

EXPERIMENTAL DIABETES INSIPIDUS IN DOGS *

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It is a well substantiated clinical observation that injuries involving the base of the cranium frequently are followed by polyuria which may or may not be accompanied by glycosuria. It is also just as well substantiated that growths which involve the base of the brain, especially the region of the third ventricle, may likewise give rise to polyuria which may be accompanied by hyperglycemia sufficient to produce glycosuria. These conditions when arising from fractures of the base of the skull generally are of short duration, but when they result from growths in the region above mentioned, may be more or less persistent.

The first experimental evidence that injuries to the base of the brain (in the region of the fourth ventricle) gave rise (under certain conditions of the animal operated on) to polyuria accompanied by hyperglycemia and glycosuria was furnished by the classic experiment of Bernard known as the Bernard piqûre. Further, it has been observed that certain piqûres in the base of the brain may give rise to polyuria alone without glycosuria. As Bernard failed to induce any glycosuria by his piqûre after section of the splanchnic nerves, or in fasting animals, our present-day interpretation of his results would be that he was dealing with an epinephrin glycosuria. However that may be, Cushing¹ and his coworkers have thrown some doubt on this interpretation, as well as on the assumption of the existence of a diabetic center in the floor of the fourth ventricle, and have brought forward much experimental evidence to show that the glycosuria induced by the Bernard piqûre is in all probability of hypophyseal origin. The same evidence is applicable to the polyuria induced by piqûres further forward in the brain.²

All workers in this field have noted that the injection of extracts of the posterior lobe cause a rise in the blood-pressure generally accompanied by a transient (more lasting than the increase in blood-pressure) polyuria. Like observations³ on the volume of the kidneys

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1. Cushing, H.: Bull. Johns Hopkins Hosp., 1913, xxiv, 40.

2. Cushing, by stimulating certain nerves of the autonomic system (Langley) which make connection with the pituitary body, and which he claims controls its secretion, was able to bring about these conditions (polyuria and glycosuria), which he explains in terms of hypersecretion of the nervous part of the gland.

3. King and Stoland: Am. Jour. Physiol., 1913, xxxii, 405.

show the following general results: Immediately following the beginning of the rise in blood-pressure there is a contraction of the kidneys, during which time the secretion of the urine is almost suspended. Following this initial contraction and anuria the kidneys begin to dilate and often attain a degree of dilatation much above the normal. Accompanying and during the time the kidneys remain dilated (about thirty minutes from a single dose) there is a marked polyuria, sometimes glycosuria. The intensity of the diuresis induced is always proportional to the degree of kidney dilatation and only lasts as long as the kidneys remain dilated. This is paramount to saying that the diuretic effect of posterior lobe extracts is due to a local dilatation of the kidney vessels, thus allowing a greater quantity of blood to pass through the kidneys per unit of time than under normal conditions, just as the diuresis induced by caffeine or strophanthus can be accounted for in terms of kidney volume.

Nearly all the investigations so far on the function of the pituitary body have brought out the fact that certain injuries of the posterior lobe or of the stalk, such as partial removal of the lobe or irritation of the stalk, frequently are followed by polyuria; sometimes, though less frequently, by glycosuria, generally transient but sometimes persisting for weeks, in which case the polyuria is accompanied by a great laying-on of fat.⁴ In two young female dogs I was able to induce a permanent polyuria (a veritable diabetes insipidus) accompanied by a rapid accumulation of fat by operating on the base of the brain as follows:

A hole about 5 mm. in diameter was drilled with an ordinary dental burr, driven by a dental engine, from the roof of the mouth up through the sphenoid bone into the floor of the sella turcica. The opening removed the posterior rim of the pituitary fossa and extended back about 5 mm. This exposed the posterior surface of the posterior lobe and the region just posterior to it. The hole in the sphenoid bone was then plugged with a gutta-percha compound such as is used for temporary fillings in teeth. The plug was placed so that it would impinge somewhat on the posterior lobe and its stalk and extend up into the third ventricle.

Both animals recovered from the effects of the operation, and the wounds healed without infection. No nasal trouble followed. No sugar was found in the urine secreted during the time of the operation, nor at any subsequent time. Only a small amount of urine was passed (about 150 c.c.) during the forty-eight hours following the operations. After the second day polyuria began to develop. One of these animals in particular (weight 6 kg.) after the fourth day required from 5 to 6 liters of water every twenty-four hours to make it comfortable and passed from 5 to 6.5 liters of urine per day for nine weeks, and in the same time gained three kilos in weight. While the animal was not eating, drinking and urinating, it simply slept and grew fat. With an abundance of water (6 to 7 liters) the amount of urine voided per twenty-four hours was about equal to the amount of water imbibed; but if water was given more sparingly (4 liters) the tendency was to pass more urine than the

4. Cushing, H.: Boston Med. and Surg. Jour., 1913, clxviii, 901.

water imbibed. If given an ordinary amount of water (300 to 500 c.c.) about 600 to 800 c.c. urine would be passed, and the animal would show signs of distress. The dog enjoyed a good appetite throughout, eating well of table scraps, etc. The sugar tolerance was high; in fact it was impossible to induce an alimentary glycosuria, the animal being able to ingest 15 gm. of glucose per kilo body weight in six hours without showing any signs of glycosuria.

The urine passed was simply a dilute normal urine (specific gravity 1.001-1.002). The amount of nitrogen eliminated when computed in terms of the food eaten and a normal amount of urine (250 to 300 c.c.) was about normal. Also the relative amounts of the different nitrogen constituents of the urine were normal. In fact, there was no change in the nitrogen metabolism. The inorganic salts were approximately normal. With a given amount of water, sufficient to maintain physical comfort (6 liters), the concentration of the urine remained about constant (specific gravity 1.001-1.002). With less water the urine tended to become more concentrated. Ordinary quantities of water, less than 2 liters per day, caused great physical discomfort.

During the animal's life after the operation (nine weeks) it gained 3 kilos (50 per cent.) which seemed to be almost wholly represented by an accumulation of fat. While it was found impossible to induce an alimentary glycosuria, the animal responded promptly to phlorizin with a copious output of sugar.⁵

The dog's temperature remained low throughout, not more than 37 C., and the state of lethargy in which it remained indicated profound hypopituitarism as defined by Cushing.

Necropsy.—The hole in the sphenoid bone included about 1 mm. of the posterior part of the pituitary fossa and extended posteriorly about 4 mm. The plug of temporary dental stopping had healed into the bone and protruded up along the posterior surface of the gland for about 4 mm. It had impinged somewhat on the nervous portion of the gland and the point of the plug was in close proximity to the stalk at its entrance into the floor of the third ventricle. The plug had exerted considerable pressure on the posterior lobe and the stalk, but not sufficient to destroy the gland, nor materially to change its structure. The anterior lobe was apparently normal and the base of the brain was perfectly clean.

Outside of the cranium the principal pathological finding was an excessive accumulation of fat, not only in the regions of the body where fat normally deposits, but all the tissues were infiltrated with fat. It was noticed before death that the heart was not working well; and when opened deposits of fat were found on the valves and in the interstices of the papillary muscles sufficient to occupy a large part of the space in the heart's cavities. In fact, all the spaces and interstices in the muscles of the body everywhere were distended with fat. The muscle cells themselves were not well nourished. All the glandular organs were infiltrated with fat, and the liver especially showed numerous necrotic areas. The kidneys were small and the cells contained an excess of fat. The glomeruli were full of fat. No marked inflammatory changes had occurred in the tubular epithelium, although the cells did not stain well.

Cushing and his coadjutors as well as nearly all other workers in this field have described the occurrence of intense polyurias, generally of short duration, following the partial removal of the nervous lobe of

5. An attempt was made to inhibit the formation of fat in these dogs by keeping them under the influence of phlorizin, but abscesses tended to form at the site of the injections, so this had to be discontinued. In fact, both animals had to be sacrificed on account of abscess formation due to hypodermic medication.

the gland and also after insult to the stalk. Some of the animals described exhibited a moderate polyuria lasting for months, accompanied with an abnormal accumulation of fat.

There is sufficient evidence now at hand to establish beyond doubt that certain manipulations of the posterior lobe, such as partial removal or injuries to the stalk, will induce a temporary polyuria and that continuous irritation of a small degree, such as slight pressure, may bring on a permanent polyuria (diabetes insipidus). Cushing⁴ evidently brought on this condition in one patient by a sellar decompression operation, in which only a small fragment of anterior lobe tissue was removed. In dogs, experimental diabetes insipidus is accompanied by marked symptoms of hypopituitarism and an accumulation of fat. From the clinical reports at hand, this rapid accumulation is not so apparent, although nearly all the other signs of hypopituitarism have been described.⁶

To form a true picture from the experimental data at hand of the mechanism which operates to induce polyuria and polydipsia is quite impossible. One might imagine that by certain manipulations of the gland, such as has been described and which are followed by polyuria and polydipsia, the posterior lobe can be thrown into a state of hypersecretion; and that the excess of the secretion acts in the same manner as the injection of posterior lobe extract. This would give rise to a general vasomotor contraction of short duration followed by a local vasomotor dilatation of the kidney vessels of a more lasting character. Such a change in the relative blood-supply between the body as a whole and the kidneys always gives rise to diuresis. In fact, all chemical compounds possessed of diuretic properties act on the vascular system in this way (caffein; strophanthus; pituitrin). Should one attempt to explain the polyuria and polydipsia arising from hypophyseal derangements, such as has been described in terms of the diuresis caused by the injection of extracts of the posterior lobe, the following explanation (more or less transcendental) seems to satisfy at least a number of the observed facts:

To conform with this generally accepted interpretation of the action of extracts of the posterior lobe in causing diuresis, the kidneys will have to be looked on as dialyzing membranes and the urine as a dialysate. This conception makes the dialyzing membranes (kidneys) permeable to all the normal constituents of the urine, and the rate of dialysis to depend on the concentration in the blood of the constituents of the urine, and the amount of the solution of these substances (blood) which comes in contact with the dialyzing membranes per unit

6. Marie and Boutier: *Rev. neurol.*, 1913, xxv, 555.

of time. Such a mechanism as this would tend to deplete the body of water as well as of the effete materials given off from the tissues into the blood, the solution of which in water constitutes the urine.⁷

Ordinarily, the circulation through the kidneys is about sufficient to permit of the passage of about 1,500 c.c. of water with its contained substances (urine) per day. To maintain life and comfort this water must be replenished from the outside, which is accomplished by absorption from the stomach and intestines. When a certain amount of water has passed from the body a disagreeable sensation begins to manifest itself in the mouth and the pharynx, which is relieved by the imbibition of water. When water passes rapidly through the kidneys or is given off from the surface of the body in large amounts, this sensation occurs at frequent intervals, and if the excretion of water is very rapid, it may be almost continuous (polydipsia). This is analogous to the sensation referable to the stomach called hunger. When the tissues begin to suffer from lack of food, some influence begins to exert itself on the stomach, causing contractions which give rise to painful sensations called hunger pains, and which are relieved by the taking of food. In diabetes mellitus the body cannot utilize one of the chief food substances (carbohydrates) and in extreme cases hunger pains are almost constant.⁸ Likewise when the kidneys permit the passage of an excessive amount of water, polydipsia results.

As already stated, diuresis results whenever an excess of blood is permitted to pass through the kidneys in a given time, as compared with the blood passing through the remainder of the body in the same time. This deviation from the normal relation of the kidney blood-supply to the tissues in general would tend to draw off the water from the body to an extent sufficient to cause polydipsia. Should the kidneys attain to a great degree of dilatation, such as often occurs after the injection of pituitrin, the elimination of water might be sufficiently rapid to cause a constant state of polydipsia, and if one were allowed to imagine a condition of prolonged dilatation of the kidneys to result, a state of polyuria and polydipsia comparable to the dog described might well result.

While this explanation satisfies quite well most of the conditions present in the polyurias and polydipsias of hypophyseal origin, both clinical and experimental, it can hardly be said that there is sufficient

7. Water and the inorganic salts are essential to life and must therefore be considered as foods. If the effete materials which result from cell metabolism appear in the urine as dialysates they must first be held in a state of solution. So it would appear that one of the functions of water in the animal economy is that of a solvent for these effete substances, and that its excretion is necessary to accomplish their excretion.

8. Luckhardt: *Am. Jour. Physiol.*, 1914, xxxiii, 313.

experimental evidence at hand to support it unconditionally, although experimental evidence in its support is not wholly wanting. We can hardly say, however, that we have sufficient evidence at hand to prove that operations on the pituitary body such as are followed by polyuria and polydipsia, or that such pathological lesions as give rise to polyuria, cause a hypersecretion of the posterior lobe of the gland sufficient to keep the kidneys in a dilated state for weeks or months. Neither have we sufficient evidence to claim that a constant hypersecretion of the posterior lobe will keep the kidneys in a state of dilatation, nor do we know that repeated doses of posterior lobe extract over a long time will accomplish any such results. In fact, Farini,⁹ P. Bioch,¹⁰ R. Balnet¹¹ and von den Velden¹² claim that in human subjects the injection of posterior lobe extracts exerts no diuretic influence at all, and that when administered to patients suffering from diabetes insipidus they reduce the amount of urine passed to or below normal. In normal dogs injections of posterior lobe extract twice daily failed to modify the amount of urine passed over a period of seven days.

Direct stimulation of the posterior lobe or of the nerves going to it generally cause a contraction of the kidneys which may last for a few minutes only (ten to fifteen) to be followed by a dilatation accompanied by diuresis, or the initial contraction may last for hours (twenty-four to forty-eight) eventually to be followed by polyuria, which argues for a dilatation of the kidneys. Frequently, while drilling through the sphenoid bone in pituitary operations, an oncometer record of the kidney volume being taken at the same time, I have observed a contraction of the kidney which sometimes continued throughout the operation with almost complete suppression of the urine. In fact, anuria may continue for forty-eight hours after the operation. Under like conditions I have noted an initial contraction of the kidney to be followed in from ten to fifteen minutes by dilatation and diuresis, and at other times and under identical conditions a dilatation of the kidneys from the first accompanied by diuresis.

While these observations seem contradictory, nevertheless, when scrutinized, their lack of agreement is more apparent than real. The experimental evidence seems to bring out quite clearly that continued stimulation (irritation) not of sufficient intensity to destroy the integrity of the gland, may give rise to a state of polyuria and polydipsia of long duration, lasting at least as long as the stimulation lasts, provided, however, the integrity of the gland is preserved. Operations,

9. Farini: *Riforma med.*, 1913.

10. Bioch, P.: *München. med. Wchnschr.*, 1914, lxi, 217.

11. Balnet, R.: *Berl. klin. Wchnschr.*, 1913, I, 2379.

12. von den Velden: *Berl. klin. Wchnschr.*, 1913, I, 2085.

such as direct stimulation of the gland for a short time only, or partial or total removal of the gland, induce a diuresis of short duration, and if we admit that the diuresis results from a setting free of an excess of the gland's secretion, as long as the effects of the excess secretion lasts. As to whether in these cases of experimental diabetes insipidus the volume of the kidneys is increased, we have no direct evidence. In fact, we have no method at hand to demonstrate whether or not such a condition exists.¹³

As for the explanation of the excessive formation of fat under these conditions, none is at hand. Carbohydrates seem to be rapidly converted into fat, which may account for the high sugar tolerance of the animals. At any rate it seems that the food value of the carbohydrates is reduced very much under the conditions imposed, and that the real condition of the body at the end is that of emaciation. In diabetes mellitus the body cannot use the sugars, so in experimental diabetes insipidus of pituitary origin in dogs the body does not seem to be able to utilize either the sugars or the fats to their full extent.

13. The theory that in diabetes insipidus some substance is liberated in the body that renders the kidney epithelium permeable only to dilute solutions, could not be made to hold in these dogs. The kidneys here were permeable to a urine, having a specific gravity of 1.010, as shown by the imbibition of salt and limiting the water supply.