

The Shattuck Lecture.

CONCERNING DIABETES INSIPIDUS AND THE POLYURIAS OF HYPOPHYSIAL ORIGIN.*

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INTRODUCTION.

Pituitary Glycosuria.

It has long been recognized that polyuria, with the appearance of dextrose in the urine—the typical symptomatic expression of diabetes mellitus, in other words—is a not infrequent accompaniment of acromegaly. The view is shared with my co-workers that this glycosuric manifestation of pituitary disease is indicative of the active stage of so-called hyperpituitarism, for in the advanced stages of acromegaly we have observed that the actual glycosuria or low assimilation limit for carbohydrates characterizing its early or recrudescing stages, usually becomes replaced by a high degree of sugar tolerance in which alimentary glycosuria can be provoked only by the ingestion of massive doses of sugar.

Certain experimental investigations with Goetsch and Jacobson¹ have shown (1) that experimental manipulations of the infundibular lobe cause a transient post-operative glycosuria, (2) that the injection of extracts of this lobe will cause glycosuria in well-fed animals, and (3) that after its surgical removal the animals acquire an increased tolerance for carbohydrates, accompanied by adiposity—an experimental condition comparable to the increased sugar tolerance shown by the clinical states of adiposo-genital dystrophy, which we therefore have come to recognize as expressions of pituitary insufficiency.

These findings offer experimental support to the view which we have advanced, that in the early glycosuric stages of acromegaly, in addition to the anterior lobe changes, an hyperplasia or functional activation of the posterior lobe occurs, which in the further progress of the disorder is often replaced by a relative functional insufficiency of this part of the gland.

Aware of the close chemical interrelation of the glands of internal secretion, we fully realize that the mellituria of hypophyseal disease may indicate some secondary change in the pancreatic islets, though as yet histological evidence of this is lacking. We feel, however, that in the diabetic conditions under discussion the pituitary lesion is the primary factor, and this is sup-

¹ Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri. Bull. Johns Hopkins Hospital, 1911, vol. xxii, pp. 165-190.

* Delivered at the annual meeting of the Massachusetts Medical Society on June 10, 1913.

ported, in negative fashion, by a series of observations with Jacobson, in which we have found that animals who have acquired a high sugar tolerance after extirpation of the posterior lobe may subsequently be deprived of the pancreas without the classical glycosuric consequences of the procedure described by Meyring and Minkowski.

Pituitary Polyuria.

It is, however, to the non-glycosuric form of pituitary diabetes that I wish on this occasion to call your particular attention, for this symptomatic expression of hypophyseal disease has almost entirely escaped general recognition.

In a monograph written two years ago,² dealing with the clinical aspects of hypophyseal derangements, comment was made on the fact that in certain cases polyuria and polydipsia may so dominate the clinical picture as to justify the designation of diabetes insipidus—a diagnosis which had actually been made, at one stage or another during the progress of the malady, in a number of the examples of dyspituitarism which were cited.

It was my intention, in conjunction with one of my assistants, Dr. Howard C. Naffziger, to make a detailed report of our personal experiences in this direction during the past few years at the Johns Hopkins Hospital and to assemble the past clinical observations which had a bearing on the subject. This intent has been anticipated in large part by the publication, from Minkowski's clinic in Breslau, of an excellent article by E. Frank,³ in the Berliner klinische Wochenschrift. This author, on the basis of a single personal observation—a case of bullet wound of the pituitary fossa—in conjunction with the available data from the literature, has taken an even stronger position in favor of the hypophyseal relationship to diabetes insipidus than we might have ventured to assume. However, the matter is of sufficient general interest to justify, I trust, the bringing before you in this Shattuck Lecture of such facts as may be added to the data which others have accumulated.

EXPERIMENTAL OBSERVATIONS.

The discovery was made by Schäfer and Magnus in 1901 that extracts of the posterior lobe of the pituitary body possess diuretic properties of high degree, the reaction following their injection being a long-continued one, associated with an increase in volume of the kidney. Subsequently Schäfer and Herring pointed out (1906) that the renal arteries are exempt from the general constricting effect exercised by posterior lobe extracts upon other vascular channels and upon unstripped muscle in general. They expressed the belief, however, that the di-

² The Pituitary Body and Its Disorders. J. B. Lippincott Co., Philadelphia, 1912.

³ Über Beziehungen der Hypophyse zum Diabetes Insipidus. Berl. klin. Wchnschr., 1912, vol. xlix, pp. 393-397.

resis which they observed was the result of a direct action upon the renal epithelium and that it was independent of the hemodynamic response to the extract, for it persists long after the secondary fall in blood pressure and recession of the kidney to its original size.

In the course of our Baltimore studies in the Hunterian Laboratory (1908-1912) it was noted that after certain experimental manipulations of the canine hypophysis a post-operative polyuria, often of some days' duration and at times reaching a tenfold increase over the normal output, was of frequent occurrence. In 1909 mention was made of these post-operative polyurias in an article by Crowe, Cushing and Homans,⁴ dealing specifically with the effects of hypophysial transplantation, and in a subsequent paper by the same co-workers* the protocols of fifty examples of experimental hypophysectomy (Series of 1908-9) were given in tabular form.

It may be gathered from these tables that oliguria rather than diuresis followed a total extirpation in the adults, though in the younger animals which survived the loss of the gland for a longer time there was often a transient increase in the amount of urine for a day or two. On the other hand, in the series of partial extirpations in which the posterior and a portion of the anterior lobe were excised, post-operative polyuria was almost always observed, and this was also true of the animals deprived of the posterior lobe alone.

Control observations showed that no polyuria ensued if the operation was carried merely to the point of a free exposure of the gland, stopping short of the final step of actual tissue extirpation. This was construed as an argument against the assumption that the procedure served to excite some predicated diuretic and glycosuric center in the adjacent floor of the third ventricle, rather than that the manipulation of the gland itself provoked the diuresis.

In the series of operations carried out in the succeeding year (1909-10)⁵ with Goetsch and Jacobson, although the experiments were reported from the standpoint of the glycosuric rather than the diuretic response, nevertheless the protocols show, in similar fashion, the usual non-appearance of polyuria after total extirpation (Fig. 1), whereas after a posterior lobe removal it was customary to observe a prompt post-operative increase in the urine, which occasionally reached an extraordinary figure for a dog, far in excess of the ingested fluids.

In the operative performances which served to induce hyperglycemia it was observed that the coincident diuretic effect of the procedure was more prolonged than the glycosuric response;

⁴ Hypophysial Transplantation following Total Hypophysectomy. *Quart. Jour. Exper. Physiol.*, 1909, vol. ii, pp. 389-400.

⁵ Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri. *Bull. Johns Hopkins Hospital*, 1911, vol. xxii, pp. 165-190.

* Experimental Hypophysectomy. *Bull. Johns Hopkins Hosp.*, 1910, vol. xxi, pp. 127-169. A tentative opinion was expressed that we were dealing solely with an anterior lobe effect—an opinion shown to be erroneous by the observations of the following year.

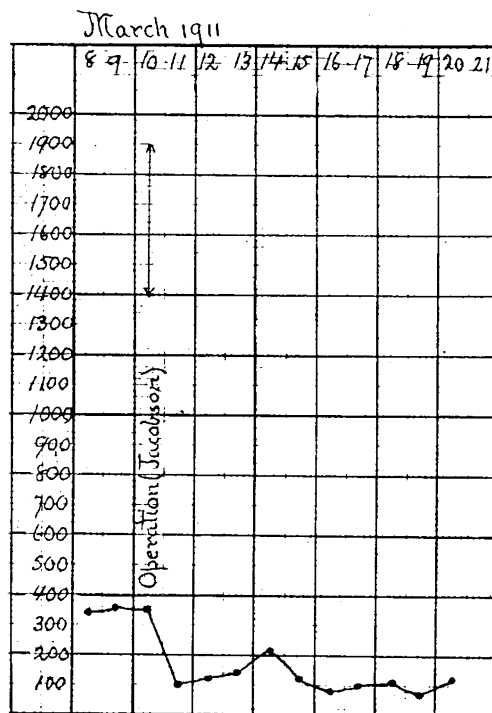


FIG. 1.

Chart showing post-operative oliguria after removal of practically the entire gland.

PROTOCOL. No. 16. Series 1910-11. 7.4 kilo. puppy. March 10: "Near total" hypophysectomy, including posterior lobe. Animal sacrificed for kymographic observations March 21.

and it was doubtless this extreme post-operative polyuria which in our earlier experiments led us to overlook the transient outpouring of sugar, so commonly noted in the second series, in which care was taken to examine the first voided specimen for the presence of a reducing substance.

We do not mean to imply that a diuretic response is invariable, but merely that it is commonly observed, and our further experiences, based on the more recent hypophysectomies conducted by Goetsch, Crowe or Jacobson during the past two years (1910-12), support the view that the clean-cut posterior lobe removals elicit polyuria with the greatest regularity. The accompanying three charts show this post-operative diuresis in its varying degrees: Figure 2, in its extreme form with an immediate polyuria of high degree—almost four liters in the twenty-four hours, succeeded by a quick fall to the normal during the next day or two; Figure 3, in less extreme form, the wave of polyuria being of somewhat longer duration; and Figure 4, in what may be regarded as an average reaction for our posterior lobe removals.

These comparatively transient experimental reactions are chiefly of interest in showing the relation of the glandular manipulations and consequent secretory discharges to diuresis. More enduring polyurias, however, occurred in four of our experiments, all of them being instances in which the hypophysial stalk was purposefully

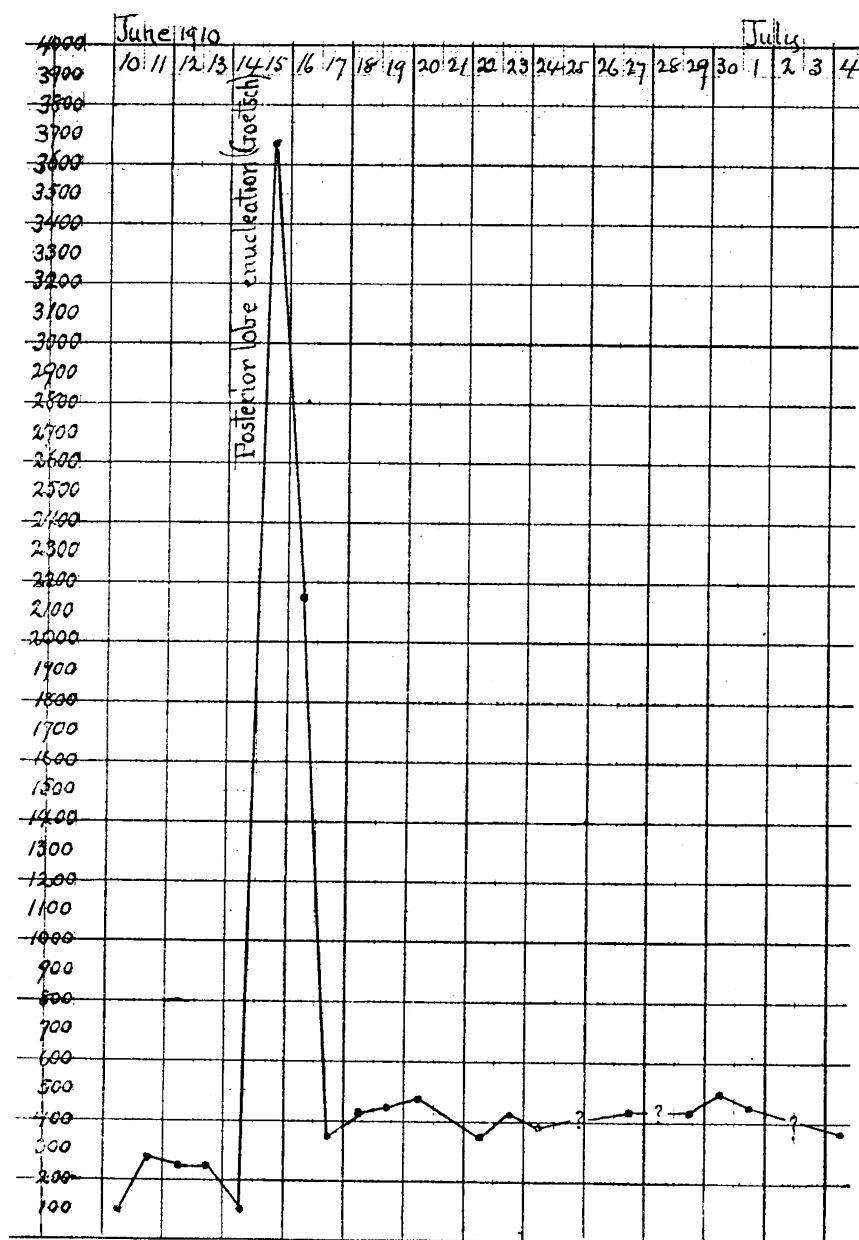


FIG. 2.

Chart showing extreme post-operative polyuria with excretion of 3700 c.c. in the first 24 hours; 2150 c.c. on the second day, with an abrupt fall to nearly the normal level.
 PROTOCOL. No. 67. Series 1909-10. Seven kilo., 10 months' puppy. Posterior lobe extirpation.

divided or obstructed, leaving the otherwise intact gland, or a large part of it, in situ. In one of these animals (a 7 kilo. fox terrier which ultimately developed characteristic symptoms of hypopituitarism after a stalk separation combined with a partial lateral removal of the anterior lobe) a polyuria varying from 675 to 1640 c.c. per diem, persisted for six months—a veritable diabetes insipidus of experimental origin (Fig. 5).

Somewhat prolonged reactions were also observed in certain experiments in Crowe's series

(1908-9) already referred to, in which we made an immediate subcortical transplant of the excised posterior lobe fragment—a measure having a certain experimental analogy to simple stalk separation, in view of the fact that the chief blood supply of the gland passes into it by way of the infundibular attachment. In two of these animals (e.g. Fig. 6) the transplant was removed on the fifteenth and twelfth days respectively, with prompt subsidence of the polyuria. In the third animal, on the other hand, the transplant was not removed and the polyuria

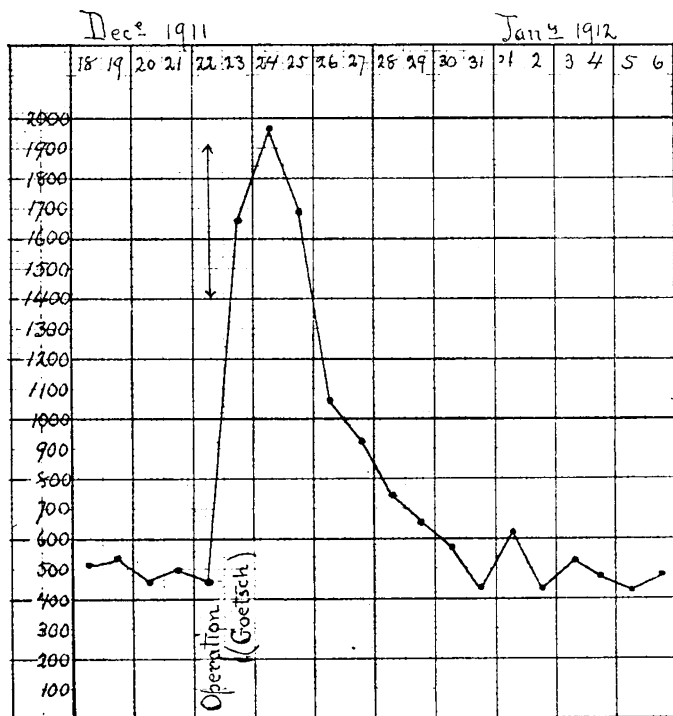


FIG. 3.

Chart showing moderately extreme transient polyuria.
 PROTOCOL. 15.5 kilo. adult dog. Eck fistula performed Nov. 10, 1911. Animal kept in good condition on calcium dietary. On Dec. 22 a posterior lobe hypophysectomy was performed, with the usual polyuria. No sugar present in the first voided specimen, which showed a lowered specific gravity of 1015, the previous and subsequent average being 1030. A pancreatectomy was subsequently performed on this animal, without glycosuria. Neither the Eck fistula nor the pancreatic operation was followed by polyuria.

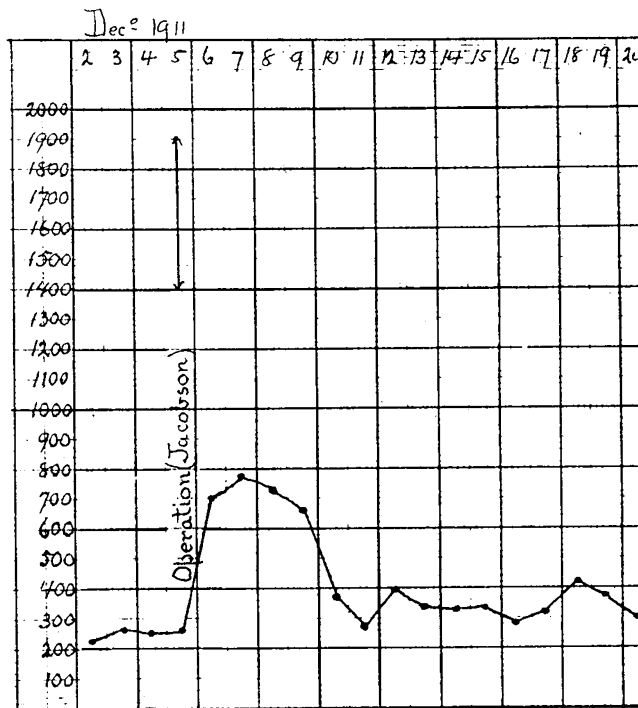


FIG. 4.

Chart showing the average moderate diuretic response after posterior lobe extirpation.
 PROTOCOL. 6.5 kilo. puppy. Operation Dec. 5, with sugar (0.6 cent. D.R.) showing on first specimen, despite the lowered specific gravity of 1012 from the preoperative specific gravity of 1028, due to the polyuria. Animal sacrificed for kymographic studies Dec. 20.

continued (Fig. 7) until the dog was sacrificed on the twenty-fourth day in order to observe the histological condition of the implanted tissue, which was thought to be viable.

Schäfer,⁶ in the course of some experiments on the effect of glandular transplants in non-hypophysectomized animals, observed that the subcutaneous implantation of the posterior lobe from one animal to another causes a transient polyuria, which subsides in a few days, coincident presumably with the absorption of the secretory products contained in the implanted tissue. It would appear, moreover, from certain observations made by Stiles, under Schäfer's direction, that the posterior lobe substance given by mouth increases the urinary output, and thus promises to be of clinical value as a diuretic. This observation also conforms with our own experiences with the oral administration of extracts.

The experimental polyurias heretofore cited have been brought about either by a direct hypophysial insult, by the injection of extracts, or by glandular implantations. An hypophysial diuresis, however, may be elicited in still another way, namely, by nerve stimulation. In some recently recorded observations in collaboration with Weed and Jacobson⁷ on the autonomic con-

trol of the gland, the chief argument for the passage of nervous impulses from the medulla through the cord to the three upper thoracic nerves and thence to the pituitary gland by way of the cervical sympathetic relays, lay in the elicitation of glycosuria from stimuli applied to this pathway. During the course of these studies, however, we commonly observed, coincident with the glycosuric response, an abundant outpouring of urine of low specific gravity; a rabbit, for example, would often excrete 15 or 20 c.c. in a very few minutes, and at times as much as 150 c.c. in the course of a few hours after stimulation of the superior cervical ganglion. A similar prompt and often excessive diuresis, provoked by the intravenous injection of concentrated cerebrospinal fluid in small amounts, was one of the facts advanced by Goetsch and myself⁸ in favor of our contention that the posterior lobe secretion finds its way into the cerebrospinal fluid. These matters are of interest in connection with the subject of emotional or neurogenic polyurias, the further discussion of which at this time would lead us too far afield.

⁷ Further Studies on the Role of the Hypophysis in the Metabolism of Carbohydrates. The Autonomic Control of the Pituitary Gland. Bull. Johns Hopkins Hospital, 1913, vol. xxiv, pp. 40-52.

⁸ Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and Its Presence in the Cerebrospinal Fluid. Amer. Jour. Physiol., 1910, vol. xxvii, pp. 60-96.

⁶ E. A. Schäfer: Die Functionen des Gehirnanhangs. Berner Universitätschriften, 1911, Heft B.

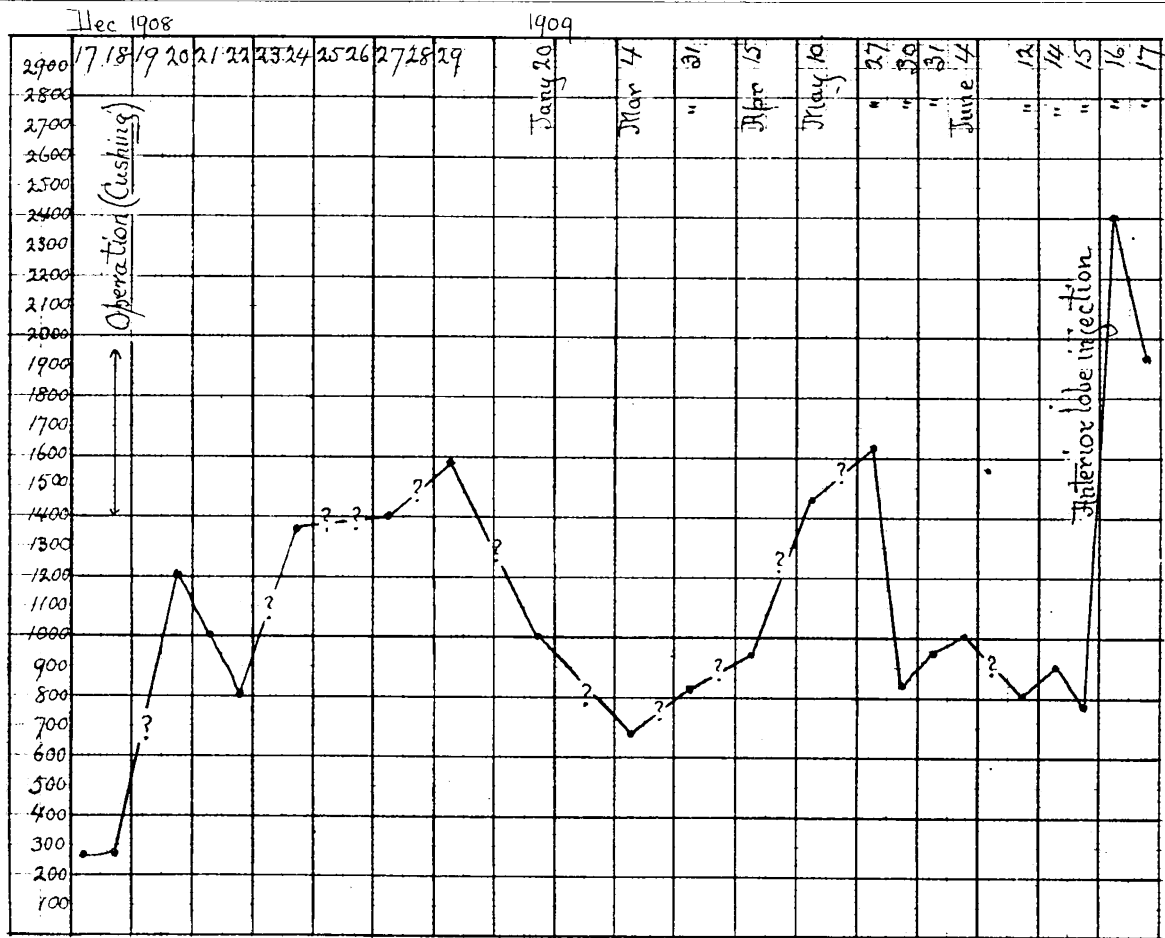


Fig. 5.

Chart showing polyuria prolonged over a period of six months after hypophyseal stalk separation.

PROTOCOL. Seven kil. fox-terrier. Dec. 18: Stalk separation with fragmentary anterior lobe removal. Polyuria observed on the six observations during the succeeding ten days and on all occasions when the amount was measured during the succeeding six months, the animal meanwhile acquiring the characteristic adiposity with drowsiness, subnormal temperature and so on, of hypophyseal insufficiency. A marked increase of polyuria followed the injection, on June 14, of 10 c.c. of a one per cent. solution of anterior lobe emulsion of bovine gland. Animal sacrificed on June 17.

Despite the suggestiveness of many of these laboratory observations it must, nevertheless be acknowledged that a long-continued polyuria of high degree, comparable to the clinical conditions of diabetes insipidus, has hardly ever been observed, though in a number of cases, after posterior lobe extirpation, animals whose pre-operative average output was *circa* 300 c.c., continued to excrete an amount two or three times as great (*circa* 700 c.c.) for the succeeding month or two.

In summarizing the experimental data it may be said that:—

1. The infundibular lobe contains, in addition to the substance capable of glycogenolysis, a chemical body or hormon capable of eliciting diuresis.

2. Under certain operative conditions which entail posterior lobe manipulations there often occurs a diuretic response, and occasionally an extreme polyuria, whereas a temporary diminution in the excreted urine is apt to follow other operative procedures, requiring an equally long anesthetization.

3. Posterior lobe implants may cause a temporary polyuria, which subsides on the removal of the implanted tissue.

4. Stimulation of the autonomic system of nerves to the gland elicits diuresis.

5. Certain operative procedures, such as separation of the infundibular stalk, and occasionally a simple posterior lobe excision, may call forth a somewhat prolonged polyuria.*

* It will be apparent to all that there exists a discrepancy in these diuretic reactions which does not apply to those accompanied by glycosuria. For in the case of the pituitary glycosurias the administration of extracts, direct glandular stimulation, or stimulation of the autonomic nerve supply to the gland, all produce glycosuria, which is recognized as an expression of glandular hyperplasia in clinical cases; whereas experimental extirpation of the gland leads to the reverse condition, namely an increased tolerance for carbohydrates, just as in clinical states an increased sugar tolerance coincides with the glandular insufficiency brought about by injury or compression by a tumor.

In regard to the diuretic response, on the other hand, though the administration of extracts, direct glandular stimulation or stimulation of the autonomic nerve supply are likewise capable of eliciting polyuria, nevertheless the experimental extirpation does not lead to the reverse of polyuria, nor in the clinical states with evident posterior lobe insufficiency do we find a diminished urinary output. On the contrary, active polyuria is not infrequently seen in clinical cases of hypopituitarism associated with a high sugar tolerance.

Thus hypophyseal glycosuria and polyuria do not go hand in hand. Explanations for this apparent discrepancy will doubtless be afforded by future studies.

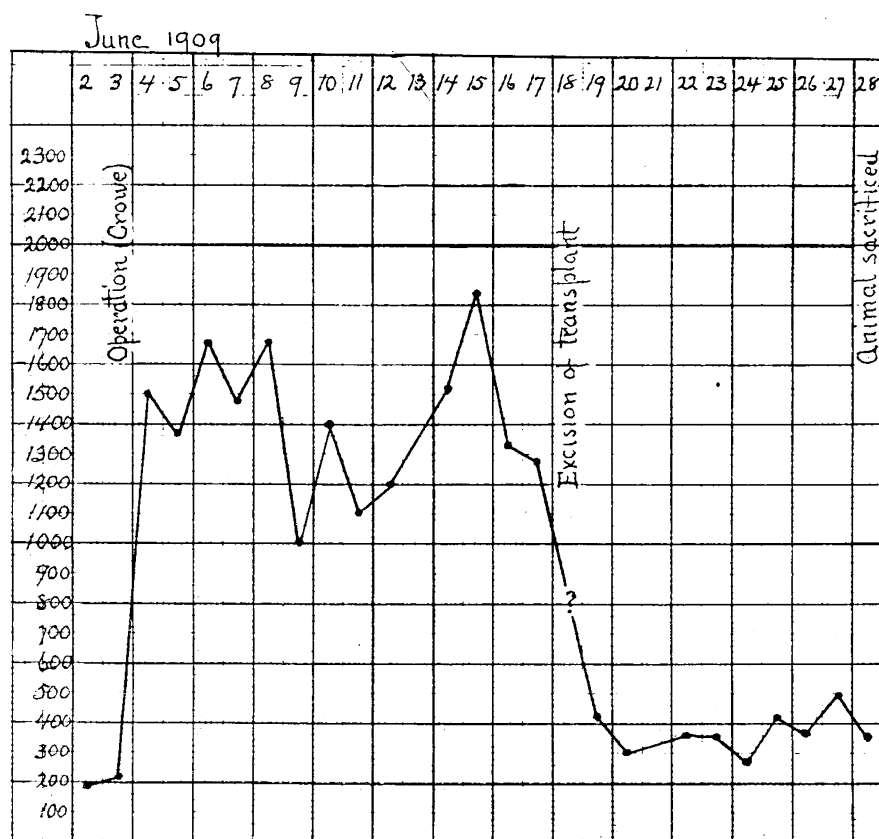


FIG. 6.

Chart showing persistent polyuria following posterior lobe reimplantation in the cerebral sub-cortex after excision. Polyuria promptly interrupted after excision of the transplant on the fifteenth day.

CLINICAL OBSERVATIONS.

Diabetes insipidus, according to our best known texts, is symptomatically defined as a long-continued disorder characterized by polyuria and polydipsia, with a sugar-free urine of low specific gravity. Two varieties of the malady are commonly recognized: the so-called *idiopathic* form, supposedly originating in the kidneys, is sharply distinguished from a *symptomatic* form, which includes not only the polyurias shown by supposedly psychopathic or hysterical individuals, but also those provoked by some emotional insult, as well as those for which there may be an actual organic neurological basis, such as cerebral trauma, syphilis or tumor.

Meyer, in 1905, considered the idiopathic form to be a primary renal polyuria due to a functional disability of the kidneys which rendered them incapable of secreting urine above a certain low specific gravity, on which basis the ingestion of salt should fail to concentrate the urine and thus should serve to distinguish true diabetes insipidus from the condition brought about by a primary polydipsia. It is held, moreover, that in cases of true diabetes insipidus deprivation of water does not check the polyuria, and some have claimed that the excretion of ingested fluids is more rapid than normal (*tachyuria*); and

this is advanced in support of the view that the disorder is a primary polyuria rather than a primary polydipsia. Others contend that the opposite condition, namely bradyuria, exists, and indeed on etiological grounds the subject is in a state of great confusion.

As will be recalled, Claude Bernard observed, fifty years ago (1854-55), that a transient glycosuria could be provoked by a piqûre at a point in the floor of the fourth ventricle between the origin of the pneumogastric and auditory pairs of nerves, and also that stimulation of a point just anterior to this so-called sugar center would occasionally produce a transient polyuria without the coincident appearance of sugar in the urine. It is natural that many have assumed the existence of some relationship between these experimental glycosuric and diuretic piqûres and certain clinical glycosurias and polyurias, particularly those of a supposedly emotional or neurogenic origin. I do not believe, however, that these conditions, so often precipitated by cerebral trauma, whether psychic or mechanical, were capable of interpretation until it was shown, in collaboration with Weed and Jacobson,⁹ that impulses which pass from Bernard's centers by way of the cervical sympathetic are

⁹ The Autonomic Control of the Pituitary Gland. Bull. Johns Hopkins Hospital, 1913, vol. xxiv, pp. 40-52.

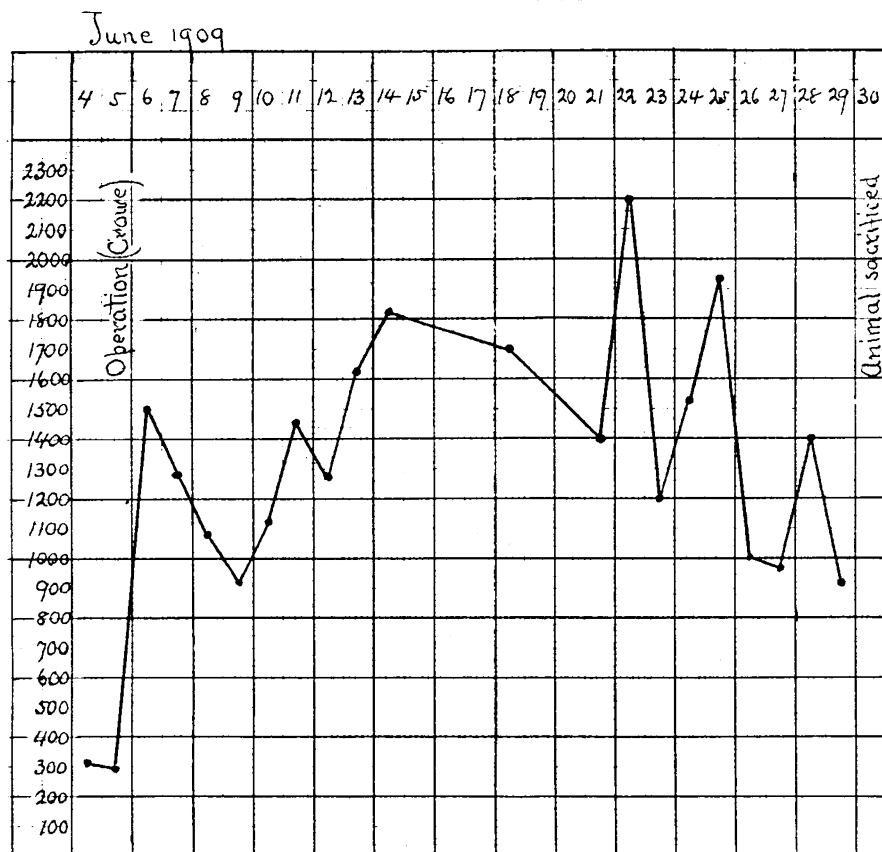


FIG. 7.

Chart showing persistent polyuria after posterior lobe reimplantation in the cerebral subcortex after excision. On all occasions during the twenty-five days following the operation, when the 24-hour amounts were measured they varied between 800 and 2200 c.c.

capable of discharging from the gland a glyco-genolytic as well as a diuretic substance.

In our somewhat extensive experience with patients who have received traumatic injuries involving the cranial base, a pronounced and enduring polyuria with polydipsia has been observed in a number of instances; and similar conditions have been reported by others. I have pointed out elsewhere that in basal fractures, even though the fissures may not actually run through the sella turcica, the pituitary body is often the seat of extravasation, which may readily account for the diuretic and glycosuric response occasionally exhibited by the recipients of severe cranial injuries. In one such individual under my care a year ago, there was intense polydipsia, with an average daily output of about 8 liters of sugar-free urine with a low specific gravity, the condition persisting for the six weeks the patient was under observation in the hospital. As was true of the experimental conditions heretofore described, so also in these cases of basilar fracture, when a glycosuric response occurs it is apt to be transient and the presence of sugar may be overlooked unless the first voided specimen is secured, whereas the polyuria is commonly of much longer duration.

Though as eminent an authority as Van

Noorden is skeptical of the possibility that a true diabetes may be thus inaugurated by trauma, a number of striking cases have been recorded by Abt and Strauss, by Wieland, by Nothnagel and by Naunyn and Lepine. In view of these authentic clinical examples and in the light of our laboratory experiences, which bring a new element into the discussion, namely the hypophysial secretion, it seems safe to conclude that a suitable injury, affecting the infundibular lobe without obvious lesion of any nerve center, may set up a prolonged polyuria, justifying the designation of diabetes insipidus.

Let us turn from this brief consideration of the traumatic polyurias to those associated with some obvious process of disease.

A review of the clinical histories included in many of the past articles upon diabetes insipidus makes it clear that a large percentage of the patients have shown symptomatic evidence of a lesion involving the base of the brain, a gummatous meningitis affecting the structures in the middle cerebral fossa being a particularly common accompaniment of the disorder. This was true of several of Fletcher's cases gathered from the Johns Hopkins Hospital records,¹⁰ and one

¹⁰ T. B. Fletcher: Diabetes Insipidus, with the Report of Five Cases. Johns Hopkins Hospital Reports, 1912, vol. x, pp. 197-247.

of his patients, subsequently under my own observation, showed characteristic neighborhood manifestations of an hypophysial lesion coupled with signs of glandular insufficiency.

The fact that tumors or other lesions in the neighborhood of Bernard's center are far less likely to be accompanied by polyuria and glycosuria than are similar lesions situated farther forward in the interpenduncular region, has long been a source of confusion, and some have even gone so far as to predicate so-called diuretic and sugar centers in the floor of the third ventricle. An observation of particular significance in this connection was commented on by Fitcher and has been recently emphasized again by E. Frank, namely the surprising frequency with which primary optic atrophy, often with bitemporal hemianopsia, accompanies the encephalitic polyurias often classified as diabetes insipidus*; indeed, the diabetes has even been looked upon by some as a cause of the optic atrophy.

As stated in my introductory paragraphs, in our considerable experience with hypophysial disorders a surprising number of the patients had either been regarded as the victims of the malady under discussion at one time or another, according to their own clinical story, or else the condition was apparent during their hospital residence. In most of these individuals the existence of a pituitary involvement was sufficiently clear, in view of the coincident local manifestations of tumor, though we are becoming familiar enough with these clinical states to recognize the evidences of dispituitarism in the absence of these telltale neighborhood signs.

However, from a critical standpoint unequivocal proof comes only through post-mortem examinations, and of these there have been a sufficient number recorded in the literature, supplemented by the evidence of our own series of cases to make a strong brief.

A number of these cases have been brought together by E. Frank; for example, a tubercle of the infundibulum reported by Hagenbach in 1882, a sarcoma of the hypophysis by Rosenhaupt in 1903, a cystic tumor below the third ventricle by Finkelnburg in 1910, and two examples of gummatous involvement of the infundibular region, both with bitemporal hemianopsia and diabetes insipidus, have been put on record by Oppenheim. Though not certified by autopsy, the situation of the lesion in many other reported cases has been reasonably definite, as was true of Frank's case—a patient who had received a bullet wound involving the pituitary fossa, with subsequent development of diabetes insipidus accompanied by adiposity and other symptoms indicative of a state of hypopituitarism.

*According to E. Frank, Kruse in 1894 reported 35 cases of bitemporal hemianopsia, 7 of them showing diabetes insipidus. Spanbock and Steinhaus in 1898 reported 50 cases of hemianopsia, 11 of them showing diabetes insipidus. Oppenheim has recorded one or two cases in which the post-mortem findings showed a gummatous meningitis, the medulla and pons being unaffected by the process.

Since the appearance of Frank's paper another example, certified by autopsy, has been recorded by Prof. Simmonds of Hamburg.¹¹ The patient was a woman of 37, in whom an intense polyuria developed some months after an operation for cancer of the breast, the amount of urine fluctuating between 10 and 19 liters per diem. The autopsy disclosed a small metastatic nodule of the growth which involved the dorsum sellae, the posterior lobe and hypophysial stalk, the pars intermedia and pars anterior remaining free. A somewhat comparable condition occurred in the case of a patient who was under my care a year ago in Prof. Halsted's service in Baltimore.

A young man, 22 years of age, entered the hospital January 24, 1912, in extremis, with a recurrent lymphosarcoma of the neck and metastases in the cranial bones. Aside from the local disturbances caused by the inoperable tumor his chief symptoms were an insatiable thirst and polyuria. Until shortly before his death, which occurred a month after his entrance, the daily amount of urine varied between 10 and 12 liters.

At autopsy a discrete nodule of the widely infiltrating growth was found by Dr. Whipple occupying the thickened stalk of the pituitary body. The kidneys were histologically normal.

In our series of something over 100 examples of primary hypophysial disease which have been carefully investigated, though many of them, particularly of the group showing hypophysial insufficiency, have shown polyuria, in six a condition existed which justified the clinical designation of diabetes insipidus, and in five of these individuals this had been one of the various clinical diagnoses advanced before admission. The following curtailed history will serve in illustration:—

On November 23, 1911, J. B., aged 48, entered the Johns Hopkins Hospital, nearly blind, in a stuporous condition and utterly disoriented.

According to the history, he had received, six years before, a frontal injury which had fractured his nose. He subsequently suffered from headaches, occasionally accompanied by nausea and vomiting. He became forgetful, had periods of somnolence and lost his potentio sexualis. He acquired an enormous appetite, and polydipsia with extreme polyuria developed. His vision began to fail, and nine months before his admission a bitemporal hemianopsia was observed. Periods of diplopia followed. Owing to the polyuria several of his many attendants had agreed upon a diagnosis of diabetes insipidus.

On examination the case proved to be a typical one of hypopituitarism with outspoken and characteristic neighborhood symptoms, though the x-ray of the sella showed normal outlines.

The body temperature was usually subnormal, often registering as low as 96; the pulse was slow, often 60; and the respiration also was greatly slowed, with occasional rhythmicities of Cheyne-Stokes type.

¹¹ M. Simmonds: Hypophysis und Diabetes Insipidus. Münch. med. Wchnschr., 1913, vol. ix, pp. 127-128.

Somnolence was one of the most striking features, and as there were frequent periods of incontinence it was not always possible during his drowsy periods to collect the full 24-hours urinary excretion. At other times, when he was wakeful and responsive and the urine could be measured, the amount was always over 5 liters, not infrequently exceeding the ingested fluids.

Though the urine from time to time contained a trace of albumen and an occasional hyaline cast was present, there was no clinical evidence of arteriosclerosis, the blood pressure almost invariably registered below 100, and functional tests of the kidneys gave normal reactions.

He was under observation for five months, and during this time efforts were made to compensate for his glandular deficiency by the administration of extracts and by pituitary implantations, with but variable success. He ultimately died from an inhalation pneumonia on April 29, 1912.

The autopsy disclosed an interpeduncular cystic tumor—the usual squamous epithelial lesion derived from an anlage of Rathke's pouch. The hypophysis was greatly flattened and contained but a few normal cellular elements. The kidneys were histologically normal. There was no arteriosclerosis.

This is a fair example of the five other cases in which the polyuria was sufficiently pronounced to justify particular study. It is, moreover, the only one of the six in which occasional traces of albumen and renal elements appeared in the urine, and I may add in this connection that none of the patients showed evidences of arteriosclerotic changes, that a persistently low blood pressure was commonly observed, and that standard functional tests of the kidneys gave normal reactions in the three patients in whom these tests were made.

Suggestive as the foregoing examples of spontaneous polyuria prove to be, there is still another case in the clinical series which is even more illuminating. In this patient an enduring polyuria was inaugurated by a transphenoidal hypophyseal operation—an experience which is somewhat comparable, as will be observed, to the experimental consequences of hypophyseal manipulations discussed in the first section of this paper. The story deserves a somewhat detailed recital.

Pituitary tumor with blindness from primary optic atrophy. Symptoms of hypopituitarism. Sellar decompression, provoking a post-operative diabetes insipidus.

Mrs. F. L., 40 years of age, entered the J. H. H., Oct. 23, 1911, with the complaint of blindness and headaches.

There was nothing noteworthy in her family or past personal history, though from childhood she had suffered more or less from cephalalgia. Her adolescence was somewhat tardy, for her catamenia, though subsequently regular, did not begin until she was 16. She married at 20, and raised a family of six healthy children, the eldest 18 years, the youngest three months of age. Four other pregnancies miscarried.

Present Illness. After her fifth confinement, four

years before admission, she began to suffer from throbbing headaches, and a few months later failure of vision was first observed. This condition progressed, and in the course of the next two years she became almost completely blind.

Subsequently her sense of taste and smell became affected, and there were occasional uncinat seizures preceded by a dreamy state with an olfactory aura (as of something scorched, as bread, rubber or meat), and followed, in the more severe attacks, by a convulsion with loss of consciousness. Of late there had been some failure of memory with depression; also marked drowsiness.

Physical Examination. A well-nourished woman, 5 feet 6 inches in height, and weighing 150 pounds. Visceral (abdominal, thoracic, etc.) examination negative. Urine normal. Blood examination (including Wassermann test) negative except for an eosinophilia of 4 per cent.; blood pressure averaged 110 mm. of Hg. No positive neurological signs aside from those of the pituitary neighborhood.

Analysis of Hypophyseal Symptoms. (1) *Neighborhood:* The cranial x-ray disclosed completely obliterated sellar outlines. *Eyes:* Pupils dilated (7 mm.); sluggish reaction to bright light. Bilateral primary optic atrophy. Blindness so nearly complete that accurate perimetry was precluded though shadows of large moving objects were at times indistinctly made out in the nasal fields. Pupillary reactions also appeared to be better from a ray of light cast on the temporal than on the nasal retina—presumably the last stage of a bitemporal hemianopsia. Complete anosmia. Uncinate gyrus seizures as recorded.

(2) *General Pressure Symptoms.* Headaches, extreme and paroxysmal and occasionally accompanied by nausea and vomiting. Some evidence of new tissue formation in the atrophic nerve heads, with obscuration of the margins and of the lamina cribrosa.

(3) *Glandular.* No skeletal change; no especial adiposity; no cutaneous change. Moderate hypotrichosis. Sugar assimilation limit 200 grams of levulose. Constipation marked. No polyuria or polydipsia. Pulse, temperature and blood pressure tended to be subnormal. Marked drowsiness. Other ductless glands negative.

November 1. Sellar decompression by transphenoidal route. The thin, bulging floor of the sella was easily removed in one large scale. The dura was incised, but instead of the expected soft struma a dense tissue mass was encountered. This was taken to be the flattened gland interposed between the operative field and the tumor. (A minute fragment of the tissue, removed for examination, subsequently showed flattened anterior lobe cells with a great increase of interstitial tissue.)

There were no surgical complications: no subsequent nasal discharge.

On recovering from the operation the patient exhibited a degree of thirst, which proved to be insatiable by the usual ward delivery of water. Not, however, until several days later did the associated polyuria become so marked as to attract especial attention (Fig. 8). Unfortunately there had been no test for sugar on the first specimen voided after the operation, though, according to the ward routine for all suspected hypophyseal cases, the 24-hour amounts were recorded, except on three days (November 13 to 15 inclusive) when some specimens were lost. After November 16 the fluid intake and output were both measured.

As the poor woman's pressure headaches continued unabated, recourse was had, a month later, to a palliative subtemporal decompression.

December 4. Right subtemporal decompression. A tense temporal lobe was disclosed. Uncomplicated healing. There was prompt and permanent relief from headaches but the polyuria, anosmia and subjective olfactory seizures continued as before and, as was anticipated, no improvement occurred in vision.

Observation on the Polyuria. (Fig. 8.) As stated, the sellar decompression of November 1 served to inaugurate an active polydipsia with polyuria. The primary wave of polyuria shown in the accompanying chart persisted for three months, the 24-hour amount of urine reaching nearly 12 liters at the crest of the wave. The polydipsia was proportionate, and though from the plotted curve it would appear that the average fluid intake was less than the renal output, the ingested water only was measured. There were, however, many days when the excretion unquestionably exceeded the ingested fluids. However, her weight during these three months varied but slightly, at the lowest being 147.5 pounds, and on February 1, at the end of the primary period of extreme polyuria shown in the chart it was again at 150, her weight on admission.

Her thirst was unquenchable and was most distressing to observe. A two-liter jar of water which siphoned to her mouth, was kept at the head of the bed, and the poor blind creature almost continuously sucked at the tube, except during her sleeping hours. It was often necessary to refill the jar every few hours.

The chart shows that only on the day of the second operation (December 4) was there a marked break in the polyuria, owing doubtless to a diminished intake and possibly, too, to the fact that some specimens may have been lost in the operating room.

At no time were there any renal elements, sugar or albumin, acetone or diacetic acid in the urine.

Functional tests of the kidneys at the height of the polyuria showed no alteration from the normal. The phenolsulphonphthalein test for tubular function showed a positive reaction in 4½ minutes, and 47 per cent. was returned in the first hour. Tests with potassium iodide, with carbol-fuchsin and with lactose all gave normal results, and the glycosuric reaction to phloridzen was likewise normal.

The specific gravity of the urine throughout the three months averaged 1005 to 1006. Practically the lowest registration, namely 1002.5, occurred on the first two days following the inauguration of a period of salt-free diet, though at this time the polyuria was not at its extreme height. Attempts to increase the urinary concentration by administering NaCl were obscured, owing to the impossibility of keeping the ingested fluids low enough for the urine to be appreciably affected by any reasonable amount of salt.

On February 1, sugar and salt were withdrawn from the dietary and the liquids were limited to 2200 c.c., with resultant rise in the specific gravity; on the first two days the excretion exceeded the ingested fluids. The restriction of liquids, however, caused so much distress that prolonged observations were unjustifiable, and at this time, moreover, there was an evident spontaneous lowering of the degree of polyuria which had preceded.

She remained in the hospital through the month of February, during which time the polydipsia mod-

erated considerably. On some occasions the 24-hour amount of urine fell almost to normal limits. She was discharged on February 24, 1912, four months after her admission. Since her discharge frequent reports of her condition have been received through her physician. There has been an occasional slight wave of thirst with polyuria amounting to three or four liters in the 24 hours, but for the most part the amount ranges around the normal.

She continues (April, 1913) to be free from her former pressure headaches, though her uncinate seizures still recur and her blindness and drowsiness remain about as before.

'Tis an ill wind, indeed, that blows no benefits, and the experience with this unfortunate patient, who presented a therapeutic problem for which we have as yet no satisfactory surgical or other solution—the presence of an interpeduncular growth, which flattens and functionally obstructs the underlying pituitary gland—at least has added something to our knowledge of an obscure malady.

Though it may not be clear in just what way the manipulation of the compressed gland served to inaugurate the polyuria, the experience offers a strong argument in favor of the view that an actual disturbance of the pituitary body itself, rather than the stimulation of some predicated diuretic center in the remote third ventricle surmounting the growth, was the inciting cause of a condition worthy of the designation of diabetes insipidus.

It may be said in conclusion that certain clinical observations, coupled with the experimental data which have been assembled, suggest not only that,

The emotional polyurias are in all likelihood the expression of a neurogenic discharge of hypophyseal secretion, but also that,

The clinical polyurias of longer duration are in many instances merely the symptomatic expression of an internal secretory disturbance brought about by injury or disease involving the hypophyseal neighborhood.

Hence, whether or not there actually proves to be a form of polyuria of primary renal origin, our present conceptions of so-called diabetes insipidus need to be recast, with especial reference to the factor of the secretory activity of the pituitary body and particularly of its posterior lobe.

Note.—Since the preparation of this paper an interesting communication under the title "Diabète insipide avec infantilisme," made by Peirre Marie and Boutier before the Société de Neurologie de Paris, has been published in the *Revue Neurologique*, 1913, vol. xxi, pp. 555-560. The case in all likelihood was one of infantilism associated with an hypophyseal lesion, though no radiographic observations were made.

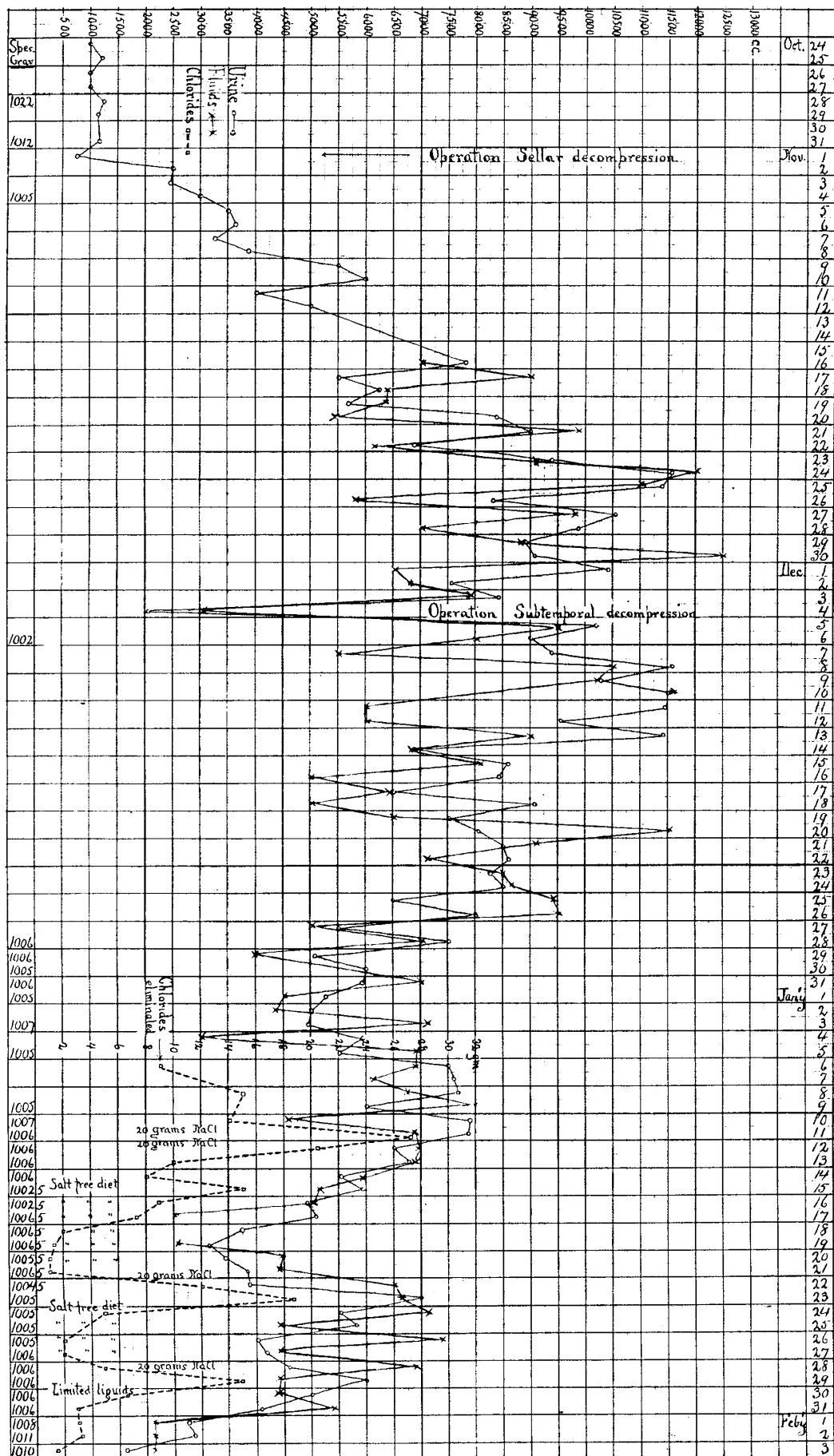


FIG. 8.