PARTIAL HYPOPHYSECTOMY FOR ACROMEGALY.*

WITH REMARKS ON THE FUNCTION OF THE HYPOPHYSIS.

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RAPID advances in our knowledge of the physiology and pathology of the thyroid gland followed on the heels of the early surgical experiences, showing the danger of total extirpation of goitrous tumors which, after the example of Kocher and Reverdin, were being subjected to operation at the hands of many. In some cases an acute disturbance (cachexia strumipriva) supervened; in others, a chronic state of malnutrition, which was soon recognized as identical with the condition "myxœdema," to which Sir William Gull had called attention.

These early clinical observations provoked studies which led to the discovery of the separate function of the thyroid gland and the parathyroid glandules of Sandström and Gley; to an understanding of the clinical manifestations not only of hyper- and hypothyroidism, but of tetany as well; to the modern methods of partial thyroidectomy for cases in which the gland is hyperactive and to organotherapy for conditions of deficient activity—one of the triumphs of experimental medicine.

Surgical experiences will doubtless come to play a similar rôle in helping to untangle the complexities of the functional disturbances of hypophyseal origin. Surgeons, however, cannot afford to enter into this new field too precipitously, not simply by reason of the peculiar inaccessibility of the gland—for operative resources will overcome these difficulties—but principally on account of the present uncertanties

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in regard to its physiological properties. We at least should profit by the lessons taught us by the earlier experiences with the operations on the thyroid, undertaken before there was a full understanding not only of the clinical consequences of total extirpation but also of the double glandular function (thyroid and parathyroid).

Surgery of the hypophysis up to the present time, with the possible exception of the case that I am about to report, has been limited solely to an attempt to remove tumors or to evacuate cysts originating either in the gland itself or in its immediate neighborhood—a period in the development of these matters comparable to the early chapter in the history of the thyroid when operations were restricted to the removal of goitrous cysts or tumors which were causing pressure symptoms. Beyond question, however, as was true of the thyroid, there will prove to be innumerable instances of more or less pronounced over-activity of the hypophysis, as well as cases of under-activity, *unassociated* with tumors; and it is necessary, before we can establish any rational basis for treatment, that we have a clearer understanding of the clinical manifestations of these states. This applies not only to surgical measures but to organotherapy as well,—for the administration of the gland or of glandular extracts, in the light of our present knowledge, must still be carried out most blindly.

I shall endeavor in this communication (1) to state briefly the existing views in regard to the rôle of the hypophysis in disease; (2) to recount the few facts which are known concerning the function of the gland; (3) to give the bare results of our own experimental work, which has served in a measure to throw light on the condition of hypophyseal deficiency (hypopituitarism); (4) to report a successful case of partial hypophysectomy for acromegaly (hyperpituitarism); and (5) to discuss the lines along which surgical measures must in the future be directed.

1. *Hypophyseal Diseases.*—To review an old story, the peculiar symptom-complex to which the name acromegaly was

given was described in 1886 by Pierre Marie; and a few years later he expressed the view, based on the post-mortem findings in certain cases, that the malady was associated with a definite enlargement of the pituitary body, either a hyperplasia or an adenomatous growth. Since then gigantism has come to be regarded as an allied condition dating from youth and likewise associated with tumor or enlargement of the gland. These observations have been followed by innumerable reports, some of them confirmatory, others opposed to Marie's view; for there have been cases of acromegaly recorded in which the hypophysis is said to have shown no pathological change, and a particularly large number of cases in which tumors of the gland or its neighborhood have been *unaccompanied* by symptoms of acromegaly.

A review of many of these latter reports, together with the study of certain patients seen in the clinic of Frankl-Hochwart, led Fröhlich to the view that a certain definite syndrome associated with adiposity and arrested sexual development was characteristic of a number of these cases of hypophyseal tumor in which manifestations of acromegaly were absent. Renewed interest in the surgery of the hypophysis followed Schloffer's proposal of a transphenoidal approach to the gland, and a few of these patients with this syndrome have since been operated upon by von Eiselsberg and others, with evident amelioration of the symptoms.

As yet, however, there has been no corroborative experimental proof of the relation either of the syndrome of Fröhlich or that of Marie to any definite alteration of the gland—far from any determination as to whether such histological alterations as have been found represented a condition of over- or under-activity. Indeed, I have been unable to gather from the writings of Marie and his associates whether, in the light of conjecture, they finally came to regard acromegaly as due to under-secretion or over-secretion of the affected gland or one of its subdivisions.

In Hochenegg's successful case of operation for acromegaly the striking shrinkage of the tissues involved in the

over-growth led Stumme, who made the full report of the case, to the natural supposition that the condition represents one of hypophyseal over-activity comparable to the over-activity of the thyroid in exophthalmic goitre. However, the marked improvement which has followed similar operations with partial extirpation of hypophyseal tumors associated with the syndrome of Fröhlich in the absence of acromegaly, has led to further confusion as to the actual part played by the pituitary body in these dissimilar states.

2. *Hypophyseal Function.*—Marie's clinical observations stimulated physiologists to a renewed interest in the gland, and it was found by Howell that the posterior lobe (pars nervosa) contained a blood-pressure raising principle and by Schäfer that a substance producing diuresis was present in the same part of the gland. Here the matter has remained practically stationary so far as the results of injections are concerned.

Since Horsley's brief statement in 1886 to the effect that he had removed the hypophysis from a few dogs without appreciable effect, there have been endless reports of investigations on animals of various species by divers operative procedures which have left the question of extirpation and its consequences a most unsettled one. Some have claimed that removal of the gland is incompatible with life; others that its loss has no effect on the physiological status of the animal whatsoever. A series of successful extirpations in dogs by a new operative method, however, has led Paulesco to emphasize again that the gland is essential to life; for after a total hypophysectomy all of the animals succumbed in the course of a few days to a definite train of symptoms (cachexia hypophyseopriva); a fragment of the gland, on the other hand, was found to have been left *in situ* in all of the animals which survived.

3. *Experiences with Experimental Hypophysectomy.*—In association with Dr. S. J. Crowe and Dr. John Homans an extensive series of observations has been made during the past year which has led us to fully support the main conten-

tion of Paulesco; namely, that at least a fragment of the gland is essential to the long continuance of life. All told, there have been over one hundred of these operations on the canine, carried out by a method very similar to the bilateral craniectomy used by Paulesco.

It is, however, upon the disturbed equilibrium of the animals that were observed for a long period after *partial* removal of the gland that I particularly wish to dwell. A number of these dogs, though kept under the same laboratory conditions as control animals, have in the course of a few months become excessively fat, and in every instance have shown marked atrophy of the organs of generation—a combination of symptoms, therefore, comparable to the clinical states of adiposity with infantilism described by Fröhlich.* It may be added that these symptoms are associated with deficiency of the anterior lobe alone and seemingly bear no relation to extirpation of the pars nervosa, though all the physiological activities of the gland hitherto recognized through injection methods are confined to this lobe. Alterations at the same time in the other ductless glands of the body are more or less constant after these partial hypophysectomies, showing the close interrelation of all of these structures—matters, however, which cannot be touched upon here.

Fully realizing that there is much that remains to be explained in regard to the function of each of the three divisions of the pituitary body, we nevertheless have been bold enough on a recent occasion,† as the result of our experiments, to advance certain views in regard to hypopituitarism and hyperpituitarism so far as the anterior lobe is concerned. Since then, through the kindness of numerous professional friends,

* There have been many other associated symptoms, which are beyond the scope of this paper—polyuria, glycosuria, amenorrhœa, impotence, etc.—all of them frequent accompaniments of the clinical conditions, whether acromegaly, gigantism or the adiposogenital degeneration, which are met with in company with hypophyseal tumors.

† The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism. The Oration at the Sixtieth Annual Session of the A. M. A. Jour. of Am. Med. Assn., July 24, 1909, vol. liii, p. 249.

the opportunity has been given of seeing several cases, particularly of hypopituitarism, many of them, in all probability unassociated with tumor.

I have purposely refrained in this brief discussion from making comment on the neighborhood symptoms of tumor in the hypophyseal region, though our diagnoses in the past have largely depended upon their presence; for I especially wish to emphasize the fact that conditions of hyperpituitarism and of hypopituitarism of greater or less degree doubtless occur frequently in the absence of tumor—as frequently, in all probability, as the corresponding disturbances in the secretory activity of the thyroid gland.

Had it not been for the presence of tumor or hypertrophic enlargement which definitely pointed out the seat of war it is improbable that we should have come to associate acromegaly or the syndrome of adiposity and sexual infantilism with a lesion of this hitherto obscure gland, particularly in view of the fact that our familiarity with its histological appearance in states of over- or under-activity is slight when compared, for example, with our knowledge of the finer anatomy of the thyroid under like conditions.

Though it must be considered merely as a working basis at present, it is my impression that the cases of the group Marie, with hyperplasia or the adenomatous condition which he and Marienesco describe, represent a state of over-activity (hyperpituitarism); whereas the cases in the group Fröhlich represent a condition of lessened activity (hypopituitarism) in consequence of invasion or compression of the gland by the tumor or cyst, on whose presence the diagnosis of the condition has heretofore rested.

The natural explanation of the improvement in the symptoms due to disturbances of glandular function (apart from the pressure or neighborhood symptoms) which has followed the evacuation of cysts or partial tumor extirpation in the cases of the Fröhlich type is, that remaining fragments of the anterior lobe have resumed their normal function, being relieved from pressure as a result of the operation.

Summary.—It may be said, therefore, that we have experimental evidence that a condition of adiposity with loss of activity or with definite atrophy of the sexual organs may follow the removal of a large part of the anterior lobe of the pituitary body. Hence it would seem probable that the syndrome Fröhlich is likewise a condition due to hypopituitarism.

Further, the experimental evidence is fairly conclusive that the sudden removal in its entirety of the epithelial lobe (pars anterior) of the hypophysis during a presumed state of health is incompatible with a lengthened maintenance of life—a matter of evident surgical moment in the treatment of hypophyseal lesions.

Finally, an additional case of operation for acromegaly in which, for the reasons which have been given, the gland was purposely removed only in part, will be fully recorded. It adds further support to the view of Stumme and the conjectures made by others in the past that acromegaly (gigantism likewise) is a condition due to over-activity of the gland (hyperpituitarism).

4. *Partial Hypophysectomy for Hyperpituitarism (Acromegaly).* CASE.—The patient, J. H., a farmer aged 38 years, kindly referred to me by Dr. Charles H. Mayo, entered the Johns Hopkins Hospital in March, 1909. He complained of frontal headache, photophobia, thickness of speech from an enlarged tongue, and increase in the size of the jaw, hands and feet.

The *family history* is good and apparently has no bearing on the case.

Past History.—Patient has always regarded himself as healthy. No illness recalled with the exception of mumps at 24, a severe attack of quinsy at 32, whooping-cough at 33, and measles when 34 years of age.

He has been married seven years and has one healthy child 5 years of age. He is not impotent but has had little sexual appetite for a year or more—a condition which he attributes to his discomforts. His average weight has been of late years 175 pounds and he has gained about 10 pounds in the last few months despite his discomforts.

Present Illness.—About eight years ago he began to suffer from periodic headaches, which have increased in frequency and severity so that now the pain has become more or less constant, with exacerbations. It is referred to the depth of the head and often passes to the back of the neck, where there is considerable stiffness and an uncomfortable drawing sensation. Soon after the onset of the headaches he began to be troubled with photophobia, particularly during the attacks of pain. Otherwise there has been no visual disturbance; no history of scotomata, squint or diplopia. There has been no impairment in hearing, no olfactory or gustatory disturbance, no vomiting, no nausea.

It was pointed out to him several years ago by his friends that his lower jaw and lips were increasing in size. The subsequent enlargement has been so gradual that the change has hardly been noticeable though he is aware that his entire head, his hands and feet have shared in the growth. Eight years ago he wore a number seven shoe and at present a number eight is rather too small and he requires a larger hat than formerly.

He has had some difficulty with mastication, owing to the failure of the teeth to meet, but the face has not felt stiff and expressional movements seem normal. Speech has become somewhat husky owing to the enlarged tongue.

He complains of dizziness on resuming an erect posture after stooping; also of numbness and tingling of the hands and feet, which are cold and clammy. He suffers from cold, particularly in winter, when his fingers look like "dead fingers." During the past two years he has felt weak and worn out through constant pain, and has been pretty much confined to the house during the daytime owing to his photophobia. His bowels tend to be constipated; there is no history of glycosuria or polyuria.

Physical Examination.—A well-nourished, muscular man. The general color is dusky, cyanotic, possibly due to prolonged indulgence in antipyretic drugs.

Head.—The characteristic features of acromegaly are evident in the accompanying photographs (Figs. 2, 3, and 9). The largest horizontal circumference of the cranium is 61 cm. The jaw is markedly undershot, although without widening of the mandibular arch. The teeth, as far forward as the second bicuspids, meet fairly well, but from here the lower dental arch projects beyond the upper fully 1 cm., the possible change of

position varying from 8 to 11 mm. The mouth can be opened at the widest only 4 cm. and the subjective sensation of stiffness is marked. There is considerable projection of the supra-orbital arches, evidently due to enlargement of the frontal sinuses.

Eyes.—Pupils are equal and react normally. The ocular movements are normal, though strong convergence causes discomfort. The sclera are slightly injected. The eyes are somewhat tilted, giving a slightly Mongolian aspect to the face. A perimetric examination shows normal fields for form and color.

Ears and hearing are normal, also sense of smell. The nose is large and broad, the lips thick. Nothing abnormal is shown in pharynx or tonsils. The tongue is large, thick and coated. The teeth are widely spaced (Fig. 3).

The thyroid is not appreciably enlarged. A few small glands in the right side of the neck and the epitrochlears are palpable.

The thorax is barrel-shaped, the costal angle about 85°. There is evident enlargement of the sternum, and the clavicles are large and prominent with unusual curvature. The chest is abnormally thick and the characteristic sloping of the shoulders with prominence of the upper spine is present. The heart and lungs are negative and there is no evidence of arteriosclerosis in the palpable vessels. Nothing abnormal is apparent in abdomen, abdominal viscera, or genitalia.

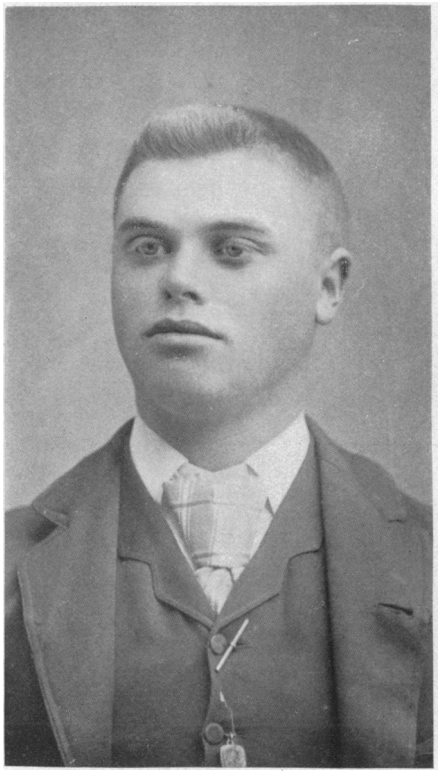
The hands and feet are large (Figs. 2 and 8), with the usual spade-like appearance due to the periosteal thickenings typical of the disease and shown by the radiogram (Fig. 4). Elaborate measurements of the fingers taken throughout show the largest circumference of the middle finger to be 8.5 cm. The hands are supple and strong, the nails normal and without ridging. The foot measures 26.5 cm. in length, the circumference of the great toe being 10.5 cm. The soft tissues of the hands, as well as of the face, feel dense as though distended with a solid œdema, which, however, does not pit on pressure.

The blood and urine are normal: no polyuria; no sugar.

A lateral radiogram of the skull shows clearly a slight enlargement of the sella turcica (Fig. 5).

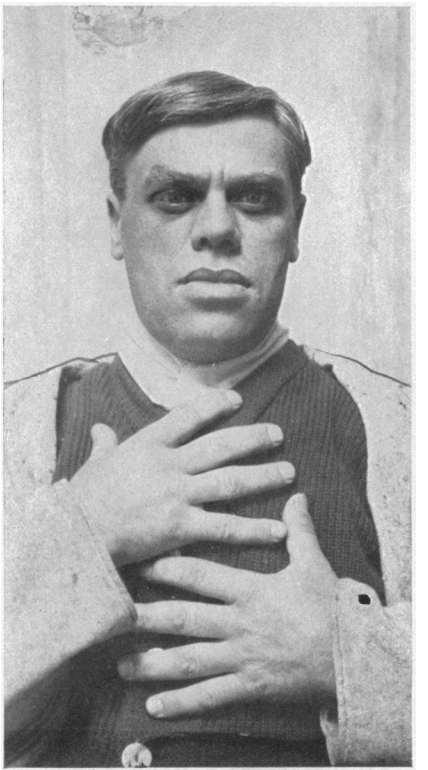
Operation, March 25, 1909.—*Preliminary tracheotomy; partial removal of the hypophysis, using transphenoidal route and osteoplastic resection of anterior wall of frontal sinuses. Closure of tracheal wound without drain.* Ether anæsthesia (S. G. Davis).

FIG. 1.

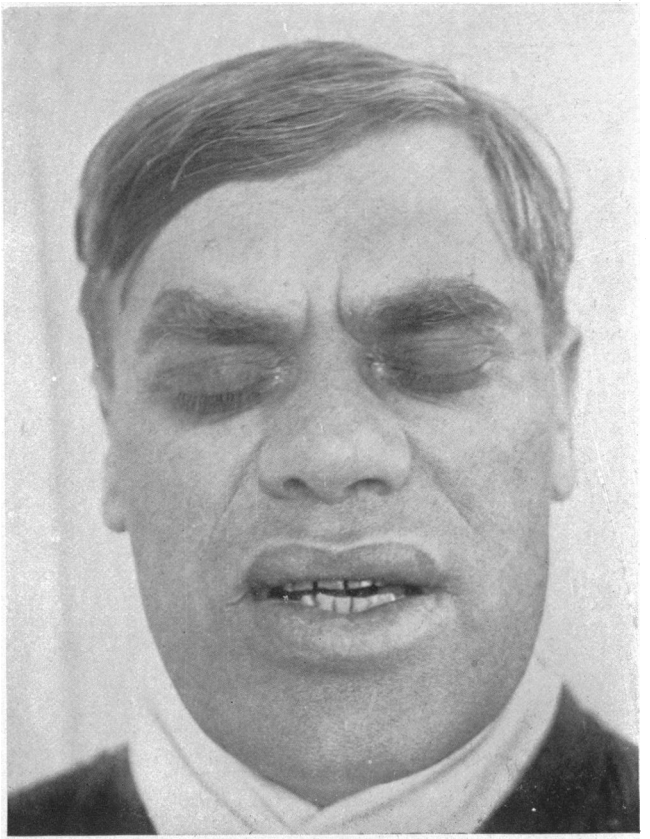


The patient some years before onset of symptoms.

FIG. 2.

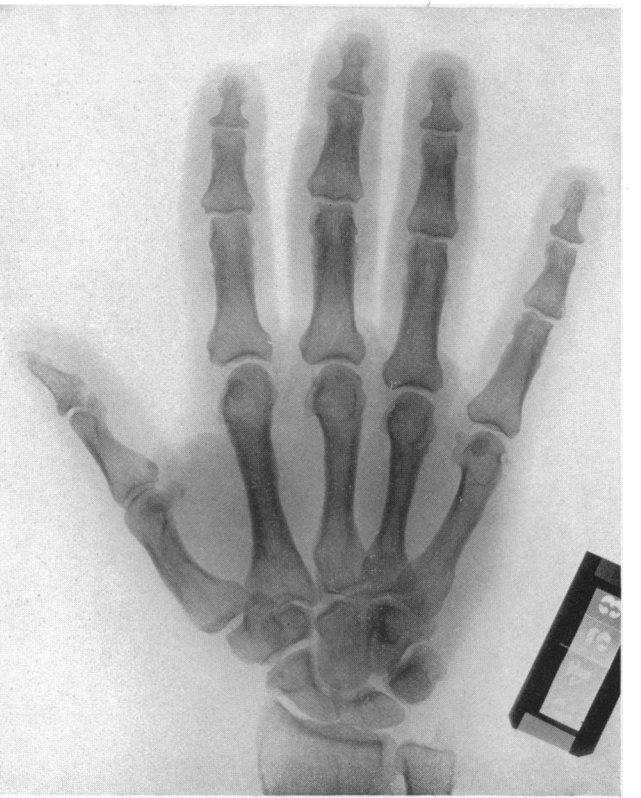


Condition on admission. (For comparison with Fig. 1.)



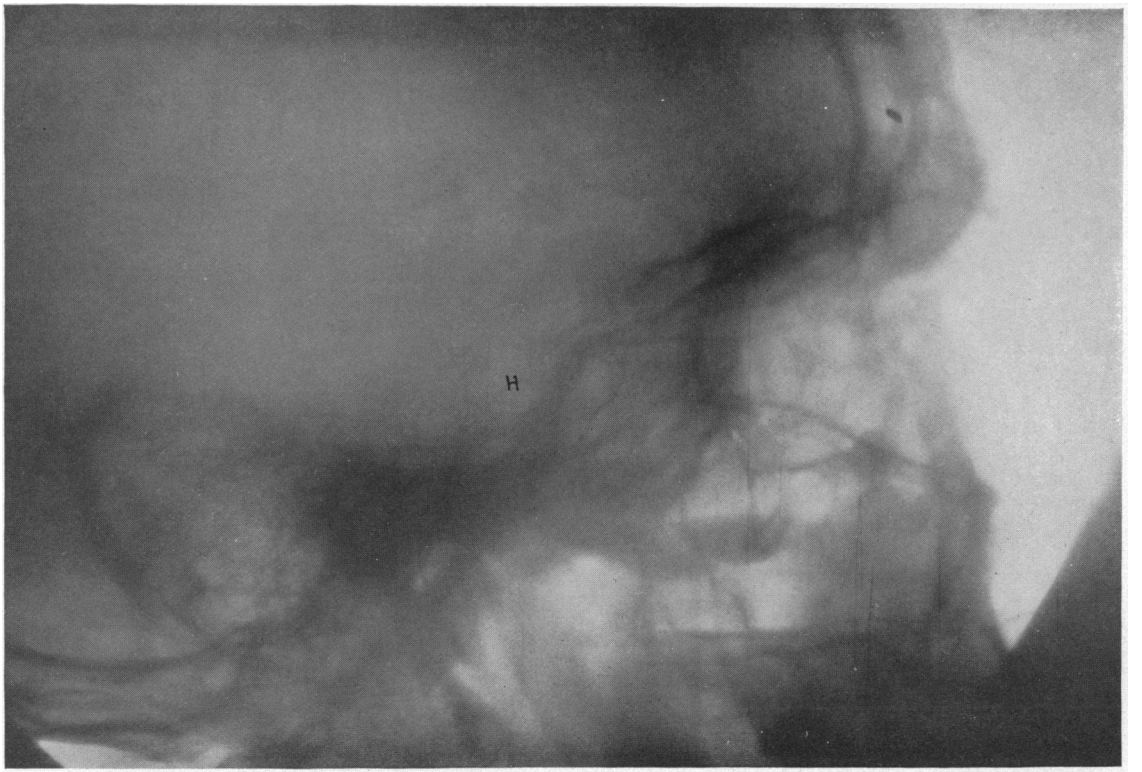
Condition before operation—photophobia. Note spacing of teeth, undershot jaw and thick lips.

FIG. 4.



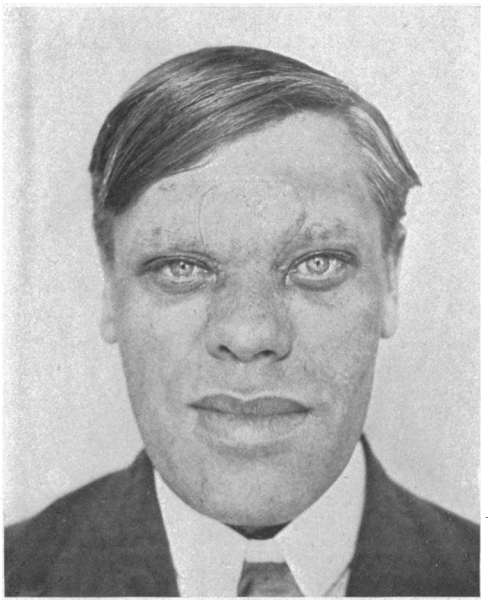
X-ray showing usual bony changes. Note thickness of soft parts.

FIG. 5.



Showing sella turcica slightly enlarged, *H*. (Size—two-thirds of original.)

FIG. 6.

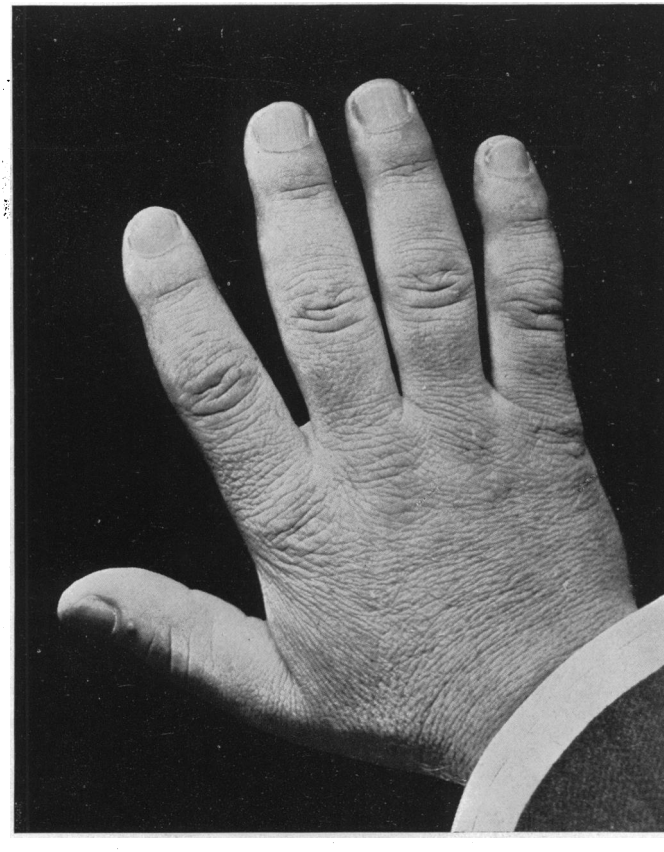


Fourteen days after operation. (To show situation of incision.)

FIG. 7.

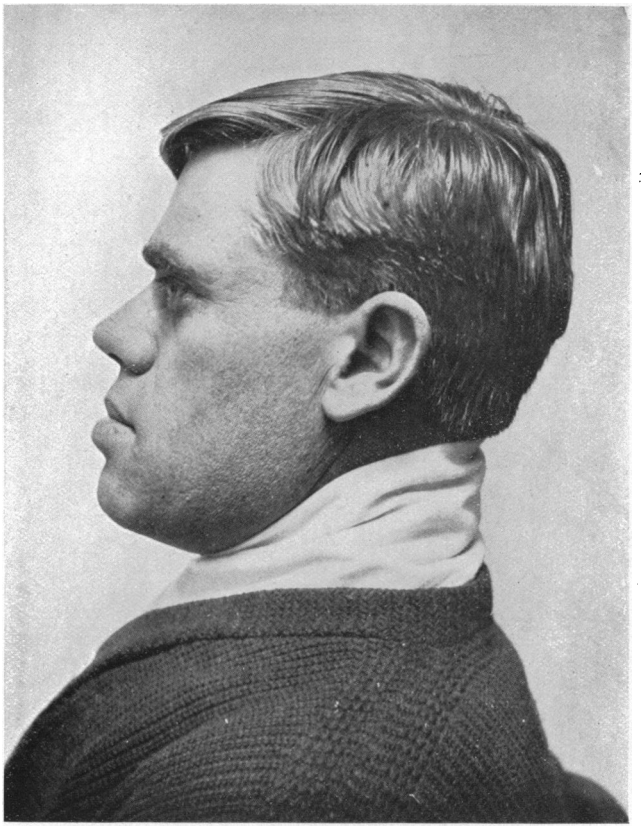
Three months after operation. (For comparison with Fig. 6.)

FIG. 8.



Right hand two weeks after operation, showing subsidence of "œdema" with wrinkling of skin.

FIG. 9.



Characteristic profile of acromegaly—condition before operation. (For comparison with Fig. 10.)

FIG. 10.

Three months after operation. Note considerable change in profile.

During the twenty-four hours prior to the operation four 15-grain doses of urotropin had been given. Possibly owing to the large tongue great difficulty was experienced in bringing about a state of surgical anæsthesia, and fearing complications from this source tracheotomy was performed. The trachea was exposed after division of the thyroid isthmus and removal of a section of the gland for histological purposes. The trachea was found filled with frothy mucus, which doubtless would have given trouble during the course of the operation. Warmed ether vapor was subsequently administered through the tracheotomy tube which was inserted through a transverse opening made between the second and third cartilaginous rings—a form of opening most suitable for immediate closure.

To prevent the entry of blood into the pharynx the posterior nares were then occluded with a sea-sponge held in place with a tape emerging from the nose in the usual way. The patient was then placed in the position of Rose; both nares were swabbed with a small amount of 10 per cent. adrenalin solution, and the sella turcica was approached as follows:

An omega-shaped incision (apparent in the photographs, Figs. 6 and 7) was made over the region of the frontal sinus, the lower legs of the incision converging toward the inner angle of the orbits whence they were continued down along each side of the nose to the lower margin of the nasal bones.

With a perforator and burr primary openings were made entering the outer side of each frontal sinus; a communication was made between these openings through which a Gigli saw was passed, and the upper edge of the proposed frontal sinus flap was cut from within outwards. Then with Montenovesi forceps the lateral incisions of the proposed frontonasal flap were carried downward through the nasal bones to their inferior margin in correspondence with the original skin incision. The median septa were divided with a few strokes of a thin-bladed chisel and the flap, consisting of anterior wall of the frontal sinus with the divided nasal bones and overlying soft parts, was broken loose and reflected downward.

The inner aspect of the enlarged frontal sinus, thus exposed, was roughened and contained many small mushroom-like, bony projections. The lining membrane appeared normal.

The ethmoidal cells were then carefully rongeured away until

a mesial channel possibly 2 cm. in diameter was made just below the ethmoidal roof and carried well back toward the posterior part of the nasal fossa. A head-light was then employed and the position of the sphenoidal cells easily determined. Their anterior wall was broken down, and on the upper and posterior aspect of their cavity the characteristic median projection of the sella turcica into these sinuses was easily detected. The thin shell of bone was chipped away with delicate strokes of a narrow chisel, exposing the spherical pocket of dura which envelopes the gland. This dural pocket was very tense and, judging from our experiences on the cadaver, was somewhat larger than normal. It was incised longitudinally and a considerable portion —possibly one-half of the exposed gland—was removed piecemeal with the aid of a delicate, long-handled curette.

Two small cigarette drains of protective were placed from the region of the sphenoidal cells, one emerging from each nostril. The frontonasal flap was replaced and secured in position by a layer of buried sutures approximating the divided frontalis muscle and galea. The tracheal wound was then closed without a drain, four fine black silk sutures being used to approximate the edges of the transverse incision, and another, later, for union of the divided thyroid isthmus. The sponge was then withdrawn from the posterior nares.

At no stage of the operation was there any disturbing loss of blood, and at no time was the operator's view submerged—possibly owing to the adrenalin. It was surprising to find how small an opening had actually been made through the ethmoidal region and how accessible the sella turcica actually proved to be after the landmarks had once been well determined.

The urotropin was continued for several days after the operation and there were no postoperative complications whatsoever. The external wounds healed *per primam*. The last nasal drain was withdrawn on the third day; the sutures were removed and the flap supported by a collodian dressing. The patient was up three days after the operation. From the first there was practically no discharge from the nostrils. An immediate subjective sensation of well-being followed the operation, with complete and permanent disappearance of the headache from which he had suffered so long.

Though anxious to return home and quite able to leave the

hospital within a week or ten days after the operation, he was persuaded to remain for seventeen days, *i.e.*, until April 11. During this interval he had called our attention to the fact that his hands seemed much less stiff than formerly; indeed, that he had not seen wrinkling of the skin such as was present for a number of years. The photograph (Fig. 8) was taken at this time in order to show this condition. There was no question but that the peculiar objective thickening of the tissues was much less marked than before. Measurements of the fingers showed that they had diminished 1 to 1.5 mm. in their circumferential measurements. His photophobia had almost entirely diminished. The one objectionable feature was the inevitable complete loss of his olfactory sense.

The patient returned to his home on a farm in the West, and after actively participating in harvesting returned to us for observation, at our urgent appeal, ten weeks later. At this time (June 24) it was quite apparent that considerable change had taken place in his appearance (*cf.* photographs, Figs. 7 and 10), seemingly due to lessened density of the tissues of face and lips. Some of the measurements seemed altered for the better. The teeth could be separated 4.5 cm. The anteroposterior movement in the lower jaw beyond the margin of the upper teeth was from 7 mm. to 11 mm. The teeth seemed to be less widely spaced. The circumference of the head was 60.5 cm. Other slight measurable alterations were made out, which possibly lay within the margin of error, so that it would be unjust at this early date to lay emphasis upon them. Before the operation my assistant, Dr. G. J. Heuer, had made an excellent plaster mask of the head and casts of the hands, which will enable us to make accurate comparative measurements in the future.

There had been no headache since the operation, very slight photophobia and only an occasional slight puffiness of the hands —much less than formerly. The speech still remained somewhat thick and the patient had no subjective consciousness of any diminution in the size of the tongue comparable to that which had occurred in the soft parts of the hands. There had been no nasal discharge. He was troubled only by the loss of the sense of smell, which had cut him off from the enjoyment of certain flavors. He had given up smoking, and now chews tobacco, and no longer cares for coffee. He had gained ten pounds in

weight, but we trust that the amount of anterior lobe removed was not sufficient to produce symptoms of physiological deficiency.

The histological examination of the fragments of anterior lobe removed correspond with what we regard as a condition of glandular activity—a matter to be reserved for a forthcoming communication.

The photographs (Figs. 7 and 10) show the absence of any operative deformity.

5. *Operative Methods.*—The various routes which have been suggested as available for an approach to the hypophysis are too well known to surgeons to necessitate or justify their being reviewed here, nor is it the purpose of this paper to do so.* There are, however, certain points in regard to these procedures in general on which a personal comment may be called for.

In the first place, most, if not all, of the operations in the past have been done for *tumors* originating in the gland itself or arising in its immediate neighborhood. These tumors, as I have endeavored to show, may be associated with evidence of hyperfunction, as in acromegaly, or, in patients showing the syndrome of Fröhlich, with hypofunction. In the presence of a tumor the main surgical indication is of course the removal of the growth, with preservation of some of the normal gland if possible, and if the tumor happens to lie well above the sella turcica so that it is visible from the side, the most natural method of approach is that which has been followed by Horsley in his series of cases; namely, a temporal and intracranial route. I have attempted to follow this route in the case of an adult woman with all the characteristic local symptoms of hypophyseal tumor, accompanied by great adiposity and amenorrhœa (hypopituitarism). Though the infundibular region was easily brought into view the tumor did not project above the dural margin of the clinoid processes,

* Comprehensive reviews of the purely surgical aspects are to be found in the "Sammelreferat," by Ernst Venus, in the Centralbl. f. d. Grenzgeb. d. Med. u. Chir. of this year, and in Proust's article "La chirurgie de l'hypophyse," in the Journal de Chirurgie, 1908, vol. i, p. 665.

and further investigation would have been foolhardy. The patient refused a subsequent transphenoidal operation which was proposed.

Nevertheless, in all of our experimental canine operations we have successfully used this intracranial method, combining it with a generous opening over the opposite hemisphere to allow for the important principle of cerebral dislocation; for with this precaution the temporal lobe on the side of the approach can be elevated without danger of compression or risk of cortical injury, since ample room for the necessary manipulations is allowed by the protrusion of the opposite hemisphere through the overlying defect in bone and dura. By this procedure the canine gland can be lifted out of its shallow envelope and, dangling in plain view, can be dealt with as desired. This, unfortunately, is not true of the human gland, and the temporal operation in all probability must remain restricted in its use either to those cases in which a benign tumor (*e.g.*, of the teratoma type described by Hecht and myself) or a hypophyseal cyst projecting into the infundibular region, can be brought into view and attacked from the side. It may prove useful, therefore, as in the case just cited, as a preliminary measure to be used for orientation of the growth before the final plan of attack is decided upon.

If, on the other hand, the lesion occupies the sella turcica and is confined within an intact though possibly distended pocket of dura, an approach from one side, as so many have pointed out, is most hazardous, if not well nigh impossible; and it is in these cases that the transphenoidal operations naturally become the ones of choice. In some instances, indeed, as in the case described by Erdheim, the tumor may actually project into the sphenoidal cells rather than into the cranial chamber. All operations, however, which open up the cranial base after traversing the nasal fossa are prone to be followed by meningeal infection, and this as much as anything else has been the element which has deterred surgeons from eager acceptance of Schloffer's operation. After all, by whatever method of approach they may be attacked little

can be expected of an operation for an epithelial tumor of the gland, beyond the temporary palliation of pressure symptoms, for at best their removal from this inaccessible region must be fragmentary and incomplete.

Now, leaving the tumor question aside and considering the probability that surgeons may be called upon in the future to treat certain of the conditions associated with alterations in the pituitary gland which are not necessarily accompanied by great enlargement, there can be but little doubt that the transphenoidal route will be most often followed. Of the various modifications of this operation a direct median approach through the nose is not only far less mutilating than any other midline operation, such, for example, as the intermaxillary or bucconasal procedure suggested by Gussenbauer and König, but also possesses the advantage over any lateral route, whether transmaxillary or intranasal, in the lessened likelihood of missing the situation of the mesially placed gland. The important factor seems to me to be a direct extracranial midline approach by the shortest possible route.

There are a number of modifications of Schloffer's nasal procedure, with either a mesial or lateral reflection of the nose, with or without opening of the frontal sinuses and with or without removal of more than the median septum and cells of the ethmoid. Schloffer in his first case deflected the nose to the side, sacrificed the internal wall of the orbit as far as the optic nerve and likewise the internal wall of the maxillary. As has been true of the attempts to reach the Gasserian ganglion, more heroic measures have naturally been employed in the earlier operations than have since proved necessary, and the method first carried out by Schloffer will doubtless undergo as many modifications at the hands of subsequent operators as the Hartley-Krause operation has undergone. For a time presumably no two individuals will approach the gland in exactly the same way, and whether it is desirable to combine, after the method attributed to Giordano, a temporary osteoplastic resection of the anterior wall of the frontal sinuses together with the osseous portion of the nose, or indeed

whether this is practicable in conditions other than acromegaly, in which the frontal sinuses are apt to be enlarged, must be left for future determination.

Hesitation to accept the transphenoidal operation on the grounds of possible meningeal infection will be lessened in the future in view of Crowe's discovery of the rapid appearance of formaldehyde in the cerebrospinal fluid after the administration of urotropin *—a matter which is of importance not only in all of these transphenoidal operations but in cases of basal fracture or in other conditions in which infection of the meninges is threatened.

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* S. J. Crowe: On the Excretion of Hexamethylenamene in the Cerebrospinal Fluid. The Johns Hopkins Hospital Bulletin, 1909, vol. xx, p. 102.