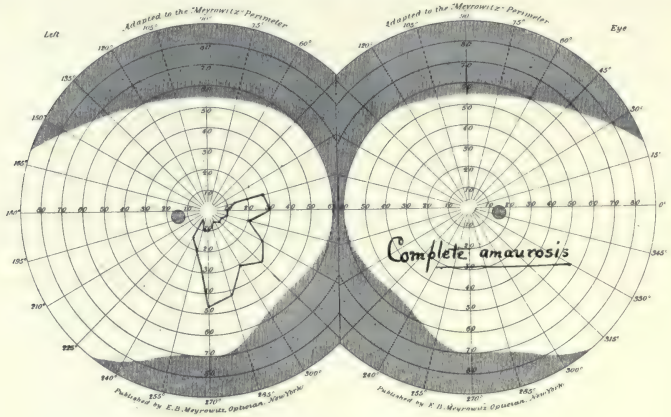


FIG. 62.—Case VII. Fields of April 9.

complains of paræsthesias, flushes, drowsiness, dizziness, tinnitus, and marked constipation. Also of left temporal headaches, nausea and pain in the back.

Physical Examination. The visceral (abdominal and thoracic) organs show no abnormalities. Cardiovascular negative. No positive neurological signs apart from those pointing to the neighborhood lesion.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood.* The X-ray (not stereoscoped) is inconclusive. It shows possibly some downward displacement of the sphenoidal

region. *Eyes:* Slight exophthalmos, more on left than right. Venules of lids full. Pupils equal: reactions better from temporal than from nasal retinæ (positive Wernicke). Fundi show primary optic atrophy on right, with tortuous vessels but no œdema: less pallor and some œdema on left. No oculomotor disturbances. Probable bitemporal field defect (Fig.

FIG. 63.—Case VII. X-ray (unreduced) after transphenoidal and subtemporal decompressions. Note low-lying sella (dotted).

57). Some weakness of right *N. oculomotorious*. Partial anosmia. No uncinate attacks. Nasopharynx negative. No epistaxis.

(b) *General Pressure Symptoms.* Persistent temporofrontal headaches. Slight obscuration from œdema of nasal margin of left disc. No vomiting. Dizziness.

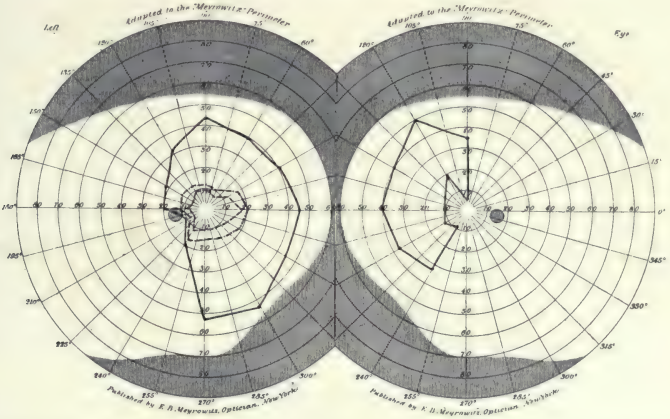


FIG. 64.—Case VII. Fields of August 28, 1911, certifying bitemporal character of the defects.

(c) *Glandular.* Patient has a small skeletal frame. Height 4 feet 11 inches. Configuration of facial bones suggestive of sphenoidal distortion (Figs. 58 and 59). Hands very short and stubby (Fig. 60): nails show no crescents. Slight suggestion of phalangeal exostoses apparent on X-ray (Fig. 61).

Cutaneous. She is very dark-complexioned. The skin over the body and extremities is smooth and soft but without special pigmentation. *Pilosity* of body (axilla and pubes)

low, but there is a growth of lanugo-like hair on the cheeks and lips. The hair of the scalp is dry and thin. *Adiposity* marked (Fig. 60), with some tendency toward lobulation, but no lipomata. Weight 154 pounds.

Carbohydrate tolerance high. Assimilation limit for lævulose 300 grams. No anterior lobe thermic tests made. *Temperature* ranges subnormal (occasionally as low as 96.2°); *pulse* variable (68–100).

Other Ductless Glands. *Thyroid:* Both lobes palpable but not enlarged. No increase of retrosternal dullness. Amenorrhœa for five months. A temporary mammary secretion from some hormone action (?).

January 12, 1911. **Operation I.** *Sellar decompression.* An uncomplicated operation by the sublabial route with submucous resection of the vomer without entering the nasal cavity. Convalescence stormy. Otitis media: orbital œdema. Nasal discharge persisted for ten days. Follicular tonsillitis on *Feb. 9.*

The headaches persisted. There was a progressive failure of vision. On *Feb. 8,* colors no longer recognized in the left eye. A month later the acuity was about 1/100.

March 29, 1911. **Operation II.** *Right subtemporal decompression.* Marked cerebral tension. Lumbar puncture (50 cc.). The fluid, concentrated to 2 cc., shows an insignificant pressure response in a rabbit but causes glycosuria and diuresis.

April 9. Headaches alleviated but visual acuity continues practically nil (Fig. 62). Decompression defect remains tense. *Discharged.*

Subsequent Notes. Her condition remained about stationary for the following three months, with an occasional headache. On *July 5* she re-entered the hospital for study. An X-ray at this time (under the advantage of the subtemporal defect) showed a very thin-walled sella of normal configuration (Fig. 63) in an unusually low position (cf. Case VIII), measuring 1.4 cm. by 0.9 cm. in depth. *Organotherapy* was instituted. Improvement soon was apparent. The charts on *Aug. 28* showed a return of vision in the right nasal field (Fig. 64). *Sept. 4:* She reports having had her first menstrual period in over two years. *Dec. 3:* Normal menstrual periods have continued.

Interpretation.—A case with the characteristic constitutional syndrome of hypopituitarism (adiposity, high sugar tolerance, amenorrhœa and the rest) together with unmistakable neighborhood symptoms (primary optic atrophy with bitemporal hemianopsia). So long as the lesion remains uncertified and so long as there is no demonstrable change in the sellar outlines, in spite of the manifest character of the symptoms, one unconsciously hesitates in the diagnosis.

This goes to show how dependent we have become on the X-ray as an aid in the recognition of these states since Oppenheim suggested its possibilities. However, we have begun to feel that a sella of this type, with thinned walls though of normal configuration, speaks in favor of a superimposed growth arising from a congenital rest; whereas the enlarged and symmetrically distended sella is characteristic of primary hypophyseal strumas, of which many examples will be given.

Two cases of presumed, and one of certified, infundibular tumor with hypopituitarism in younger individuals have already been considered in this group. Further discussion of them will be reserved until the succeeding important case has been taken up.

As a therapeutic measure the sellar decompression here availed naught, and improvement did not occur until after the subtemporal decompression, combined with organotherapy. In a case of this kind, should actual surgical investigation of the lesion be contemplated, the growth must be approached by a lateral intracranial exploration beneath the temporal lobe, with the

patient in the "overhanging brain" position of Karplus and Kreidl.[139] Should the growth be exposed and prove to be benign, as it probably is in this case, a fragmentary removal might serve to check the advancing symptoms more effectually than would the more simple palliation of a subtemporal decompression. That nothing more than a mere sellar decompression is permissible, when the lesion is primarily infundibular and the transphenoidal method of approach chosen, is demonstrated by the postmortem studies of Case VIII (Figs. 77, 78) which follows and of Case XVII (Fig. 126) of the succeeding group.

In the following case an attempted transphenoidal extirpation would merely have served to remove the flattened though still functionating residue of the hypophysis which was interposed between tumor and sphenoidal cells. The case shows, furthermore, how futile may be any measures whatsoever, even palliative ones, in the presence of an advanced lesion.

Case VIII. (Surgical No. 28200.) **Large infundibular tumor of long duration, with malignant transformation. Neighborhood and general pressure symptoms of advanced degree. Marked hypopituitarism. Terminal medullary phenomena. Subtemporal decompression without avail. Postmortem examination.**

August 6, 1911. F. H., a collegiate instructor in English, aged 41, single, referred by Dr. J. J. Whoriskey of Cambridge, Mass. *Complaint:* Blindness; headaches; adiposity; periods of coma with Cheyne-Stokes respiration.

Owing to the patient's very stuporous state and mental incapacitation only a most fragmentary history, at second hand, could be obtained. He has always been a somewhat

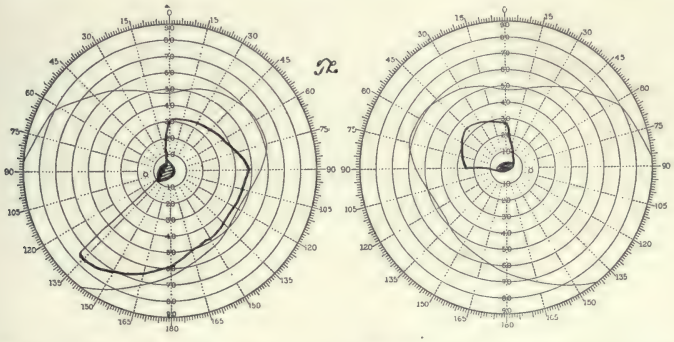


Fig. 65.—Case VIII. Fields taken elsewhere four years before admission. Characteristic stage of bitemporal hemianopsia.

odd, retiring, perhaps effeminate individual, shunning society, though much beloved by his colleagues and students for his affectionate qualities and exclusive devotion to their interests. He has always been somewhat undersized and obese, with a possible imperfection of adolescence. He has been a hard worker, of most sedentary habits. He has suffered from photophobia since childhood.

There is a vague history of a cranial injury received 7 years ago, which has left a scar over the left supra-orbital region. Two years later (1906) he had a "sunstroke" (?) while indoors, followed by unconsciousness. *Headaches* (chiefly left temporal), increasing in degree, have been more or less constant since that time, and of late years he has taken aspirin in large doses. His *vision* soon began to be impaired (1907), and various opinions were given ("toxic amblyopia," "astigmatism," "retrobulbar neuritis," etc.) as to the

cause.* Vision grew progressively worse, and he became almost totally blind 18 months ago. Nevertheless he managed to work at his collegiate tasks until the middle of the past semester, though feeling drowsy and stupid. He has become slow of speech and forgetful and there has been some obvious impairment of memory for several months. He has gained about 50 pounds in weight since 1907.

One month ago he passed into a semicomatose state with fever, Cheyne-Stokes respiration, slow pulse and a high blood pressure (240), which lasted for 24 hours. Dr. Whoriskey succeeded in arousing him by the use of stimulants. A week later there was a convulsive attack with twitching of the right arm and leg and turning of the head to the right. (Some weakness of the right side had been noted for the preceding few months.)

Physical Examination. An adipose, undersized man of middle age. He is usually in a stuporous sleep from which he can be aroused sufficiently to give vague monosyllabic answers to emphatic questions. He is completely disoriented as to time and place.

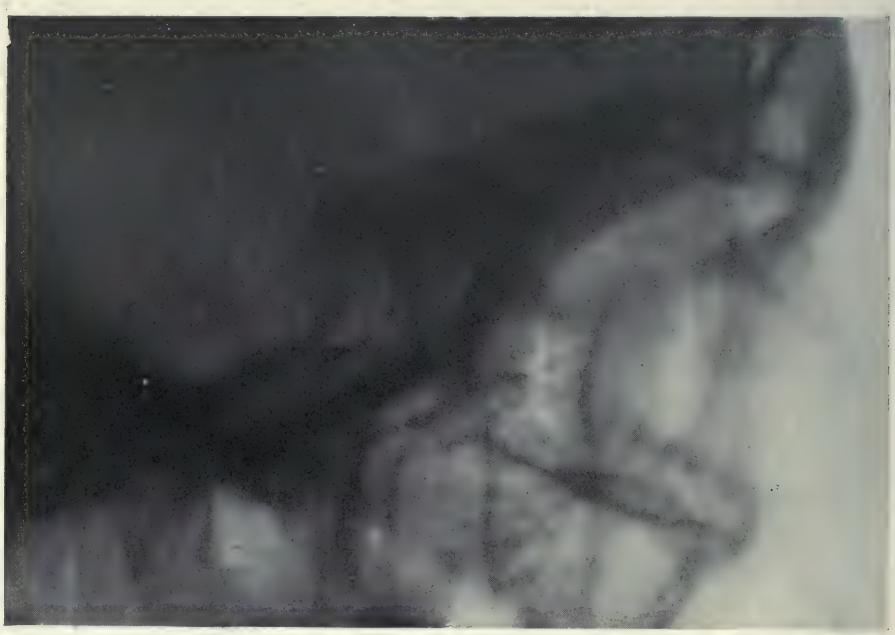


FIG. 66.—Case VIII. X-ray of sella (unreduced), showing obliteration of sellar landmarks: bony thickening of ethmoid.

Visceral (abdominal and thoracic) examination negative. Cardiovascular negative, except for a very high blood pressure (180–200). *Urine:* A trace of albumin and occasional hyaline cast. *Blood* negative. Positive neurological signs (aside from those obviously related to an interpeduncular growth) are limited to the very definite frontal lobe symptoms—impairment of memory, disorientation, stupor, disregard of amenities, and personal untidiness. He is not emotional.

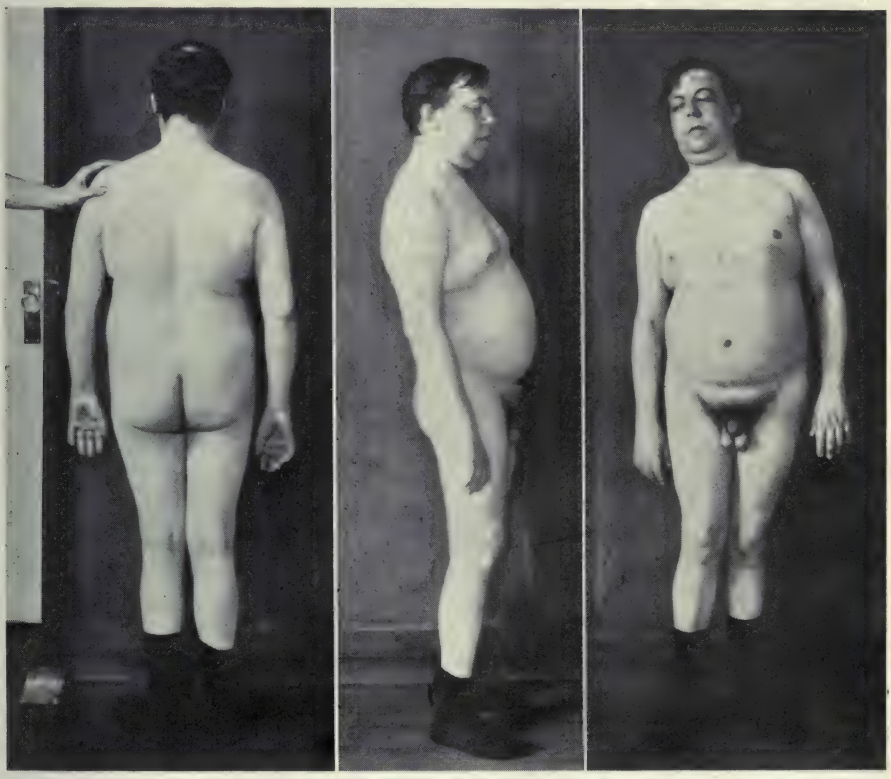
There is no objective disturbance of the right side of the body though he has complained of its being weak and numb. *Reflexes:* Deep, normal: superficial, inactive.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood Signs.* The cranial skiagram (Fig. 66) shows a marked downward distortion of the sellar region, and a faint

*I have been privileged to see most of the records of the earlier ophthalmological studies. Fields were taken in 1908, which are typical of an interpeduncular lesion, although at that time the defect in the right eye had advanced almost to blindness (Fig. 65).

shadow, which may be the unenlarged sella itself: no measurements possible. *Eyes:* Marked bilateral exopthalmos, more pronounced on right than left; positive von Graefe's sign. Bilateral primary optic *atrophy:* total blindness (originating as a bitemporal hemianopsia) (Fig. 65). Extreme passive congestion of lids and conjunctiva, with some œdema. Ocular movements performed with difficulty, and elicit *nystagmoid twitches* both to right and left. Slight divergent squint on right. Constant oscillatory movements. Pupils small; equal: no reactions. Total *anosmia.* No epistaxis: no nasal discharge. Nasopharynx negative.

(b) *General pressure symptoms* of highest grade; shown (1) on the skiagram by points of pressure atrophy of the skull; (2) by the general cranial tenderness; (3) by the extreme drowsiness and the medullary symptoms (Cheyne-Stokes respiration, retraction of the neck



FIGS. 67, 68, 69.—Case VIII. Adiposity of *typus femininus.* Note genu valgum: delicate extremities: distribution of hirsuties.

and difficulty of deglutition)—rather than by the usual triad of headache, vomiting and choked disc. Left temporal headaches, though constant, have not been severe: no vomiting. Primary optic atrophy without superimposed choked disc, though there is some obscuration of the nasal margin on the right. Pallor not marked in either disc. Veins tortuous but not dilated.

(c) *Glandular Signs.* Small skeletal frame (Figs. 67, 68, 69). Height 5 feet 6 inches. Head: tendency to maxillary prognathism (Fig. 71). Extremities small: hands (Fig. 70) delicate, pudgy, fingers tapering, joints exceedingly mobile; wears a number 6 glove. Feet small—number 6 shoe. Slight genu valgum (Fig. 67). Epiphyses ossified (Fig. 72).

Cutaneous. Delicate soft skin, with excessive perspiration, curiously limited to the face. No pigmentation. Pilosity low and of feminine distribution: always a scanty beard.

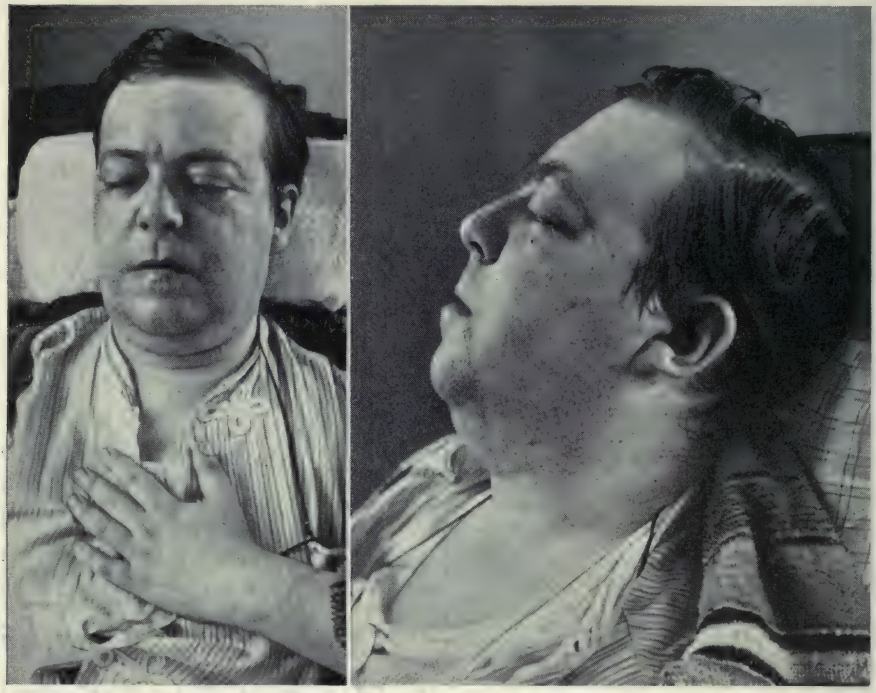
Adiposity marked: panniculus particularly abundant over abdomen, pubes, pectoral

region and hips. Large suprasternal and supraclavicular pads. He has gained 40 pounds in weight in four years—weighs 161 pounds. Extreme *asthenia*. No polydipsia or polyuria. *Temperature* (rectal) ranges above normal (99–100° F.). He has always felt "chilly and cold." Of late he has had occasional unaccountable febrile attacks. *Pulse* 90 to 100.

Carbohydrate tolerance not high. Assimilation limit for lævulose established at 150 grams (0.1 per cent. lævorotatory by the polariscope). *Thermic reaction* to anterior lobe injection inconclusive.

Other Ductless Glands. Nothing clinically observable. According to the patient's personal attendant, until recently there have been marked subconscious aphrodisiac tendencies.

August 17. **Operation.** Combined osteoplastic resection with subtemporal decompression. Extreme tension. Ventricular puncture with withdrawal of 10 cc. of clear fluid.



FIGS. 70, 71.—Case VIII. Note adiposity; exophthalmos and ptosis: Small pudgy hand; prominence of maxillary portion of face characteristic of sphenoidal distortion by an infundibular tumor.

Replacement of flap, leaving a large subtemporal defect. Practically no anæsthetic necessary. Condition remained unaltered. Cheyne-Stokes respiration persisted. Death on the third day after the operation, with hyperpyrexia (107°).

Autopsy. Extremely adipose body. The panniculus of the abdominal wall is 6 cm. in thickness and of a peculiar bright golden color. Peritoneal fat is especially abundant. The omentum is enormous and heavy and there is fat in excess everywhere throughout the mesentery, about the kidneys, pancreas and other organs. The *large intestine* shows a marked hyperplasia of lymph follicles. The *spleen* is small (120 grams) and shows no microscopical change. The *liver* is fatty: on section the cells are almost entirely replaced by fat (Fig. 73). *Pancreas* embedded in fat, which infiltrates the organ itself (Fig. 74). On section the islets are numerous, small, clearly demarcated. The cells appear normal. The *aorta* is not definitely small; it contains many atheromatous patches. *Prostate* is small: seminal vesicles large: distended with a purulent material which microscopically contains spermatozoa.

Ductless Glands. *Thyroid* is small (30 grams). On section, an increase of colloid with low epithelium (Fig. 76). One parathyroid seen: normal in appearance. *Thymus:* A greatly enlarged fatty organ with the morphology of an enlarged thymus but which on

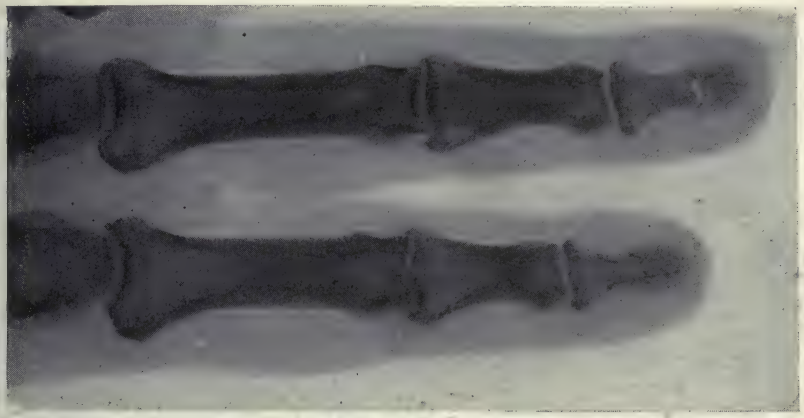
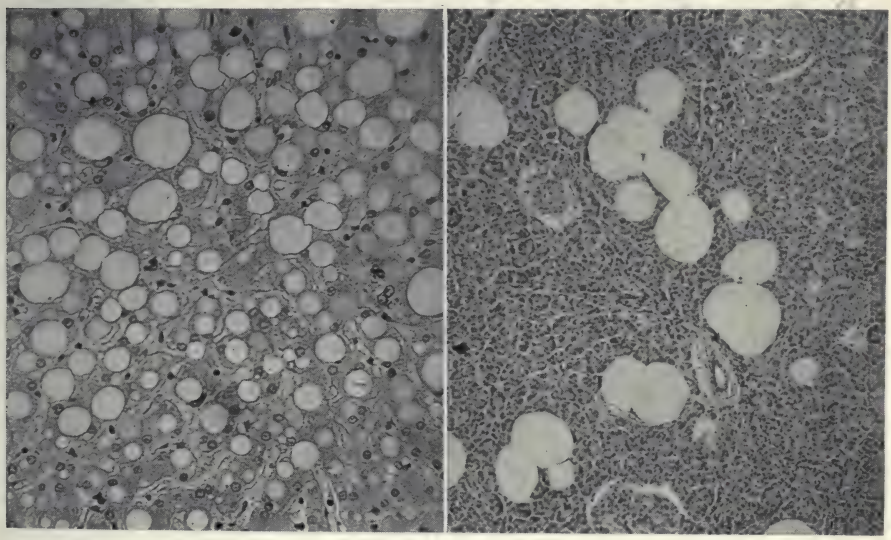


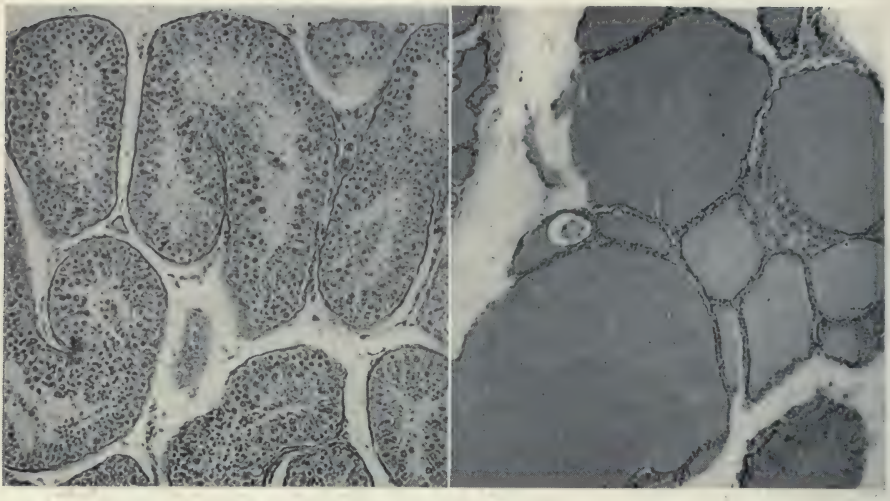
FIG. 72.—Case VIII. X-ray of index and middle fingers (unreduced). Note slight tendency to exostoses of proximal phalanges.

section shows no trace of thymic tissue. *Adrenals* very large. Right measures 6 by 4 by 1 cm. and weighs 9.6 grams; left measures 7 by 3 by 1 cm. and weighs 7.1 grams. On section, a marked change with vacuolization of cells of subcortical zones; an apparent hyper-



FIGS. 73, 74.—Showing (left) fatty liver: (right) fatty infiltration of pancreas with three islets in field (mag. 75 diams.).

trophy of chromaffin elements (medulla). *Testes* appear normal and weigh 20.6 grams each. On section they show an almost complete absence of interstitial tissue; no Leydig cells demonstrable (Fig. 75). Sertoli cells normal and tubules contain spermatozoa; also epididymis and seminal vesicles.



FIGS. 75, 76.—Showing (left) absence of interstitial cells of testes: (right) colloidal thyroid (mag. 75 diams.).

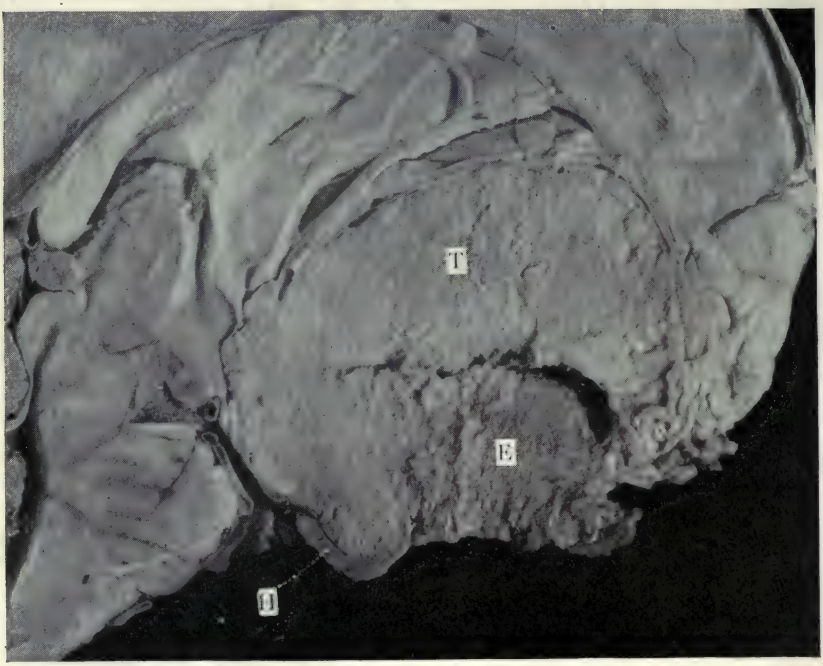


FIG. 77.—Case VIII. Median section (nat. size), showing tumor (*T*), a prolongation of which enters the sella and compresses the hypophysis (*H*). A bony extension of the growth (*E*) invades and solidifies the ethmoid cells.

The brain, after hardening by formalin injections, was removed within its meningeal capsule, with the ethmoid and sphenoid bones adherent. *Envelopes:* The skull-cap bears evidence of secondary pressure atrophy of high degree. It is pitted with many pea-sized

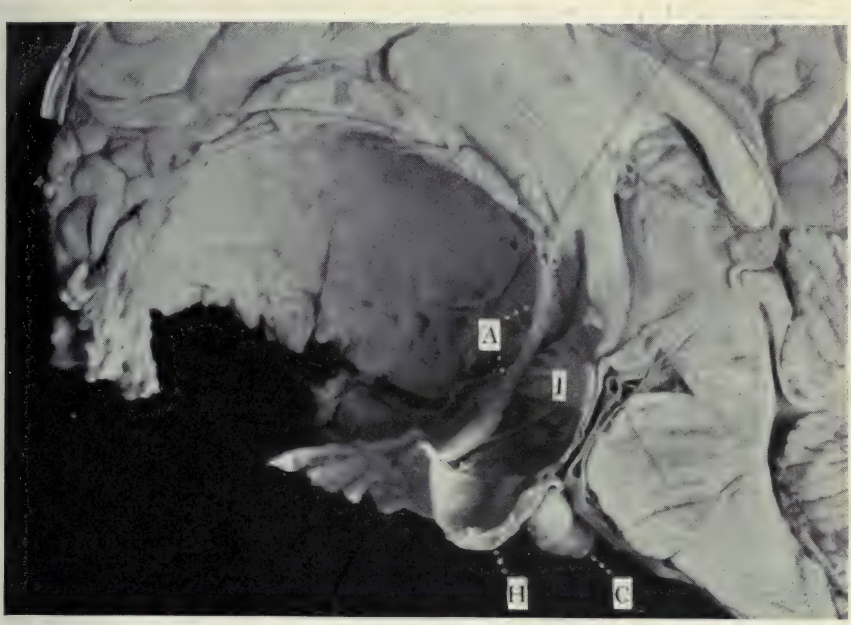


FIG. 78.—Case VIII. Nest in right hemisphere from which tumor (Fig. 79) has been enucleated, after mid-hemispheric section of brain. Note cup-shaped hypophysis (*H*) with dilated carotid (*C*) in juxtaposition; elongated infundibulum (*I*), and anterior cerebral artery (*A*).

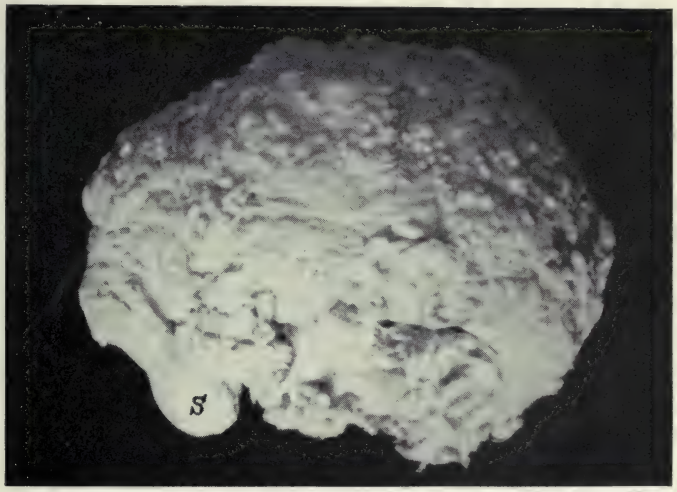


FIG. 79.—Case VIII. External surface of right half of tumor (endothelioma) after enucleation. Note granular appearance; also the portion which projected into the sella turcica (*S*).

excavations, corresponding with the cerebral herniations through the arachnoidal villi. They are particularly abundant in the left half of the calvarium (the excavations were apparent on the cranial X-ray). At the base of the skull these herniations have burst through

the foramina for the nerves, where some of them are as large as the tip of the finger. There is a marked foraminal (*F. magnum*) herniation, accounting for the terminal medullary symptoms.

The *dura* shows an extraordinary warty appearance, due to the protrusion of the many arachnoidal herniæ of Wolbach mentioned above.

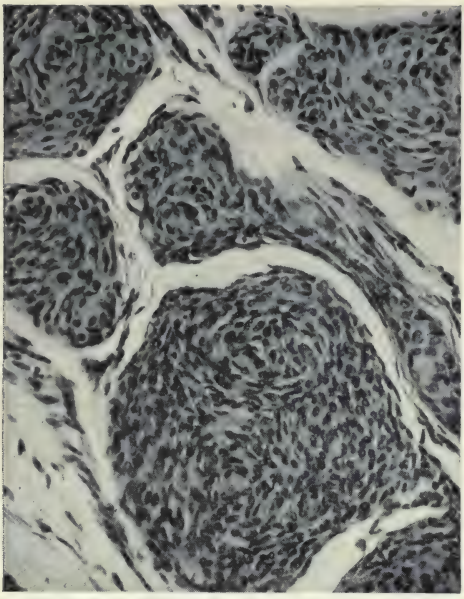


FIG. 80.—Case VIII. Section of tumor (endothelioma). (Mag. 190 diams.)

On dissecting away the much flattened sphenoidal cells the protrusion of practically a normal sized sella is seen. Its floor consists of a thin scale of bone containing some pressure perforations.

There is an enormous solid tumor mass occupying the interpeduncular region, widely dislocating all anatomical landmarks of the neighborhood. The tumor has invaded the upper part of the ethmoid, which has been partly broken away during removal (Fig. 77). This portion consists of a solid bony growth in which the optic nerves have evidently been compactly embedded (accounting for the fact that no choked disc was superimposed on the primary atrophy).

A mid-longitudinal section (Fig. 77) shows a large, sharply outlined growth about the size of a tennis ball. Its cut surface is dry, granular and of a pinkish color. Though generally spherical in shape, there are certain prolongations, one in particular which fills the

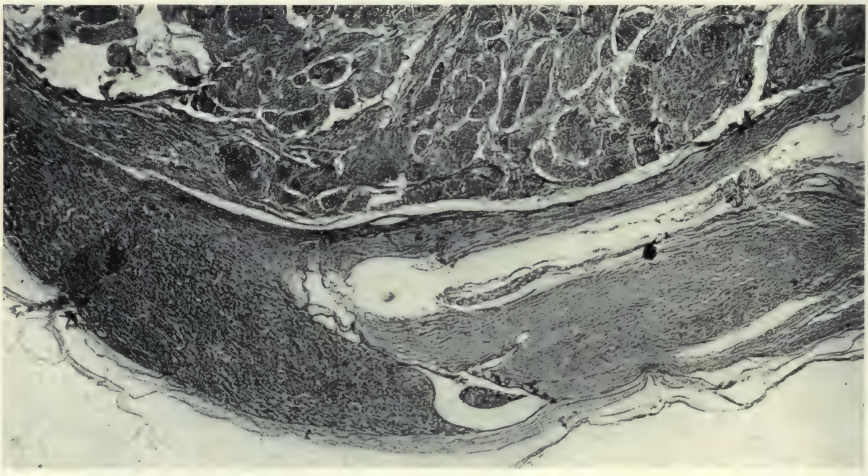


FIG. 81.—Case VIII. Showing flattened hypophysis with superimposed tumor. Note colloidal cyst in cleft and wide-meshed pars nervosa. (Mag. 10 diams.)

thinned sella and which has flattened the hypophysis to a saucershaped structure, 1.5 mm. in thickness. The infundibular stalk passes down behind the tumor (cf. Case XVII, Fig. 126, in which the tumor has pushed the stalk forward) to the posterior edge of the gland (Fig. 78). It has been drawn out to a length of 3 cm.

The *tumor* was enucleated from its bed in the right hemisphere (Fig. 79). Its surface shows a curious verrucous irregularity. Its only point of seeming attachment was on the anterior wall of the elongated infundibulum. Here it shelled out less readily, though it cannot be certified that this was the point of origin. It is somewhat moulded by the structures which it has crowded aside, the middle cerebral artery in particular having deeply grooved it. The optic nerves and chiasm have apparently been completely embedded by the growth. Most of its extension is toward the frontal rather than toward the temporal lobes. The internal carotid arteries are very large and tortuous and indent the sides of the hypophysis.

Histologically the tumor appears to be a pure *endothelioma* (Fig. 80).

The *hypophysis* (Fig. 81) is greatly flattened; the cell columns consisting in places of only two layers of cells, which have shrunk away from the greatly dilated sinusoids through the postmortem release of pressure. There is a normal proportion of acidophiles in the pars anterior. The posterior lobe is cellular: the neurogliar spaces wide-meshed but empty except for an occasional hyaline mass (Fig. 255, p. 192). There is a flattened colloid cyst in the pars intermedia.

Interpretation.—An unusual case, unlike any other in this series, though Case XVII of Group II will be found to possess certain similarities so far as the neighborhood distortions are concerned. Here, however, there were outspoken manifestations of hypophyseal insufficiency, from which Case XVII had largely escaped. The two cases differ, furthermore, in the position of the tumor, for in this case the growth lay anterior to the infundibular stalk, not behind it as in Case XVII and the tendency of its progress was upward and forward into the frontal lobes and ethmoid cells.

Though in a far more advanced degree, the local conditions are presumably similar to those postulated for the preceding case as well as for Cases IV and VI, and certified in Case III of the present group. The persistence of a morphologically intact, though thinned, sella seems to be characteristic of them all. One must not be misled therefore into the conclusion that normal sellar outlines necessarily speak against the existence of a neighborhood tumor. Sellar distention as we shall see is confined largely to patients afflicted with a primary glandular struma.

In all of these infundibular extrapituitary tumors the hypophysis itself suffers from a pressure atrophy combined with stalk obstruction, which renders both lobes of the structure functionally incompetent. Lesser grades of a similar functional insufficiency, usually with hypopituitarism, occur with tumors situated at a distance, as will be pointed out (cf. Group IV), but with the neighborhood lesions the hypophyseal deformation and compresson is far more obvious. It is important to note that with the ordinary methods of postmortem removal of the unembalmed brain a thinned-out saucer of gland, such as was revealed by careful dissection from below in this case, might easily be overlooked.

The question naturally arises as to the duration of the condition. It would seem probable, in view of the patient's skeletal characteristics, that the anterior lobe had suffered before his normal stature had been attained; it would seem probable too that the usual manifestations of adolescence had been imperfect, indicating a secondary insufficiency of the Leydig cells which antedated puberty.

Certainly some implication of the gland by the tumor was of long standing. Subsequent to and perhaps due to the trauma of seven years ago, the

dormant growth became active, with the rapid onset of neighborhood symptoms and with even more manifest indications of glandular insufficiency. These, however, were somewhat bizarre, for with the adiposity and asthenia there was not a great increase in the sugar tolerance and the blood pressure was very high. These irregularities, however, can possibly be ascribed to the extreme degree of cerebral tension and obvious medullary implication.

The postmortem studies revealed a condition therapeutically hopeless. Owing to the stupor and Cheyne-Stokes respiration a primary attack on the tumor was unthinkable, and the extensive decompression did not serve to check the medullary symptoms. It is not uncommon in these large midbrain lesions for marked hyperpyrexia to accompany the terminal phenomena.*

Case IX. (Surgical No. 28132.) **Pituitary struma with enlarged sella and uncinate gyrus seizures. Definite primary hypopituitarism with impotence, increased sugar tolerance and adiposity of feminine distribution. Improvement under glandular feeding. Transphenoidal operation.**

July 23, 1911. T. M. E., a banker, 36 years of age, referred by Dr. L. Litchfield of Pittsburgh. *Complaint:* Uncinate attacks and impotence.

Fig. 82.—Case IX. Enlarged sella (nat. size) of double contour (stereoscopic). Dorsum completely absorbed.

A number of the members of the patient's family have suffered from mental disturbances. He is one of five children. His three brothers, two of them twins, are stout and have scant beards. His grandmother was exceedingly stout (weighing 300 pounds), and other members of collateral branches of the family are stout.

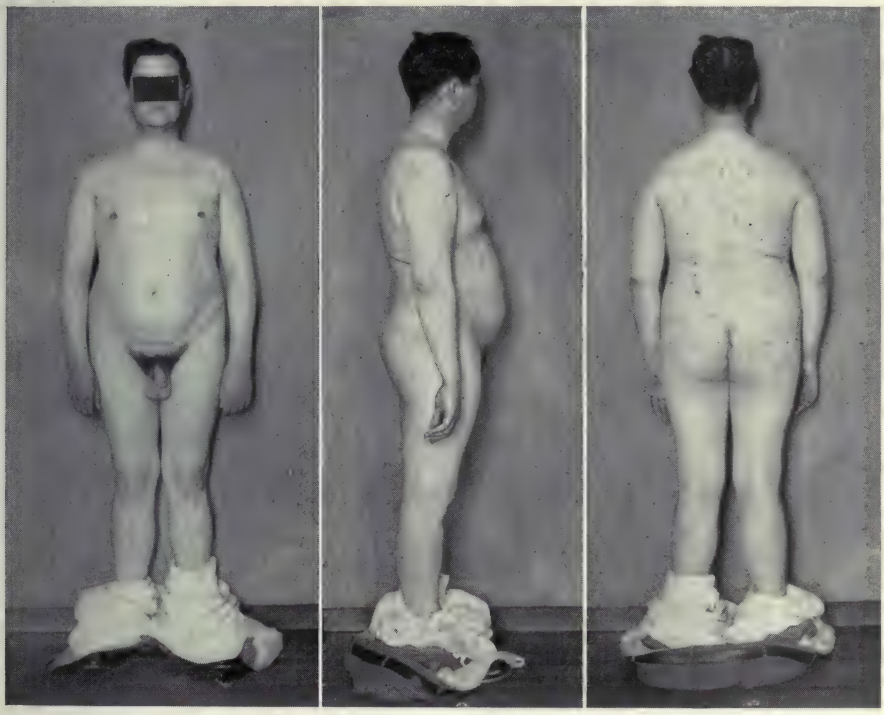
Patient is said to have weighed 15 pounds at birth and was very fat as a child. He had diphtheria at the age of 12 and typhoid at 20; otherwise no particular ailments. Habits good. He graduated from college in 1898, and has subsequently assumed large and worry-

* Frankl-Hochwart in his discussion of Eiselsberg's report (*Wiener klin. Wochnschr.*, 1909, xxii, 287) has commented upon the high post-operative temperatures of some cases he has observed.

ing business responsibilities. He married ten years ago and has one healthy child, three years of age.

Present Malady. The first disturbing symptoms (1904) were numbness of the fingers, insomnia, neuralgic headaches, and anaphrodisia. Rest and change of scene were prescribed. The symptoms continued. Malaria was contracted in Mexico in 1907. During the next few years and for long periods he often took 30 grains of quinine daily owing to dizzy spells and chilly sensations.

Uncinate Seizures. The first suspicious attack occurred in October, 1909—a definite lapse of memory for 20 minutes, with confusion and chilly sensation. In January, 1910, he had another similar seizure of longer duration—diagnosed "automatism." In February there were three attacks. In July there occurred another rather sudden loss of memory; he found his way home, and then had a severe convulsion with unconsciousness. The attack was preceded by a peculiar subjective taste and by numbness of the fingers. During the attack the face was drawn to the left and there were smacking and tasting movements



FIGS. 83, 84, 85.—Case IX. Note adiposity and disposition of hirsuties (*typus femininus*).

of the lips. There were two subsequent convulsions on the same day. Bromides were administered. Amnesia persisted for about three months. The eyes were examined at this juncture and were found negative.

In October, 1910, Dr. Litchfield prescribed *pituitary extract.* This was kept up without intermission until June 8, 1911, when the patient, feeling remarkably well, discontinued the powders but continued with the bromides. Four days later (June 12th) there occurred six mild amnesic periods (dreamy states) with gustatory sensations—"an indescribable but nasty taste and smell." Six other similar seizures on the following day. Pituitary feeding was immediately resumed. He has felt much better since and has lost 15 pounds under the treatment. Two days after discontinuing the powders on the patient's admission to the hospital, two slight uncinate attacks occurred.

He has always had an abnormally good *appetite:* has a great liking for sweets. Attempts to diet for his adiposity have naturally been lamentable failures.

He has always been sensitive to the cold—"sits close to the fire." His *skin* has always been notably free from perspiration until he began taking the pituitary powders.

Headaches have been inconspicuous. No change in vision noted. Marked *anaphrodisia* for several years and loss of potentio sexualis for two years.

He has become susceptible to attacks of depression; is forgetful, irritable and somewhat emotional. For the most part, however, he holds himself in good control, and has carried on responsible work.

Physical Examination. Of healthy appearance, though over-well nourished. Weight 200 pounds; height 5 feet 9½ inches. *Visceral, cardiovascular* and *neurological* examinations negative. Blood pressure 125 mm. Urine and blood negative.

Analysis of Hypohyseal Symptoms. (a) *Neighborhood Signs:* The stereoscopic X-ray (Fig. 82) shows a greatly enlarged sella of double contour, measuring 3.0 cm. by about 2.2 cm. in depth. The *dorsum sellæ* is obscured though identified on the 6th exposure.

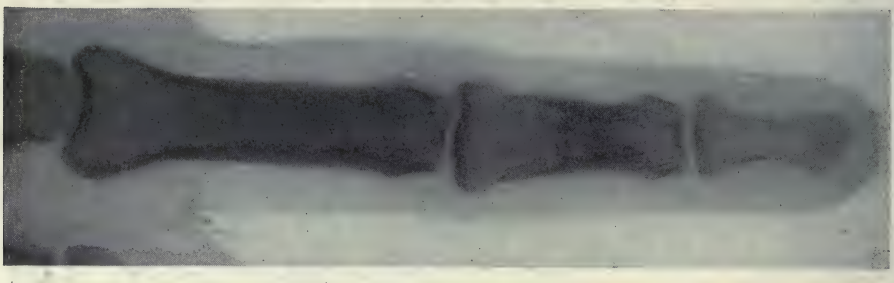


FIG. 86.—Case IX. Middle finger (unreduced) showing medullary absorption and absence of tufting.

The *eyes* are negative, though inequality of the pupils has been observed. The fields show some constriction for colors and possibly a slight tendency to an upper temporal form defect. Nasopharynx negative. Tonsils are large and cryptic: a large adenoid mass is present. No epistaxis.

(b) *General Pressure Symptoms.* None. The right frontal headaches are probably from pituitary distention. No change in the eye-grounds.

(c) *Glandular Symptoms. Skeletal:* The body shows a suggestive *typus femininus:* broad pelvis; slight genu valgum (Figs. 83, 84 and 85). Head is well formed: no prognathism; very large occipital protuberance. The epiphyses (radial, etc.) have united. The phalanges show considerable medullary absorption (Fig. 86). Teeth are normal.

Cutaneous. Skin is exceptionally smooth: pilosity low, with scanty beard, inconspicuous axillary growth and feminine distribution of pubic hair. Arms are freckled, but there is no especial pigmentation. *Adiposity* is diffuse, but panniculus is especially abundant over pectorals, hips, abdomen and pubes. Many bluish lineæ albicantiæ.

Carbohydrate tolerance high; limit something over 250 grams of lævulose. Higher dosage causes diarrhœa. With 125 grams repeated attempts to establish a therapeutic dosage unsuccessful. No spontaneous lævulosuria occurs on taking 45 grains of whole gland extract per diem with 125 grams of lævulose.

Temperature ranges about normal but has been found subnormal in the past and the *pulse* has been slow. No thermic test made. No polyuria.

No abnormalities made out in the other ductless glands, though the area of substernal dullness is unusually large.

Treatment. A sellar decompression is probably advisable, in the hope of lessening pressure disturbances on the part of the uncinate gyri—the presumable cause of the seizures. He was discharged (*July 30*) taking 15 grain powders of the gland after meals.

He reported (*August 17*) that he was feeling better than for four years past; that his temperature ranged slightly above normal, and that there was visible perspiration when exercising—not observed for a long time previously.*

INTERPRETATION.—A typical case of dystrophia adiposo-genitalis of the adult type. Had it not been for the uncinate attacks calling attention to the neighborhood, it is possible that the underlying condition would not have been recognized, as there would have been no occasion for an X-ray exposure.

FIGS. 87, 88.—Case X. Note moderate adiposity and characteristic hand.

The enlargement of the sella makes the diagnosis of a primary pituitary fault unquestionable. However, similar nutritional conditions due to states of dyspituitarism, without an enlargement or struma of the gland, unquestionably exist in a large number of individuals and pass unrecognized. Hence, had the uncinate fits not been interpreted as evidencing a regional disturbance, the case would have fallen, in our present classification, among those with hypopituitarism in Group III.

Some twelve stereoscopic plates of the patient were taken here and elsewhere, it being presumed from all of them that the posterior sellar outlines were entirely destroyed. Only after several trials at our own hands did Dr. Boardman succeed in getting negatives in which the distorted and thinned dorsum could be stereoscoped and the actual profile dimensions of the enlarged pituitary pocket determined.

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*A month later another uncinate attack occurred, and at this time the fields taken by Dr. W. W. Blair showed, for the first time, an irregular constriction of the color fields.

November 9, 1911, a *transphenoidal* operation was performed and a large mass of the tumor removed (No. 34 of the operative table, page 311). It proved to be a chromophobe struma. Uneventful convalescence. Supplementary radiotherapy.

CASE X. (Surgical No. 27798.) **Pituitary struma with bitemporal hemianopsia and enlarged sella. Definite primary hypopituitarism with impotence and adiposity of feminine type. Marked improvement in vision after glandular extirpation. Supplementary organotherapy.**

May 13, 1911. I. D., a Hebrew salesman, 30 years of age, referred by Dr. M.

FIG. 89.—Showing greatly distorted and enlarged sella of Case X (nat. size).

Allen Starr. *Complaint:* Severe headaches, loss of vision, general weakness, extreme nervousness. He had an attack of "pleurisy" 12 years ago and is very subject to "colds," there being an abundant secretion from the nasopharynx much of the time. He has been married 14 years; is without offspring.

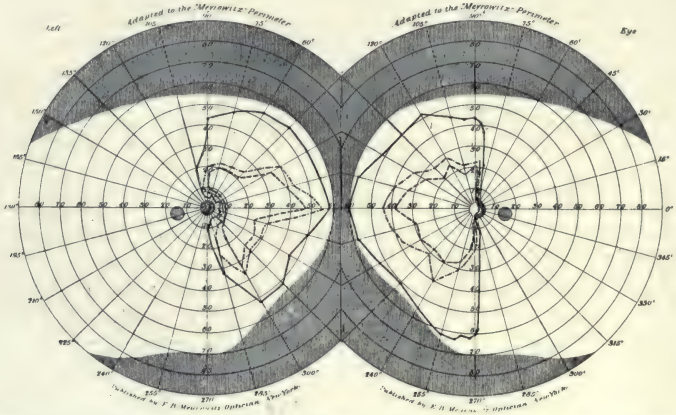
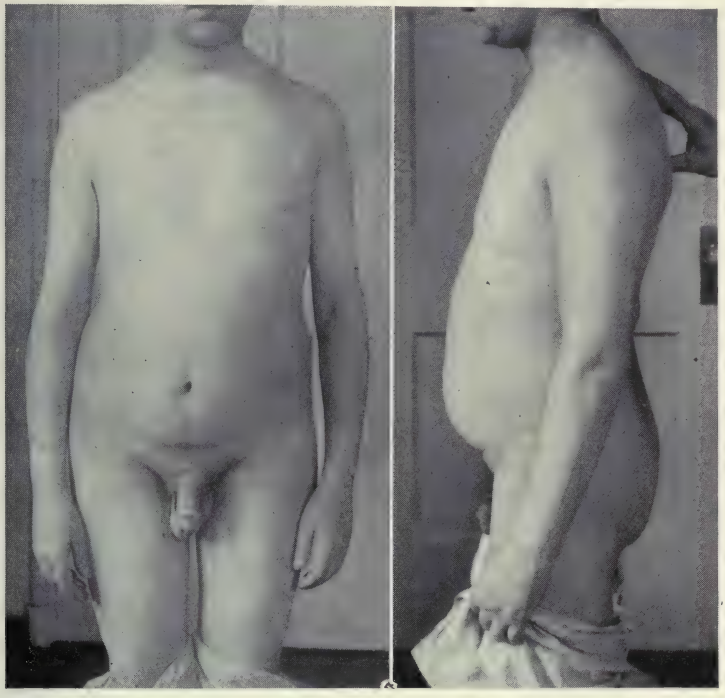


FIG. 90.—Case X. Fields on admission (0.5 cm. discs). Hemianopsia includes macula on left; spares it on right.

The Existing Malady. He associates the onset of the trouble with the first *lowering of vision,* 18 months ago, though it obviously long antedates this period. Six months later changes suggestive of a *bitemporal hemianopsia* were recognized by Dr. Ernest Sachs. These rapidly progressed to the typical bitemporal lesion which, with some fluctuation in its

extent, still persists. There has been no diplopia. *Headaches* occurred and of late have been severe and continuous. For a year he has been extremely *nervous* and easily fatigued. He has become somewhat irritable, worries excessively and becomes exhausted upon the slightest exertion.

For a year or so there has been a noticeable *anaphrodisia* and for the past several



FIGS. 91, 92.—Case X. Showing skeletal configuration and adiposity of *typus femininus* with hypotrichosis.

months he has been *impotent*. He suffers much from cold in spite of frequent subjective "heat flushes." There has been no increase in weight; no polyuria.

A few days after his admission, while gargling his throat and bending over, there was a gush of clear watery mucus from his nose (rhinorrhœa?) with lessening of the headache.

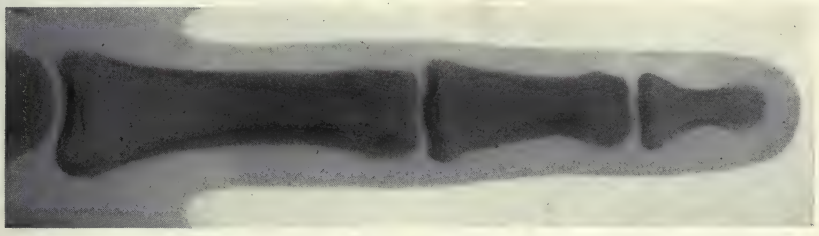


FIG. 93.—Case X. X-ray of middle finger (nat. size). Note epiphyseal lines and infantile terminal phalanges.

Physical Examination. The patient (Figs. 87, 88) is undersized, over-nourished, flabby, feeble. No abnormalities in thoracic or abdominal viscera. Neurological examination negative aside from the changes in the optic nerves and the dispositional peculiarities. No general pressure disturbances.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The X-ray (stereoscopic) shows a marked enlargement of the sella (Fig. 89) which measures about 2 cm. in depth and 2.5 cm. in its antero-posterior dimensions. *Eyes:* Bilateral primary optic atrophy. Bitemporal hemianopsia including the macula on left and sparing it on right (Fig. 90). Acuity left 5/50; right 15/50. Marked photophobia. No exophthalmos; no diplopia. Positive hemiopic pupillary reaction. There is a lowering of olfactory acuity. Rhinorrhœa (?) on one occasion. No epistaxis. Nasopharynx negative.

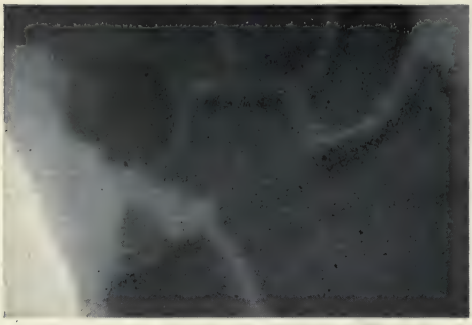


FIG. 94.—Case X. Persistence of cartilaginous epiphyses in patient aged 37. Height 165 cm.

(b) *Glandular Manifestations. Skeletal:* Patient is undersized (5 ft. 5 in.); weight 132 pounds. The body shows the characteristic *typus femininus* (Figs. 91, 92); small extremities, wide pelvis. The hands are peculiar (Fig. 87), pudgy, shapeless, hairless; the fingers long, somewhat clubbed, the terminal pads deficient and the nails curved. The epiphyses are incompletely ossified (Figs 93, 94); feet are small (wears a 5½ shoe); tendency to webbing of toes.

Cutaneous. The skin is dry, soft, velvety, and over the body practically hairless. No axillary and practically no pubic growth. The beard is scant though the hair of the scalp is plentiful. *Adiposity:* A generalized feminine distribution of panniculus, which is abundant over hips, pectorals and pubes. Large supraclavicular pads.

Carbohydrate tolerance not excessive. No great appetence for sweets. Limit for lævulose 150 grams.

Thermic reaction to anterior lobe injection not determined. *Temperature* persistently subnormal (97-98°). Slowed *pulse.* Low *blood pressure,* 115 mm. Hg. No polyuria.

Other Ductless Glands. Thyroid barely palpable. Thymus (?): A definite increase in retrosternal dullness. Some unusual axillary pigmentation. Testes show no abnormality.

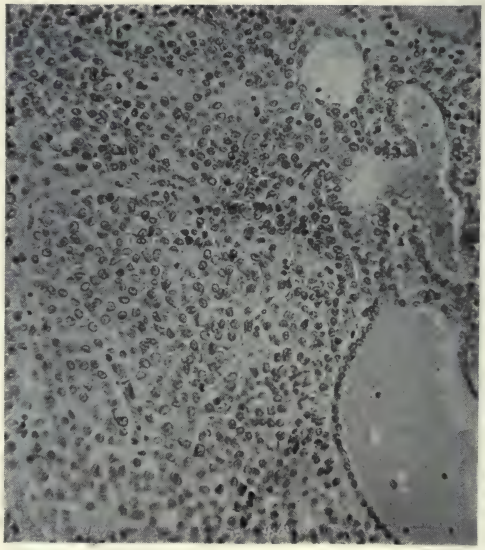


FIG. 95.—Chromophobe struma of Case X (mag. 190 diams.) showing compact cells and colloid cysts.

May 18, 1911. **Operation.** *Partial removal of struma by usual sublabial approach with submucous resection of septum.* The enlarged gland protruded into the sphenoidal cells and was covered only by thin dura and mucous membrane. There was a median small parahypophysis apparent to the naked eye. The soft tumor was under sufficient tension to cause it to extrude through the first incision made in the capsule. There was no bleeding. The operation presented no difficulties. There were no post-operative complications.

On *histological examination,* the fragments removed at operation show (Fig. 95) the usual characteristic struma, made up of closely packed masses of large chromophobe cells having sharply cut vesicular nuclei and a smooth protoplasm which stains indifferently.

On deeply stained sections a few cells are found which show some affinity for the acid stain, but almost without exception they are of the type of neutrophilic elements of pars anterior and pars intermedia, resembling the cells which multiply in the gland during pregnancy. There are many areas which contain an amorphous hyaline material, which may be the

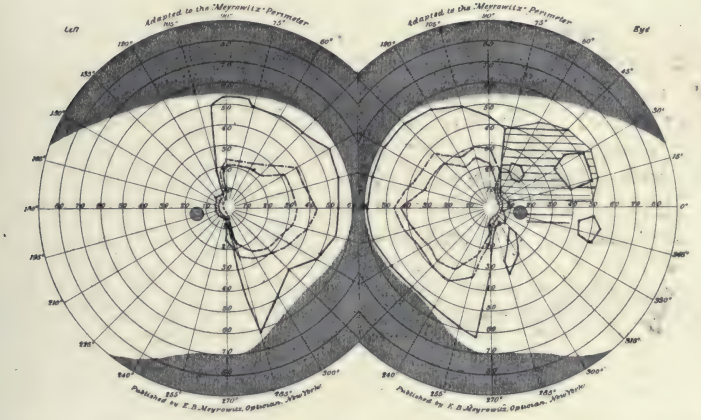


FIG. 96.—Case X. Fields 19 days after operation (0.5 cm. discs). Macula restored on left: vision returning in right temporal field.

product of cellular secretion, and there is one colloid cyst. No mitotic figures are observed. There is practically no trace of alveolar structure or supporting substances of the cell masses.

Convalescence uneventful: usual two or three days of extreme drowsiness. Polyuria of 2030 cc. in the first twenty-four hours, as in the animal experiments. No fever. Subjective improvement in vision.

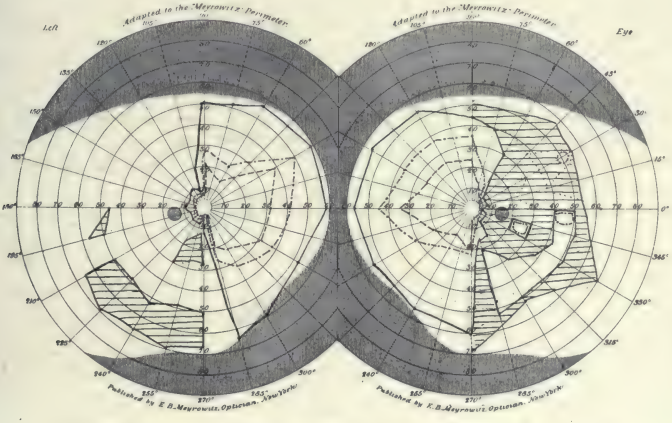


FIG. 97.—Case X. Fields 3 months after operation (0.5 cm. discs).

June 3. Patient can count fingers in each temporal field. Perimeter shows return of vision on the left so as to include macula and there are patches of vision in the right temporal field. *Acuity:* Left 15/40; right 15/30. *Organotherapy:* Two 3-grain pituitary tablets after meals.

June 6. Further improvement in vision. *Fields* (Fig. 96). *Acuity:* Left 15/30;

right 15/20. Photophobia has disappeared. Nasal examination shows an intact median septum; it would be impossible to tell that an operation has been performed. Organotherapy instituted. *Discharged.*

August 1, 1911. Reports for examination. General condition much improved. Complains of neuralgic chest pains. There has been a reawakening of potentio sexualis since taking tablets. *Fields* (Fig. 97) show further improvement.

INTERPRETATION.—This is a very typical example of primary hypopituitarism culminating near middle life, though it is quite probable that a certain degree of hypopituitarism has existed since childhood; enough to modify skeletal growth though not enough to constitute the picture of Fröhlich's dystrophia adiposo-genitalis.

The chief therapeutic indications were surgical ones, to relieve if possible the advancing pressure implication of the optic nerves. Judging from later

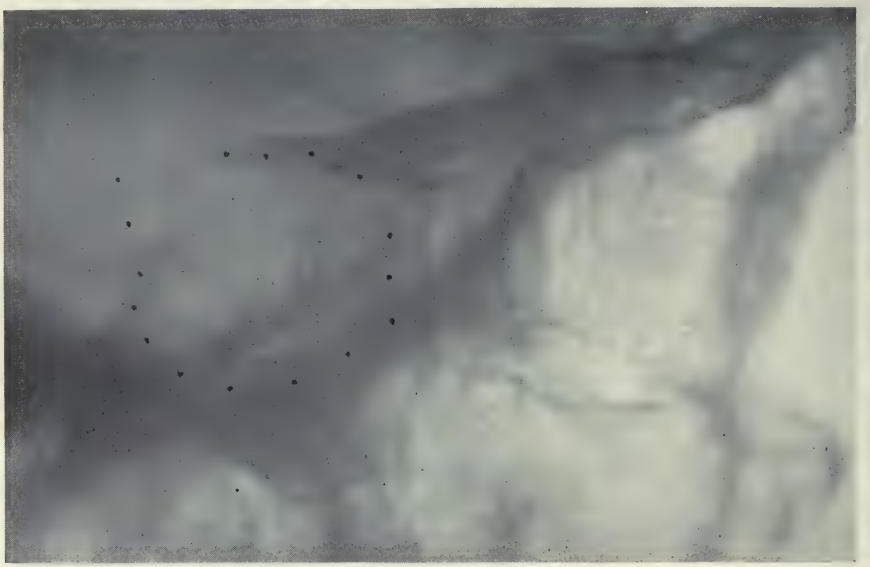


FIG. 98.—Case XI. Radiogram of sellar region (unreduced), showing the practical impossibility of correctly estimating from a single plate the outlines of the distended pocket. Dotted line drawn in from stereoscopic plates.

experiences (cf. p. 321) we should have supplemented the operation with radiotherapy as well as with the therapeutic administration of glandular extracts. The glandular (posterior lobe) deficiency itself was not great, judging from the comparatively low sugar assimilation limit, and the non-progressive augmentation of adiposity. The histological character of the struma places it in a pathological group which comprises the majority of the cases in which it has been possible to secure tissues for examination.

It is to be noted that had the patient been seen a few months earlier, before the optic nerves were seriously affected, the case would have fallen in Group III. We must fully realize, therefore, that as conditions change, these cases will naturally shift from one to another of the groups into which for convenience of the present clinical study we have subdivided them.

The next case resembles more closely Cases II and V in the rapid advance of the tumor growth. When the condition has gone so far as presumably to cause a ventricular hydrops by obstructing the foramina of Monro, thus adding serious general pressure symptoms to those already present, the therapeutic problem becomes desperate enough.

CASE XI. (Surgical No. 27619.) **Large interpeduncular extension of hypophyseal struma of long duration, with pronounced neighborhood and general pressure symptoms. Slight evidence of former overactivity and present definite glandular insufficiency (hypopituitarism). Partial extirpation of tumor. Glandular therapy.**

April 12, 1911. Miss S. E. K., a trained nurse, 36 years of age, referred by Dr. George M. McBean of Chicago. *Complaint:* Amenorrhœa, impaired vision, frontal headaches. Her family history is without note; her health as a child was good.

Present Malady. Since she was 13 years of age she has had frequent "sore throat." A tonsillectomy was performed. At the age of 15 (1890) a "benign" growth was removed from the throat by Dr. Christian Fenger.

Her *catamenia,* which began normally at the age of thirteen, continued until 1901 (aged 28), when they permanently ceased. She subsequently gained greatly in weight (from 115 to 178 pounds).

In 1908 she had a severe pneumonia. In 1909 there occurred a peculiar transitory enlargement of the lymph glands—axillary and epitrochlear. During 1909 she had occa-

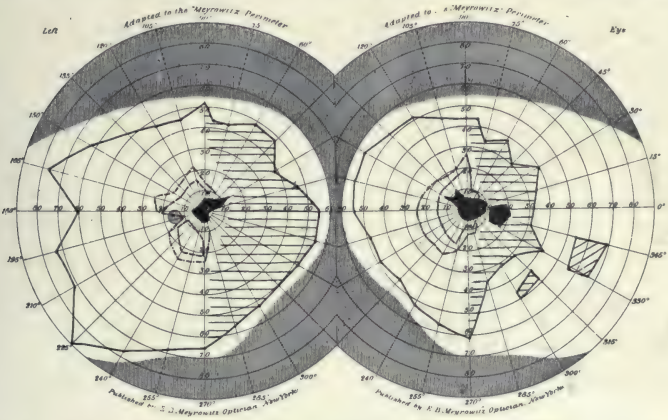


FIG. 99.—Case XI. Fields of April 12th, before operation, showing a tendency toward homonymous hemianopsia.

sional "blinding headaches" with diplopia; relieved for a time by removal of a nasal "polypus," the tissue being pronounced "sarcoma." In July, 1910, purpuric spots appeared over the lower extremities. Curettage of sphenoidal sinus in March, 1910. Three different diagnoses were made, viz., "granuloma," "sarcoma" and "myxoma." Curettage repeated by Dr. McBean April 7, 1910, with temporary improvement in vision.

Suggestive Wassermann reaction February, 1911. Vigorous antiluetic régime instituted. In March, 1911, an X-ray (Dr. Reichman) showed probable hypophyseal tumor. In April another sphenoidal polypus was removed, the laboratory diagnosis being "sarcoma of endothelial variety." She was subsequently seen by many specialists and varying opinions were given.

Failure of vision for the past eighteen months. Choked disc first observed in March, 1910. Reading vision lost for eight months. Apparent bitemporal (?) hemiachromatopsia at one time. Frequent nose-bleeds, occasionally followed by clearing vision. Improvement also occurred after each nasal curettage.

For two or three years she has been exceedingly nervous and irritable. She has nervous shivering chills. Marked dispositional change, with loss of memory and of will power. Frequent crying spells; very drowsy and torpid much of time. Obstinate constipation.

Physical Examination. An overnourished woman with large frame. Height 5 feet 7½ inches; present weight 158 pounds. No abnormalities are apparent in the cardiovascular system or visceral (abdominal and thoracic) organs. Urine negative; no polyuria. Neurological tests are negative aside from the symptoms obviously due to the hypophyseal lesion. Wassermann reaction negative. Blood examination (differential) negative; urine negative.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood Symptoms.* The X-ray (stereoscopic) shows extreme distention and enlargement of the sella turcica (profile diameter 3.5 cm. by 4 cm. in depth). The sellar floor has been destroyed and the growth pro-

FIGS. 100, 101.—Case XI. Profile with prominence of maxillary rather than of mandibular portion of face—the reverse of acromegalic profile.

jects into the sphenoidal cells and nasopharynx. There is merely a ghost of the posterior clinoid region (Fig. 98).

A retropharyngeal examination reveals a tumor partly blocking the right nares. Epistaxis has been frequent and there is a constant discharge from the nares. There is partial anosmia.

There is a bilateral *exophthalmos* with marked dilatation of the venules of the lids. Suggestive von Graefe. *Diplopia* has been present, and a slight lack of parallelism from paresis of the right external rectus is now apparent. The left pupil is slightly larger than the right. The *optic nerves* are seriously implicated. There is a tendency toward a right homonymous hemianopsia (Fig. 99) with central scotomata. (The fields, except for some color interlacing, were normal March 14, 1910). Vision reduced to 5/200 right and left.

(b) *General Pressure Symptoms.* Periods of severe blinding temporal *headaches* with nausea. Tendency to retraction of neck, recumbency bringing relief. *Choked disc* of 2 D. right and 3 D. left, apparently superimposed on a primary optic atrophy; an abundance of new tissue present. Probably some frontal lobe involvement.

(c) *Glandular Disturbances. Skeletal.* No apparent acromegalic changes in the bones. Lower jaw rather undeveloped than otherwise. Upper teeth prominent and widely spaced. No thickness of the tongue. She has noticed an *enlargement of the hands and feet*, and her mother thinks her features have become large and coarse (Figs. 100 and 101)

Cutaneous. The hair has fallen out markedly: an especial loss noted after pneumonia. No obvious general hypotrichosis. Moderate *adiposity:* she has, however, lost 20 of the 63 pounds gained eight years ago following the catamenial cessation. No polyuria or polydipsia.

The *carbohydrate tolerance* is somewhat above normal. Assimilation for lævulose 160 grams; for glucose 350 grams. She has a distinct appetence for sweets. During four days of sugar feeding tests her weight increased from 158 to 163 pounds. A positive *thermic reaction* (97.6° to 99.6° F.) followed the injection of 0.4 gram of anterior lobe extract.

The *temperature* ranges subnormal (97°–98° F.), the *pulse* also (60–80). Blood pressure normal (120–130).

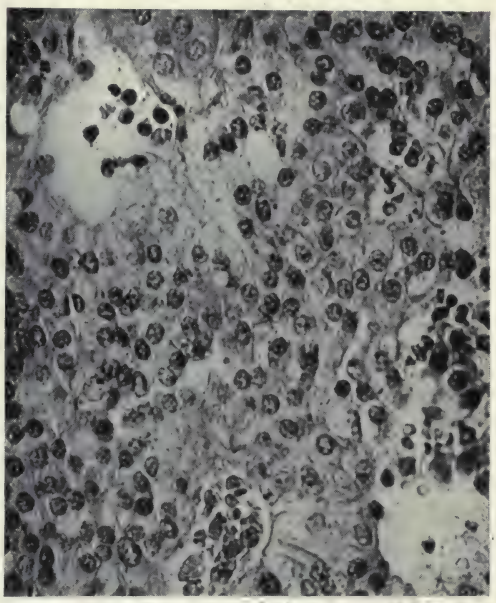


FIG. 102.—Character of chromophobe struma of Case XI (mag. 375 diams.).

Other Ductless Glands. *Thyroid* small, palpable. No increase of substernal dullness. *Ovaries* not palpable (amenorrhoea for eight years). *Adrenal* (?): A definite tendency to ecchymoses. The skin bruises very easily and there is a history of purpura. There was a marked tendency to post-operative bleeding. No pigmentation.

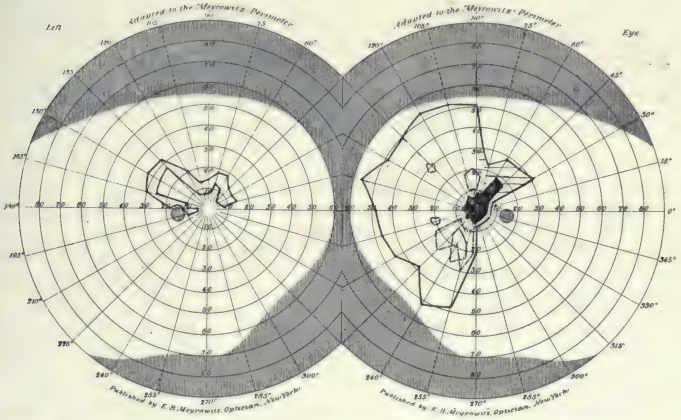


FIG. 103.—Case XI. Fields of May 12th, 3 weeks after operation, showing progressive constriction.

April 20. **Operation.** Usual sublabial approach with submucous septal resection. Large succulent tumor filling sphenoidal cells; sellar base almost completely destroyed. Partial emptying of tumor mass from enlarged sella; small protective drain; urotropin.

The *histological examination* of the tissues removed at operation shows great masses

of faintly staining cells of the neutrophilic type, containing large, sharply cut vesicular nuclei (Fig. 102). No acidophiles seen. In some areas the cells contain small and more deeply staining, less vesicular nuclei, but on the whole they are of the type of those constituting normal pars intermedia.

There was the usual post-operative drowsiness, lasting for several days. No febrile reaction. A marked subsidence of choked disc, with declining vision. Exophthalmos much less.

May 1. Administration of glandular extract begun—18 grains of whole gland extract daily; dosage established on the basis of sugar tolerance.

May 11. Noticeable improvement in mental condition. Subjectively comfortable, though there have been occasional periods of epistaxis, which have left her somewhat anæmic. With the subsidence of the choked disc the left field has become greatly constricted (Fig. 103), with practical blindness. On the right the acuity has lowered to 2/100.

Patient *discharged May 16*, taking 18 grains per diem of whole gland extract. Since its institution two weeks before, the temperature and pulse have ranged normal and there has been considerable improvement in the symptoms of hypopituitarism. No change in the neighborhood symptoms. The *prognosis* as regards further intracranial extension of the growth is most forlorn.*

INTERPRETATION.—This is another case in which a marked glandular "struma," "hyperplasia of chromophobe elements," actual "malignant transformation," or what one will, led to serious general pressure manifestations from actual invasion of the intracranial chamber. The neighborhood disturbances were consequently most pronounced, and there was a suggestive right homonymous hemianopsia which augured ill for the unfortunate young woman.

It is conceivable that there may have been an early transient period of functional hyperplasia of the gland (cf. the suggestive enlargement of the hands and feet, with coarse features, though with no acromegalic osseous changes), but certainly at the time the patient came under observation the evidences of insufficiency were full-blown (cf. the adiposity, amenorrhœa, subnormal temperature, dry skin, positive anterior lobe thermic reaction, increased sugar tolerance, etc.)

It is possible, from a surgical standpoint, that had a wide sellar decompression been performed early in the course of the disease, thus permitting a free downward extension of the struma, it might have served to prevent the bursting inward of the growth through the dural envelope into the interpeduncular space. Vision, at all events, could probably have been saved by an early operation of this type. Certainly under existing conditions surgery can confessedly do little more than scoop out such masses as fill the sphenoidal region and possibly relieve any further serious general pressure disturbances by subtemporal decompressions—not an encouraging outlook.

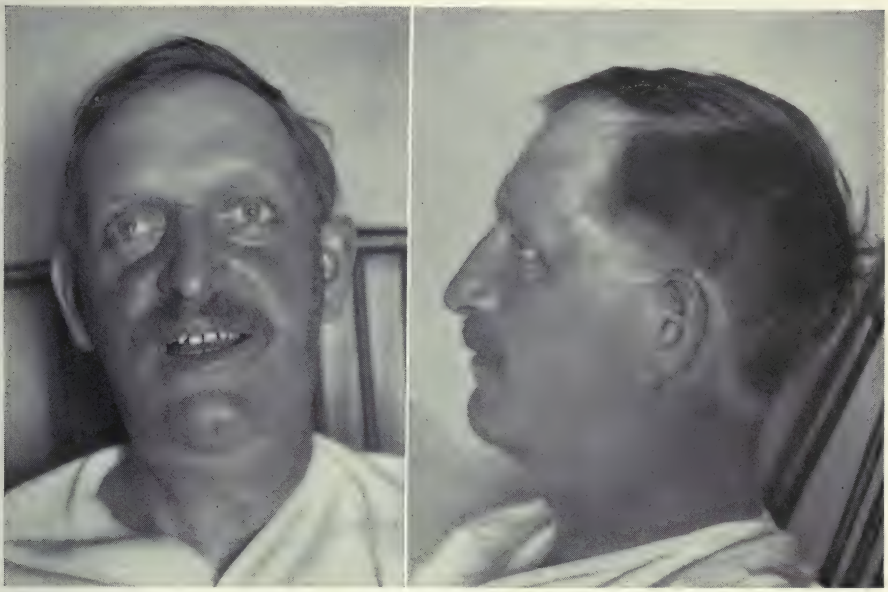
This was the first case in which we were able to determine a rational therapeutic dosage of glandular administration on the basis of the established carbohydrate tolerance. The patient improved considerably under this

* Dr. McBean reported the patient's sudden death on Oct. 20, 1911. Glandular therapy had been discontinued. A *postmortem examination*, limited to the brain, showed an extensive intracranial protrusion of the growth into the descending cornua of both temporal lobes, similar, I judge, to the condition pictured in Figs. 47, 48. A pathological diagnosis of "round-celled sarcoma" was made. It is possible, judging from later experiences, that a post-operative supplementary radiotherapy might have inhibited the further growth of the lesion.

régime, but the rapidity of the growth and the certainty of its further extension into the intracranial chamber make the ultimate prognosis exceedingly grave.

C. **Tumors with Manifestations of Former Glandular Overactivity though Present Underactivity is the Striking Feature.**—The conditions shown in Case XI suggested a possible trace of an acromegalic tendency—namely some enlargement of the hands and feet and thickening of the skin and features. In some of the preceding cases, too, (*e.g.*, Cases I and II) the evidences of former glandular activity were so outspoken as to be the dominant feature of the glandular manifestations.

The two cases which follow are also ones in which signs of present glandular insufficiency coexist with a large glandular struma, but in both patients physical indications of former hyperpituitarism are quite unmistakable. The



FIGS. 104, 105.—Case XII. Note (left) spacing of teeth; strabismus; adiposity: (right) profile with maxillary rather than mandibular prognathism.

first of them shows, perhaps as well as any other case in the series, the drift toward the ultimate glandular insufficiency which is exhibited by many of these individuals in whom some traces of acromegaly show that at the outset there was at least a transient period of hyperpituitarism. They are cases, in other words, of a mixed type—of evident d y s p i t u i t a r i s m .

CASE XII. (Surgical No. 25806.) **An extensive hypophyseal struma occasioning outspoken neighborhood symptoms with dyspituitarism. Evidences of former activity shown by slight acromegalic changes. A present marked functional insufficiency. Sellar decompression with partial extirpation of tumor. Temporary improvement.**

April 20, 1910. J. Van W., a farmer, 36 years of age, referred by Dr. Eugene Riggs of St. Paul. *Complaint:* Loss of vision, adiposity, etc.

He has been a vigorous and hard-working man of good habits. When 16 years of age he was kicked in the face by a horse but was not seriously injured. At 21 he had pneu-

monia, and at 25 typhoid. He has been subject to nose-bleeds "all his life," sometimes having them several times a week. There have been none, however, for the past year.

He has been married seven years and has four children.

Present Malady. He was slight as a young man, with an average weight of 140 pounds. During the past four years he has suffered from frontal *headaches* with occasional nausea and *vomiting*. Diplopia has been present; also much photophobia. There has been a gradual *loss of vision*. There seems originally to have been a bitemporal defect: for six months the right eye has been completely blind. He has grown large and heavy, his weight at one time exceeding 200 pounds.

Of late the headaches have become worse and the vomiting more frequent; nevertheless he has had a ravenous appetite and holds his weight. There have been periods of excessive *polyuria;* also intractable *constipation*. He has complained much of the cold; and dryness of the skin and absence of perspiration have been noted for some time. He has appar-

FIG. 106.—Case XII. X-ray (unreduced) showing large frontal sinuses and greatly distorted sella, the base (??) masked by floor of mid-cerebral fossa.

ently been impotent for a year. At present there is marked *drowsiness* with frequent yawning; also evident *mental impairment*—forgetfulness, delusions and occasional disorientation.

Physical Examination. A light-complexioned, overnourished man with somewhat coarse features (Figs. 104, 105). There are occasions when he responds intelligently, but for the most part he is somnolent, with occasional active irrational periods during which he roams about in disoriented fashion. No abnormalities are made out in his cardiovascular system or visceral (thoracic and abdominal) organs. There is marked muscular enfeeblement.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood.* The X-ray shows (Fig. 106) a great enlargement of the sella with deformation and more or less obliteration of its outlines. *Eyes:* A primary bilateral optic atrophy with right blindness and a left temporal hemianopsia including the macula. The colors interlace (Fig. 107). Visual acuity 9/100. Slight bilateral exophthalmos; a right divergent squint, with nystagmoid twitches. Pharynx not examined. *Epistaxis* frequent. There is *anosmia* and evident *frontal lobe involvement,* shown by loss of memory and power of attention, confusion, disorientation, delusions and untidiness.

(b) *Glandular Symptoms. Skeletal:* Height 5 ft. 10 in.; somewhat round-shouldered. There is little in the patient's appearance to suggest acromegaly, but an X-ray of the hands shows the characteristic changes with marked terminal phalangeal tufts (Fig. 108). The epiphyseal cartilages are fully ossified. The *teeth* are quite widely spaced (Fig. 104). *Cutaneous:* The *skin* is smooth and noticeably dry; the hair somewhat thin. There is a general and widespread *adiposity.*

He is sexually *impotent.* There is *polyuria,* the urinary output usually exceeding the fluid ingested, as: on April 23, output 1710 cc., liquids 1300 cc.; April 24, output 1980 cc., liquids 1400 cc.; April 26, output 2510 cc. liquids 2020 cc., etc. (It was difficult at times to collect the full amount as on his irrational days he was most untidy.)

His *temperature* ranges subnormal (96.6°–97° F.) and the *pulse* averages 70. A positive *thermic reaction* to an injection of 2 cc. of 5 per cent. solution of bovine pars anterior (test April 26 giving a febrile response from 98.6° [rectal] to 101° F.) with marked sweating. A control injection in a normal individual of about the same weight was negative. A posterior lobe injection (April 28) gave no thermic reaction.

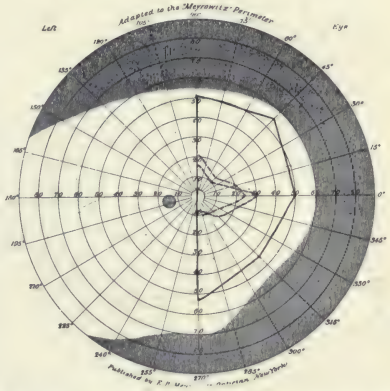


FIG. 107.—Case XII. Field of April 19th, showing hemianopsia including the macular region.

Carbohydrate tolerance somewhat increased. On April 26th 100 grams glucose gave no sugar; on April 27th 100 grams with a coincident injection of 0.1 grains of posterior lobe extract gave sugar on the first specimen. Subsequent to the operation further tests carried out during June established the assimilation limit at something over 225 grams glucose—this being the largest quantity that could be retained.

FIG. 108.—Case XII. Index and middle fingers (natural size), showing typical acromegalic changes.

Other Ductless Glands. Thyroid palpable but seemingly not enlarged. (It proved at operation to be large and colloidal.)

April 30. **Operation.** *Unsuccessful attempt to expose the sella turcica.* After a primary tracheotomy a misdirected approach to the gland was made by the transphenoidal route. The operation was badly conducted and was abandoned after a prolonged and

futile search for the landmarks of the gland. The cervical wound was closed after removing a section of the divided thyroid isthmus.

Convalescence was stormy. There were symptoms of meningitis, a superficial breaking down of the cervical wound and apparently an infected antrum. Under urotropin these disturbances subsided, and in three weeks' time his condition was as before.

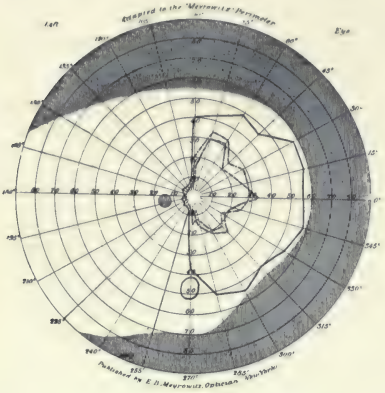


FIG. 109.—Case XII. Post-operative field of June 10th, showing return of macular vision.

May 26. **Second operation.** *Sellar decompression, with partial extirpation of tumor.* First experience without a preliminary tracheotomy. Conditions were more favorable in every respect than at the previous operation, and it was seen that the former approach had been directed too high and the main cavity of the sphenoid not opened. The projecting gland was easily identified; the base of the sella had nearly disappeared through pressure atrophy. The capsule of the gland was slit stellate fashion and a considerable mass of the struma was curetted out—enough, it was hoped, to allow for some settling down of the growth.

The *histological examination* of the hypophyseal tissue removed at operation shows (Fig. 110) closely packed chromophobe cells having a faintly staining protoplasm and large sharply cut, vesicular nuclei. No acidophiles seen. The cells have practically no interstitial or supporting tissue. The thyroid fragment shows excess of colloid.

Post-operative Notes. Recovery on this occasion was uneventful. The patient was subjectively much benefited and there was but one period of headache after the operation (*May 30th*). He became less drowsy and his mind clearer.

After *June 5th* organotherapy was instituted and 9 grains daily of anterior lobe extract were administered, probably an insufficient dosage, though under it his former subnormal temperature became normal. A perimetric chart on *June 20th* showed a return of vision in the blind half of the macular region and a widening of the color fields, but otherwise there was no change (Fig. 109).

He was discharged *June 22d*, with his discomforts apparently much lessened, though his physical state was about as before.

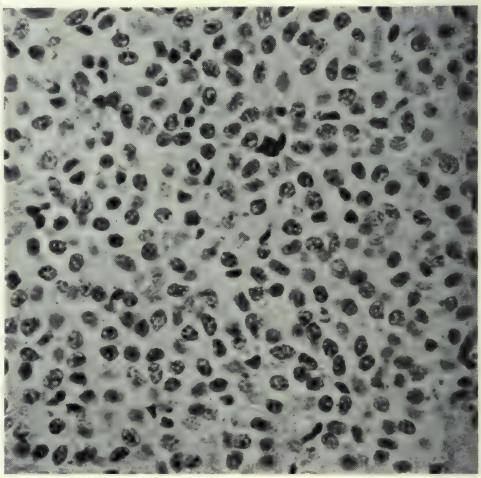


FIG. 110.—Chromophobe struma of Case XII (mag. 375 diams.).

Sept. 23 (three months later). His wife writes: "I can see a decided change and he improves daily. He complains of no pain whatsoever. His right eye has improved quite a bit and he can see much better; the other remains blind. He is taking his medicine regularly and is losing flesh. In fact he is quite a different man." A later note (*August, 1911*) states that he has begun to fail, with a return of headaches and an increase of mental symptoms.

INTERPRETATION.—A case of dyspituitarism with insignificant acromegalic changes corresponding presumably with an early stage of anterior

lobe stimulation, followed by hypopituitarism (adiposity, subnormal temperature, dryness of the skin, polyuria, impotence, increased carbohydrate tolerance, etc.), doubtless associated with the terminal functional insufficiency of the struma. The growth has the same histological features shown in most of the preceding cases of certified primary hypophyseal struma, and has doubtless invaded the cranial chamber to the same forbidding extent disclosed postmortem in Cases II and V and presumably present in Case XI.

It is of course inconceivable that a growth of this character, of this magnitude and in this situation can be entirely removed, but temporary relief, even at such a late stage, can unquestionably be gained by a sufficient sellar decompression even without a fragmentary extirpation of the tumor. It is presumable that an early removal of the sellar base permitting a downward extension of the growth might prevent or at least delay the rupture of the upper dural capsule of the gland and thus serve to save vision and lessen the likelihood of an intracranial invasion by the struma.

The patient was under observation at the stage of our experience with the canine experiments when we laid undue stress on the relation of anterior lobe deficiency to adiposity, and at the time (April, 1910) we considered anterior lobe feeding the essential need in these clinical cases. The interpretation that excessive carbohydrate tolerance is an indication of posterior lobe deficiency had not then been made. This was before the second series of canine experiments with Goetsch. Doubtless there was need in this case of whole-gland administration. The operative procedure, moreover, was just emerging from the earlier elaborate performance with tracheotomy, pharyngeal packing and extensive resection (followed in our first operation—Case XXVI, Group III) to the simpler procedure of the later cases.

The following case is included here, confessedly with some misgivings, in view of the possibility of a primary "fault" of some ductless gland other than the pituitary body. However, a demonstrable enlargement of the sella and the presence of symptoms characteristic of dyspituitarism may justify its incorporation here rather than with the cases in which the gland primarily involved is a matter of uncertainty (cf. the pluriglandular cases of Group V).

Case XIII. (Surgical No. 27784.) **Familial gigantism with adiposo-genital syndrome—obesity and amenorrhœa. Enlarged sella turcica, with oculomotor palsies and epistaxis. Internal hydrocephalus, due possibly to pineal tumor. Post-traumatic cerebrospinal rhinorrhœa. Futile surgical exploration.**

May 11, 1911. Miss M. D., aged 27, single, referred by Dr. E. C. Dunning of Caro, Michigan. *Complaint:* Frontal headaches, "nose dripping," impairment of vision, insomnia, ataxia.

The patient's *family history* is remarkable for the large size of her ancestors on the paternal side. Her father, aged 55, is over 6 feet in height and weighs 250 pounds; an uncle is equally large, and a granduncle, weighing 500 pounds, travelled with Barnum as a giant. She has three younger brothers, all of them considerably over 6 feet and weighing over 200 pounds. The patient herself, the smallest of the family, is 6 feet in height and weighs 180 pounds.

Exceedingly *obese* as a child, she developed slowly in all ways and was never considered strong. She grew rapidly, and at 12 years of age there were a few slight menstrual periods with possibly some signs of aphrodisiac precocity. *Menstruation* ceased after a year and did not return until five years later (age 18). During this interval *epistaxis*

(vicarious?) was profuse. Menses have since been regular. She has suffered from *headaches* since childhood. An amiable and appealing girl, with normal mental activities, she finally gave up attending school in 1903, owing to her intracranial discomforts and progressive physical weakness.

Present Malady. This is attributed to a severe fall down a flight of steps eight years ago (Sept., 1903) causing a *basal fracture.* It is to be noted, however, that for some months previously weakness of the right leg and some dragging of the foot had been observed. This indeed may have led to the fall, in which the fracture of the frontal base was sustained with bleeding from nose and mouth, exophthalmos and orbital ecchymoses: there were ten days of unconsciousness.

From that time there has been a more or less constant discharge of clear, watery fluid, which drips from the left nostril when the head is inclined forward. The fluid escapes at the rate of about 15 drops to the minute. From time to time the flow has ceased, and profound headaches with stupor and opisthotonoid rigidities have followed, which have been relieved by a renewed escape of fluid.

Four years ago vision in the left eye began to be impaired; and 18 months ago an external squint with diplopia gradually appeared. Ever since the injury, furthermore, there has been an increasing disability with unsteadiness and spasticity of the extremities. This, too, is aggravated by any period of cessation of the rhinorrhœa. There is some weakness of the left arm and leg, and marked static ataxia, with a tendency to fall backward and to the right. Habitual constipation.

Physical Examination. An over-tall and overnourished young woman, with an abnormally large and square head and pendulous abdomen. Abdominal and thoracic organs appear normal. No cardiovascular change. Urine and blood normal.

Neurological. There is a definite spasticity of the lower extremities with exaggerated deep reflexes, more active on the left than on the right. There is a slight left-sided (complete) hypæsthesia with lowering of muscle sense and possibly some loss of stereognostic ability. No apraxia. A positive Romberg, with tendency to fall backward (corpora quadrigemina?). Unsteady gait. Loss of superficial abdominal reflex on right. Cerebration slow.

The Cerebrospinal Rhinorrhœa. On several occasions considerable amounts of fluid were collected for examination. A rapid escape, induced by lowering the head, always occasioned a "vacuum" headache, similar to that which ordinarily follows the withdrawal of too large an amount of fluid by a lumbar puncture. Several 100 cc. amounts, however, were obtained, giving reactions of normal cerebrospinal fluid. The fluid contained a pressor substance (posterior lobe) and caused glycosuria when injected intravenously in rabbits (2 cc. in 20 to 1 concentration).

Analysis of the Glandular Manifestations. (a) *Neighborhood Symptoms.* Two possibilities, *hypophyseal* and *pineal,* must be considered. (1) An hypophyseal struma, in view of the enlarged sella (profile measurements 1.7 by 1.3 cm., Fig. 111) could account for the diplopia with third nerve involvement and for the excessive epistaxis; no anosmia; nasopharynx negative. (2) A lesion of the pineal gland could likewise account for the diplopia; also for the static ataxia with falling backward (corpora quadrigemina?), for the left-sided tremor (nucleus ruber?), and similarly for the spasticity and hypæsthesia indicating a greater involvement of the left than of the right pyramidal tract. A tumor in either situation could account for the internal hydrocephalus and secondary optic atrophy, though this is a more probable consequence of a pineal than of an hypophyseal tumor.

(b) *General Pressure Symptoms.* These were in evidence before the injury (basal fracture) and were possibly indirectly responsible for the accident. The former severe headaches have lessened and the choked disc has subsided, coincident with the escape of fluid through the traumatic communication between the dilated ventricle and the left cribriform plate.

(c) *Glandular Symptoms. Skeletal:* The patient's height is nearly 6 feet; weight 181 pounds. The head is large, square, flat, and the forehead is unusually prominent (Figs. 112

and 113). It gives a hollow percussion note. The orbits are noticeably separated. The palatal arch is very wide and low; the teeth badly set but with no spacing. The hands are narrow, rather small; the fingers long and tapering (Figs. 113 and 114): radial epiphyseal

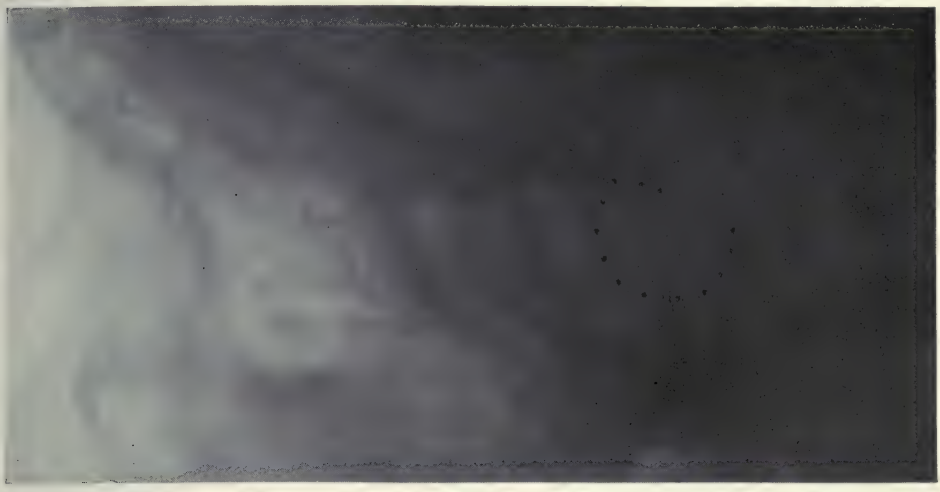


FIG. 111.—Cranial base of Case XIII (nat. size) with slightly enlarged sellar outline indicated by dots.

FIGS. 112, 113.—Case XIII. Note prominent forehead, flat vertex and broad head; also adiposity, divergent strabismus and small hand.

lines still present. The toes are congenitally anomalous and show a tendency to webbing, with rudimentary nails.

Cutaneous. Skin is dry and smooth. There has been a marked thinning of the hair of the scalp, but that over the body (thorax and abdomen) is normal, or possibly in excess of normal. *Adiposity* marked: abdominal panniculus particularly abundant.

Carbohydrate tolerance somewhat increased. Assimilation limit for lævulose 175 grams. Temperature and pulse range slightly below normal: no polyuria.

Other Ductless Glands. Pineal: A suggestion from the history of precocious libido sexualis in addition to the possible neighborhood symptoms. *Thyroid* not palpable. *Thymus:* Retrosternal dullness increased. *Adrenal:* Negative; no pigmentation. Pelvic organs small; *ovaries* not palpable.

May 25 and 31. **Operation** in two stages for exploration of pineal region. A large bone-flap was turned down, exposing the entire postcentral half of the left hemisphere. At the second session the dura was opened and the ventricle tapped. An abundance of fluid escaped: the hemisphere collapsed and it was possible to explore deeply between falx and hemisphere. The splenium was exposed but no pineal growth projected through the tentorial opening under it. Some local venous oozing obscured the field, so as to make

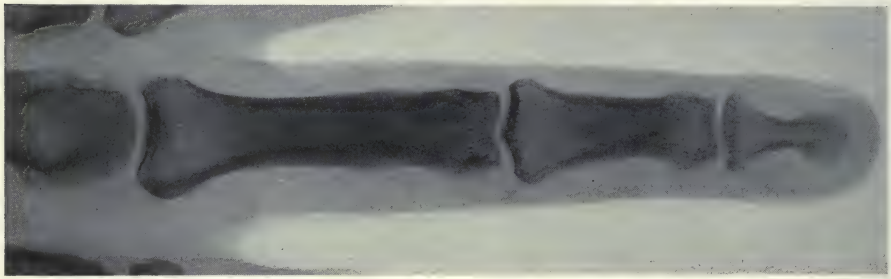


FIG. 114.—Skiagram of middle finger of Case XIII (nat. size).

further investigation hazardous and uncertain. The exploration was inconclusive beyond certifying the ventricular hydrops. Uncomplicated recovery.

Patient was discharged *June 26*, there being no especial change in her pre-operative symptoms. Daily urotropin advised, to ward off as far as possible the chance of a meningeal infection.

Subsequent Notes. *August 9, 1911.* Parents report cessation of headaches, improvement in mental condition, continuance of rhinorrhœa. *October 17.* Dr. Dunning records cessation of rhinorrhœa for previous four weeks, with marked increase of disability and with lowering of vision.

INTERPRETATION AND DISCUSSION.—We have here a case on the borderline of gigantism and, what is rare, one in which there is a familial tendency (cf. Case XXXI, Group III) in this direction. Were it not for the fact that the condition in this young woman verges well on to the field of pathology and that the X-ray shows an hypophyseal hypertrophy, one might not conjecture that the other members of the family owe their unusual stature to a dominant pituitary instability—their gigantism being purely within presumed physiological limits according to the interpretation of Launois and Sternberg.

In spite of the patient's very suggestive overgrowth, we nevertheless, from both a diagnostic and therapeutic standpoint, were between two fires—hypophysis versus epiphysis. The patient's stature, the enlarged sella, the epistaxis and oculomotor palsies were suggestive of a pituitary hyperplasia of sufficient size to give neighborhood symptoms. However, the internal hydrocephalus, with enlarged head and secondary optic atrophy, is an unusual and even then only a late consequence of a growth in this situation.

On the other hand, none of these symptoms, except the enlarged sella, are foreign to the syndrome of a lesion in the neighborhood of the corpora quadrigemina, such as a pineal (secondary or primary) tumor or hyperplasia could produce. Indeed, other neurological disturbances speak in favor of this region, and even the cerebrospinal rhinorrhœa is not against it. The single example of a brain from a patient who had been afflicted with rhinorrhœa which I have had the opportunity to examine (one in the possession of Dr. Adolph Meyer) shows a tumor of the pineal gland, there being communication between the nares and the anterior horn of the dilated right ventricle through a small opening in the right cribriform plate. There is no history of the case other than that the patient died of meningitis—the usual outcome of long-standing rhinorrhœa.

In the discussion of a subsequent group of cases (Group IV) it will be pointed out that the secondary hypophyseal disturbances—usually on the side of functional hypoplasia—become evident with most intracranial lesions which are accompanied by a long-standing obstructive hydrocephalus. In one instance (Case XLVII) the hydrocephalus, as in the case under discussion, was thought to be due to an enlargement of the pineal gland. Under such circumstances, however, the hypophysis is usually found compressed and flattened, not hypertrophied as in this particular patient. If, therefore, the possibility of a pineal tumor must be accepted in spite of the negative operative findings the lesion may represent either a secondary hyperplasia or a primary congenital tumor which is undergoing enlargement.

It is noteworthy that this patient showed what possibly may be interpreted as an indication of precocious adolescence, a condition which Marburg[176] and Frankl-Hochwart[88] are inclined to attribute to some form of pinealism. However, there are some features of the cases which they have reported, notably the adiposity, which lead me to believe that hypophyseal symptoms secondary to the hydrocephalus are confused with what may possibly be other symptoms actually of primary pineal deficiency. Moreover, as may be recalled in this connection, a number of our partially hypophysectomized dogs (posterior lobe removal) subsequently exhibited astonishing manifestations of sexual excitation.[53]

At the time of his notable monograph[249] on cerebrospinal rhinorrhœa published in 1899, St. Clair Thomson assembled the reports of a number of cases from the literature. In one of these cases (Horner's) there was a coexistent primary optic atrophy, and in view of the postmortem findings of a pituitary tumor in another case (Gutsche's), Thomson was inclined to attribute the rhinorrhœa in his patient to the same cause and suggested that in all of these patients the symptoms were possibly due to a pituitary tumor—unquestionably too sweeping a conclusion. Needless to say, these cases were all reported before the introduction of the X-ray as an aid to the diagnosis of an hypophyseal tumor.

From a therapeutic standpoint it was difficult to determine what, if anything, could be done in a surgical way for this unfortunate girl. The first indication was to afford some relief, if that were possible, for the hydrocephalus which unquestionably antedated the basal fracture and for the cerebrospinal rhinorrhœa which succeeded it. The attempt was a failure, the operation accomplishing nothing more than the certification of the existence

of the ventricular hydrops. It was inconceivable that a sellar decompression could modify the hydrocephalus in any way, and though it might have given some relief to the local neighborhood symptoms, these, in the absence of direct pressure on the optic nerves, were, as a matter of fact, not particularly distressing. The procedure, furthermore, would have been attended by a greater risk than usual of a meningeal infection, owing to the open communication between cerebral ventricle and ethmoid cells.

GROUP II. CASES WITH PRONOUNCED NEIGHBORHOOD BUT RELATIVELY INCONSPICUOUS GLANDULAR SYMPTOMS

We now come to a group of patients in whom the local pressure effects of tumor upon the adjacent structures in the interpeduncular space so far predominate as to render the evidences of functional pituitary involvement relatively inconspicuous. Indeed, had the clinical recognition of states of lessened glandular activity not been made possible by the results of experimental extirpation, the unobtrusive manifestations of dyspituitarism shown by these individuals would doubtless have passed entirely unnoticed.

Needless to say, any long-standing and slowly growing tumor of whatever sort in the interpeduncular region will in the course of time elicit characteristic localizing symptoms, whether or not the growth primarily arises from the pituitary body itself. In one certified instance (Case XVII) the lesion proved to be a benign growth arising presumably from a congenital pituitary anlage and resembling the lesion disclosed postmortem in a case already described (Case III); and in two other instances (Cases XVI and XX) the lesion though uncertified is presumably of like nature.

The seven other cases in this group are all of a similar type with a form of primary hypophyseal struma or hyperplasia (histologically certified in all but two—Cases XIV and XVIII) with sellar enlargement as the characteristic telltale of the lesion. No sellar distortion need accompany the extrapituitary (infundibular) tumors, on the other hand, though all other neighborhood signs are equally outspoken in both conditions.

In considering this particular group of cases, moreover, it is to be recalled that the present clinical subdivision of these patients is based upon the symptom-complex which each presented at the time of coming under observation. And inasmuch as, with three exceptions, all of them have been seen within a period of two years, this tentative classification fails to take into account the progressive nature of the disease.

Unquestionably in many individuals the process becomes stationary after a temporary functional over- or underactivity of the gland which nevertheless has sufficed to give clinically recognizable symptoms. In others it slowly progresses toward ultimate unmistakable hypopituitarism; and this, as I have already emphasized, seems to be particularly true of the cases in which there is a progressively enlarging adenomatous struma.

It is fully appreciated, therefore, that there are individual examples placed at present in this group which in the course of time will exhibit more outspoken clinical manifestations of glandular insufficiency. Hence their redistribution under this scheme of classification will in all probability be necessary in a few years. Indeed, in the short time since these patients

first came under observation for their tumor symptoms alone, evidences of hypopituitarism in some of them (Case XVIII for example) have become sufficiently pronounced to make, even now, the propriety of their retention in this group debatable.

It is noticeable that with one exception (Case XIV) the neighborhood, symptoms appeared at about the same age—in the vicinity of 30—in all of these patients. Though it will be pointed out that three of them (Cases XVII, XXI and XXIII) exhibit some skeletal evidences of primary hyperpituitarism (possibly dating from adolescence in Case XXIII), nevertheless the inconspicuous glandular manifestations in all show a present tendency toward hypopituitarism. Consequently such subdivisions of this group as were adopted in considering Group I need hardly be observed, and the cases therefore will be numbered chronologically, the better to appreciate the therapeutic advances which have been made. For it is in this group of cases that the results of sellar decompression are most encouraging, particularly in so far as preservation of vision is concerned.

The first three cases were observed before our experimental studies had given us any especial grasp upon the maladies under consideration, and consequently before we had learned to appreciate certain of their more essential clinical manifestations. However, the histories, though incomplete, contain matters of sufficient interest to justify their inclusion in the series.

The following case was incorporated, together with Case III, in my early report[55] as an instance of the combination of optic atrophy and sexual infantilism. The symptoms date from the adolescent period, which, as will be noted, was preceded by three severe illnesses. The history, from our present standpoint, is lacking in many details, but the following data have been culled from it:

Case XIV. (Surgical No. 17470.) **Hypophyseal struma (uncertified) with primary optic atrophy and amenorrhœa. Uncinate attacks. Subtemporal decompressions.**

March 11, 1905. Miss D. W., aged 26, a saleswoman, referred by Dr. W. C. Galloway, of Wilmington, N. C., through Dr. Hiram Woods. *Complaint:* Headaches and loss of vision.

Patient was well during her childhood except for severe typhoid at 10, measles at 11 and pneumonia at 12 years of age. She had a *single menstrual period* at 14, and subsequent examinations have shown an undeveloped uterus. There has since been an occasional watery discharge from both breasts but no vicarious menstruation: no epistaxis.

At 16 she began having more or less constant *headaches,* which have been severe for the past five years: no nausea or vomiting. There has been a gradual *loss of vision,* and she has been blind in the left eye for 4 years. For the past 3 years she has had frequent "dizzy spells" accompanied by hallucinations (seeing animals) and a sense of unreality (uncinate?). Never any loss of consciousness. There is an occasional discharge of offensive mucus "which drops in the back of her throat."

Physical Examination. A well-nourished, healthy-appearing young woman with a good color. Abdominal and thoracic viscera negative. Cardiovascular system negative. Infantile pelvic organs.

Analysis of the (Recorded) Hypophyseal Manifestations. (a) *Neighborhood.* No X-ray at this time (cf. *infra*). *Eyes:* Slight exophthalmos; slight divergent squint; bilateral primary atrophy; blindness complete in left eye. Fields of right eye, taken for form alone, show an upper temporal defect (significance not then appreciated). Acuity 20/30. Olfac-

tory sense impaired: complete right anosmia. No epistaxis. Suggestive uncinate symptoms (cf. *infra*).

(b) *General Pressure Symptoms.* Severe bitemporal headaches (probably from glandular distention rather than from general pressure). No choked disc.

(c) *Glandular Symptoms.* She has a small skeletal frame; height not recorded, weight 125 pounds. Hands delicate; fingers tapering. There is definite mental instability: she is excitable; lachrymose.

Cutaneous. Skin smooth, with a colorless, waxy appearance; some bogginess of the subcutaneous tissues (œdema or adiposity?). Panniculus abundant. Hirsuties normal. Mammary glands developed. Complete amenorrhœa.

Temperature ranges from 97° to 98°. *Pulse* slow, occasionally below 60.

March 14, 1905. **Operation.** A bilateral subtemporal decompression was performed in the hope of relieving the intracranial discomforts. It was followed by some measure of subjective relief, cessation of headaches and improvement in vision.

FIG 114*a*. Case XIV on second admission (1912). Note maxillary prognathism; peculiar pudgy hand; lack of parallelism in globes.

A year later, *May, 1906*, she returned for observation. An X-ray (Dr. Baetjer) at this time showed a greatly enlarged sella. The contracted field in the seeing eye (right) had widened. Her vague dizzy spells were accompanied by a disagreeable gustatory impression—the "taste of blood"—typical *uncinate attacks* without loss of consciousness.

Later Notes. A gynæcologist subsequently performed a double oöphorectomy and appendectomy. I have been privileged to examine the sections. The *appendix* is normal but shows an extreme lymph hyperplasia. The *ovaries* show a great number of cysts, visible to the unaided eye. Some of these cysts contain shreds of membrana granulosa. There are no perfect vesicles: no primordial ova or Pflüger's tubes: stroma in excess.

Three years later (*February, 1909*) patient reports by letter a continuance of original symptoms.

After five years (*August, 1911*) Dr. Galloway reports that her uncinate attacks have become more typical and often end with a general seizure and unconsciousness. She has

gained 20 pounds in weight. Exophthalmos and strabismus are more marked; skin sallow and dry.*

COMMENT.—It is appalling that as recently as six years ago there could have been any doubt as to the primary hypophyseal implication in this, at the time regarded as an obscure, case. It goes to show, furthermore, how it is that women suffering from these maladies come to frequent gynæcological clinics, complaining of amenorrhœa and adiposity with headache and vague nervous symptoms. Not a few of them become the victims of an exploratory laparotomy and actual oöphorectomy, for, with an open abdomen, some surgeons cannot resist the impulse to guillotine some organ on the chance that it may be the culprit.

Though gynæcologists have been guilty of this, the offense is not confined to them alone, for many of us have unquestionably looked at the *syndrome pluriglandulaire* of hypophyseal origin through the wrong end of the telescope. This case would have been a most favorable one for sellar decompression and subsequent organotherapy.

The experience in the foregoing case showed that decompression over the vault can hardly be expected to lessen the pressure disturbances of an hypophyseal growth in so far as they affect the optic nerves. Hence we were beginning to think seriously of the possibility of a direct surgical attack on the tumor itself in these conditions when the following patient presented himself. It is fortunate perhaps, in view of the aneurismal complication, that he did not accept our hesitating suggestion that an operation might be advisable.

CASE XV. (Surgical No. 20902.) **Temporal headaches; primary optic atrophy with quadrantal hemianopsia. Symptoms of dyspituitarism unrecognized. No treatment. Sudden death after four years. Autopsy. Hypophyseal struma associated with an interpeduncular aneurism.**

June 16, 1907. C. P. R., a blacksmith, 31 years of age, referred by Dr. Herbert Harlan, with the *complaint* of temporal headaches and loss of vision. He has always been a stout, vigorous man and weighs 198 pounds. There is no specific history. He has been married seven years and has two healthy children, aged five and six.

For four years he has been suffering with severe right temporal *headaches* and for some months vision has been failing in the right eye. Three years ago he was troubled with *nose-bleed*, which was brought on whenever he blew his nose. He has managed to keep at work in spite of his discomforts.

Examination shows the right pupil larger than the left with no consensual reaction from left to right. Vision in the right eye 15/200; in the left 15/20. The visual fields show a right lower nasal quadrantal defect with total loss for colors; left eye normal. There is slight exophthalmos on the right.

A tentative diagnosis of an interpeduncular growth was made, but *no X-ray* was taken. (At the time the patient was seen our attention had not been called to the nutritional disturbances accompanying these conditions and the history contains no notes bearing on them.)

January 17, 1911. (Four years later.) The patient had been lost sight of until, on this date, his physician, Dr. J. C. Pound, notified us of his sudden death and secured

*The patient re-entered the hospital February, 1912, owing to increase in pressure symptoms. A transphenoidal operation was performed, with partial removal of a chromophobe struma of the usual type (cf. No. 2 of operative table, page 308).

permission for an examination. The following further notes were secured at this time from his wife.

A vigorous course of "specific treatment" was instituted without avail, and he became a Christian Science devotee, refusing further medical attendance. There was a progressive *failure of vision*, and for the past two years a total blindness in the left eye with a marked lowering of acuity in the right. No oculomotor palsies were observed.

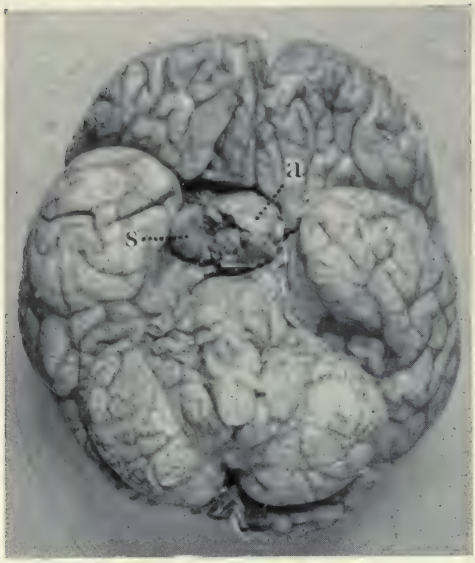


FIG. 115.—Case XV. Showing the hypophyseal struma (*A*) and adjacent aneurism (*S*).

In 1910 he began having especially severe *headaches and nausea* with attacks of *vomiting*. He became exceedingly *drowsy* and would fall asleep on the slightest provocation, often while eating his meals. He was very forgetful and oblivious of his surroundings. He had attacks of dizziness and staggering.

In spite of his discomforts and almost total blindness he continued at work until two days before his death: at that time he had an exceedingly severe headache, with vomiting, dizziness and staggering, and was brought home by his fellow-workmen. He recovered sufficiently to go to the doctor's office a few blocks away; he secured some headache tablets at a drug store, returned home and lay down in a stuporous state, from which he did not awaken.

Autopsy. (*Jany. 18, 1911*). Brain removed without hardening: sphenoidal bone not secured. A solid *tumor* the size of a pigeon's egg occupies the interpeduncular region (Figs. 115, 116). To the right of the tumor is an *aneurismal sac*, measuring about 1.5 cm. in diameter. This sac has evidently been ruptured during removal of the brain. On lifting the tumor from its bed it is seen that the optic chiasm and tracts have been pushed far to the left side, so that a *left homonymous hemianopsia* must certainly have been present (cf. Cases II and V) at some stage of the malady, though when he was examined the defect involved the lower nasal quadrant of the right eye alone. His wife's statement that vision was first completely lost in the left eye is substantiated.

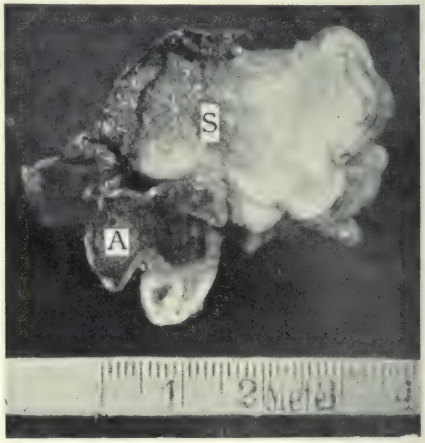


FIG. 116.—Case XV. Transverse section of struma (*S*) and aneurism (*A*). (Nat. size.)

Owing to the manner in which the brain was removed, it is impossible to tell just what were the connections of the aneurismal cavity with the carotid arteries. There is no general nor cerebral arteriosclerosis. The abdominal and thoracic viscera are practically normal in gross appearances. No macroscopical changes of note in the ductless glands.

On *histological examination* the *hypophyseal struma* proves to be of the usual type, (Fig. 117) with masses of large, faintly staining cells containing sharply cut vesicular nuclei.

The cells are purely of the chromophobe type, resembling those of normal pars intermedia. The tumor abuts against the adjoining aneurismal sac with practically no intervening capsule.

Sections of the *liver* show an extreme fatty change. The *adrenals* are practically normal. The *thymus* is represented by mere shreds of involuted thymic tissue, containing an occasional Hassall corpuscle. The *testes* show normal tubules and spermatozoa but no interstitial cells which can be identified as such.

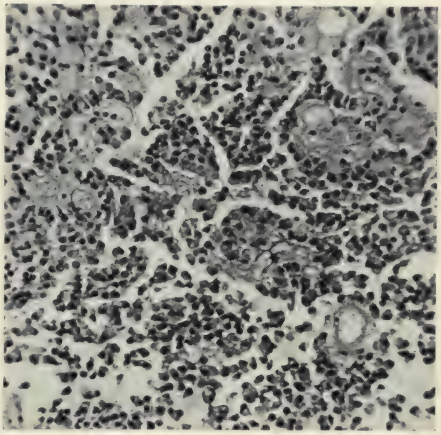


FIG. 117.—Chromophobe struma of Case XV. (mag. 190 diams.).

DISCUSSION.—The chief interest here concerns the adjacent aneurism, and it is impossible to tell which of the two lesions—the struma or the aneurism—was primary or whether they were merely of accidental coincidence. The latter would seem unlikely, not only in view of the comparative rarity of each condition alone, but also in view of the absence of arteriosclerotic disease elsewhere. To be sure, intracranial aneurisms may occur without signs of generalized vascular disease, and this seems to be particularly true of those that have been found in the interpeduncular region.

We have seen in Cases II and V that when an hypophyseal struma bursts through the enveloping dural capsule it is apt to do so to one side, toward one of the cavernous sinuses, and thus may come to completely envelop the carotid artery (cf. Fig. 47). Such an extension of the struma has evidently occurred here, as certified by the homonymous hemianopsia as well as by the postmortem findings; and it is not impossible that the arterial wall might have become weakened and absorbed by pressure, just as the dura must have been, and as bone may be even without any direct cellular invasion by the growth. This seems the most likely explanation.

On the other hand, an aneurism may actually play the same rôle as an interpeduncular tumor and by its compression effects cause outspoken hypopituitarism. Such a case is now under our observation—a patient referred by Dr. W. S. Thayer. He has arteriosclerosis, bitemporal headaches, bilateral primary optic atrophy, and the constricted fields show a tendency toward bitemporal hemianopsia. Moreover, he is rapidly growing stout, and has a subnormal temperature and pulse. However, as the lesion has not been certified and as the X-ray is negative, the case hardly deserves a more detailed recital.*

The chief interest in the following case lies in the prolonged periods of stuporous sleep, for although drowsiness and inactivity, apart from the ter-

*Comment will subsequently be made upon Lyon's excellent monograph, entitled "Adiposis and Lipomatosis," in which 20 personally observed instances of pathological adiposity are recorded. Dr. Lyon has since written to me (Dec. 1, 1910) in regard to Case VI of his series—an old man who had become extremely obese after 55 years of age. At autopsy an aneurism the size of a pea, arising from the cavernous portion of the left internal carotid artery, was found in direct contact with the pituitary body. The gland was said to be normal. The pubic, axillary and facial hair was scanty, and the testes extremely atrophied.

minal asthenia, are not unusual in the canine after experimental hypophysectomy, and are common likewise in the clinical cases, such an extreme degree of the condition is unusual.

CASE XVI. (Surgical No. 22665.) **Chronic (stationary) hypopituitarism in an adult. Infundibular tumor (uncertified) with adiposity, hunger phenomena and long periods of stuporous sleep. Marked neighborhood symptoms. Subtemporal decompression. Oganotherapy.**

July 15, 1908. Mrs. A. B. W., 56 years of age, referred by Dr. E. B. Fenby, with the complaint of severe headaches and excessive drowsiness.

Her family are all of a nervous temperament. She was not strong as a child: pleurisy at 29. She has had seven children, only three of whom are living.

Present Malady. Her symptoms are said to have been present for twenty years, since the birth of her last child, when she was very ill with phlebitis, etc. She has since suffered greatly from "nervousness" and from *headaches* which or a time, 14 years ago, were often accompanied by vomiting—"sick headaches." It was at this time that her eyesight began to fail. There were periods of *diplopia* and subsequently *blindness* in the left eye.

Eight years ago the *pelvic organs* were removed *in toto*, upon the advice of a gynæcologist, who regarded her disorder as purely hysterical.

Almost from the outset there have been remarkable recurrent periods of somnolence. The longer periods are said to have occurred, in recent years, only during the winter months, though the history does not bear out the suggestion that they are invariably seasonal (*vide* her present attack). She was under Dr. Fenby's observation during the most recent period which lasted from October, 1907, to February, 1908. During this time she actually gained in weight.

Her daughter affirms that the average duration of the sleeping periods is from four to five months each year. When in this state she will often sleep without arousing for thirty-six hours at a time. She then becomes restless and awakens sufficiently to partake ravenously of food and immediately falls asleep again. During her waking intervals she shows a nervous activity which is most wearing to her family. She has had antiluetic treatment without avail.

When first seen (at her home July 15, 1908) she was observed to be a short, overstout woman, lying on her right side in a profound sleep, which was said to have lasted since June 1. By shaking her it was possible to arouse her sufficiently to make her open her eyes and protrude her tongue: she immediately relapsed into a deep sleep.

The *physical examination* at the time revealed little beyond a bilateral optic atrophy, an oculomotor palsy, subnormal temperature, slow pulse and active reflexes. In view of the history it was conjectured that there was an infundibular growth. She was transferred to the hospital. There the X-ray shed no additional light on the condition. Wassermann test was negative.

July 17, 1908. **Operation.** A right subtemporal decompression was performed, disclosing no unusual tension. There were no operative difficulties: no post-operative complications. On July 30 she was discharged, "unimproved."

Not until a year later were suspicions aroused as to the probable existence in this patient of actual hypopituitarism. She has been examined anew from this standpoint, and the following glandular symptoms may be assembled:

Analysis of Hypophyseal Symptoms. (a) *Neighborhood.* An X-ray, February, 1911, by Dr. Deetjen, shows with particular clearness, owing to the decompressive opening, a normal sella. Superimposed, however, is the quite unmistakable shadow of an interpeduncular tumor. *Eyes:* There is a palsy of the right external and superior recti with a marked convergent squint. The left pupil is smaller than the right and does not react. There is a bilateral secondary optic atrophy, more marked on the left than right with a considerable upheaval of connective tissue: no œdema at present. *Fields:* Left, amaurosis complete; right, some constriction of the lower nasal field. Nasopharynx negative. No epistaxis. No uncinate symptoms.

(b) *Glandular Symptoms.* Skeletal frame small. Patient is short (5 ft. 3 in.), with a widespread adiposity, and weighs 168 pounds. The skin is dry, smooth and has always been notably free from perspiration: no pigmentation. The hair of the head is thin: not at all gray.

Temperature (rectal) ranges subnormal (97°–98°). Pulse also subnormal (66–70). There is polyuria (1700 to 2500 cc.): urine of low specific gravity (1010). No *carbohydrate tolerance* tests made.

Since February, 1911, she has been taking hypophyseal extract (whole gland: gr. 15 daily) combined with an equal dosage of thyroid extract. Under this treatment she has lost some weight; her temperature averages a degree higher than before; she has shown no tendency toward drowsiness. It remains to be seen what her condition will be under the organotherapy during her usual winter period of "hibernation."

COMMENT.—The extraordinary periods of somnolence exhibited by this patient are possibly nothing more than an exaggeration of the tendency to drowsiness shown by many others; for a number of them, apart from the

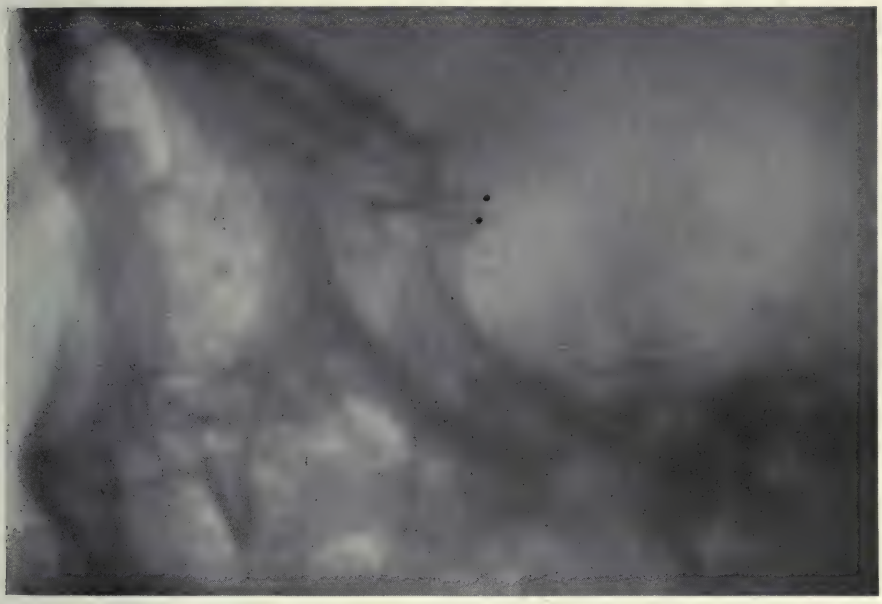


FIG. 118.—Case XVII. Showing complete destruction of sellar outlines. Dots on anterior clinoid processes.

stupor of increased intracranial tension, have been abnormally heavy sleepers.

It is of interest that Salmon,[237a] among other factors such as auto-intoxication, vascular stasis from intracranial tumor and the like, considers that pituitary diseases, whether from overaction of the gland or stimulation of the infundibulum, the floor of the third ventricle or some neighboring centre, must be regarded as an important causative agent in sleep. Purves Stewart[240a] has reported cases in which pathological drowsiness was a striking feature, and seems inclined to attribute it to an upward pressure on the infundibulum.

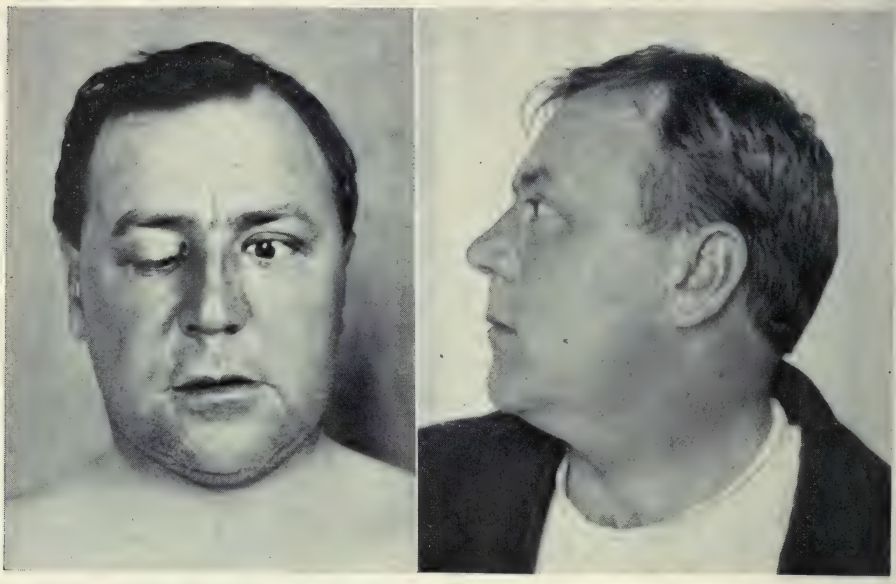
The temptation is strong to dwell upon the similarity between physiological states of hibernation and these peculiar pathological states of somnolence which are accompanied also by a subnormal temperature, slow pulse and retarded tissue oxidation (cf. p. 233). Drowsiness, it may be recalled,

is a common feature of states of experimental hypopituitarism, and there may be such a thing as a normal physiological period of glandular inactivity.

CASE XVII. (Surgical No. 24773.) **Large interpeduncular tumor (teratoma) with pronounced neighborhood symptoms overshadowing unmistakable evidences of dyspituitarism. Direct pressure involvement of the hypophysis. Two transphenoidal operations. Death. Autopsy.**

Oct. 5, 1909. J. M., a steam-fitter, aged 35, was first admitted *complaining* of headache and loss of vision. He has been a vigorous and athletic man of good habits, and is one of a large family of healthy children. He has been married seven years, and has three children, aged six, four and one year respectively.

Present Malady. Four years ago he suffered for six months from severe frontal *headaches* with occasional *vomiting*. During this period his *vision* began to fail, first in the



FIGS. 119, 120.—Case XVII. Showing (left) oculomotor palsy: patient attempting to look downward. Note (right) characteristic profile with maxillary prognathism.

left eye. There was left ptosis and diplopia. Since then the headaches have lessened, but the loss of vision has progressed, the right eye becoming affected secondarily, though with more rapid progress. The history suggests a period of bitemporal *hemianopsia*. Ocular movements have become affected in both eyes. During the past few months there has been a complete loss of libido et potentio sexualis. He has gained 27 pounds in weight.

Physical examination shows a stout, overnourished man of 5 ft. 6 in., weighing 214 pounds. He is powerful and muscular and shows no loss of physical strength. There is no arteriosclerosis. Wassermann test is negative.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The *X-ray* shows practically complete absorption of all sellar landmarks (Fig. 118). *Eyes:* There is an extensive bilateral oculomotor palsy with ptosis (Fig. 119). On the left there is total paralysis of the inferior rectus and oblique and of the superior rectus; on the right, of the external and inferior recti and both oblique muscles. The pupils are widely dilated and without reactions. The discs show a marked primary *atrophy* with superimposed choking—swelling of 1 D.—perivascular striations, new tissue formation and pigment up-

heaval. *Fields* show a complete blindness in the right eye and but a small area of retained central vision (Fig. 121) in the left; acuity 5/80.

There is complete *anosmia* and uncertain gustatory perception. Patient complains of *neuralgia* in the left trigeminal area. There is a suggestion of frontal lobe impairment (?), shown as a loss of inhibition, for he is lachrymose and over-hilarious in turn: loquacious and irrelevant. There is no disorientation, but he has been irritable and forgetful. There are no definite uncinate symptoms. In the vault of the pharynx and extending backward from the arches of the posterior nares there is a protrusion suggesting a vascular tumor. No history of epistaxis or nasal discharge.

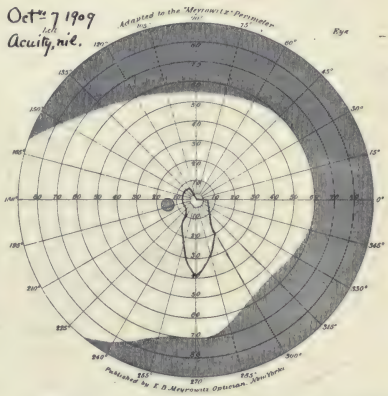


FIG. 121.—Case XVII. Field of remaining vision, 5 days before operation. Complete achromatopsia.

(b) *Glandular Manifestations. Skeletal:* Though the face, extremities and thorax show no outspoken change suggestive of acromegaly, the hands, however, are square and an X-ray betrays characteristic though incipient changes in the bones (Fig. 122). No epiphyseal lines are visible. There is a slight tendency to anterior position of the lower jaw and the tongue is over-large. There is no spacing of the teeth.

Cutaneous. Skin is smooth and of late there has been a noticeable lack of perspiration. There is no hypotrichosis but rather the reverse. A brownish pigmentation over face and hands. There is an overabundant and generally distributed panniculus (Fig. 123), the adiposity having been rapidly acquired during the past six months.

Other Ductless Glands. Thyroid palpable; possibly enlarged. No testicular atrophy, though he has become impotent.

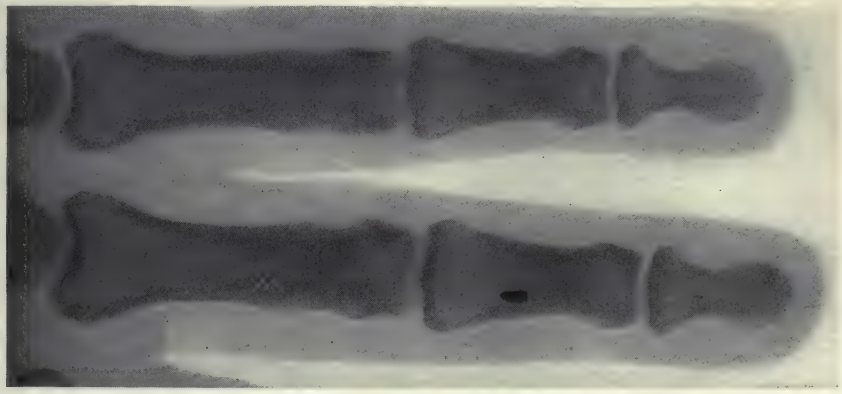


FIG. 122.—Case XVII. Middle and ring fingers showing phalangeal thickenings.

Polyuria is not apparent (cf. post-operative notes). There is no glycosuria. Carbohydrate tests were not made. *Temperature* and *pulse* are subnormal, often falling to 97° and 65 beats respectively.

Oct. 12, 1909. **Operation.** Preliminary tracheotomy (fragment of thyroid removed for examination). Deflection of nose downward according to Eiselsberg's method, with opening of frontal sinuses, giving exposure by median ethmoidal approach. Difficult orientation, owing to obliteration of the sphenoidal cells and the operator's inexperience. Com-

plete pressure atrophy of the sellar base. The bulging muco-dural covering of the tumor was finally recognized and some large fragments of a friable growth were scooped out. The cervical (tracheal) and facial wounds were closed without drainage. Uncomplicated recovery.

FIG. 123.—Case XVII. Generalized adiposis.

The *histological examination* of the tissues showed (1) a mixed tumor (teratoma) probably from a congenital anlage; (2) a colloid condition of the thyroid.

Post-operative Notes. A definite polyuria for several days, the 24-hour amount averaging over 2000 cc. and occasionally reaching 3500 cc. His weight fell to 200 pounds. The visual field in the left eye widened considerably and by *Oct. 31* colors, with standard discs, were recognized (Fig. 124). Aside from this distinct improvement in vision showing a betterment in the neighborhood conditions, there was little if any change in his symptoms. He was discharged *Nov. 1.*

Readmission, *April 18, 1910.* His subjective improvement lasted only a couple of months, and he is now having a return of headaches as severe as before. His weight has again reached 214 pounds. He is noticeably losing his hair. There is some light perception in the right eye; the left is about as before.

Thermic test with anterior lobe injection gives a positive febrile response to 102° F. (Fig. 125), a transient glycosuria and a subjective sense of well-being.

April 28, 1910. **Second Operation.** The attempt was made to carry out a more radical removal of the growth by the same approach as at the first session. The anæsthetic was very badly taken, and bleeding was considerable, necessitating packing of the cavity. A few hours after recovering from the anæsthetic the patient pulled the drains from his nostrils. This was followed by profuse bleeding, which was checked, but started afresh during the night. Primary respiratory failure with death after twenty minutes of artificial respiration.

Autopsy. Nothing noteworthy in gross, aside from the universal adiposity. The brain after hardening *in situ* was removed in its envelope with the sphenoidal bone attached. The hemispheres were divided by a longitudinal section disclosing an intraventricular clot, presumably the immediate cause of death. There is a large friable tumor mass, only the lower part of which (possibly one-third) has been removed (Fig. 126). The

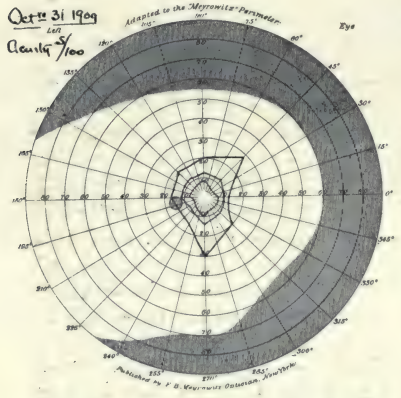


FIG. 124.—Case XVII. Field 3 weeks after operation, showing widening of peripheries with return of color perception.

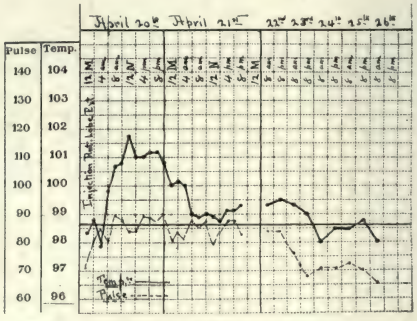


FIG. 125.—Case XVII. Typical thermic response to subcutaneous anterior lobe injection, April 20, 1910.

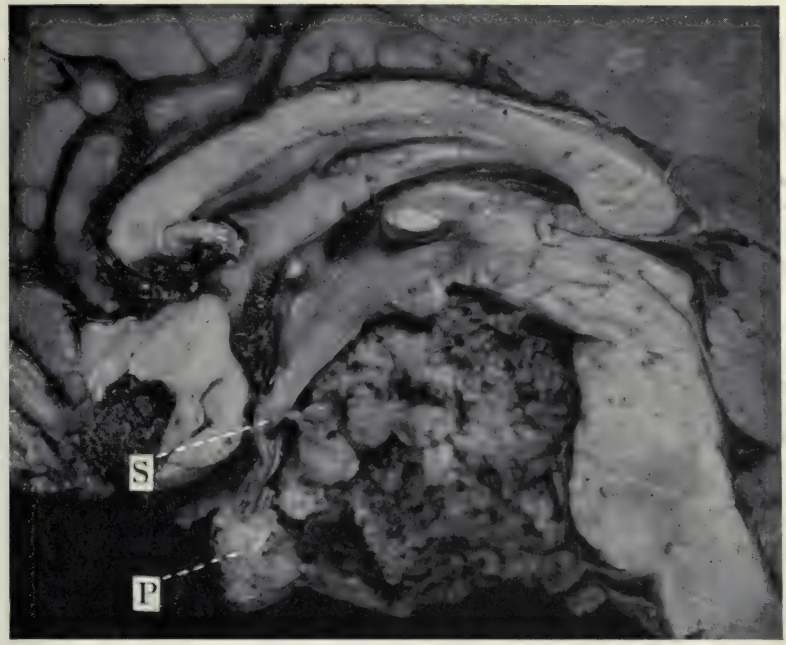


FIG. 126.—Case XVII. Mesial view of right hemisphere (nat. size) showing right half of tumor in position. Elongated infundibulum (*S*): flattened pituitary body (*P*).

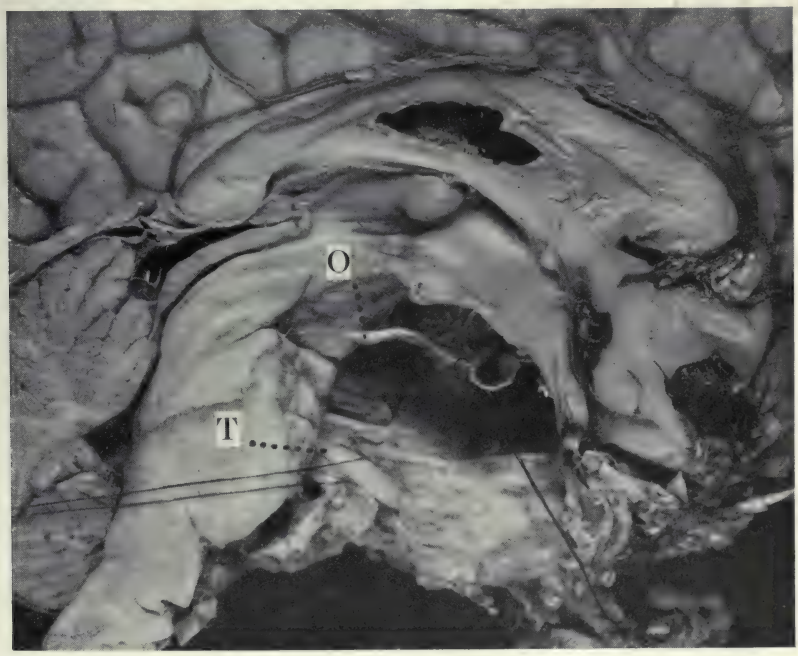


FIG. 127.—Case XVII. Mesial view of left hemisphere after enucleation of tumor mass. Note flattening of nerves, especially trigeminus (*T*) and oculomotorius (*O*), which have been held aside by threads.

growth is of spherical shape, roughly 5 cm. in diameter. It clearly has not originated from the hypophysis itself, for the flattened remnants of the gland are found by tracing down the anteriorly displaced and greatly elongated infundibulum and stalk (Fig. 126). The gland adheres to a remaining fragment of its lower dural envelope and fortunately escaped removal in the blindly conducted original attack upon the growth.

The tumor has greatly dislocated and deformed the entire mid-brain, pushing up the basal ganglia, flattening the pons and deeply indenting the temporal lobes on each side. It has occluded the foramina of Monro and caused a moderate grade of hydrocephalus, accounting possibly for the choked disc and the mental symptoms. The opening in the tentorium (*incisura tentorii*) is widely separated; its edges are everted and the growth projects considerably above it.

The cerebral deformation is best appreciated after lifting half of the enucleable growth out of its bed in one hemisphere (left) (Fig. 127). Lying in the walls of the deep cavity which is thus left, the third, fourth and sixth nerves are found greatly elongated and flat-

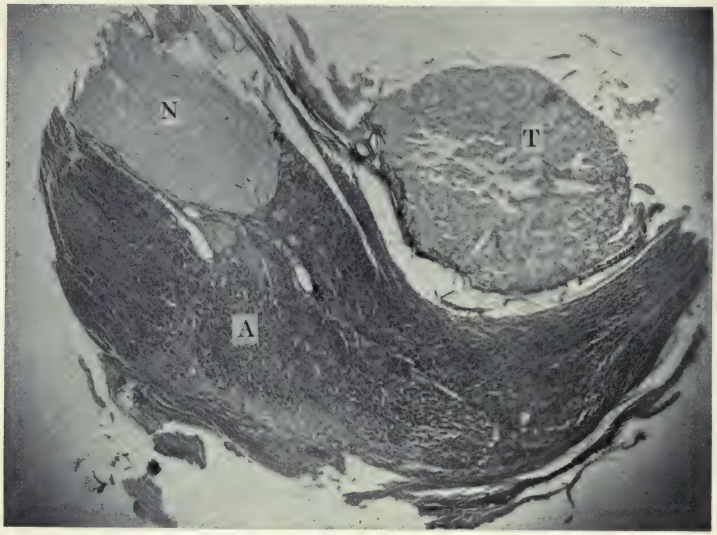


FIG. 128.—Case XVII. Low power enlargement of flattened hypophysis (compare with Fig. 126), with fragment of superimposed tumor (*T*), pars anterior (*A*) and pars nervosa (*N*).

tened. The relic of the third nerve thins out into nothing more than a wisp of tissue. The trigeminus is markedly flattened against the base (cf. the neuralgic pains). The ventricular deformation is so extreme as to have greatly elongated the infundibular stalk and to have separated it from the pons for a distance of 4 cm., whereas normally they are in fairly close juxtaposition.

Histological. The *tumor* shows the same structure throughout. It consists of embryonic cartilage containing a few bone cells with myxomatous and connective tissue. A "mixed tumor from a congenital anlage" (Dr. Welch).

The *hypophysis* (Fig. 128) shows the usual appearance of the congested, flattened gland; the cell columns of the anterior lobe are thinned, lie parallel and are separated by widened sinuses. There is the average number of chromophile elements. The pars nervosa is unduly cellular and contains the widened mesh suggestive of a hyaline content which has been dissolved by the formalin fixation.

Other Ductless Glands. The fragment from the isthmus removed at the first operation during the tracheotomy shows a colloid goitre. The gland itself is somewhat enlarged.

The *thymus* is enlarged. It shows glandular strands with much fat.

The *adrenals* are not enlarged. They show marked fatty change in the subcortical layers.

The *pancreatic islets* are prominent and numerous. There is an increase of fat in the gland itself.

The *testes* show large interstitial spaces, which, however, are practically free from normal cells of Leydig. Those that are to be made out are fatty and granular. The tubules contain spermatozoa.

INTERPRETATION.—A slow-growing interpeduncular tumor, arising from a congenital rest, which has ultimately reached an enormous size with great deformation of the adjoining structures. It has produced, on the one hand, some inconspicuous symptoms of general pressure (irregular headache and choked disc, probably from the secondary ventricular hydrops): on the other, very definite neighborhood symptoms, from local implication, particularly of the oculomotor and optic nerves, but also from a compression involvement of the pituitary gland.

The evidences of hypophyseal implication were shown by traces of an early glandular anterior lobe stimulation (?), indicated by the alterations in the bones of the hands. Later on, however, the gland became so compressed as to have its functional activity largely diminished, leading to a marked adiposity, to sexual impotence, subnormal temperature, a positive thermic reaction to anterior lobe extract, etc. A partial release from pressure through the first operation, which allowed the tumor mass to settle more into the sphenoidal region, led to some subjective relief from pressure symptoms, to some improvement in vision and to polyuria and the restoration for the time being of a normal temperature.

From a surgical standpoint, complete extirpation of such a growth is unthinkable. Palliative measures alone must be resorted to; and here, as in the case of many slow-growing cerebral tumors elsewhere, nature has given a therapeutic lead. But her methods of decompression are slow; and the optic nerves usually suffer irrevocable damage if one waits for a tumor to work its own way through the cranial chamber by pressure atrophy of bone. A surgical removal of the sphenoidal cells and the base of the sella is merely an acute method of accomplishing what the slower natural process has indicated as desirable.

There are obvious risks, however, in the transphenoidal performance, if accompanied by partial extirpation of an infundibular tumor, and particularly when the growth is of this type. For the flattened hypophysis, whose function is by no means entirely destroyed, lies between operator and tumor, and in this particular case it was fortunate that it was not extirpated with the fragments of tumor. In the discussion of Case VIII this has already been referred to.

Projecting as it did into the temporal lobe and extending well above the tentorial opening, the growth might have been exposed by a direct intracranial operation; and it is not at all improbable that a subtemporal approach such as Horsley practises combined with the "overhanging brain" position, will prove to be the better method of attack for lesions of this kind. However, the risks of such an intracranial procedure are inestimably greater than in the perfected transphenoidal operation and in either case nothing more than a fragmentary removal is possible.

Could one have known what was amiss with this patient and had surgical measures reached a stage of development which rendered intervention

permissible, the proper treatment would have been (1) to have removed the sellar base on the first indication of neighborhood symptoms (cf. Case XX), thus saving vision and relieving the hypophysis from the superimposed pressure, and (2) to have removed the benign lesion, whether by a transphe-

FIG. 129.—Case XVIII. Outline of enlarged sella turcica, showing double contour, indicated by dots. (Nat. size.)

noidal or subtemporal route, in fragmentary fashion whenever an increase in symptoms showed that the optic nerves were again becoming implicated. There is every reason to suppose that a working life might thus have been spared in comfort for many years.

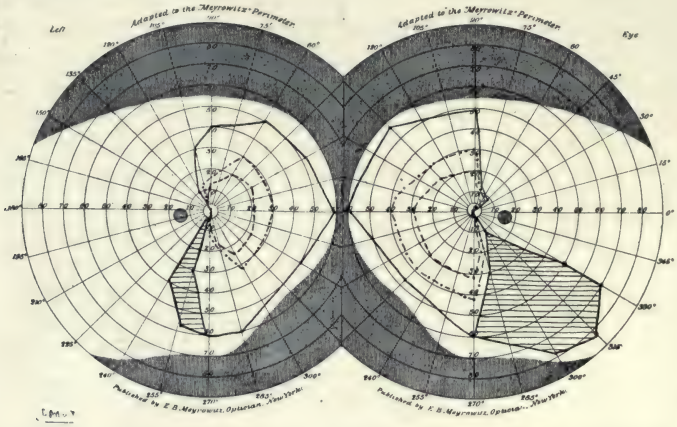


FIG. 130.—Case XVIII. Fields showing (0.5 cm. discs) bitemporal defect with inclusion of the macula. Some preservation of vision for form in lower temporal fields (shaded areas) with 4 cm. discs.

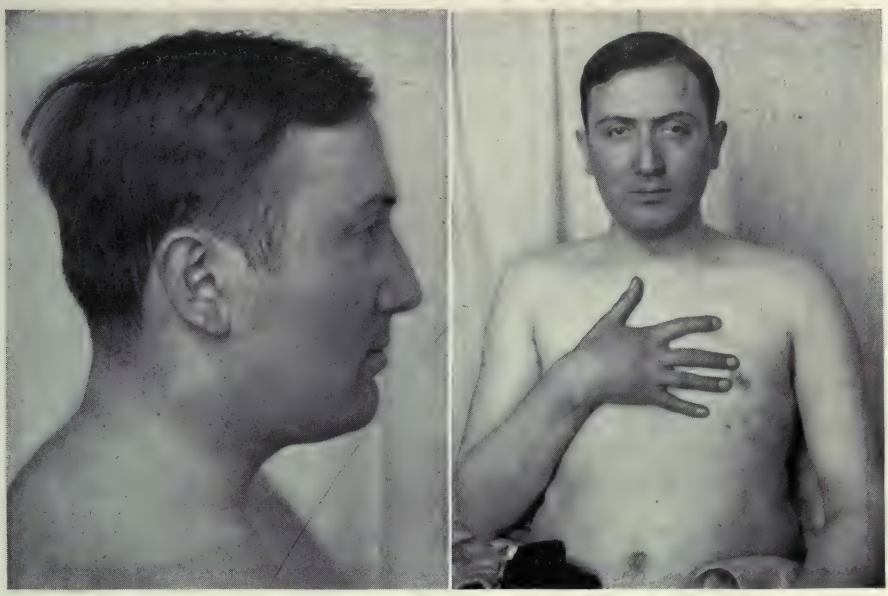
CASE XVIII. (Surgical No. 24981.) **Hypophyseal struma with optic atrophy and bitemporal hemianopsia. Glandular symptoms inconspicuous. No treatment.**

Nov. 15, 1909. A. P., an Italian, a barber 28 years of age, was referred by Dr. Alexander Duane of New York. He is one of a large family of healthy children. There is noth-

ing particularly noteworthy in his past history. He has been married two years; he has one child a year old, and there are expectations of another.

Present Illness. This he dates from an "inflammation of the eyes" four years ago, since which time his vision has not been good and he has worn glasses. An examination by Dr. Duane six months ago disclosed a *bitemporal hemianopsia*. He has suffered somewhat from early morning *headaches* which wear away during the day—never very severe. There have been occasional periods of *diplopia*. He is *drowsy* much of the time. There is no mental change. A vigorous antiluetic régime led to no improvement in his condition.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The X-ray (Fig. 129) shows an *enlarged sella turcica*, which measures 1.8 cm. in its antero-posterior diameter and 1.6 cm. in depth. *Eyes:* Both optic nerves show the pallor of a primary atrophy without choked disc. Pupillary reactions are normal, but are less pronounced to a beam of light projected on the nasal retina than to one projected on the temporal retina.



FIGS. 131, 132.—Case XVIII. Characteristic profile of long-standing hypophyseal struma. On right, note tendency toward adiposity; also large, long-fingered hand.

There is slight exophthalmos. The fields show a *bitemporal hemianopsia* involving the macular region (Fig. 130). Visual acuity, right 20/30: left 20/80. There are no other neurological symptoms.

(b) *Glandular Manifestations. Skeletal:* The patient has the characteristic facial outlines (Fig. 131) shown by several other cases in this series (cf. Cases V, VII and XI). He is about 5 feet 8 inches in height and says his usual weight, clothed, is 155 pounds; his hospital weight is 159 pounds. Skull and thorax show no acromegalic changes. The hands are large; the fingers long, smooth and characteristically tapering. The X-ray shows no suggestion of acromegalic change. The epiphyseal lines are still evident.

Cutaneous. The skin is smooth and dry. There is definite *hypotrichosis*. The nails show no change. The panniculus is abundant. *Temperature* and *pulse* during the five days of observation were slightly subnormal—97° and 60 per minute. There is a suggestive *polyuria* (2240 and 1900 cc.), of which the patient himself is aware. The specific gravity is normal. There is no glycosuria. No carbohydrate tests were made.

Operation refused.

Subsequent Examination. *Dec. 7, 1910.* He is rapidly gaining weight; now weighs 188 pounds—an increase of 33 pounds in the past year (Fig. 133). The *adiposis* is generally distributed and is somewhat lobular; there is no tenderness. There is a notable absence of perspiration. *Anaphrodisia* for the past year. Polyuria continues. The *bitemporal hemianopsia* is now complete, with no vision whatever in the temporal fields and with a notable shrinkage in the color peripheries. Visual acuity on the right has dropped from 20/30 to 15/40; on the left from 20/80 to 12/80. The exophthalmos is more pronounced and the venules of the lids are much dilated. No headache; no choked disc. The examination of the pharynx is negative. Sellar decompression advised: refused.

INTERPRETATION.—When this patient was first seen the two neighborhood symptoms of greatest diagnostic value—the enlarged sella and bitemporal hemianopsia—stood out clearly as the chief symptoms of note. There was a minimum of discomfort and the signs of glandular deficiency were insignificant. It is not unnatural that he should have wished to delay, especially as at that time we had no basis of assurance that it would be possible for him to regain some of the vision already lost.

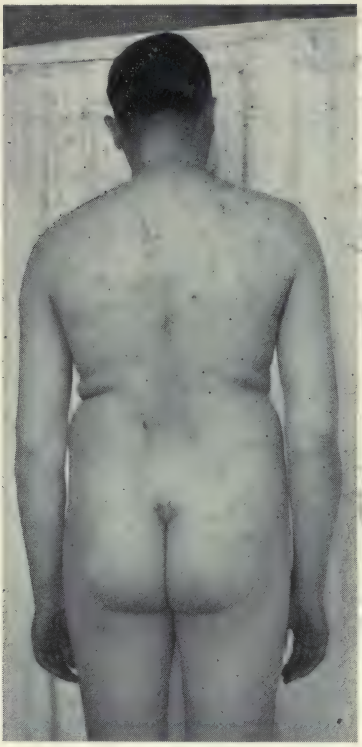


FIG. 133.—Case XVIII. Increase in adiposity beginning to be apparent on second admission.

After the year's interval not only were the local symptoms more marked but evidences of hypopituitarism were manifest, shown by the gain in weight, the anaphrodisia and increasing drowsiness.

The following case is the first in which we obtained a really satisfactory result by transphenoidal decompression of the struma:

CASE XIX. (Surgical No. 26250.) **Hypophyseal struma. Pronounced neighborhood symptoms with optic atrophy and bitemporal hemianopsia. Sellar decompression with restoration of vision. Return of hemianopsia after one year. Partial removal of tumor with improvement again in vision. Symptoms of hypopituitarism evident though not outspoken. Glandular therapy.**

July 15, 1910. A. S., a Russian, aged 27, single, a school-teacher. Referred by Dr. B. J. Beck of New York. An only child, with good health until his present illness.

The Existing Malady. For the past three years he has had severe incapacitating periodic frontal *headaches,* unaccompanied by nausea or vomiting. The headaches have of late been practically continuous.

A thorough ophthalmological examination four years ago when he was applying for a railroad position revealed no abnormality. Eight months ago he began to appreciate a subjective *dimness of vision.* This has increased. On *May 31, 1910,* an examination by Dr. C. H. May showed *hemiachromatopsia* limited to the left eye alone.

The condition was diagnosed as sphenoidal sinus disease and an operation was performed with this in mind. No improvement. The eyes have rapidly grown worse and he now reads print with difficulty even with the right eye. During his ten days' residence in

the hospital before operation there was a rapid shrinkage of the fields of vision and progressive lowering of acuity. (*July 16:* Right, 15/50; left 5/200. *July 26:* Right 10/50; left 3/200.) He has had no subjective diplopia nor observable lack of parallelism in eyes.

Physical Examination. An overnourished, dark-complexioned young Hebrew. Height about 5 feet 6 inches; weight 155 pounds. Visceral (abdominal and thoracic) examination negative. Neurological tests negative except for eyes. *Urine*, negative. *Blood*, a slight eosinophilia (5.5 per cent.).

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Disturbances.* A stereoscopic X-ray shows an enlargement of the *sella turcica*, which in profile measures 2.0 cm. by 1.8 cm. in depth (Fig. 134). *Eyes:* The left *pupil* is slightly larger than the right and

FIG. 134.—Case XIX. Showing (nat. size) enlarged sella with double contour, as indicated by dots. After a sellar decompression the lower of these outlines becomes lost.

the left cleft is narrower. There are nystagmoid twitches. Suggestive Wernicke's sign; Wilbrand prism test is also suggestive.

There is a bilateral *choked disc*, measuring 3 D. in the left eye, not measurable in the right. Oedema in both eyes superimposed on a primary atrophy of the nerves. Perimetric fields show: *May 31, 1910* (Dr. May), a temporal hemiachromatopsia of the left eye; *July 16, 1910* (Dr. Crowe), temporal hemianopsia on the left complete, including the macula, a tendency to temporal hemiachromatopsia on the right, shrinkage of field for form in both eyes; *July 26, 1910* (Fig. 135) (Dr. Crowe), a further shrinkage of the left field, with a notch in the right field for form corresponding with the earlier loss of the color fields, namely, an upper quadrantal and temporal loss of the field for form with almost complete hemiachromatopsia for colors.

No epistaxis. Nasopharynx negative; large tonsils.

(b) *Glandular Symptoms. Skeletal:* No striking changes in the skull aside from the enlarged sella. Profile rather characteristic (Fig. 136). The fingers are slightly clubbed

(Fig. 137); the crescents of the nails are covered; an X-ray shows a slight terminal tufting and traces of epiphyseal lines: nothing suggestive of acromegalic change (Fig. 138).

Cutaneous. The body is covered by an abundance of hair, said to be an inherited characteristic. On the scalp it is coarse and abundant and has not been falling out. The *skin*, however, is very dry and the patient says he never perspires. There is a suggestion of *adiposity*. Since the onset of the trouble his weight has increased from 147 to 155 pounds.

There are no subjective changes in relation to the *sexual function*. There is no history of *polyuria* and the 24-hour urine during his five weeks' residence in the hospital averaged about 1500 cc., though on several occasions it exceeded 2000 cc. The *temperature* is subnormal, often reaching 97°; the *pulse* is slow (50–70).

Tests of *carbohydrate tolerance* between *July 18* and *26* show a high assimilation limit for glucose, 350 grams causing no glycosuria. A gain of 3 pounds during the feeding tests. On *July 26*, 200 grams of glucose, coincident with 0.1 gram boiled posterior lobe extract hypodermically, gave a positive glycosuria. The subcutaneous injection of 2 cc. of a boiled 0.5 per cent. emulsion of anterior lobe extract gave a *thermic response* from 97.6° to 100° F.

Fifty cc. of *cerebrospinal fluid* obtained by a lumbar puncture (*July 27*) contained

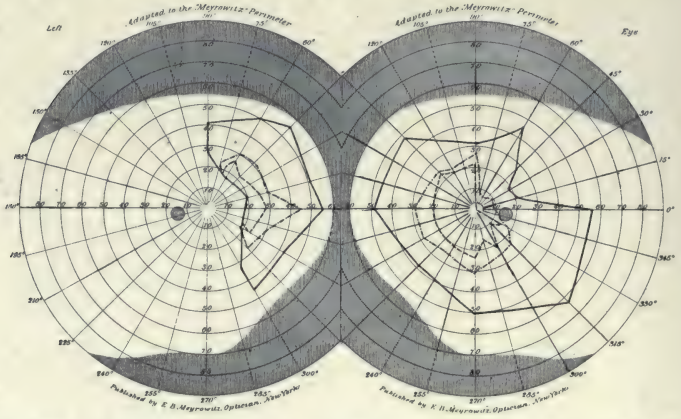


Fig. 135.—Case XIX. Fields of July 26, 1910, just before operation. Note bitemporal tendency: left eye on the way to complete blindness before right is seriously affected

a blood pressure raising substance but did not cause the usual diuresis or increased peristalsis when injected into the external jugular of a rabbit in 15 to 1 concentration.

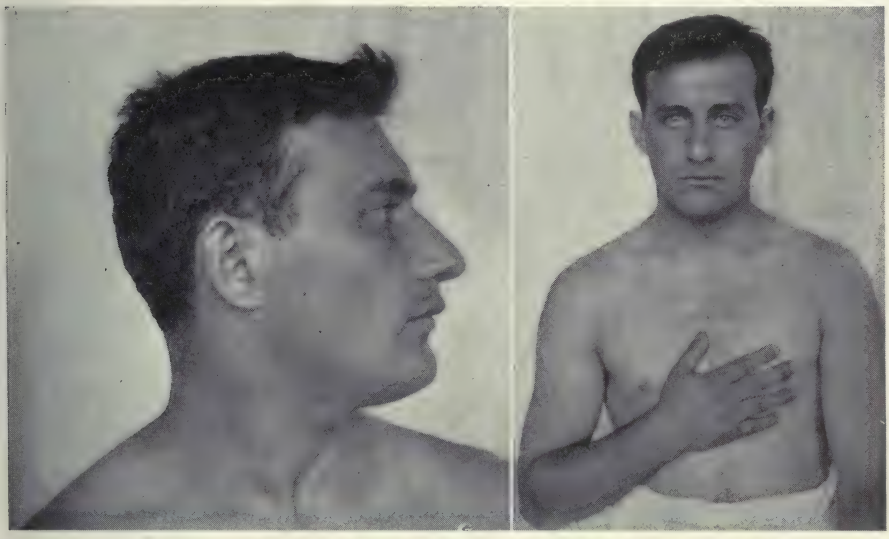
Other Ductless Glands. There is an evident enlargement of the neck, with fullness in the thyroid region. He has recently had to wear larger collars. No definite symptoms referable to thymus, adrenals or testes.

A *summary* of the hypophyseal symptoms shows, as neighborhood signs, an enlarged sella turcica, a progressive change in the visual fields toward a typical bitemporal hemianopsia, a low grade of choked disc superimposed on an obvious optic atrophy. On the part of the gland itself, a subnormal temperature, slow pulse, dry skin, increased carbohydrate tolerance with a gain in weight of 3 pounds during the progress of the tests, a tendency to adiposity—all evidencing a deficiency in metabolizing powers.

July 28, 1910. **Operation.** Anæsthetic (ether) so badly taken that after an hour's manœuvring, the thought of operating was abandoned.

August 3, 1910. Second anæsthetization. Decompression of the sella turcica for neighborhood symptoms. Anæsthetic well taken after primary scopolamine and morphia. Operation conducted without difficulty. The floor of the sella turcica was removed and stellate incisions made in the capsule of the gland. Prompt recovery without complications.

Post-operative Notes. A subjective improvement in vision was noted within a few days after the operation. Perimetric charts of *August 14* show expansion of the fields with disappearance of notch in upper quadrant of right field for form. *August 22:* Rapid filling out of fields both for form and colors in both eyes; central scotoma, however, persisting in left. *August 25:* Administration of 300 grams of glucose gave a positive gly-



FIGS. 136, 137.—Case XIX Profile with maxillary prognathism characteristic of hypophyseal struma. On right note slight grade of adiposity; peculiar clubbed fingers; pilosity.

cosuria. *August 29:* Still further improvement in fields. Patient *discharged* taking three grains of whole gland extract after meals.

Subsequent Notes. *October 31* (Dr. May): *Fields* very nearly normal except for the central scotoma of the left eye, and some constriction of the color peripheries in the

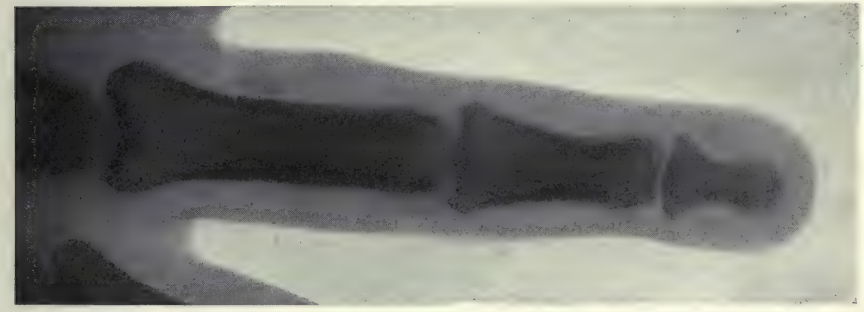


FIG. 138.—Case XIX. Radiogram of middle finger (unreduced).

right upper temporal quadrant (Fig. 139). Visual *acuity* has markedly improved: right eye 15/50; left eye 5/80.

November 15. Returns for observation. Fields show practically no constriction; the central scotoma shown in Dr. May's charts (Fig. 139) is a scotoma for red alone. *Acuity:* right 15/40; left 10/100. The subjective improvement in vision is even greater than the tests would seem to indicate.

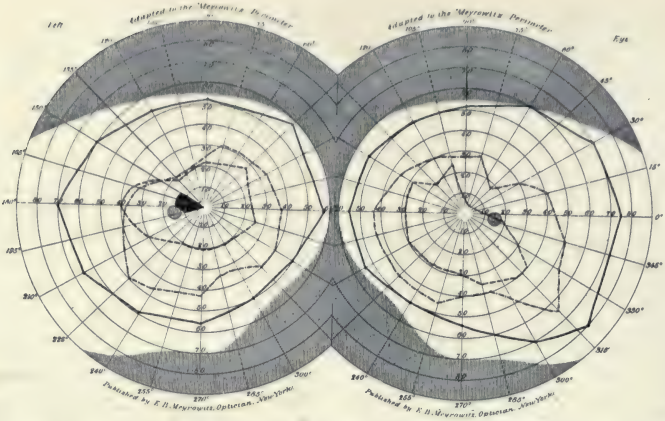


FIG. 139.—Case XIX. Fields of Oct. 31, 1910 (Dr. May), 3 months after operation. Showing almost complete restoration (cf. Fig. 135).

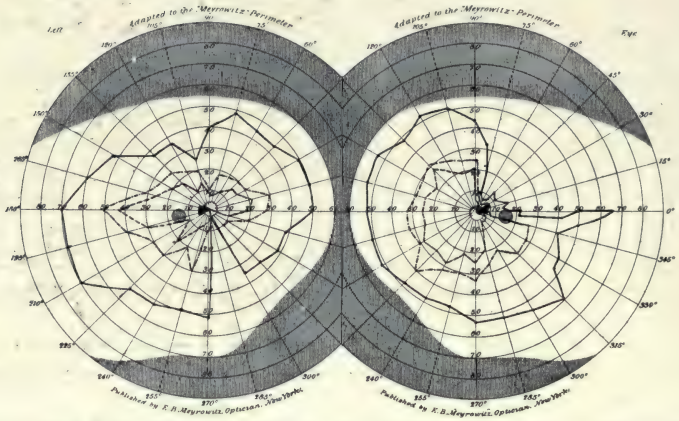


FIG. 140.—Case XIX. Fields on readmission April 21, 1911, showing return of constrictions.

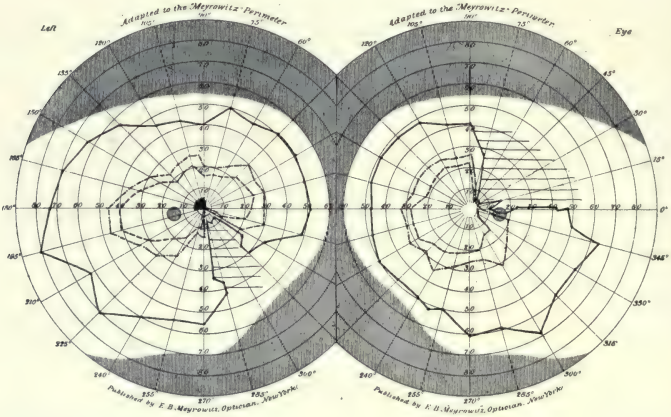


FIG. 141.—Case XIX. Fields of June 6, 1911, 14 days after second operation: 4 cm. discs now seen in previously blind (shaded) areas

There was a gain of 20 pounds in weight during the first six weeks after his discharge; present weight 169 pounds. He has been free from headaches. His temperature continues subnormal.

There is no anosmia. Nasal examination shows a small perforation just above the septum of the anterior nares, but the median septum of mucous membrane is otherwise intact throughout.

A stereoscopic X-ray shows no change in sellar outlines, except for the loss of the lower curve of the fossa due to removal of its floor (cf. Fig. 134).

April 21, 1911. **Readmission.** During the past two months there has been a return of headaches and a rather rapid lowering of reading vision, the right field now being affected more than the left. His *weight* has increased. His *sugar tolerance* is apparently higher—250 grams lævulose—and a determination of the therapeutic dosage shows that 12 grains three times a day is necessary to give lævulosuria with 110 grams of the sugar. Presumably he has been taking an insufficient amount of extract.

The *neighborhood symptoms* have again returned. The sella now measures 2.3 cm. by 2.0 cm. in depth. The fields (Fig. 140) show constriction on the left with persistence of the central scotoma and a complete upper quadrantal defect on the right, with some obscuration of the entire right temporal field. *Acuity:* left 3/70; right 10/70. The *fundi* show considerable new tissue in the physiological cups. Swelling about 1 D.

The *temperature* remains nearly normal when taking the extract, but falls to about 97° upon its omission.

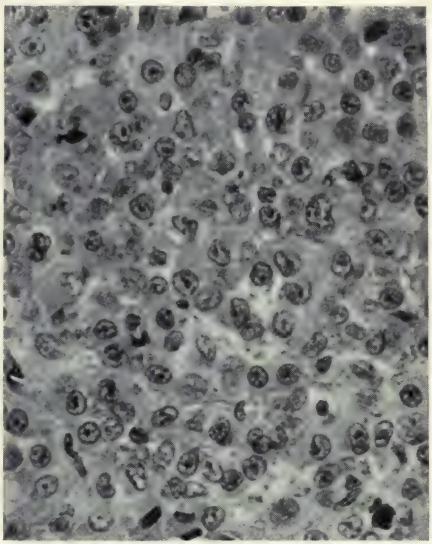


Fig. 142.—Chromophobe struma of Case XIX (mag. 375 diams.).

May 23, 1911. **Secondary Operation.** *Partial removal of pituitary struma.* The original sublabial route was followed, without loss of blood and without difficulty. It was found that a dense cicatricial membrane with an intact mucous surface, in the centre of which could be seen the scar of the original incision, covered and restrained the protruding struma. A new incision was made in this old median scar and about a thimbleful of the growth was removed, as much of the scar as possible being excised.

Convalescence was most satisfactory and there again occurred a rapid subjective improvement in vision.

June 6. Fields show (Fig. 141) a return of vision in the defective right upper quadrant; acuity has increased to 20/70 in the right eye and to 7/70 in the left. *June 15:* Still further improvement. Acuity, left 20/70; right 7/70.

The patient's organotherapeutic dosage was established at 12 grains of the whole gland extract three times a day. He was discharged *June 21*, taking this amount of the extract, which had held his temperature and pulse practically at normal for the preceding ten days.

A *histological examination* of the tissues (Fig. 142) shows the characteristic neutrophilic type of glandular struma. There is a preponderance of large cells having a neutrophilic, non-granular protoplasm and large vesicular nuclei. No acid-staining cells seen. A few thin-walled blood vessels apparent, but there is practically no intercellular tissue.

INTERPRETATION.—As in the preceding case, here also the presence of characteristic neighborhood pressure symptoms led to a clinical scrutiny which disclosed unmistakable evidences of dyspituitarism—shown by the subnormal temperature, the progressive tendency to adiposity, the high tolerance for carbohydrates and the positive anterior lobe thermic reaction. The relative inactivity of the posterior lobe reactions shown by the cerebrospinal fluid is an additional factor of interest.

There were two clear therapeutic indications: (1) surgical decompression for the relief of neighborhood symptoms, and (2) organotherapy to compensate for the insufficient glandular secretion. The first operation served its purpose remarkably well, though unfortunately for only a short time. Consequently a year later a partial glandular extirpation was necessitated. During the interval we had fortunately arrived at a more satisfactory basis for determining the necessary dosage of the glandular preparation. The patient's symptoms of hypopituitarism had evidently been increasing and a fairly large dosage was necessary to establish a carbohydrate equilibrium.

One cannot foretell the ultimate outcome, the disconcerting factor being the progressive enlargement of the struma, which appears histologically to be of a cellular type capable of extensive proliferation. In view of the choked disc, an intracranial extension of some degree has in all probability already occurred. Unfortunately we have as yet no effective means of combating the cellular hyperplasia, except by the crude measures afforded by partial surgical extirpation (cf. radiotherapy, p. 321). In many cases, however, the enlargement of the struma is slow in its progress; and it is not inconceivable that the stimulus under which the hyperplasia occurs may in time become ineffective. Meanwhile surgical measures are likely to be chiefly indicated for the preservation of vision.

In the following case characteristic neighborhood symptoms were present in the absence of demonstrable change in the configuration of the sella turcica. It resembles in this respect Cases IV, VI, VII and XVI, regarded as instances of presumable though uncertified interpeduncular lesions. Here, however, the glandular symptoms were most inconspicuous.

CASE XX. (Surgical No. 26634.) **Infundibular tumor (uncertified) with primary optic atrophy, hemianopsia and oculomotor palsies. Practically no glandular symptoms. Operation: sellar decompression. Improvement.**

Sept. 26, 1910. N. B. K., aged 32, a surveyor, was referred by Dr. S. G. Dabney of Louisville, Kentucky, complaining of blindness.

There has been a peculiar hereditary nervous trouble in his family, with a form of spinal paralysis occurring in middle life. The patient has been a vigorous, athletic young man, very susceptible to colds and sore throat; otherwise he has escaped the usual infectious diseases. Eleven years ago he had a temporary right facial palsy after "catching cold;" there was no pain or discharge from the ear. He has never had headaches, but his neck often feels stiff and uncomfortable. Four years ago he had a transient attack of diplopia, which passed off in two weeks.

Present Malady. Dimness of vision was first observed seven months ago. This rapidly increased, and in two months (February) his acuity, tested by an ophthalmologist, was; right 4/200; left 20/200. Six months ago (March) a *temporal hemianopsia* in the left eye was observed, but this was never noted in the right. At this time also there was limitation of movement in the left eye which has increased rapidly.

In August there was bare light perception in the right eye, and Dr. W. K. Holden of New York suggested the presence of an hypophyseal tumor. At this time there was an atrophic pallor of each disc. He has never had headaches: there has been no polyuria; no change in his weight, in the skin or hair; no sexual change. His average weight is 155 to 165 pounds; present weight 157 pounds. He feels in perfect health: no dullness or mental inactivity.

In spite of a negative Wassermann test he has been subjected to a vigorous antiluetic régime, with no improvement in the condition of the eyes.

Physical Examination. Aside from the neighborhood symptoms the patient seems in perfect physical condition. Thorough visceral and neurological examinations are absolutely negative. The blood is normal; Wassermann test negative. There is a tendency to polyuria without apparent polydipsia, the twenty-four-hour amounts often exceeding 2000 cc.—on one occasion reaching 2985 cc. The skin is moist and without pigmentation. There is no thyroid enlargement.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood Symptoms.* There is no deformation of the *sella turcica* (Fig. 143), which measures 1.2 cm. by 0.8 cm. in depth. The tumor,

FIG. 143.—Case XX. X-ray by Dr. S. G. Cole (unreduced) of sellar region, showing sella (dotted) of normal outline.

if one is present, lies superimposed and has given as yet no general pressure symptoms. No anosmia; no epistaxis. *Eyes:* Vision is entirely lost in the right. The left shows a temporal hemianopsia, the central vision at the time of admission being retained both for colors and for form, the acuity being 15/200. (Ten days later the central vision for colors had become lost [Fig. 144] and vision was evidently failing rapidly—acuity 12/200.) The pupils are unequal, the left larger than the right. The right pupil reacts consensually but not to light or distance, the left eye shows no reaction from the nasal (blind) retina (positive Wernicke). Consensual reaction from right to left is lost. The Wilbrand prism test is positive, showing no ocular movement.

The ophthalmoscope shows a primary atrophy without choked disc, though the veins are large and tortuous. In the left eye the atrophy seems largely confined to the nasal retina. There is a striking lack of parallelism in the axes of the eyes (Fig. 145). The right eye retains an upward fixation, but its movements can be carried out normally. The left shows a slight ptosis with weakness of all the muscles and paralysis of the superior rectus.

(b) *Glandular Symptoms.* There are no suggestions of acromegaly, infantilism or adiposity. Evidences of dyspituitarism, however, are shown by *polyuria*, a tendency to

subnormal temperature (often as low as 97°) and an increased *carbohydrate tolerance* as follows: September 29, glucose 200 grams; September 30, 300 grams; October 1, *400 grams*, without glycosuria. The subcutaneous injection of 0.2 grams of posterior lobe extract in

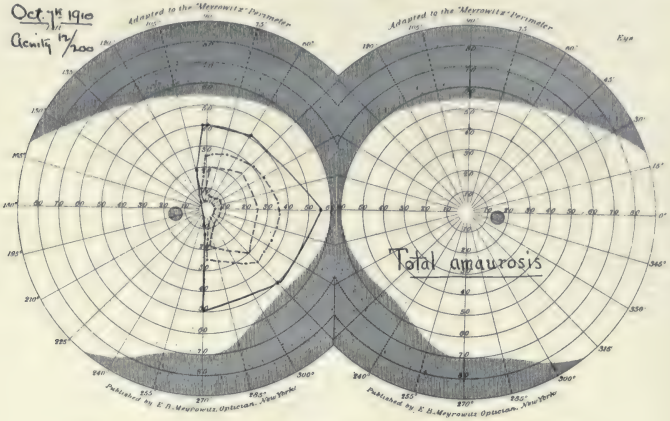


FIG. 144.—Case XX. Fields of Oct. 7, 1910, before operation.

2 cc. NaCl solution gave no febrile response and led to no spontaneous glycosuria. No *thermic response* to anterior lobe injection. A *lumbar puncture* was performed and 60 cc. of clear fluid withdrawn, without disturbance other than a slight temporary headache. The fluid gave fairly active posterior lobe reactions in the rabbit.

FIG. 145—Case XX. Showing oculomotor palsies.

Oct. 11, 1910. **Operation.** *Decompression of the sella turcica.* No operative complications: no difficulties from anæsthesia. No tissue removed. Dura enclosing tense gland split in stellate fashion.

Within a few days the patient experienced a subjective improvement in vision in the left and had some light perception in the right eye.

Oct. 21. Subjectively the eyes are much improved. The perimetric chart of the left eye shows no alteration, but the acuity has improved, to 15/100. Patient can dimly make out objects in the right nasal retina. No consensual reaction from right to left is obtained. *Discharged* Oct. 24. No glandular therapy.

Subsequent Examinations. On *Nov. 10* it was possible to demonstrate (Fig. 146) a return of vision for large objects in the right nasal field; not for colors, however. Diplopia less marked. By *Feb. 18, 1911*, the fields had widened considerably (Fig. 147). On *June 14, 1911*, condition stationary. Gaining perceptibly in weight—168 pounds at present. Polyuria and polydipsia continue as before.

INTERPRETATION.—Were it not for the evident binasal character of the optic atrophy, together with the preservation of vision in the left temporal retina and some post-operative return in the formerly blind right temporal

retina, practically assuring a median retrochiasmal lesion, one would hardly venture, in the absence of sellar deformation, to make a diagnosis of an infundibular growth.

The oculomotor disturbances are, however, additional factors, and the only other case in the series in which they were equally extensive is Case

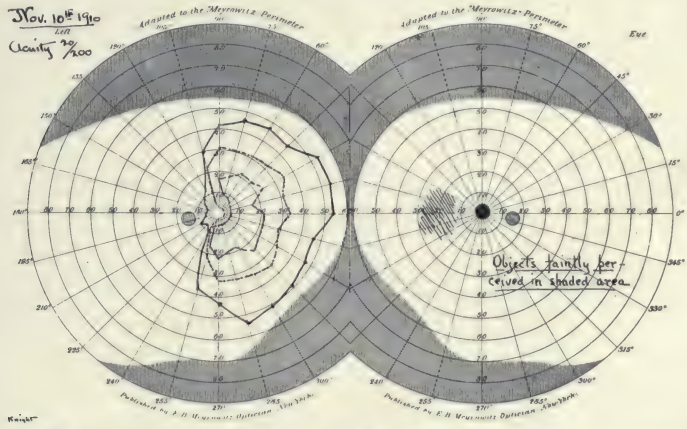


FIG. 146.—Case XX. Fields of Nov. 10, a month after operation, demonstrating the probable bitemporal character of the hemianopsia.

XVII, one of certified infundibular tumor. The sellar decompression consequently was undertaken with little expectation of improvement in the existing conditions but in the hope of sparing the gland from further pressure implication, for the extremely high sugar assimilation limit and the subnormal temperature were regarded as an evidence of posterior lobe (stalk)

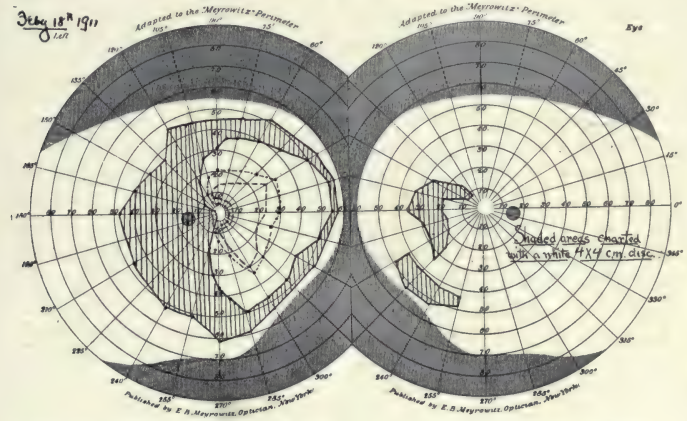


FIG. 147.—Case XX. Fields of Feb. 18, 1911, four months after operation.

implication. It was presumed that the pars anterior, in view of the negative thermic reaction, was still functionally competent. Considering the patient's extreme tolerance for sugars it is remarkable that he has not become obese.

The case falls in the same category with Case XVI, in which the lesion has been dormant—and the patient also for that matter—for years: with

Case VII in which a subtemporal decompression was finally necessary: and with Case XVII in which the lesion suddenly took on a rapid growth.

The remaining three patients in this group are of a fairly uniform clinical type. Each of them carries an hypophyseal struma of chromophrobe type—the form of tumor which numerically predominates in the histologically certified lesions occurring in this series of cases—namely, in Group I, Cases I, II, V, IX, X and XII: in Group II, Cases XV and XIX.

Case XXI. (Surgical No. 27419.) **Hypophyseal struma with primary optic atrophy and unilateral blindness. Evidences of dyspituitarism with amenorrhœa. Suggestion of slight primary hyperpituitarism. Sellar decompression. Organotherapy.**

March 13, 1911. Miss A. S., aged 34, referred by Dr. G. E. Seaman through Dr. H. V. Ogden of Milwaukee, with the diagnosis of hypophyseal tumor.

History Relating to Present Illness. When twelve years of age she had a severe fall, striking the back of her head. Her *menses* began at the age of 15 and continued with fair regularity for two years, when they ceased permanently. She weighed about 120 pounds until she was 18 or 19, when she began to grow stout, her average *weight* from that time until the past year being 180 pounds. She has recently lost 20 pounds "from worry."

Some lowering of *vision* in the right eye was first noted sixteen months ago. In four months' time the eye became completely blind. There is no record of hemianopsia, diplopia, or photophobia. There have been occasional frontal *headaches;* infrequent, however, and not severe. Attacks of "dizziness" have been distressing, with a sensation of "something rushing into the head and lifting it off."

A definite *enlargement of the hands and feet* is said to have occurred during the past year, necessitating a size larger in gloves and shoes. She has become excessively nervous and emotional and her memory has become very capricious. She has a large appetite; is constipated. There have been frequent nose-bleeds.

Physical Examination. An overnourished woman, 5 feet 6 inches in height and weighing 160 pounds. Mucous membranes pale. Complexion muddy; freckled. Visceral (thoracic and abdominal) organs negative. Blood and urine negative. Infantile pelvic organs. Routine neurological tests practically negative except for the neighborhood (pituitary) disturbances. Abdominal reflexes are absent. She is astigmatic.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Signs.* Stereoscopic X-ray plates show a much *enlarged sella,* its full extent not appreciable without stereoscopy. The antero-posterior diameter is 3.2 cm.; depth 3.0 cm. (Fig. 148). *Eyes:* Slight exophthalmos, especially on the left. Pupils equal and reactions normal to light and distance. Loss of right-to-left consensual reflex. Total blindness in right eye with primary atrophy. Some haziness of nasal margin of left disc. Slight nystagmus both to right and left. Tendency to divergent squint with eyes at rest. Perimeter shows slight constriction of left temporal field (Fig. 149). Acuity 9/15. Frequent epistaxis: nasopharynx negative.

(b) *General pressure symptoms* practically absent. Some frontal headaches; slight haziness of left disc.

(c) *Glandular Manifestations.* The stature is somewhat short but there are no striking *skeletal changes.* The epiphyses are fully ossified. The suggestive acromegalic changes with enlargement of the hands and feet involve the bones as well as the soft parts (Fig. 150). Hand rather square with slight suggestion of terminal fullness of fingers and tendency of tissues to enfold nails. Toes much facetted by shoes. Some maxillary prognathism (Fig. 151).

Cutaneous. There has been considerable loss of hair and the skin is somewhat dry. She is somewhat *adipose. Amenorrhœa* for seventeen years; infantile uterus. The *temperature* tends to be subnormal (97.5°–98°) and the *pulse* slow (70).

Other of the usual signs of oncoming hypopituitarism are wanting. There is an unusually high *blood pressure* (175–180) and no especial asthenia. There is only a slight increase

in *carbohydrate tolerance* (assimilation limit 150 grams lævulose). No thermic reaction to injections of anterior lobe extract.

March 18, 1911. **Operation:** *sellar decompression.* A simple uncomplicated case by sublabial approach and submucous resection of vomer. Dural envelope split over large

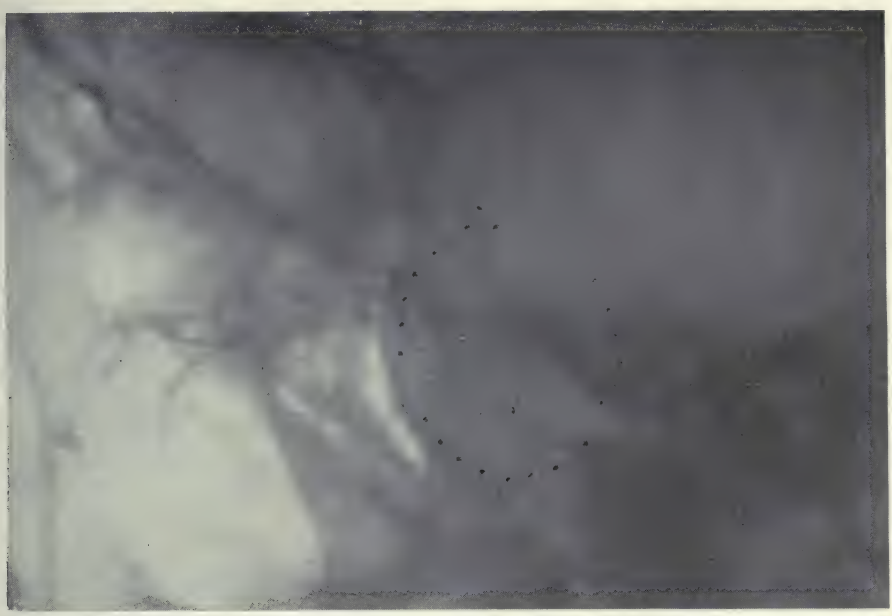


FIG. 148.—Case XXI. X-ray of sella (Dr. Hickey of Detroit) showing confusion of single plate. Dotted line marked in stereoscopically.

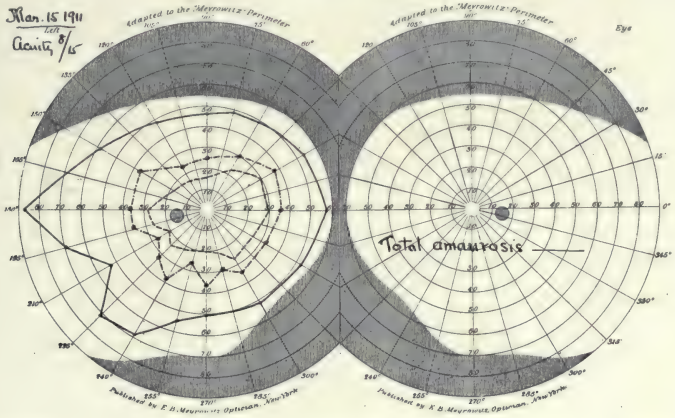


FIG. 149.—Case XXI. Fields of March 15, before operation, showing some temporal constriction of seeing eye.

bulging gland. A small fragment removed for *histological examination,* which shows the usual chromophobe struma with masses of cells having a faintly staining protoplasm and large vesicular nuclei with sharply outlined chromatin network; no acid staining cells; a few colloid globules present, but no formed acini; practically no supporting or interstitial tissue (Fig. 153).

Recovery uncomplicated. She was *discharged* after ten days (*March 28*), taking whole-gland extract.

Subsequent Notes. *April 1, 1911.* Visual acuity of left eye has improved to 15/15. A small area of vision for 3 cm. disc in the lower nasal half of the right field, showing (cf. Fig. 149) original bitemporal tendency of the lesion.

April 10, 1911. Fields for left eye have widened to normal peripheries (Fig. 154). No further improvement in right, though pupillary reaction to light can be obtained from the temporal retina (positive Wernicke).

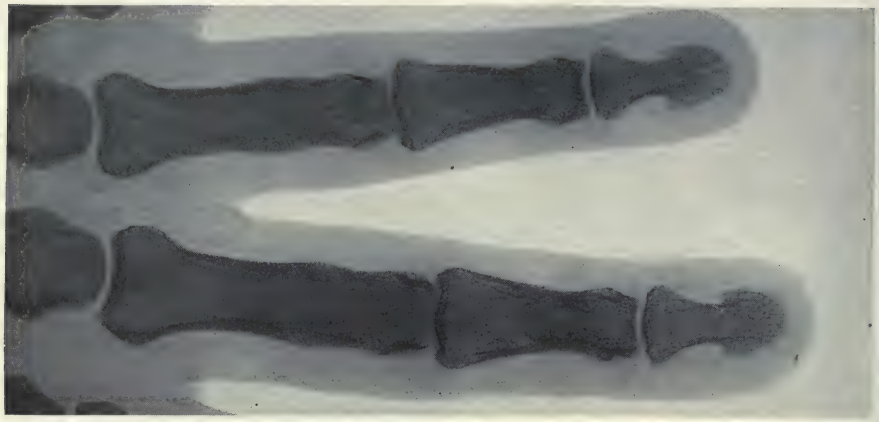
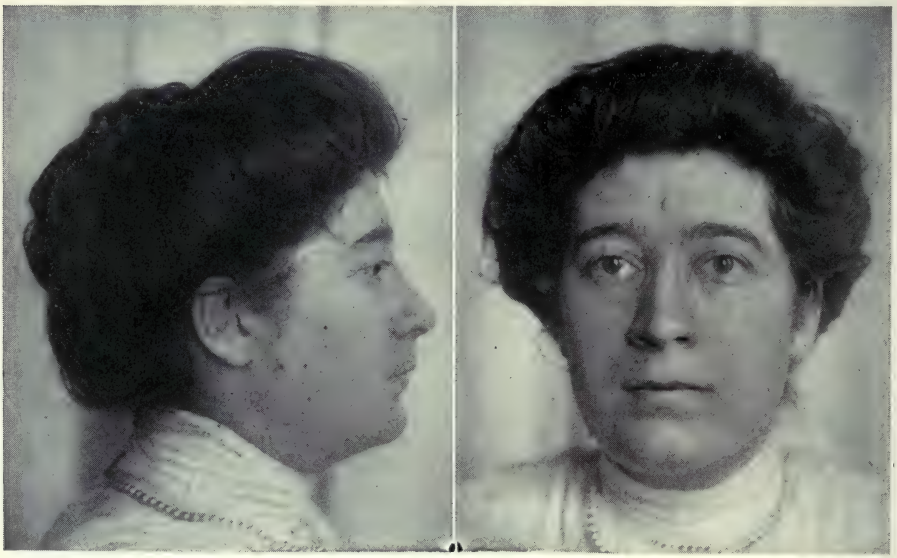


FIG. 150.—Case XXI. X-ray of middle and ring fingers (nat. size), showing tendency toward acromegalic change in thickening of first and in mushrooming of terminal phalanges.



FIGS. 151, 152.—Case XXI. Showing suggestive prominence of maxillary zone of face: also the coarse, freckled features.

July 14, 1911. Dr. Seaman reports that she has continued with whole-gland extract in 6 grain doses after meals. Her nervous and dizzy attacks continue (possibly uncinate?). There has been no further improvement in vision—indeed, possibly some concentric constriction of the field. A second operation, with further removal of struma (as in Case XIX) advised. Also radiotherapy.

INTERPRETATION.—From the standpoint of the symptoms referable to disturbed glandular activity this is a borderline case, and with some hesitation it has been placed here rather than in Group I. Had it not been for the glandular struma and the amenorrhœa, the patient's constitutional state would have passed muster as normal.

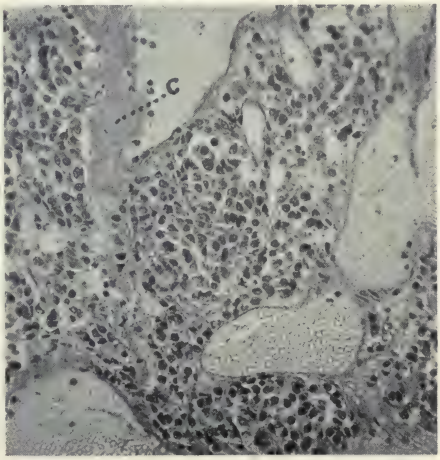


FIG. 153.—Chromophobe struma of Case XXI (mag. 190 diams.). Field showing dilated sinusoids containing colloid (*C*).

There are, however, some suggestive indications (the enlargement of the hands and feet, for example) of former hyperpituitarism, and some (the tendency to adiposity, the dry skin, slight increase in sugar tolerance, etc.) of an existing functional state the reverse of this. Though some of the usual signs are wanting, it is probable that the malady is verging toward the stage of glandular insufficiency. In view of the slight and only temporary post-operative improvement in vision and the present stationary condition, it would in all probability be wise (as in Case XIX) to operate a second time and partially empty the distended sella of its strumous contents. As it was, the operation was limited to the mere removal of the sellar base, in view of the striking relief afforded Mr. A. S. shortly before by this simple measure,—unquestionably an insuffi-

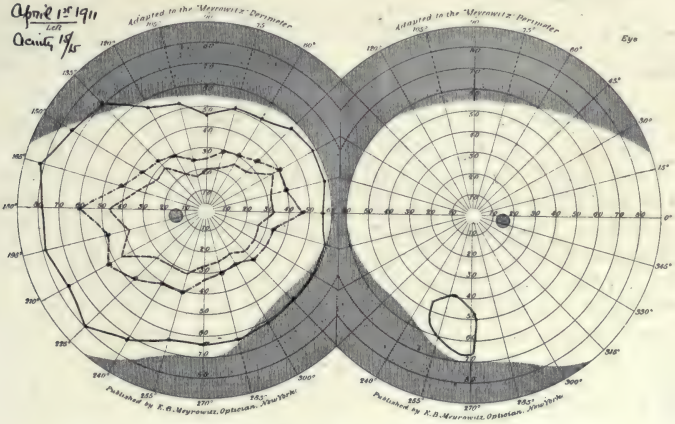


FIG. 154.—Case XXI. Fields of April 1, two weeks after operation.

cient procedure when a large glandular struma is encountered. Had we known at the time that Mr. A. S. was soon to return with renewed symptoms, necessitating a partial extirpation, this more radical step would have been taken at the first session in the patient under discussion. It is to be feared

that with further delay the glandular struma may undergo further hyperplasia and burst its confines, as in some of the cases in Group I, if it has not already done so.

In view of these experiences the distended sella in each of the following cases was partially emptied of its contents at the first operative session.

CASE XXII. (Surgical No. 27955.) **Large hypophyseal struma with almost total amaurosis following a bitemporal hemianopsia. Symptoms of dyspituitarism unusually inconspicuous. Sellar decompression with fragmentary extirpation of growth. Partial restoration of vision.**

June 11, 1911. L. H., a farmer, aged 27, referred by Dr. L. E. Fuller of Axton, Virginia, with the complaint of failure of vision and headaches. Aside from an attack of inflam-

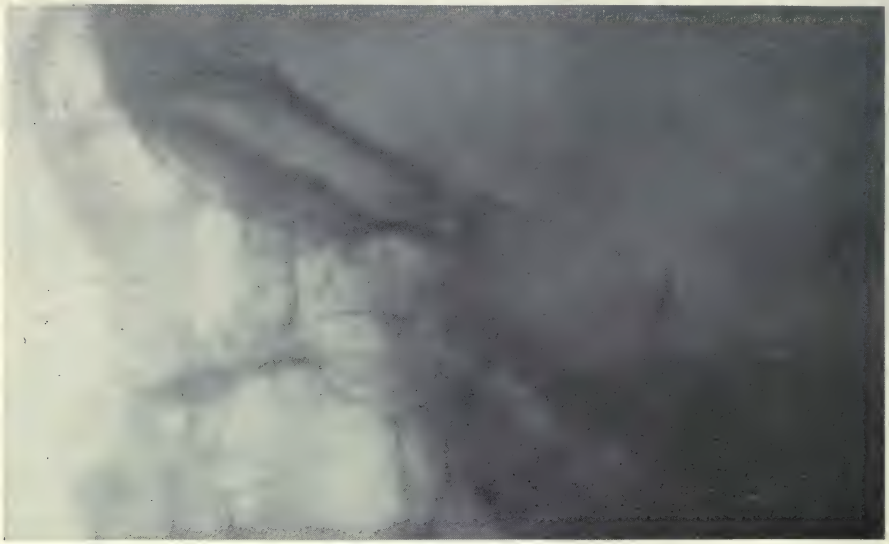


FIG. 155.—Case XXII. X-ray (unreduced) of enlarged pituitary fossa. Note shadow cast by thinned scale of dorsum sellæ.

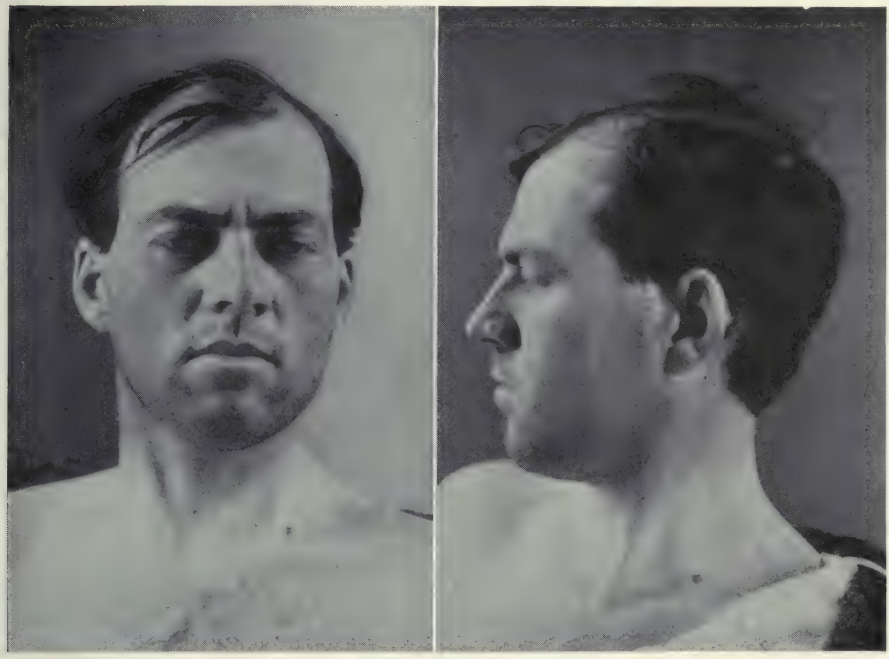
matory rheumatism he has enjoyed good health. He has been married two and a half years and has one healthy child.

Present Illness. Eight months ago he began to lose vision in the outer field of the left eye. This was soon followed by temporal headaches, which have persisted. Three months ago there was a rapid failure of vision in the right eye, with further constriction of the left fields. He can now barely distinguish large moving objects. Unable to count fingers. There has been no drowsiness; no anaphrodisia; no increase in weight.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood Signs.* The X-ray (Fig. 155) shows a greatly *enlarged sella turcica* projecting well into the sinuses and measuring 3 cm. by 2.5 cm. *Eyes:* Bilateral primary optic atrophy; visual acuity practically nil; reduced to perception of light. (The bare ability to recognize large white moving objects on the nasal fields, was lost three days after admission.) Pupils wide; right larger than left; react to accommodation, but only slightly to a beam of light on the temporal retinæ (positive Wernicke). No history of diplopia. Possibly a slight existent divergent squint. Nasopharynx negative: no nose-bleeds.

(b) *General pressure symptoms* absent. No choked disc. The headaches are doubtless due to distention of the pituitary pocket.

(c) *Glandular Signs. Skeletal:* His height is only 166 cm. (5 ft. 5⅜ in.); his weight 128 pounds. There are no recognizable skeletal changes shown by the X-ray aside from an unusually large occipital protuberance. The facial configuration suggests sphenoidal dis-



FIGS. 156, 157.—Case XXII. To show cephalic outlines suggestive of sellar and sphenoidal distortion. Note width at malar level, and on profile view slight prominence of maxillary zone of face.

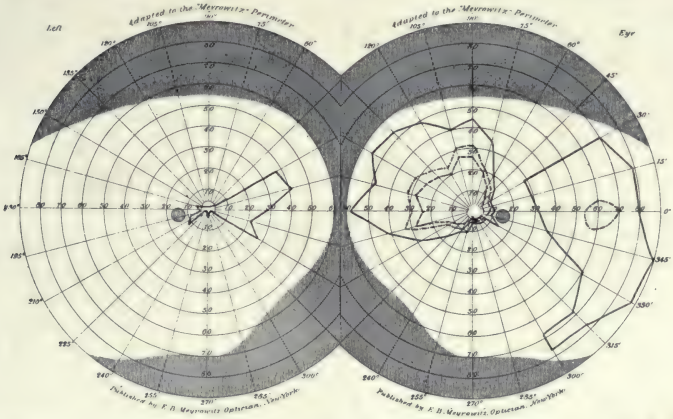


FIG. 158.—Case XXII. Fields of July 17, one month after operation, before which time there was recent complete amblyopia.

tortion (Figs. 156 and 157). The two upper *middle incisors* have never erupted, the lateral incisors being separated 0.4 mm. The fingers are somewhat tapering, and the nails without crescents.

Cutaneous. The skin is sunburned and freckled but there is no general pigmentation. It is somewhat dry, except over the hands, which are pale and moist. He is becoming bald

(a family trait), but otherwise he is rather hirsute: the beard is heavy and grows well up on the cheek-bones; eyebrows are shaggy; sternal and sacral hirsuties abundant. No outspoken *adiposity*.

The *temperature* tends to be subnormal (occasionally 97°): the *pulse* slow (60 to 70). The *blood pressure* is low (105 mm. Hg.). There is no polyuria or polydipsia. He is intolerant of sugars and vomited the lævulose administered. Sugar *assimilation limit* not determined (cf. later note).

Examination of other ductless glands reveals no functional abnormalities.

June 16, 1911. **Operation.** *Partial extirpation of struma.* The usual sublabial approach with submucous resection of vomer, etc. Large tumor, covered only by dura and mucous membrane disclosed, filling sphenoidal cells. Marked pressure atrophy of sellar base. About one-half of sellar contents removed. No bleeding. Anæsthetic well taken.

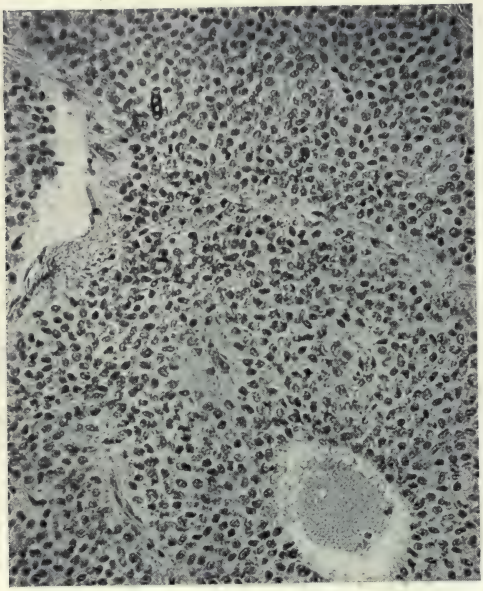


FIG. 159.—Chromophobe struma of Case XXII (mag. 190 diams.): cells in large alveoli with central colloid.

Post-operative Notes. There were no surgical complications. Subjective return of vision on the following, and improvement on each succeeding, day. On *June 21* the perimeter showed *nasal vision* in the right eye for discs larger than 4 cm.

June 29. Fields plotted with 4 cm. discs show remarkable improvement in the right eye, with return of color vision: achromatopsia in left. Wernicke reaction positive in left, negative in right eye. No nasal discharge: no headaches. Patient *dismissed*. No glandular feeding.

July 17. Returns for observation. Condition excellent. Further improvement in vision. Fields taken with 4 cm. discs (Fig. 158). He feels stronger. Blood pressure 115. Weight increasing (134 pounds) but no tendency to adiposity.

August 21. Returns for observation. Improvement at a standstill. Some return of temporal headaches. *Carbohydrate tests:* 150 and 200 grams of lævulose retained—urine negative for sugar. Patient unable to retain 250 gram dose. Tolerance therefore high, but limit not ascertained. Further subjective improvement in vision, but fields show no change from July 17th. *Blood pressure* below 100.

The *histological examination* of the fragments removed at operation shows (Fig. 159) masses of closely packed chromophobe cells with a definite alveolar arrangement, the picture suggesting that of the so-called alveolar sarcoma. The nuclei are large, vesicular, sharply cut and have an open chromatin network. There are a number of large blood sinuses between the alveoli and occasionally a central mass of colloid. At the free margin of one fragment there is a distinct basement membrane, covered by a layer of cells which are ciliated (sphenoidal?). No eosinophile cells.

INTERPRETATION.—Here the pluriglandular syndrome is—as yet—clinically unrecognizable, the hypophysis (both anterior and posterior lobes) probably being still functionally competent, despite the large struma. However, the experience with the other patients in the series similarly afflicted is enough to show what may be expected.

Notable features of the case are (1) the total freedom from the usual discomforts of distention of the pituitary capsule, probably due to the rapid pressure atrophy of an easily distensible sella, and (2) the restoration of vision after partial extirpation of the tumor, after complete blindness had ensued. This merely goes to show that despite the forebodings which an atrophic pallor of the disc occasions, one need not despair of restoring some measure of vision in many of these unfortunates, if the pressure has not endured so long that such fibres as are rendered functionally incapable of transmitting impulses merely through a "physiological block," have become completely destroyed.*

The ease with which hypophyseal symptoms may be misconstrued, even when one is on the lookout for them, is exemplified by the primary mistakes of diagnosis in the following history.

CASE XXIII. (Surgical No. 26039.) **Hypophyseal struma with primary optic atrophy and bitemporal hemianopsia. Dyspituitarism with evidences of former activity. High sugar tolerance. Chronic hypoglycæmia. Operation. Partial extirpation of growth.**

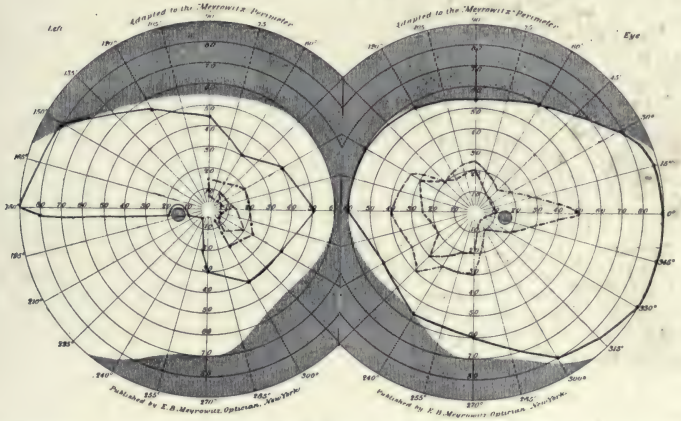


FIG. 160.—Case XXIII. Fields on first admission, June, 1910, suggesting a bitemporal hemiachromatopsia with left quadrantal form defect (misinterpreted).

June 1, 1910. B. C., a coach painter, aged 39, was referred to the hospital by Dr. C. M. Rains of Bohannon, Virginia, complaining of loss of vision. One of a large family of healthy children, he enjoyed a fair measure of health himself until his present trouble. The usual infantile infections were followed by a very severe typhoid and a secondary pneumonia at 14. He subsequently *grew very rapidly*, and at 17 measured 6 feet in height. At 23 he had another attack of typhoid and at 28 pleurisy.

Apart from these illnesses he has been well: a hard-working man of more than the average physical strength. He has used tobacco to excess and alcohol abundantly, but otherwise has had no vices. Though he works constantly with white lead and oil, he has never had any occupational colic or neuritis. He has been married five years and has one healthy child.

Present Symptoms. In March, 1909, he accidentally observed that vision in the left eye was dim. It has progressively failed. He has had occasional temporal *headaches*, but

*In No. 28 of the operative series (cf. p. 310) there occurred an immediate partial restoration of vision after two weeks of total blindness.

they have not been frequent or severe: no nausea or vomiting. *Photophobia*, with aching pain in the eyeballs, has been his chief source of annoyance.

At the time of this first admission in June, 1910, although the fields of vision (Fig. 160) aroused some suspicions, the X-ray plate was inconclusive, and expert ophthalmological opinion was emphatic that the condition was a typical *lead* or *tobacco amblyopia*. A gloomy prognosis was given: he was given large doses of potassium iodide and *discharged*, the visual acuity in the left eye having dropped markedly during the two weeks he was under observation.

August 10, 1911. **Readmission.** The patient, by good fortune, was seen by Dr. Walker in Norfolk, who found a typical bitemporal hemianopsia; and he was advised to re-enter the hospital. He has done fairly well during the intervening year, but for the past few weeks

FIG. 161.—Case XXIII. X-ray of cranial base (unreduced) showing widely dilated sella.

his sight has begun to rapidly fail. As before, dim vision and photophobia are his only complaints, though he is aware of a progressive *asthenia*.

Physical Examination. An overnourished, though healthy appearing man. The visceral (abdominal and thoracic) and cardio-vascular systems are negative.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The X-ray shows the sella to be greatly enlarged, its floor—the outlines of which remain distinct—bulging so far forward as to almost fill the sphenoidal cells (Fig. 161). Profile measurements 3.6 cm. by 2.0 in depth. A protrusion is observable in the nasopharynx. There have been no nose-bleeds or known discharge of any kind into the nares.

Eyes. No oculomotor palsies: no history of diplopia. Slight fine nystagmus both to right and left. Pupils equal in both bright and dim light. Hemianopic pupillary reaction (Wernicke) positive, right and left. Wilbrand prism test negative. *Fundi* show bilateral primary atrophy, principally involving area of emergence of uncrossed fasciculi. *Fields* show typical bitemporal hemianopsia (Fig. 162). *Acuity*, left 15/100; right 15/30.

(b) *General Pressure Manifestations.* Practically negative. Headaches inconspicuous; fluctuating; bitemporal. No exophthalmos; no choked disc, vomiting or dizziness.

(c) *Glandular Manifestations. Skeletal:* Present height 182.5 cm. (5 ft. 11⅞ in.). Patient states that at 17 his *height* was 6 feet and that a few years ago he measured, barefooted, 6 feet 1 inch. He has become round-shouldered. He is much the largest member of

his family: he *weighed* 199 pounds at 21 years of age. The *head*, though large, shows by the X-ray no suggestive acromegalic tendency in occipital protuberance or mandibular arch. The frontal sinuses, however, are somewhat larger than the average. The upper and lower dental arches meet exactly; possibly an indication of slight mandibular prognathism. *Hands* (Fig. 163) are very large, 20.5 cm. in length from tip of median finger to lower edge of radius—*type en long* of Marie. The X-ray shows (Fig. 165) some slight tufting of the terminal phalanges and shadows of the epiphyseal lines (radius) persist (Fig. 167). *Feet* are large: he wears a No. 10 shoe. The skeleton in general is not massive: wrists and ankles are not disproportionate to his size.

Cutaneous. No acromegalic thickening evident. Skin of extremities rather harsh and dry, but patient perspires freely, particularly over the face. He has never observed any œdema. The hair is abundant on the scalp, over the chest, abdomen and neck (Fig. 163): no loss of hair has been observed; beard is fairly heavy. There is an extraordinary brown *pigmentation*, practically limited to the hands; a sharp line of demarcation between the zone of dorsal discoloration and the palmar surface, which is remarkably pale. They

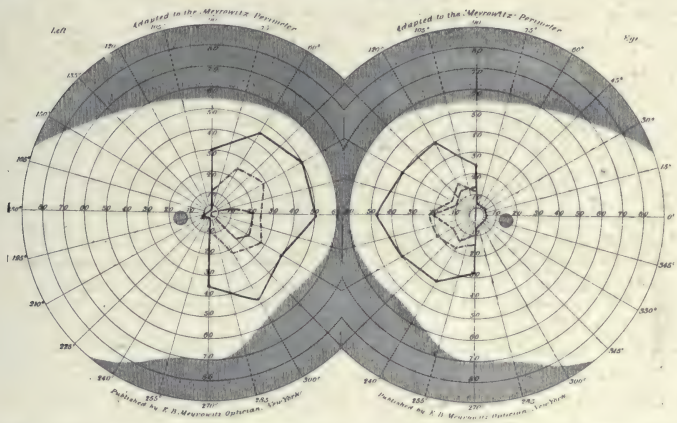


FIG. 162.—Case XXIII. Fields on readmission, Aug. 11, 1911, showing typical bitemporal hemianopsia the form fields sparing the macula.

resemble an anthropoid's hands in hairiness and coloration. *Adiposity* is quite marked, particularly over trunk, but there has been no noticeable increase in weight. Patient says he has weighed from 200 to 215 pounds for some years.

Formerly a man of great physical prowess, during the past ten years he has gradually lost his strength and *muscular asthenia* is now marked. He has considerable vague backache but no pains or tenderness of the extremities. He is noticeably *drowsy*. *Temperature* (97 to 98°) and *pulse* (70) range subnormal. *Blood pressure* 141 mm. No polyuria observed.

Carbohydrate tolerance is exceedingly high, the assimilation limit for lævulose not reached (cf. *infra*) but shown to be over 350 grams. The large doses of sugar are not distasteful.

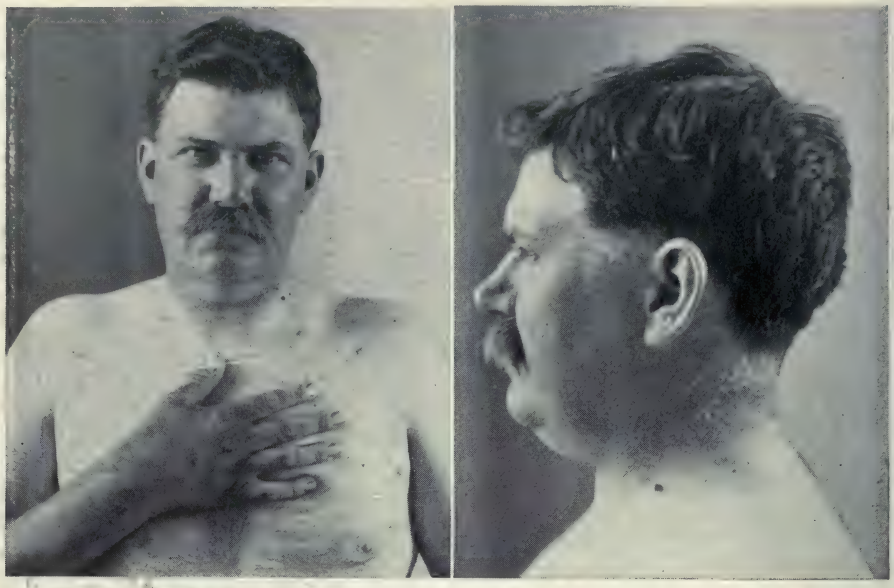
Polyglandular Manifestations. Thyroid not enlarged. No sexual incompetency has been observed. *Adrenal:* Asthenia and pigmentation.

August 15, 1911. **Operation.** Sellar decompression by infralabial and transphenoidal approach with partial extirpation of struma. Urotropin. An easy, uncomplicated operation. Recovery uneventful.

Histological study of the tissues shows (Fig. 166) the usual chromophobe struma, similar to that in the preceding cases though with the connective tissue or supporting elements somewhat more marked.

Secondary Carbohydrate Tests. On *August 24*, 350 grams, on *August 25*, 400 grams, and on *August 27*, 450 grams of lævulose gave no lævulosuria. This is the largest amount of sugar which any individual in the series has been able to retain at one dose.

On *August 29* a sample of blood was taken at 3.40 p.m. and at 3.45 p.m. the patient was given 300 grams of lævulose: an hour later, at 5 p.m., another sample of blood was taken and 2 cc. of "pituitrin" (Parke, Davis & Co.) was introduced intravenously at



FIGS. 163, 164.—Case XXIII. Note pilosity: large and deeply pigmented hand ("type en long" of Marie). On right; profile showing beginning adiposity.

5.10 p.m.: an hour and a half later, at 6.30 p.m., a third specimen of blood was taken. Sample No. 1 was shown by Dr. Jacobson to have a sugar content of 0.0394 grams; sample No. 2 to have a content of 0.053 grams; and sample No. 3 a content of 0.073 grams. Thus,

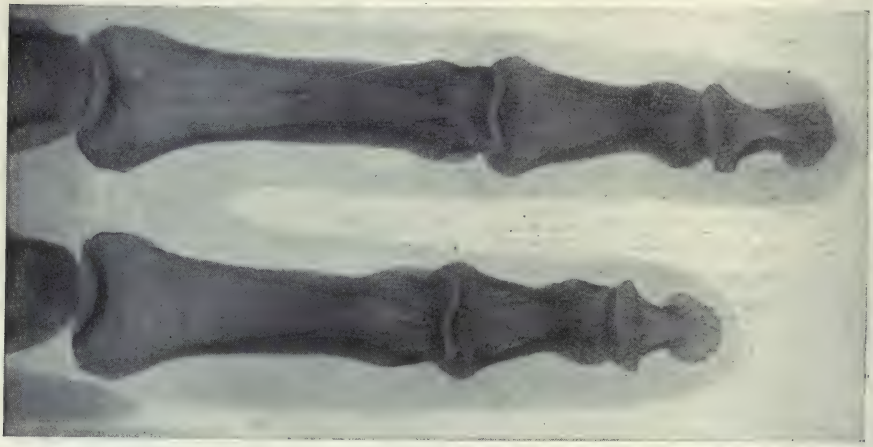


FIG. 165.—Case XXIII. X-ray of fingers (unreduced) showing large size and tendency to acromegalic changes.

an extraordinary condition of *hypoglycæmia* was demonstrated with a sugar content in the blood as low as the normal for the canine and far below that for man, even after the administration of three times the amount of lævulose usually necessary to produce a spontaneous

mellituria. Further, a dosage of posterior lobe extract, which of itself often suffices to cause a spontaneous glycosuria, failed to bring the sugar content of the blood up to the average normal. There was a subsequent marked diuresis (1375 cc. in 12 hours) and rise in blood pressure.

Patient discharged *August 31*. Nose healed; no secretion. No improvement in visual fields.

INTERPRETATION.—It will have been noted that most of the individuals heretofore mentioned in this group have been somewhat undersized, their height averaging about 5 feet 6 inches: further, that in all but two of them the symptoms, such as they were, suggestive of disturbed functional activity of the gland, were on the side of hypopituitarism from the outset. In two of the cases (XIX and XXI) there were slight though suggestive indications of a past hyperpituitarism, shown by the thickening of the tissues of the extremities, and in Case XXI by slight acromegalic alterations in the phalanges themselves.

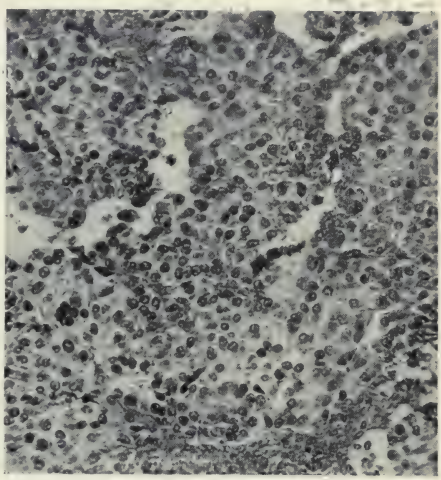


FIG. 166.—Chromophobe struma of Case XXIII (mag. 190 diams.).

In the case under discussion it would seem that an activation of the pars anterior had occurred earlier in life, accounting for the unusual size, and it is to be noted that the epiphyseal lines are still apparent at the age of 39. The natural supposition is that there may have been some tendency toward glandular instability similar to that which we have already discussed in reference to Case I, and that under the influence of an exciting cause of unknown nature the present struma began rapidly to develop.

FIG. 167.—Case XXIII. X-ray of wrist (nat. size) showing trace of epiphyseal line in patient of 39 with tendency to gigantism.

Whether or not the severe infection which occurred at the time of adolescence and which was followed by a period of rapid overgrowth can be taken as an indication of glandular stimulation in consequence of the disease is of course purely conjectural. In this patient, however, as well as in Case I, there seems to have been an early post-adolescent period of hyperpituitarism leading to physiological overgrowth—normal gigantism of Sternberg. This is taken as an indication of an hypophyseal instability which, in the later life of each of these patients, favored the adenomatous transformation which the structure has undergone.

The patient's clinical manifestations of hypophyseal insufficiency are not conspicuous and his moderate tendency to corpulence might easily escape notice. However, the extraordinary tolerance for carbohydrates which he possesses forebodes future adiposity. This is the first case in which a positive hypoglycæmia was demonstrated. So far as I am aware Addison's disease is the only malady in which a subnormal sugar content in the blood has ever been demonstrated.[253] In view of this the suggestive signs of secondary adrenal involvement—the asthenia and pigmentation—are of unusual interest.

GROUP III.—CASES WITH PRONOUNCED CONSTITUTIONAL MANIFESTATIONS OF HYPOPHYSEAL ORIGIN IN THE ABSENCE OF NEIGHBORHOOD PRESSURE DISTURBANCES.

In this group there is less reason than there was in the preceding one for presenting the cases in chronological order. Hence they will be subdivided as were the cases in Group I, and we will consider, first, those in which evidences of primary hyperpituitarism are manifest, and, second, those in which a condition of hypopituitarism was the essential factor from the outset.

A. **Cases with Existent or Past Hyperpituitarism the Striking Clinical Feature.***—The fact that nine out of thirteen of our illustrations of anterior lobe hyperplasia leading to skeletal overgrowth fall in this group is an indication that the gland in these states of outspoken hyperpituitarism, exemplified by acromegaly and gigantism, is destined, with comparative infrequency, to undergo adenomatous transformations with the development of large tumors such as we have seen in Group II.

Despite the reports in the past of occasional instances of acromegaly in which postmortem studies have shown no morphological or histological changes in the pituitary body, there can be little doubt but that in the majority of cases there occurs, at least in the active stage of the process, an enlargement from hyperplasia of the gland which serves to produce subjective discomforts even if it does not suffice to call forth local objective signs. The bitemporal hypophyseal headaches, which are the more common form of these discomforts, I am inclined to attribute solely to the distention of the sentient dural envelope of the gland. They are apt to subside when the activity of the process declines, doubtless with a return of the gland to its former size and possibly to its former appearance.

Hence there is necessarily no more reason to expect a permanent and unmistakable enlargement of a pituitary body which has once been stimulated to functional hyperplasia than there is to expect a persistent enlargement of a thyroid which has passed through a similar period of overactivity. Indeed, it is well known that the clinical manifestations of hyperthyroidism may be entirely disproportionate to the degree of thyroid enlargement, and yet an extirpated lobe may show areas of epithelial hyperplasia typical of the process.

As a rule, however, with a continuous or recrudescing hyperplasia—

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* The question of hyper- *versus* hypo-activity of the pars anterior as the essential element in producing the more characteristic features of acromegaly will be discussed subsequently (page 249). It will suffice to say here that we accept the hyperpituitarism (anterior lobe hyperplasia) view at least as the most satisfactory present conception.

true both for thyroid and hypophysis—the gland remains permanently enlarged in the form of a "struma"—to use an old-fashioned and convenient designation. For this to occur in the case of the hypophysis necessitates an enlargement of the membranous and bony encasement of the gland, and the X-ray fortunately enables us to estimate the size of the pituitary struma under these circumstances with almost greater accuracy than is oftentimes possible in the case of a thyroid struma. Indeed, as will be pointed out (Case XXVIII), a progressive enlargement can be demonstrated by successive measurements and thus the quiescence or otherwise of the process be determined.

In these cases of glandular enlargement in acromegaly the profile outlines of the expanded sella remain clear and sharply cut. There is far less tendency—possibly owing to the osteogenetic features of the malady—for the sella to become eroded by pressure atrophy and for the enlarged gland to project itself into the sphenoidal cells—a characteristic of the adenomatous strumas with hypopituitarism already discussed.

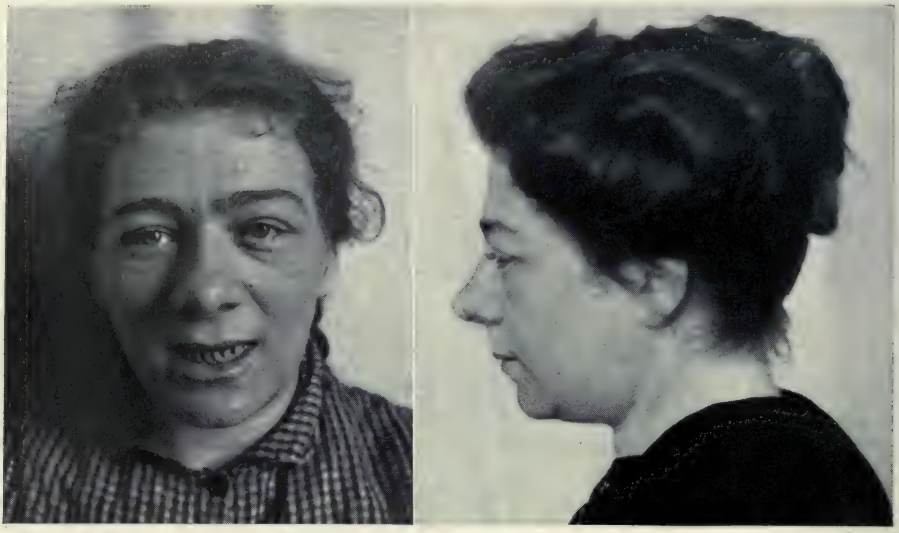
There seems every reason to believe that the glandular hyperplasia in the cases which exhibit symptoms of primary hyperpituitarism behaves in much the same way as do the hyperplasias of the thyroid, with which Marie's studies, more than any others, have made us familiar. It would appear: (1) that many cases show quiescent periods, after which recrudescence may occur; (2) that in many other cases the process actually becomes permanently checked, the clinical traces of skeletal overgrowth remaining merely as the vestige of the dormant malady; (3) that in others an ultimate condition of glandular insufficiency may supervene as the result of excessive involution which succeeds the active process; (4) that in some instances, and apparently at any stage of the process, the struma may become transformed into a rapidly growing adenomatous tumor having so-called "malignant" tendencies.

Under the last circumstance pronounced neighborhood symptoms are of course elicited, and hence under our present tentative clinical subdivision, made for the express purpose of emphasizing these local symptoms, such examples of this transformation as we have seen (Cases I and II) have already been cited. It is encouraging to believe that such an outcome is unusual.

The early acute hyperplasias are at the present day rarely if ever clinically recognized. In the case of a rapidly growing child with possibly some headache and perhaps transient glycosuria, one would hardly venture, even now, to suggest hyperpituitarism; and no more in an adult who showed some prognathism and coarseness of the tissues, unless perchance a neurological, ophthalmological or radiographic examination should disclose neighborhood symptoms. The clinical description of these states is restricted to the full-blown type which every one recognizes on the street. It is natural, therefore, that this series comprises no instances of incipient hyperpituitarism (with possibly the single exception of Case XXXVIII), though with our present knowledge of the subject it doubtless might have been possible to recognize the condition in many of these patients before the characteristic skeletal and other changes became exaggerated. It would indeed be precocious to make a diagnosis of "acromegaly" before enlargement of the acral parts of the body occurs. Still it should be possible.

Of the twelve acromegalies that we have had the privilege of studying in some detail, in only three are the manifestations of hyperpituitarism com-

paratively recent (Cases XXIV, XXV and XXXVIII) and the gland possibly still functionally overactive. In all the others the process has long since become stationary, or, and what is more common, the gland has passed into



FIGS. 168, 169.—Case XXIV. Note coarse features; spacing of teeth, deep wrinkling of brow, abundant head of hair, tendency toward adiposity, absence of mandibular prognathism.

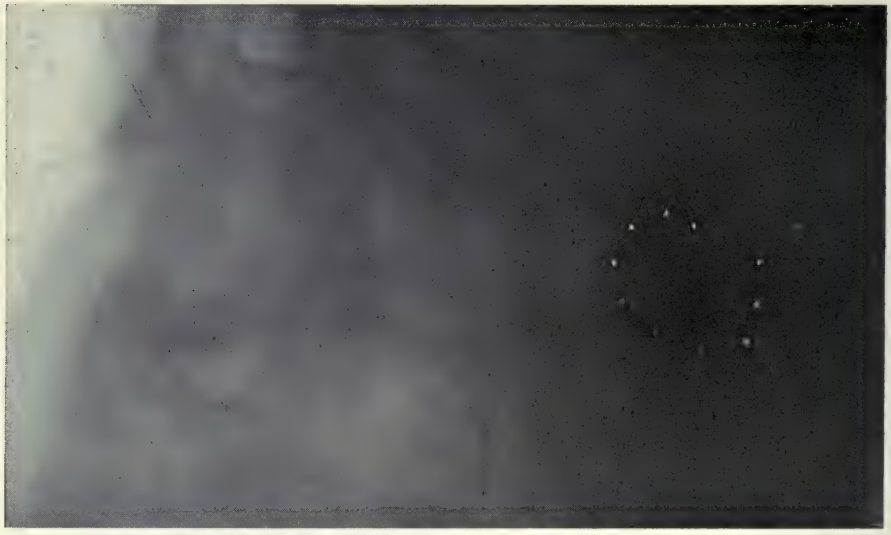


FIG. 170.—Case XXIV. X-ray (unreduced). Sellar outline indicated by dots.

a state of functional inactivity with manifest signs of dyspituitarism—notable being the tendency toward adiposity and a high assimilation limit for carbohydrates.

It is well known that spontaneous glycosurias are not uncommon in acromegalics, but our experience would lead us to believe that they occur only during the periods of functional hyperplasia. In most of these cases, as will be seen, the assimilation limit is very high—as high as in some of the unmistakable cases of primary hypopituitarism, viz., 400 grams or over of lævulose. The sugar tolerance, as will appear in the following cases, is a fair index of the age of the process as well as of the present degree of glandular insufficiency. In the first two cases it is relatively low and within normal limits. The only instance of a tolerance considerably below the normal will be found in Case XXXVIII of Group IV.

Case XXIV. (Surgical No. 27256.) **Hyperpituitarism with acromegalic symptoms of five years' duration. Enlarged sella turcica. Conditions probably still active. Sugar tolerance 225 grams lævulose. No neighborhood symptoms. No treatment.**

January 23, 1911. Mrs. C. E. T., 37 years of age, referred by Dr. C. N. Strickler of Atlanta, Georgia. *Complaint:* Numbness and pain in hands and arms with enlargement of extremities; cessation of menses; frequent urination.

Patient's mother died of cancer. In addition to the usual infections of childhood, she had typhoid and malaria as a child and a severe attack of dysentery twelve years ago.

Marital. Normal catamenia inaugurated at 13 years of age. She was married at 19 and has had five healthy children. Between her last pregnancy three years ago and the preceding one there were three miscarriages. During the past two years she has had only five menstrual periods.

She has a large appetite and a distinct appetence for sweets. She has gained 20 pounds in weight in the past two years. She has habitual constipation.

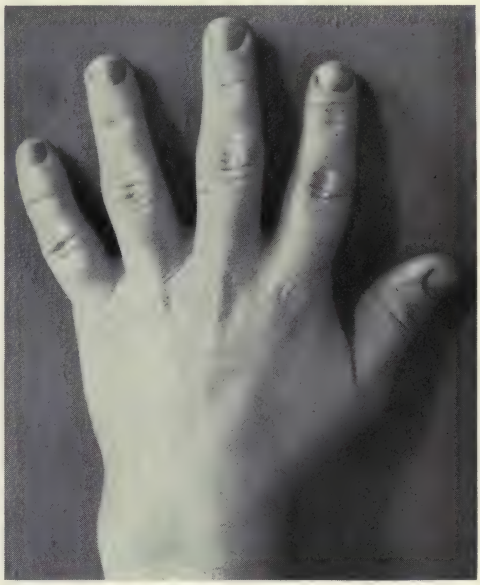


Fig. 171.—Case XXIV. Characteristic square hand: "type en large" of Marie.

The Existing Malady. This she dates from the onset of numbness and burning sensations in the fingers nine years ago, shortly after the birth of her fourth child. It is notable that during the three earlier pregnancies there was a tendency to swelling and enlargement of the hands and feet. The numbness and burning sensations have steadily increased and have been particularly troublesome of late. They first involved the thumb and first two fingers of the right hand, but subsequently spread up the arm and now involve the left hand and arm. Only once has she been without this symptom—during her last pregnancy.

Six years ago, lasting over a period of three years, she suffered from nervousness, lack of energy and extreme weakness.

An increase in the size of the extremities was first noticed five years ago, supposed at first to be merely an œdema. This has been progressive and she now wears shoes two sizes larger than formerly.

At about this time and lasting over a period of two years there was an extreme polyuria of uncertain ætiology (diabetes insipidus?). No glycosuria has ever been observed.

Formerly possessed of a delicate and clear complexion, the skin has become coarse, the complexion muddy and the features heavy.

She has been given thyroid extract without modifying her condition.

Physical Examination. A large-framed, coarse-featured woman inclined to adiposity (Fig. 168). Her *weight* is 186 pounds, attributable more to her large bony frame than to its coverings. Her breath is foul; tongue heavily coated. Visceral (thoracic and abdominal) examination negative. No unusual neurological features, though the deep reflexes are brisk to exaggeration (compare the usual inactive reflexes of advanced cases). *Blood* and *urine* negative.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The *X-ray* shows a large sella turcica, measuring in profile 2.0 cm. in depth by 1.5 cm. in its antero-

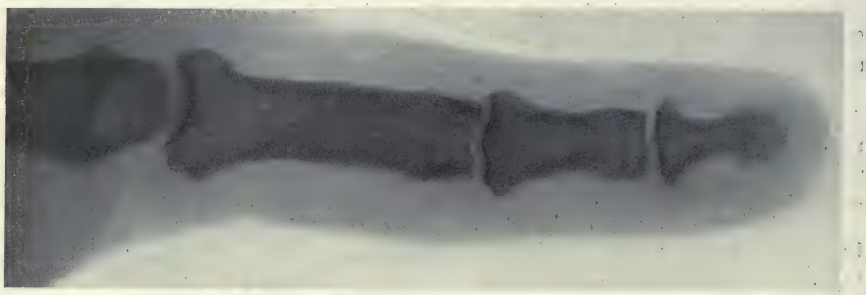


FIG. 172.—Case XXIV. X-ray of finger; acromegalic changes inconspicuous.

posterior diameter (Fig. 170). The eyes are widely separated but show no abnormalities. The visual fields are normal. Nasopharynx normal.

(b) *Glandular Manifestations. Skeletal:* Height 5 feet 5 inches. Outspoken acromegalic features. No prognathism, but the teeth are much separated (Fig. 168). The face has appreciably widened at the level of the orbits; the frontal sinus is large and there is an enlarged occipital protuberance. She stands erect without rounding of the shoulders. Clavicles and sternum are large and prominent. The chest has increased in size. The hands (Fig. 171) and feet are large; toes much facetted, many of the nails growing vertically. The X-rays of the hands show that the acromegalic changes are largely restricted to thickenings of the soft parts (Figs. 172, 173).

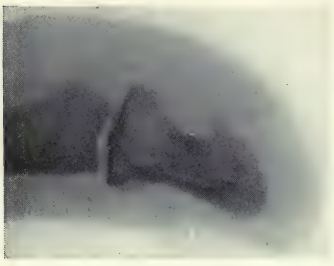


FIG. 173.—Case XXIV. X-ray of thumb showing exostoses.

Cutaneous. The skin of the face and hands is thick, coarse and, according to patient's statement, has recently become hirsute. It is moist and she perspires freely. The hair of the head is abundant. The tongue is enlarged. Evidently there is a fluctuating œdema of the soft parts, the skin at times being tense with deep creases, and at others elastic and movable, with finer wrinkles. The cutaneous glands are enlarged, with comedones over the face and back. There are a number of moles.

Though the patient is over-well nourished, there is no excessive adiposity. Her *weight* apparently fluctuates considerably, depending upon the presence or otherwise of *œdema:* a variation of 10 pounds was noted within a few days' interval while she was under observation. According to the history there has been a definite *polyuria;* not observable at present.

Carbohydrate Tolerance. Assimilation limit established for lævulose at 125 grams (1.7 grams per kilo.).

Temperature is irregular, occasionally varying from 97° in the morning to 99.6° in the evening. It usually ranges, however, slightly above normal. The anterior lobe injection gave

no thermic response and was followed by none of the discomforts usually observed in patients suffering from a glandular deficiency. *Blood pressure* is unusually low (90 to 100 mm. Hg.).

Other Ductless Glands. Thyroid not palpably enlarged. Amenorrhœa.

INTERPRETATION.—One interesting feature of the case lies in the suggestive evidences of glandular overactivity which accompanied the early pregnancies and the possible effect which repeated child-bearing may have in exciting the gland to a state of pathological overactivity, much as one sees the thyroid occasionally activated by consecutive pregnancies. Certainly any indications of hypophyseal instability—headache with psychic phenomena, accompanied by paræsthesias with swellings of the hands and feet—which accompany child-bearing should give as definite warning against its immediate repetition, as do the transient and more often recognized symptoms of hyperthyroidism.

In the absence of neighborhood pressure symptoms and in view of the fact that the process appears to be stationary or quiescent, there seems, in the present state of our knowledge, to be no clear therapeutic indication for this patient. It is possible that the condition may be approaching a state of hypopituitarism, in which case an increase in sugar tolerance will appear and organotherapy may become necessary.

The following case is likewise a relatively early one.

CASE XXV. (Surgical No. 27247.) **Hyperpituitarism with recent stationary (?) acromegalic changes. Slight enlargement of sella. No neighborhood symptoms. No treatment.**

Jan. 21, 1911. S. S., a Hebrew merchant, aged 40, referred by Dr. A. G. Eaddy of Timmonsville, South Carolina, through Dr. L. F. Barker. *Complaint:* Nervousness and constipation.

The patient comes from a family noted for its good health and longevity, and aside from his present malady he remembers no personal illness. His habits are good. He has done much hard physical labor. Has a ravenous appetite. He has been married nine years and has two healthy children.

The Existing Malady. Onset six years ago with severe headaches, dizziness, constipation, flatulence, weakness and nervousness. These symptoms have largely abated. He now complains of dull pain in his left arm and shoulder. He has noticed that his finger ring has become too small and he has required a larger shoe. No change in potentio sexualis.

Physical Examination. A tall, dark-complexioned, exceedingly hairy man, with characteristic acromegalic features (Figs. 174, 175). Height 5 feet 11¾ inches; weight 160 pounds. *Visceral* (abdominal and thoracic) examination negative. *Neurological* examination negative except for overactive deep reflexes. *Blood* and *urine* negative. Wassermann negative.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* Nothing except the slight enlargement of the sella, which measures 1.8 by 1.4 cm. in depth (Fig. 176).

(b) *General Glandular. Skeletal:* Large frame. Head large and square: X-ray shows characteristic prominence of frontal sinuses, occipital protuberance, mandible, etc. Thorax large. Slight kyphosis and scoliosis. Hands large, spadelike; fingers clubbed; usual changes on X-ray (Fig. 177).

Nose, ears and larynx enlarged; lips very thick. The heavily coated tongue is twice the normal size. Pyorrhœa alveolaris.

Cutaneous. The skin is coarse, thick, heavily wrinkled and everywhere mottled with a remarkable brownish pigmentation, particularly over groins and around navel. There is a most unusual degree of hypertrichosis (cf. Figs. 178, 179). No adiposity.

Temperature and pulse range on the average about normal. *Blood pressure* extremely low (85 to 90 mm. Hg.). No polyuria.

FIGS. 174, 175.—Case XXV. Patient at the age of 31, three years before onset, contrasted with present appearance, nine years later.

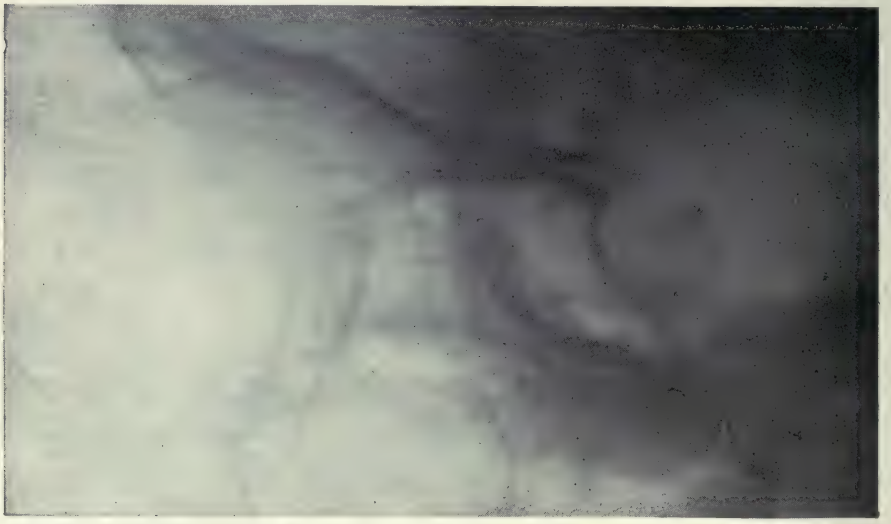


FIG. 176.—Case XXV. X-ray of cranial base (nat. size): slightly enlarged sella of double contour.

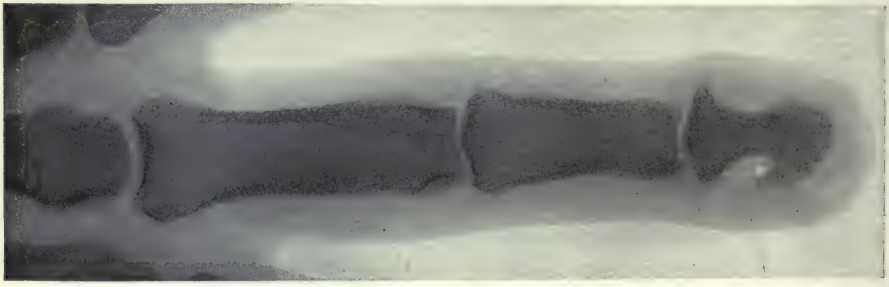


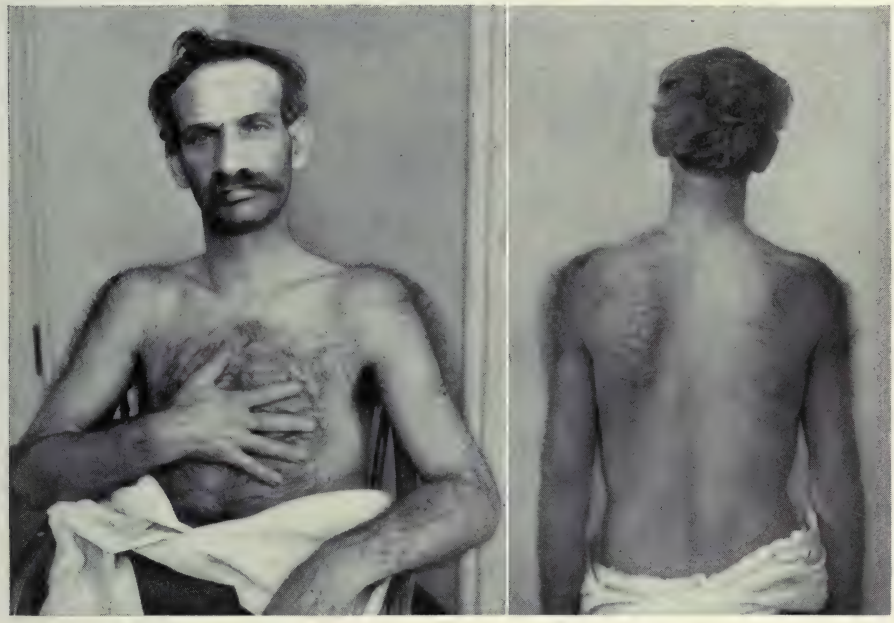
FIG. 177.—Case XXV. X-ray of middle finger (nat. size) to show exostoses.

Carbohydrate tolerance not increased. Limit for glucose 150 grams; for lævulose about 110 grams. Slight *thermic reaction* (from 98.6° to 100°) after an injection of 0.4 gram anterior lobe extract.

Polyglandular Symptoms. Thyroid palpable, possibly slightly enlarged. *Adrenal:* Low blood pressure, asthenia and considerable pigmentation of the skin. *Testes* normal; no functional alteration apparent.

Subsequent Examination. Aug. 18, 1911. Symptoms largely in abeyance, but he continues to have dull pains in arms and legs. There has been a gain of 16 pounds in weight. No further enlargement of sella shown by X-ray.

INTERPRETATION.—This acromegalic represents a fairly recent and possibly still active condition of hyperpituitarism. The extreme hypertrichosis



FIGS. 178, 179.—Case XXV. To show disposition of hirsuties: acromegalic facies and hand.

and excessive sweating are notable features. He is one of the few patients in our entire series of thirteen who still possessed a low (normal) sugar tolerance.

The case serves as a fair clinical illustration of the pluriglandular nature of the malady, resembling in many ways Case XXIX, both having enlarged thyroids, both being greatly pigmented. In this patient, furthermore, there is an exceedingly low blood pressure. This, with the pigmentation and hirsuties and muscular weakness, suggests adrenal involvement.

The following patient, chronologically the first in our series of acromegalics, was thought to be in a fairly active stage of the disease. Unfortunately he was seen before our carbohydrate studies had been made, so that this valuable measure of glandular activity is not available in the record. He was operated upon in the hope of relieving the persistent hypophyseal headaches, attributed to distention of the glandular capsule.

CASE XXVI.* (Surgical No. 23779.) **Adult hyperpituitarism of eight years' duration with outspoken acromegaly. Condition still active. Enlarged sella. No sugar tests. Operation. Partial extirpation of pars anterior.**

March 17, 1909. J. H., a farmer, 38 years of age, referred by Dr. C. H. Mayo, of Rochester, Minn. *Complaint:* Headaches, photophobia and progressive enlargement of the tongue, face and extremities.

He has been a healthy man of good habits. There is nothing noteworthy in his family or early personal history. He has been married seven years and has one child five years of age.

Present Malady. He has suffered for eight years from periodic *headaches*, which of late have increased in frequency and severity and are accompanied by marked *photophobia*. The discomforts are referred to the right temporal region, whence they radiate to the back of the neck, which "becomes drawn." For some years he has been aware that his lips,

FIGS. 180, 181.—Case XXVI. Patient at 25, before onset of the malady, contrasted with present condition.

tongue, jaw, hands and feet were slowly *increasing in size*, but does not think there has been any advance in the condition during the past two years. His weight has been increasing and he has felt weak and "worn out." He complains of *dizziness*, of a sensation of *tingling in the extremities* and of suffering greatly from cold. Anaphrodisia for the past year or two.

Physical examination shows a well-nourished man with the characteristic features of acromegaly (Figs. 180, 181). Abdominal and thoracic viscera negative. No cardiovascular changes.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The X-ray shows an enlargement of the sella turcica with thickening of its walls: profile measurements 1.8 by 1.8 cm. in depth (Fig. 182). *Eyes:* Though photophobia is extreme the pupillary reactions, ocular movements, fields, acuity and fundi show no deviation from the normal.

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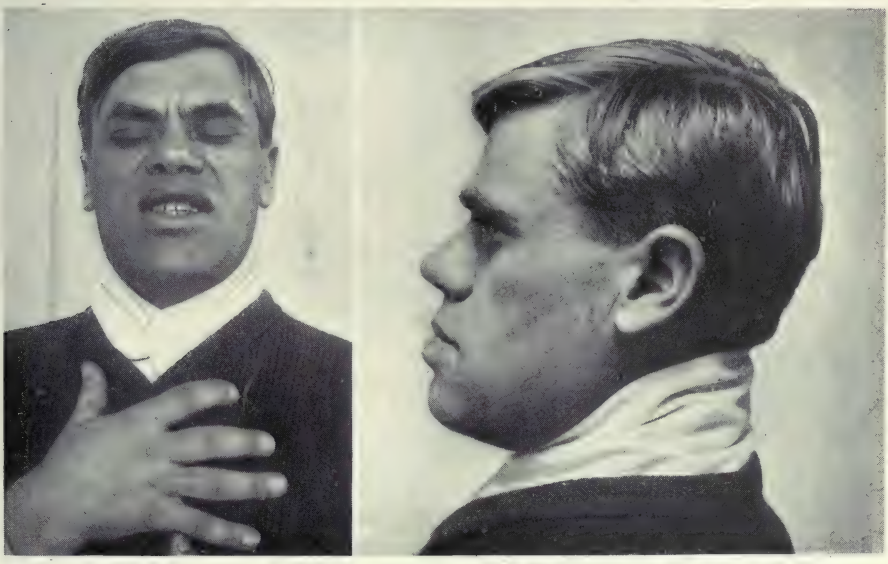
*This case has been heretofore recorded (Partial Hypophysectomy for Acromegaly) in the Annals of Surgery, December, 1909, and in the Transactions of the XVI International Medical Congress, Budapest, 1909.

(b) No *general pressure symptoms.* The headaches are attributed to distention of the glandular capsule (a view confirmed by the relief which the operation afforded).

(c) *Glandular Manifestations. Skeletal:* Height 5 feet 8 inches. Typical manifest *acromegalic changes* (Fig. 183). Skiagrams show no trace of epiphyseal lines. The hands

FIG. 182.—Case XXVI. Showing thick-walled, slightly enlarged sella (unreduced).



FIGS. 183, 184—Case XXVI. Note photophobia; spacing of teeth; full œdematous hand (cf. Fig. 186 and characteristic acromegalic profile.

and feet are much enlarged and show usual bony changes (Fig. 185). The circumference of the middle finger is 8.5 cm.; that of the great toe 10.5 cm. The lower jaw is undershot (Fig. 184), the lower incisors projecting 1 cm. beyond the upper. The teeth are widely spaced. Tongue is enormous and so fills the mouth as to seriously impede the speech; the

lips and nose are thick, the supra-orbital ridges prominent, the frontal sinues being much enlarged. The thorax is barrel-shaped, the clavicles and sternum being especially heavy and prominent. There is considerable rounding of the shoulders. There are no visceral hypertrophies nor other abnormalities to be detected.

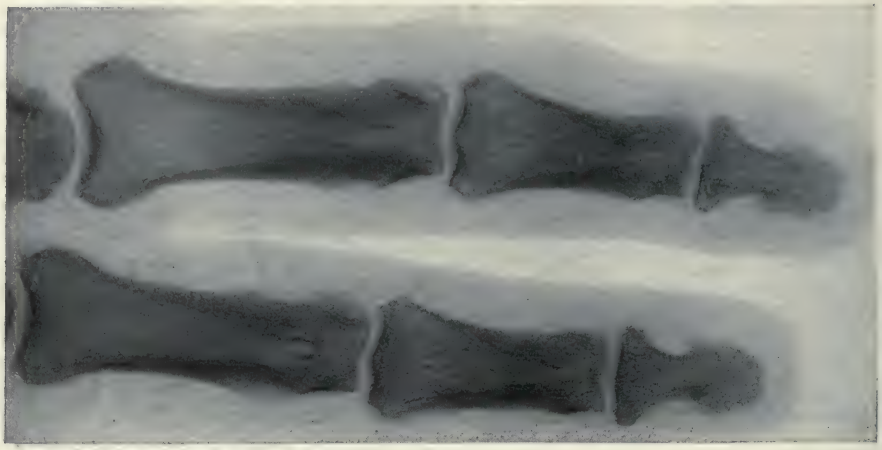


FIG. 185.—Case XXVI. Skiagraph of middle and ring fingers (nat. size), showing terminal tufting and lateral exostoses.

Cutaneous. Skin is coarse, moist, hirsute; cutaneous glands hypertrophied. The subcutaneous tissues of the hands and face feel dense, as though distended with a solid œdema. The hands are clammy and show a peculiar cyanotic duskiness, as does also the face (antipyretics?).

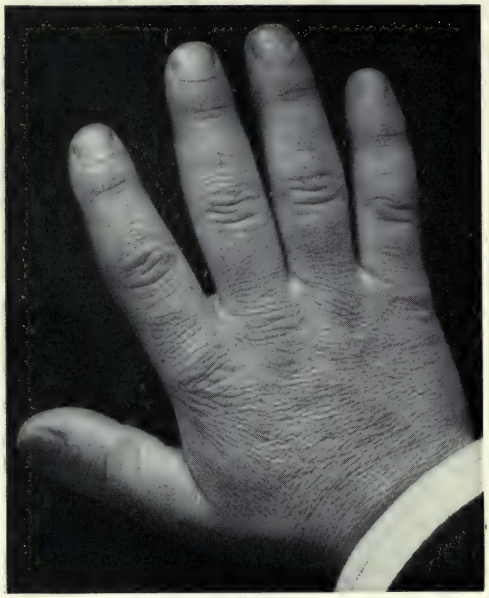


FIG. 186.—Case XXVI. Marked wrinkling of hand on post-operative subsidence of "œdema."

He is well nourished, *weighing* 188 pounds—largely skeletal, as there is no striking adiposity. The *temperature* is occasionally slightly subnormal (97° to 98°) and the *pulse* also, occasionally registering as low as 60 per minute. The urine is normal; there is no polyuria nor glycosuria. (We had not, at this time, made use of the thermic reaction or of tests of carbohydrate tolerance.)

Other Ductless Glands. There is no palpable enlargement of the thyroid; no testicular atrophy.

March 25, 1909. **Operation.** A preliminary tracheotomy was necessitated by the difficulty of anæsthetization, due to the patient's large tongue. The gland was approached by *Schloffer's transphenoidal route* after osteoplastic resection of the anterior wall of the large frontal sinuses with downward deflection of the nose. The floor of the sella was removed, the glandular capsule split and what was thought to be about one-third of the pars anterior removed. Drainage through the nostril after closure of the external wound.

A section of the slightly *enlarged thyroid isthmus*, necessarily divided during the tracheotomy, was removed for examination. The tracheal wound was immediately closed. There were no post-operative complications.

The patient's headaches promptly subsided and likewise his photophobia in large measure. Not long after the operation he called attention to the fact that his hands (Fig. 186) had lost their former stiffness and that the skin was finely wrinkled instead of being smooth and puffed—a state in which he did not remember having seen them for some years. He was discharged *April 11*.

Histological examination of the anterior lobe fragments which were removed shows (Fig. 187) a predominance of chromophile elements with normally disposed eosinophilic cells lining the sinusoidal spaces. The *thyroid* section shows a "colloid goitre."

Subsequent Note. *June 24, 1909.* Returns for observation: confident that there is a marked change in his appearance. The dense subcutaneous œdema is less marked. The measurable lessening in the size of the hands, feet, fingers, etc., is in all likelihood due to the subsidence of the œdema rather than to any skeletal change. No headaches. Complete (post-operative) *anosmia*. Letters during 1910 and 1911 record *polyuria* (2000 cc.), occasional periods of headache and photophobia. No increase in weight.

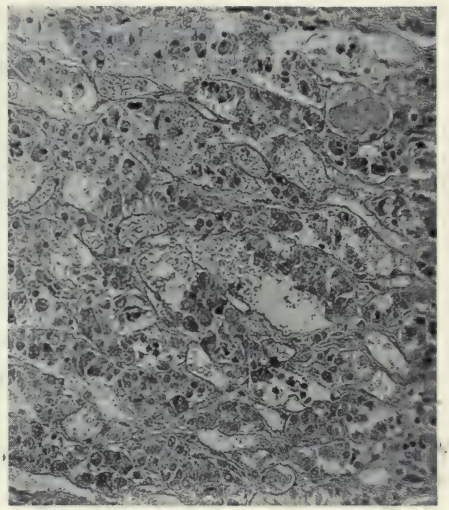


Fig. 187.—Struma with chromophile elements from Case XXVI (mag. 190 diams.).

Interpretation.—A typical case of acromegaly of eight years' slow progress and probably still advancing. The slight enlargement (hyperplasia) of the gland did not suffice to produce neighborhood symptoms. The headaches, in view of their post-operative subsidence, were, in all probability, due to distention of the sensitive dural envelopes, and would doubtless have been relieved by the mere incision of the capsule.

The operation was conducted under the belief that the condition, supposedly one of hyperpituitarism, would be benefited, as is hyperthyroidism, by partial excision. Owing to the measurable post-operative subsidence in size of the acral parts of the body, the experience naturally suggests, as do those of Hochenegg,[127] that the syndrome acromegaly is actually one of hyperpituitarism. The matter will be considered later on (page 250).

The following two cases are more obviously verging on dyspituitarism, and organotherapy is clearly indicated.

Case XXVII. (Surgical No. 27290.) **Typical acromegaly of nine years' duration. Present signs of dyspituitarism. No neighborhood symptoms. Enlarged sella. Organotherapy.**

Feb. 1, 1911. Mrs. L. C., a school teacher, 35 years of age, referred by Dr. J. H. McDuffie, of Columbus, Georgia, through Dr. L. F. Barker. *Complaint:* "Weeping navel," amenorrhœa, weakness and pains in extremities, which have become enlarged.

The patient is one of a family of five children; the others well. She was born with an allantoic fistula. There has been a continuous discharge since she was six years of age; occasionally a retro-umbilical pouch fills and causes a tumor, which can be discharged by manipulations.

Her menses began at 16 and were regular until she was 26. At this time she had a severe "sick headache" with nausea and vomiting, followed by amenorrhœa for six months. Menses returned for a time and then ceased again. She thinks she menstruated vicariously from the navel for a time. She has been married four years; never pregnant. Always a hearty eater; chronically constipated.

Existing Malady. Patient's mother called attention to her *increase in size* and weight eight or nine years ago: her rings, gloves and shoes became too small. About this time her menses first ceased. *Amenorrhœa* has persisted for the past eight years. For a year or two there has been an uncomfortable *numbness and tingling* in the face and hands. Pains in the left sciatic region have been severe and she has had substernal discomforts. There has been practically no headache.

She suffered from a physical breakdown five years ago and has since been exceedingly *nervous and emotional*. *Drowsiness* has been pronounced for the past three or four years. She complains of great physical *weakness* and cannot attend even to trifling tasks.

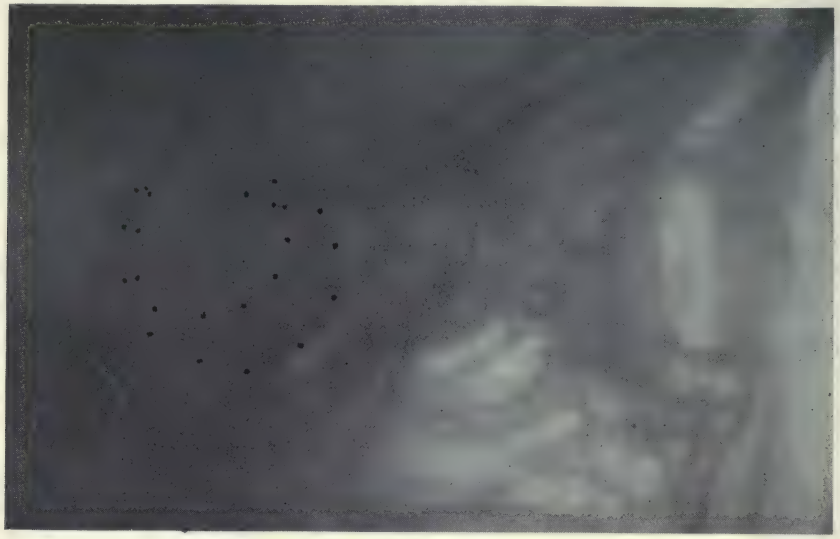


FIG. 188.—Case XXVII. Enlarged sella of double contour (nat. size).

She has taken thyroid extract for six months, with considerable improvement: she has become more energetic; the œdema of the face, eyelids and hands has subsided.

Physical Examination. A rather stout, large-framed, coarse-featured woman. Speech thick, owing to enlarged tongue. The visceral (thoracic and abdominal) examination is negative except for the *patent allantoic canal*. This discharges a bloody mucus, which has excoriated the skin surrounding the navel. She has an intermittent pulse. Cardiovascular condition is negative: neurological tests also, aside from her inactive deep reflexes. She is hypochondriacal; excessively nervous; powers of concentration impaired.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The *X-ray* shows (Fig. 188) an enlarged sella measuring in profile, 2.4 cm. in depth by 2.8 cm. in its antero-posterior diameter. No nose-bleeds. Slight exophthalmos; otherwise eyes negative in all respects. Fields normal. Nasopharynx negative.

(b) *Glandular Manifestations. Skeletal:* Height 5 feet 8 inches. Characteristic acromegalic features; slightly undershot jaw; broad nares (4 cm.). Hands show characteristic changes on X-ray (Fig. 189). Chest large; clavicles and sternum prominent. Hypertrophied larynx with change in voice. *Soft parts* of extremities greatly thickened. Tongue heavily coated and hypertrophied. *Nutritional:* Her average weight was formerly 118

pounds. Since 1907 she has been growing adipose. She now weighs 158 pounds. The skin is coarse; glands hypertrophied.

Temperature tends to be subnormal (96.5° to 98°). *Pulse* 65 to 75. *Blood pressure* very low (75 to 96 mm. Hg.). No polyuria.

Carbohydrate Tolerance. Assimilation limit for lævulose about 160 grams. *Thermic response* (to 0.4 grain of anterior lobe extract hypodermically) positive, giving a reaction from 97° to 100°.

Other ductless glands negative. No palpable enlargement of the thyroid. Amenorrhœa.

Operation for closure of the patent allantoic canal advised: refused. No surgical indications for the pituitary enlargement. Patient discharged, taking combined hypophyseal and thyroid tablets.

INTERPRETATION.—A typical case of acromegaly of ten years' duration with symptoms traceable from the patient's twenty-sixth year. There has

FIG. 189.—Case XXVII. Index and middle fingers showing terminal tufting.

been an enlargement of the gland, as shown by the X-ray, causing, however, no neighborhood symptoms.

That the former stage of hyperpituitarism is being superseded by one of relative glandular inactivity is evidenced by the existent symptoms suggestive of "hypophyseal myxœdema"—the subnormal temperature, the moderately high assimilation limit for sugars, the adiposity with increase of 40 pounds in weight, and so on. The positive thermic reaction following the injection of anterior lobe extract is regarded as an indication of present insufficiency of pars anterior.

Noteworthy are the associated congenital abnormality of the umbilical canal and the marked improvement in the symptoms by thyroid administration.

CASE XXVIII. (Surgical No. 26210.) **Typical chronic hyperpituitarism of adul life (acromegaly) of ten years' duration. Progressive enlargement of sella. No neighborhood symptoms. Glandular therapy, with marked improvement.**

July 6, 1910. J. M., a minister, 40 years of age, admitted for observation. *Complaint:* acromegaly.

He is one of a family of six children: all the others well. In 1887 he had apical tuberculosis, and on Dr. Osler's advice passed three months at Asheville, where his weight increased from 140 to 170 pounds. It was at this time that signs of skeletal overgrowth were first observed. He has since gained steadily in weight and now weighs 190 pounds.

FIGS. 190, 191, 192.—Case XXVIII. Patient before the onset of the malady (aged 18); at the time of onset (aged 26); on admission, after its full development (aged 40).

He has always suffered from catarrh and has had two septal operations. In 1908, in a fit of coughing during an attack of bronchitis, he had a severe pharyngeal epistaxis.

The Existing Malady. Formerly rather slightly built (Figs. 190–192), there has been

FIG. 193.—Case XXVIII. X-ray showing enlargement of sella (nat. size) with thickening of anterior and posterior clinoid processes, shown by double row of dots.

a gradual increase in the size of his head, face, hands and feet for about ten years. This was accompanied at first by aching pains in the bones which would banish sleep. An enlargement of the tongue with resultant thickness of speech led to such embarrassment in public speaking that he has abandoned it.

Though he has no headache at any time, he has felt drowsy, dull and mentally inactive for the past two years. He has had some attacks of suboccipital pain, acute in onset, increased by movement of the head and only relieved by lying flat or letting his head hang forward (cf. Case XXX). Some of these attacks have led to vomiting. He complains, also, of discomfort in the lumbo-sacral region. He has been aware of polyuria and of a marked loss of libido sexualis. He has an enormous (abnormal) appetite and has become particularly fond of sweets.

Physical Examination. A well-nourished man of 5 feet 8 inches, *weighing* (stripped) 190½ pounds and showing the outspoken signs of acromegaly. There is no obvious cardiovascular lesion: the visceral (thoracic and abdominal) examination is negative.

A *neurological study* gives as the only positive signs a distinct lowering of the sense of smell, the left pupil slightly larger than the right, a definite nystagmus—slow to right, rapid to left. This is possibly of some moment, in view of the attacks of suboccipital pain with vomiting. There are, however, no other signs of a cerebellar lesion (cf. Case XXXVIII). The deep reflexes are inactive.

There is a definite looseness (subluxation) of the right sacro-iliac joint, possibly due to the bony deformations and doubtless the cause of his "backache," in view of the relief afforded by strapping.

The thyroid is palpable but does not appear enlarged.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* A stereoscopic X-ray (Fig. 193) shows a considerable enlargement of the sella turcica, the fossa measuring 2 cm. by 1.5 cm. in depth. There is otherwise nothing. The fundi, perimetric charts, ocular movements, etc., show no deviation from the normal.

(b) *Glandular Manifestations. Skeletal:* The acromegalic changes are striking and typical. The occipital protuberance, the mastoid processes and supra-orbital region (Fig. 194) are much enlarged (formerly wearing a 6⅞ inch hat he now requires a 7⅜ size). The lower jaw is undershot and greatly widened, so that the teeth do not meet, though individually they are not appreciably spaced. The bones of the thorax are large and heavy, but there is no kyphosis of the upper spine. He is very erect and states that his *height has increased* from 5 feet 8¼ inches in 1897 at the onset of the malady to 5 feet 10½ inches at present. The characteristic bony changes occur in the phalanges (Fig. 195).

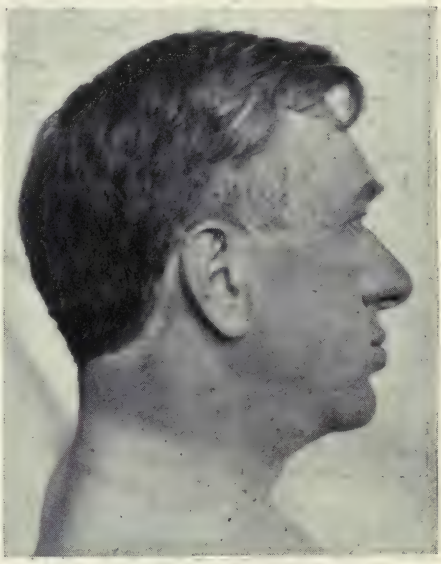


FIG. 194.—Case XXVIII. Characteristic profile with prominent supra-orbital regions.

The *skeletal coverings* are likewise hypertrophied. Notable are the thick lips, nose and ears, and particularly the subcutaneous coverings of the extremities. The tongue is huge and completely fills the mouth. The hands are square and the sort parts crowd up around the nails, obscuring the crescents (Fig. 196). The nails of the toes tend to grow vertically upward. The circumference of the middle finger at the first knuckle is 8.25 cm. (cf. 8.5 cm. in Case XXVI, 9 cm. in Case XXXI, and 10 cm. in Case XXXII). The breadth of the open palm at the knuckles is 11 cm. In the occipital region the thick scalp is puckered into heavy transverse folds.

The *skin* is thick and coarse and the cutaneous glands hypertrophied, particularly over the face. The hands and feet are continually moist and the patient perspires freely. There is a tendency to *hypertrichosis*. The *hair* is abundant, coarse and slightly gray; the

eyebrows are heavy and grow rapidly. The axillary and pubic growth is abundant, the latter spreading up to the costal angle. There is an abundant growth of coarse hair over the sacrum.

There are numerous fibroma molluscum* and a symmetrically placed subcutaneous *lipoma* at the inner side of each arm. There is a tendency to extreme looseness of the skin over the body generally, more especially over the arms and back of neck.

Tests for *carbohydrate tolerance* show an assimilation limit for glucose at about 300 grams. The patient's fondness for sweets is notable in this connection (cf. later note).

The *temperature* is markedly subnormal (96°–98°). An *anterior lobe injection* (2 cc. of a 5 per cent. solution) caused a thermic response from 97° to 99°, which persisted for

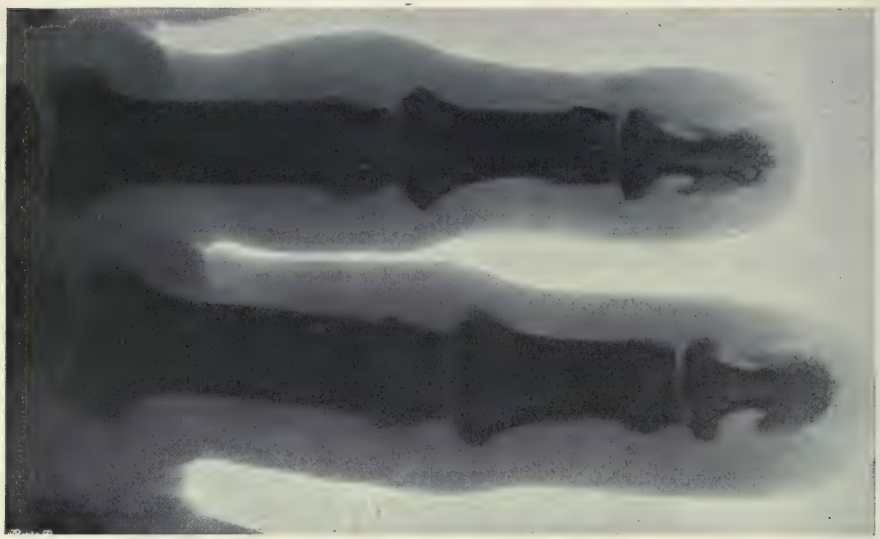


Fig. 195.—Case XXVIII. Characteristic phalangeal changes of high degree.

twenty-four hours (no local reaction). There is a definite *polyuria*, the 24 hour amount often being over 2000 cc.: one measurement of 2540 cc. exceeding the measured fluid ingested.

A *lumbar puncture*, with a withdrawal of 50 cc. of fluid concentrated to 2 cc. and injected into a rabbit gave positive results for the presence of posterior lobe secretion.

The patient left the hospital *July 18*, taking 3 grains of whole gland extract (Armour) three times a day.

Sept. 17, 1910. Re-examination. He expresses himself as much improved subjectively and is sure that his nose, tongue, lips and hands are becoming smaller. His articulation is better and he has resumed the giving of public lectures. His temperature keeps slightly subnormal, despite the extract, but he has been losing weight (6 pounds). The dosage of the extract was doubled.

July, 1911. **Subsequent Examination.** Patient in excellent condition: actively at work. Is confident of a subsidence in the size of the tongue, lips, hands and feet. He wears a size smaller shoe than has been possible for years.

An *X-ray* examination (stereoscopic) of the base of the skull shows that the *sella has definitely enlarged.* It now measures 2.3 by 2.0 cm. in its two dimensions on the plate. The enlargement, however, has occurred without pressure discomforts or the production of neighborhood symptoms.

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* The tendency toward neuro-fibromatosis is not uncommon in acromegaly. I have seen another case (not included in this series) in which the condition was quite marked. Others have called attention to the combination of Marie's and Recklinghausen's syndromes.[196]

Carbohydrate Tests. Tolerance for lævulose established at 220 grams. On this basis the sugar tolerance has greatly increased (cf. July, 1910, limit 330 grams glucose). The attempt to estimate the *therapeutic dosage* on the basis of sugar tolerance shows that it requires 12 grains of extract three times a day, by mouth, to cause a slight lævulosuria on taking 125 grams of lævulose—an amount of sugar representing his presumed normal. He still has an extreme sugar appetence. The temperature is normal, but if the extract is omitted it becomes subnormal, often 96°. His weight has not increased under the treatment.

Sept., 1911. On 12 grains of the extract three times a day he continues to feel perfectly well and is actively engaged in his professional work.

Interpretation and Discussion.—A typical case of acromegaly of thirteen years' duration and of about ten years' active progress, with an onset more or less coincident with a tuberculous lesion of the lungs. At present the glandular activity has subsided and the condition is verging

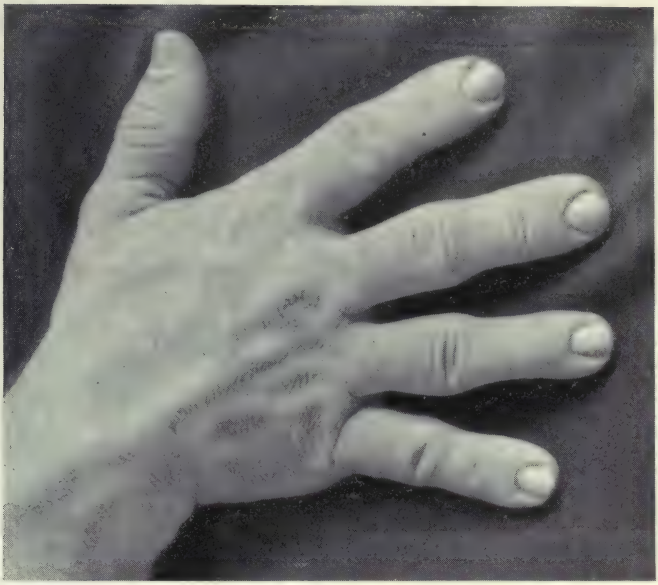


Fig. 196.—Case XXVIII. Characteristic hand: note heaping up of tissues about nails. "Type en large" of Marie.

toward hypopituitarism, as evidenced by the tendency to adiposity, the subnormal temperature, the progressive increase of carbohydrate tolerance, the slight thermic response to injection of anterior lobe extract and the evident improvement under glandular administration.

There have been no neighborhood manifestations at any time, though the enlarged sella turcica indicates the existence of a struma pituitaria. Although the dimensions of the sella have measureably increased between July, 1910, and July, 1911, in view of the absence of neighborhood neurological symptoms and the obvious present inactivity of the anterior lobe, there are no grounds for surgical intervention, either on the basis of fragmental removal of a functionally hypertrophied gland (as in Case XXVI) or of relieving pressure disturbances.

The case illustrates how it is that in the past glandular feeding in acromegaly has given inconclusive results. In most cases doubtless (as in Case XXX to follow) organotherapy has been used during the active stage of the disease and naturally without improving the condition even if it has not been aggravated. This would seem, on the face of it, to be an argument against the view that acromegaly is a condition brought about by glandular inactivity. However, accepting the reverse conception—namely, that the malady is a consequence of hyperpituitarism—there comes a period, as in this case, when the activity of the process has subsided and when there is actually need of organotherapy.

We are led to believe that the need, or otherwise, of the administration of glandular extract can be determined by the presence or absence of a high sugar tolerance; and furthermore that a rational therapeutic dosage can be determined on this basis—matters to be considered more fully later on.

The clinical evidences of the pluriglandular nature of the malady are possibly better exemplified by the following case than by any other of the acromegalic series.

Case XXIX. (Surgical No. 25977.) **Typical adult manifestations of former hyperpituitarism (acromegaly) of many years' duration. No neighborhood symptoms. Present dyspituitarism. Polyglandular syndrome. Operation for "plunging goitre."**

May 21, 1910 W. H. P., a contractor, 59 years of age, referred to the hospital by Dr. C. P. Fox, of Greenville, Tennessee, complaining of dyspnœa and cough accompanying a tumor of the neck.

The family history is without note. He is one of seven children, the others healthy. Aside from the usual infections of childhood and two attacks of typhoid (1867 and 1871) and pneumonia (1890) he has been vigorous and in good health until the present trouble. He has been married thirty-six years and has five healthy offspring.

Present Malady. About 7 years ago he began to notice an enlargement of the extremities. A year or so later, after actively threshing at harvest time, he had a sudden attack of "respiratory difficulty," and was in bed for eight weeks with some asthma-like affliction. He has never been entirely free from dyspnœa since. He then observed that his collars were becoming tight and noticed a "swelling of the throat" which caused coughing, spitting and an increase of dyspnœa. This was treated as "asthma." The *enlargement of the neck* (evidently an active goitre) became extreme, but finally subsided, leaving a small tumor, at times palpable, deep in the neck over the right clavicle.

His *dyspnœa* has become progressively worse and is aggravated by recumbency; and he sleeps in snatches, sitting upright. His former *weight* of 150 pounds increased to 201 pounds during the first two years of the malady, despite a coexistent *polyuria*—often as much as 3000 cc. during the night alone. The weight has since dropped to 153 pounds, owing to diarrhœa, inappetence and sleeplessness. No exophthalmos noted. Sweating has been profuse at times. For three years there has been a *loss of potentio sexualis*.

For the past year he has been much troubled by *burning and itching* of the extremities and nose. Never any headaches.

Physical Examination. An undernourished, cyanotic man with very dusky complexion and markedly pigmented. He is very dyspnœic: the respiration is wheezing; the voice suggestive of *a recurrent nerve palsy* (confirmed by the laryngoscope). These symptoms are obviously associated with an *intrathoracic tumor*.

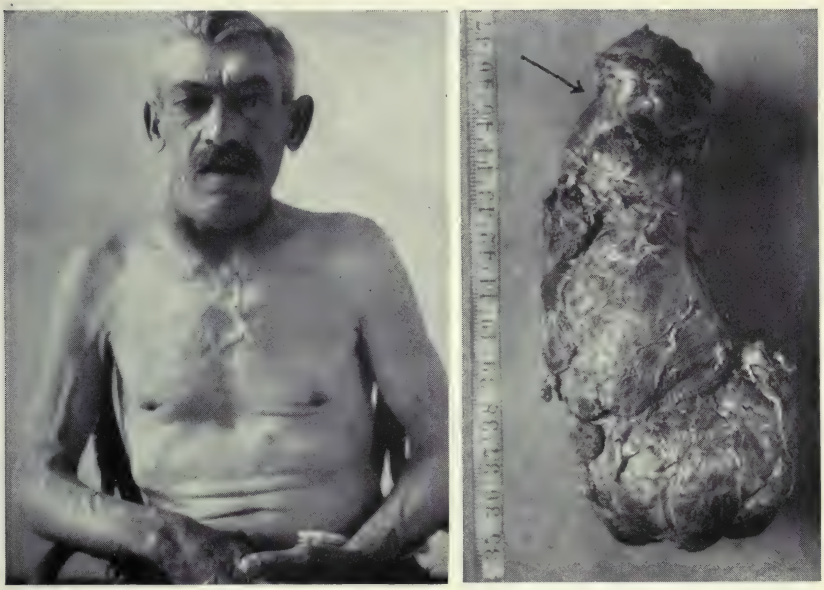
There is no palpable gland in the normal position of the right thyroid lobe; indeed, the neck is less full than is usual. A normal (?) left lobe is palpable. On forced expiration the upper end of a hard *nodular tumor* is forced into the neck from behind and below the right clavicle. A portion of the mass can be grasped by the fingers and "anchored" in

this position, whereupon respiration is fairly free. Also, on forced expiration, there occurs an extraordinary ballooning out of the cervical and supraclavicular tissues, evidently from blood filling the dilated subclavian, jugular, brachial and mediastinal veins (cf. Fig. 197). An X-ray of the chest shows a distinct shadow in the right upper thorax.

The condition at first suggested a malignant mediastinal growth, especially as there were some large hard cervical glands; but further study made it seem more probable that there had been a large goitre of the right lobe which had gradually gravitated into the chest owing to the acromegalic enlargement of the upper thoracic aperture, and which was exerting pressure against the trachea and superior cava within the chest—the *goitre plongeant* of Kocher. There is retrosternal dullness on percussion as low as the second rib. There is evident enlargement of the heart and considerable arteriosclerosis.

A neurological examination is negative throughout.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood.* A stereoscopic *X-ray* shows a moderate enlargement of the sella, which measures 2.5 by 1.5 cm. in depth (Fig. 199). No local pressure symptoms.



FIGS. 197, 198.—Case XXIX. On left, showing ballooning of neck and extreme venous stasis on forced expiration. On right, retrosternal goitre removed at operation (12 cm. in length). Arrow indicates clavicular level.

(b) *Glandular Manifestations.* The *skeletal* changes involve the skull, lower jaw, hands (Fig. 200) and feet in typical fashion. The breadth of the nose is 4.5 cm.; glove measurement 25 cm. In addition there is considerable bony thickening and forward bowing of the legs, giving an attitude suggesting the posture of Paget's disease (Figs. 201, 203). The shouders are rounded: height 5 feet 7 inches. There is a pronounced transverse abdominal groove and the characteristic gluteal flattening with many extra-transverse folds.

The *skin* is smooth, moist and *much pigmented.* The palms and soles are cold and clammy and the patient complains much of burning and itching of the extremities. There is a marked bronzing of the skin involving the head and neck above the collar line, the hands (Fig. 202) (except the two terminal phalanges, which by contrast are very pale), the arms to the shoulders, and the genitalia, and there is a large area of pigmentation between the scapulæ (not parasitic). "Fly blisters" applied in the past have left areas of deep pigmentation on the back and extremities.

The *subcutaneous tissues* are flabby, as though from loss of weight (50 pounds). Present weight 153 pounds.

There is no polyuria nor glycosuria at present. The *temperature* (97°) and *pulse* (60) range subnormal.

Carbohydrate tolerance, *July 2*, after 200 grams of glucose, negative: *July 3*, after 300 grams, negative: *July 6*, 400 grams, partly vomited; no glycosuria: *July 7*, 400 grams with stomach tube; no glycosuria.

FIG. 199.—Case XXIX. Sella of double contour (nat. size).

Other Ductless Glands. A large *thyroid* struma. The pigmentation, asthenia and low blood pressure suggest *adrenal* deficiency. No testicular atrophy.

June 10, 1910. **Operation.** Extirpation of plunging goitre, under scopolamine-morphia-cocaine anæsthesia. The tumor measures 10 by 5 by 6 cm.; it is lobular and the

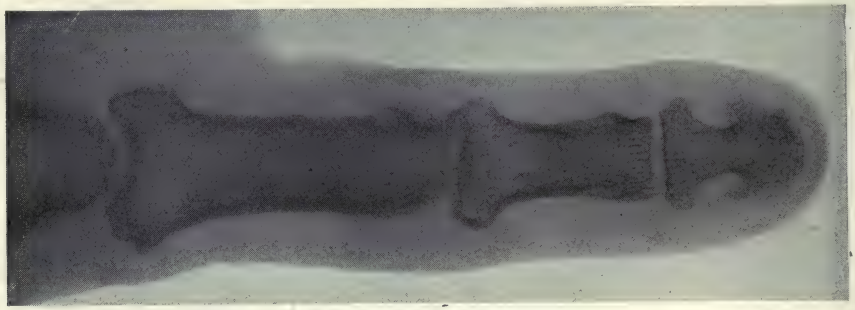


FIG. 200.—Case XXIX. X-ray of index finger (nat. size).

various subdivisions are marked off by dense fibrous bands, some of them heavily calcified. *Histologically* it is a colloid goitre with degenerative changes.

There were no operative nor post-operative complications. The subjective relief experienced was naturally extreme. He gained rapidly in weight.

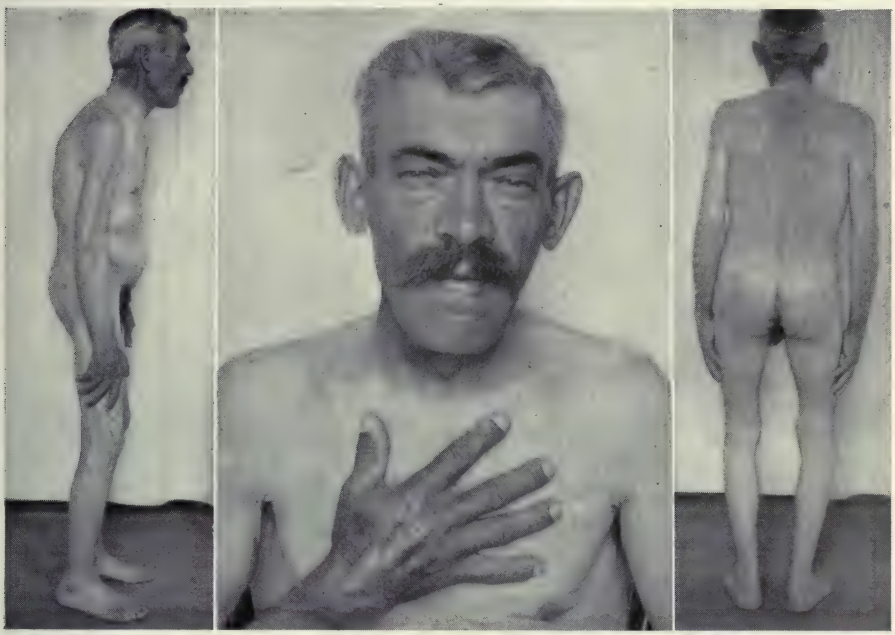
On *July 8* he was given 2 cc. of 5 per cent. anterior lobe solution intramuscularly. The *thermic reaction* was slight, from 98.6° to 100°, but without subjective discomfort other than slight headache and nausea.

No glandular (hypophyseal) therapy administered. Discharged *July 10*.

Subsequent Note. *Sept. 1, 1911.* Reports that he is in good health. Weighed 190 pounds in March, a gain of 37 pounds in eight months.

INTERPRETATION.—A case of acromegaly of more or less insidious onset and termination, leaving a condition of dyspituitarism. The condition is associated with a large goitre, which may be a manifestation of a former hyperthyroidism. A subsidence in size of the enlarged right thyroid lobe coincident with the acromegalic enlargement of the thoracic aperture doubtless encouraged the descent of the cervical gland into the chest, where it produced its own distressing neighborhood symptoms.

The patient's pigmentation and asthenia suggest adrenal insufficiency, and if this is the actual cause, the case represents a polyglandular symptom-complex. No neighborhood symptoms on the part of the hypophysis seem



FIGS. 201, 202, 203.—Case XXIX. Showing posture suggesting Paget's disease: characteristic acromegalic facies: square, deeply pigmented hand.

ever to have occurred, despite the considerable enlargement of the sella turcica.

It is evident that the active process in the hypophysis and the secondary thyroid hyperplasia have long since passed, the exceedingly high assimilation limit for sugars evidencing the present glandular insufficiency, despite the absence of adiposity which may now be expected after the removal of the intrathoracic goitre.

The patient probably needs administration of hypophyseal extract, possibly combined with thyroid extract. The immediate indications were of course purely surgical—to give mechanical relief to the pressure symptoms brought about by the displaced lobe of the thyroid.

We come now to three examples of skeletal overgrowth which presumably dates in each case from an age before epiphyseal union was complete. The first of them is a typical acromegalic with some evidences of elongation

of the long bones as well. The third case is a typical pathological giant, with insignificant acromegalic features. In the second case the two conditions are about equally manifest.

CASE XXX. (Surgical No. 26068.) **Typical chronic advancing hyperpituitarism (acromegaly with suggestion of gigantism) of fifteen years' duration. Absence of objective neighborhood symptoms. Subtemporal decompression. Glandular therapy.**

June 8, 1911. My friend, J. D. I., a collegiate instructor, 42 years of age, was admitted for study. His history discloses the fact that a younger sister has been suffering for some years with headaches, that she has a changed contour of the face and undershot lower jaw and that she was operated upon for "glands of the neck."

The patient himself has been subject since early youth to periodic headaches, formerly supposed to be digestive. He passed through the usual diseases of infancy without complication. He suffers from attacks of "hay fever" and his mucous membranes are particularly sensitive to certain odors. As a young man he was delicate-featured and light-complexioned, weighing 140 pounds in 1892, when he graduated with high classical honors and started his career as a teacher. He has since grown dark, heavy and taller, weighing now over 200 pounds (Figs. 204–207).

In 1896 an operation was performed for "enlarged cervical glands." He was married in 1898: is without offspring.

The Present Malady. The onset was most insidious, and occurred subsequent to

FIGS. 204–207.—Case XXX. Photographs of patient in 1892, aged 24, before the onset of the malady; in 1897, aged 29, at time of onset; in 1905, aged 37; and in 1910, aged 42, with outspoken acromegalic changes.

his graduation. At the time of the operation in 1896, the evidences of overgrowth had become sufficiently obvious to attract the attention of his surgeon. Not until 1900, however, did his intracranial discomforts lead him to seek medical advice on this score. He consulted Dr. O. F. Osborne, who recognized the condition as acromegaly and prescribed pituitary extract, which he has taken more or less constantly during the intervening decade, with the exception of an interval between 1904 and 1908 when thyroid extract was administered.

He experienced subjective improvement, particularly from the thyroid treatment, but at present has grown to depend on the hypophyseal preparation, his discomforts being accentuated whenever it is withdrawn. He is taking a large amount, namely, 36 grains a day (Armour whole-gland preparation).

The *headaches* have from the beginning been the most troublesome feature. Formerly they were chiefly suboccipital but of late are described as more general. When severe there is a bursting sensation, greatly accentuated by a cough, sneeze or muscular effort. They are intensified by the erect posture and are invariably relieved by lying down. They have never been accompanied by nausea or vomiting.

He complains of a sense of *mental and physical inertia*—of "logginess"—which is more and more difficult to overcome. He feels dull and sleepy most of the time. There is a sense of heaviness and numbness—"going to sleep" of the extremities. He has suffered

from shortness of breath, and had an attack of angina (?) in 1896. There is considerable nasal obstruction. Blood pressure has been low. For ten years there have been recurring attacks of corneal ulceration in the left eye. He is subject to attacks of tonsillitis, and regards himself as very susceptible to infections. He perspires freely and formerly had copious night-sweats. He has *grown two inches in height* since the onset of the trouble. There has been a progressive decline in libido sexualis for some years. The testes have diminished in size. No abnormalities in the urine have ever been noted.

Physical examination shows a heavy, 200-pound man, six feet two inches in height, with most characteristic and outspoken signs of acromegalic overgrowth. Nothing abnormal is made out in the visceral (thoracic and abdominal) examination. There is no peripheral arteriosclerosis. There is a persistently *low blood pressure*. The neurological examination is negative. The thyroid is palpable; possibly enlarged.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood.* None. The *X-ray* negative is difficult of interpretation, as the clinoid processes are prominent and thickened,

FIG. 208.—Case XXX. Skiagram after subtemporal decompression (shadow of "clip" on meningeal vessel). Note thickening of walls of sella, which is somewhat enlarged.

the estimated profile dimensions being 2.0 by 1.3 cm. in depth (cf. Fig. 208). A stereoscopic view is needed for accurate measurements.

(b) *Glandular Manifestations. Skeletal:* There are striking evidences of overgrowth in the bones as well as in their coverings. The characteristic rounding of the shoulders is absent, and it is noticeable from the increase in stature that the skeleton has enlarged throughout, giving a suspicion of gigantism—an unusual feature, which might possibly be attributed to the prolonged anterior lobe feeding.

The following figures present some contrasts and show that most of the growth took place probably between 1896 and 1900 (there has been little change since).

1892. Age 24. Height 6 ft. 0 in. Weight 140. Collar 14½. Shoes 7. Hat 6⅞.
1900. Age 33. Height 6 ft. 2 in. Weight 202. Collar 17½. Shoes 11. Hat 7⅝.

The *head* is large—27 cm. in the line from chin to vertex. The supra-orbital ridges are prominent: the jaw shows a large and thick alveolar arch, but there is no prognathism (Fig. 209) nor are the teeth spaced. The *X-ray* of the head shows an appearance which, as will be seen, was misinterpreted as an evidence of *cranial hyperostosis.* The nose shows

(Fig. 207) the characteristic narrow bridge and wide nostrils (4½ cm. in breadth). The lips are thick (the vertical width of exposed mucous membrane is 3 cm.); the tongue so large and awkward as to impede lingual speech.

The *hands* have the usual spadelike appearance; glove measurement, right 27cm., left 25.5 cm. The palms are deeply creased (Fig. 210). The nails show an absence of crescents. The fingers are supple, despite the thickened tissues. The *feet* are large—27 cm. in length and 10 cm. in breadth. The toes are much facetted by pressure of the shoes. X-rays of the extremities show the usual phalangeal changes (Fig. 211). The epiphyseal lines are obliterated.

FIG. 209.—Case XXX. Profile of acromegalic gigantism. No kyphosis or prognathism.

Cutaneous. The skin is moist, soft and smooth and without pigmentation, though the patient thinks that his complexion has darkened greatly during the course of the disease. The skin over the terminal phalanges of the fingers is white, suggesting Raynaud's constriction, and there is frequently a subjective feeling of numbness in the extremities. There is a tendency toward *hypertrichosis:* a large hirsute patch over the sacral region.

The *panniculus* is abundant: there are large pads of fat over the posterior cervical triangles. He has gained 60 pounds since the onset of the malady.

No polyuria has ever been observed, nor glycosuria. In 1900 Prof. L. B. Mendel made some studies which showed no serious perversion of the nitrogenous metabolism. *Sugar Tolerance:* Glycosuria was produced with 200 grams of glucose after negative tests with 100, 150 and 175 grams. It is to be noted that his glandular therapy had been discontinued five days before. Two cc. of *anterior lobe* solution administered hypodermically gave no glycosuria with 150 grams glucose, and a negative thermic reaction.

The *temperature* is persistently subnormal (97–98°), the *pulse* slow (60–70) and the *blood pressure* below 110.

July 7, 1910. **Operation.** The headaches were so incapacitating and persistent as to justify some surgical experimentation. It was difficult to determine their exact cause: it did not seem possible, in view of the relatively small sella turcica, that they could be due to distention of the glandular envelope, and as the X-ray had shown what was taken for an extensive thickening of the calvarium and as there was some hyperæmia and œdema of the optic nerves, we felt justified in investigating the tension conditions of the cerebral chamber.

FIG. 210.—Case XXX. Characteristic square hand (*type en large*) with deep palmar creases.

A right subtemporal decompression was performed. The bone was soft, vascular and somewhat thicker than is usual, but much less so than was anticipated. The dura was tense. There was a more abundant escape of cerebrospinal fluid than customary and some tendency of the brain to protrude. The tension, however, was far less than was expected.

Recovery from the operation was uneventful, but the headaches returned in their former intensity as soon as he assumed an upright posture.

July 16, 1910. A lumbar puncture was performed with withdrawal of 60 cc. of fluid. This fluid, concentrated to 3 cc., given intravenously in a rabbit, elicited moderate reactions typical of posterior lobe extracts—a slight pressor response and glycosuria.

Subsequent Notes. The "static" headaches, "logginess" and drowsiness persist. Inconclusive attempts have been made to establish his therapeutic dosage. One hundred grains of desiccated whole gland (Armour & Co.) have been necessary to give even a slight lævulosuria with 120 grams of lævulose (Mendel). A sellar decompression is being contemplated.

From *August 10* to *October 15, 1911*, he took *100 grains daily* of Armour whole-gland preparation, and "felt distinctly better during this period than during any period of equal length for a number of years"—with a diminution of headache, lessened sluggishness, higher blood pressure, better appetite.

INTERPRETATION.—An outspoken fifteen-year case of acromegaly with an onset more or less coincident with a cervical tuberculous adenitis. The most active growth occurred during a period of about four years, in the

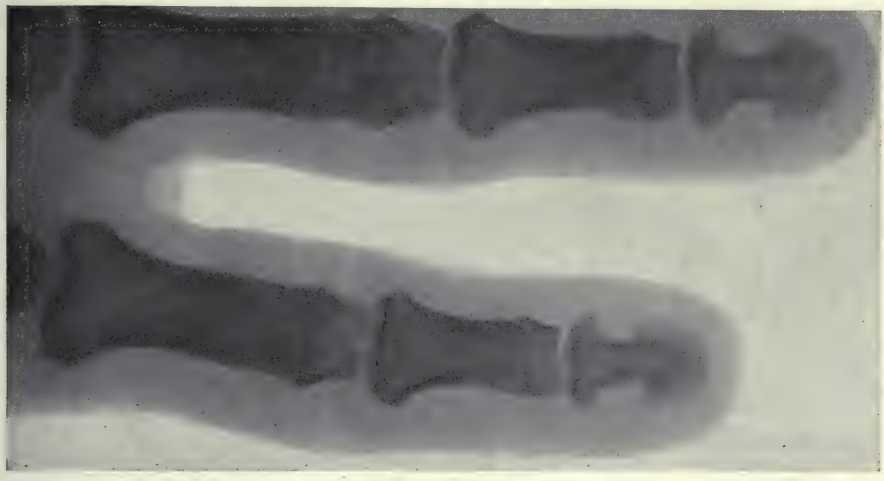


FIG. 211.—Case XXX. X-ray of middle and ring fingers showing characteristic tufting and exostoses.

patient's third decade, and owing to his increase in height it is presumable that epiphyseal union was as yet incomplete. It is notable in this connection that rounding of the shoulders and prognathism, which characterize most cases of acromegaly, are wanting. It is to be observed that he was taking pituitary (whole gland) extract during the active period of the disease.

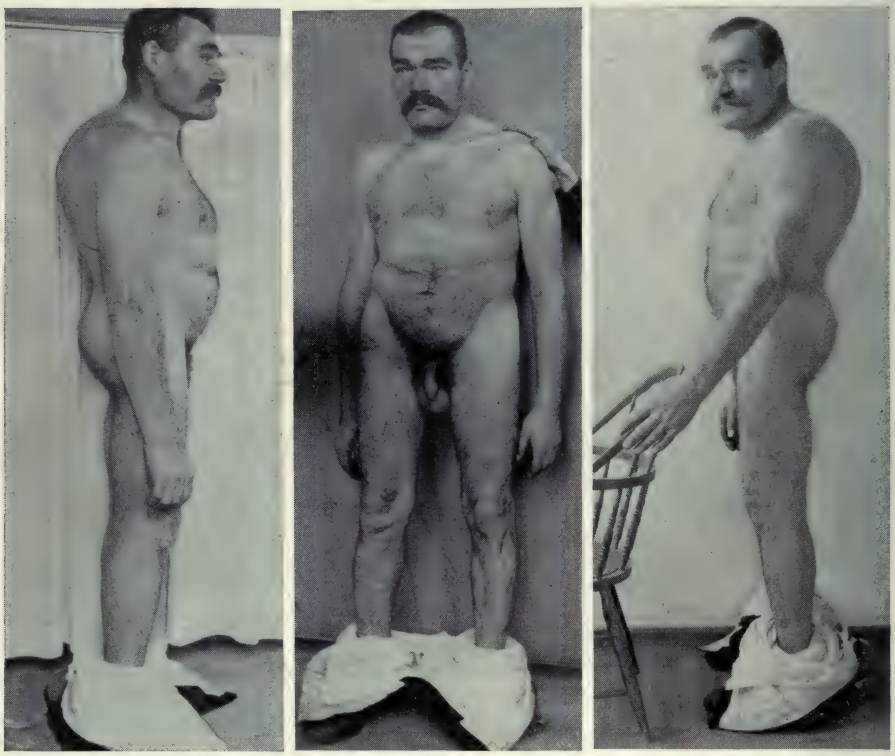
At present the active process has subsided and the condition is verging toward hypopituitarism—at least on the side of the posterior lobe insufficiency—judging from the subnormal temperature, the low blood pressure, increase in sugar tolerance and the tendency toward adiposity. The posterior lobe reactions with the cerebrospinal fluid were seemingly less pronounced than with normal (bovine) control fluids.

The static headaches, invariably relieved by recumbency, are possibly due to the emptying of the fluid contents (cerebrospinal or venous) of the cranial chamber when the patient assumes an upright posture—much the sort of headache that is experienced in the case of an individual who gets up

after a lumbar puncture before fluid reformation has occurred. The low blood pressure bears some relation to the headaches. They were unmodified by the subtemporal decompression, which is collapsed when the patient is uncomfortable and full when he is free from headache.

It seems probable, in view of the suggestive posterior lobe deficiency, coupled with the low arterial tension and the possible failure of the splanchnic field to regulate the venous pressure during the upright posture, that there is an especial need of posterior lobe administration. It is notable that he tolerates and feels benefited by such an enormous dosage of whole-gland extract—100 grains daily.

The following Gargantuan individual with an unmistakable but quiescent giganto-acromegalic syndrome has, with rare fortune, escaped from the constitutional disabilities so apt to accompany hypophyseal disease.



FIGS. 212–214.—Case XXXI. Stationary acromegalic gigantism. Height 6 ft. 1 in. despite kyphosis. Weight 247 pounds.

CASE XXXI. (Surgical No. 27011½.) **Chronic (stationary) hyperpituitarism causing gigantism with acromegalic aspects. Mendelian tendencies. Large sella turcica. No present neighborhood pressure phenomena.**

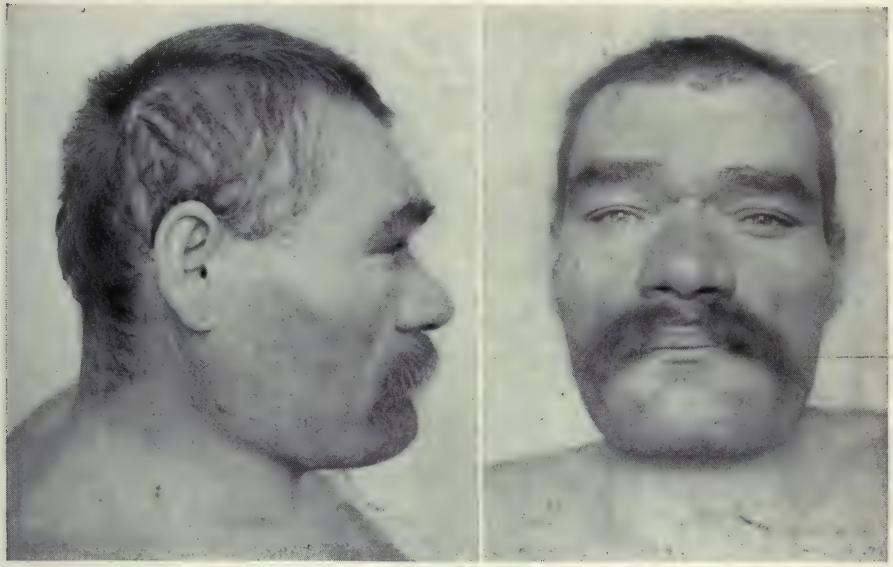
December 1, 1910. Florian F., a Hungarian, 48 years of age, a cooper by trade, was operated upon in the hospital in 1906 for hæmorrhoids, and was readmitted for the purpose of securing this record. No physical complaints.

Family history is of interest, as there seems to be an inherited tendency toward overgrowth—which would have interested François Rabelais. His maternal grandfather was a

"giant." His parents however were of average height (father 5 feet 7 inches), were healthy, and lived to be nearly seventy years old. The patient is the eldest of their nine children—three boys and six girls. One sister is large and closely resembles the patient: she has twelve children. Some of his own offspring have been over-large.

Personal History. The patient states that he is said to have been at birth as large as a year old child and that he was exceedingly fat—a veritable Pantagruel, who in turn might have stamped out the bottom of his bassinette. Owing to this adiposity he was unable to walk until three and a half years of age, and for several years afterward was unable to get up without help after having fallen. He was removed from school as "hopeless" after a three years' experience in boyhood, and was taught his present trade, at which he has since worked.

He has been noted for his physical prowess—actual as well as legendary. When a boy of twelve he was six feet tall and could lift a hundred pound weight. In 1887 he took in marriage a large woman weighing two hundred pounds. She has had three preg-



FIGS. 215, 216.—Case XXXI. Cephalic configuration in a case of acromegalic gigantism.

nancies: the first, ten years after their marriage, resulted in a child "too large to be born." A second child, a girl weighing seventeen pounds at birth (1898), survives, and now at eleven years of age is five feet in height and weighs one hundred pounds. The third—"an enormous child"—died in its first year from unknown cause.

The patient is a hard-working man of good habits. He has had but one illness which confined him to bed; viz., typhoid, when about 15 years of age. He has suffered from chronic constipation and hæmorrhoids. He immigrated to this country in 1903.

The Existing Malady (?). As related, he has been over-large since birth. He recalls no physical discomforts except for a period of ten years after his fifteenth year (1880–1890) during which he had persistent and severe bitemporal headaches and very frequent epistaxis: no concomitant nausea or vomiting or visual disturbance. There is no history of polyuria, polydipsia, sexual inappetence, etc. Seven years ago he *weighed 302 pounds*. He is chronically constipated.

Physical Examination. A Goliath, of extraordinary skeletal proportions (Figs. 212-214). He stands six feet and one inch, despite the extreme bowing of his shoulders.

He is powerfully muscular and well nourished, but there is no superfluous adiposity, his present weight being only 247 pounds. His *temperature* is subnormal, 97.2° F.; *pulse* 52.

The visceral (thoracic and abdominal) and neurological examinations show no abnormalities. There is no evidence of mental or physical deterioration.

The *head* is bilaterally symmetrical, but the face is disproportionately large (breadth at zygomatic level, 17 cm.) (Figs. 215, 216). The supra-orbital ridges, zygomatic arches, mastoid prominences and occipital protuberance are prominent and massive: the forehead is receding. The mandibular arch is heavy, but the jaw is right-angled and not undershot: the teeth, which are much worn, meet squarely and are closely set (breadth of upper arch 7.5 cm.). An under-exposed radiogram shows, nevertheless, a marked enlargement of the sella turcica (Fig. 217), measuring 2.2 cm. by 1.6 cm. in depth.

The nose is broad (5 cm. at alæ) but not disproportionately large for the face, as is often the case in straight acromegaly; and the same is true of the lips and ears. The mucous membranes are a good color, the tongue (6 cm. in breadth, protruded) hardly fills his cavernous mouth; there is no thickness of speech.

The *thorax* is huge, measuring 120 cm. in circumference over the pectorals. There is an extreme upper dorsal kypho-scoliotic curve, with a deforming hunch of the left shoulder.

FIG. 217.—Case XXXI. Print (nat. size) of under-exposed negative showing huge frontal sinuses and enlarged sella (dotted).

The *upper extremities* are gorilla-like in length and hairiness, the bones being huge, the fingers almost reaching the knees. Circumference at the wrist is 22 cm. His great callous paws are square (Fig. 218), but not with the spadelike shape of the acromegalic hand. There is no clubbing of the fingers. The nails are well formed and preserved for the hand of a laborer: they show the crescents, are not incurved, and there is no heaping up of the surrounding flesh. The breadth of the open palm is 12 cm. Circumference over the knuckles (glove measurement) is 30 cm. The girth of the middle finger is 9 cm. The X-ray shows characteristic phalangeal exostoses of hyperpituitarism (Fig. 219). No trace of epiphyseal lines.

Lower Extremities. They are straight and show the general characteristics of the upper extremities. The feet are proportionately less enlarged than the hands. The length of the right foot is 29 cm.

The *skin* is normally moist; it is coarse, exceedingly hairy, and particularly on the face shows innumerable crypts of huge cutaneous glands—like normal skin seen through a magnifying lens. There is no especial pigmentation. No tendency to adiposity.

Other Ductless Glands. The thyroid is somewhat enlarged, particularly the right lobe (colloid goitre?). Otherwise nothing. No testicular atrophy.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* There is an enlarged sella turcica but no pressure phenomena. Pupillary reactions, ocular movements and visual fields are normal. A period of "hypophyseal" headaches (age 15 to 25) with frequent epistaxis. Nasopharynx negative.

(b) *Glandular Symptoms.* Skeletal overgrowth as described, dating from early life, with hypertrichosis, etc. No evidence of a tendency toward dyspituitarism, unless the

FIG. 218.—Case XXXI. Showing contrast of two adult hands.

subnormal temperature can be so interpreted. No history of polyuria, polydipsia or glycosuria. No anaphrodisia; no adiposity.

Unfortunately an opportunity has not been given for testing his carbohydrate tolerance or for making an anterior lobe thermic test.

INTERPRETATION.—Apparently a case of early and possibly familial (Mendelian) gigantism (cf. Case XIII of Group I), with a seeming exacer-

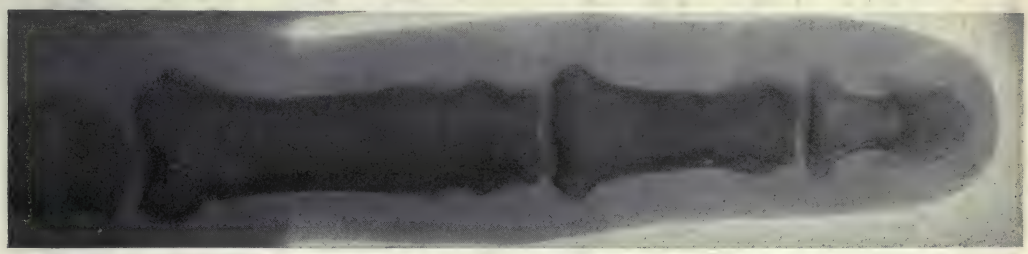


FIG. 219.—Case XXXI. Middle finger (nat. size), showing typical acromegalic changes.

bation (post-typhoidal?) of hypophyseal activity between the fifteenth and twenty-fifth years, and a present stationary condition. Though the acromegalic features of the case are manifest, the absence of the undershot jaw, of the spaced teeth, of the enlarged lips and tongue, and the general rather than disproportionate skeletal enlargement of the extremities, speak for a condition which dates from a period antecedent to epiphyseal ossification. His days have already outnumbered those of the usual "giant" and he shows no signs of the physical or mental deterioration of pathological gigantism. His colossal strength has been retained (unlike Case I).

There seem to be no superimposed clinical manifestations of dyspituitarism, judging from the anamnesis and our somewhat incomplete physical study of his present condition, no opportunity having been given to establish his assimilation limit for sugars.

The case is intermediate between acromegaly and gigantism, and the history of onset bears many points of resemblance to that of Case I in Group I. A physiological instability of the gland is apparent in both, but here there has occurred no transformation into the malignant type of adenomatous hyperplasia.

The following is a typical instance of pathological gigantism with degenerative cystic retrogression of the glandular hyperplasia.

Case XXXII. (Surgical No. 25947.) **Preadolescent hyperpituitarism with giant overgrowth. Enlarged sella, containing a cystic struma pituitaria. No neighborhood symptoms. Terminal glandular insufficiency (hypopituitarism). Death. Autopsy.**

May 15, 1910. John Turner, without occupation, 36 years of age, was referred for study by Dr. James F. Mitchell of Washington. His personal complaint is "swelling of the legs, with inability to walk."

There is nothing noteworthy in his family history. There were four other children of average height. He was much overgrown as a boy, and attended school for a short time, but his size was an embarrassment, and he became truant, never learning to read or write.

Though during his youth he had frequent shaking chills (malaria?), headaches, and many spontaneous "nose-bleeds," he considered himself well until ten years of age. He drank heavily from the age of fifteen—"a pint of whisky for breakfast"—and attributes his present discomforts to these habits and to exposure incidental to his occupation as a driver of a brick wagon. He smokes excessively. There has never been any temptation toward sexual indulgences.

He began to grow rapidly when fifteen years of age and at this time suffered much from frontal headaches. He does not know how long he continued growing. Ten years ago his health began to fail. Owing to his bulk it has become increasingly difficult for him to get about and he has become disabled in consequence of the deformation with enlargement of the knees, which prevents an upright posture. Of late he has had several attacks of "nephritis," for which he has been an inmate in various hospitals. He has always had a Gargantuan appetite, and has been free from gastro-intestinal irregularities. He suffers much from the cold and "sits over a stove" most of the year.

Physical Examination. An extraordinary prototype of the folk-lore giant—overcome by his own size (Fig. 220). He *weighs* 275 pounds: his height is estimated at about eight feet: measurement of body after death *8 feet 3 inches (251.5 cm.)*. His complexion is a peculiar grayish-white.

There is a splenic enlargement ("ague-cake"); otherwise the visceral examination (thoracic and abdominal) is negative. The heart-sounds are feeble: there is a relative mitral insufficiency: the organ is enlarged. There are no definite signs of arteriosclerosis though the retinal arteries suggest some thickening. The superficial vessels are soft and the blood pressure low. There are no varicosities.

The *urine* is variable in amount, occasionally showing slight polyuria (1900 to 2000 cc.). Specific gravity 1020. There is 0.7 gram of albumen per liter. No casts or renal elements are found. The *temperature* and *pulse* are irregular and tend to be subnormal: registrations of 96° F. are not infrequent with a pulse of from 55 to 60.

The *neurological examination* is practically negative. Though without education, he is shrewd, competent and independent. His olfactory sense is unaffected. The eyes are normal; movements unrestricted; pupils equal, with normal reactions; visual fields normal; acuity normal; discs clear. There is some arterial constriction of the retinal veins. There

FIG. 220.—Case XXXII. Note the narrow chest; large joints; hypotrichosis. Also the large size of the hands compared with those of Dr. Crowe, whose height is 5 feet 8 inches.

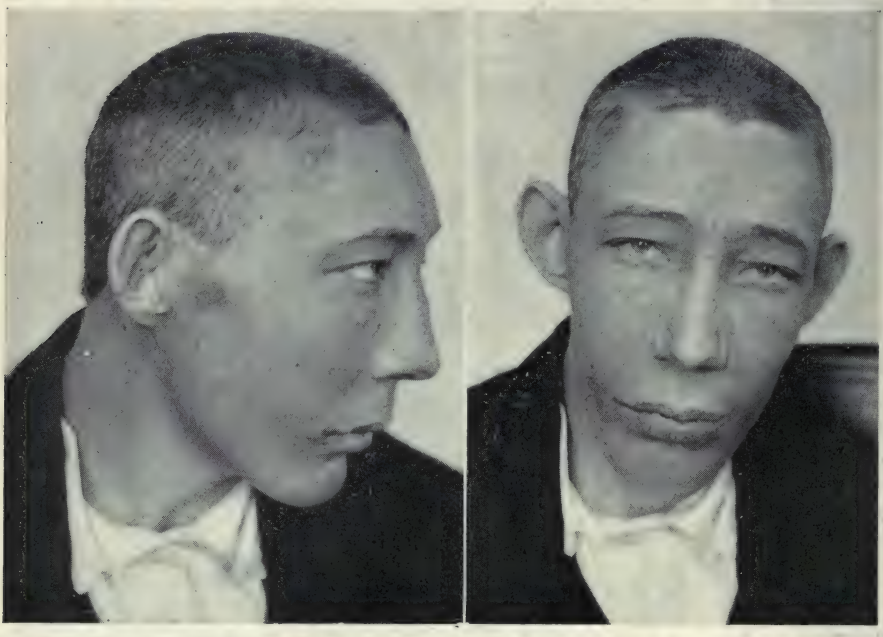
are no motor or sensory changes, though the *extreme muscular enfeeblement* is notable. The deep reflexes can not be elicited.

Cutaneous. The skin, except over the lower extremities, is as soft and pliable as that of a child, with marked *hypotrichosis:* it is very dry, and the patient says he never perspires. There is practically no beard, absolutely no axillary hair, and a very scant pubic growth. There is considerable *pigmentation.* On the parietal scalp is a verrucous fibroma 2 cm. in diameter.

The skin of the lower extremities (Fig. 220) below the knees has all the appearances of elephantiasis: it is dense, ridged, thickened, excoriated and pigmented. The malleoli cannot be palpated and the feet are much swollen.

There is an excess of *panniculus,* which is evenly distributed. Over the right hip is *an isolated lipoma* as large as a fist.

There is no disproportionate hypertrophy of the tongue, as in acromegaly. The neck is thin and the thyroid is barely palpable. The genitalia are small; the testes atrophic.



FIGS. 221, 222.—Case XXXII. Note maxillary rather than the mandibular prognathism of the true acromegalic: also posterior position of the ears.

Osseous Changes. The *skeletal* framework is enormous (Figs. 220, 224). Owing apparently to bony deformation about the joints he stands much bent at knees and hips: his gait in consequence is feeble and shuffling and it is possible for him to walk only by the aid of two heavy canes. The lower *epiphyseal line* of the radius is still observable on the X-ray plates (Fig. 225).

The *skull* shows an overgrowth, restricted for the most part to the facial bones (Figs. 221, 222). In comparison the cranial chamber seems small (61 cm. in its occipitofrontal circumference), and the calvarium is free from the exostoses and asymmetrical deformations so often described in giants. The supra-orbital regions are not especially prominent, though the mastoids are huge.

The subcranial portions of the skull are much enlarged (cf. Case XXXI). The malar bones project; the mastoids and the alveolar processes of the jaws are massive and thick; the teeth are widely spaced and irregularly placed. The facial prognathism involves the

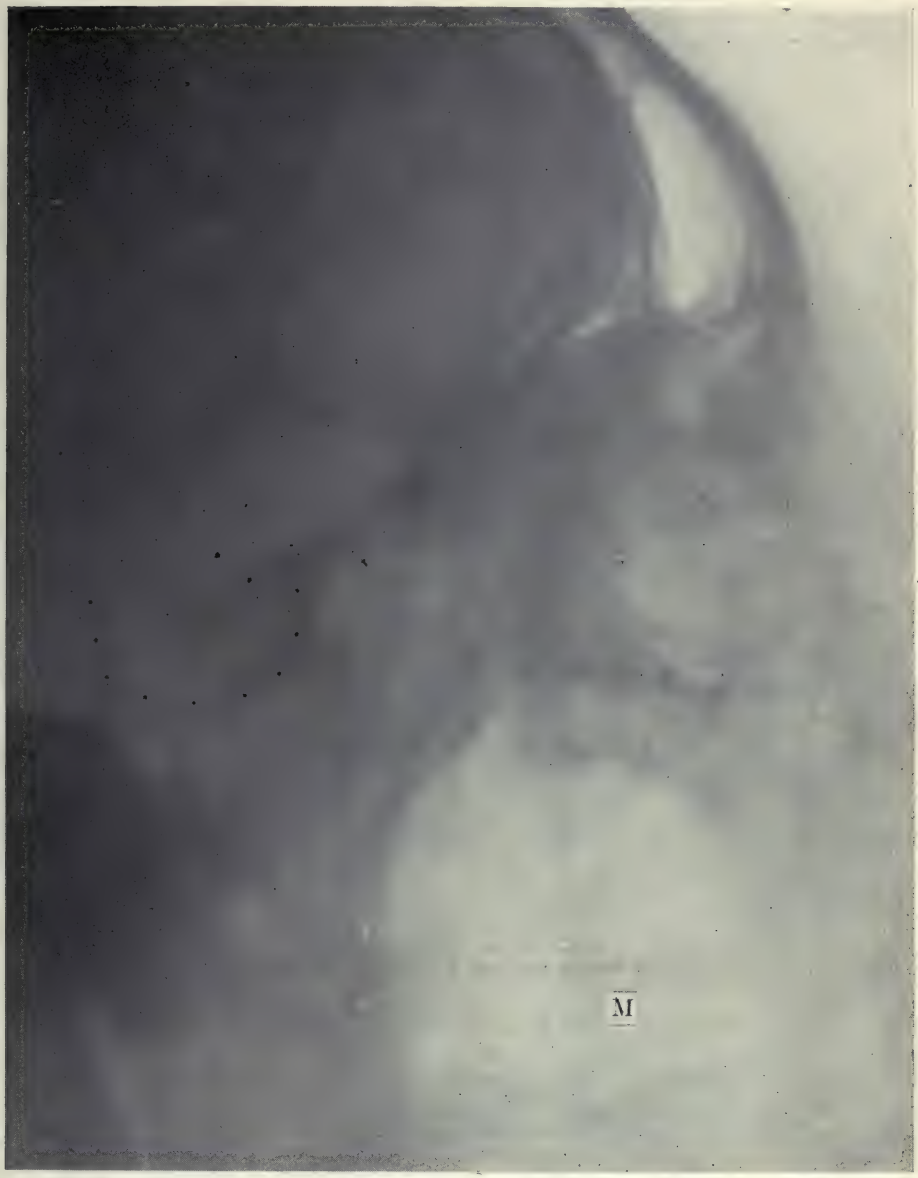


FIG. 223.—Case XXXII. Portion of cranial radiograph (nat. size) to show upward extension of frontal sinus; enormous maxillary antrum (*M* in its centre): enlarged bowl-shaped sella (indicated by dots). Note the very low position of the sella in relation to sloping orbital plate. (Photo. horizontal.)

maxillary rather than the mandibular jaw. The eyes are widely separated, the distance between the inner canthi being 4 cm., and the outer angle is 1 cm. above one-half the vertical distance from chin to vertex.

An *X-ray* of the skull (Fig. 223) shows a very large, relatively shallow *sella turcica*, measuring on the plate 2.7 cm. in its antero-posterior diameter and 1.7 cm. in depth. The maxillary sinuses are huge: also the frontal, which extend far up between the tables of the bone.

Spine, Thorax and Pelvis. The vertebral column shows considerable scoliosis and some upper dorsal kyphosis. The shoulder girdle and the chest are relatively narrow (36 cm. from the acromial end of one clavicle to that of the other). There is a marked deformation of the pelvis, the left ilium being widely flaring and thickened. The pelvic circumference below the iliac crest is 109.5 cm.

Upper Extremities. Each clavicle is 21 cm. in length. The scapulæ are large: the spines measure 20 cm., and the vertical length is 25 cm. The arm measures 110 cm. from the acromion to finger-tips: when the patient is seated in an ordinary chair the fingers rest on the floor (Fig. 224). The head of the *humerus*, palpated through the flabby deltoid, is enormous: from tuberosity to external condyle the bone measures 47 cm. The *radius* is 37.5 cm. in length. There is no limitation of motion in shoulders or elbows, but in each wrist there is a marked radial deflection, accentuated on the right by an old Colles' fracture (?).

FIG. 224.—Case XXXII. Note extreme length of arms and thighs in relation to usual 18-inch chair.

The *hands* are unbelievably huge (Fig. 225), the length from the base of the median metacarpal to the tip of the middle finger being 27 cm. The length of the flexed middle finger from knuckle to tip is 17 cm., almost the length of an ordinary hand: its circumference at the first joint is 10 cm. The fingers are tapering; not square, as in the acromegalic type. The exposed nails are well formed and very long—that of the middle finger, for example, being 2.3 cm. The crescents are well shown.

Lower Extremities. The length of the femora from trochanter to knee-joint is 62 cm. (Fig. 224). The bones are straight and well formed, but there is great enlargement of the extremities, as is true of all the long bones. The circumference of the left knee is 58.5 cm. The legs cannot be straightened at the knees; both patellæ are dislocated outward from the median position and seem to have ridden upward on to the femoral surface. There is bilateral genu valgum. There is no fluid in the joints.

The *feet* are huge and much deformed. The patient wears a child's made-over undershirt as a sock. His shoe measures 38 cm. in length. Measurements of the feet are necessarily much modified by the external œdema. The circumference over the ankle is 48.5 cm.; that of the great toe, 13.5 cm. The toe-nails are much thickened and hypertrophied.

Carbohydrate Tests. We were unable to produce glycosuria by the ingestion of glucose, so that the tolerance was never established. The ingestion of more than 300 grams provoked vomiting. A subcutaneous injection of 0.1 grain of posterior lobe extract concomitant with the ingestion of 175 grams of glucose, and again with 250 grams, led to no glycosuria; so that it is safe to conjecture that his tolerance is very high. These posterior lobe injections caused no rise in temperature.

Anterior Lobe Thermic Reaction. On June 1 an intramuscular injection of 2 cc. of 5 per cent. anterior lobe extract (Armour & Co.) caused a rise in temperature to 99.6° from its previous irregular level varying from 96° to 97° F., enduring for nearly forty-eight hours, when it again dropped to 96° F.

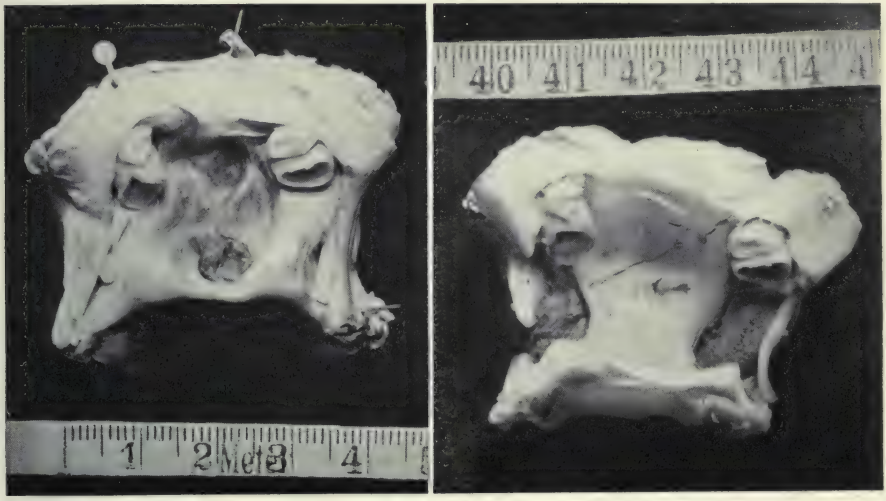
Summary of Hypophyseal Symptoms. (a) *Neighborhood Signs.* An exceedingly large sella turcica; otherwise nothing except the history of hypophyseal (?) headaches and epistaxis. Nasopharynx negative.

(b) *Glandular Signs.* The enormous skeletal overgrowth, evidencing presumably a former anterior lobe hyperplasia. This stage of overactivity has passed into a stationary or hypo-active stage, with a condition of *dyspituitarism*, shown by the tendency to adiposity, the subnormal temperature, the testicular atrophy with impotence, hypotrichosis, increased carbohydrate tolerance and positive anterior lobe thermic reaction.

The case presented no surgical indications, and as his home was so remote and his surroundings so hopeless, it seemed futile to attempt to carry out any prescribed course of glandular therapy to counteract the presumably advancing signs of hypopituitarism. On *June 18* he was discharged

Subsequent Note and Autopsy. The patient was not again heard from during life. He died six months later (*Jan. 14, 1911*). Three days later, after the body had been embalmed, permission for an autopsy was secured. It was conducted (Drs. Crowe and Sharpe) under most inauspicious circumstances.

Head. Scalp very thick (2.5 to 3 cm. on cut surface). Calvarium less thick if anything than normal: certainly no hyperostoses. *Brain* enormous, weighing 4 pounds 2.5



FIGS. 226, 227.—Case XXXII. Sella of giant Turner before and after removal of contents (nat. size). In Fig. 226 note collapsed diaphragm overlying gland and the large infundibular stalk. In Fig. 227 note great size of denuded sella with widely separated clinoids and central defect in floor (fissured fracture made during removal); also note great size of carotids.

ounces (1884 grams): convolutions normal and unusually well formed. A block of the sphenoid containing the sella removed in one piece (Figs. 226, 227). All sinuses much enlarged.

Body very adipose. Arteries remarkable throughout for their large size and absence of sclerotic thickening.

Visceral examination negative except for large size of the organs in general and an *hypertrophied spleen* (20 by 14 cm.; weight 1000 grams). *Kidneys* weigh 700 grams; markings apparent; capsule not adherent; no extensive histological change. *Liver* large, with increase of pigment. *Pancreas* small. No enlargement of mesenteric lymph glands or intestinal follicles. *Heart* weighs 520 grams.

Ductless Glands. Thyroid tissue not secured; certainly no enlargement: organ could not be palpated from below. *Thymus:* Mere shreds of fatty tissue, showing histologically a few strands of glandular structure containing an occasional shrunken Hassall's corpuscle. *Adrenals* exceedingly diminutive: located with some difficulty in extensive fatty capsule: transverse diameter only 2 mm.: no macroscopical trace of chromaffin elements: cortical

layers fairly normal in histological appearance and show no fatty degeneration of the zona fasciculata. *Testes* small: weight 15 grams, measuring 4.5 by 2.5 cm. On section there is a diffuse fibrosis. Histologically, almost complete disappearance of spermatogenous cells: mere ghosts of acini remain (Fig. 228). No interstitial cells of Leydig. *Pancreas* small: marked fibrosis: weight 70 grams: islets unusually large and numerous.

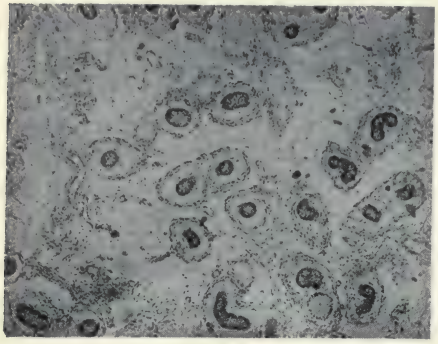


FIG. 228.—Case XXXII. Microphotograph of section of testis (mag. 40 diams.) showing extent of involution.

The *sella turcica* is much enlarged (Fig. 226). Optic nerves widely separated: carotids enormous. The upper membranous diaphragm of the sella is sunken and thrown into folds. The infundibular stalk is large and juicy. On carefully dissecting out the gland it is found to be represented largely by a collapsed cyst. The sellar base shows a central defect, partly filled by a calcareous deposit. The empty fossa (Fig. 227) measures 2.2 cm. across and 2.7 cm. antero-posteriorly.

A *histological* study of the walls of the collapsed gland shows (Fig. 229) a central cyst lined by a thin peripheral zone of cells which are of fairly normal appearance though very loosely meshed. There appears to be a definite relative scarcity of acidophile elements, though a number of characteristic eosinophiles are to be seen. The neutrophilic elements are multinuclear in many instances. No mitotic figures.

INTERPRETATION.—A case of preadolescent hyperpituarism producing gigantism and showing practically none of the osseous deformations and changes in the soft parts which typify acromegaly. On the theory of Launois and Roy the active process must have ceased before complete ossification of the epiphyseal cartilages, and it is interesting that the epiphyseal lines of the long bones are still faintly apparent. The patient, therefore, is not an "*acromegalic* giant" in the same sense as are Cases I, XXX and XXXI.

FIG. 229.—Case XXXII. Low power enlargement (40 diams.) of antero-posterior section through wall of cyst. *A*, cyst cavity: *B*, margin of chromophobe struma: *C*, flattened acidophile elements and enlarged sinuses: *D*, dural capsule.

Just when the transformation from a state of glandular overactivity to one of manifest dyspituitarism occurred the history does not make clear. Possibly it was at the time of the notable failure of strength ten years before he came under observation. In addition to the muscular enfeeblement, other evidences of present insufficiency were the dry skin with loss of axillary and pubic hair, the subnormal temperature, high sugar tolerance and marked increase in panniculus.

Individuals affected with pathological gigantism are said to die young and childless, the average age, according to Hutchinson,[132] being 21 years. There are exceptions, however, to this rule. The giant Chang is supposed

to have been 51, and the giant Palozzi, carefully studied by Levi and Franchini,[162] reached the unusual age of 66 years.

How many of these giants have shown signs of dyspituitarism before death I am unaware. Certainly the condition was obvious in the case of the giant Palozzi, for Levi states that adiposity had become pronounced and that there was a dry, pigmented skin, a subnormal temperature, muscular enfeeblement and so on. His metabolism was carefully investigated by Franchini, and some discrepancies from the normal were found, but the record of his sugar tolerance is limited to the statement that there was no spontaneous glycosuria nor did the ingestion of 150 grams of glucose suffice to produce it.

It is well known that a spontaneous mellituria, even of such a degree as to simulate diabetes and to be accompanied by furunculosis (cf. Case I) is not at all uncommon in acromegaly and gigantism; and I presume, as has already been emphasized, that during the actual period of hyperpituitarism a low sugar tolerance, if not actual glycosuria, would be found to occur in all cases.

Glycosuria, however, is but a temporary symptom, and failure to appreciate the fact that a giant or acromegalic may be in an active, a quiescent or a retrogressive stage of hyperpituitarism when subjected to studies of metabolism, doubtless accounts for the past wide discrepancies in the results of these studies. The skeletal manifestations of hyperpituitarism remain as clinical fixtures, whatever may be the subsequent course of the gland's activity—therefore, once an acromegalic always an acromegalic, even though the morbid process which stimulated the overgrowth has long since subsided. But unquestionably between the early and late stages of acromegaly as wide divergences will be found in tissue metabolism as are known to occur between Graves' disease and myxœdema.

From the standpoint of stature, the giant Turner, owing to his crippled joints, was not as strikingly tall as other recorded giants. The measurements after death, however, show that he ranks well up among the more notable cases. Thus Buhl's case (Hessler) measured 227 cm.; the giant Hugo (Launois and Roy), 230 cm.; Chang, the Chinese giant, 244 cm.; the giant Wilkins, recorded by Dana[61] and later by Bassoe,[11] 245 cm.; the giant Byrne, or O'Brien, of John Hunter fame, 249 cm., the writer's case Turner, 251.5 cm. The skeletal measurements of some famous giants are still greater: viz., the St. Petersburg giant, 254 cm. and the famous "Irish giant" in Trinity College, 259 cm.*

It is interesting that apart from their great stature many of the giants pictured in medical literature present a marked similarity of feature, which gives them a peculiar "family resemblance," almost as striking as that possessed by most acromegalics. Thus an example has recently been recorded by Lemos,[157a] and the giant Lopes of his report might well be taken for the younger brother of this giant, John Turner.

There were no neoplastic hyperostoses in this case, as in the giants Wilkins and Hessler, and no overgrowth of individual organs, aside from the enlarged spleen, which possibly was of malarial origin.

* In his article in Bouchard and Brissaud's Traité de Médicin (1905 T. x, p. 511) Souques refers to the giant Machnow who is said to have measured 284 cm. in height.

Notable is the very large and well-convoluted brain, which weighs more (1884 grams) than any other recorded brain, so far as I am aware, the maximum weight in Reid's series of 278 cases, quoted in Quain, being 1810 grams, the average for males, according to Boyd, in the fourth—this patient's—decade being 1364 grams. The brains of giants appear to be above the average weight (*e.g.* that of Wilkins 1540 grams; that of Hessler 1465 grams), though not as large as those of many individuals of average stature.

Aside from the hypophysis, the ductless gland series in the cases that have come to autopsy does not seem to have been made the subject of the especial study it deserves. As in the giant Turner, Bassoe records for the giant Wilkins a complete involution of thymus and testes: on the other hand, the adrenals were large and there was a colloid goitre, whereas Turner showed small adrenals and thyroid, the histological condition of the latter not being known. Both of them had large spleens (Turner, 1000 grams; Wilkins, 620 grams). In Turner also there was a possible hyperplasia of the islets of Langerhans, whereas the pineal gland was exceedingly small.

Of particular interest is the condition of the testis, which shows (Fig. 228) not only a complete absence of interstitial cells of Leydig but an absence of Sertoli cells as well, with little more than ghosts of the seminiferous tubules. Brissaud and Meige[28] have pointed out that gigantism and infantilism may accompany one another—contrary as this may sound. They refer, however, to the absence of secondary sexual characteristics which give a preadolescent aspect to the "grands enfants vieillots."

As regards the h y p o p h y s i s itself, it is fair to assume that there was originally an extreme functional hyperplasia of the pars anterior with subsequent cystic degeneration. These hyperplasias are capable of various transformations—here a degenerative one, whereas an example of change into the type of a "malignant adenoma" has been given in Case I of Group I.*

B. **Cases with Primary Hypopituitarism the Striking Feature in the Absence of Neighborhood Symptoms.**—These are probably the most common of all hypophyseal disorders. They are for the most part cases of manifest adiposity with correlated sexual changes—a condition which in the past, if considered as anything more than "simple obesity," has usually been ascribed to a primary gonadal disturbance.

During the past year we have seen and have made studies of a number of individuals with a clinical syndrome which in the present state of our diagnostic uncertainty one could hardly venture, without being thought an extremist, to ascribe to primary pituitary insufficiency.

Hence the records of only five of these patients will be incorporated in this report, they being selected according to age—(1) infancy, (2) before and

* Through the courtesy of Dr. Bassoe I have had the privilege of examining the many slides taken from the tumor in the case of the giant Wilkins, so carefully recorded by him. As he says, the tumor is of two types, one resembling sarcoma, the other an hyperplasia of eosinophilic elements. I do not believe, however, that the section which he has pictured (Fig. 5 of his report) fairly represents the full size of the anterior lobe, which I judge to be much enlarged. It contains many clusters of eosinophilic elements such as Erdheim has described as focal adenomata, and there is a marked invasion of pars nervosa by the pars intermedia cells. It is possible that the gland was functionally overactive until the patient's death, which was doubtless brought about by the cerebral pressure disturbances of the secondary osteosarcoma—a process which supposedly originated in the greatly hypertrophied frontal bone.

(3) after adolesence, (4) a young adult and (5) subsequent to the menopause. They are individuals in whom there has either been some significant indication of local glandular change, or who have obviously benefited by glandular administration—admitting, of course, that extract of the thyroid, of adrenal or of ovary or testes might likewise have been of some benefit. We are, of course, only at the threshhold of understanding these matters.

In the cases which we have heretofore discussed, with the exception of the few in which interpeduncular tumors had not as yet led to more or less deformation of the sellar outlines, we have leaned heavily on the X-rays as an aid to diagnosis. In the cases of acromegaly and gigantism just considered a sellar enlargement has been present in every instance, even though no actual neighborhood symptoms may have been associated with it. Here, however, with hypopituitarism in the absence not only of sellar deformation but also of all other neighborhood symptoms, we must depend solely on the presence of these constitutional disturbances which we have learned to recognize as manifestations of insufficient glandular activity.

Doubtless as many cases of nanism or infantilism are due to a primary hypophyseal as to a primary thyroid insufficiency. And doubtless, too, many cases regarded as primarily of thyroid origin—and this is particularly true of cretinoid states—may actually be due to defective hypophyseal activity, which, as is well known, is not uncommonly associated with actual enlargement of the thyroid itself.

So far as many of these types of skeletal undergrowth are concerned, it would seem more probable, in view of the presumable association of the pars anterior to processes of growth, that the activity of the hypophysis rather than the activity of the thyroid is at fault. In short, hypophyseal cretinism and infantilism are in all likelihood recognizable, though unrecognized, clinical entities.

These cases, of course, may show some enlargement of the sella, for there is no reason why the functional defect may not be accompanied by a struma, as is true of thyroid cretinism or myxœdema. Under these circumstances the diagnosis would be as easy as it is in acromegaly, for the clinical syndrome is no less unmistakable. It will be seen, however, that in all but one of the cases to be recorded the sellar measurements are below the normal average.

The clinical picture will vary according to the age at which the process has started, as well as in accordance with the extent of glandular deficiency. This is no less true of hypopituitarism without neighborhood symptoms than of hypopituitarism with neighborhood symptoms. For example, Cases III and V of Group I, had they been seen and recognized before neighborhood symptoms became pronounced, would have fallen in this subdivision of Group III as types originating from the preadolescent era. Cases VIII and IX would also, under these circumstances, have fallen here, as ones with a slight modification of the secondary changes of adolescence; and Cases VII and X as typical adult types.

The first of the following cases is one which raises the question of the *influence of trauma*. We have already seen in a number of the histories heretofore recorded that the lesion has been attributable to an injury. Whether the trauma is actually the ætiological factor or whether it is merely an ele-

ment in activating a dormant process in a gland already unstable is not always determinable. Doubtless the gland is prone to become damaged in the majority of severe cranial injuries, especially those associated with basal fractures, for the fissures are apt to run across the middle fossæ and often actually cross the sphenoidal bone and pass through the sella itself.

I incline to the belief that the transient glycosurias, which are known to accompany a considerable percentage of all basal fractures (cf. Ogden and Higgens,[199] also Kausch[140]) are due to an hypophyseal injury rather than to an injury of some supposed sugar centre. Thus we have learned from our experimental studies[100] that operative glandular manipulations of a certain kind invariably produce glycosuria. Some preliminary studies by Dr. H. J. Fitz Simmons in the Hunterian Laboratory have shown, furthermore, that an anterior *piqûre* of the rabbit's hypophysis is as certain to give glycosuria as is Bernard's posterior *piqûre* of the fourth ventricle.

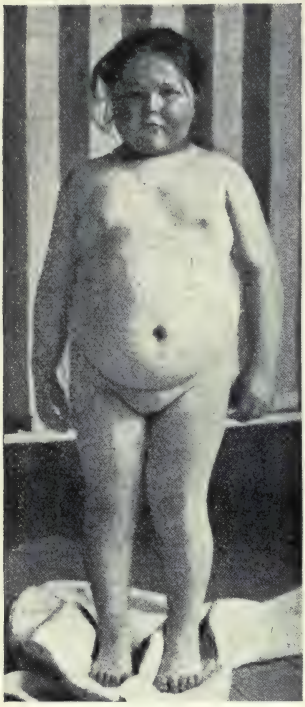


Fig. 230.—Madelung's case of bullet wound of the hypophysis (for comparison with Fig. 232).

We have, as yet, had no opportunity of studying the gland histologically in any fatal case of basal fracture which showed a post-traumatic glycosuria, though in two out of four glands kindly supplied by Dr. A. C. Harrison, there were extravasations in the posterior lobe. Unfortunately no urinary examinations had been made.*

There is one oft-quoted case—that of Madelung's[173]—of certified hypophyseal injury from a bullet wound with the subsequent occurrence of symptoms which we now recognize as due to glandular deficiency.† It is remarkable, in view of this well-known instance of proven partial destruction of the gland, that the syndrome first recognized as a clinical entity by Fröhlich was not unanimously ascribed to hypophyseal insufficiency (hypopituitarism); but this was not even suggested, so far as I am aware, until adiposity and sexual retrogression were observed in our partially hypophysectomized animals.

Professor Madelung suggests the possibility "dass die monströse Fettleibigkeit des Kindes mit der Kopfverletzung in Zusammenhang stehe," and he expresses the hope that others may report similar cases if they have encountered them. Prob-

* Since this writing we have received from Dr. John Homans the hypophysis from a patient who showed glycosuria after a cranial injury which proved fatal. The gland shows abundant extravasations in and about the posterior lobe (cf. p. 265).

† The case (Fig. 230) was that of a 9-year-old girl who had been shot in the eye with a Flobert rifle. She recovered, though with some palsy of the right arm and leg. She rapidly began to put on weight, and psychic changes were soon apparent. She became inactive, persistently drowsy, and would not participate in childish games—a backward child. Her skeletal growth was inhibited and ultimately she became exceedingly adipose. The measurements at the age of 9 were: height 124 cm.; weight 42 kilo. (almost twice the normal). Circumferences: abdomen 88 cm., thigh 47 cm., calf 30 cm., upper arm 27 cm. (cf. our Case XXXIII). An X-ray showed the bullet lodged in the sella.

ably all have encountered them. The following patient happens to be nearly of the same age, and is the physical prototype of Madelung's case.

CASE XXXIII. (Surgical No. 27970.) **Post-traumatic hypopituitarism in a child, with adiposity, high sugar tolerance and epilepsy. Organotherapy.**

June 13, 1911. Myrtle N., 10 years of age, referred by Dr. E. C. Lehnert, of Baltimore, with the *complaint* of epilepsy and adiposity.

Her father was a very stout man and died at the age of 35 of diabetes. The patient was a normal baby, but in early childhood she fell down a flight of stairs and sustained a serious *cranial injury*. She was unconscious and had convulsions for some hours. Four years ago, after an attack of scarlet fever, she began to complain of *headaches* and to have frequent *epileptiform seizures*. These are general convulsive seizures, always with loss of consciousness, preceded by a gastric aura.

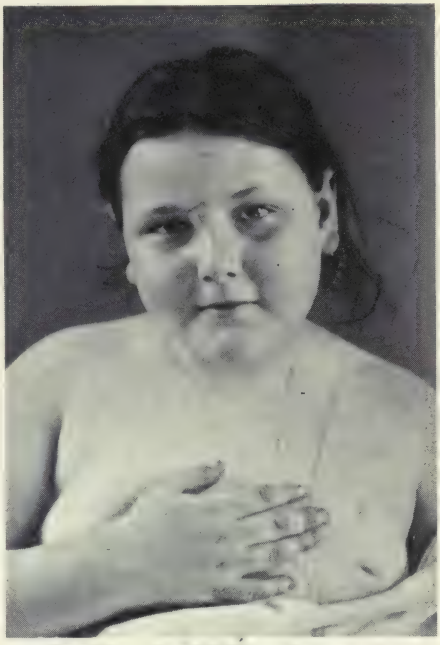


FIG. 231.—Case XXXIII. Note scar of brow; small pudgy hand with tapering fingers (cf. Fig. 243, Case XXXV).

During these four years profuse *nosebleeds* have occurred every few weeks, usually as the terminal feature of a headache and often preceding a convulsion. She has grown very *obese*, particularly in the past two years.

She has a ravenous *appetite;* "is always hungry and eats more than a grown-up"—and is "always thirsty." She complains much of feeling *weak and tired*. No impairment in vision noted. No dryness of the skin.

Physical Examination. An exceedingly adipose and apathetic child, with a traumatic scar on the forehead (Fig. 231) between the eyes.

Measurements. Height 133 cm. (4 feet 4⅜ in.); weight 53 kilo. (117 pounds); circumference of abdomen 92.5 cm., of thorax 87 cm., of thigh 56 cm., of upper arm 27½ cm., of calf 32 cm. (cf. Madelung's case).

Visceral and neurological examinations negative. Blood and urine negative. No polyuria.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood.* Sella abnormally small, clinoids heavy: fossa measures 0.5 by 0.5 cm. Marked epistaxis. Eyes, nasopharynx, etc., negative.

(b) *Glandular.* No skeletal change apparent. The extremities are small: the hand pudgy with tapering fingers (Fig. 231). The skin of the body is smooth and hairless. Adiposity is extreme (Figs. 232, 233), particularly over abdomen, hips, pectorals and pubic regions: pads of fat over clavicles and under arms. Flesh not tender.

Temperature and *pulse* not subnormal. No *polyuria* observed.

Carbohydrate Tests. Slight reduction with 100 grams of lævulose. Sixty grams given while taking 9 grains of desiccated whole gland (Armour) gave a slight lævulosuria (estimated therapeutic dosage). During the three days of straight sugar feeding she gained 3 pounds in weight (114 to 117): on starting the organotherapy she lost 6 pounds (117 to 111) during the first three days.

Subsequent Notes. *Sept. 2, 1911.* After her discharge the organotherapy was continued for three weeks and both child and mother think that the condition was much im-

proved. During this time she had one attack. The tablets were then discontinued and the attacks became more frequent—four during the past week. No increase in weight (114 pounds).

Dec. 3, 1911. During the past three months the dosage has been increased to 18 grains per diem, and the attacks have fallen, without other treatment, from 16 in August, to 9 in September, to 3 in November. Weight stationary.

INTERPRETATION.—A condition of so-called adipositas universalis in a child, following a cranial injury and associated with epi-

FIGS. 232, 233.—Case XXXIII. Showing extreme adiposity (cf. Fig. 230).

lepsy—a common enough clinical symptom-complex, but one not often attributed to hypophyseal insufficiency (hypopituitarism). We are even inclined to go farther and to regard the posterior lobe insufficiency as the paramount issue. Further comment on the relation of epilepsy to these conditions will be reserved for a later section (page 272).

The following patient, of about the same age as the preceding one, shows similar constitutional disturbances, associated, however, with some signs of skeletal overgrowth rather than dwarfing of stature—a condition

possibly related to eunuchism. Whatever may be the underlying factor, the clinical syndrome of this particular state in preadolescents is as unmistakable as the syndrome of the typus Fröhlich.

CASE XXXIV. (Surgical No. 27421.) **Preadolescent dyspituitarism without neighborhood symptoms. Epilepsy, feminism, adiposity, overgrowth. Improvement under organotherapy.**

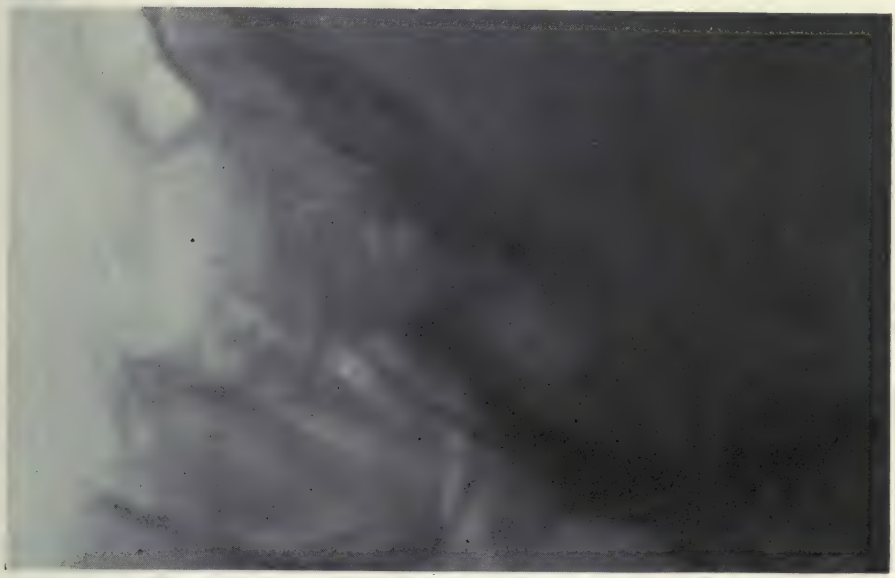


FIG. 234.—Case XXXIV. X-ray of cranial base (nat. size), showing small sella with heavy outlines and no sphenoidal cells in juxtaposition.

March 13, 1911. D. G., aged 9, referred by Dr. J. J. Putnam of Boston. *Complaint:* Adiposity and epilepsy.

The child's mother is said to have developed "diabetes" (hypophyseal?) shortly before his birth, and she died from this cause two months later. There is no history of headaches

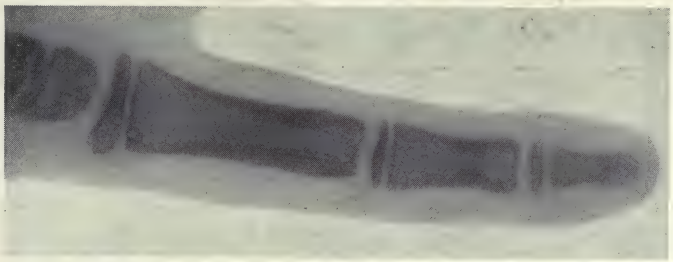


FIG. 235.—Case XXXIV.—X-ray of index finger (nat. size).

or of acral enlargements—merely that there was a very large amount of sugar in the urine.

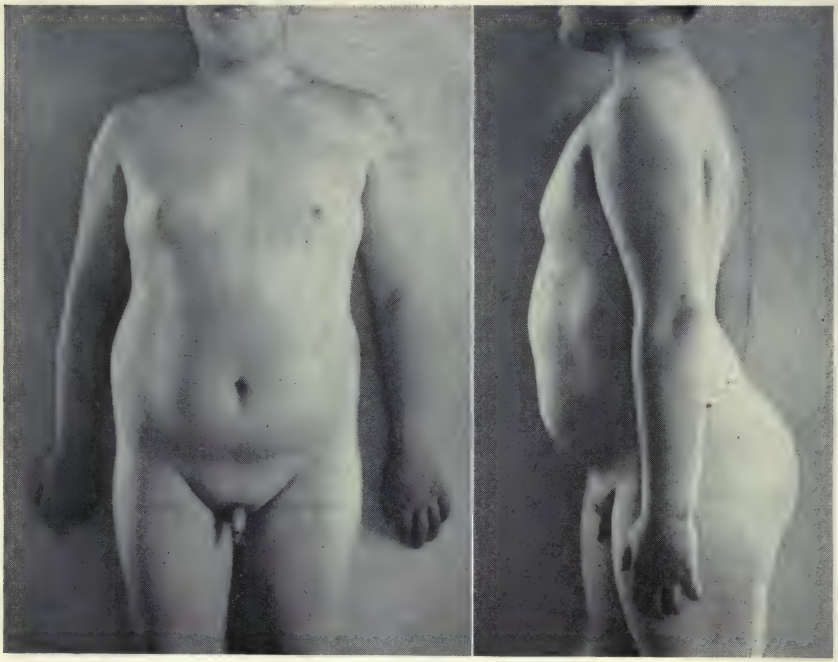
He was somewhat tardy in acquiring speech and in learning to walk—"a backward child." Until his fourth year he was rather slender and frail, but at that time he became noticeably obese, and has remained so. Physically he is quite unlike the other children of the family, nor does he resemble them in facial outline. He is lazy and inactive.

He has had three peculiar epileptiform attacks (3 years, 14 weeks and 3 weeks ago). He suffers from the cold. He has an enormous appetite, particularly for sweets. No headaches.

Physical Examination. A light-complexioned, colorless, adipose boy with a feminine configuration of the body. Visceral (abdominal and thoracic), cardiovascular and neurological examinations are practically negative. *Blood* and *urine* negative.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood.* The sella (Fig. 234) is below the normal size and shows an unusual solidity of the sphenoidal bone. *Eyes:* Slight exophthalmos. There is a suggestive bitemporal dimness of vision on rough tests, not confirmed by the perimeter. Fundi negative. Pharyngeal examination shows large tonsils and adenoids. No uncinate features noted in the epileptic attacks.

(b) *Glandular. Skeletal:* He is somewhat overgrown. *Height* 149 cm. (4 ft. 10⅝ in.): *weight* 118 pounds. No signs of epiphyseal union (X-ray) in the long bones or phalanges



FIGS. 236, 237.—Case XXXIV. Note adiposity of typus femininus and genital hypoplasia.

(Fig. 235). The extremities are tapering: wrists and ankles small. The pelvis is broad and there is some genu valgum, giving the body a feminine aspect.

The head is large, forehead prominent (wears a No. 7 hat: circumference 56.5 cm.). Profile of the face shows slight maxillary prognathism: the nose is straight, of Grecian type. Upper teeth are rather prominent. The hands are small with fat, tapering fingers; no crescents showing.

Cutaneous. The skin is dry; notably free from perspiration; smooth and delicate. There is a slight languo-like growth of hair on the face and arms: no axillary or pubic hair. No pigmentation.

He is *adipose*, with a feminine type of distribution (Figs. 236, 237) over hips, pectorals, pubes and abdomen: the supraclavicular pads are prominent. He is so large as to require the clothes of a sixteen-year-old boy. Circumference over pectorals 88 cm.; at umbilicus 90 cm.; over hips 84 cm.; thigh 55 cm.; calf 31 cm.; ankle 19 cm.

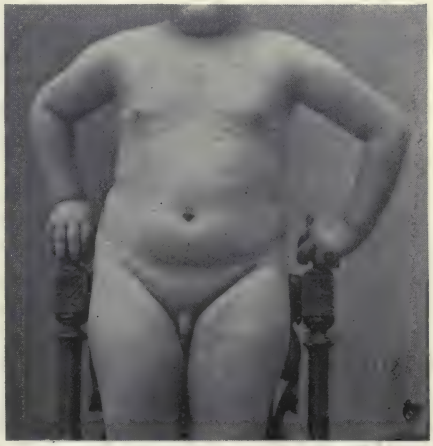
Carbohydrate tolerance high for a child of his age; assimilation limit approximately 150 grams of lævulose. No *polyuria* (800–950 cc.). *Temperature* and *pulse* average normal. *Blood pressure* 135 mm. Hg. *Thermic reaction* suggestive (97.6 to 99.6°).

Other Ductless Glands. Thyroid not palpable. The *genitalia* are undeveloped. Testes have emerged but lie hidden in the fat of the mons veneris: they are very small and soft.

Discharged March 17, taking 9 grains of whole gland preparation (Armour) daily.

Subsequent Notes. *May 26, 1911. Returns for Observation.* There is a definite improvement in the child's appearance and in his mental and physical condition: he is far more alert. The skin has become moist. His voracious appetite is better controlled and his weight has fallen to 109 pounds—a loss of 9 pounds. He has lost the "bloated" appearance of the face. He is less nervous. No convulsive attacks. He sleeps better. He is beginning to show a pubic growth of hair. The left testis has descended to the scrotum.

Establishment of therapeutic dosage on basis of sugar tolerance. While taking 9 grains of desiccated whole gland daily, 100 grams of lævulose gives a slight lævulosuria on a single specimen six hours later. Estimating that his normal tolerance should be no more than 80 grams of lævulose, he was given this amount of sugar each evening, the glandular dosage meanwhile being increased. When the amount reached 18 grains a day, a slight lævulosuria was demonstrated on a single specimen (Seliwanoff) eight hours after taking the sugar.



Kindness of Rudolf Neurath.

FIG. 238.—For comparison with Figs. 236, 237. Age 6; height 3 ft. 11 in.: weight 69 pounds.

Discharged taking 18 grains of whole gland preparation (Armour) daily.

August and September, 1911. Further improvement. He is far less lazy and inactive. His weight has dropped to 100 pounds—a loss of 18 pounds since taking the extract. There is a slight pyrexia (99°) while taking the extract.

October, 1911. Continued mental and physical improvement—"a different boy."

December, 1911. General condition continues excellent. Weight remains slow (102-105 pounds). Attendant reports a "complete mental, moral and physical awakening."

INTERPRETATION.—There are certain unusual features in this case, for it deviates somewhat from the typical instances of *dystrophia adiposogenitalis* of the typus Fröhlich. These concern more particularly the child's evident skeletal overgrowth—a condition the reverse of that which apparently occurs in the cases in which the glandular insufficiency is brought about by tumor—Cases III and V, for example. It is not improbable, therefore, that we have here an instance of anterior lobe activation combined with posterior lobe insufficiency. It is to be hoped that we may in time be able to distinguish the clinical manifestations due to over- or under-activity of the two subdivisions of the gland.

In the typical syndrome of Fröhlich we have an expression of infantilism both structural and sexual associated with adiposity of juvenile type and an hypophyseal tumor—a combined effect of deficiency of both anterior and posterior lobes. In the syndrome shown by the case under discussion we have an expression of structural gigantism

(anterior lobe hyperplasia) associated with genital hypoplasia, adiposity of feminine type and epileptoid attacks, in the absence of an hypophyseal tumor but with an evident low grade of hydrocephalus as indicated by the large head.

One of Neurath's cases[196] is almost the exact counterpart of this case (Fig. 238)—an overgrown boy of 6 years, with semi-occasional epileptoid attacks, weighing 31.2 kilo. (69 pounds), height 118 cm. (3 feet 11 inches), extremely adipose (abdominal measurements 75 cm.), genital hypoplasia, a large head and a normal sella. Neurath's two other remarkable cases are somewhat similar, and doubtless the type will come to be a definitely recognizable one.

However, as he has fully emphasized, one must not fail to bear in mind in this connection the secondary effect upon growth and corpulence occasioned by castration or destructive testicular disease in preadolescents—an effect due in all probability to activation of the pars anterior of the hypophysis. Hypophyseal hypertrophy secondary to castration is well known (Fichera, Tandler and Gross, Rössle), and the length of limb acquired by the preadolescent eunuch is, in all likelihood, a consequence of this expression of glandular interrelation.

Sternberg includes among his subdivisions of "pathological giants" conditions such as that reported by Sacchi,[220] of rapid overgrowth in a child of 9, who had attained a height of 143 cm. after the appearance of a testicular neoplasm.

Had we not already seen that similar constitutional disturbances are brought about by obvious primary hypophyseal lesions, it would be natural to ascribe conditions such as this patient presents to the consequences of partial eunuchism (dysgenitalismus).

The next case is an illustration of hyperpituitarism in a young mulatto who has passed into the adolescent period.

Case XXXV. (Surgical No. 25694.) **Hypopituitarism of young adult life (dystrophia adiposo-genitalis) with an absence of neighborhood symptoms. Glandular therapy.**

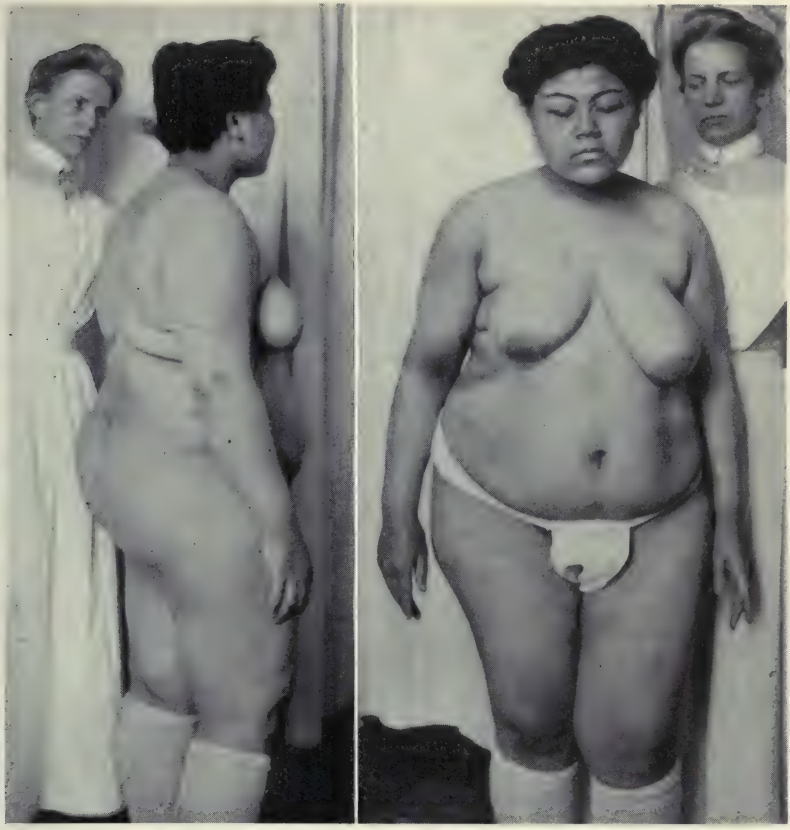
March 16, 1910. Marion B., 15 years of age, was referred to Dr. Thayer's service by Dr. William Miller, with the complaint of headache, obesity and weakness; and was transferred to us for study March 31, 1910.

For three years she has been having severe frontal headaches with attacks of giddiness and failing eyesight. She has had shortness of breath and palpitation on exertion, and polyuria. Her menses began normally in her fourteenth year, but during the past twelve months she has had only three scant periods.

No members of her family are obese and she herself was slight until a year ago. In January, 1909, she weighed (clothed) 115 pounds: in September of the same year her weight was 183 pounds, and on admission to the hospital it was 239 pounds—a gain of *124 pounds in fourteen months*. Her appetite is large: she is very fond of sweets.

Physical Examination. An exceedingly obese young mulatto with a small and delicate bony frame (Figs. 239, 240). The mucous membranes are a good color. There is marked pyorrhœa alveolaris.

Cardiovascular: The heart and vessels are apparently normal. The pulse is persistently slow (65 per minute, and occasionally falling below 50). *Visceral:* The thoracic and abdominal organs show no deviation from the normal. *Neurological:* There are no



FIGS. 239, 240.—Case XXXV. Marked adiposity (124 pound increase in fourteen months)

FIG. 241.—Case XXXV. Showing normal sella with thickened dorsum sellæ, giving double contour.

positive findings. *Gynæcological:* The cervix uteri is very small: fundus and ovaries are not palpable.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood Symptoms.* These are wanting. An X-ray shows a normal sella turcica (Fig. 241). There is considerable uniform constriction of the fields for form and the earlier fields (Fig. 242), taken on admission during a period of headache, show some color interlacing. There is no diplopia: no pupillary change: no neuroretinal abnormalities.

(b) *Glandular Symptoms. Skeletal* changes are inconspicuous. The extremities are small; the hands (Fig. 243) pudgy, the fingers delicate and tapering, the nails showing no crescents. The X-ray shows small terminal phalanges (Fig. 244). The *epiphyses* are ossified, there being but a ghost of the radial line still present.

Cutaneous. The skin is smooth and dry. The hair of the head is apparently normally abundant, but there is a very scant pubic and axillary growth. The *adiposity* is excessive and has been acquired in the space of a year, with extraordinary rapidity. It is universally distributed, though the neck is slim and disproportionately free from panniculus. The

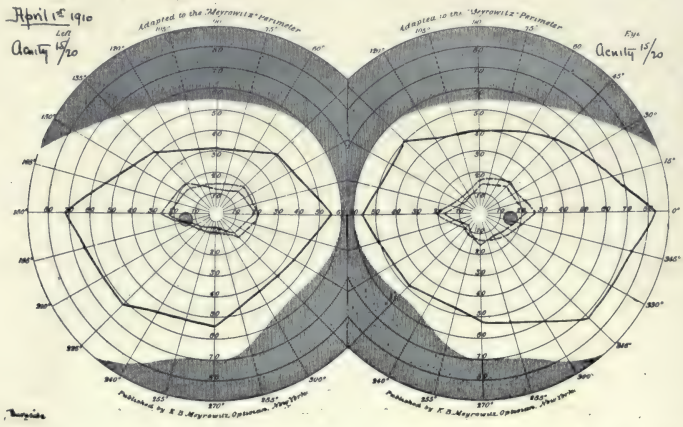


FIG. 242.—Case XXXV. Fields of April 1, 1910, showing fairly uniform peripheral constrictions.

circumferential measurements are: Neck 24 cm.; upper arm 35 cm.; chest at axillæ 100 cm.; body at umbilicus 121 cm., at hips 121 cm., thigh 74 cm., calf 40 cm. The deeper tissues are not tender: there are no discrete lipomas.

The *carbohydrate tolerance* is increased, 275 grams of glucose being required to produce a transient glycosuria. There is slight *polyuria*, the measured excretion often exceeding the ingested fluids: thus on *May 10* the intake was 950 cc., output 1250 cc.; *May 11*, intake 1000 cc., output 1840 cc.; *May 12*, intake 1000 cc., output 1350 cc.; *May 13*, intake 900 cc., output 1495 cc.; *May 14*, intake 500 cc., output 1425 cc.

The *thermic reaction* to 3 cc. of 1 per cent. solution of bovine anterior lobe (Armour) is positive, causing a response from 97.6° to 102° F. A control posterior lobe injection on two occasions gave no thermic response. The *temperature* and *pulse* range subnormal.

Other Ductless Glands. The thyroid is not enlarged. There has been a suppression of the menses and the pelvic organs are apparently undeveloped.

Treatment. The patient was discharged *June 24*, taking whole gland extract in small doses: viz., 3 grains with her three daily meals.

INTERPRETATION.—This case is one of a not uncommon type—a young individual in whom a rapid development of extreme corpulence has been associated with headaches and amenorrhœa. There may possibly be some

intracranial process remote from the infundibular region, as in the cases to be recorded in the succeeding group. The clinical syndrome, however, is that of primary hypopituitarism with involvement of both lobes, as the positive thermic reaction to anterior lobe injections, the high sugar tolerance, adiposity, polyuria, subnormal pulse and temperature, would indicate.

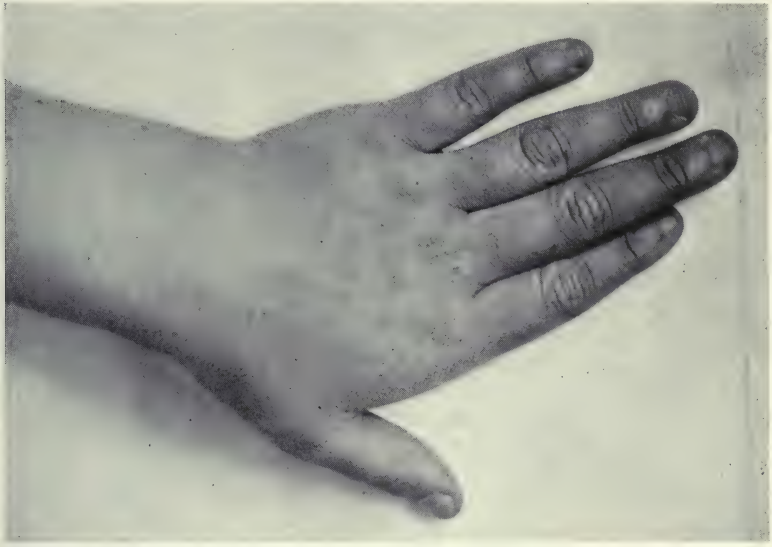


FIG. 243.—Case XXXV. The typical tapering hand of adolescent hypopituitarism (cf. the *type en large*, Fig. 196, and the *type en long*, Fig. 163, of Marie).

It is of interest that while in the medical ward on a very restricted diet her weight fell from 239 pounds on March 16th to 225 pounds on March 31st, at the time of her transfer. Following her hypophyseal test injections there was a loss of four pounds, due, we presumed, to an activated metabolism, her

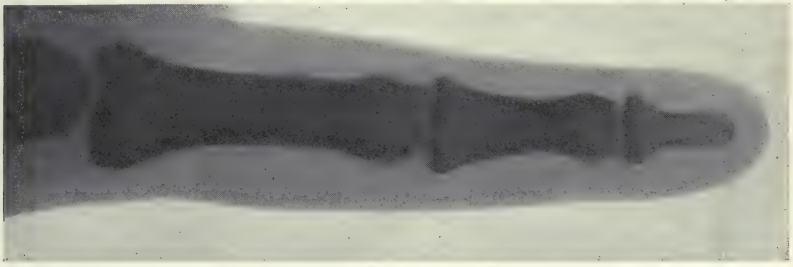


FIG. 244.—Case XXXV. Finger of patient aged 15; showing closure of epiphyses and small terminal phalanx.

weight falling to 222 pounds. During the subsequent ten days of sugar feeding (starting at 50 grams and increasing 50 grams a day to 300 grams) she rapidly regained weight up to 232 pounds.

Obviously the primary therapeutic indication for this patient's condition is glandular feeding and, being one of our earlier experiences, unques-

tionably an insufficient dosage was given. It is in such conditions that thyroid extract has proved of value in the past, doubtless prescribed on the supposition that the adiposity, dry skin, loss of hair and subnormal temperature were expressions of hypothyroidism.

It is, of course, well known that thyroid preparations have the property of increasing metabolism, but whether this occurs through an activation of the hypophysis or by supplying an actual thyroid want it is at present difficult to tell. Certainly hypophyseal preparations have an equal if not a greater power than thyroid extracts in accelerating metabolic processes, and unquestionably it is best to give extracts of the gland which is primarily at fault.

The following case represents a similar condition occurring in the next decade. There are certain radiographic changes in the sella suggestive of a glandular transformation.

Case XXXVI. (Surgical No. 26225.) **Adult advancing hypopituitarism with amenorrhœa, adiposity and enlargement of the sella turcica. Improvement under glandular therapy. Subsequent sellar decompression.**

July 10, 1910. Mrs. L. H. B., a bookkeeper, 24 years of age, was admitted for study complaining of headaches, amenorrhœa, dryness of the skin and rapid gain in weight.

She has one paternal aunt who is heavy, but her family otherwise incline to be tall and slender. She was sickly as a child. At the age of 2, following measles, there was an otitis media, and the left ear has been discharging ever since. In addition to the usual infantile infections she had pneumonia at the age of 10, followed by articular rheumatism. She had chorea at 12, and for a number of years afterward suffered from "fainting spells," which are very suggestive of epilepsy. She has chronic catarrhal trouble and suffers from tonsillitis.

Her menses began at 12 and have always been irregular. She married at 16, and had a healthy child a year later. She has been divorced for seven years. For the past two years amenorrhœa has been complete.

Present Malady. She began having *headaches* about eight years ago; usually severe, occipital, and often followed by nose-bleed. Following a severe mental shock four years ago she ceased menstruating: her last catamenia was in *May, 1908*. Her average weight up to December, 1908, was 130 pounds, and during the following six months there was a sudden unaccountable *increase of 60 pounds*.

In *May, 1909*, she was given *thyroid tablets* for her adiposity. Their administration led to extreme nervousness, palpitation and excessive perspiration, and they were discontinued after she had lost 25 pounds in weight: this was regained soon after stopping the tablets.

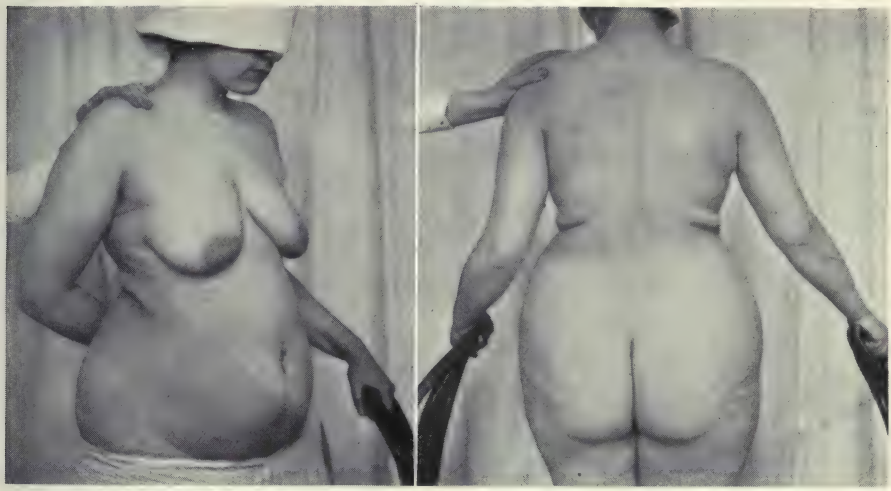
She has an inordinate *appetite*, and complains much of dullness and drowsiness: she is easily fatigued. There has been a marked *change in disposition* with great irritability, lapses of memory, etc. She has observed transient *swellings of the hands and feet* and the skin is dry and hot. Her hair has been falling out: the nails have become brittle.

Physical examination shows a woman of 5 ft. 7 in., weighing 203 pounds (Figs. 245, 246). Visceral organs (thoracic and abdominal) negative. Cardiovascular negative. There is an old discharging otitis media, giving some labyrinthine symptoms with a positive reaction on caloric tests. *Urine* negative. *Blood:* Slight leucocytosis. Wassermann negative. *Blood pressure* 105 mm.

The *neurological* examination is negative throughout, aside from the nystagmus, which is doubtless associated with the labyrinthine disease. There is, however, a history of diplopia. The ophthalmoscope shows a suggestive haziness of the nasal margins of both

discs, but there is no measurable swelling. There are perivascular streaks which suggest the possibility of an old choked disc. The veins are slightly full and tortuous. The fields show slight interlacing (Fig. 247).

Pelvic examination shows a small and slightly displaced uterus. The ovaries are palpable, movable and apparently normal.



FIGS. 245, 246.—Case XXXVI. Note adiposity (60 pounds increase in six months); small head and neck, wrists and hands.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* A stereoscopic *X-ray* shows an enlarged sella measuring 1.7 by 1.4 cm. in depth. A peculiar dense shadow is thrown by its contents (Fig. 248). This is particularly striking when compared with other cases in which, even though the sella turcica appeared greatly enlarged, the

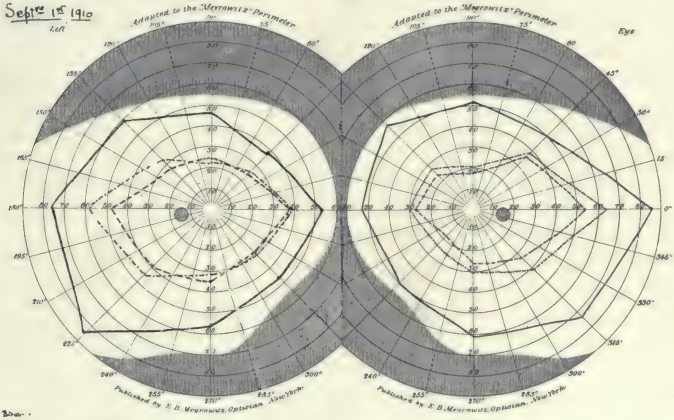


FIG. 247.—Case XXXVI. Fields showing slight constriction with some color interlacing on left.

contents did not interrupt the rays. There is no optic atrophy: no deformation, though slight constriction of the visual fields: no paresis of ocular muscles (note history of diplopia). *Epistaxis* has been frequent in the past.

(b) *General Pressure Symptoms.* Persistent headache: haziness of discs with signs of an old process: color interlacing.

(c) *Glandular.* No skeletal changes. Extremities small. Hands and fingers of tapering type. The skin is subjectively "dry and burning," and there is a notable absence of perspiration—the more striking in view of midsummer heat and her obesity. The hair is thinning. There is an excess of panniculus, especially over abdomen and hips; face, neck and extremities remaining largely exempt: it has been rapidly accumulated.

Carbohydrate tolerance high: 250 grams of glucose gave an atypical reduction but 300 grams were necessary to produce positive glycosuria with fermentation reaction.

Complete *amenorrhœa. Temperature* ranges subnormal (96° to 98°): *pulse* variable (60 to 90). Positive anterior lobe *thermic reaction* (cf. Jan. 27, 1911).

July 16. A *lumbar puncture* was performed and 50 cc. of fluid removed. Two centimeters of this fluid in a 5 to 1 concentration gave fairly characteristic posterior lobe reactions. Following the puncture there was an increase of headache and a definite 24-hour *thermic response* (similar to that of an anterior lobe injection) from 98° to 101.6°, with a gradual return to the subnormal point of 97°.

July 18. She was *discharged,* taking 3-grain powders of whole-gland extract after meals.

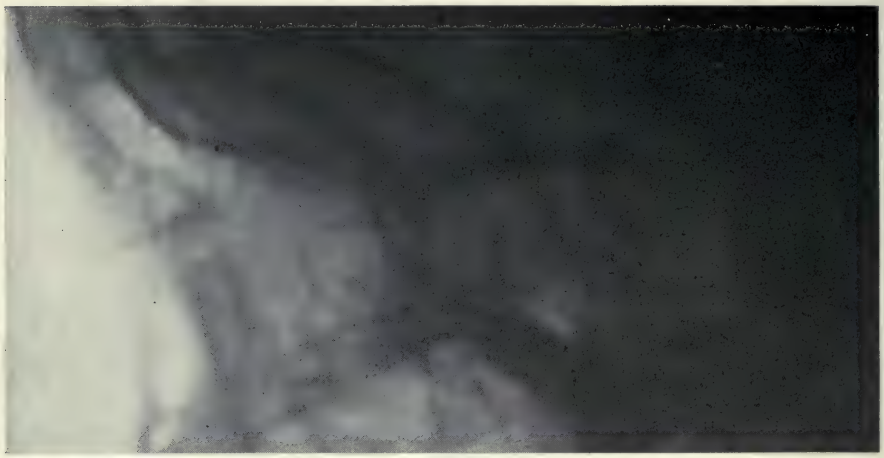


FIG. 248.—Case XXXVI. Skiagram showing solid shadow cast by entire sellar region without bony deformation: either an ossified sellar cup or actual calcification of the gland itself.

This was one of our earlier attempts at glandular administration. The experience was as follows:

Therapeutic Notes. During the following three months the extract was taken and then discontinued and resumed again, to compare the subjective symptoms. The patient kept careful record of the urine, temperature, etc., throughout.

During the first two weeks she experienced disturbing cutaneous sensations of "flushing" with some visible perspiration. Her temperature ranged about a degree higher—nearly normal. Her headaches were less, though she still felt mentally dull, listless and dazed. There was evidently some effect upon the gland, for there was a temporary return of diplopia.

On discontinuing the extract the headaches returned: some photophobia was observed for the first time, and her temperature fell again and ranged around 97° F.

After a two weeks' interval the extract was resumed in the original small dosage, with about the same result. This was continued during the summer. In *October,* with the thought that the chronic suppurative process in the ear might bear some relation to her glandular disease, a radical *mastoid operation* was performed, eliminating this disturbing element.

In *January, 1911,* she re-entered the hospital for further study. She had taken no

extract since October. Her weight was 200 pounds: the headaches were constant: she was forgetful and very irritable, and there was a general sensation of *muscular weakness.* Temperature 96° to 98°.

It was found that her *sugar tolerance* had greatly increased, the assimilation limit for lævulose then being 320 grams—a higher weight of sugar than had represented the limit for glucose six months before.

With 0.4 gram of boiled posterior lobe extract given hypodermically in 2 cc. of water a 200-gram dose of lævulose gave a positive lævulosuria. No thermic reaction. A few days later, however, 0.4 gram of boiled anterior lobe extract given under the skin gave a *positive thermic reaction* (Fig. 249), with profuse sweating and headache.

Discharged Jan. 28, taking 6 grains of the whole gland after meals. This was gradually increased, and by March she was taking 10 grains after meals, with 5 grains of thyroid extract.

Aug. 1, 1911. Under this dosage she has kept in very fair condition during the year. Her weight has remained below 200 pounds, the skin moist, the temperature about normal.

As an experiment she discontinued the extract for six weeks during the heat of June and July. The change was very noticeable, with return of headaches, dry skin, subnormal temperature, irritability, and her weight increased to 210 pounds. On resuming treatment she lost 11 pounds in the first ten days.

A number of *skiagrams* have been taken during the intervening year. All show the same peculiar opacity of the pituitary pocket, and the more recent ones indicate that there has been an increase of a millimeter or two in its dimensions (cf. p. 186).

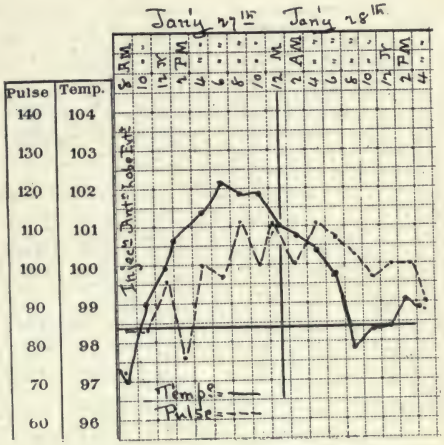


FIG. 249.—Case XXXVI. Thermic reaction to subcutaneous injection of boiled pars anterior emulsion, indicating anterior lobe insufficiency.

INTERPRETATION.—A case of rapidly acquired adiposity with headaches, drowsiness and amenorrhœa, a high sugar assimilation limit, which could be lowered by the coincident injection of posterior lobe extract, and a subnormal temperature with a positive thermic reaction to anterior lobe injections—characteristic signs, in other words, of insufficiency affecting both lobes of the gland.

In addition, the X-ray disclosed a sellar enlargement and a peculiar opacity of its contents: subjective improvement, furthermore, occurred under the therapeutic test of glandular feeding. A few years ago the association of her symptoms with hypophyseal disease would hardly have been suspected.

As in the majority of the cases with adiposity, the condition seems to be one of incomplete tissue metabolism—of ineffectual burning up of the stored food products, and particularly of the carbohydrates. The subnormal temperature is possibly an indication of this, and its presence is the more remarkable in view of the dry skin and absence of perspiration which these individuals often show. It is a feature, however, common to states of insufficiency of other ductless glands—of the thyroid, for example, and possibly also of the adrenal or thymus.

In view of the persistent headaches, it is possible that a sellar decompression may be advisable, and this at present is under consideration.* It might serve also to liberate the gland from a possible confinement by an ossified pituitary pocket or actual calcification of the gland, such as Dercum and McCarthy[64] and Krauss[150] have described. For similar reasons a sellar decompression was performed in Cases VI, VII and XX, and also in the following case.

Case XXXVII. (Surgical No. 26679.) **Adult hypopituitarism with extreme corpulence (Dercum's disease) and high carbohydrate tolerance. Suggestive neighborhood symptoms. Operation: sellar decompression. Organotherapy.**

Aug. 4, 1910. Mrs. M. B., a widow, aged 55, was referred to the hospital by Dr. William Fountain of Greenville, N. C., complaining of adiposity and pains in her feet and knees.

She is a woman of good habits and no notable past illnesses. She has led a regular and hard-working life. Her menstrual history relates no irregularity. She has borne five healthy children. Her menapause occurred at the age of 42, without incident.

Present Malady. Formerly not a heavy woman, she began, six years ago, to rapidly *increase in weight*, until she exceeded 300 pounds. During this period she has had a more or less constant, dull frontal *headache*, often associated with attacks of *vertigo*. There has been a sensation of revolving to the right during these attacks and she has fallen a number of times. She has never lost consciousness. *Vomiting* preceded by nausea has accompanied several of the more severe headaches.

She becomes easily fatigued and feels very weak. There has been considerable *loss of memory* and she is inclined to worry over trifles. She has had some tinnitus and there has been a progressive diminution of visual acuity. The flesh has been generally tender and bruises easily: there have been aching pains in knees and ankles. She has had some numbness with "pins and needles" sensations in her left hand and arm.

She has had polydipsia and *polyuria* for at least three years, with increased frequency of micturition, necessitating her getting up three or four times during the night. She is *drowsy* most of the time and tends to sleep "whenever she sits down." Her hair has fallen out rapidly during the last few years and is "dry and brittle."

Physical examination shows an exceedingly obese woman *weighing 302 pounds* (Figs. 250, 251) with normal thoracic and abdominal viscera so far as they can be examined. Cardiovascular and neurological condition is practically negative, except for the neighborhood signs to be mentioned. The deep reflexes are not obtainable. There is a tendency toward a subnormal temperature (often registering as low as 96.5°F.). The pulse occasionally falls to 60. *Blood* and *urine* negative.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood.* The sella is slightly enlarged, measuring 1.7 cm. by 1.3 cm. in depth (Fig. 252). The posterior clinoid processes appear to be thickened and irregular.

Eyes. There is a definite slight exophthalmos of the left eye, the pupil of which is dilated and the palpebral cleft wider than on the right, with positive von Graefe and Joffroy signs. The pupillary reactions are normal. The perimetric chart shows a definite upper quadrantal homonymous notch in the left color field (Fig. 253). Both discs are pale and

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**Subsequent Note.* She re-entered the hospital *Oct. 20, 1911*, with the further complaint of headaches (right temporal) and considerable lowering of vision. The fields showed a marked increase in constriction: low grade of choked disc (bilateral).

Oct. 24, 1911. Operation. Sellar decompression, with removal of a few fragments of gland for examination: these showed a *chromophobe struma* with no eosinophile elements. At the same time blood was taken for sugar estimation, and showed (Jacobson) 0.060 per cent. sugar—a moderate hypoglycæmia (cf. Case XXIII).

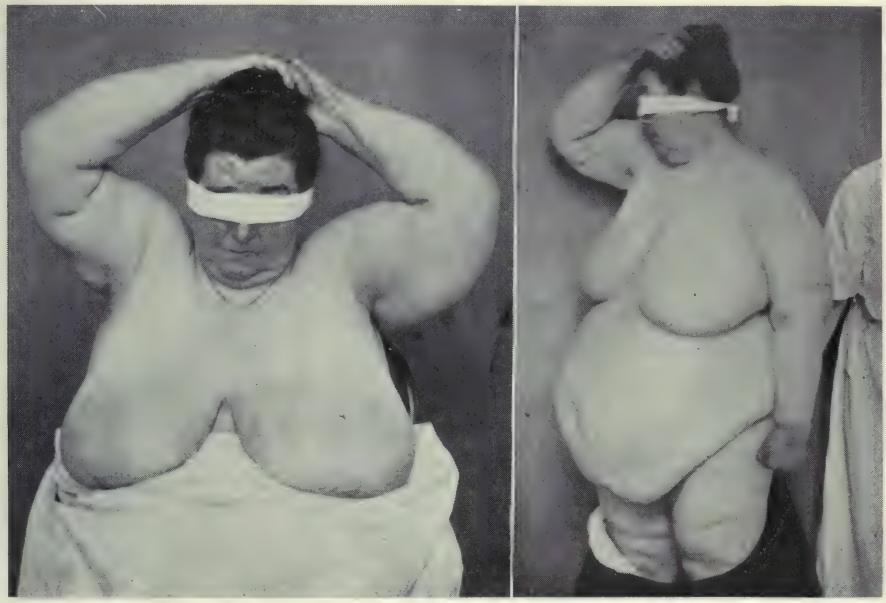
She made a prompt recovery from the operation, with immediate and complete cessation of headache—the most striking case in this respect that we have seen. She left the hospital seven days later, and resumed her work.

show a slight haziness of the nasal margin with some distention and tortuosity of the veins. The acuity has been progressively lowering: at present (corrected) it is 10/40 for both eyes.

(b) *Glandular.* The skeletal frame is small, particularly the hands and feet. Height 5 feet 6 inches. The head is well formed; the face not particularly fleshy. *Lipomatosis* of the subaural and cervical regions is marked. The breasts are huge and pendulous; the abdomen elephantine. There are no circumscribed lipomata. The upper arms are fat and when raised the panniculus hangs in huge folds.

The lower extremities at first glance resemble elephantiasis, but there is no hypertrophy of the skin. The fat of the extremities is tender on pressure. The skin is soft, smooth, dry and somewhat pigmented over the more exposed areas. There is a very scant axillary and pubic growth of hair and that of the head is much thinned.

Carbohydrate tolerance is exceedingly high: limit not ascertained. On *August 13*, 200 grams glucose, on *August 14*, 300 grams, and on *August 16*, *400 grams gave no glycosuria.*



FIGS. 250, 251.—Case XXXVII. Extreme obesity ("adiposis dolorosa") attributable to hypopituitarism.

On *August 22*, 0.1 gram of posterior lobe extract, injected after giving 200 grams of glucose, caused no glycosuria.

The *temperature* is persistently subnormal (occasionally as low as 96° F.): the *pulse* is slowed (occasionally below 60). No *polyuria* observed.

The patient returned to her home, taking 3 grains of desiccated whole-gland preparation for the following five weeks.

Oct. 6, 1910. **Readmission.** Subjectively she has experienced marked improvement. She has had practically no headaches and has lost 25 pounds in weight (present weight 273 pounds). She has perspired freely under the treatment—the first time in some years. The organotherapy was discontinued on her readmission, whereupon there was a definite return of headaches and nausea, dullness and drowsiness. The general physical and neighborhood symptoms showed no alteration from the conditions observed on her previous admission.

On *Oct. 14*, a subcutaneous injection of 0.2 gram of desiccated anterior lobe extract boiled in 2 cc. of salt solution was followed by *no thermic response.* There was no local reaction nor constitutional disturbance.

Oct. 25, 1910. **Operation.** By the sublabial approach a sellar decompression was performed, on the view that there was possibly a superimposed lesion causing posterior lobe obstruction. The anæsthetization caused anxiety, owing to the patient's weight and respiratory difficulty while lying on her back.

The bony projection of the sella was finally identified and the floor removed. The gland was considerably larger than expected. The enveloping dura was slit, stellate fashion. No fragments excised. Closure without drainage.

Recovery was uneventful, aside from a transient hæmaturia from overdosage with urotropin. The temperature was 100° for 24 hours and then fell to its previous subnormal level.

Glandular therapy (9 grains of whole gland: Armour) was resumed on *Nov. 1.* As on the previous occasion it led to a definite increase in the amount of urine, though even with the extract the 24-hour amounts were never large.

Carbohydrate Tests. On *Nov. 10,* 300 grams of glucose gave no reducing substance. On *Nov. 14,* 400 grams led to a transient glycosuria on the first specimen (it is to be noted

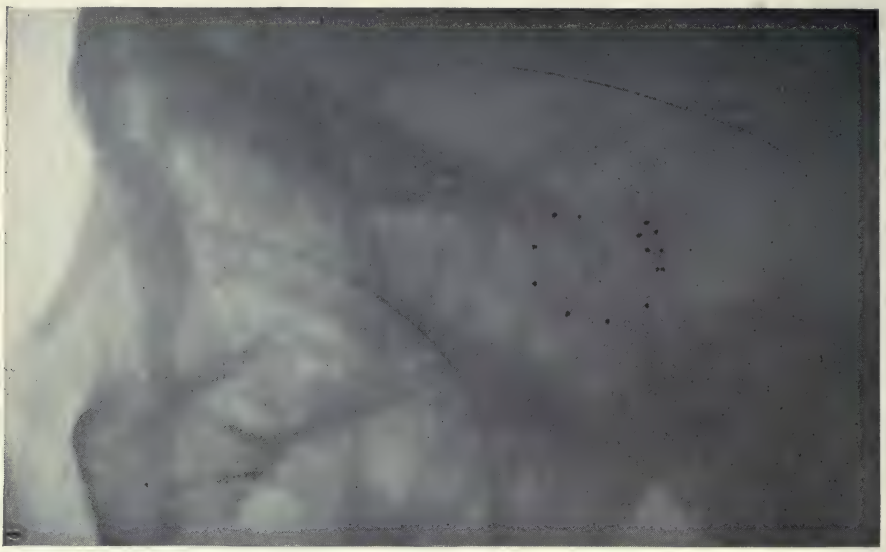


FIG. 252.—Case XXXVII. Slight enlargement of sella. Outlines indicated by dots (nat. size).

that the earlier test of *August 16* with this dosage caused no glycosuria, these later tests having been made during a period of glandular administration which doubtless influenced her tolerance). Coincident with the sugar tests she gained 6 pounds.

There was some subjective improvement in vision. The fields of *November 10* (Fig. 254) show some diminution of the constriction.

She was *discharged* November 15, her weight having dropped to 259 pounds—a loss of 47 pounds since her first admission.

Subsequent Notes. *September 8, 1911.* She has continued to take whole gland extract with only a few intermissions. She has an occasional slight headache. Her weight has progressively fallen and is now 242 pounds (clothed), a loss of over 60 pounds during the year.

INTERPRETATION AND DISCUSSION.—An individual, in whom extreme adiposity was acquired after middle age, the clinical picture being that of Dercum's disease, though the dolorous features were associated rather with

intracranial discomfort than with any unusual tenderness in the areas of increased panniculus.

There are certain features of the case which point with some definiteness toward a pituitary involvement. In the first place, the neighborhood

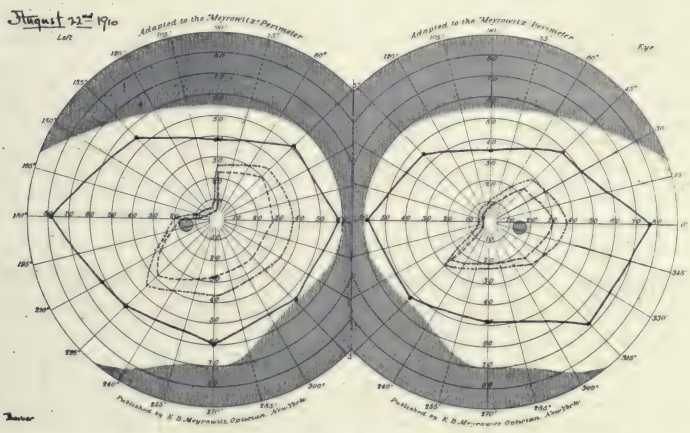


FIG. 253.—Case XXXVII. Fields before operation, showing some constriction and a tendency to a left homonymous color defect.

symptoms (a slightly enlarged sella; homonymous quadrantal achromatopsia; the gland demonstrably under tension at operation, etc.) though inconspicuous, nevertheless indicate some local disturbance, possibly an infundibular lesion. Further, the extraordinary carbohydrate tolerance, which could be

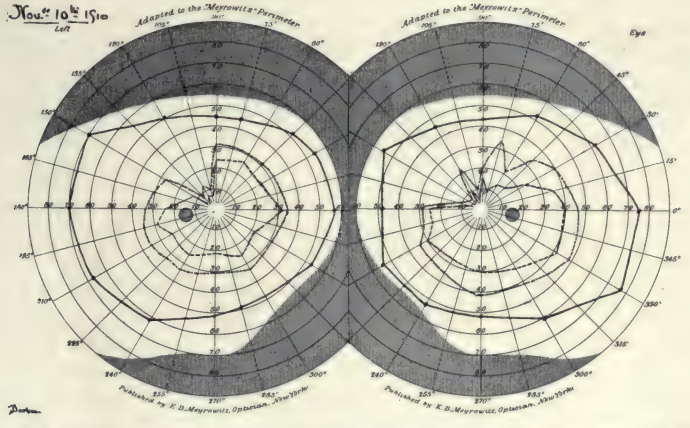


FIG. 254.—Case XXXVII. Fields showing some widening of peripheries but persistence of the left upper quadrantal color defect.

lowered by glandular feeding, and the apparent increase in tissue metabolism under organotherapy, are also evidences of primary hypophyseal deficiency —a deficiency limited to the activity of the posterior lobe, if the negative thermic response to anterior lobe injection can be relied upon.

The case was observed and the effects of glandular feeding tried before we had any lead as to means of estimating the dosage, and in all probability the patient has been taking an insufficient quantity of the gland and possibly requires posterior lobe extract alone. Nevertheless, her improvement even under the small dosage was convincing.

It can hardly be gainsaid that a number of the individuals reported as instances of *adiposis dolorosa* are actually examples of disturbed metabolism secondary to disease of the ductless glands. The very fact that thyroid administration has served in many cases to activate metabolism is, in a measure, indicative of this.

It is probable, furthermore, and indeed we have had clinical evidence to support the view, that thyroid extract is actually of benefit in cases of adiposity primarily hypophyseal. It is very probable, indeed, that an extract of any one of the ductless gland series might be of benefit under these circumstances. However, there can be little doubt but that the administration of the gland primarily at fault in the polyglandular syndrome is therapeutically indicated above all others.

I judge that Dercum and his associates have begun to feel disposed toward accepting an hypophyseal origin for certain at least of the cases described as "adiposis dolorosa," a condition which must, as Lyon[171] has clearly shown in his admirable paper on adiposis and lipomatosis, cover a large number of conditions and which can hardly be accepted, therefore, as a so-called clinical entity. Indeed, in one of Lyon's patients recorded as a typical instance of the malady, an aneurism compressing the pituitary body has since been found at autopsy (personal communication). Another case with postmortem examination recorded by Dercum and McCarthy[64] I should judge to have been a typical case of hypopituitarism with genital dystrophy, epilepsy, etc. Postmortem examination disclosed an hypophysis enveloped in a subdural calcareous layer (cf. Case XXXVI) and compressed by an intrasellar tumor, tentatively regarded as an "adeno-carcinoma." Doubtless equally careful postmortem investigations would reveal hypophyseal abnormalities in many other cases. In his recent thesis[102] Grahaud, a pupil of Launois, has included Dercum's malady among the adiposities of hypophyseal origin.

It will be recalled, that since Vitaut's studies of adiposis dolorosa, a certain grade of mental change has become accepted by Dercum himself as one of the four cardinal symptoms of this malady. Hence it is interesting to observe that practically all of the cases of hypopituitarism which have been heretofore cited in our series have exhibited some degree of psychic disturbance, varying from nervousness to epilepsy and actual mental derangement.

There are, of course, innumerable intracranial maladies which serve to secondarily inhibit the activity of the pituitary gland through cerebrospinal fluid stasis or through vascular disease, as we shall indicate in the following section. It is probable, however, that pituitary deficiency, like thyroid deficiency, may actually elicit signs of mental instability irrespective of any gross encephalic lesion, and there can be little doubt but that many of the psychasthenias and neuroses of one sort or another will prove to be associated with ductless gland disturbances, more particularly with those of hypophyseal origin.

GROUP IV.—CASES IN WHICH REMOTE RATHER THAN NEIGHBORING INTRACRANIAL LESIONS HAVE LED TO SECONDARY DISTURBANCES OF THE GLAND.

This proves to be a limitless group and one to which practically no attention, so far as I am aware, has heretofore been paid. Four or five cases selected from a large number will suffice as illustrations. Naturally only those in which a postmortem examination of the gland has been possible are of conclusive value.

By a fortunate circumstance our hypophyseal studies have been made in a service which is composed largely of individuals suffering from encephalic tumors of most diverse types. Through the courtesy of the pathological department my assistants and myself have been given the privilege of making our own first-hand studies of the nervous systems of patients who have come to autopsy in this service, and we have made it a practice to harden the brains *in situ* by carotid injections of formalin for the especial purpose of studying the cerebral deformations produced by tumors.

For the past several years, since our interest has been aroused in hypophyseal matters, we have removed and sectioned the pituitary body thus hardened in all cases, and it was soon observed that even macroscopical changes in the gland often accompany growths which are situated at a distance. In nearly all subtentorial tumors, for example, some degree of hypophyseal deformation with flattening of the structure is an almost invariable finding.

No sooner had we observed the occurrence of adiposity in some of our experimentally hypophysectomized animals and realized that it was a manifestation of glandular deficiency than it became clear that clinical evidences of hypopituitarism in association with intracranial growths were passing unrecognized before our eyes.

It has long been a subject of comment that individuals with tumor cerebri often retain their weight and general nutrition to a surprising degree, despite the more or less pronounced headache and vomiting. This rule applies to adults as well as to children, but is perhaps more striking in the latter. In a series of over twenty preadolescents with cerebellar tumors and internal hydrocephalus the majority have been, as the histories relate, "well nourished," and not a few of them quite adipose. The same is true for many infants—at least for those who have received reasonable care—who are afflicted with so-called essential hydrocephalus. Furthermore, there are symptoms other than mere adiposity to which attention has been called in adult cases—among them amenorrhœa[191] and anaphrodisia; and the subnormal temperature and slow pulse of these individuals may properly be merged in this same syndrome.

In a number of these patients we have made tests of the carbohydrate tolerance and have found it to be modified, just as in cases of hypopituitarism when the gland is subjected to the direct compression of a tumor. One or two patients have shown an assimilation limit of over 400 grams of lævulose. For obvious reasons, therefore, it has become a routine of our neurological examinations to analyze the possible hypophyseal manifestations under an especial heading.

We at first supposed that the mere distention of the third ventricle, with the consequent flattening of the gland, was a sufficient explanation of these symptoms of glandular deficiency, and it was not until the apparent demonstration, with Emil Goetsch,[59] that the posterior lobe secretion possibly discharged into the cerebrospinal fluid, that we had a full realization of the mechanism by which an internal hydrocephalus can obstruct the secretory activity of this part of the gland. For cerebrospinal fluid stasis becomes

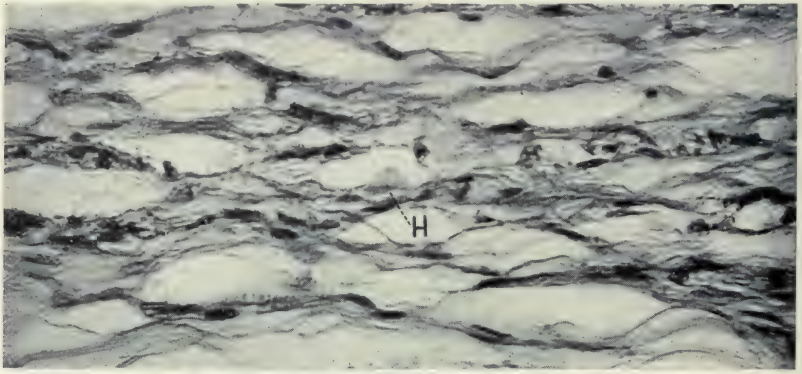


FIG. 255.—Showing separated interneurogliar spaces characterizing posterior lobe obstruction. A single globule of hyalin at *H* remains undissolved. (Mag. 375 diams.)

equivalent in its effects to an experimental obstruction of the stalk or to the compression of an immediately superimposed infundibular tumor.

It was in the fluid from the case of hydrocephalus which will be reported that we first demonstrated the presence of a substance which gives the reaction characteristic of posterior lobe extracts themselves. All of the cerebrospinal fluids—some 40 or 50 specimens from man as well as the normal bovine fluid—which we have subsequently examined have, as a matter of fact,

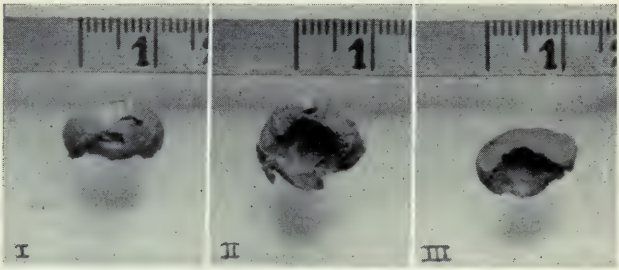


FIG. 256.—Characteristic scaphoid distortion of gland from case of cerebral tumor with hydrops of third ventricle. (I) Posterior view showing cystic clefts, (II) upper view, (III) transverse section.

been shown to possess similar properties. One naturally clings, however, to the belief that in the retained fluid of obstructive hydrocephalus the secretory products will be found in excess of the amount contained in normal fluids.

This, confessedly, we have not demonstrated one way or the other to our entire satisfaction, for there is such variability in reaction to posterior lobe extracts shown by individual animals that it is not only difficult to

establish a standard physiological response for a given dosage—we have used for the most part rabbits—but it is also difficult to compare the cerebrospinal fluid reactions with those of a known dosage of posterior lobe extract in a single individual, for the reason that second injections, as Howell first pointed out, are less effective than primary ones.

However, as will have been apparent from the case reports already given, we are working in the direction of attempting to use the reactions obtained from the lumbar cerebrospinal fluid of individuals suffering from dyspituitarism as a measure of their hypophyseal (posterior lobe) activity. If, by dependable physiological tests, a deficiency of the secretory products of the posterior lobe can be demonstrated in the circulating cerebrospinal fluid, it will prove of inestimable value in the diagnosis of such cases of hypophyseal adiposity as show no telltale neighborhood symptoms to aid in their recognition.

This seeming digression relates only to the posterior lobe and its method of discharge, for this portion of the gland must obviously feel the effects of a cerebrospinal obstruction more than the pars anterior.

The infundibular stalk in these cases of hypopituitarism due to ventricular hydrops is apt to appear succulent and thick to the unaided eye, and the microscope will usually disclose a widely separated neurogliar meshwork (Fig. 255) which betrays a stasis of hyaline secretion, even though few of the soluble globules remain in the tissues undissolved by the processes of fixation and staining. Furthermore, under these circumstances one is apt to see not only an active invasion of pars nervosa by pars intermedia cells (cf. Fig. 265), but also an excess of colloid in the pars intermedia, often collected into large cysts visible to the naked eye.

As the anterior lobe doubtless discharges its secretory products directly into the blood stream of its large sinusoidal spaces, it is consequently less affected by cerebrospinal fluid disturbances than it is by vascular or possibly by nervous influences. Still, however slight may be the alterations of its physiological activity under the influence of ventricular hydrops, its anatomical deviations from the normal are apt to be considerable. When they have been hardened *in situ* before removal the scaphoid-shaped glands retain their deformed configuration (Fig. 256); and the histological picture proves equally characteristic of the process. The cell clusters instead of being roundish on section appear flattened and lie in concentric layers (cf. Figs. 272 and 315), separated by distended sinusoidal spaces, for a more or less marked venous stasis is an early feature of the general increase of intracranial tension.

A. **Distant Lesions with Hydrocephalus and Hyperpituitarism.**—From this preamble it will be surmised that grades of functional hypopituitarism, affecting chiefly the posterior lobe, are the usual consequence of obstructive hydrocephalus. For a time we were under the impression that this was the only type of functional disturbance that could be thus produced, though such cases as our XXXIV and those recorded by Neurath[196] suggest the possibility that dyspituitarism with overgrowth from anterior lobe hyperplasia may occur in young individuals with moderate grades of hydrocephalus (cf. p. 177).

We have had, however, one example of outspoken hyperpituitarism in an adult (acromegaly) which occurred in association with an unsuspected cere-

bellar cyst. Whether the hypophyseal hyperplasia was merely a concomitant process which bore no relation to the obstructive hydrocephalus, or whether the gland had been aroused into its state of pathological overactivity as a secondary result of the cerebellar lesion, cannot be positively certified. I incline toward the latter view.

CASE XXXVIII. (Surgical No. 25827.) **Typical recent hyperpituitarism of adult life (acromegaly), of a year's duration, with some neighborhood symptoms and associated with an unsuspected large cerebellar cyst, confusing the clinical picture. Operation. Death. Autopsy.**

April 25, 1910. H. M. B., a chemist, 33 years of age, referred by Dr. A. C. Forman of Bayonne, N. J., was admitted with the complaint of frontal headaches, increase in the size of the features and extremities, vertigo and nervousness.

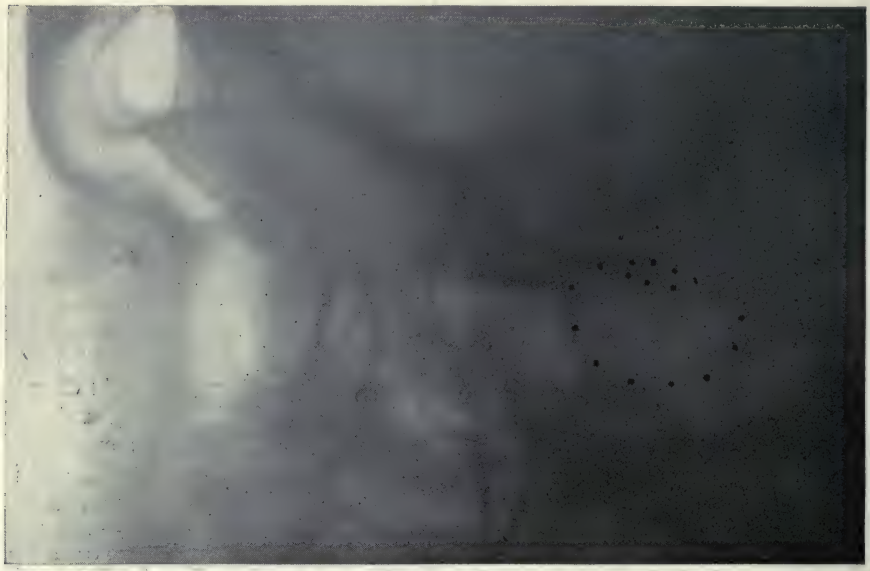


FIG. 257.—Case XXXVIII. X-ray of enlarged sella (nat. size). Note enlarged frontal sinus.

He has always been notably healthy and vigorous. He has been married seven years and has one child 3 years of age.

Present Malady. Two years ago he began to have shooting pains in his head (vertex), brought on by coughing, lifting or straining at stool. For a year he has been very constipated and has suffered from indigestion. There has been some polydipsia and polyuria; no glycosuria has been observed.

Three months ago an attack of "grippe" confined him to bed for a month and during this illness he suffered much with suboccipital headaches and stiffness of the neck. These discomforts have largely disappeared, though he has remained very "nervous." There have since been three *peculiar upsets* (February 6, March 5 and March 10) with nausea, vomiting (epistaxis or hæmatemesis?), retching, hiccoughing and subconsciousness. On each occasion his life was despaired of owing to the consequent exhaustion. Since April 1 he has been fairly well and has been at work, in spite of a constant bitemporal headache.

For a year his relatives have observed an *enlargement of the features.* Though aware that he has had to wear a larger hat and glove, that his tongue feels large and thick, and though his dentist says his teeth have separated, the patient himself has not been conscious of any marked alteration in his appearance.

He has been noticeably unsteady on his feet for a year and has had considerable vertigo. There has been no anaphrodisia or impotence. In January, 1910, he weighed 183 pounds; he has lost 26 pounds. He perspires over-freely.

Physical Examination. A tall, rather undernourished but healthy appearing man, weighing 157 pounds and standing over 6 feet. There are outspoken evidences of acromegaly. The temperature and pulse are normal. There are no cardiovascular changes. The abdominal and thoracic viscera appear normal.

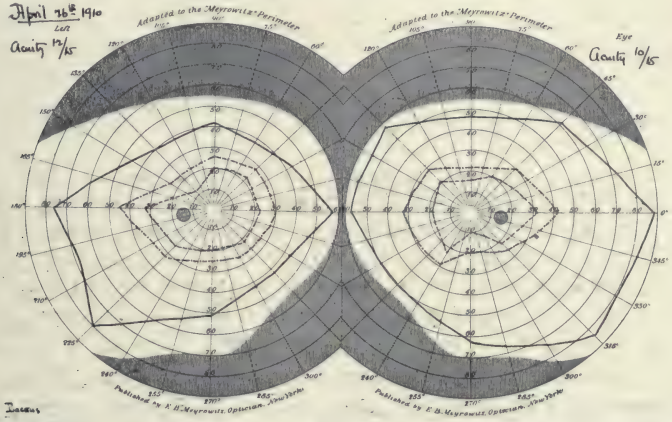


FIG. 258.—Case XXXVIII. Fields showing constriction with suggestive upper quadrantal color defect on left.

FIGS. 259, 260.—Case XXXVIII. Note pronounced acromegalic facies with spacing of teeth, prominent supra-orbital ridges, mandibular prognathism, etc.

Neurological examination shows nothing abnormal aside from his unsteadiness, which is said to be much less marked than formerly. There is a positive Romberg: no ataxia of the arms.

The thyroid is palpable and seems enlarged, necessitating a larger collar for the past year.

Analysis of Hypophyseal Symptoms. (a) *Neighborhood Manifestations.* The X-ray shows a considerable enlargement of the sella, which measures 2 cm. by 1.5 cm. in depth

(Fig. 257). *Eyes:* The visual fields are somewhat contracted and show a suggestive color defect in the left temporal field (Fig. 258). (By an unaccountable oversight the eye-grounds were not examined.) The right pupil is slightly larger than the left. There are no oculomotor disturbances: no history of diplopia. There is slight bilateral nystagmus.

FIG. 261.—Case XXXVIII. Middle finger (nat. size), showing no change other than slight termina tufting, the enlargement chiefly confined to the soft parts.

(b) *Glandular Manifestations.* The typical changes of an early *acromegaly* are shown chiefly by an enlargement of the tongue, of the nose (breadth 5 cm.), the ears, lips and hands (glove measurement 23.7 cm.), and by the clubbed toes.

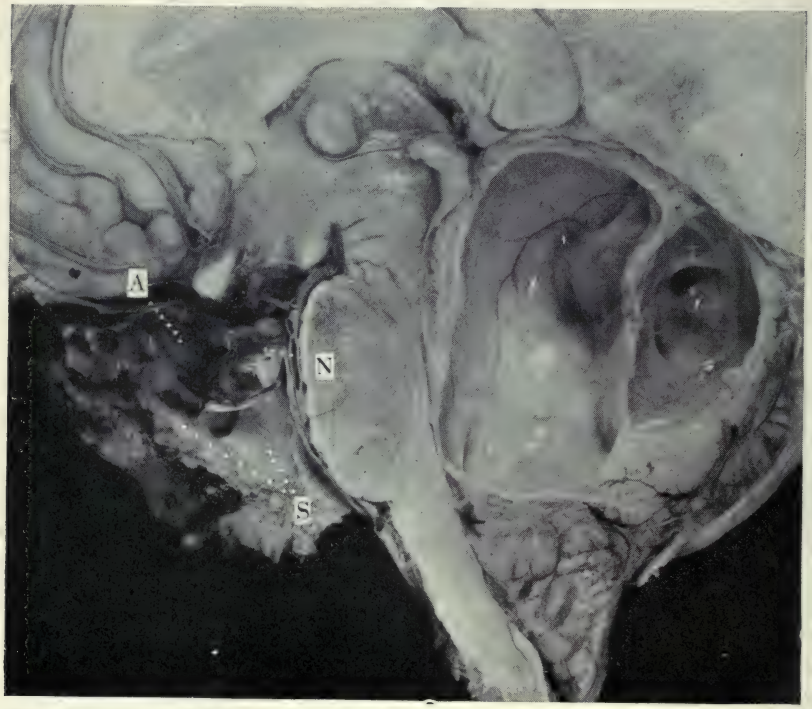


FIG. 262.—Case XXXVIII. Median section of brain stem (nat. size). Note large multilocular cerebellar cyst; flattening of pons and medulla; cerebellar herniation, necrotic pars anterior (*A*), intact pars nervosa (*N*), sphenoidal cells (*S*).

The supra-orbital, occipital and mastoid regions are prominent and the lower jaw is enlarged, with marked separation of the teeth and slight mandibular prognathism (Figs. 259, 260). There is considerable forward bowing of the shoulders. An X-ray of the hands shows that the changes are chiefly confined to the soft parts (Fig. 261).

The skin is moist, with free perspiration: there is a tendency to *hypertrichosis* with abundant sacral hirsuties. There is polydipsia and *polyuria*, the urine varying from 1880 to 2260 cc.

Tests of Thermic Reaction. On *April 27* the usual 2 cc. of 5 per cent. anterior lobe (ox) solution was given hypodermically. This precipitated one of the patient's peculiar attacks with intense headache and stupor, nausea, dizziness, sweating, vomiting with hæmatamesis, hiccoughing and a slowing of the pulse from 84 to 60. There was no elevation of temperature.

This distressing upset would have given us great apprehension had it not so exactly simulated his three earlier attacks. The hiccough persisted for forty-eight hours, but the headaches shortly disappeared and he was unusually bright and comfortable.

Carbohydrate tolerance between 100 and 75 grams of glucose. Thus, on *May 1*, after 100 grams of glucose at midnight, sugar in considerable amount was present in all specimens passed the following day. On *May 5*, *6* and *7*, glucose in 25, 50 and 75 cc. doses respectively caused no glycosuria. On *May 8*, 100 grams again produced glycosuria.

An operation was decided upon, the intention being to excise a portion of the presumably overactive anterior lobe. On the morning set for the operation the patient complained of an oncoming severe headache, and his wife said that she would have anticipated one of his familiar acute attacks. It is quite possible, therefore, that the operation was badly timed, though there seemed no particular reason for postponement, and it was hoped that it might serve to ward off the attack, if one were actually about to occur.

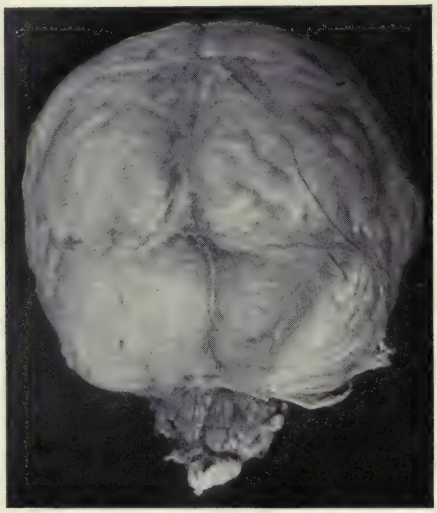


Fig. 263.—Case XXXVIII. Posterior view of brain removed in its envelopes after fixation. Note extreme foraminal herniation of cerebellum.

May 10, 1910. **Operation.** Sublabial approach with removal of the sellar base. Opening of dilated third ventricle mistaken for a cyst, and accidental severance of hypophyseal stalk. Death with symptoms of acute cachexia hypophyseopriva combined with medullary failure.

Under scopolamine-morphia-ether anæsthesia an attempt was made to conduct the operation without a preliminary tracheotomy. The anæsthetist experienced great difficulty, owing to the large tongue, and finally there was a complete closure of the glottis, resulting in extreme cyanosis and cessation of breathing (doubtless due to medullary pressure by the then unsuspected cerebellar cyst). An emergency tracheotomy, with transverse tracheal incision, was performed and, after a few moments of artificial respiration, spontaneous breathing was resumed.

There was naturally some question as to the advisability of proceeding, but the patient's condition after a short interval seemed unaffected by the upset and there appeared to be no essential reason for postponement.

The approach to the sella proved unusually simple, easy and bloodless. The sphenoidal cells were opened, disclosing a large sellar protrusion, covered by a thin scale of atrophied bone. This was carefully picked away with nasal rongeurs, thoroughly exposing the large dural capsule.

With a knife-hook the capsule was incised and the gland bulged through the opening. In order to obtain a better exposure of the pars anterior the incision was carried upward to the very edge of the bone defect, when there occurred a sudden gush of fluid.

For a moment it was thought that a pituitary cyst had been opened, but the collected fluid proved to be clear and the cavity from which it came was so deep as to make it almost certain that a bulging third ventricle had been opened. It is probable that the stalk was broken off during the examination of this cavity. The contemplated removal of a portion of the presumably hyperplastic pars anterior was abandoned.

The tracheotomy tube was removed and the sublabial and cervical wounds were closed without drainage. Practically no anæsthetic was required subsequent to the tracheotomy, and by the end of the operation the patient was semiconscious and conversing. Urotropin régime instituted.

Post-operative Notes. He passed a fairly comfortable afternoon, taking sips of nourishment and assuring us that he was entirely free from his usual discomforts. In the evening he vomited once and complained of some headache. His pulse was somewhat feeble and his blood pressure registered only 90. On the second day he was pale and drowsy but took nourishment well.

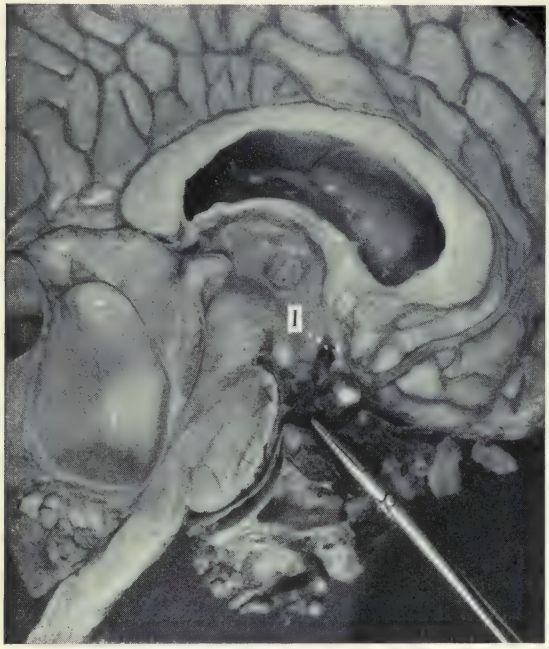


FIG. 264.—Case XXXVIII. Median section (reduced). Clamp, placed in line of operative approach, overlies the necrotic pars anterior and points to the broken infundibular stalk. Its cavity is plugged by a small blood clot (*I*). Note dilated ventricle.

For the following three days his condition remained much the same, with restlessness, feeble pulse, respiratory rhythmicity, hiccoughing and vomiting. On the morning of *May 13*, his respiration became feeble, shallow and sighing. An elevation of temperature to 107.2° per rectum preceded death.

Postmortem Examination. The brain was hardened *in situ* and removed in the intact meninges, leaving adherent that portion of the cranial base which included the operative field. This was clean, free from blood-clot and without signs of infection.

On making a median section a large unsuspected cerebellar cyst (Fig. 262) was disclosed. This had produced an internal hydrocephalus of moderate degree with the usual bulging of the third ventricle, which had been momentarily mistaken for an hypophyseal cyst at the operation. There was the usual degree of cerebellar herniation through the foramen ovale (Fig. 263) accounting for the medullary symptoms.

The *Hypophysis.* The infundibular stalk had been broken off just above the gland (Fig. 264). The gland itself was considerably enlarged: the anterior lobe soft and necrotic in appearance.

Histological examination shows that the *pars anterior* has completely degenerated, there being no stainable anterior lobe cells, with the exception of a minute cluster (shown on serial sections) near the upper portion of the pars intermedia. These may possibly represent acidophile cells, though this is uncertain. The degenerated lobe takes a heavy diffuse eosin stain.

The *pars intermedia* shows a marked hyperplasia. Where it adjoins the degenerated pars anterior there are a number of cysts apparently containing thin colloid. There has been an extreme invasion of the posterior lobe by unaltered pars intermedia cells, bearing the usual resemblance of this type of investment hyperplasia to a malignant process (Fig. 265).

There is a suggestion, too, of a condition of stasis of the *pars nervosa*, which is unusually cellular, its neurogliar meshwork distended. Most of the spaces are empty but some still retain hyaline masses, a large number of which are to be seen in the tissue near the broken stalk.

Other Ductless Glands. The *adrenals* were large. They show histologically an apparent medullary hyperplasia, and there is a marked vacuolization of the cells occupying the intermediate layer, only a few normal cells being visible.

There was a large persistent *thymus* which has the histological appearance of an infantile gland. It is not invaded by fat. The Hassall corpuscles are very large and numerou:

The *pancreas* show an unusual number and considerable enlargement of the islets.

The *thyroid* was somewhat enlarged and shows an excess of colloid. The *parathyroids* are infiltrated with fat but the cells seem unchanged.

The *testes* show a large increase of interstitial tissue; the cells of Leidig are unusually numerous and occupy about one-fourth of the field.

There is a *lymphatic hyperplasia* of the intestines. The liver on section shows no marked change.

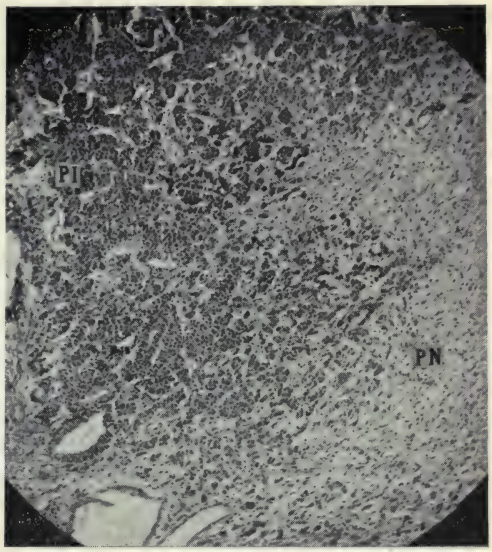


FIG. 265.—Case XXXVIII. Microphotograph from margin of pars nervosa (*PN*), showing invasion by cells of pars intermedia (*PI*).

INTERPRETATION. — An instance of acute hyperpituitarism. Pointing in this direction are the hypophyseal enlargement, the acromegalic overgrowth chiefly of the soft parts, the moist, hairy skin, the low sugar tolerance and the normal, or slightly elevated, temperature. Further, there was no thermic response to a pars anterior injection, which merely served to accentuate the symptoms, much as thyroid extract may aggravate the symptoms of Basedow's disease.

The mixed symptoms of dyspituitarism, such as characterized the eleven other acromegalics in this series, were notably absent—dryness of the skin, adiposity, sexual changes, high sugar tolerance and so on.

The condition coincided so thoroughly with our preconceived notions of an early stage of hypophyseal hyperplasia that the one bizarre physical sign—the patient's static ataxia—was not given its just dues. Unfortunately the eye-grounds were not examined—one of the unaccountable oversights which occur when attention is drawn away from the possible to the obvious in making a physical examination. It is probable that there was a choked disc, and this finding might have led us to consider more fully the likelihood of a concomitant cerebellar lesion. Still it is doubtful whether we should

have been led into a suboccipial exploration even in this event, for the temptation would have been great to attribute the attacks of headache, vertigo and vomiting to glandular intoxication, particularly since one of these seizures was brought on by administering glandular extract.

An equally lamentable feature of this case is the technical fault committed at the operation—an experience which more than any other factor has led us to desist in the larger number of our subsequent operations from little more than the mere removal of the sellar base, unless the X-ray has unmistakably shown a large struma. For such an accident as stalk division, particularly with a coincident shutting off of the circulation to the gland from below (unavoidable in a transphenoidal sellar decompression), must necessarily lead to an anæmic necrosis of practically the entire anterior lobe.

This has been our experience in the canine after the placement of clips on the infundibular stalk, causing complete shutting off of the arterial supply: for, as Goetsch and Dandy have shown, the anterior lobe has no collateral circulation (cf. page 7). Their studies, which were undertaken after our experience with this patient, have demonstrated that the posterior lobe, including all of the pars intermedia, is supplied by the vessels which enter from behind, and this part of the gland alone, therefore, would retain its vitality under the circumstances of this operation.

The patient's terminal symptoms, barring the high temperature, were very much akin to those of acute experimental cachexia hypophyseopriva, such as follow total anterior lobe removal in the canine. The evacuation of the cerebrospinal fluid should have offset rather than aggravated any symptoms on the part of the cerebellar cyst, much as a ventricular puncture would have done. There was no escape of fluid after the first few hours, owing, as shown postmortem, to a small clot which plugged the opening (Fig. 264).

The complete degeneration of the anterior lobe cells prevented their histological study, and though this part of the gland was obviously enlarged, no conjecture can be made as to the preponderance or otherwise of acidophilic cells. The extraordinary feature, of course, is the extreme invasion of posterior lobe—like a malignant epithelial ingrowth—by pars intermedia cells which have undergone no hyaline change, although there is an abundance of hyalin near the severed stalk.

This pars intermedia hyperplasia resembles the alterations seen in the canine gland after experimental obstruction and, doubtless, was incited by the existent obstructive hydrocephalus; for it is hardly likely that it could have occurred in the last thirty-six hours of life.

The marked foraminal herniation (Fig. 263) which the brain showed sufficiently accounts for all the respiratory disturbances and for many of the terminal phenomena. It is fortunate that we were not led to withdraw the lumbar fluid for purposes of study. Still this might have spared us the tragedies of the larger operation which was undertaken.

Cases in which the cause of the hydrocephalus and its secondary functional glandular deviations are but a matter of diagnostic conjecture are, of course, far more numerous. But so long as the exact pathology of the condition remains uncertified, it would be unwise to surrender to them the amount of space in this section which their discussion would require.

As a rule the evidences of glandular derangement point merely toward insufficiency of posterior lobe secretion, as will be seen. However, in a few instances there have been constitutional manifestations which appeared to indicate some measure of a coincident anterior lobe hypoplasia.

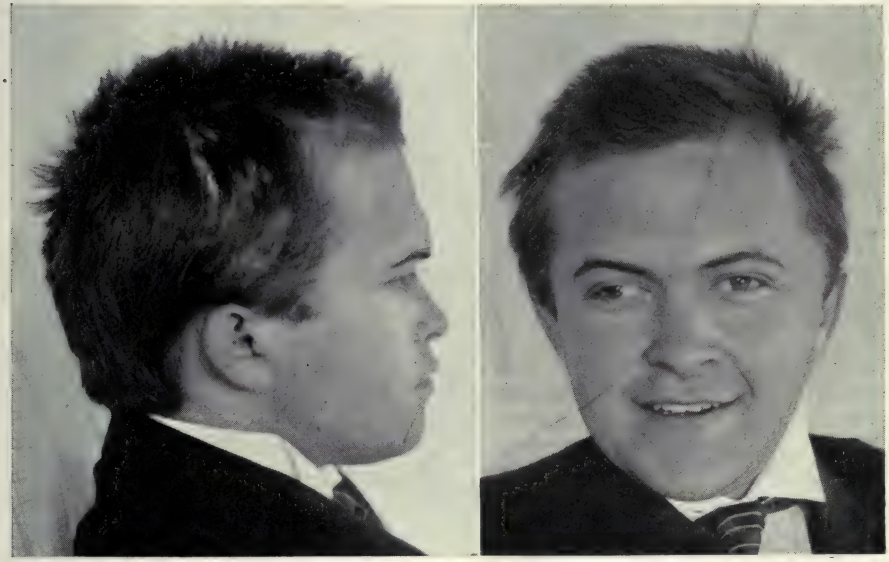
An illustrative case of this type of dyspituitarism with hydrocephalus of uncertified origin may be briefly given.

CASE XXXIX. (Surgical No. 21840.) **Dyspituitarism with enlarged sella accompanying marked hydrocephalus and pronounced cerebellar symptoms. Decompression operations.**

January 20, 1908. S. G., aged 20, entered Dr. Barker's service complaining of spasticity and weakness of the legs.

He is of a "high-strung and nervous" parentage. Many of his relatives are exceptionally tall: grandfather and two uncles over six feet; father 6 feet 2½ inches: brother 6 feet 4 inches.

He weighed 12 pounds at birth. Aside from the usual infections of childhood, he was fairly well as a boy, though noticeably "clumsy," fat and "chubby." He entered college



FIGS. 266, 267.—Case XXXIX. Showing hydrocephalic configuration of head with projecting frontal sinus.

three years ago (aet. 17), but withdrew after a year, owing to "forgetfulness and inability to concentrate his mind."

Present Malady. For five years there has been a progressive weakness and spasticity of the legs, so that he stumbles in walking. He has been having frequent "bursting headaches," occasionally with nausea and vomiting. His head has been enlarging. He is very *drowsy* and has an *enormous appetite*. Polyuria has been observed. Diplopia has been present for some time.

Physical Examination. A healthy-appearing, tall, somewhat adipose young man, with a leonine and evidently hydrocephalic head (Figs. 266, 267). Weight 168 pounds. Visceral examination (abdominal, thoracic, cardiovascular) negative. *Blood* and *urine* negative.

The *neurological examination* shows a divergent squint of the right eye with subjective diplopia: right pupil larger than left: bilateral *choked disc* with new-tissue formation

and secondary atrophy. The fields show color inversion. Acuity, right 6/60; left 32/60. Slight nystagmus: marked *static ataxia:* gait very unsteady: Romberg positive: some incoordination of arms: deep reflexes exaggerated throughout, with ankle and knee clonus: no sensory disturbances.

He has had a number of *epileptiform convulsions* with unconsciousness.

Hypophyseal Manifestations. *Skeletal.* Height 179 cm. (5 feet 9 inches). The head measures 66 cm. in circumference and is somewhat asymmetrical, the cranium appearing fuller on the right: no exostoses. The supra-orbital arches are very prominent and the sinuses enlarged, as in acromegaly. There is no prognathism: no spacing of the teeth. The skull gives a hollow note on percussion.

The *X-ray* shows the wavelike appearance from atrophy through convolutional pressure which characterizes the calvarium of cases of long-standing hydrocephalus. The sella is enlarged. The radial epiphyses are incompletely ossified. The hands are of the "type en long" of Marie. The extremities are cold, clammy, cyanotic—they often feel "numb and painful."

Cutaneous. The skin is moist: without abnormal pigmentation. There is a tendency to hypertrichosis. Panniculus is overabundant.

Carbohydrate tolerance high: assimilation limit for lævulose (1910) not reached owing to regurgitation of the sugar. *Temperature* ranges between 96.5° and 98°. *Pulse* is somewhat slowed.

Numerous **operative measures** were resorted to before relief from the obstructive hydrops was afforded. Thus, on *Jan. 21, 1908*, a right subtemporal decompression was performed; on *March 12, 1908*, a left decompression and exploration of the interpeduncular space, disclosing merely a bulging third ventricle; on *Jan. 18, 1909*, lateral ventricular drainage to the scalp; on *Feb. 23, 1910*, a suboccipital exploration, in view of the apparent increase in cerebellar symptoms.

During this interval he has become very stout, his weight exceeding 200 pounds.

The last operation has apparently served to overcome all the pressure manifestations, which have now (*Sept., 1911*) been in abeyance for a year, with the decompressive areas collapsed.

INTERPRETATION.—An internal hydrocephalus of some years' duration and of slow progress, occurring in a young man whose family shows a strain in which skeletal overgrowth is dominant.

The hydrocephalus was presumably due to a posterior lesion (of corpora quadrigemina or pineal body?), implicating the pyramidal tracts and possibly the superior cerebellar peduncles. It led to a marked thinning of the skull and enlargement of the head, but at the same time there occurred a definite increase in stature.

The X-ray shows an enlarged sella and ununited epiphyses. The external cutaneous manifestations are also suggestive of pars anterior hyperplasia, but coincident evidences of dyspituitarism, naturally attributable to posterior lobe obstruction, are shown by the adiposity, the subnormal temperature and pulse, the high carbohydrate tolerance and enormous appetite.

Though it is conceivable that the pineal body may be implicated, either by a tumor of the gland itself or by a secondary compression from an adjoining lesion, it is idle to speculate upon this (cf. Cases XIII and XLVII).

B. **Distant Lesions with Hydrocephalus and Hypopituitarism.**—Despite the frequency of outspoken manifestations of hypophyseal deficiency in association with hydrocephalus, whether secondary to tumor, to inflammatory disease, or of the "idiopathic" variety, I have found only three articles on

the subject in the literature, one of them having been published, I find, prior to my first comment upon the subject.

In 1909 Marienesco and Goldstein[182] made a report upon two cases of hydrocephalus with adiposity of the typus femininus and genital hypoplasia, one in association with a cerebellar cyst and the other accompanying an hydrocephalus of uncertain ætiology. Subsequently Goldstein[101] made a further note upon three patients with presumed meningitis serosa who exhibited suggestive manifestations of hypophyseal disease. He appears, however, to regard the evidences of glandular involvement as a possible means of differentiation between meningitis serosa and brain tumor and does not suggest that the same symptoms may occur in both conditions. His three patients were all young hydrocephalics with typical constitutional features of dystrophia adiposo-genitalis; but it is obviously impossible to exclude tumor, particularly of the infundibular variety, without a postmortem examination. Six illustrations of the syndrome in slightly hydrocephalic children have also been given by Babonneix and Poisseau.[5]

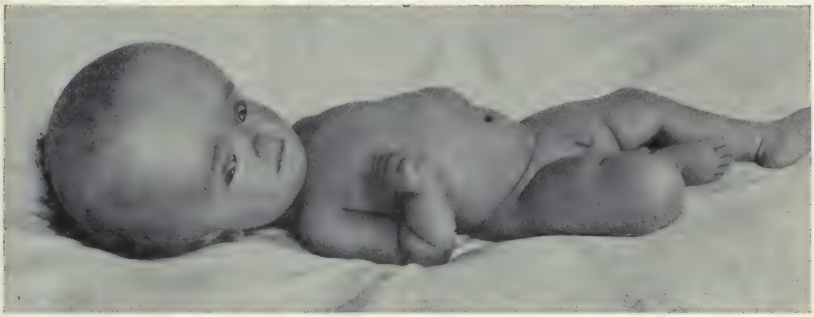


FIG. 268.—Case XL. Characteristic over-well-nourished, hydrocephalic child.

Of interest in this connection, also, is Marburg's report[176] of a patient with tumor of the pineal body who exhibited adiposity and sexual infantilism—a syndrome similar, in other words, to that supposed to typify certain hypophyseal tumors and which we have come to ascribe to glandular deficiency, or hypopituitarism. In consequence of this finding, Marburg ascribes to the pineal gland a functional activity similar to that which our studies have led us to associate with the pituitary body.

Needless to say, a pineal neoplasm of any considerable size must lead to a secondary hydrops ventriculorum and to stasis of posterior lobe secretion. Hence it may be expected ultimately to give symptoms of pituitary deficiency which will unquestionably be similar to those which occurred in Marburg's case. With due appreciation, therefore, that the pineal gland may possess functions with which we are unfamiliar and that in conditions of disease it may give clinical pictures which may some day be capable of recognition (cf. Case XLVII of Group V), Marburg's conclusions, based on a single case, must be accepted with certain reservations, for some at least of the symptoms are so easily explained on another and simpler basis.

From the discussions of certain of the preceding cases (*e.g.* XXXIV, XXXVIII and XXXIX) it will have been apparent that we are approaching

a possible clinical differentiation of the functional derangements of the separate lobes of the hypophysis. Thus a posterior lobe insufficiency from hydrocephalus may cause the usual disturbances of metabolism with adiposity, and yet the anterior lobe may, at the same time, be overactive and excite overgrowth and stimulate sexual activity. The clinical combination of adiposity with genital hyperplasia rather than with genital hypoplasia is, therefore, possible. The latter, however, is far more common.

From a large number of cases which have manifested symptoms of hypopituitarism three have been selected, as they illustrate the condition in infancy, in adolescence and in adult life. In the first, the hydrocephalus was of the "essential" or unexplained variety; in the second and third, it was produced by the obstruction of a tumor.

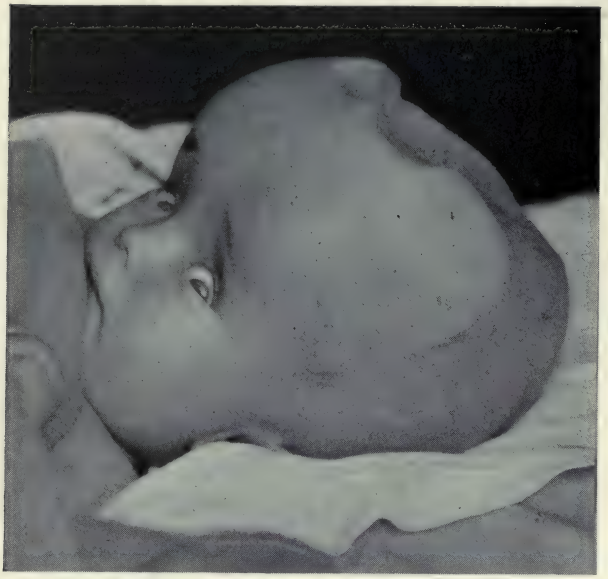


FIG. 269.—Case XL. Showing collapsed ventricles emptied by lumbar puncture.

CASE XL. (Surgical No. 25849.) **Pituitary deformation in a case of congenital hydrocephalus associated with adiposity.**

April 27, 1910. Lloyd H., 10 months of age, was referred by Dr. McPherson of Tonawanda, N. Y., with the complaint of hydrocephalus.

A full-term, supposedly normal, breast-fed baby of healthy parents.

After an illness with convulsions at five weeks of age, there occurred a rapid enlargement of the head, almost to its present size.

Physical Examination. An over-well-nourished, hydrocephalic child (Fig. 268), weighing 28 pounds and with the characteristic facies of the malady. Circumference of head 66.5 cm.

The skin was dry and shiny; the hair very thin and sparse. Only the two lower incisors had erupted. The fingers were especially delicate, tapering and transparent. *Temperature* (rectal) was irregular, often subnormal (97°–100°F.).

The usual preliminary steps were taken to determine the situation of the obstruction. By various single and combined (lumbar and ventricular) punctures it was shown that *the ventricle could be emptied by a lumbar puncture* and hence that a free communication already existed between the ventricular cavities and the subarachnoid spaces, indicating the futility of the usual methods prescribed for ventricular drainage.

It was also shown that *large amounts of the fluid could be withdrawn* (600 cc. or more at a time) by either route without upsetting the child.

All the specimens of fluid were found to show the reactions characterizing posterior lobe extracts. The specimen first removed from the ventricle, however, gave more active reactions than any subsequent ones. The fluid would reaccumulate in from six to eight hours.

It was shown, furthermore, that urotropin injected into the ventricle did not subsequently appear in the urine, whereas, when taken by mouth it promptly appeared in cere-

brospinal fluid and urine. Obviously the cerebrospinal fluid "block" lay between the subarachnoid spaces and the intracranial sinuses—circumstances under which some form of drainage such as that advocated by Payr, or the retroperitoneal method which I have suggested, is indicated.

July 2. **Operation.** Laparotomy: establishment of *communication between arachnoid and retroperitoneal spaces* by small trephine opening in fifth lumbar vertebra. The

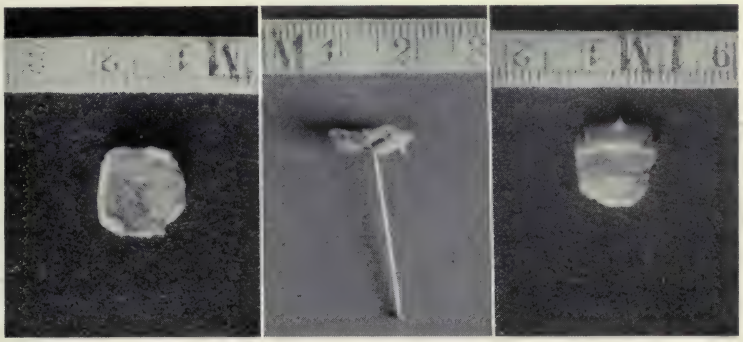


FIG. 270.—Case XL. Showing distorted hypophysis (nat. size). (I) Upper view; (II) posterior view with colloid-filled cleft showing; (III) lower view, a square of adherent dura with central point of vascular attachment left attached to anterior lobe.

head remained collapsed (Fig. 269) for eight days and the condition seemed favorable, as there were no abdominal symptoms.*

Unhappily, at the end of this period the drain became occluded. A second operation as undertaken and led to a fatality on the following day.

July 20. **Postmortem Examination.** The brain, hardened *in situ* and removed within the meninges, showed an extreme grade of dilatation of all ventricles, the aqueduct being 4 mm. in diameter and the foramen of Magendie large and patent.

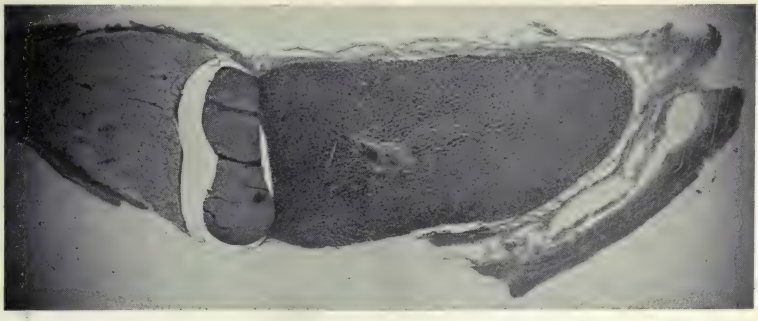


FIG. 271.—Case XL. Antero-posterior section of hypophysis, showing colloid cyst in cleft.

The third ventricle was much distended and the hypophysis greatly flattened (Fig. 270), a large colloid cyst occupying the cleft (Fig. 271). The cellular columns of the pars anterior gave the usual appearance of these flattened glands (Fig. 272).

The *body* showed an excess of panniculus and much fat about the abdominal organs. The larger viscera were negative. The *ductless glands* showed no obvious deviation from

* It is interesting, in view of the known action of posterior lobe extracts (and therefore of cerebrospinal fluid, as we believe) on smooth muscle, that three of our earlier cases of retroperitoneal drainage for hydrocephalus died from intussusception.

the normal for a child. The *adrenals* and *parathyroids* were, perhaps, larger than usual. The *thymus* also was large and there was an abundance of lymph adenoid tissue elsewhere. *Histologically* the glands, with the exception of the hypophysis, showed no especial change. The *liver* was exceedingly fatty.

Interpretation.—An extreme grade of hydrocephalus, presumably due to an obstruction of the pachymeningeal outlets of the fluid from the subarachnoid spaces. A flattened and congested, though physiologically active gland, with obstructive insufficiency of the posterior lobe leading to a lowered metabolism with adiposity.

It is possible that the sparse hair and delayed dentition of these hydrocephalic children may likewise be an expression of deficient posterior lobe

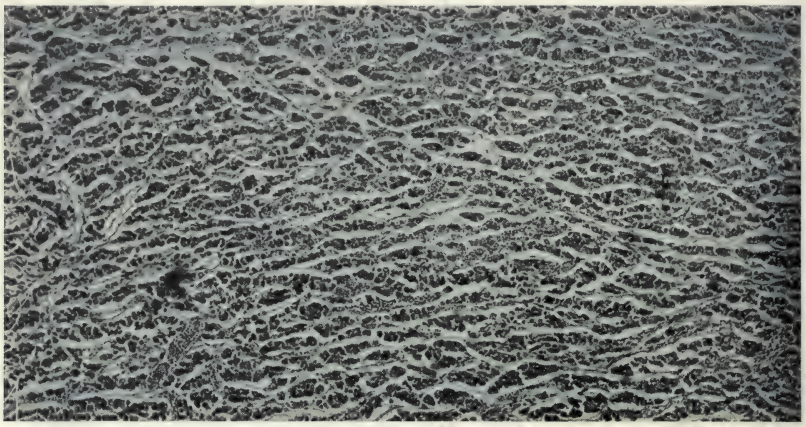


Fig. 272.—Case XL. To show flattening of pars anterior cell columns in hydrocephalus (mag. 75 diams.).

secretion, for in two or three of them a rapid growth of hair and early eruption of teeth has occurred soon after a successful drainage.

Case XLI. (Surgical No. 22013.) **Obstructive hydrops ventriculorum due to a glio matous cerebellar cyst. Deformation of pituitary body with colloid cyst. Hypopituitarism Operation. Autopsy. Status thymo-lymphaticus.**

February 24, 1908. Francis S., 2 years of age, was referred by Dr. Charles G. Jennings, of Detroit, with the complaint of hydrocephalus.

The child, apparently healthy, had been weaned at 6 months and artificial feeding begun. Several gastro-intestinal upsets occurred and there was thought to be some indications of *rachitis*—epiphyseal enlargements, head sweating, delayed dentition and failure of closure of fontanelles.

Three months before admission, following a severe *cranial trauma*, the head began to enlarge, with bulging of the unclosed fontanelles. The musculature of the body became weak, the pupils dilated, and there was a convergent squint. Nausea and vomiting occurred, and was attributed to gastro-intestinal derangement.

Physical Examination. A well-nourished child, weighing 25 pounds, with a hydrocephalic *enlargement of the head* (53.5 cm. in circumference). There was considerable *rigidity* of the extremities, with exaggerated deep reflexes; a bilateral abducens weakness; an atrophic pallor of the discs, and a declining *papillœdema* without measurable swelling. The hands were used awkwardly and with considerable *incoördination* and tremor.

A series of double *ventricular and lumbar punctures* were performed to determine if possible the situation of the obstruction. The tension of the fluids was equal, but it was not possible at first to empty the ventricles from below. This subsequently became possible, and it was thought that a communication had been established between ventricle and subarachnoid space, the view being that as a result of the trauma some adhesions, from a mild inflammation, extravasated blood or a serous meningitis, had partially occluded the iter or foramen of Magendie. The presence of *a tumor was not suspected.*

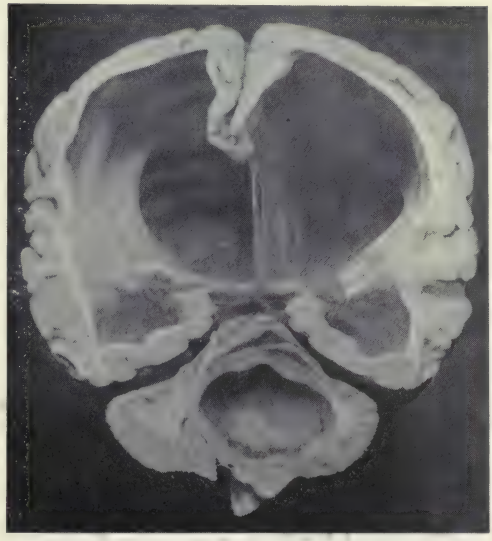


FIG. 273.—Case XLI. Showing cerebellar cyst with glioma in its upper wall: extreme hydrops ventriculorum.

The child improved markedly and on *April 18* was discharged. The betterment continued and the condition seemed to be at a standstill until September, when the earlier symptoms returned, with nausea and vomiting. There was some further enlargement of the head.

April 19, 1909. **Readmission.** There had been an evident advance in the process, with an enlargement of the head to 63 cm. and typical hydrocephalic facies.

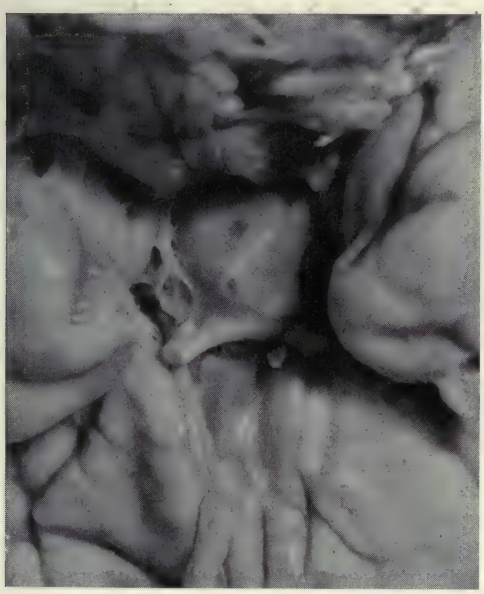


FIG. 274.—Case XLI. Showing the widely distended third ventricle (nat. size), with point of attachment of hypophyseal stalk.

The other symptoms were as before—spasticity with exaggerated reflexes, a positive Babinski, strabismus and muscular weakness, the child being unable to sit up or to hold up its heavy head.

In addition, there was a positive though slight *nystagmus*, and the movements of the arms had become definitely *ataxic*. Despite the supposed gastrointestinal disturbances the nutritional condition was excellent with a tendency to *obesity*.

April 29. **Operation.** A suboccipital exploration disclosed a large central cyst, in the wall of which a shell of tumor was apparent. A portion of this wall was shelled away and the wound closed. The excellent recovery from the anæsthetic was followed three hours later by a sudden collapse associated with *hyperpyrexia*.

Autopsy. Body of a child showing an overabundant panniculus.

The *brain* was hardened *in situ* and on section (Fig. 273) showed the cyst with its mural shell of gliomatous tumor, and the ventricular hydrops. The third ventricle and infundibulum were widely dilated (Fig. 274).

The *hypophysis* was flattened, its stalk elongated, and a large colloid cyst occupied

the cleft (Fig. 275). *Histological* studies showed the usual cellular condition of the pars nervosa with hyperplasia of pars intermedia commonly seen in obstructive cases. The pars anterior was flattened, with the cell columns compressed and lying in concentric rows.

Ductless Glands. The *thymus* was much enlarged, the two lobes extending out over the pericardium: it was pale on section and there were a number of small opaque areas. The gland showed histologically practically no retrogressive changes: the Hassall's corpuscles were very large and numerous. The *pancreas* appeared normal. On section the islets were large and very numerous. The *adrendls* appeared normal. The *thyroid* was small and pale. The acini contained an excess of colloid for the gland of an infant.

The *spleen* measured 7 by 4 by 2 cm. and showed a great enlargement of Malpighian corpuscles. The lymphatic tissue of the intestine was in excess and the mesenteric glands were enlarged. The *aorta* appeared exceptionally small and delicate.

Anatomical Diagnosis. Status lymphaticus: obstructive hydrocephalus: gliomatous cyst of cerebellum.

INTERPRETATION.—Hydrocephalus was the dominant clinical symptom, though the causal agency by which it was produced—a cerebellar tumor—was not suspected until a year after the child first came under observation.

FIG. 275.—Case XLI. Showing hypophysis like an inverted mushroom, with large colloid globule extruded from cleft.

Were the postmortem examination in a case of this kind limited to the examination of the abdominal and thoracic organs, the sudden death after anæsthesia with hyperpyrexia would naturally be attributed to the obvious status thymo-lymphaticus. This has been commented upon in the discussion of Case V—an adult in whom the condition was still more striking.

In all probability the thymic state was not merely coincidental. It is more likely that it represented a polyglandular manifestation of ductless gland involvement, the hypophysis, in all likelihood, being the member of the series primarily implicated.

The pituitary derangement was in the nature of an obstructive posterior lobe insufficiency causing a moderate grade of hypopituitarism, and, as has been seen, this condition of the gland represents the form of functional disorder which is most commonly associated with a persistent thymus even in adult life.

CASE XLII. (Surgical No. 26128.) **A large endothelioma of the right hemisphere causing hydrops of the third ventricle and hypopituitarism. Operation. Death. Characteristic polyglandular lesions.**

June 20, 1910. Ida J., colored, aged 23, married, was referred to us by Dr. Campbell, of the Manhattan State Hospital, with the complaint of "brain tumor"—a diagnosis certified by an exploratory operation.

Tumor History. The intracranial symptoms began with *headaches* in 1904, at the age of seventeen. She was married in 1906, and has never been pregnant, though she was supposed to be so from the onset of *amenorrhœa*, which occurred soon after her marriage and which has persisted.

In 1907 there were headaches, *vomiting* and impairment of vision. In 1909 weakness of the left arm and stiffness of the leg occurred, and a tender, pulsating swelling appeared over the right parietal region. There were also focal *irritative movements* of the left face. Later left hemi-hypæsthesia was observed.

In December, 1910, a *local exploration* of the parietal swelling showed an area of pressure atrophy of the skull overlying a vascular dural endothelioma, a fragment from the surface of which was removed. The symptoms progressed unabated.

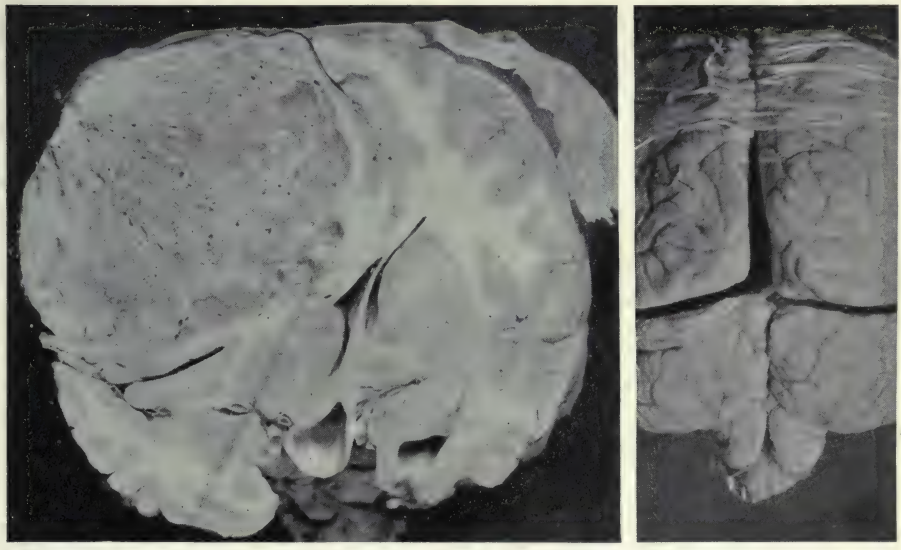
Physical Examination. An exceedingly stout young colored woman (Fig. 276), 5 feet 3 inches tall and weighing 160 pounds, presenting the full-blown symptomatology of a localizable cerebral tumor. General pressure symptoms were extreme —severe *headache, vomiting,* practical *blindness* from secondary atrophy, etc. The localizing symptoms, which need not here be gone into, were definite for a large centrally placed cortical growth in the right hemisphere.

Hypophyseal manifestations were shown by the extreme *adiposity,* dry skin, subnormal temperature, slowed pulse, low blood pressure and amenorrhœa.

FIG. 276.—Case XLII. Hypophyseal adiposity accompanying brain tumor.

June 25th. **Operation.** Primary stage with exposure of growth; excessive bleeding and many periods of respiratory cessation, requiring artificial respiration. *June 30,* attempted second stage, which was abandoned after excessive bleeding during the early efforts to begin the enucleation. Death from respiratory failure some hours later.

July 1. **Autopsy.** The body showed a superabundance of panniculus and fatty



FIGS. 277, 278.—Case XLII. Left: Showing enormous endothelioma causing cerebral distortion and hydrops largely confined to the third ventricle. Right: Posterior view of brain showing extreme foraminal herniation of cerebellum.

changes in most of the organs. Larger viscera practically negative, except for the adiposis. The liver in particular showed marked fatty degeneration.

The *brain* showed (Fig. 277) a large vascular *dural endothelioma* of the right hemisphere, which had led to a marked cerebral distortion with a wide hour-glass dilatation (Fig. 279) of the third ventricle.

Ductless Glands. The *pituitary body* was much flattened and the posterior lobe and cleft were largely replaced by a large retention cyst of colloid (Fig. 280). The *thyroid* was enlarged and colloidal. The *adrenals* showed little miscroscopic al alteration, except for the lipoid change of the zona fasciculata. The *ovaries* were large, 5 by 2½ cm., and cystic. Only one fully formed Graafian follicle was apparent; the rest were minute and undeveloped. There was a "persistent" *thymus* measuring 9 by 7 by 2.5 cm. It contained an unusually large number of Hassall's corpuscles of various sizes and shapes.

FIG. 279.—Case XLII. Hour-glass distention of third ventricle.

FIG. 280.—Case XLII. Upper view of flattened hypophysis showing empty colloid cyst of posterior cleft.

INTERPRETATION.—The patient presented symptoms of hypophyseal deficiency comparable in their clinical aspects to those produced by experimental ("almost total") hypophysectomy or to clinical instances of infundibular tumor directly compressing the gland.

Needless to say, the pressure here was due to the intermediation of the cerebrospinal fluid, which caused a dilatation of the third ventricle, obstructed posterior lobe secretion and flattened the anterior lobe.

In a case of this kind there are, of course, no neighborhood hypophyseal symptoms, and the X-ray does not show an enlargement of the glandular pocket; hence the blindness, for example, is due to an atrophy secondary to the high grade of choked disc, not to a primary atrophy from direct pressure on the nerves.*

The hypophyseal manifestations must be clearly distinguished from the

*Oppenheim (Charité-Annalen, 1890—Lehrbuch IV Aufl. S. 946) first called attention to the bladder-like distention of the third ventricle, which he presumed might be a cause of pressure atrophy and bitemporal hemianopsia—a doubtful explanation.

tumor symptoms on which they are superimposed. They are in all likelihood attributable to the hydrops of the third ventricle which from the outset would naturally inhibit the secretory function of the gland. I say 'naturally' rather than 'necessarily,' for in Case XXXVIII of this Group the pars anterior at least seemed to have been stirred into activity by the obstruction, with resultant signs of acute acromegaly.

GROUP V.—CASES EXHIBITING A POLYGLANDULAR SYNDROME.

With some hesitation a separate group has been made under this heading, for the purpose of including a number of patients exhibiting unmistakable evidences of ductless gland disorder, in whom, however, the hypophyseal manifestations did not so far predominate as to justify the assumption that the extensive general glandular derangement had its origin in this particular gland.

Although in some of the patients the intracranial symptoms were sufficiently marked to bring the pituitary or pineal gland under strong suspicion, and though some showed marked improvement under hypophyseal therapy, nevertheless the clinical syndrome of each shows peculiarities which conform with none of the standard types heretofore given.

It is, of course, fully appreciated that in almost all of the cases which have been included in the four preceding groups there have been evidences of the participation of more than one of the ductless glands. This has been emphasized in many of the case reports—numbers V, XXIX and XXXII, being good examples—and will be again referred to in the section on symptomatology. It does not always require a postmortem examination to make this clear, for gross alterations in thyroid and testis may be apparent, and secondary functional disturbances on the part of the more inaccessible glands —of interstitial cells of Leydig, pancreatic islets, thymus, ovary and adrenal— are often symptomatically recognizable.

In acromegaly, for example, the frequent coexistence of a goitre, the early glycosuria, amenorrhœa, pigmentation and asthenia, suggest, in one or another of the cases, participation of thyroid, pancreatic islets, ovary and adrenal; and whether these organs are all involved at the outset by the underlying biochemical disturbance—which doubtless is the background for many ductless gland disorders—or, what is more probable, become secondarily implicated during the compensatory readjustment of metabolic processes consequent upon the primary derangement of the gland in question, does not modify the fact of the pluriglandular nature of the malady.

The same holds true for primary states of hypopituitarism, for here again characteristic changes, which are presumably secondary, occur throughout the ductless gland series; but the facts related in connection with the cases comprising Group IV would tend to give additional assurance that a primary hypophyseal derangement is capable of bringing about a functional unsettling of the entire glandular series.

The close physiological interrelation of these structures has been abundantly emphasized on experimental grounds, notably by Pineles[207] in 1899 and later by Eppinger, Falta and Rudinger.[69] Clinicians, however, with the possible exception of the French school, have been slow to

appreciate the symptomatic significance of the facts which their studies have elucidated.

In the case of thyroid and parathyroids, of pituitary and pineal bodies, of adrenals, thymus, pancreatic islets, testis and ovary, any disturbances of function, whether in the direction of increased or of lessened activity, will doubtless occasion reciprocal alterations in one or another, if not in all, of the correlated glands. These alterations may produce changes which are clinically recognizable, or, on the other hand, changes which the miscroscope alone can detect. Nevertheless, despite the inevitable ultimate polyglandular nature of the picture from the pathological point of view, a primary disturbance of each one of these glands, whether in the direction of overactivity or underactivity, doubtless will be found to possess its own characteristic clinical syndrome which differs from that of each of the other glands.

The various syndromes associated with *primary glandular insufficiencies*, owing partly to the possibility of their experimental reproduction, are the better known. Thus, cretinism and myxœdema, Addison's disease, pancreatic diabetes, parathyroid tetany, and the eunuchoid state are clinically recognizable states due to primary deficiency of individual glandular structures; we may now add to this list the "dystrophia adiposo-genitalis," which we have laid at the door of hypophyseal deficiency and possibly also the hypothymism experimentally reproduced by Klose and Vogt, as well as the hypopinealism of Frankl-Hochwart.

The reverse states—those due to *hyperactivity of the individual glands*—are as yet beyond experimental reproduction, and partly for this reason they are not so well understood in their clinical aspects, hyperthyroidism being the one notable and unquestioned example, though acromegaly and gigantism and the status thymicus are commonly accepted as expressions of primary hyperpituitarism and hyperthymism.

It is not to be overlooked that the ætiological incident lying back of the primary glandular involvement, particularly in the case of the functional hyperplasias, is in most instances still in obscurity. We can readily explain a state of lessened activity when an individual gland is the seat of disease—such as occurs in adrenal tuberculosis—or when a gland is affected by compression, as in many cases of hypopituitarism, but the source of the stimulus, biochemical or otherwise, leading to states of overactivity is less apparent.

As in the case of hyperthyroidism, bacterial toxines may play an important rôle, and a history of an antecedent infectious disease was obtained in a number of our cases of supposed hyperpituitarism. It is possible, too, that states of malnutrition, auto-intoxications, trauma, a disturbed vascular or nervous supply to the gland, or oft-repeated physiological hyperplasias, such as accompany pregnancy, may represent the ætiological incident in certain cases. However, these things are as yet largely conjectural, and the single fact remains that there is probably a fairly definite clinical symptom-complex for a primary involvement of each of the ductless glands, whether the involvement is of such a character as to excite, on the one hand, an excessive secretion or, on the other, to diminish functional activity.

In some cases, however, the symptomatology may be so confused that it is impossible, with our present limited knowledge, to tell which of the indi-

vidual glands is actually the primary seat of disease. We may in time be able to determine this by the slow therapeutic test of feeding the active principle of one gland after another; or a more expeditious method may be supplied by the immediate reactions which follow the subcutaneous or intravenous injections of various extracts.

In brief, *the term "polyglandular syndrome" indicates merely that secondary functional alterations in members of the ductless gland series occur whenever the activity of one of the glands becomes primarily deranged. Further, the term as here employed is restricted to those cases in which it is difficult to tell which of the structures is primarily at fault.*

The following two cases will serve as illustrations. The second of them represents a clinical syndrome which cannot be uncommon, for we have seen two other examples, one, however, being sufficient for this report.

CASE XLIII. (Surgical No. 26405.) **A syndrome suggestive of pluriglandular insufficiency, involving hypophysis, thyroid, adrenal and ovary. Marked improvement under pituitary administration.**

June 8, 1910. Miss M. B., 40 years of age, entered Dr. Barker's service, complaining of variable symptoms. She was subsequently transferred to us for special hypophyseal studies.

Her mother had a "goitre" and "rheumatism." All of the eleven children of the family, except one brother who died of phthisis, are living and, with the exception of the patient, are well.

Personal History. She was always delicate as a child, with more than the usual share of maladies—measles, scarlet fever, whooping-cough, tetanus (?), three attacks of inflammatory rheumatism at the ages of 6, 13, and 27, pneumonia, and "of course" malaria. Her menses began at 13 and were regular until three years ago, since which time there has been complete *amenorrhœa*.

Present Malady. This she dates from an attack of influenza nine years ago, which led to inappetence, indigestion, constipation and pronounced psychic disturbances—confusion, irritability, forgetfulness. She has since suffered from insomnia, nausea and occasional vomiting.

Her skin has gradually become harsh, and a peculiar œdematous thickening and swelling has taken place in the subcutaneous tissues, chiefly in the neck, but extending over the face as well. Pruritus of the extremities has been marked. Her hair has become thin, dry and gray.

Her speech and her body movements have become slow, and, formerly very lively and buoyant, she has felt too dull and indisposed "to do anything or go anywhere." Despite the œdema of the tissues she has lost 10 pounds in weight. She suffers greatly from the cold.

Physical examination shows a delicate and poorly nourished woman of small stature with a senile appearance.* There is a peculiar boggy *œdema* of the nose, lips and cervical tissues, giving her an extraordinary expression, accentuated by her markedly receding chin. These tissues do not pit on pressure, but feel firm and elastic.

The skin has a yellowish tinge: it is harsh, finely wrinkled and dry and there are areas of *pigmentation*. *Hypotrichosis* is marked. The hair of her head is thin and brittle and there are patches of alopecia. The eyebrows are scanty: there is practically no pubic or axillary hair. The tongue is thickened, coated, rubbery and considerably enlarged: there is marked pyorrhœa alveolaris.

* Her appearance resembled, though in lesser degree, the remarkable cases of "progeria" described by Jonathan Hutchinson and by Hastings Gilford (The Disorders of Postnatal Growth and Development, London, 1911).

Her *temperature* is markedly subnormal, often falling to 96.6°, and the *pulse* slow, occasionally 50. *Blood* (Wassermann, etc.) negative except for a slight anæmia. *Urine* normal: no polyuria. *Blood pressure* low.

Visceral examination (thoracic and abdominal), and also *neurological* tests practically negative. The reflexes are brisk to exaggeration. The joints everywhere show an *hypertrophic arthritis*, but the process seems inactive at present. There is a general enlargement of the palpable lymph glands.

Ductless Glands.—An *X-ray* of the cranial base shows an exceedingly small (8 mm. by 10 mm.) but normally placed sella. The *thyroid* is somewhat enlarged; suggestive myxœdema. There is an apparent increase in retrosternal dullness. *Adrenal:* Pigmentation, low blood pressure, asthenia. *Ovary:* Complete amenorrhœa.

Therapy.—On the assumption that the patient was suffering from myxœdema, thyroid was given for three weeks after her admission, with no change in her condition. At the end of June hypophyseal preparations were administered in place of the thyroid extract. A complete transformation occurred, with a rapid disappearance of the œdema, a softening of and return of moisture to the skin, and a nearly normal temperature and pulse; but most marked of all was the change from her former drowsy and inert mental condition to one of lively buoyancy in which she began for the first time to show interest in her surroundings. The pyorrhœa rapidly cleared up and the apparent enlargement of the tongue subsided. On *July 24* there was a *return of menstruation*—its first occurrence in three years.

An outcrop of *zoster* on *Aug. 2* in the left fourth cervical skin-field temporarily interrupted her convalescence, but by *Aug. 16* she was up, walking about and feeling again "a different person."

At this time the pituitary feeding was discontinued for the purpose of establishing her *sugar assimilation limit*. She was unable to retain a larger amount than 200 grams of glucose, which caused no glycosuria.

On *Aug. 19* a *thermic reaction* test with 0.1 gram anterior lobe extract (Armour) led to a marked fall in temperature to 96° F., rather than to the expected rise, and caused a subjective return of her former distressing subjective symptoms, with some mental confusion, a tight feeling in her head, the former chilly sensations and so on. On *Aug. 21* the glandular feeding was resumed, with a prompt restoration of subjective well-being.

By the time of her discharge (*Aug. 23, 1910*) she was again mentally bright and lively; her skin was moist and smooth, and a fine growth of hair was beginning to appear over the former areas of alopecia.

Subsequent Note.—With an occasional intermission she has been taking the extract continuously, and writes that she remains in excellent condition, with active mental processes, her hair growing rapidly and her weight increasing (*Aug. 24*, 96 pounds; *Oct. 1*, 101 pounds; *Nov. 16*, 113 pounds). There was a second scant outcrop of herpes zoster on the left side over the lower ribs a month after her departure. Normal menstruation has continued.

INTERPRETATION.—The case is a confusing one at best, and were it not for the very definite improvement in her condition under pituitary extract there might be no reason for thinking that the hypophysis rather than thyroid or ovary, for example, was chiefly responsible for the constitutional disturbances which she presented. Whether the polyglandular upset was a consequence of the widespread chronic arthritis or whether the arthritis was caused by the disturbances in metabolism resultant to a primary ductless gland disease must be a matter, as yet, of pure conjecture.

It is presumable that hypophysis, thyroid, adrenal and ovary are all at fault and that extracts of any one of these glands might be beneficial, though the hypophyseal therapy proved more efficacious than thyroid extract,

which was the only other form of opotherapy tested. If an hypophyseal derangement of some kind was actually causal in the symptom-complex, this at all events did not conform to the usual type of hypopituitarism. For adiposity was lacking, though there was a high sugar tolerance, and further uncertainty is offered by the negative thermic reaction and the aggravation of symptoms which followed an anterior lobe injection. The essential feature of the condition seems to have been one of multiple insufficiency involving several of the glands.

A corresponding symptom-complex has been designated as *insuffisance pluriglandulaire* by Claude and Gougerot,[44] who ascribe the condition to the combined functional deficiencies of several of the organs of internal secretion. Similar states have been described by others. We do not feel, however, that the perpetuation of the term, as the designation of a clinical entity, is justifiable unless qualified by full appreciation of the fact that the pluriglandular implication usually indicates a primary fault of one, and a secondary derangement of other correlated structures.

As Delille[63] has pointed out, particularly in relation to hypophyseal disease, "insuffisance pluriglandulaire" may occur either in association with primary hyperpituitarism or primary hypopituitarism. The polyglandular syndrome, in other words, is more apt to be a combination of functional deficiencies of some members of the series and functional hyperplasias of others, these changes being regarded by Alfred Kohn[148] rather as evidences of glandular antagonisms than as vicarious or reciprocal activities.

Case XLIV. (Surgical No. 26399.) **Polyglandular syndrome with suggestive involvement of pituitary, adrenal and testicular glands and possibly of thymus and thyroid.**

August 14, 1910.—Tony W., a Russian, a laborer, 24 years of age, unmarried, was admitted through the Dispensary to Dr. Barker's service July 17, and was subsequently transferred to us for study. His complaint was "weakness."

Family and past histories without note. He has heretofore always been well.

Present Illness.—He has been losing strength for a year and has been unable to work. At present he cannot walk without great exhaustion. The asthenia is so marked that he has difficulty even in dressing himself.

Physical Examination.—An overnourished man, weighing 180 pounds, with a slowed *pulse* (averaging 60, occasionally reaching 40), and a subnormal *temperature* (96.4 to 98°). Mucous membranes are a good color, the tongue is coated, the teeth decayed, with pyorrhœa alveolaris.

He is dull and *somnolent*, sleeping much of the time. His *skin* is swarthy and much *pigmented*, the discoloration being accentuated on the face and hands, axillæ, areolæ, umbilicus and genitals. It is, furthermore, dry and smooth and he perspires hardly at all. There is practically no axillary and pubic hair. *Panniculus* is abundant.

Cardiovascular.—There is a striking enfeeblement of the heart sounds, with a soft systolic precardial murmur. Low *blood pressure*. The *urine* is normal and the *blood* also, except for a slight eosinophilia (6 per cent.). Wassermann test negative.

Visceral examination (thoracic and abdominal) negative. Liver and spleen are not palpable.

Tuberculin injection causes a slight prolonged 36-hour pyrexia to 100.5° at highest point, associated with an extreme slowing of the pulse.

Carbohydrate tests impossible, as the taking of more than 100 grams of glucose leads to vomiting. There is evidently an atony of the bladder, as the patient may void only once a day and then a large amount—2000 cc. on one occasion: no demonstrable polyuria, however.

Neurological Examination. — Though the gait and station are normal there is an extreme *asthenia*. The grip is exceedingly feeble and the patient states that it requires great physical effort to extend the fingers after making a fist. He can raise himself on his toes only five times in succession: he cannot lift a twelve-pound weight from the floor, etc. The facial muscles are weak.

Electric responses are normal, though irritability is slightly diminished, but there is no tendency to fatigue: no tetany—*i.e.* neither the reactions of myæsthenia nor myatonia (Dr. H. M. Thomas). The deep reflexes are not obtainable even on reinforcement. The superficial and visceral reflexes are normal but there is complete loss of corneal and pharyngeal responses. There is a slight Romberg with a tendency to fall backward.

The cerebral nerves are normal. The eyes show no change beyond a slight contraction of the visual fields. There is definite *hypæsthesia* of the body to painful stimuli.

Ductless Glands.—*Hypophysis:* The head is large with a very broad cephalic index. The lower jaw is undershot. The hands and feet are over-large and square. The X-ray shows a moderate *enlargement of the sella turcica*. Cutaneous changes and adiposity of insufficiency. *Thyroid:* Not palpable. *Thymus:* No retrosternal dullness. *Adrenals:* Cutaneous pigmentation, asthenia, low blood pressure. *Testes:* Small: the patient is impotent.

The injection of 1.1 gram of boiled anterior lobe on *August 20*, and of 0.2 gram on *August 24*, gave a *negative thermic reaction*, but caused polydipsia and temporary polyuria; no sugar.

Therapy.—Under pituitary administration there occurred a striking improvement in the patient's condition; his muscular tone improved; his somnolence lessened. He gained 14 pounds in weight during his hospital residence. Discharged *Sept. 2*, and has not been subsequently heard from.

INTERPRETATION.—Certain features of the condition were suggestive of myæsthenia and myatonia, his physical weakness being almost more pronounced than in any, even of the outspoken cases, of primary hypopituitarism in our series. However, the general enfeeblement, comprising the cardiac as well as skeletal musculature, resembled rather the asthenia of Addison's disease, and the medical diagnosis lay between *adrenal tuberculosis* and *incipient acromegaly*.

It is of interest to recall that Tilney (1907) reported a case which was designated "asthenic bulbar paralysis," in which an adenoma of the hypophysis was found postmortem; and Fontanel (1905) and Marienesco (1908) have each recorded other examples of this disease with pituitary enlargement.

Evidently in this patient the entire chain of ductless glands was functionally deranged, and it is doubtful which of them may have been primarily affected. The pigmentation, the unusual weakness and the positive tuberculin reaction naturally suggest the adrenal,* though the enlarged sella, indicating the existence of an hypophyseal struma, and the improvement under pituitary feeding favor the hypophysis as the primary offender.

The patient was irritable and refractory, and elaborate studies such as the case needed were impossible. The more striking symptoms are the muscular weakness with abolished deep reflexes, the pigmentation, the subnormal temperature and pulse, the tendency to adiposity, the

* We have since (Dec., 1911) studied a very similar case in which a marked *hypoglycæmia* (0.0235 per cent. sugar) was found by Jacobson. Judging from the experiences of Porges this would suggest that the adrenal element was dominant (cf. Case XXIII).

somnolence, the impotence and the dry skin—symptoms many of which could accompany a primary disturbance of the function of several of the glandular series with the inevitable secondary involvement of the remainder of the group.

It is not impossible that some form of opotherapy other than hypophyseal would have led to a subjective improvement of corresponding degree.

In the following three cases the intracranial symptoms were sufficiently definite to lay the burden of responsibility upon the hypophyseal or pineal gland, and yet in all, the glandular manifestations were so bizarre, so unlike those presented by the cases which have been recorded in the preceding groups that they have been placed apart in this group of cases with a polyglandular syndrome.

They unquestionably represent types of ductless gland disease of a different order from those commonly recognized, and give an opportunity for collecting the facts recorded in relation to pinealism and the possible hyperplasias of adrenal and interstitial cells of Leydig.

Case XLV. (Surgical No. 27140.) **A syndrome of painful obesity, hypertrichosis, and amenorrhœa, with over-development of secondary sexual characteristics accompanying a low grade of hydrocephalus and increased cerebral tension. Pituitary, adrenal, pineal or ovary? Subtemporal exploration and decompression.**

Dec. 29, 1910.—Miss M. G., a Russian Jewess, single, aged 23, was referred to us by Dr. De Witt Stetten of New York.

One of a numerous and healthy family, she was well until 16 years of age, having been free from the customary children's ailments.

The Present Malady.—Her *menses*, which began at the age of 14, were regular for two years and then, 7 years ago, suddenly ceased, coincident with attacks of temporal headache, pain in the back and swelling of the feet.

FIG. 281.—Case XLV. Showing hirsuties of lip and forehead.

Her *vision* began to fail at this time. There have since been periods of diplopia. Nausea with vomiting has occurred with the more severe headaches. She has had more or less intracranial discomfort ever since; often aching pains in the eyes. Dizziness and unsteadiness have been marked at times.

She has become stout, her *weight* increasing from 112 pounds two years ago to 137 pounds at present. *Other noteworthy symptoms* have been insomnia, tinnitus, extreme dryness of the skin, frequent sore throat, shortness of breath, palpitation, purpuric outbreaks, marked constipation, sudden attacks of dizziness with falling, a definite growth of hair and mustache during the past few years with marked falling out of the hair of the scalp. She feels chilly and cold all of the time and suffers from insomnia rather than from drowsiness. Muscular weakness is extreme and there is much complaint of backache and epigastric pains.

Physical Examination.—A young woman 4 feet 9 inches in height, of extraordinary appearance. Her round face is dusky and cyanosed and covered with a fine growth of hair, which is particularly noticeable on forehead and upper lip (Fig. 281). Mucous membranes are of bright color despite her frequent bleedings.

Visceral (abdominal and thoracic) and *cardiovascular examinations* negative except for high tension of the pulse.

Neurological examination reveals practically nothing other than the signs of intracranial pressure.

There is a definite tendency toward *hæmophilia*. The skin bruises easily and large spontaneous *ecchymoses* occur frequently. *Epistaxis* is almost a daily occurrence. She has bleeding hæmorrhoids. Lumbar puncture, pricking of ear, etc., cause a wide subcutaneous extravasation.

Blood.—No abnormalities. R. B. C. 5,300,000; W. B. C. 12,000. Hgb. 85 per cent. Coagulation time 3 minutes. Wassermann negative; also for cerebrospinal fluid. *Blood pressure* high, averaging 185 mm. *Temperature* and *pulse* normal.

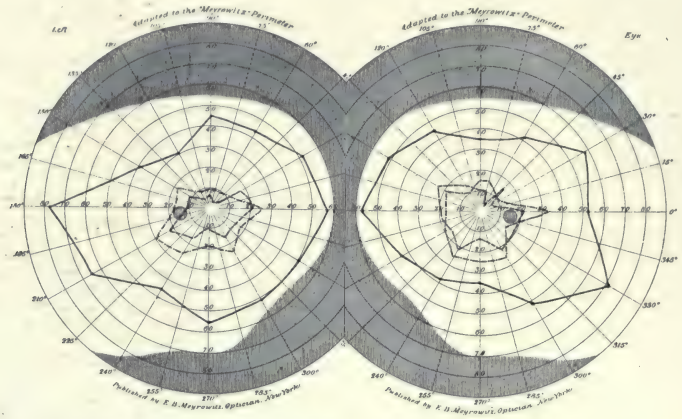


FIG. 282.—Case XLV. Fields with constriction and color interlacing.

Analysis of Hypophyseal Manifestations.—(a) *Neighborhood Symptoms:* The stereoscopic X-ray shows what appears to be a somewhat thinned-out sella of normal configuration but of small size, measuring only 1.0 cm. by 0.9 cm. in depth.

Eyes: Slight bilateral exophthalmos, greater on left than right. The optic nerves are congested and show a low grade of choked disc with no atrophic pallor. No present oculomotor palsies, though diplopia has occurred. *Fields* show constriction, particularly of temporal margins, with interlacing of colors (Fig. 282). *Acuity:* Left and right 10/40.

Epistaxis has been frequent for years, often excessive, with daily nose-bleeds. There has occasionally been a sudden discharge of clear fluid (rhinorrhœa?) in amounts sufficient to soak a handkerchief. Direct examination of pharynx negative.

(b) *General Pressure Symptoms.* Pressure headaches: a low grade of choked disc: color interlacing: nausea and vomiting: dizziness: pain in eyeballs: exophthalmos.

(c) *Glandular Symptoms. Skeletal:* A low stature (144 cm.) and delicate framework: extremities small, fingers tapering: nails long, well formed, no crescents. Her head squats on her high shoulders: she has the attitude and figure of a full-term pregnancy (Fig. 283).

The epiphyseal lines (radial and phalangeal) are still radiographically visible (Figs. 284, 285). The *teeth* are widely spaced, notched, and suggest Hutchinsonian change.

Cutaneous. Skin during the past few years has become rough and dry and has a blue and dusky appearance. The body and extremities show an especial degree of cyanosis. There are a number of large subcutaneous ecchymoses over the lower extremities. The

lineæ atrophicæ over the abdomen are of a deep brownish-purple color (cf. Fig. 283). There is considerable *pigmentation*, particularly of eyelids, groins, pubes and areolæ. Mucous membranes clear.

Hair of the head is thin and sparse. There is an abundant new growth of fine black hair over forehead, cheeks and upper lip. The hair of the eyebrows and temporal regions merges (Fig. 281). A fine hirsuties over back and hips.

The *subcutaneous tissues* feel boggy and tense. *Adiposity*, particularly limited to the abdomen, is marked and of recent origin. It is very painful and tender (adiposis dolorosa). No lipomata, but the fat is coarsely nodular.

Carbohydrate tolerance high. Assimilation limit for lævulose about 200 grams. Slight *thermic reaction* to anterior lobe injection of 0.2 gram hypodermically, with sensation of warmth and profuse perspiration.

Other Ductless Glands. *Pineal:* Possibly early "Frühreife;" hypertrophic genitalia; hypertrichosis; low grade of hydrocephalus. *Thyroid:* Right lobe somewhat enlarged; patient has noticed an increase in the size of her neck, which is partly from fat, however. *Adrenal:* Extreme pigmentation; asthenia; high blood pressure; tendency to bleeding; possibly the hypertrichosis. *Thymus* negative. *Ovaries* not palpable: infantile uterus; complete amenorrhœa.

There were no clear *therapeutic indications* except for the relief of intracranial pressure and in view of the tendency to bleeding a decompression was thought unjustifiably hazardous. She was discharged *Jan. 31, 1911*, and returned again for further study on *July 28th*, her condition largely unchanged, though the visual fields were even more constricted and vision was lowered to 15/70 left and 15/100 right.

Sept. 6, 1911. **Operation.** Right osteoplastic resection combined with subtemporal decompression; lumbar puncture; attempted exploration of interpeduncular region by overhanging brain method. Satisfactory view of space not obtained. Negative findings except for unusual thickness and vascularity of diploë, and tense and wet brain with low grade of hydrocephalus.

Recovery was uncomplicated and an unexpected degree of relief was afforded by the decompression.

Subsequent Notes. A month later: no further headaches; subsidence of neuroretinal œdema; blood pressure low (130-140); sleeping better; a loss of 12 pounds in weight.

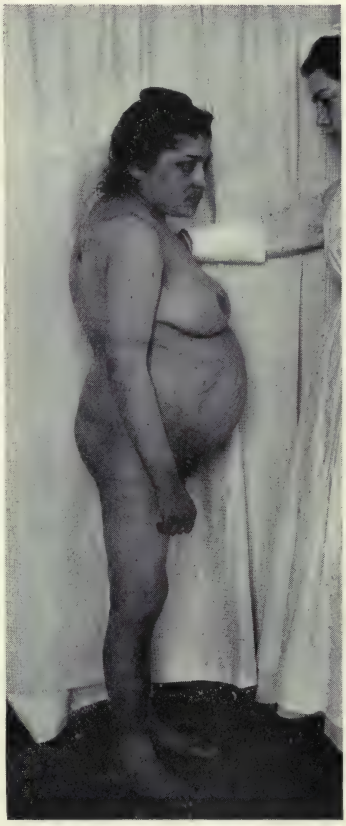


FIG. 283.—Case XLV. Showing small stature, adiposity, cyanosis, purplish lineæ atrophicæ.

Despite this improvement in the signs and symptoms of her intracranial disorder, she continued to complain of backache, of pain in the left side and swelling of the extremities.

An exploration of the adrenals is under consideration.

COMMENT.—The syndrome shown by this patient exemplifies the fact that terms such as Bartels' *dystrophia adiposo-genitalis* and Dercum's *adiposis dolorosa* may be made to include cases which neither of these writers intended to come within the scope of these designations. All of the cardinal symptoms of both of these maladies were shown—skeletal undergrowth,

adiposity and sexual dystrophy on the one hand, painful and tender adiposis with asthenia and psychic disturbances on the other.

The case is an instance of the combination of intracranial pressure symptoms with amenorrhœa, adiposity and low physical stature—a syndrome which might well be due to hypophyseal deficiency. But here, however, the similarity to the cases of hypopituitarism, which have been heretofore discussed, ends, and instead of the sexual infantilism of reversive type with which we have be-

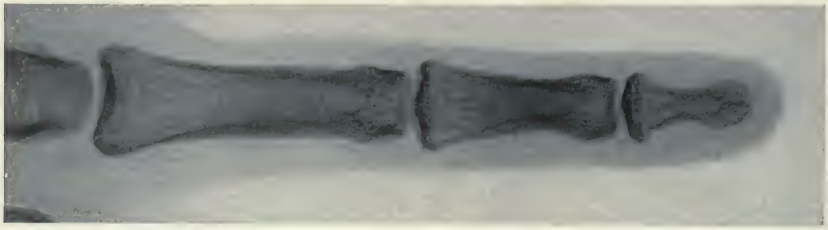


FIG. 284.—Case XLV. X-ray of middle finger (unreduced) showing traces of epiphyseal lines.

come familiar, the patient shows the secondary sexual development, mammary and genital, of a multipara, with unusual and recently acquired hirsuties.

A symptom-complex of this type has been described in association with certified *adrenal lesions*, which makes it appear that the adiposo-genital syndrome may occur with derangements of other of the ductless glands than the hypophysis itself. The following case recently reported by Launois, Pinard and Gallais[154] will serve in illustration.

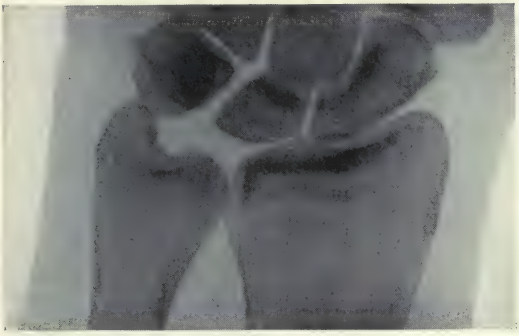


FIG. 285.—Case XLV. X-ray of wrist showing incomplete epiphyseal ossification.

Their patient was a young woman of 19, with increasing weakness, lumbar pains and various nervous and mental disorders. The skin was harsh, dry, of a grayish-brown tint and covered with brush-like, bluish scars from stretching by the excessive and rapidly acquired panniculus. She had grown a beard and mustache, and resembled a man of 25 more than a female of 19. There was a double choked disc. A tumor finally became palpable in the left hypochondrium, and at autopsy this proved to be *a malignant adenoma of the left suprarenal gland.*

Other cases with precisely the same syndrome have been recorded in the past by Linser (1903),[168] Bulloch and Sequeira (1905),[30] Guinon and Bijon (1906),[105a] Bortz (1909),[23] and Bovin (1910).[23a] In all of them adenomatous or hyperplastic adrenal tumors have been found and in some instances the constitutional transformation of the afflicted individual into an adipose and hirsute creature has been extraordinary. This has been particularly striking in some of the preadolescent patients who have shown a premature development of the sexual organs and accessory genital structures together with an astonishing hypertrichosis.

It will thus be seen that we may perchance be on the way toward the recognition of the consequences of *hyperadrenalism.* Heretofore the only recognizable clinical state associated with primary adrenal disease has been the syndrome of Addison, and the grouping of these cases may possibly add one more to the series of clinical conditions related to primary maladies of the ductless glands.

Though the following case shows some of these same features of possible hyperadrenalism, nevertheless the intracranial symptoms suffice to give reasonable assurance of an interpeduncular lesion, and had there been hypotrichosis and adiposity the history would probably have been included with those of Group I (cf. Cases III to VII).

CASE XLVI. (Surgical No. 27409.) **Infantilism with sexual precocity, hypertrichosis, pigmentation, amenorrhœa, deficient mentality, uncinate fits and asthenia. Exploratory operation.**

Feb. 13, 1911. Miss N. S., aged 19, referred by Dr. R. F. Ellegood, of Wilmington, Delaware. *Complaint:* Convulsive seizures loss of vision; asthenia.

There is a family history of some nervous disorders. The patient was an unusually large and healthy baby. She is said to have received, during childhood, a severe blow on the forehead; there are no present evidences of this injury. She is said to have had St. Vitus' dance at seven.

Present Malady. As long as she can remember, she has been troubled by disturbing lapses, accompanied by a *sense of unreality:* she often insists that she "is some one else and has beautiful dreams."

Since her sixteenth year she has had attacks suggesting *petit-mal* with dreamy states, often as many as five or six a day. Of late the attacks, which are usually preceded by a disagreeable *gustatory impression,* have become more infrequent and more severe, with momentary loss of consciousness and falling. They have been regarded as "hysterical."

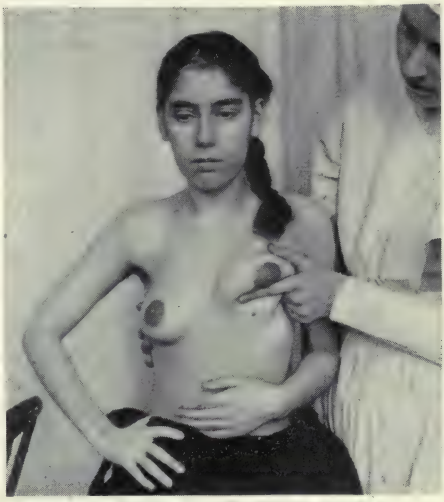


FIG. 286.—Case XLVI. Undersized young woman; childish aspect. Note supernumerary nipple and low growth of hair on forehead.

She has suffered from frontal *headaches* for some years: they are now less severe. For the past year there has been some stiffness and rigidity of the right leg. Her *vision* has been failing for a year, and acuity is now very low: she has frequent periods of *amaurosis.*

Her *mentality* is of a low order: memory poor: she is often irrational and is occasionally disoriented. She has been given an abundance of chloral and bromides.

There is a history of *infantile precocities.* Her adolescence is said to have been normal: she became plump, and there was an unusual mammary development. The *catamenia* began at 14, but have been irregular, and she has not menstruated for the past six months. Examination showed infantile pelvic organs.

During the past year an abundant new *growth of hair* has appeared, particularly on the face and arms, and her skin has become much *pigmented.* Excessive *sweating* of the extremities has been a troublesome symptom. She has been exceedingly *drowsy* and feels excessively weak. There is marked inappetence.

Physical Examination. A dark-complexioned, undersized, hirsute young woman with the stature of a child of 13 (Fig. 286). *Weight* 90 pounds. There is a pigmented *supernumerary nipple* below the left breast. Visceral and cardiovascular examination negative. *Temperature* ranges above normal (98.6° to 99.6°); *pulse* 80. Blood pressure low (82 mm.).

FIG. 287.—Case XLVI. Small, normally formed sella (dotted outlines).

Neurological tests show exaggerated knee jerks; also an extraordinary indifference or actual insensitiveness to painful cutaneous stimuli. There is a slight muscular spasticity and disability of the right side: some static ataxia: she walks unsteadily and with a broad base.

FIG. 288.—Case XLVI. Small, delicate hand, in contrast with hand of adult of same age.

Blood and *urine* negative.

Analysis of Hypophyseal Manifestations. (a) *Neighborhood Symptoms.* The X-ray shows a small sella turcica (Fig. 287).

Eyes: Bilateral *primary optic atrophy* with almost total amaurosis: at present can barely count fingers. History suggests that vision was first lost as a right *homonymous hemianopsia.* Pupils dilated; right larger than left. Fluctuating oculomotor palsies with diplopia. *Characteristic uncinate attacks.*

Pharyngeal examination shows large tonsils, but vault negative. No epistaxis.

(b) *General Pressure Symptoms.* Former severe headaches: slight œdema of the atrophic discs.

(c) *Glandular Signs. Skeletal:* Stature infantile. Height 58 inches (147.5 cm.) Cranium small (55 cm. in circumference) but shows no abnormalities. Hands small, infantile (Fig. 288); the epiphyses have ossified and the radial lines are barely apparent (Fig. 289).

Cutaneous. Skin moist, dusky, freckled: large, deeply pigmented areolæ. *Hypertrichosis* marked: the hair of the temporal regions almost meets the eyebrows (Fig. 290) and there is an abundant, fine, dark growth over arms, shoulders, legs, hips and back. Axillary and pubic growth heavy. Nails small and show no crescents.

There is no history of adiposity: greatest weight 110 pounds two years ago.

Extreme *drowsiness and asthenia* have been marked features of her condition.

Carbohydrate Tolerance. Below 150 grams lævulose. *Thermic response* to injection of 0.2 grams anterior lobe extract negative.

Other Ductless Glands. *Thyroid* palpable; not enlarged. *Adrenal* (?): Pigmentation, asthenia, low blood pressure and hypertrichosis. *Thymus:* Sternum prominent; possibly an increase of dullness. *Luteal:* Amenorrhœa; full and precocious development of secondary characteristics of sex.

March 11, 1911. **Exploratory subtemporal operation.** Under the impression that the uncinate fits and the primary optic atrophy spoke emphatically in favor of an infundibular tumor, despite the absence of sellar distortion, a subtemporal exposure of the interpeduncular region was made by combining a left osteoplastic flap with a lumbar puncture and the head-down (*ueberhängende gehirn*) position of Karplus and Kreidl. There was no interpeduncular tumor.

Recovery was uneventful. There was an appreciable improvement in her mental condition and a cessation of the dream states, for which no explanation can be given.

She was discharged *March 23:* no response has been made to subsequent inquiries.

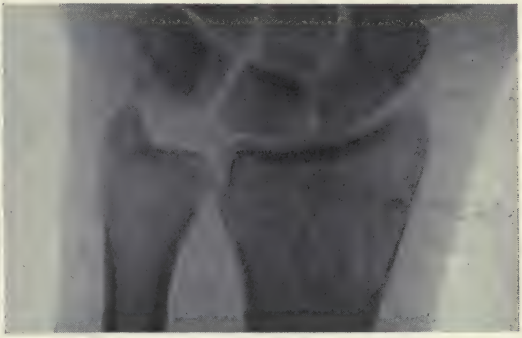


FIG. 289.—Case XLVI. Note united radial epiphysis with bare trace of line.

INTERPRETATION.—As in the preceding case here too there are uncertainties as to the primary seat of the evident polyglandular disorder.

From the standpoint of the *hypophysis* there are certain factors which suggest a combination of anterior lobe deficiency and posterior lobe overactivity. There is no enlargement of the sella turcica—on the contrary, the X-rays hows the fossa to be rather small, and possibly there may be an hypoplasia (primary or secondary) of the pars anterior accounting for the small stature. Furthermore, an exploration giving a good view of the interpeduncular field disclosed no tumor. Though tempted therefore to incorporate this case among those of Group I exhibiting infantilism, it seemed inappropriate to do so without further explanation of some of the bizarre symptoms—the hypertrichosis, the aphrodisiac tendencies, the unusual character of the neighborhood signs.

FIG. 290.—Case XLVI. Profile: note freckling and low growth of temporal hair.

The possibility of primary *pinealism* must be fully admitted. Certain glandular symptoms support the view of primary pineal disturbance, notably the hypertrichosis and the sexual precocities, to which Marburg and Frankl-Hochwart have called particular attention in these cases. They are usually

associated with a congenital tumor of the pineal gland, and the supernumerary nipple in this patient possibly speaks in favor of some such tendency.

Some of the symptoms, however, which have been attributed to a pineal tumor—notably the adiposity—I am inclined to attribute to a secondary hypophyseal derangement due to the ventricular hydrops, which is an almost inevitable consequence of a growth in the pineal region. It may be recalled, too, that in our first experimental canine series[53] some of the dogs with primary posterior lobe defects exhibited striking aphrodisiac tendencies—the reverse, in other words, of the condition shown by the animals in whom nearly total extirpation had been performed. Moreover, hypertrichosis and sexual precocity have been described in connection with adrenal lesions: hence for the present it is impossible to speak with any degree of assurance of this or that gland as primarily at fault, when confronted by a syndrome of this type.

The same uncertainties apply in equal measure to the following case:

Case XLVII. (Surgical No. 28326.) **A syndrome of precocious sexual adolescence, overgrowth, adiposity, hypertrichosis and asthenia, with a low grade of hydrocephalus and optic atrophy, suggesting involvement of pineal, hypophysis and interstitial cells of testis. Pineal exploration negative.**

Sept. 2, 1911. Alfred K., 8 years of age, referred by Dr. Alexis Carrel of New York. *Complaint:* Loss of vision and abnormal development of sex.

There is nothing noteworthy in the history of his antecedents. Patient is the only child. A very difficult labor: a 7½ pound baby with a cephalhæmatoma and with a "cast" in the left eye.

A healthy babyhood: no maladies except "summer complaint" at 18 months and chicken-pox in the third year.

Present Syndrome. Though always somewhat larger than the average he became especially stout at the age of three. No abnormality was suspected until, in his fourth year (1906–7), there occurred a definite *loss of vision*, the left eye being first affected and a year later the right.

For three years (1906–8) he suffered much from headaches and frequent projectile vomiting. At this period he acquired an *abnormal appetite* ("would eat as much as a man"); there was a marked *increment in growth*, and he became very *adipose*. In 1907 an adenoid operation was performed.

By *Feb., 1908*, he had become blind, but after four months normal (?) vision was gradually regained. There followed periods of temporary amaurosis until *May, 1909*, when vision was permanently lost. Some *static ataxia* was first noted at this time.

It was observed at birth that his genitalia were over-large. In 1909–10 (aged 6) he acquired his *secondary sexual characters*, with an adult masculine voice, axillary and pubic hair and overdevelopment of the genitalia. His mother states that he has an unusually affectionate disposition.

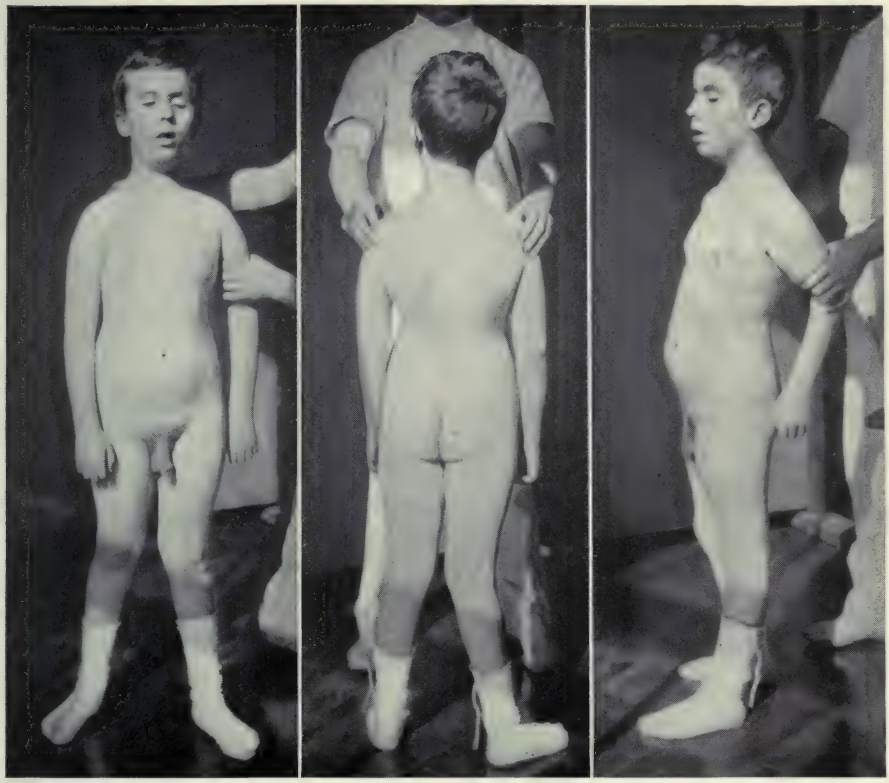
At the age of 6 also there was an acceleration of skeletal growth far exceeding the normal for his age. He then reached his present size and weight.

Since his fourth year he has been dull and drowsy. For the past year articulation, mastication and deglutition have become affected: there is drooling, increasing asthenia and unsteadiness. There have been periods of deep stupor and at best he sleeps all day if not aroused: much yawning and "nose rubbing."

Physical Examination. A child, looking twice his age—overgrown (5 ft. 6 in.), adipose (95 pounds), blind, large-headed, with hypertrophied genitalia and the so-called adenoid expression.

Visceral (abdominal and thoracic) and cardiovascular examinations negative. *Positive neurological signs* as follows: optic atrophy with total amaurosis; right pupil larger than left; ptosis on left (Fig. 295) with divergent squint; ocular movements restricted in all directions; nystagmus to left; pupillary reactions present, despite the total amaurosis. *Blood* and *urine* negative (former polydipsia and polyuria). *Temperature* and *pulse* range slightly above normal.

Analysis of Glandular Symptoms. *Skeletal:* A peculiar configuration for a child, due to his unusual height of 143.5 cm. (normal for 8 years = 122.3 cm.), the adult size of the



FIGS. 291, 292, 293.—Case XLVII. Note stature; large head; small extremities; genu valgum; genital hypertrophy.

head, the narrow sloping shoulders, the "knock-knees" and the delicate, tapering, childlike extremities (Figs. 291–293).

The *cranium* is of the "Türmschädel" type, bilaterally symmetrical, of adult size, 57.5 cm. in circumference. The *X-ray* shows a small sella, perched, however, on a solid base without underlying sphenoidal cells (Fig. 294).

The face is large, showing maxillary prognathism; the palate is high and narrow; the upper teeth project and are somewhat spaced. The larynx is large.

The *extremities* are small, delicate and tapering, the hands particularly so (Fig. 295), their length from wrist to tip of middle finger being only 14.5 cm. The *epiphyses* are cartilaginous throughout (Fig. 296).

The toes are somewhat anomalous: the great toe projects beyond the others, which are relatively smaller than normal.

Cutaneous. The skin of the face is rough, coarse, full of comedones with a beginning mustache. There is excessive secretion from the cutaneous glands with a most offensive odor. There is a widespread growth of fine black hair over the trunk, particularly over the back and hips. The pubic and axillary hair is abundant and has been clipped.

There is marked *adiposity* (Fig. 295) with a feminine distribution, the panniculus being especially abundant over pectorals, pubes, hips, supraclavicular regions and inner aspect of thighs. Circumferential measurements: neck 32 cm.; over pectorals 75 cm.; abdomen 72 cm.; hips 77 cm.; thigh 45 cm.; calf 28.5 cm.

Carbohydrate Tolerance. One hundred grams lævulose negative: no larger amounts given. Blood shows normal sugar content.

The Individual Glands. The *pineal* is suggested by the hydrocephalus, static ataxia with tendency to fall backward (corpora quadrigemina?), the oculomotor (nuclear?) palsies and nystagmus: the *hypophysis*, by the overgrowth, the primary optic atrophy, the oculomotor (peripheral?) palsies, the peculiar character of the sphenoidal shadow, and the adiposity, which might, of course, be secondary to the hydrocephalus.

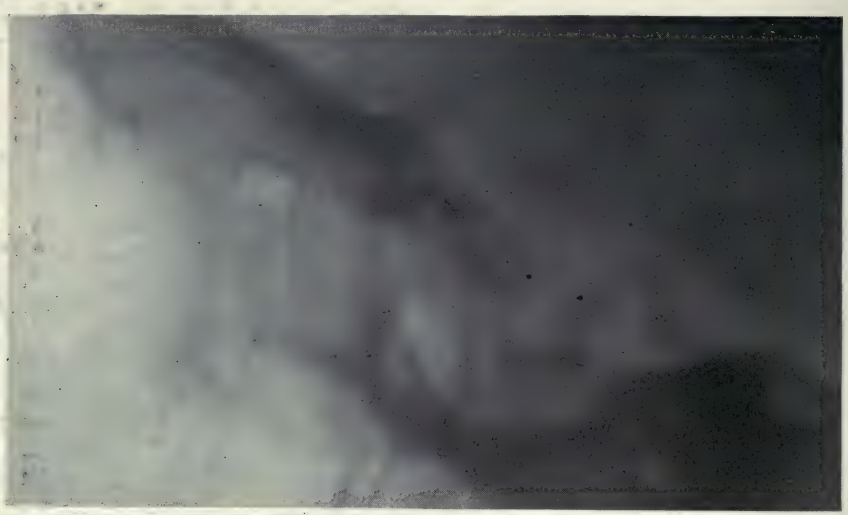


FIG. 294.—Case XLVII. X-ray of sellar region (unreduced) showing normal though small fossa surmounting a non-cellular sphenoid. Dots on anterior and posterior clinoids.

The *thyroid* is not palpable, nor are there clinical evidences of its participation. There is no increase in retrosternal *thymic* dullness. There are no specific *adrenal* signs.

The *testes* are small, but there is a hyperplasia of the genitals, and the *secondary sexual characters* are fully developed—a condition which has been variously attributed to pineal and to adrenal lesions as well as to a primary hyperplasia of the interstitial cells of Leydig. The adiposity may likewise be a feature attributed to hypophysis, pineal, adrenal or testis.

Sept. 7, 1911. **Operation.** Under a tourniquet an osteoplastic flap was made corresponding with the posterior half of the right hemisphere. The dura was opened, and a ventricular puncture made, collapsing the ventricle (250 cc.).

The occipital lobe was easily dislocated outward, bringing the splenium into view. The tentorium was split to the right of the sinus rectus, exposing the upper surface of the cerebellum and venæ Galeni.

The structures were all of normal appearance: there was no tumor of the neighborhood. The flap was replaced and the wound closed without drainage.

A small section of the testis was excised for examination. This shows *a preadolescent type of tubule without formed spermatozoa, but the interstitial cells of Leydig are in excess* (Fig. 297).

There were no post-operative complications. The patient was discharged on Oct. 6, his condition unchanged. An exploration of the interpeduncular region was urged, and, should this fail to disclose the lesion, a callosal puncture was proposed for relief of the hydrocephalus. The proposal was not accepted by the parents.

Comment.—Here, again, is a pluriglandular syndrome of unusual character, the definite intracranial symptoms throwing the burden of suspicion upon either pineal gland or pituitary body as the primary seat of the derangement, whereas an hyperplasia of the interstitial cells of the testis, suggested by the precocious genital development and certified by the histological findings, adds further confusion to the symptom-complex.

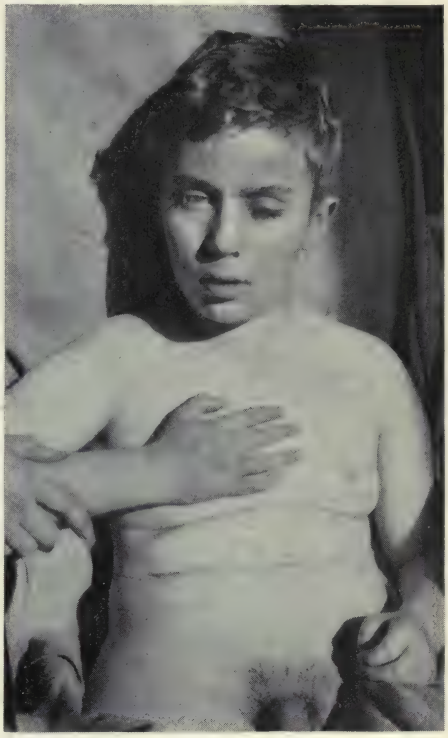


Fig. 295.—Case XLVII. Note adiposity, oculomotor palsies and small tapering hand.

The clinical manifestations relating to each of these structures may be assembled.

The Hypophysis.—Certain neighborhood symptoms point to this structure—the primary optic atrophy and the oculomotor palsies, which are of a peripheral rather than a nuclear type. The sella, however, is small and of normal configuration, the suggestive anomaly shown by the X-ray being in the nature of an opaque shadow cast by the sphenoidal bone where the sinuses usually show open spaces. This may represent merely one of the sphenoidal variations to which Gibson[97] calls attention, or may indicate the presence of a tumor arising from a craniopharyngeal rest, of the kind Erdheim has described. Such a lesion, however, could hardly account for the intracranial symptoms, especially for the hydrocephalus.

If the hypophysis is actually implicated by an adjacent tumor, it must be a superimposed growth in the interpeduncular space. Such a lesion, however, would have provoked primary hypopituitarism, and with this familiar syndrome the constitutional disturbances do not conform.

So far as the secretory symptoms are concerned, the picture is the reverse of that characterizing preadolescent hypopituitarism, for there is precocious overgrowth, both skeletal and genital, and hypertrichosis rather than the delicate hairless skin which accompanies hypophyseal insufficiencies. The subnormal temperature of this state is wanting, and a delayed rather than a precocious adolescence is to be expected.

Hence, if hypophyseal, the condition is one of preadolescent hyperpituitarism, but in this event one would certainly anticipate an enlarged sella. This view can be reconciled with existing conditions only on the possible basis of a functional hyperplasia of an accessory craniopharyngeal gland.

THE PINEAL GLAND.—The neighborhood symptoms favoring this structure were dominant, and consequently it was the primary object of surgical intervention.* The static instability, of the type characterizing a lesion of the corpora quadrigemina, the oculomotor palsies and the internal hydrocephalus, all pointed to a posterior lesion, though, to be sure, upon this view a secondary rather than a primary optic atrophy would have been expected.

Our knowledge of the secretory function of the pineal—Descartes' seat of the soul—is scant. Under the stimulus, however, of Otto Marburg's elaborate anatomical studies in 1909, the past two years have

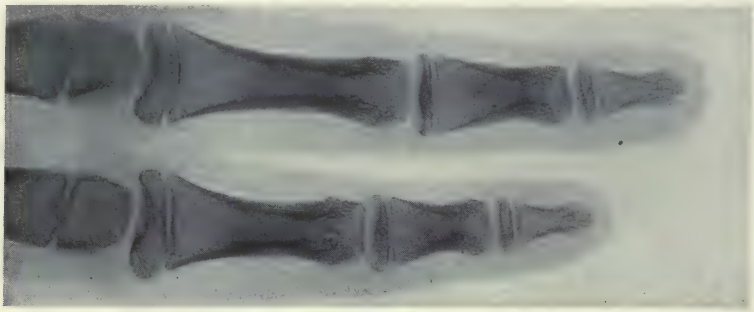


FIG. 296.—Case XLVII. X-ray of middle and ring fingers (unreduced).

witnessed an activation of interest in the structure, the data having recently been collected in full by Arthur Münzer.[194]

Experimental studies have as yet disclosed no definite physiological properties, either by injections or by extirpation methods, a number of successful epiphysectomies by Exner and Boese[79] having shown negative results; and in our own experiments, if there are any symptoms produced by a pineal extirpation they have so far eluded us.

As has been true of other glands of internal secretion—hypophysis, adrenal and thyroid, for example—the first information concerning function has come through clinical observations of the syndrome exhibited by patients suffering from proven hypertrophies or tumor of the gland, of which teratoma and cysts are the more common form.

The pineal gland doubtless shows its chief functional activity in childhood, a significant involution of the structure occurring at puberty. The constitutional secretory disturbances, so far as they have been recognized, include a form of so-called cerebral adiposity, which Marburg[175] ascribes to hyperpinealism, though it must be realized, on the basis of the

* So far as I am aware, this and the exploration in Case XIII represent the first surgical exposures of the pineal region in man. Though in both cases the findings were negative, the feasibility of the procedure was clearly demonstrated, and had a benign tumor actually been present, as was suspected, it would have been more accessible for surgical removal than, for example, is a lateral recess tumor.

adiposities due to posterior lesions causing internal hydrocephalus (cf. Group IV), that this could well be the expression of a secondary hypophyseal deficiency mechanically brought about by a ventricular hydrops.

Hence pineal enlargements, whether associated with a functional hyperplasia or hypoplasia, may be provocative of a tendency toward adiposity. However, there is another even more striking symptom which cannot be attributed to the hypophysis, for certain types of pineal tumor are characterized by an extraordinarily precocious puberty, of a type precisely similar to that exhibited by the patient under discussion.

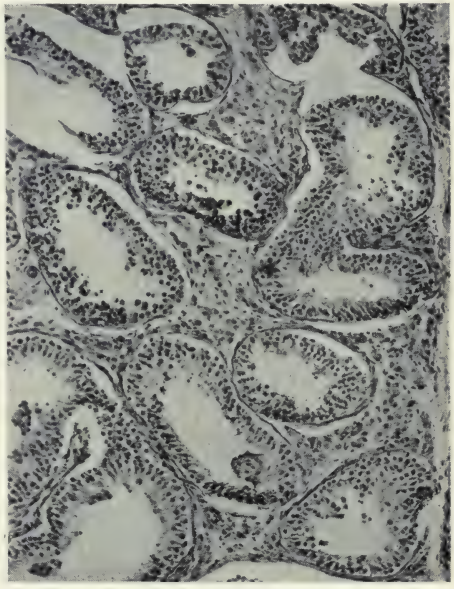


Fig. 297.—Case XLVII. Section of testis (mag. 75 diams.). Note preadolescent type of tubule and great excess of interstitial cells.

Frankl-Hochwart,[88] who was probably the first to make a correct diagnosis of the condition during life, on the basis of the constitutional rather than neurological symptoms, has assembled a few of the certified cases from the literature. He regards the syndrome as an expression of hypopinealism. In his words: "When in a young individual (boy) in addition to the general pressure symptoms of tumor and the local signs of involvement of the corpora quadrigemina, there occur an abnormal increase in stature, an unaccustomed growth of hair, obesity, drowsiness, a premature genital and sexual development with evident precocity of adolescence (*geistige Frühreife*), one must think of a pineal gland tumor (teratoma)."

The Interstitial Cells of the Testis.—In preadolescent states of hypopituitarism, as we have seen, there is a tendency toward the persistence of sexual infantilism, or at least toward an imperfect or delayed acquirement of the so-called secondary sexual characteristics (cf. Case VIII), just as in states of hypopituitarism which occur after puberty there is a tendency toward a reversive condition, with testicular hypoplasia, impotence, amenorrhœa and some measure of loss of the secondary characteristics already acquired (cf. Case X). We have seen, too, that in these states a histological degenerative (?) change occurs in the interstitial cells of Leydig.

In our patient, on the other hand, these cells are shown to be increased, and such a condition does not occur, so far as is known, as the result of a primary hypophyseal lesion. To be sure, illustrative cases of undoubted hyperpituitarism in childhood have been rare, and it may be found that premature sexual ripening characterizes this condition. Certainly the definite tendency to gigantism in this patient speaks in favor of a functional hyperplasia of the anterior lobe.

Many of the true giants, however, show some sexual infantilism (cf. Case XXXII) with incomplete secondary characteristics of sex; so that for the present the possible effect of hyperpituitarism in causing a secondary hyperplasia of the interstitial cells must be left undetermined. It may be said, however, that there would seem to be some antagonistic action between pineal and hypophysis in relation to the sexual glands.

Had it not been for the evident intracranial symptoms which this child showed it might naturally have been surmised that the symptoms were due to a primary *hyperorchidism* rather than to an hyperplasia of the interstitial cells secondary to changes in another gland. In this connection such a case as the following reported by Sacchi[220] is of moment:

> In association with an enlargement of the left testis puberty occurred in a boy at 5 years of age. At 9 his height was 143 cm. (5 ft. 6 in.), his weight 44 kilo. (97 pounds)—almost the same as that of our patient at the same age. He had an unusual physical and muscular development, with a black beard 5 cm. in length and full sexual development. The tumor was excised and was called an alveolar carcinoma (possibly an interstitial cell tumor?).

Thus, functional derangements, whether primarily of pineal or of testicular origin, may seemingly elicit this clinical phenomenon of early pubescence with skeletal overgrowth. Moreover, there is an adrenal syndrome, as discussed under Case XLV, which may give to the individual a somewhat similar aspect. Doubtless the uncertainties regarding these matters will be cleared up in the near future.

PART III

GENERAL REVIEW OF INCIDENCE, SYMPTOMATOLOGY AND TREATMENT

INCIDENCE

After the long recital, in the preceding section, of case reports subdivided into groups, based possibly with too great emphasis on tumor manifestations, it seems advisable to assemble the data relating to incidence, symptomatology and treatment, so that these subjects may be discussed as features of hypophyseal disease in general rather than as expressions of individual cases.

Among the factors of an incidental nature which deserve especial comment are inheritance, developmental defects, trauma, physiological epochs of life, and infectious diseases.

Inheritance.—It is probable that there are strains, which run through families on Mendelian laws and which betray the existence of ductless gland irregularities unrelated to any post-partum influences. The question of an inherited instability of the hypophysis has already been briefly considered in the attempted interpretation of certain of the case reports—notably of Cases I, XIII and XXXI, all of them individuals with a dominant familial tendency toward skeletal growth exceeding the average normal.*

It is a far cry from experimental genetics with *pisum sativum* to the conditions found in *homo sapiens*, even in such a comparatively simple factor as height. However, there can be little doubt but that dominant and recessive growth characteristics are governed both for man and the edible pea on a similar basis. Laws have been established for certain of the better known inherited tendencies which border on the clinical domain, as albinism, night and color blindness, brachydactylism, hæmophilia, deaf-mutism, cataract, and so on—and it is interesting, in our present connection, that there are authentic instances of familial diabetes, both insipidus and mellitus.

One patient concerning whom I have been consulted, but whose history is not included in this series, is an intelligent young man of 24, who has evident manifestations of genital dystrophy, and whose secondary sexual characteristics have never appeared. His father, who is a physician and inter-

* There are on record histories of inherited gigantism (de Neuville: Nains et Géants. *Revue des Revues*, Jan., 1898, *cit.* Bassoe); but Bateson, in his *Mendel's Principles of Heredity* (1909), makes no reference to them among the various inherited deviations known to occur in man. He emphasizes, however, that there are many elements which enter into the single "character" we call height.

One need but recall that Goliath of Gath had a giant brother whose staff was as thick as a weaver's beam, and that Goliath's four sons were giants, one of them with twenty-four fingers and toes (II Samuel, xxi, 16–22; I Chronicles, xx, 4–8). Doubtless, too, Rabelais based his story on something more than folk-lore.

ested in heredity, has traced a tendency to the condition through several generations, there being two distinct strains in the family—a "virile type" with early hirsuties; and a smooth-skinned, comparatively hairless and what he calls "girlish type" in which adolescence is delayed usually until the seventeenth or eighteenth year, as was true of himself and his brother. The variations in this family apparently descend in sex-limited fashion to the males, similar to the descent of such dominants as hæmophilia and color-blindness.

It would seem, therefore, that there may be certain inherited deviations which may in all likelihood be attributable to transmissible ductless gland properties; and, as has been suggested in discussing the cases which showed these traits, a functional glandular instability may exist in these individuals which makes them more susceptible, under stress, to alterations which border on the pathological.

Apart from any inherited constitutional peculiarities, five of the patients in this series have shown some minor CONGENITAL DEFECTS—rather too large a proportion to be merely coincidental. In Case XXVII there was a persistent allantoic canal. In Cases X and XIII the toes were short and malformed with a tendency toward webbing. The median maxillary incisors were wanting in Case XXII, and Case XLVI showed a supernumerary nipple.

It has been suggested that in certain individuals there may be some inherited instability of the gland which makes it susceptible to alterations which border upon the abnormal so far as its functional activity is concerned. Such periods of stress may occur during the course of the more serious physiological epochs of life, through accidental or operative glandular mutilations, or as a consequence of disease, notably infections.

Unquestionably TRAUMATISM plays a certain rôle, for in six of the patients in this series (Cases V, VIII, XII, XXI, XXXIII and XLVI) the early symptoms were apparently incited by an antecedent cranial injury. It will be noted that they are all patients with subsequent hypopituitarism, associated in all but one instance with an interpeduncular tumor.

The incidence of trauma in relation to intracranial tumor in general is well recognized, and represents, roughly, about 15 per cent. of our series of some 300 cases. Whether the injury is actually causal or merely serves to stir into activity a latent process, is of course uncertain.

Physiological Epochs.—A d o l e s c e n c e , p r e g n a n c y and the c l i m a c t e r i c doubtless represent periods of life in which occur the most striking and abrupt of all the physiological alterations to which mankind is heir. In some animals there are other more notably seasonal states, such as h i b e r n a t i o n , which can be placed in the same category. These conditions are often coupled with more or less definite clinical manifestations on the part of the ductless gland series—changes which, for obvious reasons, have been recognized in the sexual glands and thyroid, but which have been largely unobserved in the case of the other glands, owing to their inaccessible position.

This is particularly true of the hypophysis, for though experimentalists have shown that the interrelation between the interstitial cells of testes or ovary and the pituitary body is a most intimate one—far more intimate than with the thyroid, for example—the utter inaccessibility of the struc-

ture, which has precluded investigation by prescribed clinical methods, as well as the unfamiliarity with the symptoms brought about by its states of over- or under-activity, has left the whole subject in obscurity.

Puberty.—The possibility that, coincident with the adolescent period, there may be functional alterations in the hypophysis has not, so far as I am aware, been clinically suggested or histologically demonstrated. However, there are reasons for believing that at this age demonstrable changes occur which, in association with a primarily unstable gland, may so upset the biochemical processes of the body that they cross the boundary from a purely physiological state to one which borders on the pathological (cf. Case I).

The rapid increase in stature which occurs during the adolescent period is in all likelihood due to an hypophyseal hyperplasia.* The same factor may well account for the occasional spontaneous glycosurias characterizing this period of life; and it is not improbable that during this epoch the tolerance for carbohydrates is actually low in all individuals, as is possibly true also in pregnancy, in which state a transient physiological hyperpituitarism is more clearly demonstrable, as we shall see.

It is conceivable, furthermore, that the acquirement of secondary sexual characteristics, which Tandler,[244] Hanes[117] and others have definitely shown to be related to the interstitial cells of Leydig in the testis, may in some way be dependent upon a primary hypophyseal stimulus—a conjecture which would seem to receive some support from the bizarre cases of early sexual development with certain types of hypophyseal or pineal tumor. The reverse condition—namely, failure to acquire secondary sexual characteristics, stunting of growth and a high rather than a low tolerance for sugars—due to hypophyseal insufficiency is easily produced by partial experimental extirpation in preadolescent animals.

Hibernation.—Here the possibility of a controlling hypophyseal factor is equally conjectural, though it is a natural assumption—granting the low tissue metabolism of these states—that the ductless gland series, which so intimately affects metabolic processes, is functionally dormant.†

In clinical conditions of hypophyseal deficiency somnolence is a conspicuous feature. It is suggestive, at all events, that in both the physiological state of hibernation and the pathological condition of hypopituitarism there is a tendency toward unwonted sleep, a subnormal temperature and slowed pulse, a lowered metabolism with diminution of the carbon dioxide output, a definite hypæsthesia of the body to painful stimuli, and, in the males at least, an hypoplasia of the sexual glands. In the clinical states, moreover, these symptoms can be largely alleviated by glandular administration.

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* Tandler[244] has observed that normal individuals in whom adolescence has occurred at an early age remain, as a rule, short-limbed, whereas those with a tardy adolescence are long-limbed. In other words, early sexual development indicates early closure of the epiphyses: delayed puberty (of which artificial eunuchism represents the extreme example) suggests delayed epiphyseal union.

Rotch and Smith[218a] have approached the subject of epiphyseal union as an indication of physiological development from quite a different point of view.

† Gemelli has found in the marmot that after hibernation the hypophysis, presumably awakening from a state of functional inactivity, shows an apparent cellular hyperplasia with mitotic figures.

Hansemann, in the same animal, found during hibernation no interstitial cells of Leydig; but when the dormant period had passed these cells increased so greatly in number that the testis on section resembled a sarcoma.

This matter has been briefly discussed in relation to the history of a patient (Case XVI) in whom long periods of somnolence were seemingly seasonal. It is not improbable that a periodic functional exhaustion of the gland may bear some relation to normal sleep, the causation of which has been the source of much speculation among physiologists.

Pregnancy.—In this state the hypophyseal relationship is somewhat more clear. Hypertrophic changes in the gland with cellular hyperplasia have long been noted (Compte (1898),[47] Launois and Mulon (1903)[153] and others). Furthermore, that functional alterations occur comparable to those which more obviously affect the thyroid has been surmised from the remarkable cases which from time to time have been recorded (von Reuss *et al.*) of fleeting bitemporal hemianopsia during the last weeks of the multiparous gravid state, as well as from the not infrequent cases in which hypertrophy of the turbinates (66 per cent. Freund; 85 per cent. Zacharias) and temporary enlargement of the lips and nose, with thickening of the tissues of the hands and feet, have suggested acutal transient acromegalic changes.

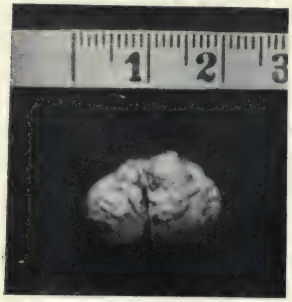

FIG. 298.—The full, rounded gland of pregnancy, weight 89 cg., with the disproportionately small posterior lobe showing above. Primipara: death from postpartum hæmorrhage.

Pointing, too, in the same direction are the not infrequent glycosurias of pregnancy; and I am under the impression that a notable increase in stature has been described as occurring occasionally in young pregnant women.

Thanks to the conclusive studies of Erdheim and Stumme,[74] the question of functional hypertrophy has passed beyond the stage of conjecture. These authors have demonstrated, by actual measurement of 150 glands of pregnant women, not only the occurrence of a definite color change from grayish-red to white, but also an increase in the size and weight of the structure. Thus the average weight of the gland of primipara was found to be 84.7 cg., the observed maximum being 110 cg.; whereas the average of nullipara was 61.8 cg., with a maximum of only 75 cg. After parturition there occurs a subsidence, the involution being complete at the termination of the period of lactation. With a succeeding pregnancy a further augmentation takes place, the glands of multipara averaging 106 cg., with an observed maximum of 165 cg. (Fig. 298).

What is more important, definite histological changes are apparent in the pars anterior, where there occurs a multiplication of large neutrophilic elements which are apparently derived from the normal chromophobe cells (Hauptzellen). The acidophilic cells no longer dominate the field, and such of the characteristic eosin-staining elements as are to be found are seemingly crowded away from the sinuses which they once lined (Figs. 299, 300). It is many months after parturition before the acidophiles regain their former predominance.

In the pars anterior of pregnant dogs, cats and rabbits, as well as of the few human glands that we have examined, the picture described by Erdheim and Stumme has been present. Moreover, a marked hyperplasia may also be seen in the epithelial investment of the pars nervosa—at least this has been observed in the canine gland.

In this connection the demonstration by Ott[201a] and by Schäfer[227] and Mackenzie[172a] of a powerful galactogogue substance in the posterior lobe should be recalled. Of interest also is the fact that posterior lobe extracts have a specific action upon smooth muscle and particularly upon uterine fibres, intravenous injections in pregnant animals almost invariably producing abortion. It is not impossible, therefore, that normal parturition may be incited by the secretion of the hyperplastic gland, which reaches its culmination in the last month of the gravid state and which periodically discharges with the menstrual cycle.

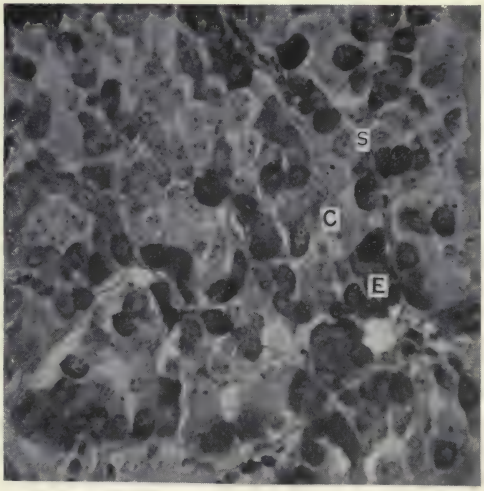

FIG. 299.—Section from centre of pars anterior of healthy young adult (Bensley fixation; iron hæmatoxylin), to show disproportion of eosinophiles (*E*) lining the sinuses (*S*), the chromophobe cells (*C*) being centrally placed.

It is apparent from the foregoing that within normal functional limits wide anatomical variations may occur. It is readily foreseen, therefore, that ultrafunctional transitions with some manner of secretory perversion may be easily acquired. For example, repeated involutions from the chromophobe hyperplasias of the Erdheim and Stumme type may bring about a physiologically inactive condition of the gland which borders on the pathological; and thus a measure of hypopituitarism may in all probability account for the excessive adiposity, loss of hair, asthenia, subnormal temperature and so on, not uncommonly seen in women after multiple pregnancies. On the other hand, the transitory clinical manifestations of glandular overactivity already mentioned may persist, or even increase, after the termination of the pregnancy.

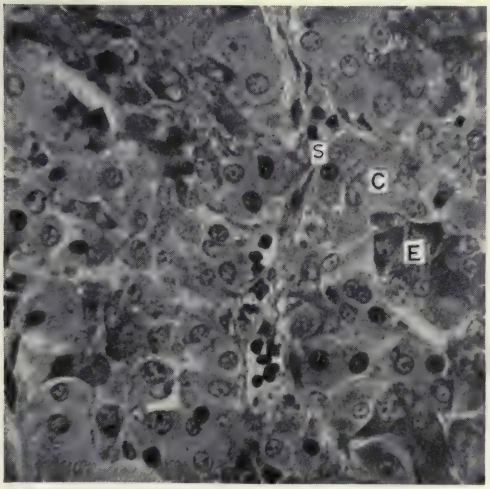

FIG. 300.—For comparison with Fig. 299. Gland of full-term pregnancy, showing predominance of chromophobe elements (*C*) which now line the sinuses (*S*), the few eosinophiles (*E*) being crowded to the centre of the cell columns (Bensley fixation; iron hæmatoxylin).

Thus in two patients in our series (Cases II and XXIV) a glandular hyperplasia apparently incited by pregnancy overlapped the pathological and led to fixed acromegalic changes with ultimate secondary

hypopituitarism. Again, in Case VII there may have been some relationship between the disease and the preceding multiple pregnancies, though the patient showed no definite clinical traces of an overactive stage, unless the X-ray of the fingers (Fig. 61) may be so interpreted. The main features from the outset were those of glandular insufficiency, and it is notable that menstruation after a long period of amenorrhœa was re-established by organotherapy.

The gonadal and hypophyseal interrelation is, of course, far more complex in the female than in the male, in whom but one element—the cells of Leydig—is concerned, whereas in the female both interstitial cells and corpus luteum exercise an important rôle in interglandular relations.

Infections.—The incidence of acute infectious processes is apparent in a number (seven at least) of our cases, more notably among the individuals exhibiting primary hyperpituitarism. This possibly could be expected from analogy with the thyroid, for more or less outspoken hyperthyroidism is far from an infrequent accompaniment or sequel of acute febrile processes.

In two of the acromegalics (Cases XXVIII and XXX) the onset of symptoms was coincident with a tuberculous infection. In Cases II and XXIX also there was an immediate history of some obscure pulmonary affection. In another (Case XXIII) it is evident that the overgrowth followed a severe typhoid and pneumonia at the age of 14, though the present tumor manifestations with signs of glandular insufficiency and dyspituitarism did not appear until the 38th year. Messedaglia (1908)[187] in his elaborate monograph has fully commented on this ætiological factor, one of his patients likewise having had an antecedent typhoid.

Emphasis has been laid, especially by Delille,[63] upon the fact that histological changes are apparent in the hypophysis of individuals who have succumbed to infections. This we have noted in our canine series, for what we regard as a functional hyperplasia of the posterior lobe is commonly seen after distemper or meningeal infections. Gemelli, Guerrini, Rénon, Thaon and others have also described anterior lobe hyperplasias which have been occasioned by experimental infections, and according to Delille the changes which occur in rabbits after the inoculation of the typhoid bacillus are particularly striking. Undoubtedly the gland normally reacts to bacterial intoxications, and the fact that animals subjected to a partial hypophysectomy are so susceptible and so unresistant to infections is possibly attributable to the deprivation of some antagonistic substance which the intact gland is capable of evolving.

If these alterations, therefore, actually represent functional hyperplasias brought about by the need for some antitoxic property contained in the gland's secretion, it is not unlikely that other manifestations of functional activity will in some cases prove to be clinically observable, just as they are in association with the functional hyperplasias of pregnancy.

For example, there seems to be a general impression among physicians that particularly *in typhoid a notable augmentation of skeletal growth may take place* when the illness affects young adolescents. Though there seem to have been no specific studies—at least of common knowledge—relating to these matters, nevertheless there have been occasional comments in the literature upon the surprising increment in stature which has occurred during convalescence of young individuals from typhoid—in extreme cases amount-

ing, in a few weeks, to two inches or more. Under these circumstances, moreover, the rapid growth of the long bones has not infrequently been associated with tenderness over the epiphyseal zones, and transverse atrophic striæ (*vergetures*) due to stretching of the skin may even occur in the neighborhood of the joints.

An interesting assemblage of these cases has been made by Jean Chanal,[38] who attributes the phenomenon to a direct effect of the bacillus of Eberth in stimulating the epiphyses to unusual activity. It, however, seems much more probable that the condition is attributable to a functional pituitary hyperplasia with liberation of the pars anterior hormone of growth in unusual amounts.

Arteriovascular Lesions.—These, under certain conditions, may unquestionably jeopardize the activity of the gland by a diminution of its blood supply, despite the abundant provision which nature has made against any such mischance by surrounding the structure with an arterial and venous circle.

We have observed one striking example in a young woman of 36 with extensive cerebral endarteritis, presumably of luetic origin. Following an attack of hemiplegia, definite evidences of hypopituitarism occurred—a rapid gain in weight from 114 to 187 pounds, amenorrhœa, a subnormal temperature and slowed pulse. Though the X-ray showed a normal sella, there were definite chiasmal symptoms, with homonymous hemianopsia, headaches, choked disc on a primary optic atrophy and so on. A subtemporal decompression was performed. Nine months later there was another and fatal hemiplegic attack, and a postmortem examination showed an extensive obliterative endarteritis of the internal carotids and Willisian vessels.

SYMPTOMATOLOGY

In reassembling the symptoms manifested by these various patients, they will be taken up *seriatim* in the same order in which they are presented in the individual case reports, namely, as (1) neighborhood symptoms, (2) general pressure manifestations, (3) the secretory or glandular symptoms proper, and (4) the polyglandular manifestations.

THE NEIGHBORHOOD SIGNS AND SYMPTOMS

These, let it be emphasized again, serve merely as an occasional "sign-post" to the lesion, and so long as the road continues unfamiliar it is well to stop and read carefully the directions. By so doing one may learn to take the proper path when the directions are confused or when the sign-post is actually wanting.

Subjective Discomforts.—These deserve first consideration. They are probably much more marked when the gland itself is the seat of hyperplasia or tumor than when the growth is interpeduncular and intradural, as is the case with the majority of the benign lesions causing primary hypopituitarism. Only in an advanced stage do the latter growths occasion intracranial discomforts of any severity.

These HEADACHES, usually bitemporal, often severe and persistent when there is considerable glandular hypertrophy, are presumably due to the

distention of the glandular envelope. Our operative experience with Cases XXVI and XXXVI would seem to point conclusively in this direction, for the subjective discomforts were immediately relieved in each case by splitting the tense capsule of the gland, which was only moderately enlarged. This suggests that distention of the pituitary capsule is a not infrequent cause of some of the common periodic cephalalgias of obscure origin.

The pituitary headaches are quite different in type from those incited by a general increase of intracranial tension such as occurs when the hyperplastic gland has burst through its envelopes and extended widely into the cranial chamber (*e.g.* Cases II and V). Under these latter circumstances one may expect to find some measure of choked disc superimposed on the primary optic atrophy.

It is notable that the pituitary headaches proper often subside coincident, presumably, with a stationary process or with a full distention of the dural capsule and widening of the sella. It is remarkable, however, that the fossa can become greatly enlarged by slow pressure distortion with but a minimum of discomfort (*e.g.* Case XVII) even at the outset.

A few of the patients have suffered from cephalalgia of less clear origin. In one acromegalic in particular (Case XXX) severe racking headaches occur only when he is in an upright position and subside promptly with recumbency. Possibly the abnormally low blood pressure may play some rôle in this, the discomforts resembling those which follow lumbar puncture with withdrawal of large amounts of fluid.

Photophobia is another frequent source of complaint (*e.g.* Cases XXIII and XXVI). It is often associated with deep orbital discomfort and sensitiveness of the eyes to pressure.

Deformation of the Sella Turcica.—X-ray studies of the pituitary fossa, to which attention was first called by Oppenheim in 1899,[201] have proved a most useful adjunct to the investigation of hypophyseal disease.

Isolated single-plate examples of marked sellar deformation accompany a number of the more recent case reports, and special studies of the subject have been made by Fuchs,[92] Erdheim,[71] Giordani,[99] Jaugeas,[133] Köhler[147] and by Fisher.[84] Schüller's admirable atlas (1905)[233] should also be consulted.

Sellar deformations, however, are merely of accessory value to the symptomatic manifestations, for we must realize that both extreme hyperpituitarism (*e.g.* Case XXXVIII) and extreme hypopituitarism (*e.g.* Case VII) may exist with but little if any alteration in the shadow cast by the bony encasement of the gland (Fig. 301).

There are three types of the pathologically deformed and enlarged sellas which may be distinguished: (1) those associated with thickening of the clinoid processes and dorsum ephippii; (2) those with thinning from pressure absorption of these parts, and (3) those with more or less destruction of all outlines. There are, of course, many subvarieties and much overlapping of these types, and a radiographic study of the subjacent sphenoid, as Gibson's studies[97] would indicate, is of importance as well as the mere configuration of the sella itself.

The First Variety.—Here the enlargement is accompanied by thickening of the walls, and as this type is confined to the cases of acromegaly and gigantism (cf. Cases XXIV to XXXII) which are uncomplicated by adeno-

matous struma formation, it is probable that the bony thickenings are merely a feature of the tendency toward osseous overgrowth. In one instance (Case XXX) there had been such a degree of bony overgrowth as to mask the actual enlargement of the sella until this was made evident by stereoscopic plates.

Unquestionably, in almost all cases of acromegaly and gigantism, even without the secondary tumor formation shown by Cases I and II, certain evidences of pressure atrophy of the sellar dorsum and base will occur, for a process of bone absorption always accompanies the osteo-formative process. This is apparent in the thinned floor of the sella in Case XXXII (Fig. 155), but a much eroded floor and dorsum is far more characteristic of:

The Second Variety.—That marked thinning with perforations of the sellar floor as well as of the dorsum may occur in acromegaly is shown

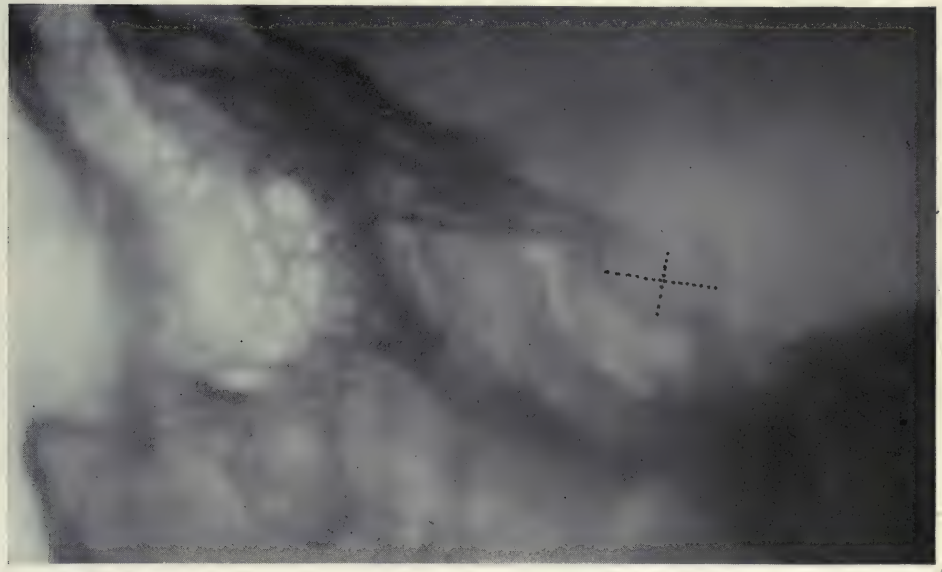

Fig. 301.—Fairly normal sella (nat. size) with average large profile measurements (1.5 cm. by 0.9 cm. in depth). Taken after subtemporal decompression in a case of brain tumor. (For comparison with the distorted shadows accompanying the case reports.)

by the accompanying figure (Fig. 302), but such a condition is comparatively rare in this disease unless the hypertrophic gland has undergone the terminal metamorphosis into an adenomatous struma (as in Cases I and II).

These great distentions with absorption of bone from pressure atrophy are far more common in the cases of advanced hypopituitarism (Figs. 148 and 161 of Cases XXI and XXIII furnish good examples) associated with a primary glandular struma. In the earlier stages there occurs a simple spherical distention (cf. Fig. 129, Case XVIII, Fig. 134, Case XIX, Fig. 82, Case IX, and Fig. 89, Case X); whereas in the advanced stages there is an extreme spherical ballooning out of the fossa, which projects far into the sphenoidal cells, the bony capsule being so thin as to cast a hardly perceptible shadow.

In THE THIRD VARIETY there occurs a more or less complete absorption of the dorsum and a downward dislocation of the base, so that the sellar landmarks, with the usual exception of the anterior clinoid processes, are effaced. This change may be brought about either by the transformation of a primary glandular hyperplasia into the type of malignant struma which is capable of bursting its dural capsule and invading the cranial chamber (Fig. 106, Case XII), or conversely by the downward pressure of an interpeduncular growth which deforms and absorbs the subjacent sphenoidal bone by its progressive enlargement (Fig. 118, Case XVII).

Neither of these processes, however, is incompatible with the preservation of a fairly distinct sellar shadow of average size, though the walls are

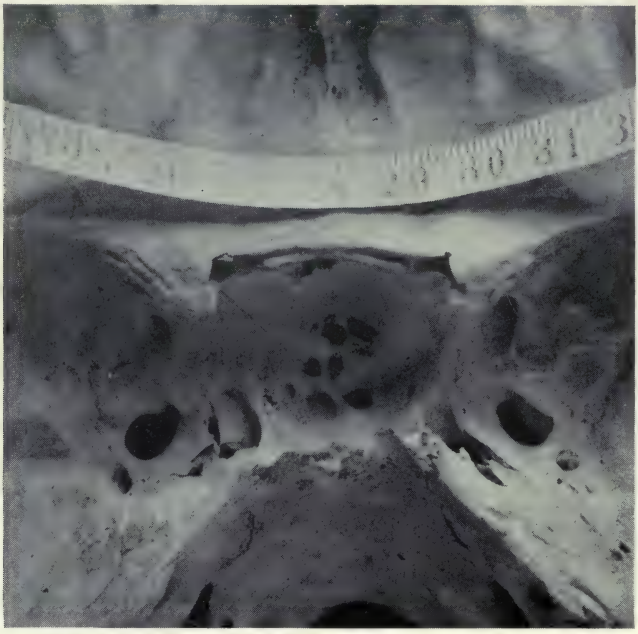

FIG. 302.—Photograph of sella turcica of an acromegalic with hypophyseal struma, from the pathological department of the Johns Hopkins Hospital (natural size). Note the extreme separation of the anterior clinoid processes with narrowing of optic foramina: the fragmentary and eroded condition of the dorsum sellæ: the several perforations in the sellar base. (Compare X-ray Fig. 304.)

apt to be thinned and show erosions. It may be exceedingly difficult in some cases of this type to identify the outlines on a single plate, the more so since there is apt to be a general downward displacement of the entire sphenoidal region. Hence many exposures from different angles may be necessary, and it is not an uncommon experience, after several plates have shown a supposedly complete absorption of the dorsum sellæ, to unexpectedly secure a negative on which the fine line of a thinned and elongated dorsum is clearly apparent (Fig. 155, Case XXII).

The chief difficulty in radioscopic interpretation is unquestionably met with in these cases of superimposed extrapituitary growths. Only when the growth has led to a marked sellar deformation, as in Case XVII, are the

X-rays of great diagnostic value in cases of this type, for we have seen (*e.g.* Case VIII) that the sella may be fairly well preserved, even though the tumor is enormous and has been of long duration.

Equally important, and more difficult to interpret, are the abnormally small sellas which accompany the primary glandular hypoplasias of the young (cf. Figs. 234 of Case XXXIV, 287 and 306). It has been our experience in these conditions that unusually heavy shadows are cast, particularly by the dorsum sellæ. Exceedingly small fossæ are occasionally seen (Fig. 303).

The subject unquestionably deserves further investigation with the aid of stereoscopy, and "snap-shot" exposures possible with the modern quick plates make cranial radiography a new and important field. Some preliminary studies have been made in this direction in collaboration with Dr. Walter Boardman.

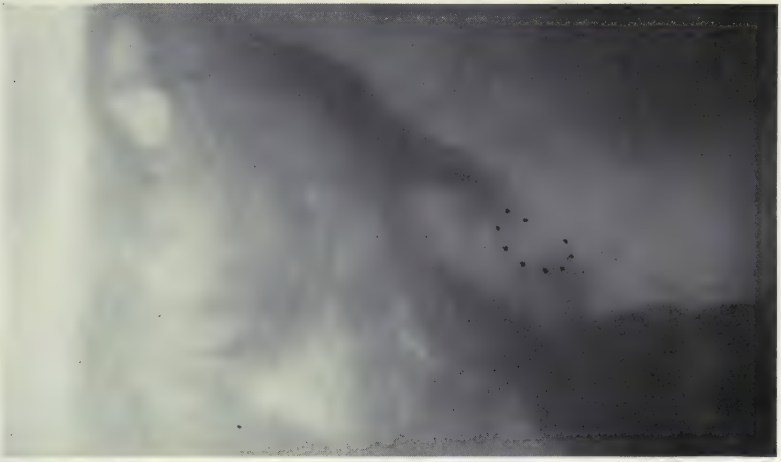

FIG. 303.—Radiogram of extremely small sella of an undersized young adult with presumed primary hypopituitarism.

Radiographic Interpretations. There are, of course, a multitude of variations even in presumably normal states, variations which affect the position of the sella as well as its size. Needless to say, a direct lateral view on a single plate may show no trace of the pocket, for in long-standing lesions the sphenoidal region is apt to become depressed downward so that the sella is hidden by the zygomatic arches or obscured by the shadows which are cast by the floor of the temporal fossæ (Fig. 304).

Under these circumstances *stereoscopic plates* are absolutely essential, and indeed they are desirable in all cases, the head being tilted slightly so that one may look directly into the fossa. Only in this way can the full depth of the pocket be clearly made out, and this is particularly true of lesions associated with ballooning of the sellar floor which has allowed the gland and its capsule to project far into the sphenoidal cells. It is often necessary to make repeated exposures from different points of view, for it is disconcerting to secure a negative which discloses a well-formed, though displaced and thinned-out, sella when previous ones have seemingly shown a complete obliteration of the structure.

This has been our experience in one or two instances in which subtemporal decompressions have been performed owing to the presence of general pressure symptoms, a subsequent radiogram having brought into clear outline a previously obscured sella.

Profile radiographic measurements exceeding 15 mm. anteroposteriorly and 10 mm. in depth may be looked upon as indi-

cating an enlargement (cf. Fig. 301), and, as our cases have shown, the adult profile dimensions may vary from a sella of this size to one considerably over 30 millimeters. The skeletal measurements, given by Arthur Keith[141] for the normal, average 10 to 12 mm. antero-posteriorly, 14 to 15 mm. transversely and 8 mm. in depth. A slight magnification naturally occurs on the X-ray plate.

Usually a greatly enlarged sella may be expected when neighborhood symptoms are pronounced, though, as stated, this is not necessarily true of primary interpeduncular tumors. On the other hand, neighborhood symptoms may be absent and yet the sella be large, as is true not only of most of the acromegalics and of the giant in this series, but of some of the cases of hypopituitarism as well (*e.g.* Case IX).

With an undistended sella there is often a single clear basal outline, but a *double contour* is often apparent (*e.g.* Figs. 129 and 134) when there has been any considerable dis-

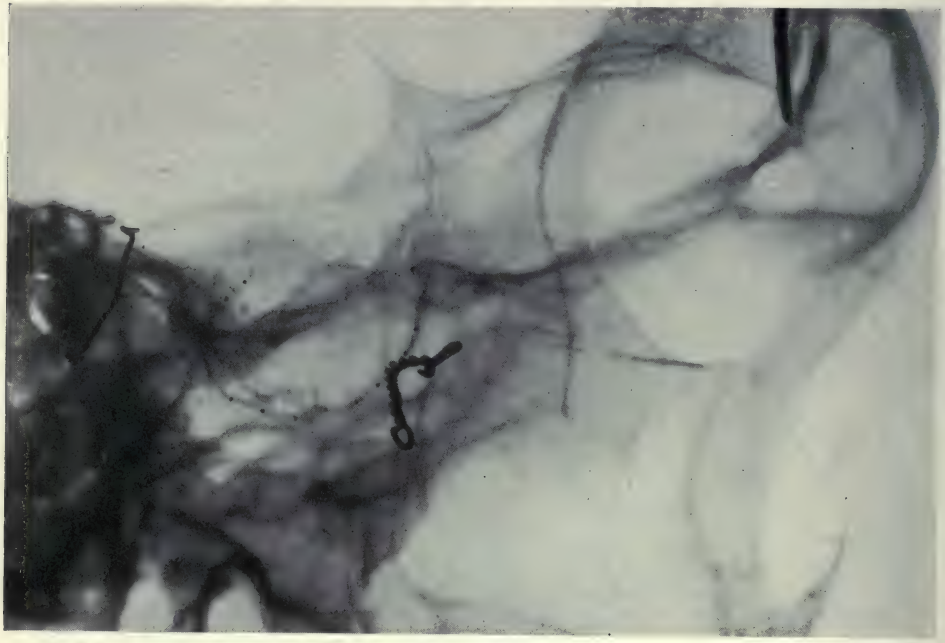

FIG. 304.—Lateral X-ray of cranial base shown in Fig. 302. Dotted line indicates sellar contour, only recognizable with certainty by stereoscopic view.

tention of the fossa. The inner line corresponds with the lateral openings of the fossa; the outer and lower with the downward median bulge of the sellar floor. The lower line will ultimately disappear or become indistinct when the distended floor has undergone absorption from pressure atrophy. However, even with extreme thinning of the base, good stereoscopic plates will often show a trace of this outer line bulging downward almost to the floor of the sphenoidal cells.

Under such circumstances the operator need not expect to enter recognizable sphenoidal cells in approaching the gland from below, for as soon as the anterior sphenoidal wall is opened he will come directly down upon the gland, covered with little more than thinned scales of bone and mucosa. Needless to say, too, the lower of the curvilinear lines will be seen to have disappeared from a negative taken after a sellar decompression.

It is our impression that single plate exposures should be made by focusing directly over the hypophysis perpendicular to the sagittal plane, whereas stereoscopic exposures should be made from the side and above, so that one may look down into the fossa.

Though the patients in our series have been under observation a comparatively short space of time, it has been noted in the interpretations of the case reports that a measurable progressive enlargement of the sella occurred in one or two instances. Thus in Case XIX, one of chromophobe struma with incipient hypopituitarism, the measurements increased from 2.0 by 1.8 cm. to 2.3 by 2.0 cm. in nine months; and again, in Case XXVIII, one of acromegaly, there was a measurable increase from 2.0 by 1.6 cm. to 2.3 by 2.0 cm. between July, 1910, and July, 1911.

It is presumable, therefore, that serial radiograms may under some circumstances be of value in determining whether or not the hypertrophic condition of the gland is advancing. Could this have been determined in some of the cases in this series (*e.g.* Cases XI, XII, and XXI) and a prompt sellar decompression have been performed, the patients might have been spared their present loss of vision—often the most distressing outcome of the malady.

We have seen that, as the result of pressure absorption, defects will be found in the sellar base; and with successful stereoscopic plates they may actually be seen in favorable cases. They may be multiple (Fig. 302) or there may be a single median opening, as in the case of the giant Turner (Fig. 227). Such defects in the sellar base were found by Levi (1909)[160] in some museum preparations of acromegalic skulls, and were interpreted as indicating a persistent craniopharyngeal canal—a conclusion which must be accepted with reservations, inasmuch as a histological examination of the contents of the canal is necessarily precluded in the dried specimens.

Visual Disturbances.—These are the most common and, needless to say, the most serious of all neighborhood signs. The OPTIC NERVES are particularly apt to suffer, whether from an extension of a hyperplastic struma beyond the sellar confines, or from the effects of a primary infundibular growth. Consequently the degree of implication of chiasm, nerves or tracts bears no direct relation to the size of the sella.

Thus in most of the acromegalics (Cases XXIV to XXXII inclusive) there was an enlarged sella without visual disturbance. On the other hand, in the patients with primary hypopituitarism and chromophobe struma (Cases XIV to XXIII) the visual disturbances were usually profound, though in occasional instances (*e.g.* Case IX), even of lesions of this type with marked sellar enlargement, the optic nerves have thus far escaped.

The ATROPHY is a so-called primary one and the disc shows no œdema except in the late stages, when the growth has reached such a size as to lead to general pressure phenomena—due, in the vast majority of instances, to an occlusion of the foramina of Monro with resultant hydrops lateralis ventriculorum. This complication usually brings on pressure symptoms with some abruptness, with an increase of headache and possibly vomiting; and under these circumstances a choked disc may become superimposed on the atrophic nerve head (*vide* Cases II and XI).

Still, even this sequel cannot produce a neuroretinal œdema if the nerves are completely enveloped in the tumor mass (cf. Case VIII), for the sheath

of Schwalbe can no longer be distended by the tense cerebrospinal fluid—a strong argument in favor of the mechanical *versus* the toxic theory of so-called optic neuritis of tumor.

Of the 23 patients with tumor manifestations, only one (Case VIII) had become completely blind in consequence of a primary atrophy, though another (Case I) was nearly so, and in Case XXII a short period of total amaurosis preceded the operation, which led to a prompt restoration of partial vision. In only one individual in the whole series of patients subjected to operation is the condition uninterruptedly progressing toward blindness—this is an instance of superimposed choked disc with a secondary atrophy (Case XI) following an intracranial extension of the lesion.

It is safe to say that the amblyopia associated with a primary atrophy more often represents a physiological block to light impulses than an actual destruction of the nerves, as the post-operative restoration of vision in previously blind eyes in a number of individuals of the series exemplifies.*

Some degree of EXOPHTHALMOS has been shown by almost all of the patients with tumor: it is rare in the absence of a definite growth. Presumably, therefore, it is purely a local stasis phenomenon (cavernous sinus?) and bears no clinical relation to a sympathetic stimulation or to an associated hyperthyroidism.

Perimetric Deviations.—Some distortion of the visual fields has been demonstrable in all but two of the twenty-three patients showing pronounced neighborhood symptoms (Groups I and II). However, the supposedly typical bitemporal hemianopsia with a vertical meridian which bisects the macula is conspicuously rare in the series. Indeed, in the twenty-one cases there are only three instances of fairly symmetrical bitemporal field defects (namely, Cases X, XVIII and XXIII), and it was fortuitous that the patients happened to be seen in exactly this stage of the process.

Of the remaining eighteen patients, one (Case VIII) was blind on admission, doubtless after a bitemporal hemianopsia, and another (Case XXII) was nearly so, though some vision returned in the nasal fields after the operation. Eleven of the patients (Cases I, V to VII, XIV to XVII, and XX to XXII) were blind in one eye, the process having started as a bitemporal defect in six instances, as an homonymous defect in four and being uncertain in two (Cases XIV and XXI). One of the patients (Case II) showed a typical, and another (Case XI) a fairly typical homonymous hemianopsia.

It becomes apparent from this brief summary, in the first place, that homonymous defects, or tendencies in this direction, are at least half as frequent as bitemporal ones. Indeed, they are possibly quite as frequent; for in a number of the patients who have been referred to us the diagnosis has been based solely on

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* In a patient, totally blind, operated upon in October, 1911, since these paragraphs were written, a large hypophyseal cyst was opened. Four hours later vision had so far returned in one eye that she was able to count fingers (No. 29 of operative table).

Another patient, with a typical bitemporal hemianopsia, showed normal fields the day after operation (No. 40 of operative table).

the existence of a bitemporal hemianopsia, and doubtless there are many in whom an homonymous defect, even though coupled with pallor of the discs, would not have been regarded as equally significant.

Attention has been called by several writers to the coincidence of homonymous hemianopsia with hypophyseal and chiasmal lesions. In the three patients in whom the source of the lateral pressure was disclosed postmortem (Cases II, V and XV) the glandular struma had burst its capsule and extended upward along the left side of the chiasm in two of them, producing a right homonymous defect, and to the right side, with a left homonymous defect in the other.

It is apparent, in the second place, that unilateral amblyopia may occur with but little if any perimetric deviation in the field of the opposite eye (cf. Cases V and XXI).

Finally, and what is perhaps of greater clinical significance, mere tendencies toward temporal defects must be carefully looked for, particularly defects limited to the color peripheries, if one wishes the perimeter to serve in making a diagnosis before the time when crude finger-tests suffice to demonstrate a complete hemianopsia.

Heretofore perimetric investigations of these conditions have been confined largely to the observance of advancing lesions, and, as the process is notably slow, often extending over years, the sequence of the changes is rarely observed. Hence, an exceptional opportunity is given the surgeon to study reversals of the process, which occur at a more rapid rate after the nerves have been in a measure released from pressure by operative procedures.*

A sufficient number of charts have been reproduced with the foregoing histories (*e.g.* Cases X and XIX) to show the method of progress of a hemianopsia. The primary defect usually first involves the color boundaries alone in one upper temporal quadrant. This is followed by a more or less complete temporal hemiachromatopsia, possibly with a "slant" in the upper temporal form field, which gradually spreads downward until most of the temporal field is involved. In all cases the color fields are involved first: the form fields later. The macular area is often spared for a long time, but finally it becomes implicated in turn, first in its temporal half. Finally, the whole central area enters the blind field, and the nasal field in turn progressively shrinks away from the centre. It is to be emphasized that rarely are the two eyes affected in equal degree, and also, that after operation, restorations occur in reverse order.

Though there are, of course, variations and exceptions, this sequence is fairly typical of the progress of the constrictions in the cases with a bitemporal tendency. Hence, it can be readily appreciated that the chance is small of encountering a patient in a stage of the process when a vertical meridian, including the macula, demarcates the blind from the seeing field symmetrically in the two eyes.

J. H. Fisher,[84] in an interesting study of nine cases, reported largely from an ophthalmological point of view, and Arnold Josefson,[135] in his report of

* This will be made the topic of a detailed report in the series of papers in collaboration with Dr. G. J. Heuer on field distortion in cases of brain tumor.

eleven carefully observed patients, both call attention also to the fact that the temporal fields, at least those for form, appear to be lost from above downward.

Abnormal PUPILLARY CONDITIONS are, of course, closely linked with the optic atrophies and perimetric changes. A definite hemiopic pupillary reaction (Wernicke) and a negative oculomotor response to the prism deflection of an image to the blind half of the retina (Wilbrand) may be expected only when half blindness is complete; and, as I have just said, it is unusual for the patient to be seen at exactly this stage of the process. A positive Wernicke reaction can be of value only in the rare cases in which the use of the perimeter is for one reason or another precluded.

In many of the patients, some measure of OCULOMOTOR IMPLICATION was either suggested by the history of periods of double vision, or was obvious from palsies apparent at the time of admission. This is particularly true of the cases with pronounced neighborhood symptoms, due to interpeduncular lesions, whether primary or arising from an extrasellar extension of a pituitary struma (cf. Cases I, VI, VII, XII, XVII, XX). It is notable that even with an extreme distention of the pituitary fossa from a lesion which presumably remains intrasellar there may be no implication of the oculomotor nerves.

Slight nystagmus has been frequently observed even when the ocular movements have been unaffected by palsies.

Other evidences of local implication of the cerebral nerves may accompany extrasellar lesions. ANOSMIA may be complete in such advanced cases as Numbers V, VIII and XI, and in one patient, not included in the series, as the history is somewhat incomplete, anosmia with primary optic atrophy and adiposity were the only signs of the lesion. Post-operative anosmia is a necessary sequel (cf. Case XXVI) of Schloffer's method of surgical approach to the gland, but is obviated by the lower transphenoidal method to be described.

Occasionally trigeminal neuralgia is a source of complaint (*e.g.* Cases XIV and XVII), and Fig. 127 shows the nerve compressed by an interpeduncular growth. Large extrasellar tumors likewise may press upon the cerebral peduncles and cause spasticity (cf. Cases III and V) or add to that which the pressure of an internal hydrocephalus may already have elicited. If the cranial indentation is more marked on one side than on the other there may be an especial exaggeration of the deep reflexes on the contralateral side (Case VIII).

Similarly the uncinate region is not infrequently indented by the growth, and characteristic uncinate seizures with a gustatory or olfactory aura are surprisingly common, there having been seven examples of this type of epilepsy in the series (cf. p. 272).

Evidences of frontal lobe involvement also occur as a result of the direct implication of the lower fore-brain by an enlarging growth (cf. Cases V and VIII). Symptoms thus produced, however, are apt to be merged with the mental deviations attributable to disturbed glandular activity, to be described in a later section (p. 270).

Nasopharyngeal Signs.—Finally, it must not be forgotten that there may be signs and symptoms referable to the nasopharynx. A history of troublesome epistaxis is very common, and the bleeding may be excessive (*e.g.* Cases XI, XII and XIII). It is not unusual for patients to mention an

occasional unexpected and intermittent discharge of mucus into the pharynx (*e.g.* Case X). This probably explains why so many of these unfortunates have been subjected to prolonged treatment for supposed primary sinus disease: doubtless, too, many of the recorded instances of primary optic atrophy in supposed association with disease of the sphenoidal cells may be thus accounted for.

Our operative experiences have shown us the true nature of the process, for in four or five instances, on removing the anterior wall of the sphenoidal cells, a retained mass of tenacious white mucus has been expelled from the cavity at each side of the protruding sellar base, which extended so far downward into the cells as to partly occlude the sphenoidal foramina. A similar retention of mucus has been disclosed postmortem in two individuals (Cases V and VIII) in whom transphenoidal operations had not been performed. Occasionally a temporary relief from discomfort may follow the spontaneous discharge of this mucus, as related in some of the case reports (*e.g.* Cases I and X).

A complete physical examination should always include the retropharynx. In a few of our cases (XI, XVII and XXIII) an actual protrusion of the tumor could thus be seen, and in another, a nodule was visible which was taken for an enlarged pharyngeal hypophysis.

In view of the unquestionably close relation of many states of dyspituitarism—particularly those of primary glandular insufficiency—to lymph hyperplasia (status thymo-lymphaticus), it is quite probable that there may be a tendency toward adenoid formation in the pharynx, irrespective of the presence of a pharyngeal rest (p. 6) such as Civalleri and Erdheim have described. A number of our patients with primary hypopituitarism have shown large tonsils and adenoids, and in several of them previous operations had been performed. Doubtless in an extensive adenoid operation the pharyngeal hypophysis can be removed with the median tonsil itself. But whether this can have any influence on the economy, one way or another, is conjectural.

In two of the patients (*e.g.* Cases IV and V) with infantilism, Dr. Crowe observed in the pharynx a small median cleft or pit, which we at first interpreted as a relic of Rathke's diverticulum. In all probability, however, it represents the *bursa pharyngea* of Killian (1888),[143] which lies somewhat posterior to the pharyngeal hypophysis and has a different developmental origin, representing presumably the position of the notochord.

Cerebrospinal Rhinorrhœa.—This was discussed at some length in relation to Case XIII, the only instance in the series of true cerebrospinal fluid escape, which must be distinguished, of course, from rhinorrhœa of accessory sinus origin. Boyd[24] has reported a case, evidently one of hypopituitarism with strumous degeneration ("sarcoma") of the gland, which was associated during life with a true cerebrospinal rhinorrhœa. It is notable that after transphenoidal operations there is no persistent mucous discharge. Indeed, there is surprisingly little rhinorrhœa of any kind after the first few days, and the experience with Case XIX shows that the mucous membrane quickly covers the area of denudation.*

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*In three of our later cases (Nos. 36, 38 and 40 of the operative table) there has been a temporary post-operative cerebrospinal rhinorrhœa with recovery.

THE GENERAL PRESSURE SYMPTOMS

These have been considered in part in relation to the subjective discomforts which accompany sellar distention. However, the diagnostic error which led us to overlook a cerebellar cyst in Case XXXVIII serves to illustrate the ease with which pressure disturbances from a general increase in intracranial tension may be misconstrued. Doubtless every patient with pituitary manifestations, in whom there is any suggestion of pressure symptoms, should be scrutinized with the possibility in mind either of an intracranial extension of an hypophyseal struma or of a coincident growth elsewhere.

The condition is easily recognized when a choked disc is superimposed on a primary atrophy (*e.g.* Cases V and IX), but it must be borne in mind that a large intracranial extension of an infundibular tumor (as in Case VIII) may so envelop the optic nerves as to prevent the crowding down of cerebrospinal fluid under tension into Schwalbe's sheath. Hence, even with extreme tension from a large tumor and secondary hydrops of the lateral ventricles a neuroretinal œdema—ordinarily the most reliable sign of tension—may be wanting.

Headache, therefore, may be the only symptom, for vomiting—an inconspicuous feature, indeed, of most intracranial tumors—is particularly unusual in these patients. There are, however, certain telltale signs of pressure which are of value. Among these are the extracranial evidences of venous stasis, shown by the fullness and tortuosity of the palpebral venules as well as of the larger veins of the scalp. The X-ray also is of value in this connection, for it may show not only the signs of pressure enlargement of the diploetic channels but also points of pressure atrophy brought about by the small arachnoidal herniations of Wolbach.

An operative prognosis hinges very largely on the presence or absence of these signs of a general increase of intracranial tension, which may be so extreme (Cases V and VIII) that measures directed toward its relief, irrespective of the hypophyseal implication, are largely futile.

THE GLANDULAR MANIFESTATIONS

Modifications of Skeletal Development.—The rôle of the hypophysis in growth is of primary interest, and before briefly analyzing the conditions presented by the patients in this series it is advisable to review the present interpretation of the glandular relationship to body stature.

Experimental investigations, as we have seen (p. 15), have thrown merely a negative light on the matter in so far as they have made clear that hypophyseal deficiency—presumably of pars anterior—inhibits complete skeletal development; and it has been suggested that this may be due to a consequent lowering of the phosphorous and calcium content of the blood.

So far as I am aware, there is only one certain experimental method of inciting skeletal overgrowth, namely by early castration, and it is probable, after all, that, as Tandler suggests, the skeletal elongation characterizing eunuchism is merely an expression of a secondary hypophyseal hyperplasia.

No one has definitely succeeded in simulating a fixed state of functional overactivity of any member of the ductless gland series, whether by feeding experiments or by heterogeneous transplantations.

Unquestionably there is some chemical process at work behind the actual glandular hyperplasia (Vassale, Cagnetto *et al.*), and until this can be determined we must not only await the experimental reproduction of states of functional overactivity but must also continue to speak of the glandular change as the primary incident in the process.

In order to acquire a definite knowledge of these processes it has been necessary to turn to the study of such clinical syndromes as are presumed to be an *expression of overactivity* of one or another of the glands of internal secretion; and only in the case of hyperthyroidism have we any fairly clear views.

Acromegaly and gigantism have not unequivocally been proven to be expressions of hyperpituitarism (anterior lobe hyperplasia), and still more circumstantial and less convincing is the evidence which couples hyperadrenalism with the syndrome of hypertrichosis, adiposity, pigmentation and high blood pressure; hyperpinealism with a syndrome of precocious sexual development, overgrowth and adiposity, to which further reference will subsequently be made; and hyperthymism with the status thymo-lymphaticus.

So far, however, as functional hyperplasia of the other ductless glands is concerned—of the parathyroids, pancreatic islets, corpora lutea and interstitial cells of Leydig—we are as yet completely in the dark, though it is quite probable that the clinical expression of states of exaggerated secretory activity of each of these glands will some day be pointed out.

On the other hand, the clinical *expression of primary deficiency* on the part of the individual glands is better understood, partly because definite clinical syndromes are more easily coupled with postmortem demonstrations of destructive lesions than with demonstrations of hyperplasias, and partly because a state of glandular deficiency can be experimentally produced with comparative ease.

Skeletal Overgrowth.—It must be confessed that the view attributing the skeletal changes of acromegaly and gigantism to a functional hyperplasia of the pars anterior, with the production of an excessive or perverted type of secretion, is not universally accepted (*e.g.* Parisot's recent analysis[203]), for though testimony accumulates in its favor, proof positive has possibly not as yet been afforded.

Conceptions of Acromegaly. There have been four different views which deserve consideration.

(1) Marie, at first regarding the process as a general dystrophy, in his later papers (1888-89) attributed it to diminished hypophyseal function.*

(2) Massalongo (1892), Tamburini (1894), Benda (1901), Modena (1903) and Fischer (1910) have championed the view that the condition is due to hyperfunction and is often associated with an hypertrophy or adenomatous hyperplasia of the gland, for it is not produced by destructive or malignant growths.

According to Benda, Lewis, and Erdheim, the elements chiefly concerned in the hyperplasia are the eosinophilic cells, and there may actually be no gross enlargement of the gland.

(3) Gauthier (1892), Strümpell (1897), Vassale (1902), Guerrini (1905) and Cagnetto (1907) regard the acromegalic changes as due to some underlying nutritional disorder which affects metabolic processes, the hypophyseal enlargement being a consequence and not the cause of the malady. (This view, of course,

* In a personal communication (August, 1911) Professor Marie says: ". . . . qu'après avoir passé par l'une et l'autre hypothèse,je n' ai plus actuellement aucune position précise dans cette question, et je me demande si la solution n'est pas sur une voie un peu differente. C'est à dire que la fait important consiste pent-être moins dans la *quantité* du fonctionnement de l'hypophyse que dans les *modifications* et les *altérations* de la *sécrétion*."

must be accepted by all, though it is something of a quibble, for just as in hyperthyroidism, there must be some underlying biochemical disturbance which brings about the glandular hyperplasia).

(4) A few, as Silvestrini, Arnold (1894), Warda (1901) and Petrén (1907), on the basis of presumably negative hypophyseal findings, conclude that acromegaly bears only an accidental relation to pituitary lesions.

Parisot (1910), emphasizing the reciprocal relations of the genito-thyro-hypophyseal triad, does not consider that an hypophyseal lesion, though of frequent occurrence, is alone sufficient for the production of the characteristic syndrome of acromegaly. However, in view of Erdheim's findings (1909) of an eosinophilic hyperplasia of an accessory glandule in a case of acromegaly, the hypophysis itself being normal, all other negative hypophyseal findings must be accepted with reservations.*

Certainly most of the circumstantial evidence in our possession points in the direction of an oversecretion, whether normal or pathological; and this is at least the most acceptable present working hypothesis.

The *arguments favoring the hyperpituitarism conception of acromegaly* may be assembled. 1. In the first place, in the only known conditions associated with skeletal overgrowth one usually finds an hypertrophic enlargement of the gland or a histologically demonstrable hyperplasia—primary in the case of acromegaly and gigantism, secondary in the case of eunuchism.

2. Moreover, experimental extirpations of the hypophysis, with resultant glandular deficiency, have been shown to retard skeletal growth, and comparable effects are known, clinically, to be the consequence of glandular implication in tumor, injuries or processes of disease in young individuals.

3. Again, as the cases in this series illustrate, acromegaly tends in the long run toward a state which our experiments have shown to be brought about by glandular insufficiency—adiposity, high sugar tolerance and so on—and the fact that a low assimilation limit for carbohydrates characterizes the early stages of the disease suggests a coincident period of functional hyperplasia.

4 Further, partial removal of the presumably hyperplastic pars anterior in certain cases of advancing acromegaly, notably in those of Hochenegg and in a case of my own (Case XXVI), have led to seeming remissions in the symptoms, in the same way that partial removals of the hyperplastic thyroid in Basedow's disease induce remissions in the symptoms of hyperthyroidism.† Conversely, hypophyseal feeding has been shown to cause an accentuation of symptoms.

However, even if we accept these arguments favoring an original anterior

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* Acromegaly may occur in association with other diseases of the nervous system. In Case XXXVIII it accompanied a cerebellar cyst with hydrocephalus. Nicolas and Favre[196a] describe its occurrence in a case of Recklinghausen's disease, and a similar coincidence of the two maladies has been present in a patient recently observed in Dr. Barker's service. It may be noted in this connection that several of the patients (*e.g.* Case XXVIII) have shown fibroma molluscum—a feature of acromegaly to which Marie called attention. Petrén[205] and others have described cases with syringomyelia.

† The improvement that has been observed in patients with hypopituitarism (dystrophia adiposo-genitalis) after partial removal of the struma is not actually an argument opposed to this view, though it has been advanced as such.

Under these circumstances we are not dealing with an anterior lobe hyperplasia—at least with one of chromophile elements—but rather with a chromophobe struma or with a tumor compressing the gland. Naturally the removal of some of the growth may allow the compressed pars anterior elements to regain in a measure their functional activity.

lobe hyperplasia, there can be but little doubt that in the greater number of cases as the malady progresses glandular insufficiency supervenes. A somewhat similar view was advanced in 1894 by Tamburini,[243] that the process occurs, in two phases, with a primary stage of glandular overactivity which later, through some toxic action of the secretions from the gland, has a deleterious effect on the constitution. Thus, if I understand him correctly, the transition stage into dyspituitarism which we regard as an evidence of beginning secretory insufficiency, he attributed to the elaboration by the diseased organ of some substance harmful to the organism and leading to a condition of cachexia.

Our studies on carbohydrate tolerance have shown with some conclusiveness that in acromegaly the individual's capacity to assimilate sugars progresses from a state in which carbohydrates are rapidly metabolized to one in which they are merely stored; in other words, from a state in which there is either a low assimilation limit or an actual hyperglycæmia with glycosuria to one in which alimentary glycosuria is difficult or impossible to elicit. This would appear to be the strongest argument in favor of the transitional character of the disease from hyper- to hypopituitarism, on which such great emphasis has been laid throughout this study.

The transition doubtless may occur at a stage of the malady before the skeletal manifestations of hyperpituitarism have become outspoken, and thus the acromegalic changes may be inconspicuous (*e.g.* Case XII); or it may occur after the characteristic fixed bony changes have become full-blown (*e.g.* Case XXVIII); or it may possibly not occur at all and the disease may run a self-limited course after a stage of hyperpituitarism, with the restoration of a fairly normal glandular activity (*e.g.* Case XXXI). It must be kept in mind, therefore, that the osseous changes on which the diagnosis is usually based are not the disease itself but merely the expression—necessarily a permanent one—of a period of the malady in which hypersecretion with skeletal overgrowth occurs.

Whatever interpretation may finally be given these much-discussed matters, one point at least is now generally accepted, namely, that the skeletal changes in gigantism and acromegaly are expressions of the same morbid influence—whether or not this influence is related to a perversion or otherwise of the hypophyseal activity.* Thus Massalongo's generalization (1892)[183] that acromegaly is delayed gigantism, has been amply endorsed by Woods Hutchinson (1898)[132] and others.

The formula of Brissaud and Meige (1895),[27] *"L'acromégalie est le gigantisme de l'adulte, le gigantisme est l'acromégalie de l'adolescent,"* was changed by Launois and Roy (1904)[155] for the better into *"Le gigantisme est l'acromégalie des sujets aux cartilages épiphisaires non ossifiés, quel que soitl eur âge."* Thus, if all giants are not acromegalics, they are destined to acquire their attributes with advancing years, provided epiphyseal ossification occurs before glandular overactivity subsides.

Certain recorded cases are interesting in this connection. Thus, Claude (1897) reported a case of acromegaly in a girl of 19, of usual height, with

* The distinction drawn by Guinon and Sternberg is rather an academic one. They attribute gigantism to an exaggeration of a normal process, whereas they regard acromegaly as an actual disease.

skiagrams showing complete ossification of the cartilages, the supposition being that gigantism would have resulted had the epiphyses not become united at this unusual age. A similar observation was made by Franchini and Giglioli in the case of a young girl evidently acromegalic, who was but fourteen years of age. Doubtless without the demonstration of precocious epiphyseal union, all cases of acromegaly which have been described as occurring in childhood are contestable.

It is sometimes difficult to say where gigantism ends and acromegaly begins (*e.g.* Cases XXIII and XXX), for many giants ultimately acquire acromegalic features and many acromegalics (*e.g.* Cases I and XXXI) show undoubted manifestations of gigantism. My own explanation, based on the view of transient hyperpituitarism, has been indicated in the comments upon these cases.

The disease, in short, *is the expression of a functional instability of the pars anterior, doubtless brought about by some underlying biochemical disturbance which leads to the elaboration of a perverted or exaggerated secretion containing a hormone that accelerates skeletal growth* (of the long bones if epiphyseal union is incomplete, of the acral parts if epiphyseal ossification has taken place). *Since the functional disturbance is probably a fluctuating one, with periods of increase and remission*—as is known to be true of hyperthyroidism—*epiphyseal ossification may occur during a period of quiescence in the disorder. A subsequent recrudescence with resumption of the perverted functional activity will then serve to superimpose acromegalic manifestations on primary gigantism.* Acromegaly, in other words, cannot precede gigantism but always occurs, as in our typical example (Case I), as gigantism which has become acromegalized.

It is, of course, possible that the condition, as in some giants, may progress for years without remissions, but it seems probable from our study of the cases in this series that the ultimate tendency in all instances is toward a final and permanent state of relative glandular inactivity.

With this interpretation, therefore, the skeletal changes typifying acromegaly persist, though the actual malady has ceased, just as exophthalmos may persist though hyperthyroidism has ceased. We shall see that in conditions of primary hypopituitarism in young individuals, the hormone of growth presumably being wanting, there is failure on the part of the bones to elongate even though the epiphyses remain open.

There have been 17 individuals in our series who have shown a definite tendency either to skeletal overgrowth as a whole (4 cases) or to bony enlargements of the acral parts alone (13 cases). The former, therefore, fall in the category of gigantism, and in all of them the symptoms can be traced to a fairly early period of life. Should a condition of hyperpituitarism supervene in an individual in whom epiphyseal union possibly has been delayed until the beginning of the third decade or later, an increase in stature naturally could occur even at this late date (cf. Case XXX). However, in all of the ten outspoken acromegalics of this series epiphyseal union (radial) was complete, without a trace of the lines of ossification. In the adult individuals (*e.g.* Cases XII and XXI) who showed evidences of dyspituitarism—*i.e.*, present glandular inactivity with a trace of former overactivity shown by suggestive acromegalic changes—the epiphyses likewise were closed.

In the overgrown individuals exhibiting no acromegalic tendencies it is interesting to note that traces of the epiphyseal lines are still demonstrable (Case XXIII at 39 years; Case XXXII at 36 years; Case XIII at 27 years of age)—an evidence possibly of delayed closure. However, though the radial line is still apparent in these individuals, phalangeal ossification is complete, and the natural explanation of their failure to acquire acromegalic tendencies —as they have been acquired, for example, in Cases XXX and XXXI—is that there has been no recrudescence of hyperpituitarism since the epiphyseal fusion occurred.

These 17 cases with more or less skeletal overgrowth comprise six females and twelve males. All of them are white: we have seen no definite instances of acromegaly in the negro race. Nine of them, it will be observed, were exempt from neighborhood symptoms, though they all showed enlarged sellas. Of patients showing pronounced tumor symptoms only two (Cases I and II) had outspoken acromegaly, so that it may be inferred that the transformation of a functionally hyperplastic anterior lobe into a malignant struma is relatively infrequent.

Throughout this discourse little has been said regarding skeletal changes other than those affecting the sellar configuration, the phalanges of the hand and the radial epiphyses. These, however, are the three most useful and most convenient sources of information, at least where adult types of overgrowth are concerned.

The condition of the phalanges is a particularly dependable sign. From the external appearance of the hands we would not have ventured, in Cases XII, XVII and XXI, to predict that the X-ray would betray evidences of former, even slight, hyperpituitarism; for it is probable that the thickenings of the soft parts may in a measure subside, whereas the bony exostoses are necessarily permanent. Even in the more advanced cases, when phalangeal alterations are conclusive, there may be no mandibular prognathism, no spacing of the teeth, no rounding of the shoulders, no sternoclavicular enlargement and but little change in the cranial configuration.

Arthur Keith (1911)[141] has pointed out a definite resemblance between the configuration of the acromegalic skull, with its undershot jaw, large frontal sinuses, etc., and that of prehistoric (Neanderthaloid) crania, and further emphasizes, as did Freund in 1782, the anthropoid characteristics as a possible evidence of atavism. He has shown that the separation of the teeth is not so much due to an enlargement of the jaws as to a heaping up of the alveolar arches—an effect of mild traumatism in stimulating bony overgrowth; and the phalangeal and other exostoses he attributes to a similar cause in association with the points of musculotendinous attachment.

Skeletal Undergrowth.—For skeletal development to be modified by glandular insufficiency the process must take its start before full stature is attained. Naturally, the more marked cases are those in which the glandular insufficiency occurs before adolescence, though a state of hypopituitarism which is inaugurated even later in the second decade will doubtless dwarf the stature. This is true, likewise, of deficiency in other members of the ductless gland series—in the thyroid, the adrenal and the thymus, as is known both from clinical and experimental observations.

Though resulting largely in an academic discussion as to the significance of terms, the question of skeletal infantilism, dwarfism or nanism has aroused much interest, particularly among French writers. Lorain, some years ago, characterized as "infantilism" an arrest of development which affects the mass of the individual rather than any special organ, causing nothing more than disability, delicacy and smallness of the body, and a genital dystrophy (cf. Case IV) such as may result when tuberculosis or the cardiopathies affect young adolescents. The individual, in other words, is merely an adult in small mould.

Brissaud (1907)[26] objects to calling this condition "infantilism" and agrees with Meige that the term should be restricted to an anomaly of development in which the general morphological characteristics appertaining to infancy persist in a subject who has passed the age of puberty.*

A similar discussion, it will be recalled, has been raised by Strümpell in regard to skeletal overgrowth—true giants being merely overgrown individuals, whereas pathological giants are those suffering from morbid gigantism.

On Brissaud and Meige's interpretation the condition "infantilism" includes other factors than stature, notably the development of the generative organs. Hence, infantilism is a term which might be ascribed not only to the giant Turner of this series but to all the patients with hypopituitarism in whom the glandular deficiency antedates full adolescence (*e.g.* Cases V and XIV).

Recently, Meige and Bauer (1911)[184] have further elaborated this subject, and Bauer has introduced the term chétivisme to distinguish the infantilism of Lorain—an arrest of development with conservation of the relative adult proportions of the body—from true nanism or infantilism, in which certain morphological characteristics of infancy are retained. "Nanisme complet" is the superlative of "chétivisme," just as cretinism is of myxœdema.

Most of these discussions of the French school have centered around the developmental consequences of hypothyroidism, and the rôle of the hypophysis has entered but little into them. In the comment upon Case IV of this series—spoken of as a case of infantilism of the type Lorain—mention was made of the fact that Levi has described a typical instance of the condition (Fig. 39) in which there were marked radioscopic sellar changes; and it is quite probable that pituitary insufficiency may play a part in these, as it does in the dystrophies of a different type associated with adiposity, which have been more the subject of interest in late writings.

Innumerable examples of skeletal undergrowth, coupled with sexual dystrophy, have been recorded in the medical literature, and there are doubtless divers ætiological factors which give rise to divers types, in many of which the pars anterior of the hypophysis may play an insignificant rôle or, indeed, none at all.

To select a single instance, Byrom Bramwell[25] records, in his admirable Clinical Studies, a case entitled "Infantilism: No Apparent Cause."

> A sexually and physically infantile man (Fig. 305) with the appearance of a pre-adolescent but who was actually 27 years of age. His body was hairless and there was no beard. The genital organs were infantile: the voice juvenile. He was but four feet tall. Adiposity was marked: weight 67 pounds. Mentality unaffected. His only complaint was of occasional headache.

One may compare the body configuration of this individual with Figs. 83 and 236 of Case IX and Case XXXIV—the small tapering extremities and characteristic distribution of the adiposis. In view of the similarity of the condition to dystrophia adiposo-genitalis, the case is suggestive of preadolescent hypopituitarism without neighborhood symptoms. (An X-ray, December, 1911, disclosed an abnormally small sella; Fig. 306.)

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* *Vide* the discussion before the Société de Neurologie de Paris in 1900 on the occasion of Babinski's presentation of a case of what we should now call dystrophia adiposo-genitalis. (*Revue Neurologique* 1900, VIII, p. 533.)

It is not unlikely that under the terms *ateliosis* and *progeria*, introduced by Hastings Gilford[105] to designate "continuous youth" and "premature old age," examples of pituitary disease may have been incorporated. It will be recalled that C. A. Herter[124] described a type of infantilism which is clearly attributable to chronic intestinal infection;* and Osborne and Mendel[185] have shown that feeding young rats with isolated proteins markedly inhibits their growth though normal weight is maintained. Other ætiological factors have been fully considered in an excellent paper by George Peretz.[204a] Hence it is unwise to lay too great stress on anything other than the possibility of an indirect hypophyseal participation in the dwarfed stature characterizing the many types of infantilism.

Of the 38 individuals comprising the first three groups of our series—instances of supposed primary hypophyseal disturbance—there are 21 in

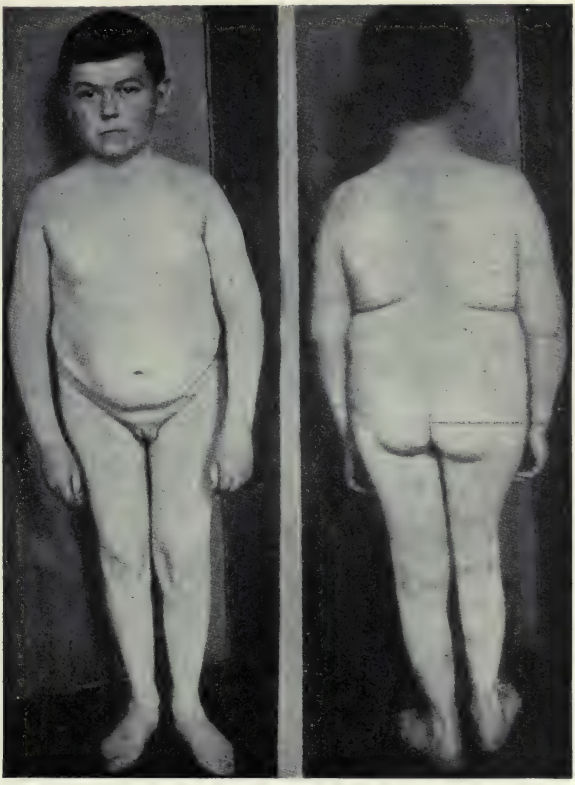


FIG. 305.—Byrom Bramwell's case of "infantilism." Aged 27; height 4 feet (122 cm.).

whom the process from the outset was presumed to represent a condition of glandular underactivity. In eight of these the condition originated at a sufficiently early age to definitely modify stature (Cases III, IV, V, VIII, X, XIV, XXII), though none of them would be called dwarfs, and the ex-

*Through the kindness of Dr. Francis H. McCrudden of the Rockefeller Institute, I have had the opportunity of studying, from an hypophyseal standpoint, two of Herter's original patients, and though it is possible that a disturbed pituitary function may be an element in the infantilism, there can be but little doubt that the nutritional disorder is the underlying factor.

pression "infantilism", if used, could apply only to the interrupted puberty of some of them. It is notable, however, that all of the 21 individuals have a moderately low stature, averaging in the neighborhood of 5 feet 6 inches (168 cm.).

When hypopituitarism dates from the adolescent period there occur changes other than the mere failure of full development of the long bones. Apart from the feminine disposition of the associated adiposis, to which further reference will be made, the males actually possess a feminine type of skeleton, with broad pelvis and a certain degree of genu valgum. Notable, too, is the smallness and delicacy often shown by the extremities; and the tapering type of hand (Fig. 243) contrasts markedly with the *"type en long"* (Fig. 55) of gigantism and the *"type en large"* (Fig. 196) of acromegaly which Marie has differentiated.

In most of these cases the X-ray shows not only a tapering terminal phalanx but also persistent epiphyseal lines or well marked traces of them. It is interesting that under these circumstances, with every opportunity for bony elongation, the "hormone of growth" which is in excess in hyperpituitarism, is wanting.

Some of these individuals, furthermore, in whom the hypopituitarism is associated with a large struma, bear a certain undefinable facial resemblance (*e.g.* Cases V and XVIII), which appears to be due to what has been spoken of in the case reports as a maxillary prognathism, in contradistinction to the mandibular prognathism characterizing acromegaly. It is my impression that this is brought about by some deformation with forward displacement of the sphenoidal bone in consequence of the marked sellar distention, which slightly increases the prominence of the maxillary portion of the face.

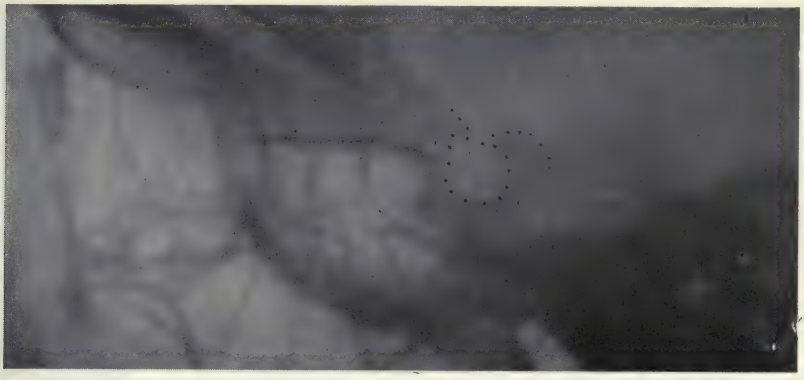
Cutaneous and Subcutaneous Changes.—The hypertrophic alterations which occur in the skeletal coverings in hyperpituitarism, particularly those of the epidermis itself, are familiar. These external thickenings, which are largely responsible for the coarse features of acromegaly, include not only an increase in the size of the hair follicles, but also an hypertrophy of the papillæ with enlargement and activation of the secretory glands, so that the skin becomes greasy and moist.

There is also an augmentation in the connective tissue of the subcutis, which may even extend to and involve the muscles, giving the tissues a dense, boggy feel, with an apparent increase in depth of the furrows of face and hands. The tendency to hypertrichosis is marked in many of these individuals (*e.g.* Case XXV) during the period of activity of the process.

With the transition to glandular insufficiency a certain retrogression in the cutaneous expressions of the malady may take place, such a retrogression as is hardly possible in the case of the bony hypertrophies. This process is a very slow one and may escape notice except on the part of an intelligent and observant patient. Such a change has undoubtedly occurred in one of the outspoken acromegalics (Case XXVIII) of the series; and a postoperative change of the same character which occurred more rapidly in Case XXVI makes it appear that a large part of the thickening and bogginess of the subcutaneous tissues must be due to an accompanying œdema (cf. Case XXIV).

The cutaneous features of primary hypopituitarism are quite the reverse. Here the skin, except in the older patients, is smooth, transparent and notably free from moisture. In some instances (cf. Cases III and XXXIV) it has a peculiarly infantile smoothness, and may even suggest a subcutaneous œdema, which, however, does not pit on pressure. Though the hair of the scalp may be abundant, it is otherwise on the body, for the axillary and pubic hair may be almost completely wanting, or, in the males, may assume a feminine type of distribution. The nails are apt to be small, thin and underdeveloped and, as Crowe has pointed out, do not show the crescents at their base. When hypopituitarism originates in adult life there is a tendency for the hair, even of the head, to become thinned.

Pigmentation is a conspicuous feature of many of the adult states (cf. Cases XXIII and XXIX), and, as it is apt to be associated with asthenia and



Kindness of Dr. Byrom Bramwell.

FIG. 306.—Small sella of case of infantilism, shown in Fig. 305.

a low blood pressure, it is natural to ascribe it to an associated adrenal insufficiency, though it hardly reaches the degree of bronzing seen in some of the Addisonian examples of adrenal tuberculosis.

ADIPOSITY.—The acquirement of an excessive subcutaneous deposit of fat is one of the notable clinical features of many of these cases, and often so far dominates the picture as to lead to its inclusion in the various designations of the malady—adiposis dolorosa, adiposis universalis, dystrophia adiposo-genitalis, adiposis cerebralis. A remarkable series of examples has been gathered from the literature by Eugene Grahaud (1910).[102]

When actually of hypophyseal origin, we are inclined to attribute the accumulation of fat to a posterior lobe insufficiency. All of the patients in the series who, after a period of primary hyperpituitarism, began to show evidences of lowered glandular activity, have acquired some measure of adiposis, and an increase in weight has been an early feature in the larger number of those exhibiting signs of primary hypopituitarism.

The tendency to adiposity shown by dogs surgically deprived of a large part of the gland has already been described (p. 14) as a feature of experimental hypopituitarism which we have come to couple with the acquirement of

a high sugar tolerance. The extraordinary power of these animals, and their clinical counterparts, to assimilate excessive amounts of sugar can be accounted for in no other way than by the transformation of the carbohydrates into fat.

It has been pointed out that during the sugar feeding tests, in states either of experimental or clinical hypopituitarism, the individuals show a rapid accretion in weight (*e.g.* Case XXXV); and noteworthy in this connection is the demonstration of a markedly subnormal sugar content in the blood in one of the patients at least (Case XXIII).

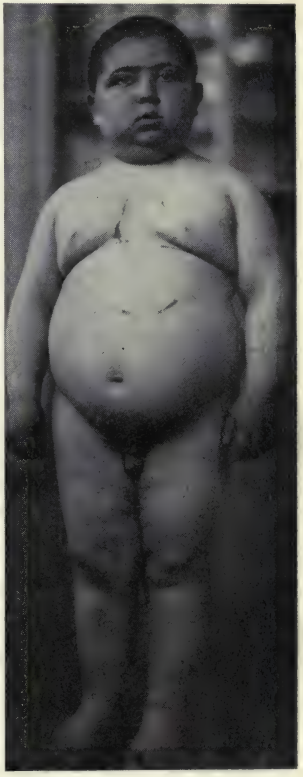
It would seem, therefore, that the sugar metabolizing powers of the body are largely in abeyance; and the associated subnormal temperature, with subjective chilliness and drowsiness, would appear also to indicate a low ebb of tissue oxidation. The condition, as heretofore stated, shows many points of resemblance to hibernation, which may therefore represent a purely physiological cycle of glandular inactivity.

We have attributed this particular symptom-complex of adiposity, high sugar tolerance, subnormal temperature, slowed pulse, asthenia and drowsiness to a secretory deficiency of the posterior lobe; and a further argument in favor of this view is the reverse condition—namely, the emaciation, spontaneous glycosuria with hyperglycæmia, and the slightly elevated temperature—which follows posterior lobe administration. This counterpoised state can be brought about experimentally even in a normal animal by the injection of posterior lobe extract in excessive amounts; and a number of the case reports (*e.g.* XVI, XXXIV and XXXVI) speak in favor of a similar, though less striking, effect produced by administering glandular preparations by mouth in conditions of glandular insufficiency due to morbid states.

The adiposity of hypopituitarism is a generalized one—not limited solely to the panniculus—though its bedside recognition is necessarily restricted to the character of the subcutaneous disposal. The fat shows, postmortem, certain peculiarities of color and consistency which suggest a different chemical composition from "normal panniculus;" and it is worthy of a differential analysis. It furthermore invades the organs, and, in the liver particularly, there is often an extraordinary replacement of the cells by fat globules (cf. Fig. 73).

It is, of course, well known that an increased deposition of fat may occur in association with deficiencies on the part of other of the ductless glands than the hypophysis. This is true of the sexual organs, of the thyroid, and possibly, too, of the pineal and adrenal glands. However, "hypophyseal adiposity" would appear to be far the most frequent type, due in all probability to the fact that the posterior lobe secretion, which contains, as we have shown, what may be regarded as a hormone essential to carbohydrate metabolism, is so easily obstructed by divers intracranial lesions. This has been discussed in considering the patients included in Group IV (p. 191); and emphasis was laid on the fact that any cerebrospinal fluid obstruction is, in its effect upon the infundibular stalk, equivalent in a measure to the direct pressure implication of a superimposed tumor. From this point of view most cases of adipositas cerebralis—a term introduced by Schuster in 1900, according to Frankl-Hochwart—are, in reality, of pituitary origin.

Childhood Types.—The so-called cerebral adiposity—in all likelihood an adiposity of hypophyseal origin—is particularly common in youth; and when coupled with genital dystrophy and skeletal underdevelopment, as is often the case, and when manifestations of intracranial disorder are present, its recognition becomes easy. In all cases the disposition of fat is fairly universal, with perhaps an especial predilection for the loins, the inner parts of the thighs, the pubes, abdomen, and pectoral, submental and supraclavicular regions. In an interesting study with the report of three striking examples, Neurath[196] has referred to these individuals simply as "Fettkinder" (Fig. 307).



Kindness of Rudolph Neurath

FIG. 307.—Adiposo-genital dystrophy with hydrocephalus following scarlet fever. Age 10: height 109 cm. (normal 130 cm.); weight 36.8 kilo. (normal 30.2 kilo.).

Though some measure of adiposity is a clinical feature shared by all of these cases, nevertheless there are a number of types distinguishable on the basis of other factors. These types differ chiefly in the character of dysgenitalism which they display and in the presence or absence of overgrowth. Thus, in the type of Fröhlich (*e.g.* Case III), coincident with an hypophyseal tumor there is a stunting of growth as well as an hypoplasia of the genitals —the "syndrome hypophysaire adiposo-génital" of Launois and Cléret.[152] In the type described by Marburg there is no pituitary growth; but an internal hydrocephalus, such as may result from a pineal tumor, is accompanied by skeletal overgrowth and a precocious hyperplasia of the sexual organs (*e.g.* Case XLVII). In a third type of hydrocephalic, in the absence of an hypophyseal tumor the obesity and skeletal overgrowth are associated with a genital hypoplasia (*e.g.* Case XXXIV).

Our early experiments demonstrated that adiposity may occur as a consequence of partial glandular extirpation (of anterior lobe, as we thought at first,[53] but of posterior lobe, as we now believe[100]), and it may be assumed, therefore, that in clinical cases the deposition of fat is due to deficiency rather than to any perversion of secretion, even in the cases of large glandular strumas.

On this basis it is evident that a tumor is not essential to the clinical condition described by Fröhlich, for a primary posterior lobe hypoplasia may elicit the same constitutional manifestations. Moreover, as has been indicated in the discussion of the cases comprising Group IV, an internal hydrocephalus is equally capable of producing an insufficiency of posterior lobe secretion, and, at the same time, may apparently either stimulate (*e.g.* Case XXXVIII) or inhibit anterior lobe activity. Hence, coupled with the obesity we may have the combination of overgrowth with sexual precocity (Case XLVII) or the

reverse (Case XXXIV), or of undergrowth with sexual precocity (Case XLVI) or the reverse (Case III).

Adolescent Types.—These are particularly interesting when they occur in the male, for when the condition dates from puberty it is associated either with a *juvenile skeletal configuration* or with *outlines of feminine type.* In the latter cases there is a corresponding disposition of the panniculus, so that the appearance of physical feminism is striking, even including the topography and scantiness of bodily hirsuties (*e.g.* Case V).

There are no good illustrations in our series of this male juvenile type, of which the case reported by Mixter and Quackenboss[189] is a good example. The feminine type is exemplified by Cases V, VIII and X of the series.

Of the many forms of obesity which occur in young women there are no especial features other than the coincidence of amenorrhœa and pituitary neighborhood symptoms, which can be pointed to as distinguishing the adiposities of hypophyseal origin from those due to other agencies.

Adult Types.—In these the adiposity need not be outspoken, but I desire to again call attention to the ultimate tendency toward an abnormal deposition of fat shown in all cases of acromegaly or gigantism. This, coupled with an increased sugar tolerance, is often the first indication of supervening dyspituitarism with insufficient posterior lobe activity. All the patients in Group III, with the exception possibly of Cases XIV and XV, exhibited this tendency, and it was a notable feature of Cases I and II of Group I.

In a few of these individuals there has been some disposition for the fat to occur in lipomatous masses (cf. Cases I, XXXI and XXXII), whereas in the others the adiposis has been evenly distributed.

Possibly no clinical condition of adiposity has been more closely observed than that to which attention was first called by Dercum, under the term adiposis dolorosa, and renewed interest has been aroused in this syndrome by the recent studies of the hypophysis and the demonstration that adiposity is a consequence of experimental ablations.

The matter has been commented upon in relation to Case XXXVII of this series, and in other of our patients Vitaut's four cardinal symptoms of Dercum's disease have been present—the adiposity, tenderness and pains, asthenia, and psychoses. The condition is far more common in women than in men: in the former it is apt to be associated with menstrual disturbances, and the menopause seems to be a particularly predisposing factor.

It is probable that under the caption adiposis dolorosa maladies characterized by obesity of diverse origin have been described. Unquestionably, however, a number of them must be due to hypophyseal deficiency. A pituitary glioma was found by Burr[31] in 1900 in a typical example of the disease. In one of Dercum's cases, McCarthy (1902)[64] found an adenocarcinoma of the pituitary body, with testicular hypoplasia. Price (1909)[210] has reported two cases, in one of which there was an inflammatory lesion involving both thyroid and hypophysis and in the other proliferation of the thyroid with slight changes in the hypophysis. Again, in Lyon's interesting series of cases,[171] a postmortem examination of one of the patients, subsequent to his report, showed an interpeduncular aneurism pressing upon and interfering with the function of the hypophysis. Finally, one of the most remark-

able examples in the literature is that given by Launois and Clèret (1910)[152] of a young woman whose weight increased in a few years from 59 kilo. to 117 kilo. In the pituitary body, which was only moderately enlarged, a homoplastic epithelial tumor which greatly distorted the remaining normal glandular elements was found at autopsy.

However, in other supposed examples of Dercum's disease which have come to autopsy there have been no demonstrable changes. In one extraordinary case that I had the privilege of seeing during life, with Dr. Hickling of Washington—the patient weighing considerably over 300 pounds—a postmortem examination disclosed no obvious hypophyseal lesion, but the brain showed an extreme convolutional atrophy, and the case may be termed one of "adiposis dolorosa cerebralis" of other than hypophyseal origin.

Carbohydrate Tolerance.—On the factor of sugar tolerance, particularly from a diagnostic standpoint, we have leaned heavily throughout this report. The main facts bearing upon the relation of the gland to the assimilation of carbohydrates may be here assembled.

It has long been known that glycosuria is a frequent though not an invariable accompaniment of acromegaly and gigantism—conditions which, for reasons heretofore given, we feel justified in ascribing to hyperpituitarism. Hypophyseal glycosurias, however, as von Noorden (1910)[197] has pointed out, show marked variations in their intensity, differing in this respect from those due to pancreatic disease. These variations can be explained, we believe, on the following basis.

In our canine experiments it was noted that a transient spontaneous glycosuria was often the immediate sequel of certain operative manipulations involving the posterior lobe, but contrary to our expectations further study showed[100] that instead of a persistent lowering of the assimilation limit for sugars the tolerance ultimately rose and remained far above normal. This was shown, moreover, to be a consequence of posterior rather than of anterior lobe deficiency.

It was subsequently observed that patients suffering from unmistakable hypophyseal deficiency associated with destructive pathological processes similarly showed a high, often an extraordinary, tolerance for sugars—these usually being patients who had acquired or who were acquiring adiposity. Further, a majority of the individuals who exhibited evidences of overgrowth from hyperpituitarism (acromegaly and gigantism) were found to possess not a lowered but a high tolerance—an indication of the fact that at least so far as the posterior lobe was concerned they were passing from a state of increased glandular activity to one of lowered activity. They were, in other words, acquiring symptoms of dyspituitarism.

The matter was further tested, both in the laboratory and clinic, by atoning for the functional deficiency through the administration of glandular extracts. It was found, as Borchardt had previously observed, that the intravenous injection of posterior lobe extracts in normal animals could produce glycosuria, and, what was more to the point, that the assimilation limit, which had been greatly raised in consequence of the experimental removal or obstruction of the posterior lobe, could be again lowered to a normal, or even to a subnormal, level by injections or oral administration of extracts (those of the posterior lobe proving far more efficient in this respect than

those of pars anterior, of thyroid or of adrenal). Subsequently it was demonstrated, with Jacobson, not only that the glycosurias produced by administering extracts are associated with hyperglycæmia, so that they do not act after the manner of phloridzin, but also that in states of high tolerance (hypopituitarism) an actual h y p o g l y c æ m i a * may be present. Needless to say, the effect of ether was eliminated in the experiments.

Nor is this all, for during the course of these studies it was found that the cerebrospinal fluid contains a substance which seemingly possesses all the physiological properties of extracts of the posterior lobe itself, the natural assumption being that the secretory products of the posterior lobe—so closely associated with carbohydrate metabolism—are actually excreted into the cerebrospinal fluid.† Hence, it becomes easily understood that any intracranial lesion which serves to obstruct this fluid will prevent the entry of the secretion, dissolved in its fluid medium, into the circulation. This readily explains the accompaniment of the syndrome of dystrophia adiposo-genitalis with diverse intracranial maladies, particularly those complicated by a hydrops of the third ventricle.

The obscurities in regard to encephalic glycosurias, such as those experimentally produced by a *piqûre* (Bernard) as well as those observed clinically in association with tumors or cerebral injuries (cf. p. 172), have been discussed in the paper with Goetsch and Jacobson.[100] A number of so-called sugar centres other than that in the fourth ventricle have been postulated by various investigators, one of them having been assumed to lie in the tuber cinereum. But it must be borne in mind that other of the ductless glands—thyroid, parathyroid, adrenal, etc.—likewise play an important rôle in sugar metabolism, as experimentally shown by the studies of McCurdy,[172] Eppinger, Falta and Rudinger,[69] Underhill and Clossen[252] and others.

Clinically, most of the conditions which have been fully studied lie in the direction of the hyperglycæmias and glycosurias. The glycosurias of pregnancy (Reichenstein)[214] are a notable example; and, as we have suggested, those of adolescence may also be due to a functional glandular hyperplasia which, in all probability, may account for the rapid skeletal growth which occurs at this period of life.

We have already referred to the frequent coincidence of mellituria with pathological hyperplasias such as accompany the early stages of acromegaly. This is especially true of the acute cases—the "acromégalie fruste" of the French[212a]—though it is also a common feature of the early stages of acromegaly of less rapid onset.

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* Most chemico-physiological studies of the sugar content of the blood under diverse conditions have been restricted in the past to states of hyperglycæmia. Porges, however, has demonstrated that a significant hypoglycæmia occurs after adrenal extirpation, and Frank and Isaac have shown that phosphorus produces the same effect.

Underhill,[253] with Kleiner and others, has shown that hydrazine, a drug which, like phosphorus, has a toxic effect on the liver cells, likewise produces hypoglycæmia and can even prevent the glycosuria which a pancreatectomy would otherwise produce.

The fatty transformation of the liver cells with hypoglycæmia in states of hypopituitarism suggests that in this condition likewise there is a disappearance of liver glycogen.

† Carlson and Martin,[33] it must be acknowledged, have failed to substantiate our views in regard to the presence of the secretion in the cerebrospinal fluid. We hope to explain the discrepancies between their and our own results.

In our series we have seen but few examples of early hyperpituitarism, indeed only one patient (Case XXXVIII) with a lævulose tolerance which might be considered below the normal—less than 100 grams. In two others (Cases XXIV and XXV) the tolerance was approximately normal, whereas the remaining acromegalics (Cases XXIX, XXX and XXXII) showed an assimilation limit which averaged up to 400 grams of glucose or lævulose—about as large an amount as can possibly be retained by the most amiable stomach. These individuals had all begun to show definite evidences of hypopituitarism —subnormal temperature, dry skin, adiposity, low blood pressure, etc.

In many of the outspoken cases of primary, rather than secondary hypopituitarism, the high assimilation limit has been even more marked, one of these patients (Case XXIII) being able to retain 450 grams of lævulose with no resultant melituria; and in this case the existence of a persistent hypoglycæmia was demonstrated.

As stated, we have come to regard the sugar tolerance of these individuals as a measure of posterior lobe activity, and it is possible that the degree of hypopituitarism may be determined by an estimation of the sugar content of the blood rather than by the more tedious production of alimentary glycosuria through feeding tests. Certainly the former method would be easier for the patient and more applicable to children, whose stomachs are usually intolerant of large amounts of ingested sugar. However, many of the patients, as has been noted in the case reports, display a definite hunger for starches and sugars, and the acknowledgment of an abnormally "sweet tooth" is common.

It has been remarked that in some cases of acute glandular hyperplasia the polyuria and glycosuria may so dominate the clinical picture that the associated secretory manifestations of other sorts may be long overlooked. We may, of course, meet with lesions of the gland which are accidental autopsy findings and which may never have produced clinical symptoms referable to the pituitary neighborhood. Such a case as the following must make us realize the ease with which an hypophyseal lesion may escape notice. How often in cases of supposed pancreatic diabetes the pituitary gland has been examined I do not know.

Case XLVIII. (Surgical No. 21026.) **Gumma of the hypophysis with glycosuria and polyuria, diagnosed as diabetes mellitus.**

July 14, 1907. E. N. R., a merchant, 32 years of age, admitted with the complaint of headaches. He is one of a family of ten healthy children. The father was a diabetic.

The earlier history is without note. His habits are good. He has been married eight years: he has three healthy children and his wife is pregnant (a healthy child was born three months later).

Present History. Three years ago he had a double otitis media: a mastoid operation was performed without disclosing an abscess. Two years ago he had severe occipital headaches for several weeks, diagnosed as "meningitis." Owing to continued intracranial discomforts, he has been unable to resume his occupation.

Six months ago the headaches were attributed to nasal obstruction, but a septal operation served only to aggravate them. A month later a second attack of otitis media occurred, with rupture of the right drum. Two months ago, after a shaking chill, he had a transient left hemiplegia with great increase of cephalalgia. Since that time, nausea, vomiting, intense headache and vertigo have persisted. His temperature has been subnormal.

Physical Examination. A short, rather overnourished man, weighing 143 pounds, with a pasty complexion, suffering acutely from cephalalgia. There is slight exophthalmos and a low grade of choked disc. Both ears show old perforations—not discharging: no labyrinthine symptoms. There is subjective numbness of the fingers of the left hand, worse during the intense headaches. The examination is otherwise practically negative. The urine is normal: temperature 97°; pulse 70.

A right temporo-sphenoidal abscess was suspected.

July 15. **Operation.** A right subtemporal decompression was performed, with exploration of the tympanic roof and temporal lobe. The dura was very tense. There was a great excess of fluid in the meningeal spaces. The temporal lobe was punctured: the needle entering the ventricle withdrew a large amount of clear fluid. *Operative diagnosis:* serous meningitis (?).

The patient made a most satisfactory recovery from the operation, and was discharged July 24, completely free from his former symptoms. He was able to resume his business affairs.

Nov. 13, 1907. **Readmission.** On a recent life insurance examination sugar was found in the urine, and he returned to the hospital for examination. He has gained 13 pounds in weight. P o l y u r i a and p o l y d i p s i a have been noticed for the past eight weeks, with some return of headaches, with mental confusion, a slowed pulse and a bulging of the area of decompression, which, up to this time, has remained collapsed.

On examination, a definite polyuria is demonstrated: 3150 to 3500 cc. per diem. Sugar is present in the urine in considerable amounts (49 to 52.5 grams). There is no acetone nor diacetic acid.

He responded well to a diabetic diet and was discharged Nov. 30. *Diagnosis:* Diabetes mellitus (?).

Subsequent History. After leaving the hospital he did very well for nine months. In *August, 1908*, there was a sudden return of intense frontal headache, vertigo and vomiting, attributed to dietary indiscretion. He became very drowsy, irrational and disoriented: there was Cheyne-Stokes respiration, projectile vomiting, thick speech, static ataxia, tremor, incoördination of movements, etc. The polyuria persisted. There was no choked disc. A cardiovascular examination was absolutely negative: no arteriosclerosis of the retinal vessels. He continued in this condition until death, which occurred at his home *December, 1908.*

Postmortem Examination. The brain, with the pituitary body, was removed and brought to us for study. There is a marked nodular arteriosclerosis of the cerebral vessels. The leptomeninges are thickened. The basal ganglia (the right especially) show lacunæ from old areas of softening. A s y p h i l o m a, large enough to be distinctly visible to the naked eye on section, involves the anterior and intermediate lobes of the pituitary body.

The above record serves as a woeful example of diagnostic errors. Syphilis was absolutely unsuspected and a vascular sclerosis limited to the cerebral arteries was not considered likely, as the retinal vessels were normal.

It cannot be certified that there was no pancreatic lesion (it is to be noted that his father was a diabetic), but the prompt disappearance of sugar and the persistence of the polyuria, suggesting diabetes insipidus, make it seem probable that the pituitary lesion was responsible for the urinary disturbance. Doubtless the same may be true of other cases which in the past have been diagnosed as diabetes mellitus or insipidus. Assuredly the glycosurias of pregnancy, of adolescence and of cranial traumatism (cf. p. 172) are often in all likelihood as definitely of hypophyseal origin as are those accompanying the early stages of acromegaly. Conditions such as the autopsy disclosed in this patient lend support to this contention.

The relation of glycosuria and polyuria to cranial injuries is a particularly interesting one. The studies made some years ago by Ogden and Higgens[199] of 212 patients suffering from recent cranial injuries, show that in something over 20 per cent. of the severe cases a transient glycosuria may be expected. Indeed, that actual diabetes may be caused by trauma is now recognized, and half of the 50 cases collected by Ebstein were attributed to injuries of the head. Von Noorden (cit. Abt and Strouse[1]) has described a severe case following fracture of the base, with a fatal termination within ten months.

Our conjecture that at least the transient glycosurias of these cases are due to an associated injury of the pituitary body receives some support from

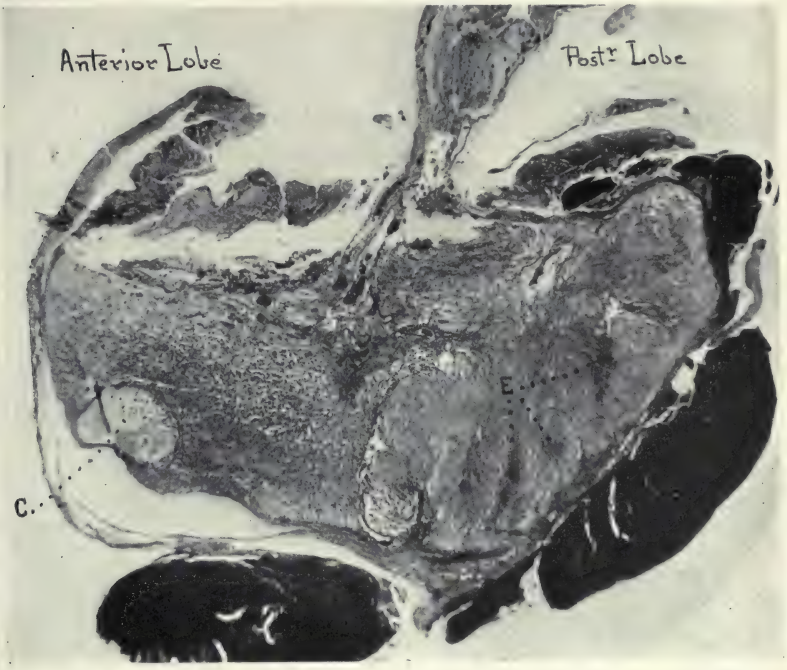

FIG. 308.—Pituitary body from fatal case of basilar fracture with glycosuria. (Mag. × 9; iron hæmatoxylin.) Note free hæmorrhages surrounding posterior lobe (black areas); also multiple extravasations (*E*) in pars nervosa. The anterior lobe, containing cyst (*C*), is free from extravasations: the acidophiles stain black.

the condition of a gland which Dr. John Homans has recently sent for study. The patient died a few hours after the reception of a severe cranial injury, the urine having shown sugar. There are multiple extravasations of blood in and about the hypophyseal posterior lobe, the pars anterior remaining free from evidences of contusion (Fig. 308).

Polyuria and Polydipsia.—As was pointed out in an earlier section, extracts of the posterior lobe were shown first by Schäfer and Magnus to possess diuretic properties of high degree.

In our experimental canine hypophysectomies a post-operative polyuria of some days' duration usually occurred. The amount of urine of some

animals—even of puppies—exceeded 2000 cc. in the 24 hours. This was particularly marked in a number of dogs in whom the excised gland was immediately reimplanted in the cerebral subcortex.[54] In a few instances the polyuria persisted from two to three weeks and subsided as soon as the autotransplant was excised.

We formerly believed that in these experimental conditions the polyuria was probably an anterior lobe effect. In this we were doubtless mistaken. Schäfer[223] has observed that the oral administration of posterior lobe substance in animals causes an increase in the urinary output and, with Stiles, he has shown that it may be used clinically as a diuretic. He found, moreover, that the subcutaneous implantation of the posterior lobe of the gland from one animal to another causes a transient polyuria, which subsides in a few days, coincident, in all probability, with the complete absorption of the secretory products which the implanted tissue contained.

It will have been noted in a great number of our case reports that a period of polyuria and polydipsia has been observed at one time or another during the progress of the disease; and various authors have likewise commented on the occurrence of an increased urinary output in association with interpeduncular tumors. Doubtless the condition has been entirely misinterpreted by many of us in the past.

It is significant that intracranial tumors and cerebral syphilis have long been recognized by clinicians as frequent accompaniments of diabetes insipidus; and, what is still more to the point, primary optic atrophies and hemianopsias have been observed, according to Futcher,[93] in a large number of the recorded cases.*

Thus, the patient, whose history follows, entered the surgical service with a presumptive diagnosis of brain tumor, but the polydipsia and polyuria so overshadowed her other symptoms that she was transferred for study to the medical side, where a diagnosis of *diabetes insipidus* was made.

Case XLIX. (Surgical No. 14698). **Interpeduncular tumor (uncertified). Definite neighborhood symptoms. Diagnosed as diabetes insipidus.**

Aug. 10, 1903. Mrs. M. C. S., 57 years of age, was referred by her son, a physician in Washington, with a diagnosis of presumable brain tumor.

Present Malady. In February, 1901, she began to suffer from *discomforts* in the right trigeminal region, and also from *uncinate attacks* with subjective gustatory and olfactory sensations (the smell and taste of tainted meat), accompanied by nausea and *excessive thirst.*

After a temporary subsidence these symptoms returned (March, 1903) in accentuated form. At this time, severe pain in the right eye was followed by *oculomotor paralysis,* ptosis and a gradual loss of vision. Under the mistaken belief that the symptoms were due to a frontal sinusitis the sinuses were drained, without avail.

In March, also, the intense thirst with marked polyuria reappeared, possibly with glycosuria at the outset (though this has never been assured), for a great number of intractable carbuncles appeared over the body.

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*Claude Bernard, as will be remembered, thought that stimulation of a point in the floor of the fourth ventricle, just anterior to his so-called sugar centre, would produce polyuria. Eckhard, Kahler and others subsequently found that lesions of other areas in medulla or cerebellum had a similar effect. Clinical experience, nevertheless, goes to show that pathological processes, such as tumor, when situated beneath the tentorium, are far less likely to elicit polyuria than those occupying the interpeduncular space.

Physical examination showed a fairly stout woman with a dry and somewhat *pigmented skin* and a remarkably *slowed pulse*, varying from 50 to 70. The right optic nerve showed *primary atrophy* with complete blindness. The left disc was pale. No perimetry: no X-ray.

The *urine* showed a specific gravity occasionally of 100, and marked *polyuria* (6390 cc. in 24 hours). Urea estimated at 9.958 grams: no sugar nor albumen. On many days the total excess of urine over ingested fluids was more than 2000 cc.; measurements over long periods, however, showed the amounts to be practically equal.

She improved greatly under iodides and was discharged with the *diagnosis* of *cerebral syphilis and diabetes insipidus.*

In all probability in such cases the polyuria is due to the excessive elaboration of the hormone contained in the pars nervosa secretion which activates renal secretion. Confessedly, however, there is some difficulty in satisfactorily explaining the diuresis which may accompany hypopituitarism, for one would suppose that individuals in stages of glandular insufficiency would show, more consistently than they do, a lowered urinary output.

In a number of our surgically treated patients an unaccountable postoperative polyuria of extreme grade has occurred. In one individual (No. 34 of the operative table) with a struma, moderate signs of hypopituitarism, and normal urinary output, *an extreme diabetes insipidus promptly followed a simple sellar decompression.* The polydipsia and polyuria persisted for the three months the patient was kept under observation. During the first month, the 24-hour excretion often exceeded 10, and occasionally 11 litres: it subsequently fell to about half this amount.

Diabetes insipidus, moreover, is not infrequently observed after cranial injuries. At this writing, we have a patient under observation with a recent (3 weeks) fracture of the base, who has suffered from an insatiable polydipsia since the time of the injury and who continues to have a daily output of urine averaging over 6 litres, but showing no glycosuria. Nothnagel[198] has described a similar and often quoted case. Our patient was not seen until 48 hours after the injury and it is possible that an immediate transient glycosuria may have been overlooked.

Variations in Body Temperature.—With few exceptions, the patients in our series have not only complained of suffering from cold but have shown an actual tendency to hypopyrexia. The exceptions comprise the early acromegalics (*e.g.* Cases XXIV to XXVI inclusive) and a few of the patients showing neighborhood symptoms, but in whom the manifestations of secretory disorder were inconspicuous. Our interpretation has been that the subnormal temperature was merely one of the many evidences of the lowered metabolic activity characterizing hypopituitarism; and its prevalence in the series is an indication of the fact that the majority of the cases are ones with present glandular insufficiency.

It is to be recalled that a subnormal temperature has been shown (p. 14) to be a characteristic feature of the experimentally produced insufficiencies; that this lowered temperature can be raised to the normal level or over by glandular administration; and, finally, that a definite thermic reaction to the subcutaneous injection of extracts of anterior lobe occurs in animals in whom a deficiency of this part of the gland has been produced. These responses are equally characteristic of the clinical states of insufficiency.

In individuals who show the subnormal temperature of hypopituitarism, a sufficient dosage of whole gland preparation serves to restore the normal temperature, which again drops to a subnormal level if the preparation is withdrawn. Good examples of this are furnished by Cases XXVIII and XXXVI.

So far as the thermic reaction to pars anterior injection is concerned we cannot, as yet, speak with any especial emphasis. Much as the carbohydrate tolerance is a measure of posterior lobe activity in cases of hypophyseal disease, so we have hoped that the thermic response to anterior lobe injection would be available as a measure of pars anterior activity. In the first place, no thermic response or local reaction follows the subcutaneous injection of boiled saline suspension of anterior lobe extracts in normal individuals. When there is a definite insufficiency, however, a thermic reaction of brief duration (resembling in many respects a positive tuberculin reaction) will occur. Examples of these reactions accompany a few of the case reports (Figs. 125 and 249).

Subcutaneous injections of posterior lobe extracts, on the other hand, in cases of hypopituitarism, elicit no thermic response—at least, no response comparable to the anterior lobe effect, though a local reaction is common and a small core of necrosis may occur at the point of injection, due presumably to the vascular constrictive effect of the active principle. Further study is necessary before these reactions can be given any wide clinical application.

Blood Pressure Changes.—As might be expected in view of the known pressor response to glandular extracts, a low arterial tension proves to be a common manifestation of the states of hypopituitarism. The systolic pressure is often below 100 mm. of Hg., even in fairly vigorous individuals, but in the stage at which they begin to complain of asthenia the pressure may register, from time to time, as low as the seventies. A notable example is afforded by our acromegalic giant (Case I).

Even in the case of the patients in whom the gland (anterior lobe at least) was still hyperactive, as in the more recent victims of acromegaly (*e.g.* Cases XXIV and XXV), the pressure was low at the time they were observed. It should be recalled, in this connection, that cardiovascular changes not infrequently accompany progressive acromegaly of long duration (Phillips[206]). This is suggestive of the fact that a high pressure pulse may have been a feature of the condition during the early period of glandular overactivity.

There are a few notable exceptions in the series to the low pressure registrations characterizing states of glandular insufficiency. Thus in Case VIII there was a high tension pulse with other unusual accompaniments of hypopituitarism, such as sweating. In this patient, however, the glandular symptoms were secondary to a large intracranial tumor which doubtless served to modify the usual picture through the elicitation of medullary phenomena. Another notable exception is Case XLV; and here the polyglandular symptoms were sufficiently bizarre to make it seem possible that a condition of hyperadrenalism was present. Indeed, the low blood pressure, with asthenia and pigmentation, of a number of the cases in the series suggests that even when the malady is unquestionably hypophyseal in its origin a secondary change in adrenal activity, verging toward inactivity, may be responsible for these symptoms.

It is to be observed that a s l o w e d p u l s e is likewise a feature of the cases of hypopituitarism throughout the series. The blood examination, moreover, has shown that many of the acromegalics had a slight e o s i n o - p h i l i a, in corroboration of the observation of Messedaglia.

Drowsiness and Torpidity (Hypersomnia).—It has been shown experimentally not only that subnormal temperatures occur in animals deprived of a considerable portion of the gland, but also that after total extirpations the fall in the body temperature may be so great under some conditions as to almost reach that of the surrounding medium. Accompanying these more extreme states brought about by operative deprivation of the gland there is apt to be a profound somnolence, insensitivity to painful stimuli, slowing of pulse and respiration, and, as both Crowe and Goetsch have observed, continuance of the cardiac pulsation, in some cases for many hours after apparent death, the organ often remaining excitable long after removal from the body.

Comment has already been made (p. 233) on the suggestive resemblance of these states of extreme hypopituitarism to the conditions which are known to exist during hibernation, and the fact that hibernating animals acquire some measure of adiposity before entering their long period of somnolence, during which their pulse, temperature, respiration and sensitivity are all subnormal, suggests that a seasonal physiological lowering of the activity of the gland may be in some measure responsible for this little-understood condition. It has even been suggested that normal sleep may bear some relation to resting periods of hypophyseal activity, some animals exhibiting a periodical dormant phase—diurnation, as it is called—intermediate between sleep and hibernation, from which they arouse merely under the stimulus of hunger. In this connection the somnolence of sleeping sickness is naturally recalled.

A most notable example of seemingly seasonal hypersomnia is exhibited by Case XVI, in the discussion of which some reference to the subject has already been made. The same tendency, though in less marked degree, has been characteristic of almost all of the cases of hypopituitarism in the series, many of the patients showing an inclination to doze throughout the twenty-four hours: in others the somnolent periods occurred in more or less definite cycles, with intervening days of fairly normal responsiveness. When these patients become aroused their mental processes are reasonably clear, provided the frontal lobes have not been impaired by pressure. They are apt to prove most reliable and amenable patients, though naturally there is much of the Rip van Winkle in their mental attitude.

In certain instances, however (*e.g.* Cases I, II, V, VIII, XI and XII), there has been a sufficient increase of cerebral tension, due to the intracranial invasion of the growth, to possibly account for the drowsiness; for the somnolence of tumor and of hypopituitarism are not unlike, and may indeed be attributable to the same cause. In both states frequent yawning is a characteristic feature.

It is conceivable, of course, that in both conditions the somnolence may, after all, be due to a secondary hypophyseal inactivity. No attempt has been made to definitely determine this by therapeutic tests in the cases of actual neoplasm, but in states of hypopituitarism associated with a primary pituitary lesion glandular therapy notably improves the mental activity

and lessens the drowsiness (*e.g.* Cases XVI and XXXVI), just as it serves to modify the other expressions of glandular insufficiency.

Still more striking is the effect of glandular administration in conditions of experimental hypopituitarism. We have seen torpid animals in states of extreme hypophyseopriva roused within a short time to a seemingly normal activity by a subcutaneous injection of glandular extract. It would be interesting to observe the effect of similar injections upon animals in the period of hibernation.

A reverse picture, with the exhibition of sleeplessness, would be expected to accompany the functional hyperplasias, but of this we can speak with less definiteness. The only patient in the series (Case XLV) who complained of wakefulness had a somewhat bizarre polyglandular syndrome and high blood pressure. In the few patients (Cases XXIV to XXVII) with still active acromegaly (hyperpituitarism) a peculiar nervous restlessness was manifest which would hardly have encouraged sleep. However, in the advanced cases which had begun to show evidences of insufficiency (*e.g.* Case XXX) drowsiness was as marked as in the individuals in whom hypopituitarism associated with a large struma was the primary process.

Insensitivity has been mentioned as a feature of experimental states of hypopituitarism. It has also been observed in a number of the clinical cases, it having been possible to operate in some instances (*e.g.* Cases IV and XLVI) with almost no anæsthesia and in the majority of the more advanced cases with a minimal amount.

Constipation, often obstinate, is a very common accompaniment of glandular insufficiency. This might be expected in view of the known effect of posterior lobe extracts in stimulating peristaltic activity. We have seen improvement in this respect when glandular therapy has been established on the measured basis calculated to overcome the degree of insufficiency.

Psychic Disturbances.—In one form or another psychic irregularities have manifested themselves in the larger number of the patients. From an ætiological point of view these symptoms fall in two categories: (1) those due to the involvement of temporal and frontal lobes by the pressure distortion of a growth, and (2) those due solely to the effect, on the one hand, of an excess or perversion of glandular secretion, or, on the other, of an insufficiency of secretion. The former have been mentioned (p. 246) with the neighborhood signs; the latter, on which especial stress will be laid, are an expression of deranged hypophyseal function.

(1) An Evidence of Cerebral Involvement.—The line of least resistance for an enlarging struma is upward into the cranial chamber, for the dural envelope of the gland above and at the sides, where it is unsupported by the bony sella, is naturally the first to yield under distention. In the discussion of the hemianopsias it has been pointed out that the capsule may give way at one side, so that the invasion may occur with a lateral rather than a mesial distortion of the chiasm.

An extreme illustration of the way in which frontal and temporal lobes become invaded is afforded by Case V, and Cases II, XI and XII likewise furnish good examples. Fortunately, it is the orbital gyri of the frontal lobes which are primarily affected, and consequently the intellectual proc-

esses may be but slightly impaired. However, in some instances (*e.g.* Case XII) a change in disposition, enfeeblement of memory, disorientation, untidiness and other signs pointing to an inhibition of prefrontal function are fully apparent. Notable always is the utter lack of appreciation of and complete indifference to the existing condition.

These pressure effects are even more inevitable in the case of infundibular growths of extrasellar origin (*e.g.* Cases VIII and XVII). Still, it is remarkable how long mental balance may be retained in the presence of these slowly enlarging growths, even when cerebral, and particularly frontal lobe, deformation is pronounced and there is complete pressure destruction of the intervening olfactory and visual pathways.

(2) An Expression of Hypophyseal Derangement.—(a) *With hyperpituitarism:* Here certain temperamental changes are often apparent, with wakefulness, lack of concentration, indecisiveness, irritability, distrust and so on—psychasthenic states which are not unlike those with which we are familiar in moderate grades of dysthyroidism. Case XXVII is a good example.

When hyperpituitarism dates from early in life, the contrast with former capabilities is less pronounced, the individual usually having been deficient in educational training from the outset. Thus, pathological giants, as a rule, have a low intellectuality, though, as was true of the giant Turner, they may be shrewd and independent. It took Holofernes five years and three months to teach Gargantua his A, B, C's backwards.

(b) *With hypopituitarism:* Of these states examples may be given which show all gradations of disturbance, from mild psychoses to extreme mental derangements with epilepsy.

It was noted in an earlier section that animals deprived of a large portion of the gland subsequently showed evidences of disturbed mentality, not infrequently associated with a tendency to convulsive seizures. These symptoms we have regarded as a manifestation of glandular insufficiency, for they do not occur in animals subjected to the same operative manipulations, but in whom the extirpation has been restricted to a small fragment of the gland.

In the clinical cases these derangements are naturally more apparent. In the milder grades of dyspituitarism, such as some of the acromegalics have exhibited, inability to concentrate, impairment of memory, and so on, have been noted by the more intellectual patients (*e.g.* Cases XXVIII and XXX), in one of whom, however, all the former powers of mental activity seem to have been restored with the readjustment of a physiological balance through glandular administration.

In most cases of hypopituitarism sufficient to cause adiposity, some deviations from the normal intellectual level may be expected. The condition may be linked in some way with the drowsiness, but it would seem to be more than this alone. It may be recalled that Vitaut regarded psychic derangements as one of the cardinal symptoms of Dercum's adiposis dolorosa, many instances of which, as we have pointed out, may be attributable to an hypophyseal deficiency. Psychic disturbances of greater or less degree have been common in our series, and are particularly well shown by some of

the patients (cf. Cases VI and XXXIV) in whom there have been no general pressure manifestations to confuse the actual glandular symptoms.

Epilepsy.—Particularly important is the relationship of convulsive seizures to the states of glandular deficiency. The possibility that an undue excitability of the cerebral cortex may be a consequence of posterior lobe insufficiency is novel to the subject of epileptiform convulsions.

Seven of the patients with existent hypopituitarism (Cases II, IV, V, IX, XIV, XXI and XLVI) had unmistakable uncinate gyrus seizures.* In all of them there was an interpeduncular extension of the growth, which doubtless pressed upon and thus irritated the adjoining uncinate gyri. In one of the patients (Case IX), indeed, the gustatory fits represented the single neighborhood manifestation (aside from the enlarged sella) of the malady, and their true character had been recognized for some years, though the underlying factor of an hypophyseal struma had been unsuspected. In a number of these patients the seizures were restricted to the subjective gustatory and olfactory impression with a dreamy and unreal sensation without subsequent convulsion: in others, a convulsion usually followed.

General epileptiform seizures, without recognizable uncinate factors, occurred in six of the other patients included in the series, though it is possible that some of them may actually have had inconspicuous gustatory impressions. However, with a single exception (Case VI), they were cases with supposedly primary glandular hypoplasia, so that the element of tumor with secondary uncinate deformation can be disregarded as a predisposing factor. Thus, all told, thirteen patients in the series, with existent hypopituitarism, have shown epileptiform tendencies—a percentage too large to be purely coincidental.

Attention may be drawn to two patients in particular (Cases XXXIII and XXXIV). Case XXXIII, regarded as an instance of hypopituitarism following a fracture of the base in which the pituitary body was damaged, not only showed all the usual constitutional signs of hypophyseal deficiency, but the patient had been having convulsive attacks with great frequency. Under glandular administration, with no other treatment, the seizures fell from thirty in the preceding month to fourteen, and to five in the following months. In Case XXXIV, regarded as an instance of primary hypoplasia of the gland, with epileptiform tendencies, under glandular feeding the patient has gone for nearly a year without attacks.

Without further observation, it would be unwise to lay too great stress on these few experiences, though they are undoubtedly suggestive of a possible predisposition to cortical instability as a consequence of hypophyseal insufficiency. It has been a source of comment by many students of epilepsy that the terminal stage of certain types is often accompanied by an extreme lowering of temperature and slowing of the pulse. Moreover, many of these unfortunates, as is well known, are obese and have ravenous appetites, just as is the case with many of the patients with demonstrable hypopituitarism. We have shown that in some instances there is a high sugar tolerance. The following case of epilepsy might pass for one of hypopituitarism.

* Three later patients, not fully reported but included in the operative table, also had uncinate attacks.

CASE L. (Surgical No. 27752.) **Epilepsy with constitutional manifestations akin to those of dyspituitarism.**

May 3, 1911. John McC., aged 16, entered the hospital with the complaint of vertigo, convulsions and adiposity. His antecedent family and personal history is without incident. There are seven brothers and sisters, who are well. He is the fourth child.

He is said to have been a 15-pound baby, and has always been obese and large for his age. He attended school until a year ago, but was notably backward. For the past two years there has been a rapid increase in weight, and he has also grown rapidly. At 14 he weighed 200 pounds; his present weight is 275 pounds. He is a very heavy eater with an

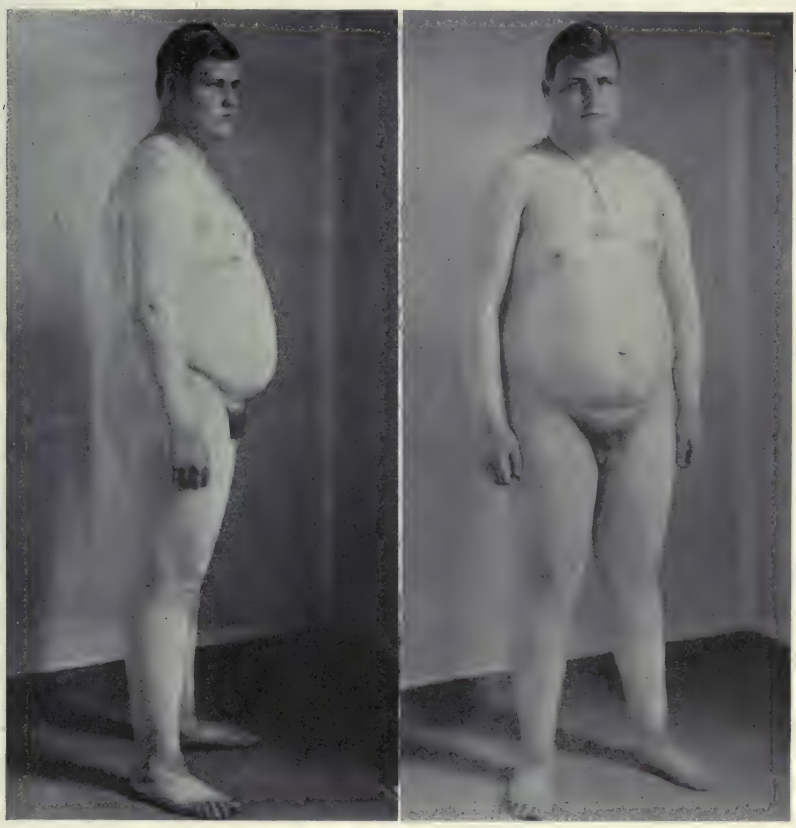

FIG. 309.—Case L. Adiposity and epilepsy of dyspituitarism. Age 16; height 6 feet; weight 275 pounds.

especial fondness for carbohydrates. No polyuria has been observed. He is sexually undeveloped for his age. There has been no cranial trauma.

For two years he has been having epileptiform seizures, without preceding aura. There are occasional petit-mal attacks, accompanied by a few moments of vacancy, but with no subjective sensory impression. He has taken a large amount of bromides.

Physical examination (Fig. 309) shows a large, adipose boy, measuring 6 feet in height and weighing 275 pounds. He is of average mentality, fairly alert and interested in his surroundings, and shows no especial tendency to drowsiness.

The visceral and cardiovascular examination is negative. The *sella turcica* is possibly below normal size.

Carbohydrate Tolerance. The exceptionally high assimilation limit for lævulose could be lowered by the coincident administration of glandular extracts. Thus, 200 grams of lævulose, which taken alone was negative, gave a positive lævulosuria while the patient was taking 12 grains of whole gland extract three times a day: 175 grams gave a positive lævulosuria when the patient was taking 18 grains of hypophyseal extract three times a day.

The *temperature* and *pulse*, previously subnormal, ranged slightly above normal after beginning the treatment.

Under the continued administration of these large doses of glandular extract there was some reduction of weight, and with this single therapeutic measure the attacks have for six months been greatly ameliorated.

One may reassemble *the data in regard to the possible relation of hypophyseal insufficiency to epilepsy* as follows.*

1. Horsley, it will be recalled, in his first experimental hypophysectomies in the canine, observed no post-operative changes whatsoever in the condition of the animals. They were, however, used subsequently as subjects of cortical stimulation, and he noted that the motor cortex was unusually excitable.

2. As already stated, we have observed a tendency to epileptiform convulsions in a number of our animals kept for long periods after partial hypophysectomy—animals that ultimately exhibited symptoms which we attribute to glandular insufficiency.

3. The study of a series of cases of hypophyseal disease in man has shown that epilepsy—a symptom unobserved in states of hyperpituitarism—is a frequent accompaniment of clinical conditions in which an insufficiency of the gland is manifest. Moreover, that the brain, under these circumstances, is possibly over-excitable, is suggested by the number of individuals in whom gustatory attacks have occurred under the influence presumably of a direct local irritation of the adjacent uncinate cortex by the enlarged gland.

4. As is well known, epilepsy is a frequent sequel of cranial injuries. In certain types of injury, as the common bursting fractures of the base, the pituitary body is prone to be damaged.

5. If, as we believe to be the case, the posterior lobe secretion normally enters the cerebrospinal fluid and thus comes to be in solution in a fluid which subsequently bathes the cortex, it is possible that its diminution from hypophyseal disease or injury may unfavorably affect the activity of the cortical cells. On this basis it is conceivable that a local scar which involves, or a tumor which presses upon, a given area of the cortex, may prevent the access to the cells of a substance which is essential to their functional stability.

6. Many individuals, supposed to be suffering from so-called genuine or essential epilepsy, present manifestations of a nutritional disorder—a tendency to adiposity and a high sugar tolerance, coupled with a lowered temperature and pulse rate—closely akin to the constitutional state which characterizes hypophyseal deficiency. In some of these individuals the administration of hypophyseal extract has served to moderate the seizures from which they previously suffered.

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* It is of interest that Wenzel (1810) (cited by Biedl) looked upon the collection of colloid in the hypophysis as the cause of epilepsy.

SYMPTOMS REFERABLE TO OTHER OF THE DUCTLESS GLANDS

These are so frequently manifest that a separate note in which they have been assembled has been included under the glandular features of each of the individual case reports.

They have been regarded as indications of a more or less widespread functional alteration of chemically interrelated structures which has been brought about by the primary hypophyseal disorder. Moreover, in the preamble to one of the earlier sections, where certain cases were recorded (Group V) in which the symptoms were of such varied type that it was doubtful which of the glands, if any, was primarily at fault, reference has already been made to the significance of the polyglandular syndrome. In short, every hypophyseal disorder elicits polyglandular manifestations, not, however, in the sense of Claude and Gougerot, from hypoplasia of a number of the glands, but apparently from atrophy of some and hyperplasia of others. Further, as Delille has pointed out, we may find a suggestion of *insuffisance pluriglandulaire* combined either with hyperpituitarism or with hypopituitarism.

It has been shown by many that total experimental ablation of thyroid (Rogowitsch, Hofmeister, Comte, Herring), parathyroids (Parhon, Goldstein and Pepere), testes (Fichera, Cimoroni, Tandler and Gross), pancreas (Cushing and Goetsch), or adrenals (Alquier, Boinet, Marenghi) will occasion secondary histological alterations in the hypophysis, usually of an hypertrophic nature; and symptomatic evidences, at the same time, of a functional hyperplasia may be apparent.

Experimentation, furthermore, has shown that the reverse is true—namely, that secondary changes occur in other members of the series as a consequence of a primary hypophyseal defect; and it is natural to suppose that some of the symptomatic manifestations of these states are attributable to such secondary factors. Moreover, if these functional readjustments occur so promptly as a consequence of surgically produced deficiencies of one or another of the glands, equally marked changes would be expected in the case of primary functional deficiencies of the selfsame glands, brought about by disease.

The Sexual Glands.—Unquestionably the interrelation between hypophysis and testis or ovary appears, on clinical grounds, to be more intimate than that between any other two members of the series. However, it must be confessed that the evidences of disordered function of these organs are promptly appreciated by the patient, whereas disorders of thyroid or adrenal, for example, are often difficult of interpretation even by the trained physician who is on the watch for them. Hence, symptoms referable to the reproductive functions may apparently long antedate those attributable even to the hypophysis itself, unless the pituitary neighborhood symptoms, through tumor formation, become pronounced before the functional activity of the gland is seriously impaired.

The case reports abound with examples of imperfectly acquired secondary sexual characteristics when the hypophyseal lesion antedates puberty (*e.g.* Cases III, V, VIII and X), and of resultant amenorrhœa or impotence with retrogressive sexual changes when the malady develops after the acquirement of adolescence (*e.g.* Cases I, VII, XI and XXXII).

In the testis—and doubtless the same is true of the ovary, whose functions are still more complex—there are two factors to be considered, the interstitial cells of Leydig and the cells of Sertoli or spermatogenous epithelium. The former are undoubtedly related to the acquirement of the secondary masculine characteristics of sex.* Thus, it is well known that cryptorchids, though impotent, may acquire their full secondary characteristics, the retained or ectopic testes showing an abundance of the interstitial cells of Leydig, whereas the tubular epithelium remains undeveloped.

As a consequence of preadolescent castration, on the other hand, both elements are removed: reproduction is impossible and the acquired characters of sex fail to appear. Under these circumstances the special growth features of eunuchism, as Tandler has pointed out, may be a consequence of the hypophyseal hyperplasia which is known to follow castration.†

It is known that the interstitial cells of Leydig are abundant in the fœtus and diminish progressively until birth, remaining stationary until the onset of puberty, when they again increase in number. It has been our impression that subsequent to a partial hypophysectomy in the puppy there is a notable and permanent diminution in the number of these cells, many of which appear to undergo a fatty change. In our later experiments, conducted by Goetsch, one testis was removed at the time of the hypophysectomy and saved as a control for the other, which was examined some months later when the animal was sacrificed.

The interesting studies by Hanes[117] have been particularly conclusive in showing that the mammalian testicle elaborates an internal secretion necessary to the normal development of secondary sexual characteristics for which the interstitial cells of Leydig are, in all probability, solely responsible. Unfortunately, from an experimental standpoint, the disposition of these cells—

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* Before the VIII International Congress of Physiologists (September, 1911) Steinach showed examples of artificially male rats. He had removed the ovaries from young females and had implanted the testes from young males into their anterior abdominal walls, with permanent change of sex characteristics, the subjects growing into normal masculine individuals.

† Tandler and Gross,[245, 246] if I understand them correctly, were led originally to regard the condition typified by the syndrome dystrophia adiposo-genitalis as due to a primary genital hypoplasia.

Tandler's interesting studies of the Skopzen sect of eunuchs, combined with observations upon castrated animals, led him to interpret some of the syndromes that we have described, as evidences of a primary inactivity of the Leydig cells (*dysgenitalismus*) with secondary hypophyseal hyperplasia and developmental disturbances of a eunuchoid nature. Eunuchoid characteristics with hypoplastic testes were unquestionably present in Cases XXXII and XXXIV of our series.

Objections to this view are many. In the first place, in most cases the hypophyseal enlargement or struma long antedates the manifestations of dysgenitalismus (*e.g.* Cases X, XXII and XXIII), and when the latter are present from puberty, as in Case V, the skeletal changes of eunuchism are absent. Again, the testicular changes which occur after experimental hypophysectomy show that dysgenitalismus may be a secondary process, with persistence of sexual infantilism, in puppies, and retrogressive changes in the adult animals. Furthermore, were the condition due originally to a testicular insufficiency, it would hardly be expected that hypophyseal opotherapy, as in Case XXXIV, would cause such decided improvement in the condition.

Tandler's more recent view is expressed as follows: "*Dass der Kastrat länger werden kann, verdankt er dem Ausfall der frühzeitigen Reife* (*i.e.*, with delayed epiphyseal union). *Dass er aber länger wird, verdankt er wohl der Hypophyse.*"

as is true of the pancreatic islets—is such as to make it impossible to observe the consequences of their ablation apart from the other cells of the organ.

However, some confirmation of the views expressed by Hanes is afforded by cases in our series in which alterations in the cells of Leydig and Sertoli have occurred secondary to hypophyseal lesions.

Three histological types of testis may be distinguished, of which the following cases are examples. In one (Case XLVII), the interstitial cells were unusually abundant, and the patient, though only seven years of age, had fully acquired his secondary characteristics—enlargement of the genitals, pubic and axillary hair, adolescent beard, masculine voice and so on. Nevertheless, the section of the testis showed a preadolescent type of tubule without spermatozoa (Fig. 310).

In another (Case VIII), the patient, though of middle age, had never fully acquired his secondary characters of sex. Possessing a feminine type of adiposity, hirsuties and so on, he nevertheless had been sexually active, and the testes showed fully developed tubular epithelium with spermatozoa. However, there was a paucity of interstitial cells, none of which could be identified as cells of Leydig (Fig. 311).

In the third type, illustrated by a patient aged 36 (Case XXXII), there was not only an absence of the secondary sex characteristics, as evidenced by the childish voice, absence of beard and so on, but the patient, at the same time, was impotent. The sections showed an absence of both elements with as marked a lack of development of the tubules as is seen in the undescended type of testis and, at the same time, with a complete absence of interstitial cells which abound in the cryptorchid gland (Fig. 312).

Tendencies in the direction of one or another of these types have been seen in most of the males in our series. The picture shown by the first of the illustrations, with hyperplasia of interstitial elements, is, doubtless, the most rare, though a disproportion in this direction conceivably takes place as a consequence of X-ray exposure, which appears more specifically to affect the spermatogenous epithelium. We have had a number of clinical examples of the second variety, namely, of individuals of the typus femininus who were sexually active but in whom the internal secretion from the Leydig elements was, presumably, subnormal; and in two of these patients (*e.g.* Cases IX and X) the testicular condition is, doubtless, verging on to that of the third type, as evidenced by the onset of impotence. In one of them (Case X), after operation, and with the institution of glandular therapy, there has been a return of libido et potentio.

After secondary characteristics of sex have been fully acquired, the reversive tendencies are less striking, though, in the majority of cases, by the time hypopituitarism has begun to be apparent, the patient has already become aware of anaphrodisia and possibly of impotence. This is true even of some of the acromegalics who have begun to show dyspituitarism; and under these circumstances the condition is the more noticeable, for the reason that many of these individuals (*e.g.* Case I *et al.*) in the early stage of their hyperpituitarism show an exaggerated libido.

That which holds true for the testes applies, also, in all probability, to the ovary, namely, that there are two, and indeed possibly more, glandular elements to be considered. Far less is known of ovarian than of testicular function, and

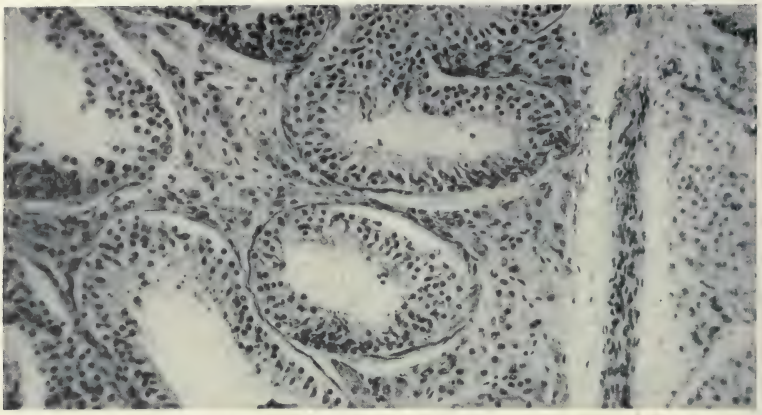

FIG. 310.—Section of testis (mag. × 140) of Case XLVII, a patient exhibiting precocious secondary characteristics. Note excess of interstitial tissue and abundance of interstitial cells of Leydig. Seminiferous tubules of preadolescent type.

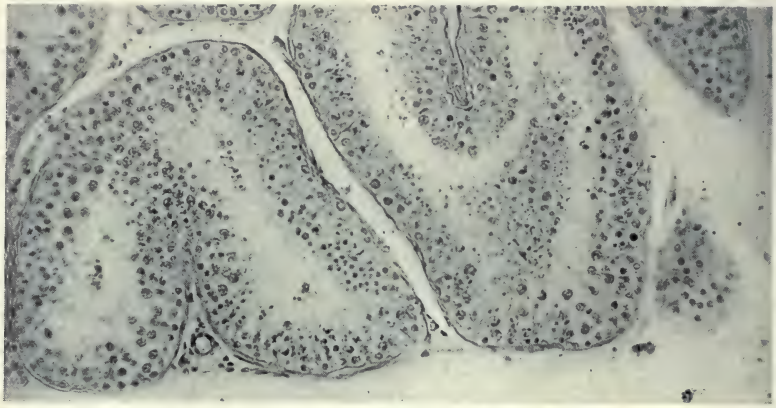

FIG. 311.—Section of testis (mag. × 140) of Case VIII, a patient who had never acquired complete secondary characteristics. Note paucity of interstitial tissue with no cells of Leydig. Seminiferous tubules fully developed.

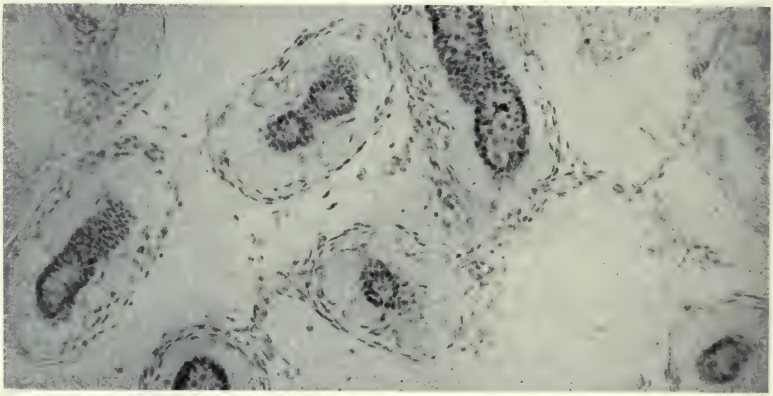

FIG. 312.—Section of testis (mag. × 140) of Case XXXII, a patient showing excess of interstitial tissue but no interstitial cells of Leydig. Seminiferous tubules completely involuted. Patient both impotent and without secondary characteristics.

unquestionably the physiological complexities and the number of hormones are greater in the case of the female gland. Not only the process of ovulation itself, but the formation of the corpus luteum of pregnancy, is a factor to be considered apart from the interstitial cells of the gland, which, in all probability, play a rôle similar to that of the cells of Leydig in the male. The existence of such cells in the ovary has been fully described by Limon.[167]

Reference may be made in this connection to two recent cases (included in the operative table but not in the case reports). Both were married women of middle age, with large, doubtless primary, hypophyseal strumas, and neighborhood symptoms of many years' duration. Neither of them was adipose. In both, there were indications of incomplete pubescence; the breasts were undeveloped and neither had ever had any axillary or pubic hair. One of them had been castrated at twenty years of age, upon the presumption that her constitutional peculiarities were primarily of ovarian origin. The ovaries were said to have been small and cystic. The other had borne children. Therefore, as has been shown to be true of the male, the reproductive function of the female may not be impaired, even though full secondary sexual characteristics have not been acquired.

Another patient (Case XIV) in the series had also been castrated on the view that her amenorrhœa was the primary element in the malady, but, as in the case just mentioned, her hypophyseal symptoms were, if anything, aggravated by the procedure. Though she was 26 years old, the ovaries were small and cystic and there were no fully developed Graafian follicles. However, the large interstitial cells were abundant, and it is to be noted that, unlike the two patients above mentioned, her adolescent characteristics were fully developed.

These three illustrations suggest that, in females as well as in males, the glandular element which is responsible for the physical changes of puberty, differs from that which is concerned with ovulation and reproduction and may, possibly, be a function of specific interstitial cells.

The relation of hypophyseal disorders to the physiological activities of the ovary, other than those concerned with the acquirement of adolescent characteristics, is unquestionably a very close one, and amenorrhœa is an early symptom whether the disorder is on the side of over-function or of under-function. In many of the cases of acromegalic women recorded in the literature since Marie's early cases, menstrual irregularity or cessation has been noted as the first observed symptom (*e.g.* Case II). To this rule, however, Cases XXIV and XXVII of our series prove to be exceptions.

One naturally recalls, in this connection, the hypophyseal hyperplasia of pregnancy and the coincident abeyance of the catamenia. Under these circumstances the gonadal interrelationship with the other glands becomes additionally complex; and the hormone which incites the hypophysis to its unusual functional activity is, in all likelihood, furnished by the new-formed corpus luteum.

However, one can hardly attribute cessation of the menses solely to a functional hyperplasia or to pathological hyperpituitarism. In the latter event it would be expected that catamenia would return as the condition

(*e.g.* Case II) passed over into the stage of glandular insufficiency. Furthermore, amenorrhœa is an early symptom likewise in cases of primary hypopituitarism, though, to be sure, some of those incorporated in our series show suggestive evidences of early and transient acromegaly (*e.g.* XI and XXI).

In only one of the patients in the series (Case VIII) has menstruation been re-established after a long period of abeyance. This is an instance of primary hypophyseal insufficiency caused, supposedly, by a superimposed tumor, and catamenia returned after decompressive measures which were directed toward the liberation of the compressed gland.

Catamenia may return, of course, after operation in many cases of brain tumor, in the presence of which amenorrhœa is a common symptom, as Axenfeld,[3a] Müller,[191] Cushing,[55] Rosenberger[218] and others have emphasized. None of these authors, however, have clearly pointed out that the symptom may be due to hypopituitarism from cerebrospinal fluid obstruction which the operation serves to relieve.

The Thyroid.—Definite histological alterations in the thyroid gland have been observed by many in animals subjected to experimental hypophysectomy (p. 10). It is our impression that a transient active hyperplasia occurs as the result of a total or nearly total extirpation, and that this condition is ultimately succeeded—if the animal survives for any length of time—by a functional involution, in which an excess of colloid and low epithelium is shown under the microscope. The hyperplasia suggests that the two glands are capable of a synergic action; in other words, that "either can, to some extent, in case of need, function vicariously for the other" (Hoskins[129a]). The later transition into a colloid state, however, is difficult to reconcile with this view.

On clinical grounds, changes in the thyroid, next to those in the sexual glands, are most commonly observed. Furnival (cited by Paulesco) found only five thyroids which could be considered normal out of 24 cases of acromegaly. Conversely, Schöneman, in a study of the pituitary body in 85 cases of goitre, found marked alterations in all but one instance. The two glands have some histological points of resemblance, and, unquestionably, they play an important rôle in metabolism and have a somewhat similar influence on skeletal growth.

In all of the cases in our series in which a microscopical examination of the thyroid has been possible (fifteen in all), the gland has been found to have a low epithelium with excess of colloid—a condition which, on Marie's view, may be an indication of some preceding period of hyperplasia. In no instance have we seen evidences of active hyperplasia, but it is of interest that in two of Hochenegg's patients with acromegaly and partial glandular extirpation a subsequent enlargement of the thyroid occurred (Exner[77]). All of our cases, it will be noted, are ones which, at the time of examination, were evidencing signs of glandular insufficiency, and the thyroid, even of Case XXVI—the nearest approach to active hyperpituitarism of any case from which thyroid tissue was obtained—showed the same histological picture.

In their gross morphology the glands have varied all the way from the large plunging goitre of one of the acromegalics (Case XXIX) to the small impalpable gland of a patient with primary preadolescent hypopituitarism. It is my impression that the gland is most apt to show enlargement in indi-

viduals with clinical evidences of past hyperpituitarism—suggesting, in other words, that the same underlying biochemical factor causes an hyperplasia of both structures, rather than that the thyroid assumes a compensatory and vicarious rôle for the hypophysis.

In none of the cases, furthermore, have there been symptomatic evidences of hyperthyroidism. To be sure, some degree of exophthalmos is common (*e.g.* Cases I and XI), but this is, in all probability, a neighborhood effect of the tumor.

We have observed no recognizable changes in the parathyroid glandules in any of the fatal cases, nor have there been symptomatic evidences of their participation in the general glandular disorder. However, their relation to calcium elimination has been pointed out by MacCallum and Voegtlin, and the hypophysis, too, is supposed to be linked in some important way with the normal utilization of this substance (*vide* the

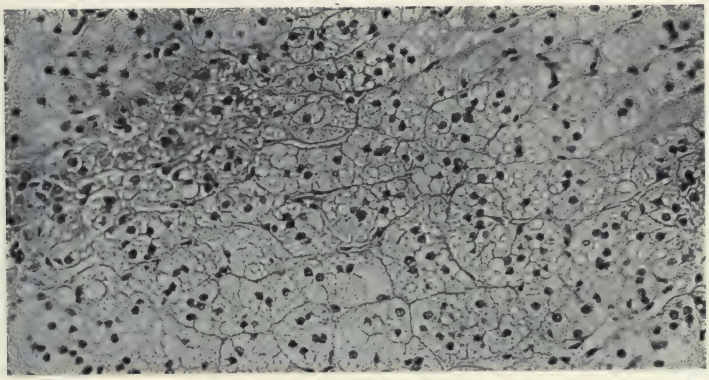

FIG. 313.—Vacuolization of zona fasciculata of adrenal in hypopituitarism (mag. × 190).

relation of the gland to the growth of bone). This is a matter which must rest upon further studies of mineral metabolism rather than upon purely symptomatic observations.

Adrenals.—As pointed out in many of the case reports (*e.g.* Cases I, XXIII, XXV and XXIX), symptoms are often present which are very suggestive of functional insufficiency of the suprarenal bodies — pigmentation of the skin, asthenia, low blood pressure, and to these may be added hypoglycæmia. These symptoms have been more pronounced in the individuals with dyspituitarism in whom evidences of former hypophyseal hyperplasia were evident. For example, in the giant Turner (Case XXXII) they were particularly outspoken, and at autopsy the adrenals were found to be exceedingly small and to possess a minimum of medullary substance. However, in the case of the ductless glands, size is no indication of functional over- or underactivity, and great morphological variability has been shown by the tissues of the autopsy series.

As is true of the experimental states of hyperpituitarism, so in the clinical cases the adrenals which we have had an opportunity of studying histologically have shown an abnormal vacuolization (a lipoid change?) of the cells of the zona fasciculata of the cortex (Fig. 313).

Attention may be drawn to two of the cases with a polyglandular syndrome in which the gland primarily at fault was indeterminable. In one of them (Case XLIV) the symptoms resembled, in many respects, those of Addison's disease, and in the other (Case XLV) what was regarded as a reverse picture, suggesting hyperadrenalism, was commented upon. This patient and one other (Case VIII) are the only ones in the series in whom an abnormally high blood pressure was observed, and it is noteworthy that the latter patient—in whom functional hypopituitarism was brought about by an extrasellar interpeduncular growth—was found, postmortem, to have unusually large adrenals with an apparent hyperplasia of the medulla.*

The Thymus.—Our clinical experience would lead us to believe that in cases of primary hypophyseal insufficiency there is apt to be a persistent and enlarged thymus when the process dates from the preadolescent era, and possibly that there is some hyperplasia of the involuted gland in cases which appear to have originated in adult life. This corresponds, roughly, with our experimental findings in the dog, for a seeming enlargement of the thymus, especially rich in Hassall's corpuscles, has been found in most of the animals, puppies as well as adults, who have long survived an extensive deprivation of the hypophysis.

In the clinical series a notable illustration is given by one patient (Case V) who succumbed to the effects of the anæsthetic and in whom the status thymo-lymphaticus of Paultow was found postmortem, with an amazing lymph hyperplasia throughout. It will be noted that practically the same condition was observed in a child (Case XLI) in whom the hypophyseal deficiency was produced by an obstructive hydrocephalus; and, in all probability, it is therefore a secondary consequence of the pituitary lesion, rather than merely a coincidental disorder.

There are, however, many exceptions to the rule that an excess of thymic tissue will be found in patients with outspoken hypopituitarism. In Case VIII, for example, though a greatly enlarged and fatty gland was clearly distinguishable, no thymic tissue was found on section: also in the giant Turner (Case XXXII) the thymus proved to be completely involuted. On the other hand, in Case II, one of acromegaly, in Case XVII, one of dyspituitarism with a mixed infundibular tumor, and in Case XXXVIII, one of acute acromegaly associated with a cerebellar cyst, there was found a persistent thymus with lymph hyperplasia of the intestines.

The Pancreas.—In an earlier paper[58] the opinion was expressed that the disturbances of carbohydrate tolerance, known to occur in clinical cases and observed in the hypophysectomized animals, might possibly be due to a secondary change in the pancreatic islets—in other words, that they might merely be one of the varied expressions of the polyglandular nature of the malady. However, later studies[100] showed that the posterior lobe itself was intimately associated with carbohydrate metabolism, and that such a thing as ''hypophyseal diabetes'' was possible, irrespective of any recognizable change in the pancreas itself.

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*The relation of tumors (hypernephromata) and hyperplasias of the adrenal cortex to other ductless glands, and especially to abnormalities and deviations of sex characteristics, has been fully presented by Ernest E. Glynn[99a] in a recent paper in which a large number of cases are assembled.

In one experiment Goetsch removed all but a duodenal fragment of the pancreas, and, after the temporary glycosuria had subsided, a partial hypophysectomy (including the posterior lobe) was performed. The animal showed the usual post-operative cycle to be expected in the case of an animal with a normal amount of pancreas—namely, a temporary lowering and a subsequent great increase of the sugar assimilation limit.*

It is probable, therefore, that changes in the pancreatic islets are less essential to these disturbances in sugar metabolism than we had supposed. Goetsch, nevertheless, has found that there are definite post-operative histological alterations in the gland, which, however, are more apparent as a loss of secretory granules in the cells of the acini than as a change in the islets of Langerhans themselves.

In eight cases (all, with the exception of Case XXXVIII and Case VIII, ones of hypopituitarism, accompanied by a high sugar tolerance) we have been able to study the pancreas, and, except for the unusual infiltration with fat, no definable change has been observable. Possibly in all of them the islets have been more in evidence than in the average supposedly normal gland; and this, on *a priori* grounds, might speak in favor of a high rather than of a low assimilation limit for sugars.

The Pineal.—Unfortunately, in our experimental series the pineal body was not studied as a routine of the postmortem investigation. In the cases examined, however, it certainly showed no hyperplasia, nor were any microscopic deviations from the normal recognized.

Neither has any definite change been noted in the clinical cases, though an occasional cystic degeneration has been present (cf. Fig. 317), with no accompanying symptomatic disorder, however, on the part of the sexual functions.

The gland is undoubtedly of physiological importance, and, as related in the discussion of Case XLVII, has an unquestionable interrelation with the other glands of internal secretion. This has been particularly emphasized by Marburg and Frankl-Hochwart, and it would appear that there is a measure of antagonism, in so far as sexual development is concerned, between hypophysis and epiphysis. However, it must be confessed that the syndrome of supposed pinealism has been observed only in connection with tumors of the gland which have led to an obstructive hydrocephalus and thus of necessity to secondary hypophyseal disturbances (cf. Bailey and Jelliffe[6a]).

A number of successful canine pineal extirpations by W. E. Dandy in the Hunterian Laboratory led to no recognizable post-operative symptoms; and this has also been the experience of Exner and Boese.[79] Furthermore, no specific reactions have been observed (Dixon and Halliburton; cit. Münzer[193]) to follow the injection of pineal extracts. Certainly nothing comparable to the precocious sexual development in clinical cases of presumed dyspituitarism has been reproduced by extirpations of the gland in young animals. On the other hand, it may be recalled that de Cyon (cit. Bauer[12]) noted that electrical stimulation of the hypophysis caused erections in some animals; and an abnormal sexual excitation (erotomania) was apparent in a number of our animals[53] after partial hypophysectomy.

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*Experiments are being undertaken in the reverse direction, namely, with a primary hypophysectomy followed by a pancreatic extirpation.

THE HYPOPHYSEAL LESION

The bare enumeration of the diverse changes which have been described as occurring in this dualistic organ would be a hopeless task. Unquestionably the structure is capable of great histological alteration at different ages and under different physiological and pathological stimuli. Consequently even the physiological "normal" for the gland under all circumstances beggars description; and until investigators agree upon some more uniform method of fixation and sectioning than is generally observed, still less can be expected from descriptions of pathologically altered glands of which the weight and configuration have not been recorded, in which the accessory glandules have not been investigated and in which the arrangement and relative proportion not only of the various pars anterior elements but also of those of pars intermedia and pars nervosa have been determined from sections made in random directions.

Fixation of the tissues *in situ* and removal of the sphenoidal bone together with the brain in its envelopes is oftentimes essential to a complete study, and this is particularly true of the cases complicated by tumor. In Case VIII and Case XVII, for example, the thinned and displaced gland at one edge of the tumor might easily have escaped notice had the usual method of removal of the unhardened brain been practised. Conversely, an extrasellar growth arising from an accessory glandule, as in Erdheim's remarkable case,[72] might easily be overlooked in an examination restricted to the usual intracranial study, without investigation of the sphenoidal cells. Since an investigation of these accessory structures has become a routine, Goetsch has found evidence of hypertrophic changes in the dural parahypophysis which he and Dandy have described,[62] both in the canine after experimental removal and in a number of the clinical cases.

Even in the case of the actual enlargements to which the gland is subject and the tumors peculiar to its vicinity there has been great disparity in the interpretation as well as in the nomenclature applied to the lesions.*

However, on developmental as well as on histological grounds we may usually distinguish (1) the homoplastic growths of the pituitary body proper—the hypertrophies or adenomatous enlargements or so-called strumas of the gland itself—and (2) the extrapituitary or heteroplastic tumors, which arise usually

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*Various classifications of hypophyseal growths have been made by Creutzfeldt (1909),[51] by Courtellemont (1911),[48] by Roussy and Clunet (1911)[219] and by others. Courtellemont, for example, divides them into three groups: (a) the epithelial tumors, with which he includes not only the heteroplastic growths with a pavement type of epithelium, but also the various adenomatous strumas which originate from the gland itself; (b) the non-epithelial tumors; and (c) the specific, tuberculous or luetic lesions.

Creutzfeldt has shown that out of 55 cases of tumor *without* acromegaly, 34 per cent. were growths from a craniopharyngeal anlage, whereas of the cases of tumor *with* acromegaly 82 per cent. were homoplastic growths, *i.e.*, adenomas, strumas, etc., of the gland itself.

In 97 cases collected from the literature by Frankl-Hochwart,[87] the tumor was described in 13 as a carcinoma (7 of them originating from an epithelial relic of the original pouch); in 13 others as an adenoma, 9 of these being designated as strumas; in 27 as a sarcoma (1 myxosarcoma, 5 angiosarcomas, 1 perithelioma and 8 endotheliomas); in 15 cases cysts were encountered; in others there were various lesions—3 gliomas, 2 teratomas, 7 tubercles, 3 gummas, 1 chondroma, 1 steatoma, etc. In addition there were 15 cases in which the hypophysis was secondarily implicated; by osteosarcomas in 7, by meningeal endotheliomas in 4, and in 4 by a glioma or sarcoma of the cerebral substance.

from some neighboring anlage, often, doubtless, from some developmental relic of the pharyngeal or infundibular diverticula—the craniopharyngeal duct tumors.

The latter implicate the gland proper only by compression, and if hypophyseal symptoms are produced they are almost invariably those of hypopituitarism: the former may be associated with clinical signs of hyper-, of hypo- or of dyspituitarism.

(1) **The Hypophyseal Strumas.**—In the case of the actual pituitary enlargements we must distinguish the physiological from the pathological hypertrophies of the gland. Functional enlargements are best exemplified by the alterations which have been shown to accompany pregnancy. Hypertrophic changes, furthermore, accompany a variety of diseases, as we have seen. They are commonly found in the aged, as well as in patients who have succumbed to chronic maladies; and in all probability under these circumstances they merely represent evidences of former periods of hyperplasia and not an existent active functional enlargement.

All manner of histological alterations appear in glands examined as a postmortem routine—invasion of the posterior lobe by anterior lobe cells, colloid accumulations, increase in connective tissue elements and what not. Often in these various glands one sees focal hyperplasias—namely, small clusters of closely packed cellular chromophile elements, either acidophilic or basophilic, described by Erdheim as anterior lobe adenomata.

The dividing line between these physiological hyperplasias and those which may be considered pathological—*i.e.* capable of producing symptoms attributable to an excess or perversion of hypophyseal secretion—is, for obvious reasons, not sharply drawn.

In the case of acromegaly we incline to the view of Benda, Dean Lewis and others, so emphatically upheld by B. Fischer,[83] that the malady is actually an expression of hyperpituitarism and is attributable to the eosinophilic elements of the pars anterior. However, as acromegaly in its early and active stage is rarely fatal, the exact histological changes which occur in this period may long remain a source of dispute, unless perchance precocious surgical extirpations will serve in time to elucidate the subject, as they have done in the case of hyperthyroidism.

In only three of our cases of presumed hyperpituitarism without tumor have we had the opportunity of examining the tissues. In one (Case XXVI) the condition might well be termed a pathological anterior lobe hyperplasia composed mainly of eosinophilic elements (Fig. 187); in another (Case XXXVIII), though the enlarged anterior lobe itself was necrotic, there was a marked invasion of the pars nervosa by proliferating epithelial cells of the investment (Fig. 265), suggestive of a functional hyperplastic change; in the third (Case XXXII) the gland, formerly much enlarged, as the distended sella would indicate, had undergone a degenerative process, and little remained of the original structure beyond the narrow encasement of a large collapsed cystic cavity (Fig. 229) by pars anterior tissue.

Whatever the histological picture might prove to be in the existing stage of the malady in the remaining acromegalics in our series, unquestion-

ably the pituitary body of each of them has undergone an hypertrophic change at one time or another, for in every instance the process has produced a demonstrable enlargement of the sella turcica. The small sellas have been restricted to cases of obvious hypopituitarism—those in which superimposed cysts or tumors have caused an obstructive glandular insufficiency (*e.g.* Case VII) or in which a presumed primary glandular hypoplasia has occurred (*e.g.* Case XXXIV).

It would appear that any of these functionally unstable glands may, under a certain biochemical stimulus, assume adenomatous characteristics, and doubtless most individuals afflicted with acromegaly face the possibility of such a transformation. Under such circumstances a rapid cellular proliferation takes place; the sella turcica becomes thinned and distended, the dural capsule ruptures, and the cellular mass invades the intracranial chamber. These adenomatous strumas, however, rarely assume malignant characteristics in the usual sense of the term "malignancy." Vessels and other structures which lie in their course are merely enveloped or pushed aside, not invaded; metastases are rarely if ever found; mitotic figures are conspicuously absent.

This form of transformation, which, owing to the neutrophilic character of the cells, we have called a *chromophobe struma*, is the type of lesion which has been certified by operation or autopsy in twelve of the individuals of the series who have had actual glandular enlargements. It doubtless corresponds with the malignant adenoma or sarcoma of many earlier writers. Indeed, the tendency still prevails to call these lesions round-celled sarcoma (cf. Case XI).

Attention should be drawn to the fact that these extreme hypertrophic transformations coexist apparently only with clinical manifestations of glandular insufficiency, no matter what the preceding syndrome may have been—even outspoken acromegaly or gigantism. Moreover, in the transformation all, or practically all, of the eosinophilic elements—to which in all likelihood the preceding acromegalic changes are attributable—become lost.*

The 12 cases in our series in which such an adenomatous struma has been certified by operation or autopsy naturally fall in Groups I and II, owing to the elicitation of pronounced neighborhood symptoms. Though in every case the existent symptoms were those of glandular insufficiency, the preceding glandular manifestations were variable. Thus one individual was an acromegalic giant (Case I) in whom the symptoms of hyperpituitarism dated from a preadolescent age; while in another (Case II) the adenomatous struma was the terminal feature of adult acromegaly. Moreover, slight indications suggestive of transient preëxisting hyperpituitarism were observable in Cases XI, XII and XXIII. In Cases V, IX, X, XV, XIX, XXI and XXII, on the other hand, the manifestations from the outset were entirely those of glandular insufficiency, with a syndrome which could hardly be attributed to a perversion or excess of secretion from the cells of the struma itself.

* Franchini's view of a dualistic process in acromegaly, as I understand it, attributes the terminal, or cachectic stage, of the malady to the toxic effects of a perverted secretion which accompanies this adenomatous transformation. This, however, seems hardly likely, in view of the fact that the symptoms of these glandular strumas are so closely akin to those of obstructive or of experimental hypopituitarism.

In their histological configuration these adenomatous strumas show considerable variation, their chief point of resemblance lying in the neutrophilic character of the cellular elements rather than in the anatomical disposition. The strumas may consist merely of a more or less loosely packed body of epithelial elements with no demonstrable supporting connective tissue and no blood vessels (cf. Fig. 34). In some cases they show a certain alveolar disposition, the cells being massed about a central core containing colloid (Fig. 159). Others show a sinusoidal structure with a vascularity more like that of the normal gland (Fig. 153), and in these vascular spaces it is not uncommon to find colloid. Still others show more or less of a papillary glandular structure, one of our later operative cases (No. 29 of the operative table) being a good example (Fig. 314). There are certain features of some of the histological pictures, particularly of those which show this glandular or papilliform arrangement, which would suggest that some of the growths take their origin from the pars intermedia.*

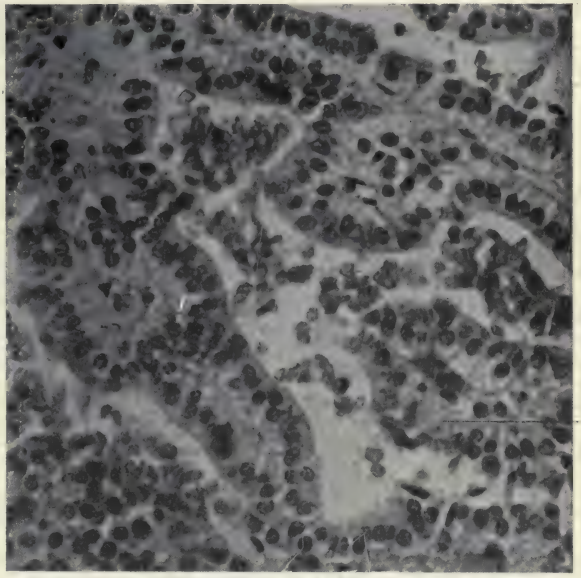


FIG. 314.—Chromophobe struma (No. 29 of table) with papillary arrangement of cells (mag. × 375).

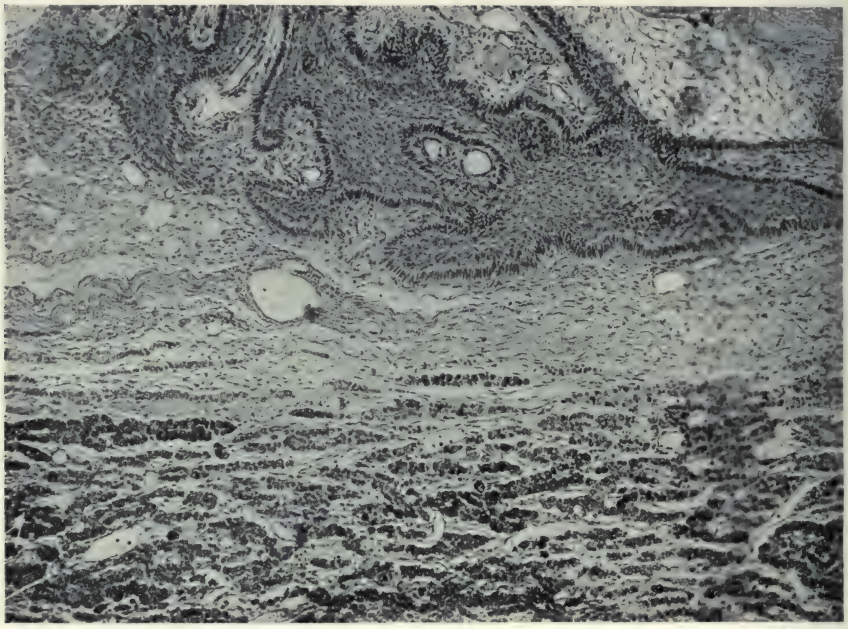
These strumas, naturally, may undergo a degenerative metamorphosis with cystic softening, as illustrated in Case XXXII, or one may encounter true cysts of variable size and with variable contents, from a watery or colloidal to a bloody or thick, chocolate colored fluid, resembling the cysts which originate in the thyroid. Such lesions present, of course, the most favorable condition for surgical intervention. We have had one example, in a blind patient, of a large hæmorrhagic cyst (cf. No. 29 of operative table) which was successfully evacuated, with the immediate return of partial vision.

(2) **Accessory or Extrapituitary Tumors.**—These, as heretofore stated, are, more strictly speaking, true neoplasms which implicate the hypophysis, if at all, merely through the agency of compression. Two types may be dis-

* Reference has been made in connection with Group V to the changes in the gland which occur as the result of obstructive hydrocephalus, and it has been noted that these changes chiefly affect the posterior lobe, and particularly its epithelial investment. This part of the gland undergoes what appears to be an hypertrophic change, doubtless in the effort toward a compensatory hyperplasia, for similar changes are seen in the fragments of the pars intermedia which are left after experimental extirpations. The most marked alterations of this type, however, have been experimentally produced by the placement of a "clip" on the infundibular stalk.[100] A similar increased cellularity of the pars nervosa has been observed by Morawski[100a] after stalk division in monkeys.

tinguished: those which arise from some congenital anlage related to the development (infundibular or pharyngeal) of the pituitary body and those which originate from other structures in the sellar neighborhood.

As Erdheim[71] was the first to emphasize, it is not at all uncommon to see near the superior or inferior portion of the hypophyseal cleft, inclusions of pavement or ciliated cells which lie within the gland and which, presumably, represent "rests" of the primitive ectodermic diverticulum (Rathke), and from which epithelial growths or cysts might be expected to originate. Similar epithelial rests are to be found below the adult sella in the line of the craniopharyngeal canal; and doubtless the most conclusive illustration in the literature of a growth arising from such an anlage is that given by Erdheim,[72] who found, in a case of acromegaly, a tumor occupying the sphenoidal cells



Specimen received from Dr. Grenville Rusk.

FIG. 315.—Section of congenital heteroplastic tumor (adamantine epithelioma) showing portion of tumor with squamous epithelium. Note compression effects on anterior lobe at lower part of section (mag. 75 diams.).

below the pituitary fossa, composed largely of eosinophilic elements, the superimposed hypophysis itself being practically normal.

Though mentioned by many as of frequent occurrence, there have been no illustrations in our series—at last none certified histologically—of the heteroplastic tumors with epithelial elements of pavement type which often undergo kerato-hyaline changes and assume adamantine characteristics. In his admirable monograph[71] Erdheim described seven of these tumors from the museum collection in Vienna, and record of similar growths has since been made by Strada,[241] by C. J. Lambert in a case of Farnell's,[80] and by others. They are comparatively rare lesions. We have had the opportunity of studying the sections of a typical case described by Rusk (Fig. 315).

Though they do not form metastases, doubtless many of these growths have in the past been called carcinomas.

We have, however, met with one example of a tumor arising apparently from an anlage at the extreme upper end of the pituitary cleft. From its cellular arrangement and colloid content, it evidently originated from an inclusion in the pars intermedia infundibuli, for it surmounted a normal, though compressed, anterior lobe. Similarly placed lesions of variable size have been described by Saxer, Boyce and Beadles, Erdheim and Dean Lewis.[164] The resemblance to thyroid tissue in certain areas of the sections may be very striking (Fig. 316).

Other heteroplastic growths, which contain mixed tissue elements of a teratomatous nature, occur in the same situation. Hecht (1909)[119] and others

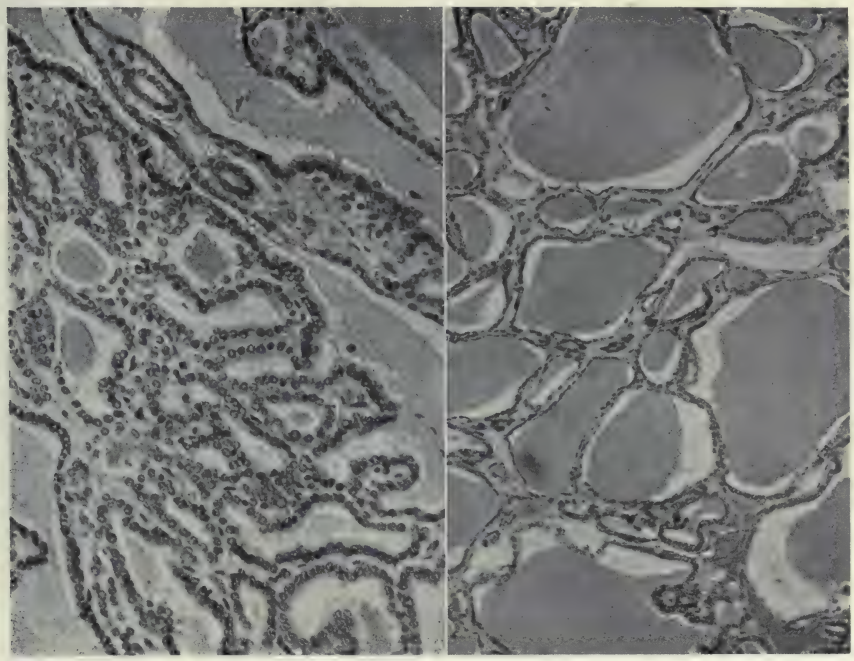


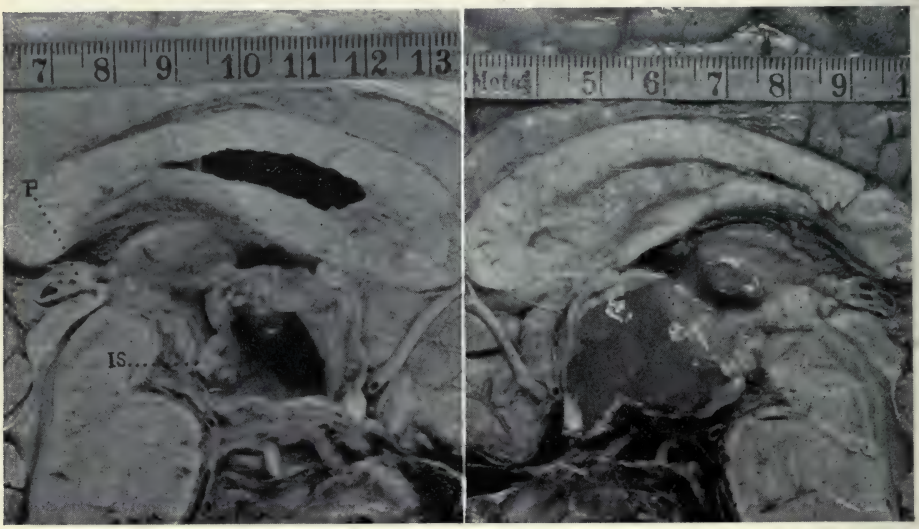
FIG. 316.—Sections (mag. × 190 and × 90) from an extrapituitary struma resembling thyroid, presumably originating from pars intermedia.

have described such growths, and two certified examples occur in our series (Cases III and XVII). In both of them the tumor elements were composite; and, as the infundibular stalk and the gland were dislocated forward (Fig. 126) and upward, the growth in each case was presumably an inclusion tumor arising from a relic of Rathke's pouch.

Less clear is the source of origin of some of the infundibular lesions, of cysts in particular, two examples of which (not included in the case reports) have been observed. In one of the patients a bitemporal hemianopsia had been produced by a median thin-walled bilocular cyst the size of a walnut, which appeared to take its origin from the anterior wall of the infundibulum (Figs. 317, 318). The cysts were filled with a yellowish

gelatinous substance, and projecting from the walls were numerous verrucous nodules composed of squamous epithelium. The underlying hypophysis showed but little change and the sella was normal, though there was a persistent craniopharyngeal canal connecting sphenoidal cells and pharynx—the only example of this anomaly in our series. The glandular symptoms were inconspicuous.

In the other patient, who showed marked hypopituitarism with a complete primary optic atrophy, the cyst was a large multilocular affair, causing marked dislocation of the mid-brain structures. Here, also, the cyst walls showed verrucous projections of the same character. The greatly flattened hypophysis occupied a sella of normal configuration. It is presumable that developmental aberrations may occur in relation to the neurohypophysis,



FIGS. 317, 318.—Papillary infundibular cyst (left empty: right with gelatinous content) which surmounted a normal sella containing a normal pituitary body (not shown). Cyst is anterior to and arises from the infundibular stalk (*I S*). Note wartlike projections from walls (squamous epithelium): also cystic pineal gland (*P*).

just as they occur in relation to the epithelial portion of the gland, and that they may serve as the starting point for these papillary infundibular cysts, which Langer,[151] Strada[241] and others have described.

Doubtless, however, many of the interpeduncular tumors which secondarily implicate the gland arise from other than a developmental infundibular anlage. Thus, in Case VIII a large endothelioma, probably of dural origin, was the offending agent; and Schnitzler[231] has described a similar case in which he thought the tumor arose from the sellar diaphragm, as it may have done in our patient. In like fashion, other heteroplastic tumors originating in adjoining structures may be responsible for clinical symptoms of glandular insufficiency, owing to pressure deformations of the gland; and it is possible that slowly growing lesions of this type may be the underlying factor in those of our cases with hypopituitarism in which pronounced neighborhood symptoms occurred, accompanied by small sellas (*e.g.* Cases VI, VII, XVI and XX).

In SUMMARY: we have certified the lesion in 29 of our cases. There have been 23 homoplastic epithelial growths or strumas originating from the gland itself. Of these, the struma in two cases of comparatively recent acromegaly was relatively small and showed an apparent hyperplasia of normal anterior lobe elements; while in a third, a giant who was showing signs of ultimate glandular insufficiency, an obvious former anterior lobe enlargement, had undergone a cystic degeneration. The 20 other cases all showed large strumas of chromophobe cells, with coexistent symptoms of hypopituitarism. With the one exception of a large hæmorrhagic cyst (No. 29 of table) the tumors have been solid affairs.

There have been 6 heteroplastic or extra-pituitary tumors. Of those originating in all probability from a developmental rest, two were teratomas which had dislocated the gland and infundibulum forward and upward, and two, infundibular cysts which had dislocated the same structures downward and backward. In addition, there has been one superimposed endothelioma, which, possibly, arose from the superior dural diaphragm.

So far as the character of these growths concerns the much-mooted question of clinical hyperpituitarism *versus* clinical hypopituitarism, it can be said that no case of acromegaly has been associated with a heteroplastic tumor except one in which a glandular hyperplasia and a cerebellar cyst were coexistent: furthermore, that in all cases of acromegaly in which a large homoplastic chromophobe struma was demonstrated, evidences of glandular insufficiency had begun to be apparent.

On the other hand, manifestations of primary hypopituitarism always accompanied the heteroplastic tumors which served to compress the gland, and were often an accompaniment, also, of the large chromophobe strumas. These enlargements may occur, therefore, in glands that have not undergone the primary hyperplastic transformation to which acromegaly is commonly accredited.

TREATMENT

From a therapeutic standpoint we are confronted by a variety of problems, some of which call for mere symptomatic medicinal measures, some for operative relief, and some for the administration of glandular extracts to make up for a deficient secretion. It is necessary to determine, therefore, for each case, just what the local conditions may be, and, so far as possible, what is the existent stage of glandular activity.

One patient may need merely a sellar decompression to alleviate the headaches of capsular distention (*e.g.* Case XXXVI), another may require partial extirpation of a struma to relieve chiasmal pressure (*e.g.* Case XXIII), another, who has no neighborhood symptoms, may require merely glandular feeding (*e.g.* Case XXXIV).

On the other hand, combinations of these measures may be needed. Thus, one and the same individual (*e.g.* Case VII) may urgently require a

subtemporal decompression for the relief of general pressure symptoms, and subsequently the sellar floor, or even a portion of the large struma, may be removed by a transphenoidal route to save the chiasm from further damage: at the same time the X-rays may be employed to check further cell division of an active chromophobe struma, the patient meanwhile receiving glandular administration to supply the secretory deficit. Hence the treatment of these cases is neither strictly surgical nor medical, but various measures must be adopted according to the immediate demands of the individual problem.

SURGICAL PROCEDURES

Unquestionably in the present state of our knowledge of hypophyseal maladies operative procedures are indicated in the majority of cases when the nature of the disorder is finally recognized; for the diagnosis, as a rule, is still largely dependent on the presence of neighborhood pressure disturbances, for the relief of which recourse must be had to mechanical or operative therapeutics.

It is conceivable that the day is not far distant when our present methods of dealing with hypophyseal enlargements, with scalpel, rongeur and curette —new as these measures actually are and brilliant as the results may often be—will seem utterly crude and antiquated, for it is quite probable that surgery will, in the end, come to play a less, rather than a more important, rôle in ductless gland maladies. This Utopia, however, will be reached only when a sufficient understanding of the underlying ætiological agencies enables us to make more precocious diagnoses.

In the present state of our knowledge surgery admittedly constitutes our chief source of defense against the advances of the larger number of recognizable pituitary maladies. Being so, it is well to understand the possibilities as well as the limitations of operative measures in the various types of hypophyseal diseases which present themselves and which are not amenable to relief through medicinal therapy.

In view of the variable conditions which may be encountered, variable procedures may be called for—those directed toward the palliative relief of general pressure symptoms; those whose object is to lessen the excessive secretion of a gland in a state of hyperpituitarism by partial removal, after the accepted manner of treating Graves' disease; those directed toward the relief of neighborhood pressure symptoms. There can be no one standard operative measure suitable for all cases.

1. **To Meet General Pressure Disturbances.**—These, as we have seen, may be so extreme as to urgently demand palliative relief before a possible direct attack on the tumor can be thought of. The problem is the same as in the case of inaccessible tumors situated elsewhere, for which a cranial, and preferably a subtemporal, decompression is indicated.

This measure has been called for in a number of our cases, and in some of the earlier experiences (*e.g.* Cases III, XIV and XVI, or Nos. 1, 2 and 3 of the table)* before the practicability of exposing the sellar region was demon-

*In this section, when Arabic numerals are used to designate the surgically treated cases, they refer to the cases as arranged chronologically in the table (p. 308), where it can be told, by the presence or absence of Roman numerals, whether the histories have been presented in full in Part II.

strated, operative measures were confined to a palliative craniectomy. After a bilateral decompression in No. 2 an interval of seven years elapsed before there was a sufficient advance in symptoms to call for a direct attack on the lesion, which at the time of the patient's first admission was not thought to be possible.

Unquestionably a decompression should have been the primary step in Case II (No. 9), for the experience with Case V (No. 17), which resulted fatally, and with Case VIII (No. 26), in which the measure did not serve to modify the terminal pressure symptoms of the large growth, show that it can be postponed until too late a stage of the disorder. Latterly in several patients a primary subtemporal decompression, which was urgently indicated, has been followed by a transphenoidal operation, with partial tumor removal or evacuation of a cyst (*e.g.* Nos. 29 and 38 of the table). Conversely, in some instances a transphenoidal operation, which proved futile owing to the high position of the tumor, has had to be supplemented by a subtemporal exploration combined with a decompression (*e.g.* Nos. 18, 32 and 34 of the table).

All told, out of the 43 patients subjected to operative measures *subtemporal decompressions* (occasionally bilateral) have been performed upon 16, merely on the basis of general pressure symptoms. In some cases the measure was unavailing, owing to the late stage of the process (*e.g.* Nos. 5 and 17); in others, owing to a mistaken interpretation of the local conditions (*e.g.* No. 11). In other cases in which, as events subsequently proved, there was marked intracranial extension of a rapidly growing struma the measure would unquestionably have been advisable (*e.g.* Nos. 7 and 20). One reason for a subtemporal, in addition to a sellar, decompression in the case of these extensive proliferations is to offer a better chance for radiotherapy, as will be explained later.

Confessedly it cannot always be told whether the severe headaches are due to general pressure symptoms or to local distention of the hypophyseal pocket. This is particularly true when primary optic atrophy has occurred and there is no choking of the disc to guide one. In No. 11, for example, the subtemporal decompression did not modify the supposed pressure headaches. Conversely, in Nos. 4 and 33 the headaches were immediately set aside by a sellar decompression, as has been described.

2. **To Combat Functional Hyperplasia.**—Whether the process in *hyperthyroidism* is due to an excess of normal thyroid secretion or to a perversion of secretion, it has, nevertheless, been found that partial extirpation of the hyperplastic gland serves, in many cases, to alleviate the constitutional symptoms of the disorder, and it is a natural conclusion that similar measures might, in like fashion, modify the symptoms of *hyperpituitarism.*

This was first suggested by Schloffer[228] as a possible means of checking the progress of acromegaly, and it was with this idea in mind that the operation was conducted in our Case XXVI—a patient in whom there proved to be a chromophile struma, as was anticipated, according to the views of Benda. Not only was there an immediate relief of subjective discomforts, but the acromegalic manifestations, so far as the thickening and œdema of the soft parts were concerned, showed marked amelioration. Similar beneficial effects were observed in one or two patients with supposedly active acromegaly operated upon by Hochenegg.

However, in our patient the former discomforts after a year largely returned, and it cannot be said that the experience is anything more than suggestive of what may possibly be accomplished in early and aggravated cases of acromegaly. No one, of course, would suggest that in patients with stationary acromegaly, such as Cases XXVIII, XXIX and XXXI, an operation is indicated, for the formerly hyperplastic glands have, doubtless, undergone involution, leaving these individuals in a condition either of fairly normal equilibrium or of actual glandular insufficiency.

In view of the fact, therefore, that hyperpituitarism, so far as glandular oversecretion is concerned, is a condition which tends to right itself, it must remain for the time-being a matter of uncertainty as to whether or not, in the absence of a degree of hyperplasia sufficient to cause neighborhood symptoms, operative measures can hold out any promise of permanently controlling the disorder.

When, however, neighborhood symptoms have arisen owing to the extreme enlargement of the gland due to the formation of an adenomatous struma whether or not there have been antecedent symptoms of acromegaly, the surgical aspects of the matter stand on firmer ground.

3. **To Afford Relief to Neighborhood Symptoms.**—This implies an actual attack on the lesion itself, either to partially remove it or to give more room so that it may continue to enlarge without jeopardizing the adjoining structures, among which the optic nerves are of chief moment. Admittedly, an interpeduncular tumor, whether it has originated as a pituitary struma which has burst its capsule, or has arisen from an extrapituitary anlage, cannot possibly be removed in its totality; and unless the neighborhood symptoms are provoked by a cyst which can be effectually drained, the best that can be accomplished is a fragmentary extirpation, or removal of the sellar floor and opening of the capsule, to encourage further growth to take place in a downward direction into the sphenoidal region.

The various types of variously situated tumors and glandular enlargements which have been pictured in the case reports serve to illustrate the fact that no one operative method can serve for all cases in which neighborhood symptoms have occurred. Before reviewing the measures, therefore, which have been followed in the several cases of our own series, it is necessary to consider, in some detail, two separate factors of importance to the surgical problem: (a) *the routes of access to the sellar and interpeduncular regions* and (b) *the method of dealing with the lesion when it has been exposed.* Though the latter is, unquestionably, the factor of prime moment, the former, alas, is the one on which chief stress has been laid by most operating surgeons whose interest has been aroused in the subject; but, after all, a demonstration of accessibility was necessary before a discussion of local treatment could be worth while.

The evolution of the operative procedures, from the earlier mutilating ones to far more simple measures, bears many points of resemblance to the progressive development of the delicate operations which have come to be employed in the exposure of other equally inaccessible intracranial structures. Of these, the Gasserian ganglion operation furnishes a good example, for it will be remembered that in some of the earlier procedures such radical measures as resection of the superior maxilla were undertaken, whereas, the present method which is generally employed is comparatively simple, free from hazard and leaves no visible scar whatsoever.

(a) *Concerning the Method of Approach.*—The character of the hypophyseal operations, which have come to be used for man, recalls the methods of experimental hypophysectomy on animals as attempted at various hands. The outcome, however, under the two conditions has been different, the experimental method, at least in the canine, resolving itself into a preferential intracranial approach conducted under the temporal lobe, rather than one from below through the mouth, whereas, in man a median operation from below (transphenoidal) will remain in the majority of cases, unquestionably, the operation of choice; for, under circumstances of experimentation, one is dealing with normal structures and with no increase of intracranial tension, whereas in the clinical cases the tumor is often sufficiently large to prohibit the degree of cerebral dislocation necessary to bring the interpeduncular space into view.

Intracranial Methods of Access.—In spite of their extreme difficulty, the earliest operations were nevertheless undertaken by this route. Thus, Caton and Paul (1893[36]), acting on Horsley's suggestion, were the first to attempt a lateral subtemporal operation, in the progress of which the orbit was exenterated. Horsley, himself, is said to have consistently followed a subtemporal route, one akin to that which Caselli, Paulesco and ourselves have used in experimental hypophysectomies: and there can be no doubt but that, in some cases, particularly when coupled with a counter-decompression (Silbermark, 1910[235]) or with the overhanging brain position (Karplus and Kreidl, 1910[139]), such a procedure is the only possible one by which certain of the superimposed extrasellar (interpeduncular) lesions can be approached.

Intracranial procedures of inconceivably radical nature, by a frontal approach, have been proposed by Krause (1905),[149] by Hartley and by Kiliani (1904)[142]—procedures which expose the chiasmal region by elevating the frontal lobes after a large bilateral osteoplastic frontal resection with ligation of the longitudinal sinus. Borchardt (1907)[22] alone, so far as I am aware, has ventured to put their suggestion into practice.

In six of our cases an attempt has been made to expose the interpeduncular region by the lateral and subtemporal method (Nos. 18, 19, 27, 32, 36 and 43), with but a modicum of success. They were all patients with large tumors, access to which was impossible by the transphenoidal route, owing to the interposition of a flattened gland. Extreme difficulties were encountered, owing to the great tension, and in only one (No. 32) was a partial extirpation possible. In the others, the operation was abandoned as a simple decompression. This method of approach is indicated when, in the presence of marked neighborhood symptoms, the X-ray shows a fairly normal sella: and in one unfortunate patient (No. 37) it was shown, postmortem, that no other method could by any possibility have exposed the lesion and relieved the symptoms.

Transphenoidal Methods of Access.—These are conveniently divided into the superior nasal (Giordano, Schloffer, Eiselsberg, Kocher, *et al.*) and inferior nasal (Kanavel, Halstead, Hirsch) types.

An operative approach, with osteoplastic resection of the anterior wall of frontal sinus and nose, was proposed many years ago (1897) by Giordano.[98] This was improved upon by Schloffer (1906),[228] who, by a transphenoidal and extracranial method, was the first to report a fairly successful operation, performed in March, 1907.[229] A transphenoidal operation had, of course, been practised by many in experimental work, though owing to the cranial configuration of the lower animals it necessitated a buccal approach to the sphenoidal region, with splitting of the palate after the method used by some rhinologists for operative treatment of infections of the sphenoidal sinuses, rather than one through the face with deflection of the nose.

Buccosphenoidal operations, similar to those used in animal experimentation, were proposed by Koenig (1900),[146] in which the superior maxillæ were separated and the hard palate chiselled away. Loewe (1905)[170] suggested a similarly radical procedure, with bilateral separation of the maxillæ after deflecting the nose. These proposals of such severe and disfiguring operations are, to-day, interesting only from a retrospective point of view.

With constant modification and progressive improvement the method of Giordano and Schloffer has been accepted and carried out by many. In Schloffer's first operation, the nose was turned down to the right, and the turbinates, the mid-septum, the wall of the orbit and maxillary sinus, and the left nasal process of the superior maxilla, together with the ethmoid cells, were excised—an exceptionally radical performance, as can be judged. A similar but somewhat less extensive operation was employed by Hochenegg (cited by Stumme[242a] and Exner,[76] 1909) with exenteration only of the septum and turbinates—a method followed in my first transphenoidal case (No. 4).

Eiselsberg's adaptation of the method was likewise somewhat less mutilating. He at first exposed the field through what he called a "tuning-fork incision," with a vertical cut in the mid-forehead, the lateral wings being carried alongside the nose with subsequent temporary resection of the frontal sinus and exenteration of the nasal cavity. This procedure, as described by Proust (1908),[211] was followed in my second operation (No. 5), and was also practised by Lecène (1909).[156] Eiselsberg has since (1910)[68] considerably modified the method in favor of one in which the nose is deflected to the side.

It is evident that there is great danger of meningitis after such extensive procedures, especially when they necessitate removal of the ethmoid cells, and Moszkowicz and Tandler (1907)[190b] suggested a two-stage operation, with turning in of a pedunculated flap of skin from the forehead, which is plastered back into the region of the cells "to lessen the risk of infection!"

All of the foregoing operations necessitate more or less *décortication du visage*, to use the descriptive French term; and not only are they needlessly mutilating, but they are apt to leave permanent nasal deformations. There have been many modifications, varying from Schloffer's high operation with resection of the frontal sinus, to ones of lesser magnitude, such as Kocher (1909)[145] has practised, with the deflection merely of the nose itself to one side. In all of these procedures, extensive facial incisions and more or less complete removal of the bony structures from the nose are required. Many

of them, moreover, deprive the patient of his sense of olfaction (cf. Case XXVI)—an annoying, though possibly trifling, sequel of the procedure.

Further modifications, which lessen the severity and magnitude of these measures, have been the result of anatomical investigations by rhinologists. Kanavel (1909)[137] demonstrated the practicability of an approach through the inferior nares, the nose being turned upward by an external curvilinear incision through the nasolabial junction of the face, the turbinates and part of the septum being removed—a method practised in individual cases with success by Mixter (1910)[189] and by Kanavel and Grinker (1910).[138] As perfected and successfully employed by Hirsch (1910),[126] a still more simple endonasal route (in two or three stages), with primary resection of the median septum and subsequent opening of the sphenoid through a single nostril after the method of Hajek,[108] may be applicable to certain cases. Fair access to the sellar base is given, and in the rarer cases in which a cyst is present the surgical results in the hands of a skilful rhinologist are just as promising from this as from a more radical approach. Indeed, local anæsthesia may be all that is necessary.

Acting on the suggestion of Kanavel's investigations, A. E. Halstead (1910)[113] was the first to use a sublabial instead of an infranasal incision, and this has been adopted in the evolved transphenoidal measure which we have come to employ. As is true of all difficult operative procedures, the performance becomes progressively simplified by the combined suggestion and experience of many, and the method of approach which has been followed in our last 20 or more cases has resolved itself into the following measure, which, with practice and the proper tools, should offer no great difficulties of execution.

Steps of the Combined Method Favored by the Author.—The Anæsthetic. Of the many accessory factors of importance, that relating to the anæsthetic deserves especial consideration. Though Hirsch has shown that in his endonasal operations the sellar floor may be reached and removed in one or more stages under local anæsthesia, unquestionably most surgeons and most patients would prefer a general anæsthetic, provided it did not add an element of hazard to what in itself is regarded as a dangerous operation.

In some of our earlier attempts, particularly with the acromegalics, we experienced great difficulty in administering the anæsthetic (ether) owing to the enlarged tongue and its tendency to obstruct the glottis. Consequently, in four of these patients (Nos. 4, 5, 6, and 7) premeditated recourse was had to a preliminary tracheotomy; and in another patient (No. 8) we were urgently forced into this measure owing to a sudden respiratory cessation, brought about by an unsuspected implication of the medulla.

In all of these cases, however, at the end of the session the transvers tracheal incision and cervical wound were immediately closed without drainage and the chief objection to the procedure was the unnecessary prolongation of the operation. At the time, it may be observed, we were needlessly apprehensive concerning the possible escape of blood into the posterior pharynx.

Conditions arose, however, in Nos. 5 and 7 which necessitated subsequent operations, and, as it was feared that a secondary tracheotomy would

be attended with difficulties, No. 5 was intubated at the second stage; while in No. 7 not even this precaution was found to be necessary, for it had begun to be evident that the simplified operation was practically bloodless. Had this not been so we should have resorted in the end in all cases to Meltzer's insufflation method in preference to the tracheotomy.

Owing to an ingenious device introduced by Dr. S. G. Davis, who has etherized nearly all of these patients, it has become possible to quietly and safely anæsthetize even the individuals with an extreme lingual hypertrophy. Through a hollow metal tube, soldered to the blade which depresses and holds forward the tongue of the excellent "combined mouth-gag and adjustable tongue depressor" devised[234] by E. C. Sewall of San Francisco, warmed ether vapor is conducted directly to the opened glottis. As the pharynx is freely exposed by the apparatus, any collection of mucus can be sponged away during the course of the operation, and the anæsthetist is well away from the field. There have been no complications attributable to the etherization in any of our thirty-two transphenoidal operations.

A still greater bugbear of all transphenoidal procedures has been the possibility of inducing an infectious meningitis, and many of the fatalities in the thirty or more cases recorded in the literature have been due to this complication, even when the cerebrospinal space has not actually been opened and the operation has been confined to the partial extirpation of a struma.

As a matter of fact, this risk proves to be comparatively slight when the operation is performed by a method which obviates removal of the turbinates and extensive laceration of mucous membrane; and even the existent risk is greatly lessened by the application of S. J. Crowe's discovery[52a] that *hexamethylenamin* finds its way into the cerebrospinal spaces. Consequently, as a routine in all of our operative cases this drug in doses up to 60 grains in the 24 hours is given by mouth on the day preceding and for some days after the operation.

In four of our cases (Nos. 36, 37, 38 and 40) the cerebrospinal space was opened, leaving a subsequent cerebrospinal rhinorrhœa. In Nos. 36 and 38 the flow ceased after a week or ten days with no symptoms of meningitis. No. 40 recovered after a severe meningitis starting on the 10th and lasting until the 22nd day after the operation. In No. 37 the infection was inaugurated by a series of severe sneezes on the 9th day and proved fatal, despite the use of urotropin, on the 13th day. There has been no suggestion of meningeal complication after any of the other 29 transphenoidal procedures.

The Surgical Procedure. — With the patient prepared and anæsthetized in the manner described, the shoulders are slightly elevated so that the head drops back in a moderate Rose position, and the posterior nares are occluded in the usual manner by a sea-sponge, after which a cotton pledget wet with adrenalin is inserted in each nostril.

The upper lip is drawn up and Loewe's transverse incision, first advocated by Halstead for hypophyseal operations, is then made across the labial frænum. The incision, which need not be more than 2 cm. in length, is carried down to the anterior nasal spine of the superior maxilla, and then by blunt dissection the soft parts are scraped back on each side from the lower margin of the bony nasal opening until the cartilaginous septum is exposed.

From this point on, the performance should be entirely a submucous one, the membrane being separated from the bony and cartilaginous septum on each side, as in Killian's[143] method of submucous resection, adopted also by Hirsch. In favorable cases, indeed, there need be no injury to the mucous membrane on either side, and the entire operation may be conducted without entering the nasal cavity: however, owing to the firm perichondrial attachment at the anterior margin, a slight tear through the mucous membrane may occur on one side or the other at this point.

A deep, smooth retractor 1.8 cm. in breadth and 6 cm. in length is then introduced on each side between the freed mucous membrane and the median cartilaginous and bony septum. The separation of this pair of retractors will give sufficient room for the easy removal of the necessary strip of septum in a few large pieces. This will include most of the vomer, the lower edge of the median plate of the ethmoid and a small strip of cartilage, in removing which Ballenger's swivel knife may be conveniently used. Usually—invariably when acromegalic changes are present—the anterior maxillary spine must be rongeured or chiselled away, and a bleeding point (*canalis incisivus*) will often be exposed, necessitating the placement of bone wax: otherwise the performance is practically bloodless.

With the original retractors still in place, a series of dilating plugs, running up to a diameter of 1.8 cm., are then introduced, separating the retractors to each side and thus serving to slightly flatten the turbinates—a step which offers difficulties only in certain cases of acromegaly when the bones of the nasal passages are much hypertrophied. The two retractors are then withdrawn, their place being taken by a bivalve speculum, the blades of which are about 7 cm. in length and 1.8 cm. in breadth. This holds itself in position and frees the hands of the assistants.

From this point the use of a head-light is essential, and it will be found that ample room is provided for a clear median view between the separated layers of mucous membrane in the depths.

The sphenoidal attachment of the septum is then identified and the "prow" of the vomer underlying the sphenoidal cells may be removed, though this is not always necessary. With experience, the sphenoidal sinuses are easily identified, but it is well, in all cases, to keep the angle of approach low and to follow the posterior margin of the vomer, so as to minimize the chance of entering the posterior ethmoidal region through mistake.*

* The chief danger in the transphenoidal operation lies in mistaking the direction of approach, owing either to exceptionally small sphenoidal or to exceptionally large ethmoidal cells, into which the floor of the ethmoidal plate may dip, much after the fashion of the sella into the sphenoidal sinuses. Despite all precautions, I have been guilty of this error in one of our recent cases (No. 37).

The patient proved to have an infundibular cyst (Fig. 317), which should have been approached by the lateral subtemporal route; and though the sella was but slightly enlarged it was determined to remove its floor, with the object of giving the supposedly compressed gland some measure of pressure relief. The angle of approach was directed too high, and led into the ethmoidal region, where unusually large cells were encountered and where a projection of the cribriform plate, mistaken for the sella, was opened. Only after splitting the dura did an escape of cerebrospinal fluid show that the operation had been misdirected.

Though a cerebrospinal rhinorrhœa was established, under hexamethyl', no ill consequences were apprehended. However, on the 9th day, after a series of severe sneezes a meningitis set in, which proved fatal on the 13th day.

The postmortem examination showed a *persistent craniopharyngeal canal associated with unusually large ethmoidal and unusually small sphenoidal cells*—a condition which the stereoscopic X-ray plates had failed to clearly demonstrate.

When the body of the sphenoid has been identified, the anterior and lower walls of the sinuses are chipped away with long-handled nasal rongeurs, and after the cells have been freely opened and the lining mucous membrane removed there is rarely any difficulty in recognizing the sellar protrusion, even when there is no pathological enlargement of the fossa. The radiograms will, of course, have previously shown whether or not the sphenoidal cells are present and how far the distended sella projects into them.

The floor of the pituitary fossa is then removed in turn, this usually amounting, in the case of a tumor, to nothing more than the chipping away of thin bony scales, which are often the only remnant of the ballooned fossa. With a "knife-hook," which can be inserted through the capsule and drawn outward, a crossed incision is made in the dural encasememt of the gland or tumor, and such a degree of extirpation as may seem advisable is then carried out, as will be more fully discussed later.

Needless to say, every step of the procedure must be conducted under the eye of the operator. It would be quite unjustifiable here, as in a similarly deep and difficult trigeminal operation, to make advances in a field obscured by vascular oozing. The cavity, likewise, should be left perfectly dry before withdrawal. This can be assured, with the exercise of sufficient patience, by momentary tamponing with gauze pledgets or by the placement of adrenalized cotton. Pledgets moistened in hydrogen peroxide also have admirable styptic properties. When such bleeding as may follow the partial extirpation of a struma has been completely checked, the bivalve speculum is withdrawn, the deflected septal linings of mucous membrane fall together, and the short incision in the lip is closed with two or three cat-gut sutures.

In our earlier four or five cases, a cigarette drain was used, leading from the denuded gland through one of the nares, but this has been found to be unnecessary, and, indeed, with an intact mucous membrane its placement is impossible unless it is led out through the sublabial incision. Hence, in our recent operations, drainage has been omitted, for the procedure, though an intranasal one, is actually conducted, in many cases, without entering the mucus-lined nasal passages. It is remarkable how little reaction there may be after such an operation and how insignificant may be the amount of subsequent nasal discharge. For example, one of our patients (Case XXXVI) left the hospital and resumed her occupation within a seven days' interval after a simple sellar decompression. An examination of the nares, after a week or ten days, makes it difficult to believe that such an operation has been performed.

The mucous membrane, however, may occasionally be torn, particularly if difficulty is experienced in freeing its perichondrial attachments at the anterior margin of the cartilaginous septum. A small septal perforation, consequently, may, in some cases, be found at this point, but such defects are of little moment. Needless to say, the operation leads to no nasal deformity whatsoever, even when the strip of septum, together with its lining mucous membrane, is completely removed. Naturally, in a late secondary transphenoidal procedure (*e.g.* No. 12 and No. 32) it is difficult or impossible to preserve the membranous relic of the original septum.

This operative method is, to all intents and purposes, similar to the endonasal method which Hirsch has recently described and which he has success-

fully practised in a number of cases. However, the external opening is twice as large as in the endonasal operation; the procedure is median from the outset, it is conducted, in favorable cases, without entering the mucus-lined nasal cavity, it can be carried out in one session, and it is somewhat less mutilating, inasmuch as the turbinates are merely flattened temporarily and not removed.

I cannot help feeling that one needs all the room possible and that every step must be absolutely under the operator's direct vision. This does not necessarily apply to the simple cases resulting in mere cyst evacuation, though even these cases may present difficulties (*e.g.* Nos. 37 and 40), but it does apply to the larger number of cases in which identification of the tissues as they are exposed by the dural incision is absolutely essential for further safe manipulations.

This preferential *transphenoidal approach with sublabial incision and submucous septal resection* is necessarily a mid-line operation, but this does not imply that it is impossible to lose one's way either in an upward or downward direction. Some sense of disorientation is particularly apt to be felt in the presence of anomalous anatomical conditions—a factor always to be reckoned with in the not infrequent lesions (as in No. 37) arising from a congenital anlage (cf. footnote p. 299).

I formerly thought it very unlikely that there would be any occasion for a transphenoidal operation when the sphenoidal sinuses were absent or imperfect, as Gibson[97] has shown they may occasionally be. In Fig. 234 of Case XXXIV a type of sella is shown which surmounts such a non-sinusoidal sphenoid, and we have seen several other examples in cases of epilepsy with adiposity.

A similar anatomical variation—unsuspected before the operation—was met with in No. 40 of the operative table. Though the sella of this patient was large (Fig. 319) it was exposed only after an extensive rongeuring away of densely cancellated bone a centimeter in thickness, and, by the time the dura was exposed, sufficient confusion in orientation had arisen to cause uncertainty as to whether we had kept so low as actually to have gone through the basilar process. Consequently, a "silver clip" was inserted between the exposed dura and bone, and further advance was abandoned. An X-ray examination the following day showed the clip lying in the floor of the sella turcica, and the operation was resumed at a second stage after six days. The previously exposed dura was opened, and, by good fortune, a cyst was encountered and evacuated.

(b) *Concerning Methods of Dealing with the Lesion.*—We have learned from the foregoing that the pituitary body can, with reasonable safety, be brought within reach of the operator's instruments by an approach through the sphenoidal cells, whether the elaborate procedure of the Schloffer type be employed or that of the other extreme advocated by Hirsch. Though the operation will unquestionably undergo further modifications at various hands—all of them tending toward greater simplicity and safety—doubtless in the majority of cases suitable for surgical treatment the preferred avenue of approach will continue to be an anterior transphenoidal one.

However, the mere technical triumph of exposing the contents of the sella turcica by one or another method is far from the most important consideration. The *crux* of the situation lies in the manner of dealing with the

pathologically modified gland when it has been brought into view; and the experience with the series of cases which has been presented has shown that the operator will often be confronted with problems other than the mere evacuation of a cyst or extirpation of a part of a strumous enlargement of the gland occupying a distended sella. Were this all, the matter would be a simple one.

Indeed, could the presence of a cyst be assured, a mere sphenoidal puncture could be made off-hand, after the manner of a "Hirnpunction," by anyone possessing a sufficient knowledge of the anatomy of the sphenoidal region and a good spacial sense. However, intrahypophyseal cysts are rare—only one example (No. 29) of a type essentially favorable for a transphenoidal operation having been encountered in our full series—and in the case of a solid tumor or interpeduncular cyst the matter is far more difficult.

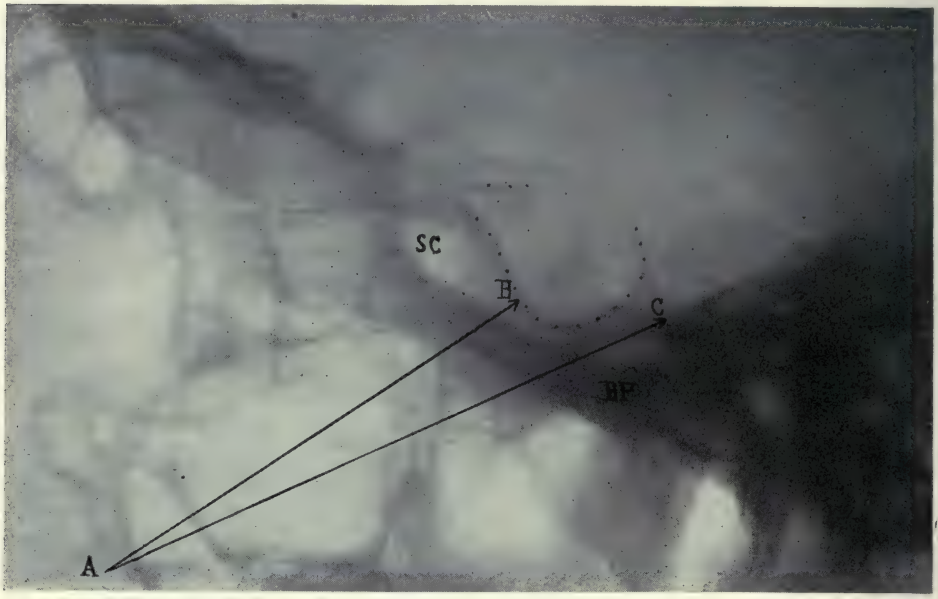


FIG. 319.—Distended sella of No. 40 (dotted). Small sphenoidal cells (*S C*). Enlarged basilar process (*B P*) extending in front of sella. Actual and correct line of approach (*A B*); apprehended line (*A C*).

The lesions, themselves, and their neighborhood manifestations, are so variable that there can be no one standard operation applicable to all cases. Hence the TRANSPHENOIDAL PERFORMANCE may resolve itself into any one of the following procedures. An infrasellar tumor arising from an hypophyseal rest may be encountered and removed; a mere sellar decompression with splitting of the glandular capsule may be performed; intrapituitary cysts may be found and evacuated; a fragmentary extirpation of a glandular struma or tumor may be combined with the sellar decompression.

On the other hand, a SUBTEMPORAL OPERATION may be clearly indicated, for the purpose of a simple cerebral decom-

pression, or for the evacuation of a superimposed extrapituitary cyst or partial removal of a similarly placed tumor. Moreover, the two avenues of approach — intracranial and extracranial — may be combined, either for the purpose of furnishing the lesion with additional room for expansion or to facilitate the effectiveness of radiotherapeutic measures, in the manner to be described.

Sellar Decompression.—This procedure promises much, I believe, for the future, if, by the aid of radiographic plates and by a further close study of the early symptomatic glandular manifestations, we can come to make more precocious diagnoses. As yet, one cannot venture to predict from incipient neighborhood symptoms that the disordered gland is destined to undergo an extensive strumous metamorphosis; and in only one patient in the series (Case XXXVI) was this assumed to be the case, for persistent "pituitary headaches," with a suggestive progressive enlargement of the sellar outlines, were regarded as sufficient justification for a simple decompression. As events proved, the operation was in the right direction, for the headaches immediately ceased after the stellate incision of the glandular capsule, which was under considerable tension.

Unquestionably, any measure which may serve to lessen the tendency of a glandular struma to burst its capsule and invade the cranial chamber will be a blessing, and it may be assumed that the usual tardy relief which nature affords, by the slow distention and protrusion of the pituitary fossa into the sphenoidal cells, can be accelerated by surgical removal of the sellar floor.

As a result, the line of least resistance for the enlarging gland will be in the direction of the sphenoidal cells rather than in the direction of the cranial chamber, and thus the optic nerves, or even the brain itself, may be spared the effects of pressure from which they would otherwise ultimately suffer. Occasionally, as in the remarkable case recorded by Boyd,[24] an hypophyseal struma may decompress itself by extensive destruction of the base of the skull, but, as a rule, this is a late effect which occurs only after the intracranial extension has been extreme.

As has been shown in the case reports, even when there is a large struma a mere decompression alone without any glandular extirpation may serve in certain cases to relieve pressure against the optic nerves and to restore, in large part, their power of transmitting impulses. However, this measure alone does not always suffice, as exemplified by Case XXI; and in Case XIX a subsequent operation, with removal of glandular tissue, was necessitated some months later owing to a secondary failure of vision. Doubtless radiotherapy might have served to obviate the secondary operation had we, at the time, realized its efficacy in checking further growth of a denuded struma.

When there is any question as to the character of the tissue which is brought into view by the dural incision, especially if there is a possibility that it may be a flattened hypophysis, the operation must be abandoned merely as a decompression, and an intracranial approach substituted at a later session. This has been our experience in several cases, and it is possible that in some of them the primary operation served, in a measure, to release the compressed gland from the superimposed pressure, with resultant improvement in its

secretory capacity. It may be seen, on consulting Fig. 78, that in an earlier stage of the malady such a step might have preserved the functional integrity of the gland.

It is conceivable, moreover, that in some of the individuals with primary hypopituitarism associated with an abnormally small pituitary fossa, a simple sellar decompression might serve to improve the activity of the imprisoned gland.

Partial Extirpation.—The problem is fairly simple in the case of a greatly distended sella occupied by a large chromophobe struma, such as was encountered in most of the cases comprising Group II of our series. Provided the intracranial extension has not been extreme, these cases, above all others, are favorable for the transphenoidal operation.

With the wall of the sphenoidal cells removed, one may often come directly down upon the protruding growth (*e.g.* Cases I, IX, X, XI, XII, XIV, XIX, XXI, XXII, XXIII and Nos. 30, 31 and 42 of the table), covered by little more than mucous membrane, upon the slightest injury to which the soft mass will begin to extrude itself.

As most of these characteristic strumas possess a very small amount of interstitial supporting substance and have a relatively low vascularity, the soft tissue is easily spooned out with but slight bleeding. It is well to restrict the extirpation to that part of the tumor occupying the floor of the enlarged sella, and the amount which can be safely removed must depend upon circumstances and the operator's judgment. No one, of course, can for a moment believe that an interpeduncular growth of a size sufficient to give neighborhood symptoms is capable of being removed in its entirety.

Often the immediate relief from the neighborhood pressure manifestations may show itself as prompt improvement in vision, even when but a small amount of the struma has been removed (*e.g.* Cases X, XIX and XXII). At times, however, improvement may be less immediately obvious, particularly when, as in Case IX, the optic nerves are not implicated. In a few instances in our series an existent bitemporal constriction of the fields remained stationary, and in one patient (Case XI) progressive loss of vision was uninterrupted despite a generous extirpation.

Cyst Evacuation.—Here the problem is still more simple, but unhappily one cannot expect to encounter intrapituitary cysts in a very large percentage of cases. There has been only one lesion of this type (*e.g.* No. 29) in our entire series. In a collection of 25 operations which Toupet[251] recently gathered from the literature, glandular cysts were found in only four or five instances; and it is probable that they are not to be expected in any greater frequency—perhaps in even less frequency—than similar metamorphoses in the case of strumas of the thyroid gland.

Another type of cyst, with an accumulation of cerebrospinal fluid which appears to occupy the local arachnoidal spaces, may be encountered, and its evacuation offers particular risks, owing to the possibility of a subsequent meningeal infection.

Such a condition has been met with in three cases in our series (Nos. 36, 38 and 40), and in all of them a temporary cerebrospinal rhinorrhœa occurred, followed, in one instance (No. 40), by a severe meningitis, from which the patient fortunately recovered under hexamethylenamin. In each of these

patients, symptoms of hypopituitarism were combined with a large sella and neighborhood pressure disturbances (bitemporal hemianopsia), and in each there was an immediate post-operative improvement with widening of the visual fields.

The exact pathology of these cysts remains somewhat obscure, though the appearances suggested a circumscribed chronic arachnoiditis. In none of the cases was there any observable glandular tissue, merely a thin dural membrane separating the cystic spaces from the distended floor of the fossa. At the operation, such an accumulation of fluid in a tissue meshwork is, of course, readily distinguished from a dilated third ventricle. From a diagnostic standpoint, however, apart from the operative findings, the two conditions may be difficult to differentiate, for we have evidence to show that a ventricular hydrops can actually lead in the young to an enlargement of the sella.

The cysts which arise from an infundibular anlage (cf. Fig. 317) are obviously out of reach by a transphenoidal operation, as the pituitary body itself is interposed and the sella may be of normal configuration.

Subtemporal Measures.—Though the transphenoidal operation is to be preferred when the radiograms disclose an enlarged and bulging sella, nevertheless, even under these circumstances, the surgical problem becomes complicated when the operation does not bring one directly down upon an obvious cellular or cystic struma but upon an intervening and flattened hypophysis.

A blind attempt at partial tumor removal, under these conditions, would serve only to damage or possibly extirpate an important glandular structure still capable of some functional activity (cf. Figs. 77 and 126). Hence, if the character of the tissue, which is exposed on incising the dural capsule, leaves any doubt in the operator's mind as to whether he has exposed a flattened gland or an actual growth or glandular struma, it is best to remove a small fragment for microscopical examination, and to postpone further measures until a subsequent session (*e.g.* Nos. 18, 32, 34 and 36), temporarily abandoning the operation as a simple sellar decompression, which, of itself, as has been indicated, may be of considerable therapeutic benefit.

When one is confronted with uncertainties of this sort, all the room possible is essential; and this is one reason why the small avenue of approach, to which the operation is restricted by the endonasal route, may give unnecessary hazard. Still another reason why the rhinologist should hesitate to attack these cases unless he acts in coöperation with a neurological surgeon or is himself prepared to follow up his transphenoidal operation by some intracranial measure, is the possible necessity, under these circumstances, of a subsequent craniotomy.

It is to be acknowledged, however, that in the majority of cases in which the lesion is inaccessible from below, the need for some intracranial measure will have been obvious from the outset, for in many of the patients pronounced neighborhood or even general pressure symptoms are so disproportionate to the alteration in sellar configuration as to make an interpeduncular and extrasellar lesion seem probable. Still, this is not always determinable.

We learned in some of our early experiences that a subtemporal decompression gave considerable relief to patients who were suffering from the effects either of heteroplastic interpeduncular tumors or from

an intracranial extension of actual glandular strumas (*e.g.* Nos. 1, 2, 3, 15 and 18). Others who were not given the advantage of this measure (Nos. 7, 16 and 21) would doubtless, as events proved, have been benefited thereby. Still others (Nos. 17 and 26) carried lesions which had advanced to such a stage that the measure was futile; and in No. 11 the operation gave no relief and was evidently ill-advised.

In several of the later cases (Nos. 18, 19, 27, 32, 36 and 43) a subtemporal exploration was attempted in combination with the decompression—a far more elaborate procedure, which possibly deserves an especial word of description, though I do not feel that the technical features of the measure are by any means as yet perfected.

An osteoplastic resection is necessitated, and though the lesion is median, so that either side may be used, the right is to be preferred, as the least important hemisphere will thus need to be dislocated. The posterior leg of the incision should be carried down to the zygoma, removal of which is desirable as in the case of the ganglion operation, for one must get as far under the temporal lobe as possible, to avoid an unnecessary degree of cerebral compression from elevation of the lobe. Naturally, the very conditions which call for the operation are ones often coupled with an increase of tension, and a wide opening of the dura in correspondence with the bone-flap is needed to permit of sufficient dislocation.

In the cadaver, as is true of the normal living brain, after the cerebrospinal fluid has been evacuated by a lumbar puncture, and especially if the patient is placed head down (the overhanging brain position of Karplus and Kreidl), it is an easy matter to over-ride the edge of the tentorial opening and to bring the third nerve, hypophyseal stalk and carotid artery into view. However, when there is increased tension, it is a far more difficult procedure, even with complete withdrawal of fluid by lumbar puncture—a measure which, fortunately, entails far less risk to these individuals than to those afflicted with tumors situated elsewhere.

In the only case in our series in which the region was brought clearly into view (No. 19), there proved to be no interpeduncular tumor. In four instances (Nos. 18, 27, 36 and 43) the tension was so great that even with the low temporal approach, the degree of elevation of the temporal lobe which was thought justifiable did not permit of a view over the tentorial margin. In another (No. 32) a large struma was exposed only after vertically incising the tentorial edge; and in view of the important structures, such as the carotid artery, which may be completely enveloped by these hypertrophic growths, an extensive lateral extirpation, such as is possible by a median transphenoidal operation, would have been foolhardy. In only one patient in the entire series (No. 37), did postmortem study indicate that a lateral subtemporal operation would have offered the only chance of surgical relief. This case proved to be one of infundibular cyst surmounting a normal gland and producing a bitemporal hemianopsia.

We have thus seen that the chief service of surgical therapy in hypophyseal maladies is to afford relief to neighborhood symptoms. A lesser service has been shown to be the palliation of the manifestations of

increased intracranial tension, just as in the case of tumors originating elsewhere. Surgery may come to render a third service in the partial extirpation of the gland in states of hyperpituitarism; and there remains a possible fourth service that may be rendered in states of hypopituitarism through:

4. **Glandular Implantations.**—Under circumstances of profound secretory insufficiency, operative measures may be a necessary adjunct to the transplantation of a gland from another source, should this prove, on further experience, to be a more effective and satisfactory way of atoning for the secretory deficit than prolonged administration of extracts.

At the present time, however, one cannot speak with any great definiteness concerning these matters. Such transplantations as were found, in our experimental work,[54] to be of therapeutic benefit were made in animals who had been acutely deprived of the gland by operation, and the most successful implantations, moreover, were made in the cerebral subcortex.

The procedure has been followed in a single case in our series (No. 38), seemingly with success (cf. p. 320).

Tabulation of Surgical Experiences.—For convenience of reference, the 43 cases subjected, at the present writing, to one or another operative procedure, have been gathered chronologically in tabulated form (pp. 308–313). Only the first 28 relate to patients whose histories have been given in full in the case reports comprising Part II of this treatise. The remaining 15 have come under observation since the completion of that section, and have been included partly to bring the operative results, so far as possible, up to date and also because some of these later cases illustrate certain surgical problems which did not arise in the earlier cases of the series.

There can be no doubt but that, in some respects, a critical analysis of an individual experience with a new and difficult surgical problem, is more valuable than the assembled results of the experiences of many, even though the total number of observations may be the same. According to Hirsch,[126] in the first 53 cases recorded at various hands there were 21 fatalities, and, in all probability, the list includes a large number of isolated experiences in which there was a favorable outcome, for these are more likely to enourage prompt publication.

With the possible exception of Victor Horsley, whose results are not available, Hirsch has had the largest individual experience, confined though it has been to a single operative measure. In his last report (1911) he gives statistics of 12 operations, with two fatalities and a fatal issue in a third case with mistaken diagnosis—a mortality, in the patients with actual hypophyseal lesions, of 16.6 per cent. The experience of others, with the exception of Eiselsberg and Hochenegg, has been limited to one or two cases only, and, doubtless, the high mortality shown by the collected series is attributable partly to the individual operator's relative unfamiliarity with the various appropriate measures for different conditions and partly, in all likelihood, to the fact that, in most of the patients heretofore subjected to operation, the condition was far advanced before it was recognized or before radical measures were thought justifiable.

The table shows that in our series of 43 patients, taken as a whole, 61 operations, many of them desperate measures of last resort, have been per-

TABULATION OF OPERATIVE EXPERIENCES

With Cases Arranged in Chronological Order According to Date of First Hospital Admission

No. Patient	Date of operation	Character of operation	Surgical complication	Result	Lesion
1. Case III	(1) Feb. 21, 1902	Left subtemporal decompression	None	Unaltered	Infundibular teratoma, with the syndrome of Fröhlich and internal hydrocephalus
	(2) Mar. 8, 1902	Right subtemporal decompression	None	Improved	
	(3) Mar. 17, 1902	Suboccipital decompression	None	Aggravated	
2. Case XIV	(1) Mar. 14, 1905	Bilateral subtemporal decompression	None	Improvement for 7 years	Chromophobe struma with adiposo-genital dystrophy
	(2) Feb. 15, 1912	Transphenoidal operation by route favored since June, 1910.	None	Transient loss of vision. Subsequent improvement	
3. Case XVI	July 17, 1908	Right subtemporal decompression	None	Unaltered	Infundibular cyst or tumor (uncertified) with dyspituitarism
4. Case XXVI	Mar. 26, 1909	Modified Giordano-Schloffer transphenoidal operation with tracheotomy. Partial extirpation	None	Improved	Chromophile struma with acromegaly
5. Case XVII	(1) Oct. 12, 1909	Modified Schloffer-Eiselsberg transphenoidal operation with tracheotomy. Partial extirpation	None	Temporary (6 mos.) improvement	Large interpeduncular mixed tumor with dyspituitarism
	(2) Apr. 28, 1910	Halstead-Kanavel sublabial approach with intubation	Post-operative intracranial bleeding	Death	
6. Case VI	Apr. 21, 1910	Halstead-Kanavel approach with tracheotomy. Sellar decompression	None	Improved	Interpeduncular tumor (uncertified) with dyspituitarism
7. Case XII	(1) Apr. 30, 1910	Halstead-Kanavel approach with tracheotomy. Operation not completed	Infected antrum	Unaltered	Large chromophobe struma with intracranial extension. Dyspituitarism
	(2) May 26, 1910	Same approach without tracheotomy. Partial excision of struma	None	Temporary slight improvement	

8. Case XXXVIII.....	May 10, 1910	Modified Halstead-Kanavel approach. Tracheotomy necessitated. Sellar decompression	Accidental stalk separation: anterior lobe necrosis	Death 4th day. Medullary compression	Early acromegaly. Cerebellar cyst: internal hydrocephalus
9. Case II.....	June 4, 1910	Halstead incision with submucous resection of septum. Favored approach without tracheotomy. Sellar decompression	Fatal pressure phenomena	Death 2nd day with medullary symptoms	Chromophobe struma with intracranial extension. Acromegaly
10. Case XXIX.....	June 10, 1910	Excision of intrathoracic goitre	None	Marked improvement	Stationary advanced acromegaly with polyglandular signs
11. Case XXX.....	July 7, 1910	Subtemporal decompression	None	Unaltered	Advanced acromegaly with hypopituitarism
12. Case XIX.....	(1) July 28, 1910	Abandoned from difficulty with anæsthesia	None	Unaltered	Chromophobe struma with dyspituitarism
	(2) Aug. 3, 1910	Scopolamine. Favored approach (sublabial incision with submucous resection). Sellar decompression	None	Marked improvement; restoration of vision	
13. Case XX.....	Oct. 11, 1910	Favored transphenoidal approach. Sellar decompression	None	Improved: restoration of vision	Interpeduncular cyst or tumor (uncertified)
14. Case XXXVII.....	Oct. 25, 1910	Favored transphenoidal approach. Sellar decompression	None	Improved: restoration of vision	Interpeduncular cyst or tumor (uncertified): adiposis dolorosa
15. Case IV.....	Nov. 26, 1910	Subtemporal decompression	None	Improved	Interpeduncular tumor. Infantilism
16. Case I.....	Dec. 17, 1910	Favored transphenoidal approach. Sellar decompression. Partial excision of struma	None	Improved	Chromophobe struma with dyspituitarism. Acromegalic gigantism
. Case V.....	Dec. 27, 1910	Subtemporal decompression	Fatal pressure phenomena	Death	Chromophobe struma with intracranial extension. Adiposo-genital dystrophy
. Case VII.....	(1) Jan. 12, 1911	Favored transphenoidal approach. Sellar decompression	Orbital abscess	Unimproved	Interpeduncular tumor (uncertified) with hypopituitarism
	(2) Mar. 29, 1911	Subtemporal decompression	None	Relief of pressure symptoms with return of vision	

TABULATION OF OPERATIVE EXPERIENCES.—*Continued*

No. Patient	Date of operation	Character of operation	Surgical complication	Result	Lesion
19. Case XLVI	Mar. 11, 1911	Combined subtemporal exploration and decompression. Overhanging brain position: negative findings	None	Improvement	Polyglandular syndrome
20. Case XXI	Mar. 18, 1911	Favored transphenoidal approach. Sellar decompression. Partial extirpation of struma	None	Improvement in vision	Chromophobe struma with dyspituitarism
21. Case XI	Apr. 20, 1911	Favored transphenoidal approach. Sellar decompression. Partial extirpation of struma	None	Temporary amelioration	Chromophobe struma with intracranial extension: dyspituitarism
22. Case X	May 18, 1911	Favored transphenoidal approach. Sellar decompression. Partial extirpation of struma	Otitis media	Marked improvement	Chromophobe struma with adiposo-genital dystrophy
23. Case XIII	May 25 and May 31, 1911	Exploration of pineal region in two stages	None	No improvement	Gigantism with presumed pineal lesion and hydrocephalus
24. Case XXII	June 16, 1911	Favored transphenoidal approach. Sellar decompression. Partial extirpation of struma	None	Improvement, with restoration of vision after blindness	Chromophobe struma with hypopituitarism
25. Case XXIII	Aug. 15, 1911	Favored transphenoidal approach. Sellar decompression. Partial extirpation of struma	None	Improvement	Chromophobe struma: dyspituitarism
26. Case VIII	Aug. 16, 1911	Urgent subtemporal decompression for intracranial pressure	Exaggeration of pressure symptoms	Death 3rd day	Large interpeduncular endothelioma. Hypopituitarism
27. Case XLV	Sept. 10, 1911	Subtemporal exploration and decompression	None	Improved	Polyglandular syndrome. Adiposo-genital dystrophy; hydrocephalus
28. Case XLVII	Sept. 12, 1911	Exploration of pineal region. Osteoplastic resection: drainage of ventricle	None	Unimproved	Polyglandular syndrome: gigantism: sexual precocity: hydrocephalus

29. Surg. No. 28382.....	(1) Sept. 19, 1911	Subtemporal exploration and decompression	None	Unimproved	Cystic degeneration of chromophobe struma. Genital dystrophy
	(2) Oct. 11, 1911	Favored transphenoidal approach. Sellar decompression: evacuation of cyst	None	Improved: immediate restoration of vision after blindness	
30. Surg. No. 28485.....	Oct. 12, 1911	Favored transphenoidal approach. Sellar decompression. Extensive extirpation of struma	None	Great improvement	Hypophyseal struma with genital dystrophy
31. Surg. No. 28552.....	Oct. 19, 1911	Favored transphenoidal approach. Sellar decompression. Partial removal of struma	None	Marked improvement: restoration of vision. Radiotherapy	Chromophobe struma: intracranial extension. Acromegaly
32. Surg. No. 28563	(1) Oct. 20, 1911	Favored transphenoidal approach. Sellar decompression. Fragmentary removal of struma	None	Unaltered	Large struma with intracranial extension. Dyspituitarism
	(2) Nov. 4, 1911	Subtemporal exploration and decompression: fragmentary removal of struma	None	Unaltered	
	(3) Nov. 23, 1911	Second transphenoidal operation	None	No improvement until after radiotherapy	
33. Case XXXVI.....	Oct. 25, 1911	Favored transphenoidal approach. Sellar decompression. Partial removal of struma	None	Immediate improvement	Chromophobe struma: genital dystrophy: adiposity
34. Surg. No. 28624.....	(1) Nov. 1, 1911	Favored transphenoidal approach. Sellar decompression. Partial removal of struma	Post - operative diabetes insipidus	No improvement	Chromophobe struma: genital dystrophy: blindness
	(2) Dec. 4, 1911	Subtemporal decompression	None	No improvement until after radiotherapy	
35. Case IX.....	Nov. 9, 1911	Favored transphenoidal approach. Extensive extirpation of struma	None	Improved	Large chromophobe struma. Uncinate attacks: adiposo-genital dystrophy

TABULATION OF OPERATIVE EXPERIENCES.—*Continued*

No. Patient	Date of operation	Character of operation	Surgical complication	Result	Lesion
36. Surg. No. 28672.....	(1) Nov. 9, 1911	First-stage subtemporal exploration	None	Unaltered	Large interpeduncular growth (uncertified): general pressure signs: uncinate fits: primary optic atrophy, etc.
	(2) Nov. 18, 1911	Sellar decompression by favored transphenoidal route. Evacuation of cyst	Temporary cerebrospinal rhinorrhœa	Improved	
	(3) Dec. 7, 1911	Second-stage subtemporal operation, leaving decompression. Overhanging brain position	None	Further improvement	
37. Surg. No. 28747.....	Nov 21, 1911	Favored transphenoidal operation attempted. Misdirected approach owing to anatomical peculiarities: opening of ethmoidal plate	Meningitis	Death on 13th day	Infundibular cyst with dyspituitarism: bitemporal hemianopsia
38. Surg. No. 28818.....	(1) Nov. 30, 1911	Right subtemporal decompression for urgent pressure symptoms	None	Improved	Hypophyseal cyst with hypopituitarism: diabetes insipidus: bitemporal hemianopsia
	(2) Dec. 15, 1911	Sellar decompression by favored transphenoidal route. Evacuation of cyst	Temporary cerebrospinal rhinorrhœa	Immediate improvement in neighborhood signs	
	(3) Feb. 2, 1912	Subcortical implantation of gland of newborn	None	Great improvement in glandular signs	
39. Surg. No. 28861.....	Dec. 9, 1911	Suboccipital decompression for presumed cerebellar syndrome (cf. No. 8) with marked pressure symptoms	None	Relief of pressure symptoms	Cerebellar syndrome with enlarged sella and internal hydrocephalus. Hypopituitarism

40. Surg. No. 28986.....	(1) Jan. 4, 1912	Attempted sellar decompression by favored transphenoidal route: abandoned	Anatomical peculiarities	Unaltered	Hypophyseal cyst: enlarged sella: bitemporal hemianopsia. Puerile type of hypopituitarism
	(2) Jan. 19, 1912	Secondary operation with evacuation of cyst	Meningitis	Immediate restoration of vision: recovery	
41. Surg. No. 29020.....	Jan. 8, 1912	Right subtemporal decompression for pressure symptoms	None	Slight improvement	Interpeduncular tumor (uncertified). General pressure signs: blindness following bitemporal hemianopsia: uncinate symptoms
42. Surg. No. 29117.....	Jan. 27, 1912	Favored transphenoidal operation with sellar decompression and partial extirpation of struma	None	Improvement in vision. Radiotherapy	Hypophyseal struma: enlarged sella: bitemporal hemianopsia. Slight acromegaly: dyspituitarism
43. Surg. No. 29162.....	Feb. 1, 1912 Feb. 7, 1912	Two-stage subtemporal exploration: lumbar puncture. Overhanging brain position. Decompression	None	Great improvement	Interpeduncular tumor (uncertified). Enlarged sella: uncinate seizures. General pressure symptoms. Slight dyspituitarism

Numbers 29 to 39 of the above table include cases which have come under observation subsequent to the completion of Part II of this monograph in September, 1911, and before the completion of this last section in February, 1912. Hence, with the exception of the histories of two patients (No. 33, Case XXXVI, and No. 35, Case IX) who were not operated upon when first seen—namely, before September, 1911—the detailed report of these more recent histories has not been included.

Between February 1 and April 1, while the manuscript has been in press, there have been nine additional cases, most of them with lesions demanding operative intervention.

formed, with an operative mortality of about 10 per cent. for the entire series. In a few instances, the impending fatal issue was definitely hastened by the operation. In two cases (Nos. 17 and 26), with the patients *in extremis*, the fatality followed subtemporal decompressions carried out in the attempt to combat advanced general pressure symptoms. In two others (Nos. 8 and 9) death occurred on the second and fourth day after a misjudged transphenoidal operation, when actually some cerebral decompressive measure was called for. In No. 5, a second attempt, after a long interval, to partially excise a large heteroplastic tumor led to a fatality from intracranial extravasation. In the remaining and sixth fatal case (No. 37) death from meningitis on the thirteenth day was due to a faulty approach occasioned by an erroneous regional diagnosis, this being the only instance in which a fairly livable existence was definitely shortened by the operation.

Thus, *in* 29 *actual attacks on the lesion by the transphenoidal route, there have been four deaths* attributable to the operation—a mortality for this procedure of 13.7 per cent. In all probability, with our present greater familiarity with these conditions, the fatal outcome in these four cases could have been avoided. However, in three of them the result would have been the same without operation, and under desperate circumstances both patient and surgeon may feel forced to accept extreme hazards.

Especially to be regretted is the single experience (No. 37) in which, through misinterpretation of the conditions, a transphenoidal rather than a subtemporal route was chosen; and in carrying out the procedure a technical blunder was made, leading to a fatal meningitis. In the cases which were actually favorable for a transphenoidal attack, the mortality figures have been negligible; and with improving diagnostic capabilities past errors should be avoided.

The transphenoidal operation will doubtless come to be regarded as an operation comparatively free from risk. Unquestionably, its performance is less hazardous than is the exposure and partial enucleation of pituitary lesions by the subtemporal route or measures such as the exploration of the pineal region. No fatalities have occurred in the series after these measures, admittedly for the reason that, with the exception of No. 32, in no instance was it found feasible to attempt the partial extirpation of an exposed lesion.

But, even including the unfavorable with the more favorable cases, a mortality ranging around 15 per cent., as in our series and in that of Hirsch is encouraging, in view of the present relative inexperience of us all. As is true of the Gasserian ganglion operation for major neuralgia, which showed for the first 100 cases in the literature a mortality equally high, so with the pituitary operations the figures should improve until a consecutive 100 cases can be given the benefit of surgical measures without a fatality, as we have found to be possible in the case of the trigeminal operation—unquestionably, on technical grounds, the more difficult of the two procedures.

In résumé : The operation of choice for the majority of cases, as being less mutilating and yet one which furnishes as wide an avenue of approach as any, is a transphenoidal operation through a median inferior nasal opening, reached by a sublabial incision and a submucous resection of the vomer, the turbinates being flattened but not removed. The essential precautions are (1) to be correctly oriented in regard to the sphenoidal cells so as to avoid a

misdirected approach to the posterior ethmoid region, where a projection of the cribriform plate may suggest to the inexperienced the hypophyseal floor; (2) to be sure of the local conditions by a careful stereoscopic study of X-ray negatives and to operate under their guidance; (3) to have perfect anæsthesia; (4) to have the courage to withdraw for a second session in case there is any uncertainty as to the character of the tissue exposed after incising the pituitary capsule.

The operation of second choice—a subtemporal procedure—may be necessary in the case of a superimposed lesion with small sella, or when with an enlarged sella a flattened gland is interposed. As a rule, this means little more than a decompression, though in favorable cases it may be possible to expose and partially remove a struma or to evacuate a cyst by this lateral method of approach.

Surgical measures resolve themselves (1) into a sellar decompression (a) for persistent hypophyseal headaches, (b) for the purpose of encouraging the extension of a glandular struma in the direction of the sphenoidal cells rather than into the cranial chamber; (2) into the partial removal of an hyperplastic gland in the active stage of hyperpituitarism; (3) into the partial removal of a tumor or struma for the relief of neighborhood symptoms; (4) into a subtemporal decompression for the palliation of pressure symptoms when an intracranial extension has occurred; (5) into a subtemporal or sellar decompression, or both, to permit of the more favorable and direct application of radiotherapy; (6) into the exposure of the brain or of some other organ in case of marked hypopituitarism, for the purpose of implanting a viable gland.

OTHER THERAPEUTIC MEASURES

Glandular Administration.—For a number of years sporadic attempts have been made to apply Brown-Séquard's principle of organotherapy in the treatment of acromegaly, for this condition, and its cousin gigantism, long remained the only maladies which with any degree of probability could be ascribed to an hypophyseal disorder. Beneficial results were occasionally observed, but more often they were negative, or, indeed, the treatment was actually harmful, as experiences reported by Rénon and Delille and by Parisot would indicate.

This we can now the better understand, for only when hyperpituitarism has passed over into the stage of glandular insufficiency will a rational basis exist for pituitary feeding. In the active stages of acromegaly one would expect symptoms to be exaggerated, just as thyroid administration exaggerates the clinical signs of exophthalmic goitre.

It was our experience with the series of experimentally hypophysectomized dogs to find that animals suffering from a known deficit of glandular secretion could be benefited by injections of extracts, by glandular feeding or by implanta-

tions of hypophyses from other sources. Frequently after a complete hypophysectomy, a subcutaneous or intravenous injection of the emulsion of a single fresh gland would temporarily arouse to apparently normal activity a somnolent animal in whom a subnormal temperature betrayed the onset of cachexia hypophyseopriva. Other animals in whom "nearly total" removals had been performed could by glandular administration be permanently tided over the critical post-operative period in which acute symptoms of glandular insufficiency augured a fatal issue, the remaining fragment of gland in the meantime undergoing a compensatory hyperplasia until it sufficed for the physiologcal needs of the animal, at which time the glandular feeding could be safely discontinued. Similarly an immediate auto-transplantation of a totally excised gland served the same purpose, it having been found[54] that the exposed cerebral cortex was possibly the place most favorable for a successful implantation. It has seemed to us, furthermore, that the characteristic hæmodynamic, thermic and other reactions known to follow injections of extracts are more pronounced in animals suffering from some degree of glandular deprivation than in animals with a normally active gland.

One result of these early experiments, as heretofore stated, was the shedding of light on the symptomatology of states of hypopituitarism which had hitherto been somewhat obscure, and consequently it was a natural conclusion that the same therapeutic measures found to be of service in the experimental states might be employed with corresponding benefit in the human cases. The manifestations of glandular deficiency, whether or not they are accompanied by neighborhood symptoms or by evidences of pre-existent overactivity with more or less marked acral overgrowth, are—as heretofore pointed out—a tendency to a subnormal temperature, dry skin, loss of hair, a slowed pulse, a lowered blood pressure, asthenia and an increased assimilation limit for carbohydrates often associated with a tendency to adiposity. Other less striking symptoms are constipation, polyuria and variable psychoses with a tendency to epileptiform seizures.

Unquestionably these symptoms can be ameliorated by glandular administration in one form or another. In view of the fact that the malady is a polyglandular one, as has been emphasized, the administration of extracts of glands other than the one primarily involved—at least of glands such as adrenal and thyroid, which show secondary deficiencies—may be of service. Examples are given in the case reports of patients definitely improved by thyroid feeding, and in the case of a eunuchoid giant with signs of secondary hypo-adrenalism (asthenia, pigmentation and low blood pressure) I have seen marked benefit from adrenal administration.

There can be little doubt, however, that the administration of extracts of the structure primarily at fault gives the best therapeutic results, but in the case of the hypophysis not only are the extracts difficult to prepare and standardize, but the proprietary preparations are as yet so expensive as to preclude the prolonged administration in sufficient doses for all needy patients.

In our early experiments we prepared our own powdered extracts from the three hypophyseal subdivisions—pars anterior, pars intermedia and pars nervosa—by careful dissection of fresh glands, obtained at the abattoir, from swine or cattle. We found the preparations from the mercantile houses to

be somewhat less dependable in their clinical results; and laboratory tests of the preparations have shown a wide variability in reaction.

Ingestion Methods.—Doubtless for prolonged glandular feeding—at least until the active principle of one of another portion of the gland comes to be synthetized—the dry powdered extracts secured after passage of the fresh gland through a Buchner press are the most convenient.

In the present state of our knowledge dependence must be had for the most part on whole-gland administration, for in the majority of cases in which the structure is subjected to the effects of pressure, both divisions of the gland are alike rendered functionally insufficient. We may, however, expect the time to come when the symptomatic manifestations of underaction of one or another portion of the gland will be sufficiently well recognized to justify the administration of extracts of that division alone.

Admittedly there is great difficulty even in determining the rational dosage of extracts for patients obviously suffering from insufficiency of the entire structure. The same difficulty, indeed, faces us in the therapeutic employment even of the more familiar extracts of the thyroid gland, the dosage of which is roughly established for the individual case only after experimental trials with the given preparation.

As shown by Hunt and Seidell great inaccuracies in the case of thyroid medication are due to the wide variations in the iodine content of the thyroid of the sheep, the animal which usually furnishes the extracts used for medicinal purposes. In all probability, one is even less likely to obtain preparations of uniform activity in the case of a gland such as the pituitary body, of whose chemistry little is known and whose active principle doubtless varies greatly at different times of the year and under different physiological conditions.* In the lack of a definite symptomatic telltale of the degree of hypophyseal insufficiency we have had recourse to the carbohydrate tolerance as a measure of the deficit, and so far as our experience has gone, this furnishes us with the only rational estimate of the requisite dosage of a given preparation.

Comment has been made on the fact that, in experimental as well as in clinical conditions of hypopituitarism associated with a high sugar tolerance, the assimilation limit can be lowered by the coincident administration of glandular extracts, particularly of those obtained from the posterior lobe. Thus in hypopituitarism the rational dosage of glandular extract to be administered by mouth can possibly be determined by giving the individual daily an amount of

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* Of the several proprietary preparations which we have used, the largest experience has been had with Armour & Company's preparation. Their three-grain tablets, either of whole gland or of anterior or posterior lobe substance, actually contain only one grain (0.06 gram) *of the desiccated bovine gland.*

The Burroughs Wellcome & Company two grain "tabloids" each represent only 2 grains (0.13 gram) *of the fresh substance*—an exceedingly small dosage. Judging from our own preparations in the Hunterian Laboratory, obtained by extracting with the Buchner press, each fresh bovine gland gives 0.013 gram (0.2 grain) of powdered extract. Thus a tablet containing 1 grain of the desiccated substance would represent the extractives of about five fresh glands.

Before prescribing, *it should* therefore *be clearly understood just what is indicated by the given weight of a proprietary tablet,* whether it implies a certain amount of fresh gland substance of desiccated gland substance, or refers only to the actual bulk of some mixture used in the process of manufacture.

glucose or lævulose sufficient to produce a temporary mellituria in a normal individual of equal body weight; meanwhile an increasing amount of the extract is administered daily, until, under the conditions of increased carbohydrate tolerance which the patient exhibits, hyperglycæmia occurs with a trace of sugar in the urine.

On this basis, in a number of our patients (*e.g.* XI, XXVIII and XXXVI) the sugar tolerance has been effectively used as a measure of the organotherapeutic dosage. However, some patients are intolerant of the sugar tests, and it has been impossible in others, even with prohibitive doses of extract by mouth, to produce a lævulosuria with amounts of lævulose supposedly representing the normal assimilation limit per kilo. of the individual's weight.

One of the acromegalics with present dyspituitarism (Case XXX) is a notable example of this, for the consumption of 100 grains of the Armour whole-gland preparation three times a day fails to give lævulosuria with the coincident administration of 200 grams of lævulose. Remarkable to say, however, with this formidable dosage of the extract which he has continued to take for some months he experiences definite subjective benefit. In all probability cases with such pronounced deficit deserve glandular implantation.

As recorded in some detail in the "subsequent notes" of the case records, many of the patients, since our first attempts in this direction in the fall of 1910, have been given routine glandular feeding, for in a large percentage of the cases in which surgical measures are indicated for the relief of neighborhood symptoms there exists an obvious secretory deficiency which calls for supplementary glandular medication.

Specific reference may be made to a few of the patients in whom organotherapy with administration of extracts by mouth was obviously beneficial. In Case VII, although the pressure symptoms were alleviated by the surgical measures, definite improvement in the manifestations of glandular insufficiency did not occur until glandular feeding was instituted, and under this régime menstruation was re-established after a year of amenorrhœa. Similarly in Case X there was not only marked improvement in the general constitutional conditions due to the glandular deficit, but under the combined surgical and organotherapeutic measures there was a return of libido et potentio sexualis after long abeyance.

In only a few of the patients has the tendency to adiposity been definitely controlled, though under the treatment there has been a considerable loss of weight in some instances, particularly in patients with primary hypopituitarism in the absence of tumor. Thus in Case XXXVI, as related in the history, with each period of glandular administration there occurred a loss of five or six per cent. in weight, which was quickly regained on interrupting the treatment. It is recognized, of course, that extracts of other ductless glands than the one primarily involved in these patients may similarly stimulate tissue katabolism, and in several of the more adipose individuals a combination of thyroid and hypophyseal feeding has been instituted, largely because of the expense of long-continued pituitary administration. In some

instances, however, (*e.g.* Case XLIII) attempts to combine the extracts caused disturbing symptoms.

A particularly good example of loss of weight under pituitary feeding is given by Case XXXIV, a youth with adiposo-genital dystrophy. Under the continued use of the extract, not only has this boy's weight diminished 18 pounds (15 per cent.) with loss of his former feminine outlines, but there has been a complete mental and physical regeneration as well. Axenfeld, Elschnig and Fleischer have recorded similar instances of improvement in individuals exhibiting the syndrome of Fröhlich. However, only since experimental counterparts of these conditions brought about by glandular extirpations made it clear that the clinical manifestations were actually those of glandular insufficiency has the rational application of pituitary administration been possible; and it is to be expected that instances of the beneficial effects of organotherapy in these states, such as Eason[65] has recently described, will soon multiply in the literature.

Unquestionably in many of the earlier feeding experiences a dosage was used which did not suffice to markedly affect the adiposis. Nevertheless, even with the amounts that were given, a definite symptomatic amelioration was usually apparent in other directions. The case records show that the body temperature is apt to regain its normal level, that the blood pressure becomes higher, constipation less troublesome, and that there is less drowsiness and often a marked improvement in mental activity. Comment has been made also on the amelioration of symptoms in certain cases of epilepsy which were suggestive of hypophyseal origin.

A good illustration of the general improvement in the whole physical and mental tone under the régime of continued organotherapy in the dosage, established for the patient's particular case, of 12 grains of the dried whole-gland preparation three times a day, is given by Case XXVIII, an acromegalic with beginning signs of glandular insufficiency.

However, the therapeutic administration of extracts by mouth is fraught with many disappointments. Attention has been drawn to the fact that a prohibitive dosage of 300 grains daily was needed in Case XXX to give the subjective benefit which other patients with glandular insufficiency experienced with far smaller amounts; and there have been examples in the series of individuals in whom the glandular administration by mouth was so ineffectual that recourse was had to:—

Hypodermic Administration of Extracts.—It was estimated by Goetsch during our studies of experimental canine hypopituitarism that the subcutaneous administration of posterior lobe extracts was more effective in lowering the assimilation limit for sugars than the administration by mouth in the proportion of four to one, and that in about a ratio of two to one the intravenous administration was more effective than the injection of the extract in the tissues.

The subcutaneous method of administration alone sufficed to arouse one of the patients (Case IV)—an example of infantilism of the type Lorain—to some measure of wakefulness and mental activity. Still more striking has been our experience with a recent case (No. 38 of the table).

In this patient the degree of somnolence, approaching unconsciousness, with subnormal temperature (often ranging about 96°), slow pulse and respiration, and low blood pressure, was extreme.

Soon after his hospital admission, owing to a period of Cheyne-Stokes respiration we were led, under the mistaken idea that these were pressure phenomena, into an emergency subtemporal decompression, for which, however, no anæsthetic was necessary. No increase of tension was disclosed by the operation.

The patient was subsequently given glandular extract by mouth in large doses, with but little if any improvement. It was found, however, that he could be aroused for a day or two by sporadic injections of extracts, and these were given from time to time when the somnolence was of such a degree as to cause particular anxiety.

After some weeks we ventured to undertake a transphenoidal operation, and, fortunately, an hypophyseal cyst was found and evacuated. There was an immediate restoration of normal mental and physical conditions, due, as we thought, to the liberation of a compressed gland by the operative manipulations. However, after a transient lucid interval of ten days, he lapsed again into his former profound torpor.

Glandular feeding was resumed, but as it again proved ineffective even in large doses, recourse was had to consecutive daily injections of boiled whole-gland extract in a dosage representing 2 grains of the desiccated preparation.

The result was amazing. He roused completely, and for a period of two weeks seemed normal in every respect, mentally active and physically vigorous.

Owing to the increasing soreness from the injections, however, they could not have been continued for a much longer period, and finally the hypophysis from a newborn child, the victim of a birth hæmorrhage, was implanted in the subcortex of the temporal lobe at the site of the original decompression, and it was found possible to discontinue the injections without the patient's relapsing into his former somnolent state.

Glandular Transplantation.—The experience recounted above represents our first attempt in man to supply a functional deficit by hypophyseal implantation. The case was an ideal one for the experiment, for the destruction of the gland through cystic degeneration had seemingly been almost complete and without complication from other factors, such as cerebral compression. The symptoms were verging toward the familiar cachexia hypophyseopriva which follows extirpations of the canine gland. The tissue which was secured for transplantation, through the co-operation of Dr. J. W. Williams, was unfortunately not obtained as soon after the infant's death as might have been desired, and it was feared that the results of the implantation would be merely equivalent to the introduction of such an amount of the active principle as the gland actually contained, with a result no different from that which would have followed the transplantation of a gland from another species.

Though from all clinical indications it would seem that the implanted fragment remains viable and has assumed a sufficient measure of functional activity in this particular patient, the only unequivocal proof of this, namely, the extirpation of the fragment with consequent return of the former outspoken symptoms of deficiency, is of course not to be thought of.

Although in the case of thyroid deficiency successful transplantations have been made at the hands of Kocher and others, the whole question is still very unsettled. Doubtless much may be expected from these measures in the future, and successes in this direction will be particularly gratifying if they serve to free these unfortunates from the bondage of a life-long continuance of glandular administration.

In order to insure the greatest probability of a successful implantation, it would seem that the best plan of procedure would be, after the method of Harrison, Carrell and Burrows, to secure a growth *in vitro* of the tissues to be implanted. When a gland is finally secured which can be cultivated in the plasma of the prospective host, the growing fragments may then be injected into the most favorable tissue, possibly even hypodermically, with a probability of "taking." Under these circumstances the survival of the fragments can be foretold with a measure of definiteness which does not pertain to the haphazard implantation of a gland which possibly may find the new soil unfavorable.

Radiotherapy.—In none of the cases recorded in full in Part II was recourse had to the X-rays as a means of controlling the advance of a strumous hyperplasia. However, in some of our more recent cases (*e.g.* Nos. 31, 32, 34, 35, 42) the results have been so encouraging as to justify a word in regard to this therapeutic adjunct to the operative measures.

Certain observations, notably those of Gramegna,[103] Béclère[15] and Jaugeas,[133] scanty though they are, nevertheless show that in certain forms of hypophyseal tumor prolonged röntgenization has a notable effect in ameliorating the neighborhood symptoms, due in all likelihood to a definite shrinkage of the growth. A widening of the constricted fields of vision serves as a reliable index of any diminution in the size of the struma.

These results are explicable on the ground of the elective sensitivity of certain cells to the action of the Röntgen rays; and it would appear that neoplastic cells of epithelial type are particularly prone to undergo atrophy without inflammatory reaction under prolonged exposures. Hence, in view of the fact that the surgical measures at our disposal are merely palliative and directed toward neighborhood symptoms alone, and in the case of an advancing struma are in no sense curative, it is possible that radiotherapy should often be employed as a supplementary measure.

It would seem that the treatment is particularly suited to the type of rapidly enlarging struma which we have described as characterizing most of the cases comprised in our Group II. In view of the encouraging experiences with some of the later patients, it is lamentable that individuals, such as Cases I, XI and XII, with far advanced lesions, were not given the benefit of these measures.

In several cases after almost complete blindness vision has been restored under the combination of partial surgical removal of the struma and subsequent repeated exposures. In two or three cases (*e.g.* Nos. 32 and 34) in which the pressure symptoms remained marked despite the partial emptying of the sella—so marked indeed that subsequent subtemporal decompressions were performed—radiotherapy has led to an evident diminution of all of the tension phenomena.

After these operations conditions are particularly favorable for the therapeutic employment of the rays, which it has been our custom, under Dr. Baetjer's guidance, to give on alternate days, through the nares and at the side over the temple. The direct impingement of the rays on the denuded lesion is rendered possible after a sellar decompression, and the subtemporal

bone defect likewise, in all probability, makes their lateral application more effective than would be the case were the skull intact. Under normal circumstances, with an interposed bone, Jaugeas has estimated that the radiotherapeutic dose absorbed by the hypophysis is only $\frac{1}{5}$ to $\frac{1}{10}$ of that absorbed by the skin.

It is, of course, to be recalled that the earlier encouraging reports by Schwartz, Freund, Cook and others concerning the beneficial effects of the rays in exophthalmic goitre have seemingly failed of substantiation upon a more extensive experience, although the exposures unquestionably were shown in some cases to have diminished the size of the gland to a certain extent.

Hence we must be prepared for a like disappointment in the case of the hypophyseal strumas. It is to be recalled, however, that we are dealing in the two instances with quite different types of epithelial hyperplasia; and it is possible that the progressive multiplication of cells in the case of the hypophyseal lesion may be no less effectively checked, under the influence of repeated exposures to these mysterious rays, than is cell division of the spermatogenous epithelium of the testis.

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