

DIABETES INSIPIDUS

Ketil Motzfeldt, M. D., University Clinic,
Christiania, Norway.

Diabetes insipidus has for centuries been recognized as a distinct clinical entity, the main symptom of which is polyuria without pathological content in the urine. The etiology, however, has been obscure.

Older writers have distinguished between an "idiopathic" and a "symptomatic" form, while more recent authors have sought by the functional kidney tests to establish a distinct division between primary polyuria and primary polydipsia. It has also been suggested to reserve the term diabetes insipidus for the "true" cases, that is for the primary polyurias due to an insufficient ability of the kidneys to produce a concentrated urine.

During recent years new viewpoints have been advanced of far reaching significance for the conception of the etiology and pathology of this disease, — views that have been reflected in the therapy, which at present seems to be more promising than has previously been the case. Although many obscure questions remain to be solved, it now appears justifiable to classify the disease as a disorder of the pituitary body. There are many cases in which this cause is beyond doubt, and probably the majority of the "true" diabetes insipidus cases will turn out to be of pituitary origin.

It has long been known that polyuria often occurs after traumatic lesions of the skull, and that it is a frequent symptom of certain nervous diseases, organic as well as functional.

Claude Bernard's celebrated piqure (1854) threw some light upon these facts, and he believed that he had discovered a "centre" for diabetes insipidus. Later investigations, however, have shown that polyuria will result from lesions of many other parts of the nervous system.

These observations gained in importance, as Magnus and Schäfer (1901) showed that the pituitary extracts had certain diuretic properties. This statement has led to considerable confusion and it has but recently been recognized that the effect really is antidiuretic.

Clinically the direct relationship between diabetes insipidus and the pituitary body was first pointed out by Frank (1912), and during the few years that have elapsed since, similar cases have been reported where this relationship is unquestionable.

As far as our present, limited knowledge goes, the most frequent pathological findings are tumors, syphilis and tuberculosis.

The pituitary adenomas, which are the most frequent causes of acromegaly, only exceptionally lead to polyuria, and little is known about the effect of the pituitary cysts. In most of the cases there have been found malignant tumors, either of the neighborhood, secondarily involving the pituitary, or in the gland itself. Metastases from cancer are especially prone to locate in the hypophysis.

The frequency of a syphilitic history in these cases has long been known. Anatomically the usual finding is syphilitic basal meningitis. This probably in some way interferes with the functional activity of the hypophysis. In a few instances there were syphilitic lesions of the gland proper.

In many of the cases of diabetes insipidus on record the patients have been suffering from pulmonary tuberculosis, but this fact has not attracted much attention. Of recent years careful anatomical investigations, however, have shown actual tuberculosis of the pituitary body, sometimes with total destruction of the gland.

These changes are easily overlooked, and in some cases the lesion has not been discovered until the microscope has revealed it. Negative findings, where the hypophysis has not been specially examined, therefore, amount to little.

There are, furthermore, as I have reason to believe, a certain number of cases due to atrophy or congenital hypoplasia of the gland. It is well known that polyuria often sets in during or after acute infectious diseases, and also how apt the ductless glands in general are to be damaged by infections. It is a common experience, gained in experimental as well as in clinical surgery of the hypophysis, that polyuria often occurs after removal or injury to the gland.

Most writers on this subject have supported the theory that these conditions have acted as stimuli for the pituitary, in accordance with the views of Magnus and Schäfer. But as there are some cases where the entire gland has been destroyed, we are obliged to drop this hypothesis and assume a hypo-function of the gland. Some cases have shown a total destruction of the posterior lobe, while the anterior has remained intact.

During the past four years, or since attention has been directed to the pituitary body as concerned in this disease, there has not been reported a single

autopsy finding in which this gland has not been in some way involved.

These cases are not numerous and they are scattered in the literature of many countries, and a presentation of the features common to them has not yet been given: By making retrospective diagnosis in the older diabetes insipidus literature I have been able to add a number of cases where the pituitary origin can be regarded as pretty well established. On this basis I will now outline some features of the clinical picture. It has been surprising to see how relatively clear-cut and uniform this condition is, when facts which were previously considered of minor importance are taken into account. The picture is in general agreement with what the textbooks give as the symptoms of diabetes insipidus, without any regard to the pituitary origin. Adiposity is frequently mentioned, but it seldom reaches any extreme degree. In the few cases where it has been tested, there has been found a high carbohydrate tolerance. Almost as common as adiposity is sexual underdevelopment, the degree of which will be dependent as well upon the seriousness of the disease as upon the age at the onset. If the polyuria sets in during childhood, puberty will very likely be delayed or entirely lacking and the patient remain in a more or less pronounced infantile state. When the onset has come in adult age, regressive changes in the sexual organs have sometimes been noted. Impotency and amenorrhoea are among the most constant symptoms, and usually set in simultaneously with the polyuria which in most instances starts quite suddenly. The secondary sex characteristics show the same changes. The growth of hair in the

axillae and on the pubes is scanty, and even marked loss of hair may come on shortly after the onset, though this is comparatively rare. The growth of the beard is apt to be scanty and slow, while there are usually no changes in the hair on the head, and the eyebrows are also intact. This last mentioned fact is in distinction from hypothyroidism, where the "eyebrow sign" is said to be of value.

These patients usually suffer from constant fatigue and are troubled with a never-ceasing lassitude; in other words there is a more or less marked asthenia. In many cases psychic alterations also take place, such as somnolence and apathy, sometimes accompanied by depression and melancholia.

The skin is usually dry and these patients perspire very little. Another valuable sign is the slightly subnormal temperature. Apart from these general manifestations there are certain symptoms which are directly pointing to the hypophysis, such as enlargement of the sella turcica and bitemporal hemianopsia. Neither of these findings are very frequent, and negative results do not speak against the pituitary diagnosis. The combination of polyuria and hemianopsia has long been known, and the visual disturbance is often of a peculiarly short duration, the *hemianopsia fugax*. All the distressing symptoms of an intracranial tumor may of course be seen in some cases.

It could not be expected to find all or even the majority of the above mentioned symptoms and manifestations in each case. However, I believe it will be very rare, in cases of primary polyuria, not to find anything pointing towards the pituitary body. There seem to be two fairly distinct types: the obese,

indolent; and the lean, infantile type. The family history does not give definite information, although some instances have shown a pronounced hereditary tendency. The complaint, which causes the patient to consult the doctor, is almost invariably polyuria, but when the degree is only slight the most distressing feature has been weakness or headache, and very rarely, eye troubles.

This varying picture will naturally suggest a disease of different ductless glands, but space will not permit me here to enter into a discussion of the intimate relationship between these glands. However, all of these signs can, with apparent probability, be referred to the hypophysis.

As mentioned, pathological experience has shown that it is no longer permissible to assume an excess of pituitary secretion. It will therefore be of interest to see how the disease compares with the hypofunction of the gland. The picture of this condition has of late been brought out in an admirably clear way,—by Cushing's work especially. It is sufficient to point out what he regards as the four cardinal symptoms:

1. High carbohydrate tolerance.
2. Subnormal temperature, slow pulse, low blood pressure.
3. Drowsiness and sleepiness.
4. Asthenia.

Anhidrosis, scanty growth of hair, sexual hypoplasia, impotency and amenorrhoea also belong to the picture, and it is now pretty well established that Froehlich's syndrome, the dystrophia adiposo-genitalis, is due to hypopituitarism.

The correspondence is so striking and obvious indeed, that further comment is unnecessary. Here I

wish, however, to emphasize that it is not unusual to see very marked cases of adiposo-genital dystrophy; or other cases of hypopituitarism with a normal output of urine. The functional activity of the posterior lobe seems to be well specialized.

Usually the diagnosis is easy when the conditions just emphasized are taken into consideration.

It is doubtful whether a subcutaneous injection with some pituitary extract is of diagnostic value, as the antidiuretic effect seems to be a general physiological action, not limited to the cases of pituitary insufficiency.

Psychic treatment or forced restriction of water, sometimes valuable in primary polydipsia, has not proven efficacious in "true" cases. A diet poor in chlorides and nitrogen has been the main treatment and has been able to lower the output to a certain extent. On the whole, however, the treatment has been rather unsatisfactory; none of the drugs recommended is of special value. Opium will sometimes decrease the thirst and in that way lower the output without exerting any influence on the concentration. The only remedy which has power to check polyuria and concentrate the urine is the extract of the posterior lobe of the hypophysis. A subcutaneous injection with an ampoule of some of the usual commercial preparations will probably be sufficient to exert a very marked influence on the output. This effect will usually show in a few hours and reach its maximum in 4-5 hours. Unfortunately the effect is not lasting and the output will probably be high again the next day. There are, however, cases on record where the diuresis has been checked for weeks afterwards. The injections are well borne; paleness,

slight headache and ringing in the ears may occur, but only last for a few hours.

Intravenous injections are not advisable as they may lead to collapse.

As this treatment cannot be kept up for a long period, it would be a great advantage if treatment by mouth might prove of some value. This mode of administration is far less efficacious, but is without discomfort and, as far as our present knowledge goes, is free from danger, even in large doses. Such treatment, therefore, can be carried on indefinitely.

The sufficient dose has to be tried out in each case, and as a rule very large doses are required, the amount of active material absorbed from the intestinal tract being evidently very small. The commercial dry preparations will very likely prove inefficient. Wherever possible the treatment should be tried with fresh material from the abattoir, as well for economical reasons as for the fact that the dried preparations are less potent. As it is very difficult, at least in pronounced cases, to check the 24 hour amount of urine in this way, it will probably be the best plan to confine the therapeutic aims to securing a normal output during the night and thus relieve the patient of one of the most distressing features—the restless nights.

One patient who has been under my care for the past two years has been very much improved by an intermittent pituitary feeding. She has taken from two to seven fresh pituitary bodies from cattle every evening. The output has hereby been checked during the night,—usually decreasing from nearly 2500 cc. to approximately 300 cc. At the same time the general state of health has improved consider-

ably, adiposity and drowsiness having disappeared, and menses have been re-established. Feeding the anterior lobe alone does not lead to this effect. This patient also shows another interesting feature. At present one hypophysis will have the same effect as, two years ago, could not be obtained by less than seven glands. The most satisfactory explanation of this fact will probably be that the hypophysis of the patient during the functional rest by the extraneous help has gained in secretory ability. This would be analogous to the explanation of the increased sugar tolerance in diabetes mellitus after alimentary rest, and is more in harmony with the laws of general physiology, than the usual assumption that the pituitary extracts stimulate the pituitary body.

This is an entirely new field for organotherapy, and only the future can tell how many cases will be benefited by treatment along these lines.

In the syphilitic cases an energetic antiluetic treatment will often prove of lasting value. The cases due to tumor have to be treated according to general surgical principles. In one case where the patient presented some evidence of brain tumor, the output was checked by a lumbar puncture.

As previously mentioned there has been confusion as to the effect of the pituitary extracts on the flow of urine. Recent clinical investigations, and among them my own work, have, however, shown quite definitely that the extracts from the posterior lobe physiologically serve to secure a normal concentration of the urine. I have gone more deeply into this question experimentally and my results indicate that this action is exerted on the sympathetic nervous system, especially on the vaso-motor nerves for

the renal vessels. These results may lead to a broader view of the polyurias. When the sympathetic system does not get its normal stimuli, as is the case in organic lesions with destruction of the posterior lobe of the pituitary body, polyuria will result. In functional disorders of the nervous system polyuria of varying degree and duration is frequently seen. The most satisfactory explanation in these cases seems to be to assume a temporary lack of tone of the vasomotor fibres in the sympathetic nervous system. The "urina spastica" of the old observers is probably rather a "urina atonica," indicating a lowered tone of the renal vaso-constrictors. Possibly these pathological polyurias of varying severity and of apparently different origin, ranging from the occasional polyuria of the neurotics to the polyurias of extreme degree in diabetes insipidus, can be linked together by the sympathetic nervous system.

Though this field is in urgent need of further investigation, it has become clear that diabetes insipidus is merely a symptomatic evidence of disordered pituitary function, and that it is due to a deficit of secretion. In consequence, administration of pituitary preparations will be the proper therapy.