Het mechanisme van de diabetische polyurie. Een vergelijking met andere klinische vormen van polyurie
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SUMMARY

Introduction
It is generally accepted that polyuria of diabetes is caused by osmotic diuresis. Opinions differ however, whether the osmotic effect of glucose takes action in the blood or in urine. Thus there is no certainty about the position of polyuria of diabetes amidst the other forms of polyuria to be encountered in patients. It is remarkable, that the urine of thirsty dehydrated diabetic patients is not maximally concentrated. A better understanding of the mechanism of polyuria of diabetes may possibly give some indications about the losses of salt and water in diabetic coma.

Chapter 1
In former ages the diagnosis of diabetes mellitus was founded solely on the symptom of polyuria of sweet tasting urine. In later years diabetes decipiens and renal glucosuria, both missing the polyuria, were described.

By various authors the following causes of polyuria of diabetes are proposed:

a. Polyuria caused by primary thirst and polydipsia.
In favour of this supposition could be that the urine of the patient with diabetes mellitus is not maximally concentrated in dehydration.

b. Polyuria caused by the osmotic effect of glucose in the urine. Polyuria is found only when a certain quantity of glucose appears in the urine. It does not coincide with a high blood sugar level, provided there is little excretion of glucose due to rising of its renal threshold.

c. The influence of a rise in blood sugar level with subsequent migration of water from the intra- to the extracellular space is discussed.
Possibly the secretion of antidiuretic hormone could be hampered by the relative higher water content of the extracellular space with hydremia, notwithstanding the dehydration. As a, this could be the reason, that the urine is not maximally concentrated.

d. Polyuria is caused by an increase in urinary solutes. A parallelism between excretion of glucose and urinary volume is often found, however, exceptions regularly occur. As a rule, the percentage of urinary glucose does not exceed 10 percent. GABRIOLOVE found a better correlation between urinary volume and the added osmotic effect of excretion of glucose and salt, as between urinary volume and excretion of glucose only.

BRODSKY and RAPOPORT found, that thirsty diabetics react after hypertonic infusions with a diuresis in the same manner as normal controls. A certain correlation existed between the urinary volume and total urinary solutes; a maximal concentration was attained only with very low urine flows.

e. In the opinion of MAINZER polyuria of diabetes occurs only in patients with symptoms of acromegaly. The hypophyseal anterior lobe would produce a diuretic fraction in excess. The findings of von HANN and WERMER make it plausible that the anterior lobe has a diuretic influence. Some authors supposed, that thyrotropic hormone was the diuretic agent in anterior lobe extracts. Following the introduction of ACTH in clinical medicine, it was discovered that this hormone has a definite diuretic action in patients with hypophyseal insufficiency. We were in a position to illustrate this with some clinical examples. Thus we should reckon with the possibility, that an increased secretion of ACTH and adrenal cortex hormone, caused by the ,,stress” of the disordered diabetic state, is in itself capable of promoting diuresis in these patients.

However we did not find a diuretic effect of injected ACTH in hypophysectomized rats.

Chapter 2

A short survey is given of former and present conceptions of renal function. The theory of H. W. SMITH and collaborators is described. It is pointed out that at present there are no indications of any functional significance of renal anastomoses as found by TRUETA and PRINZMETAL.
could be hampered by a lack of a cerebellar space with the brain. As a result, this could be concentrated.

Solute solutes.

The urinary volume is the same as can occur. As a rule, the urinary volume and glucose and salt, as be- come concentrated.

Some diabetics react after the same manner as normal people when the urinary volume concentration was attained.

Diabetes occurs only in about 10 percent.

There is a diuretic fraction in the urine. Some authors suppose a diuretic agent in antec- diuretic, as found by Tnup~.

Some authors suppose the action of ACTH in clinical thio- We were in a few examples. Thus we increased secretion of by the „stress” of the injection of injected ACTH in

The changes in renal blood flow and glomerular filtration rate following administration of ACTH and cortisone in adrenal insufficiency are discussed.

Chapter 3

The mechanism of excretion of glucose is discussed. Several objections against the concept of maximal tubular reabsorption and excretion (Tm), especially those of Gösta Ekehorn, are described. Glucose appears in the urine before the tubular mechanism of reabsorption is working at its maximal capacity. The renal threshold for glucose is lower with falling than with rising blood sugar levels. Nielsen thought this an artefact, due to renal dead space. It is however still not certain this is indeed the case.

The relation between glomerular filtration rate and excretion of glucose is discussed.

Three different renal thresholds for glucose are defined, the minimal threshold, the line threshold and the maximal threshold. The aglucosuric blood sugar level of Földi has no clinical importance.

Gluconic filtration rates can be measured by determining the relation between the excretion of glucose at two different blood sugar levels, both above the maximal threshold. The value found concurs approximately with that of inulin and thiosulphate.

Smith’s method of measuring activity of individual nephrons is described. His conclusion is, that a vicarious clearance does not exist in the human kidney; there are no resting nephrons.

Tm does not change with alterations in renal blood flow. Insulin depresses Tm, thyroxin increases it. Testosterone and DOCA have no effect; at the moment it has not yet been decided, whether ACTH has any effect on Tm.

The reason is given, why glucosuria is found so seldom in acute tubulopathy. Sometimes less glucose than expected according to filtration rate and tubular reabsorption is excreted during diabetic coma. In these cases it is supposed that passive back diffusion of glucose occurs as well; the tubular wall has become permeable by shock and anoxemia.

There are two different species of renal glucosuria:
Type 1: with low renal threshold for glucose and low Tm.
Type 2: with low renal threshold but normal Tm.

According to Reubi, type 1 is congenitally acquired, type 2 is caused by an increased variation in activity of individual nephrons,
damaged by some toxic influence. However, Bradley thinks type 2 hereditary.

In some diabetics with lowered renal threshold for glucose Robinson and Gray did not find a tubular maximum of reabsorption. As a rule $Tm_g$ in diabetics is somewhat increased.

Glomerular filtration can be measured experimentally by blocking glucose reabsorption with phlorizin. Identical values as with the creatinin and inulin clearance measured are obtained.

It is pointed out, that an extreme osmotic diuresis never causes an increase of existing glucosuria.

Chapter 4

The Hickey and Hare test for clinical differentiation of polyurias is described.

Polyurias with generally low specific gravity: Diuresis after ingestion of water or alcohol, cold diuresis and starvation polyuria are discussed.

The syndrome of diabetes insipidus is not a nosological entity. A case of diabetes insipidus sensu strictiori is described; a case similar in some respects to psychogenic polydipsia, is discussed. We observed two cases of hereditary pitressin resistant diabetes insipidus, in one of these the aminoaciduria was increased.

Two cases of so-called water losing nephritis were investigated with the Hickey and Hare test. Undoubtedly this syndrome will be recognized more often in the future. As not all patients described elsewhere and by us had a chronic nephritis, it is proposed to call this syndrome water losing kidney.

Diabetes mellitus and diabetes insipidus sensu strictiori seldom occur together. We observed one case, the diagnosis was doubtful however because of resistance to pitressin.

In acromegalics a polydipsia and polyuria is often found. We observed one case without glucosuria, having a normal antidiuretic mechanism according the Hickey and Hare test. At present there is no good explanation of polydipsia and polyuria in these cases; a disturbance in posterior lobe function certainly does not exist in all patients.

An initial diuresis after one injection with ACTH in some patients with anterior lobe insufficiency is described. This diuresis is of 24 hours duration and was found only in the two patients, whose adrenals reacted to an ACTH stimulus normally with regard to circulating eosinophils.
ADLEY thinks type should for glucose amount of reabsorption. 
dentally by blocking values as with the tained.
uresis never causes differentiation of poly-
ysis after ingestion of lyuria are discussed. llosological entity. A xribed; a case similar discussed. We observed diabetes insipidus, in
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Two other patients, the one with hypophyseal myxedema, the other with an approximately normal basal metabolic rate, had no initial diuresis. One patient with hypophyseal insufficiency and slight diabetes insipidus following operation for acromegaly had a dubious initial diuresis, in this case there was no eosinophil response in the ACTH Thorn test. The diabetes insipidus in this patient was aggravated by continuous administration of ACTH.
It is suggested that for the occurrence of initial diuresis adrenals, which give a normal ACTH Thorn test, are essential.
In one case (pat. K.-K.) we found during continuous administration of ACTH a somewhat increased diuresis compared with the pretreatment period. We think this is caused by an indirect diuretic action of ACTH in increasing the urinary solutes load, as suggested earlier by LEAF and MAMBY. Perhaps this is, in combination with the normalisation of renal hemodynamics, also the cause of the aggravation of diabetes insipidus in the patient mentioned above.
Several authors think thyrotropic fraction is the diuretic factor of anterior lobe extract. However in our cases mentioned above, there seemed to be a better correlation with normal adrenal cortical function than with thyroid function in occurrence of initial diuresis after ACTH.
Experimentally, the polyuria following administration of thyrotropic hormone disappears in a few days; this is presumably caused by formation of an antihormone (WILKINS). It is thus apparent, that an eventual impurity of the ACTH preparation used in containing thyrotropic fraction could not be of etiologic significance in the prolonged increase of diuresis during continuous ACTH therapy in the two patients mentioned above.
*Other polyurias:* Isosthenuria occurs in patients with chronic glomerulonephritis and in the final stage of essential hypertension. It is found also in extreme osmotic diuresis and in the healing phase of acute tubulopathy. Polyuria with urine of high specific gravity is found only in diabetics. Specific gravity may vary in diuresis of treatment of heart failure and in patients with hypercalciuria.

*Chapter 5*

The results are given of an inquiry into an eventual diuretic effect of ACTH in hypophysectomized rats. These were entirely negative. The increase in diuresis found in one experiment with very young
rats could indicate an indirect diuretic effect of ACTH; possibly these animals could not yet concentrate their urine as adult rats, an increase in urinary solutes would then result in increased urinary volume. However we were unable to obtain the same result in adult hypophysectomized rats.

Chapter 6

The opinions as to the cause of polyuria of diabetes are reviewed again in connection with own observations. That polyuria should be a sequel of polydipsia is thought improbable, as commonly diabetic patients with and without acidosis can be found in whom the loss of water was more important clinically than the loss of salt. In a number of brittle diabetics no correlation was found between excretion of glucose and urinary volume though considerable quantities of glucose were lost with the urine. Correlation between urinary volume and urinary solutes in mMols was often, though not always, apparent. The excretion of glucose, urea and salt were compared in a small number of diabetics and persons with renal glucosuria at the out-patient department. Of course these were not strictly identical cases before the glucose tolerance test was done, owing to different hydration and dietary habits. We found no correlation between the excretion of glucose and salt in diabetics and persons with renal glucosuria in the cases observed. The daily excretion of glucose is more important than the urinary percentages in judging the seriousness of glucosuria. The percentage is dependent to a certain degree on the output of water. However, when a considerable quantity of glucose is excreted, the output of urine increases; the urinary glucose percentage remains high. One of the factors responsible for polyuria in diabetes is the increased quantity of urinary solutes. The excretion of salt in the various phases of the metabolic disturbance of diabetes is discussed. Referring to the facts discussed in chapter 4 in connection with an eventual diuretic effect of ACTH a short survey is given of what is known with regard to hypophyseal and adrenal function in diabetics with good and poor control. The possibility, that polyuria of diabetes originates in an increased production of endogenous ACTH, in itself a sequel of the stress of the disordered metabolic state, is looked into.
of ACTH; possibly urine as adult rats, in increased urinary same result in adult diabetes are reviewed that polyuria should be, as commonly dia-
phoresis found in whom the with the loss of salt.
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We obtained an indication of the functional activity of the post-
rior pituitary gland during polyuria of diabetes by means of the 
Hickey and Hare test. In all cases of diabetic polyuria no anti-
diuretic response on infusion with hypertonic salt could be obtained. 
This clearly indicates, that in all patients the posterior lobe was secre-
ting antidiuretic hormone at its maximal capacity, though the con-
centration of their urine was not maximal.
The conclusion can be drawn that the secretion of antidiuretic hor-
mon is not hampered by the relative hydremia caused by hyper-
glycemia, as water migrates from the cells to the extracellular space. 
The only explanation of the fact, that the urine of these diabetic patients 
with normal concentrating ability was not maximally concentrated in the 
period of dehydration, can be, that diabetic polyuria is an osmotic diuresis. 
This osmotic diuresis finds its origin in the increased demand for 
water, necessary for excretion of considerable quantities of glucose, 
salt, urea, and fatty acids. Distal water reabsorption becomes ins-
sufficient as more and more glomerular filtrate passes the proximal 
tubule not reabsorbed. This is why the urine is not maximally con-
centrated in the disordered diabetic state.
Some remarks are made about the place of thirst in the diabetic 
syndrome.
It is remarkable, that patients with longstanding diabetes may have 
high blood sugar levels and high urinary percentages without any 
sensation of thirst. 
In recently discovered diabetes there is often no correlation between 
the presence of thirst and fasting blood sugar levels, as we could 
demonstrate.
As hyperglycemia does not considerably increase the osmotic 
pressure of the plasma, it is conceivable, that prolonged moderate 
hyperglycemia no more evokes thirst. A necessary condition for 
this is that the increased quantity of urinary solutes can be excreted 
by the kidneys without the occurrence of an osmotic diuresis and 
its accompanying losses of salt and water. 
A thirsty diabetic patient, not acidotic, with moderate metabolic 
disturbance and forced respiration by mouth due to nasal obstruc-
tion, is discussed. According to the antidiuresis obtained in the 
Hickey and Hare test no water deficit existed; recovery without 
fluid therapy was uneventful. 
Some patients are described with hypernatremia and hyperchlore-
mia in diabetic (pre)coma or during its treatment. In these cases
the water shortage was more important relatively than the salt loss. Isotonic saline is not the repair solution of choice in this condition. Advantages and drawbacks of fructose administration in these patients are discussed. Instead of isotonic saline, for instance the hypotonic solution of Nabarro, containing 130 meq. natrium, 100 meq. chloride and 30 meq. lactate in 1000 ml. water (Chloret. natr. 5.85 grams, lactas natr. 3.36 grams, aqua dest. ad 1000) can be given. It is pointed out, that every patient is diabetic coma forms a different metabolic problem. Therapy should always be individualized, both regarding combat of the acidosis with insulin and the disturbance of water and salt metabolism.