CREATIN AND CREATININ EXCRETION IN DIABETES MELLITUS

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PRELIMINARY

In spite of a large amount of work by many investigators our knowledge of diabetes is limited, so limited indeed that it is still defined in terms of its most important clinical symptom:—‘ A chronic disease in which “grape-sugar” is excreted in the urine ’ (Von Noorden).

In many previous investigations the output of total nitrogen has been more or less thoroughly studied, but without any very important results being obtained. In the majority of instances the patients investigated were not confined strictly to one diet during the period of experiment, with the result that great variations in the output of nitrogen were observed. Further, in many cases the diet during the experimental period was—owing to the nature of the disease—very rich in protein. This abundance of protein in the diet naturally leads to a very marked output of nitrogen in the urine, to such a degree indeed that any slight variations which might have occurred from alterations in metabolic processes would be entirely obscured.

Von Noorden, although he recognises that this high elimination of nitrogen is mainly due to the amount of protein ingested, still affirms that a diabetic excretes more nitrogen than does a healthy man on the same diet.

Two causes are put forward to account for this increased excretion of nitrogen:—

- (a) Loss of nitrogen from underfeeding; the diabetic being unable to utilise carbohydrate and thus to save protein, an increased catabolism of the latter takes place.
- (b) Loss of nitrogen from toxogenous protein catabolism; the clinical picture of diabetic coma suggests that this may occur.

Lusk¹ and others have shown the output of nitrogen, particularly in relation to the sugar output, may yield results of great clinical (prognostic) importance. They have shown that after the removal of the pancreas in dogs—whether these be fasting or on a meat diet—there is a constant elimination of nitrogen (N) and dextrose (D) in the urine (Minkowski), and these two substances are always present in the same proportion every day; there are 2·8 grams D for 1 gram N—D:N : 2·8:1. Since each gram of nitrogen in the urine represents a destruction of 6·25 grams of protein in the body, it is evident that 2·8 grams of dextrose may arise from 6·25 grams of protein, or protein yields 45 per cent. of dextrose. Lusk (*loc. cit.*) determined the amount of sugar phloridzinised dogs would produce when gelatin was supplied, and found a higher D:N ratio of 3·65:1, which represented a sugar production from protein of nearly 60 per cent. This higher ratio has been found in human diabetes when the patient is on a diet of protein and fat (Mandel and Lusk), and also in dogs when both pancreas and thyroid have been removed (Falta).

The variability of the D:N ratio in different animals and in the same animal under different circumstances cannot yet be definitely explained. Falta suggests that the extirpation of the pancreas and thyroid gland leaves the adrenals highly active, furnishing a secretion which tends to promote the formation of sugar. Mandel and Lusk assume the existence of two different chemical combinations of protein and sugar—an alpha-colloid dextrose representing the sugar in the 2·8 ratio, and a beta-colloid dextrose representing the additional percentage of the protein when the 3·65 ratio is present, the ratio depending on the combustion of the latter. The higher ratio has been termed the 'fatal ratio,' as it shows a complete intolerance for carbohydrates, a lower ratio indicates hope for the patient. It is recommended as a matter of routine in practice that the patient should be placed on a strict carbohydrate-free diet and on the second day the D:N ratio determined.

Cathcart² in a recent paper has, as the results of many experiments using diets of varied nature, put forward the hypothesis 'that carbohydrates are absolutely essential for intracellular synthetic processes in connection with protein metabolism.' In his investigations he used the output of creatin—not a normal constituent of healthy urine—as the index of protein catabolism. This substance was chosen because it is constantly present in the urine during starvation (Cathcart³, Benedict⁴). Cathcart (*loc. cit.*) found that when the diet consisted only of carbohydrates or was one comparatively rich in carbohydrates, although it might be relatively

low in Calories, no creatin was ever found in the urine. He also found that, even when the feeding followed a period of starvation,—which had led to the appearance of creatin in the urine,—that on a carbohydrate diet the creatin immediately disappeared. On the other hand, if carbohydrates were completely absent from the diet or present only in very small quantity, even when the intake of Calories was abnormally high, creatin appeared in the urine; and, if the feeding followed a period of starvation, the output of creatin instead of diminishing, as when carbohydrates were used, increased in amount. As a result of these experiments the hypothesis above mentioned was formulated, the suggestion being that the presence of carbohydrates in proper form is essential before the anabolic processes in connection with the utilisation of protein in the body can take place. In support of his contention he brought forward much collateral evidence.

An experiment performed on myself at Dr. Cathcart's request has considerable significance in connection with this point. A strict carbohydrate and creatin-free diet was taken, consisting of 10 eggs, $\frac{1}{2}$ lb. butter, and one diabetic loaf (6 oz.). The Caloric intake was ample. The figures obtained were as follows:—

Exam.	Amt. urine G.C	Sp. gr.	React.	Total Nitrogen	Creatinin	Creatinin	Creatin
1.	Sample	1018	Acid	1.3 per cent.	0.21 per cent.	0.21 per cent.	Nil
2.	1,400	1020	„	13.6 grams	1.567 grams	1.5 grams	0.067 grams
3.	1,200	1018	„	17.1 „	1.536 „	1.4 „	0.136 „
4.	1,150	1025	„	17.0 „	1.9 „	1.9 „	Nil

The first examination represents the analysis of a sample of urine when on ordinary mixed diet.

The second and third are the results obtained while the special diet was being taken. As will be seen, creatin was found.

The fourth examination was made after the addition of carbohydrate to the diet. Creatin had disappeared.

Another exactly similar experiment carried out on Dr. Cathcart had the identical results.

Since diabetes is the disease in which carbohydrate metabolism is notoriously faulty (*vide supra*), it was thought that even on a creatin free diet creatin would be present in the urine of diabetics in large amount. This has proved to be the case. It was further thought that alterations in the output of creatin might prove of value from the prognostic standpoint; that a diminution in the output would indicate that the utilisation

of carbohydrate was improving, or, if the output increased, that the disease was increasing in severity. This expectation has not, however, been realised.

In the acute forms of diabetes mellitus there is complete loss of power to burn dextrose, and probably the tissues do not retain glycogen. Such an organism must exist at the expense of protein and fat as sources of its potential energy. But in diabetes a major portion of the ingested protein is convertible into sugar, which is carried away in the urine, and this may contain a large proportion of the potential energy of protein available for cell life. To compensate for this the protein metabolism increases (as much as three to five times); but fat metabolism remains the mainstay of the life of the diabetic as it does of the fasting individual. In diabetes the protein metabolism is abnormal, and conditions varying in severity also arise in which the end-products of fat metabolism, such as beta-oxybutyric acid, aceto-acetic acid and acetone, do not burn, but accumulate within the organism and are eliminated in the urine.

Voit believed that protein breaks up into a nitrogenous portion convertible into urea, and a non-nitrogenous portion which as sugar or fat can be used by the organism. Embden and others, however, have pointed out that the amino-acids are convertible into dextrose, and that they probably are the source of urinary sugar in diabetes. Pflüger, on the other hand, believed that the sugar came from fat.

The literature shows that a certain number of observations have been made in connection with the excretion of creatinin in diabetes. Creatin on the other hand, has received less attention. Indeed, the only reference found with regard to the latter in diabetes consists of the brief mention of two cases by Shaffer,⁵ in both of which it was found.

Prior to the introduction in 1905 of Folin's method of estimating urinary creatinin and creatin many observers had worked at the subject. The results are fully discussed by recent writers: Von Noorden, Mellanby,⁶ Shaffer (*loc. cit.*), and others. The latter gives an outline of the more important findings, and adds that these must be accepted with caution on account of the methods employed.

Von Noorden states that it was early recognised that the excretion of creatinin was increased in diabetes, up to 2 grams per diem; an increase said to be due to the condition of nitrogenous metabolism obtaining in diabetics; the patient eats a great deal of meat and possibly breaks down his own muscle substance. In the same section this writer, referring to Folin's paper,⁷ in which this author demonstrated that the urinary

creatinin has both an endogenous and an exogenous origin, remarks 'that it would be extremely interesting to know whether or not the endogenous creatinin of diabetics ever shows considerable variations from the normal 0.4 gram—0.6 gram per diem.'

Bunge⁸ states that the patient does not excrete more than a healthy man on a purely meat diet, viz., 2.163 gram per diem.

Folin (*loc. cit.*) first observed that the amount of creatinin excreted in the urine by a normal individual is quite independent of the amount of protein in the food, and of the total nitrogen in the urine; the amount excreted from day to day is practically constant for each individual under similar conditions of health and muscular activity. Shaffer (*loc. cit.*) has further found that the hourly excretion of creatinin is also a constant quantity, and is quite independent of the amount of urine passed, or the amount of protein ingested. Folin (*loc. cit.*) has also shown that the chief factor determining the amount of creatinin eliminated is the live body weight of the individual. Wolf and Shaffer⁹ have confirmed a further statement made by Folin and Klercker that the excretion of creatinin is wholly unaffected by the ingestion of creatin.

On the other hand, the experiments of Noël Paton¹⁰ and Cathcart² have shown that there is in all probability a very close connection between the output of creatinin and creatin. In one experiment of Cathcart's it was shown that with a rise in the output of creatin there was a marked fall in the output of creatinin. There is also a certain amount of evidence to show that under certain circumstances the ingestion of food containing creatin is followed by a rise in the output of creatinin. The following short experiment performed on myself bears on this point. A diet containing 480 grams meat was taken on the day succeeding a creatin-free diet. The figures were as follows:—

Exam.	Amt. urine	T. N.	Total Creatinin	Creatinin	Creatin	Remarks
	c.c.	grams	grams.	grams		
1.	1600	10.7	1.68	1.68	Nil	Creatin-free diet
2.	1500	15.7	2.347	2.17	0.177	Abundant flesh diet

As will be seen creatin was excreted on this abundant flesh diet, and this occurrence was associated with a rise in the total nitrogen and creatinin outputs.

It has already been mentioned that Folin (*loc. cit.*) believes that the amount of creatinin excreted in the urine is a constant quantity for the individual, and independent of the nitrogen intake, or of the total nitrogen passed in the urine.

The figures in the tables accompanying this paper also indicate a connection between the creatinin excretion and the nitrogen intake, and they further show that the output of creatinin in diabetics is by no means always greatly exaggerated, even when a highly nitrogenous diet is being taken.

Von Noorden gives conflicting figures when considering the effect of diet on the daily output of creatinin; with a mixed diet of 0·8 gram—1·2 gram per diem; with vegetable diet 0·61 gram—0·86 gram. He quotes Macleod and Long. The former obtained higher values:—with 'mixed meat diet' 2·098 grams, and with 'creatin-free' food 1·064 grams. The latter found 0·9 gram in vegetarians.

The dietaries of the patients examined for this paper were rarely excessive in flesh content, and in a large majority of the cases a creatin-free food was given, the persistence of creatin in the urine during these periods must have been due to causes other than the food ingested.

The earlier estimates of creatinin excretion during muscular work vary, and are probably of little value on account of the defective methods employed. Von Noorden states that excessive muscular work may cause creatin to appear in the urine. Cathcart, Kennaway, and Leathes¹¹ found that even severe work does not cause a rise in the urinary creatinin when the diet is ample. Shaffer's work¹² led him to express the opinion that the amount of muscular activity is in itself entirely without effect upon the amount of creatinin excreted.

Quite recently Graham Brown and Cathcart,¹³ in a paper, in which the literature on this point is reviewed, found that stimulation of muscle might actually decrease the amount of total creatinin (creatinin + creatin) extracted. Mellanby (*loc. cit.*), on the other hand, states that work has no influence on the creatin content of muscle. Pekelharing and v. Hoogenhuyze¹⁴ found that rigor mortis, heat rigor, and 'tonus' led to an increase of creatin in muscle.

So far as this investigation is concerned, the influence of muscular work on the urinary creatinin and creatin excretion may be ignored. The patients examined—with one exception—being all hospital in-patients either entirely at rest in bed or only doing the light work of the wards.

Creatin when present in a creatin-free diet is a product of pure endogenous origin, and is never found in the urine as an excretory product under normal conditions (Folin). It can, however, be readily caused to appear, its chief source of origin being the muscle tissues.

Voit believed that it was present in urine alkaline when passed (Von Noorden). This has been shown to be incorrect.⁵

The latest contribution to the literature on the subject of creatin excretion is an article by Noël Paton,¹⁰ who shows that in the urine of birds creatin takes the place of creatinin, and is an end product of metabolism, and that increased creatin excretion indicates an increase of muscle catabolism.

The urinary creatin excretion has been examined in certain diseases. In nephritis it is said to be increased, and was at one time thought to accumulate in the blood and be a factor in uraemic poisoning (Von Noorden). This, however, has been denied, as it probably never occurs in sufficient quantities, and it is a less toxic substance than creatinin. Turner¹⁵ refers to recent work by Donath, who records the results of his experiments into the convulsion-producing properties of the substances found in the blood and urine of epileptics. When injected into guinea-pigs and dogs creatin proved innocuous; creatinin, on the other hand, produced convulsions.

A sample of urine from a female patient, who died of diabetic coma, was examined, and the creatin value was distinctly high. Total creatinin 0·0448 gram per cent. Preformed creatinin 0·0224 gram per cent., and creatin 0·0224 gram per cent. It has also been noticed that in those cases in which the acetone and diacetic acid tests were most marked the creatin values were highest (e.g. Table VIII).

Mellanby (*loc. cit.*) tabulates the excretion of creatinin and creatin in various pathological conditions affecting the liver; he found that the output of creatinin in hepatic disease is markedly sub-normal on account, he believes, of depressed hepatic function, while in cancer of the liver creatin is excreted in large quantities; in cirrhosis and engorged livers on the other hand, creatin excretion is not affected. This writer is of opinion that the liver is intimately connected with the production of creatin and the excretion of creatinin. The creatin excretion in pathological states other than those already mentioned has been examined by other workers. Shaffer⁵ mentions the following conditions, in all of which there is probably a breaking down of muscle tissue; acute fevers, the acute stages of exophthalmic goitre, tumour cachexia. The largest output found was in women during the first week post-partum. Finally, in the graver forms of blood diseases the creatinin values are low, and creatin has been found in lymphatic leucaemia (Shaffer) and myelogenic leucaemia (Von Noorden).

The following then appear to be the conditions under which creatin may occur in the urine as an excretory product. Starvation, excessive

muscular work on an insufficient diet, heart disease with failure of compensation, certain forms of liver and blood diseases, nephritis, Graves disease, fevers, tumour cachexia, epilepsy, and during the early days of the puerperium.

In the series of cases examined for this paper all these conditions may be excluded.

The methods employed for the various examinations connected with this paper were:—Total nitrogen (Kjeldahl), creatinin and creatin (Folin);¹ sugar (Pavy). In order to acquire familiarity with these methods three patients suffering from diabetes were taken. These were all undergoing hospital treatment and were improving. The figures are not tabulated, but it may be stated that creatin was always found in the urines, and that the total nitrogen and creatinin excretions were not high. An attempt was made—as will be noted in the various protocols—to test the various patients with a diet which was absolutely free from either creatinin or creatin. Such a diet, free from carbohydrate and yet palatable, was impossible. Accordingly, from time to time a diet was used which—although free from creatinin and creatin—was rich in carbohydrates. As such a diet is quite unsuited for a diabetic patient, the results obtained were, on the whole, very unsatisfactory. This diet consisted of:—eggs, milk, cream, oatmeal, cheese, butter, diabetic bread, water. The tables may now be appended.

TABLE I—Female aet. 53. Weight, 7 st. 10½ lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar grams.	Total nitro- gen grams.	Total creati- nin grams.	Creati- nin grams.	Creatin grams.	Remarks
June 18...	7,360	1045	Acid	268	39.7	1.008	0.883	0.125	Ordinary mixed diet
22...	4,460	1033	Acid	85.6	24.9	1.517	0.624	0.893	Third day after diabetic diet begun
„ 25...	4,206	1034	Acid	91.0	23.9	1.345	0.715	0.630	„ „
„ 28	4,265	1040	Acid	125.4	24.3	1.531	0.597	0.934	Creatin-free food previous day
„ 30...	6,423	1039	Acid	122.8	27.3	1.284	0.661	0.623	„ „
July 4...	3,922	1039	Acid	121.3	19.6	0.901	0.431	0.470	„ „
„ 12...	2,842	1032	Acid	67.6	21.5	1.705	0.824	0.881	After diabetic diet for 4 days Weight, 7 st. 11 lbs.

1. The presence of sugar in the urine, unless in concentrations of above 5 per cent., does not materially affect the estimation of creatinin and creatin, provided always that the conditions laid down by Folin are strictly adhered to.

NOTES ON CASE I

This patient had been the subject of diabetes for six years. Before its onset she was a big, well-nourished woman weighing 15 st. (her own statement).

Polyuria was often excessive, and the output of sugar large. Acetone frequently occurred. There was a well-marked double cataract. The urine was first examined soon after her admission to hospital, while she was still on an ordinary mixed diet. The sugar and total nitrogen eliminated were both high. The total creatinin, on the other hand, rather low. The influence of withholding carbohydrate is seen at the second and third examinations, the total creatinin values are distinctly higher, the creatin readings showing a marked increase.

On creatin-free food a gradual fall in the excretion of creatinin and creatin may be observed, but the glycosuria increased and the diet was not persisted in.

The last examination was made after a return to diabetic diet; the total creatinin values were again increased. The weight was fully maintained during the period of observation.

TABLE II.—Female aet. 16. Weight, 7 st. 6½ lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
May 22...	960	1034	Acid	28.5	7.4	0.562	0.531	0.031	Diabetic diet
" 25...	1,620	1033	Acid	44.9	14.7	0.465	0.453	0.012	Creatin-free diet
" 27...	1,136	1033	Acid	39.8	12.2	0.370	0.329	0.041	" "
" 31...	1,648	1035	Acid	41.2	15.9	0.388	0.316	0.072	" "
June 18...	995	1029	Acid	14.2	8.4	0.576	0.548	0.028	Diabetic diet Weight 7 st. 6¼ lb.

NOTES ON CASE II

The first examination was made after the patient had been in hospital for three weeks. The glycosuria still persisted, but the other symptoms were in abeyance. The history dated back some ten months, but at no time had the illness been acute, and she was still fairly well nourished.

On ordinary diabetic diet the first analysis showed a low output of total nitrogen and creatinin. On creatin-free food the amount of total nitrogen eliminated suddenly shot up, and this was associated with a rise in the output of sugar and creatin. Creatinin itself is rather diminished. The sudden rise in the total nitrogen and creatin excretions during the period creatin-free food was being given may be explained by the fact that the diet was badly borne, and weight rapidly lost (5½ lbs. in five days). The last examination was made after the loss in weight had been made good, and the patient again on strict dietetic treatment. The total nitrogen output was again low, as was also that of creatinin.

TABLE III.—Male aet. 39. Weight, 13 st. 9 lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
May 13...	3,000	1028	Acid	47.8	32.4	2.88	1.68	1.2	Diabetic diet
" 19...	2,500	1031	Acid	35.4	37.5	3.74	2.22	1.52	" "
" 30...	2,600	1027	Acid	36.3	42.6	3.85	2.22	1.63	" "
Nov. 24...	13,000	1030	Acid	335.6	56.6	3.21	1.98	1.23	Ordinary mixed diet
" 26...	15,690	1033	Acid	506.7	47.07	2.28	1.47	0.81	" "
" 30...	10,000	1038	Acid	240.0	39.2	3.78	1.60	2.18	" "
Dec. 3...	11,080	1035	Acid	250.0	65.3	4.66	2.59	2.07	" "
" 10...	10,520	1037	Acid	311.5	37.8	2.89	1.77	1.12	" "
									Weight 13 st. 8 lbs.

NOTES ON CASE III

This was a case of acromegaly diabetes. Acromegaly and diabetes are so frequently associated that some close connection between the two diseases must exist. Von Noorden mentions five cases of acromegaly, four of which were complicated with diabetes. Various explanations to account for this relationship have been put forward. Some maintain that two entirely separate pathological conditions co-exist; others believe the glycosuria occurring in acromegaly to be produced by the pressure of the pituitary tumour on the fourth ventricle. A third view is that it is due to loss or increase of an internal ferment. Mayo Robson and Cammidge (16) state that chronic pancreatitis has been repeatedly observed in association with acromegaly, and are of opinion that the glycosuria in this disease is due to morbid changes in the pancreas.

When the patient first came under observation there was no glycosuria, but it soon appeared with all the classical symptoms of diabetes. The first three examinations were made when diabetic treatment was being tried, and the values of total nitrogen, creatinin, and creatin were all high. The patient then developed diphtheria, and it was four months later that the subsequent examinations were made. The enormous polyuria was the most striking symptom on his return, together with an appetite and thirst that can only be described as insatiable. On account of the latter no diet could be rigidly adhered to. He passed great quantities of sugar, the maximum being reached at the fifth examination. The total nitrogen eliminated reached great heights, the figure at the eighth examination being particularly noticeable; at the same time the total creatinin (creatin + creatinin) touched the highest level.

Creatin was always found in considerable amount.

It is worth observing that in spite of the man's symptoms the weight did not alter materially, and apart from the excessive craving for food he was quite comfortable,

TABLE IV.—Male aet. 30. Weight, 9 st. 12 lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
May 13...	1,050	1020	Acid	Nil	18.1	1.843	1.57	0.273	Rich meat diet carbohydrate free
" 19...	920	1022	"	Nil	16.7	1.267	1.16	0.107	"
" 30...	1,365	1018	"	Nil	21.8	0.84	0.84	0.00	Eggs, milk, less meat
June 3...	1,194	1020	"	Nil	21.4	0.79	0.79	0.00	"
" 5...	910	1025	"	5.0	15.7	0.618	0.58	0.038	Creatin-free diet
" 6...	1,120	1027	"	8.3	16.3	0.613	0.57	0.043	"
" 10...	870	1018	"	Nil	16.9	0.948	0.948	0.00	Mixed diet, with limited carbo- hydrate Weight, 9st. 12½ lbs.

NOTES ON CASE IV

This was apparently a case of so-called alimentary glycosuria, one in which a fair tolerance for carbohydrates existed. Lusk (v.s.) has pointed out that this condition must not be confounded with true diabetes. It occurs when the sugar holding capacity of certain organs is reduced or over-strained as when an excessive quantity of sugar is ingested.

When the patient first came under observation, sugar had been absent from the urine for eight days; this disappearance took place after twelve days' treatment. The diet consisted of protein

and fat, no carbohydrate being given. The presence of creatin at this time may have been entirely due to the excess of meat ingested (v.s.), but it is probable that the want of carbohydrate in the diet was also a determining factor. When eggs were substituted for some of the meat and milk added, the creatin disappeared, and at the same time the total creatinin diminished.

A creatin-free diet was now given and sugar again appeared in the urine. Creatin also reappeared, but the total creatinin excretion was somewhat reduced.

It is difficult to explain the reappearance of creatin on this carbohydrate rich diet, especially when the experimental work on dogs, referred to later, is taken into account. But in this case there is probably some definite pathological state underlying the condition, a state which only permits of the combustion of a certain (limited) amount of carbohydrate. If this limit be overstepped hyperglycaemia and glycosuria occur, and it may be that at the same time some catabolic process (possibly toxic) is originated which leads to a breaking-down of muscle protein and the appearance of creatin in the urine. The last examination made in this case was during a period of ordinary diet with limited carbohydrate. Both sugar and creatin were absent, and the total creatinin value was lower than that found when no carbohydrate was allowed.

TABLE V.—Female aet. 3. Weight 27½ lbs.

Date	Sp. gr.	React.	Sugar grams. per 1000	Total Nitro- gen. per cent.	Total Creati- nin. per cent.	Creati- nin. per cent.	Creatin. per cent.	Remarks	
October 12	...	1028	Acid	20.0	0.42	0.023	0.015	0.008	Ordinary mixed diet
„ 13	...	1028	„	20.8	0.33	0.022	0.014	0.008	„ „
„ 19	...	1029	„	21.7	0.40	0.056	0.017	0.039	Creatin-free diet
„ 20	...	1032	„	25.0	0.53	0.022	0.010	0.012	„ „
„ 21	...	1033	„	29.4	0.58	0.026	0.008	0.018	„ „
„ 22	...	1035	„	33.2	0.73	0.013	0.005	0.008	„ „
„ 23	...	1033	„	30.0	0.79	0.016	0.007	0.009	„ „
„ 26	...	1030	„	28.7	0.99	0.023	0.015	0.008	After two days on ordinary diet. Weight 28 lbs.

NOTES ON CASE V

The first point of interest here is the age of the patient. On account of this the output of urine for the twenty-four hours could not be ascertained, and the table represents percentage values except for the sugar which is expressed in grams per 1,000 c.c. Diabetes at this age is rare. Amongst 1,360 private patients who consulted Pavy the disease began under ten years of age in only eight cases. The youngest patient Pavy had under his care was an infant aged 12 months. (17.)

The history in this case was of 8 weeks duration only, the chief symptom noted by the mother being excessive thirst.

It was easy to keep this patient on a creatin-free diet, but the glycosuria tended to increase. The total creatinin output, however, diminished.

The course of the illness was rapid, death ensuing from coma, at the end of six weeks after she first came under observation.

TABLE VI.—Male aet. 32. Weight 7 stone 13 lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
Oct. 15 ...	2,103	1025	Acid	55.1	10.6	0.455	0.428	0.027	Diabetic diet
„ 27 ...	2,160	1028	„	50.5	15.4	0.619	0.591	0.028	„ „
„ 30 ...	2,100	1028	„	44.6	13.8	0.612	0.584	0.028	„ „
„ 31 ...	3,520	1030	„	102.0	18.3	0.564	0.529	0.035	Creatin-free diet
Nov. 1 ...	3,200	1032	„	112.0	10.9	0.331	0.280	0.051	„ „
„ 2 ...	3,240	1032	„	111.7	10.4	0.298	0.247	0.051	„ „
„ 3 ...	2,100	1028	„	41.4	9.7	0.425	0.402	0.023	Diabetic diet, modified Weight 8st. 0 lbs.

NOTES ON CASE VI

This patient had been in hospital for five weeks before he came under observation. He was doing well on a strict diabetic diet, but the glycosuria was still marked. Although the intake of flesh was considerable, the readings are not high; the total creatinin excretion being low, and the nitrogen elimination well within normal limits. On a creatin-free diet the amount of urine and sugar passed both increased; the total creatinin output on the other hand was lower. On the day following the application of creatin-free food there was a rise in the output of total nitrogen; this rise, was however, transitory.

The final examination shows the effect of a diabetic diet with the addition of small quantities of carbohydrate. It is again evident from this table that a diabetic even on a rich nitrogenous diet need not excrete excessive amounts of nitrogen and creatinin.

TABLE VII.—Male aet. 33. Weight, 8 st. 6½ lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
Nov. 9 ...	4,830	1039	Acid	182.4	14.8	0.710	0.648	0.062	Ordinary diet; acetonuria
„ 11 ...	3,500	1042	„	115.5	15.3	1.070	0.850	0.220	do. do.
„ 12 ...	2,700	1040	„	91.8	10.05	0.820	0.653	0.167	Ordinary diet; no acetone
„ 16 ...	800	1055	„	45.0	7.9	0.759	0.338	0.421	Diabetic diet; no acetone
„ 17 ...	1,140	1040	„	23.1	14.6	1.084	0.534	0.550	Diabetic diet; acetonuria
„ 19 ...	800	1040	„	17.6	6.9	0.608	0.242	0.366	Diabetic diet; marked acidosis
„ 23 ...	760	1039	„	16.1	6.2	0.787	0.242	0.545	Carbohydrate and alkali; marked acidosis
„ 24 ...	1,650	1042	„	82.5	11.7	1.025	0.557	0.468	Carbohydrate and alkali; acetonuria
„ 26 ...	3,500	1045	„	157.5	22.0	1.869	0.942	0.927	Ordinary diet; no acetone Weight, 8 st. 0½ lb.

NOTES ON CASE VII

For some days this patient was seriously ill, and unfortunately left hospital (of his own accord) before his condition was considered safe, and before a creatin-free diet could be tried.

The amount of urine passed showed considerable variations as did also the output of sugar and total nitrogen, the latter being generally low.

The acetonuria present at the outset disappeared, and a carbohydrate-free diet was given. This reduced the glycosuria but led to an increase in the output of creatin, and a marked acidosis, the breath having the typical smell. Carbohydrates and alkalis were pushed, and the acidosis gradually disappeared. The various readings in this case were somewhat irregular, probably on account of the extreme perversion of metabolism present.

TABLE VIII.—Male aet. 37. Weight, 7 stone 9 lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
Nov. 16 ...	3,400	1038	Acid	170·0	11·9	0·669	0·350	0·319	Ordinary diet ; trace acetone
„ 17 ...	3,400	1035	„	163·2	17·0	0·800	0·498	0·302	Ordinary diet ; no acetone
„ 19 ...	3,444	1036	„	61·0	17·1	0·986	0·478	0·508	Diabetic diet ; no acetone
„ 23 ...	3,410	1037	„	92·0	15·6	1·031	0·470	0·561	„ „
„ 24 ...	2,850	1036	„	81·2	18·8	1·184	0·652	0·532	„ „
„ 26 ...	3,000	1040	„	78·1	17·9	1·447	0·698	0·749	Diabetic diet , acetonuria
„ 30 ...	3,350	1039	„	75·9	17·7	1·517	1·609	0·908	„ „
Dec. 3 ...	3,750	1038	„	92·5	27·0	1·728	0·738	0·990	Carbohydrate and alkali ; acidosis
„ 10 ...	3,700	1040	„	85·1	25·2	1·913	0·773	1·14	„ „
„ 15 ...	3,100	1037	„	71·3	19·9	1·573	0·550	1·023	„ „ (less)
„ 16 ...	3,500	1038	„	157·5	14·7	0·741	0·413	0·328	Ordinary diet ; no acetone Weight 7 st. 6 lbs.

NOTES ON CASE VIII

Like the preceding case this patient was acutely ill for some days, and in the same way left hospital before a creatin-free diet could be given.

He had suffered from diabetes for four years, with well-marked symptoms, and at the time of examination was considerably reduced in weight.

On ordinary diet he was progressing favourably, though a large amount of sugar was still being passed. When the urine became free of acetone a diabetic diet was tried. The immediate result of this was to reduce the glycosuria, but a marked and progressive rise in the excretion of creatin took place, together with all the signs of acid intoxication. This high elimination of creatin was most marked when the acidosis was at its height. The effect of a nitrogenous (meat) diet on the total creatinin excretion is well shown.

TABLE IX.—Male aet. 50. Weight, 9 st. 4 lbs.

Date	Sp. gr.	React.	Sugar grams per 1,000 c.c.	Total Nitro- gen per cent.	Total Creati- nin per cent.	Creati- nin per cent.	Creatin per cent.	Remarks
December 16 ...	1038	Acid	28.0	0.30	0.0144	0.012	0.0024	Modified diabetic diet
" 18 ...	1045	"	23.4	0.40	0.0289	0.025	0.0039	" "
" 20 ...	1042	"	37.02	0.36	0.0167	0.013	0.0037	Creatin-free diet
" 21 ...	1047	"	32.06	0.58	0.0328	0.029	0.0038	" "
" 23 ...	1043	"	35.7	0.40	0.0249	0.021	0.0039	" "
" 24 ...	1040	"	36.3	0.36	0.0212	0.016	0.0052	" "
" 27 ...	1042	"	31.2	0.33	0.0197	0.014	0.0057	" "
" 29 ...	1040	"	32.2	0.40	0.0265	0.019	0.0075	" "
Weight, 9 st. 4 lbs.								

NOTES ON CASE IX

This patient was the only case in the present series who was not an hospital in-patient. He was a tailor to trade, and attended at the out-patient department. When first seen he was on a modified diabetic diet, carbohydrates being restricted as far as possible, and under this treatment he was doing well. An effort was made to measure the quantity of urine passed in the twenty-four hours, but the results were unsatisfactory, so that only percentage amounts are represented in the table. It was apparent, however, that there was considerable polyuria. His illness dated back five years, but had never been severe, and he was always able to follow his employment. The figures obtained are fairly uniform. Creatin was always found, and tended to increase slightly with creatin-free diet, this increase being associated with a rise in the output of sugar.

TABLE X.—Male, aet. 22. Weight, 8 stone 6 lbs.

Date	Amount urine c.c.	Sp. gr.	React.	Sugar gram.	Total nitro- gen gram.	Total creati- nin gram.	Creati- nin gram.	Creatin gram.	Remarks
Dec. 4 ...	2,900	1,039	Acid	80.0	17.1	1.155	0.715	0.440	Diabetic diet
" 5 ...	2,950	1,038	"	81.2	17.1	1.173	0.716	0.457	" "
" 6 ...	2,950	1,034	"	82.6	23.6	0.982	0.581	0.401	" "
" 7 ...	2,950	1,035	"	97.3	20.0	0.805	0.486	0.319	Creatin-free diet
" 8 ...	2,850	1,036	"	88.3	19.9	0.943	0.561	0.382	" "
" 9 ...	2,850	1,035	"	91.2	19.9	0.741	0.451	0.290	" "
" 10 ...	2,800	1,040	"	100.8	18.4	0.696	0.414	0.282	" "
" 11 ...	3,200	1,036	"	102.4	19.9	0.708	0.464	0.244	" "
" 12 ...	3,000	1,035	"	84.0	21.4	1.020	0.504	0.516	Diabetic diet
" 13 ...	2,800	1,038	"	81.2	20.6	1.004	0.506	0.498	" "
Weight 8 st. 7 lbs.									

NOTES ON CASE X

A history extending over two years was given by this patient. When first seen he was on diabetic diet, but the polyuria and glycosuria were still abundant. The total creatinin output on this diet cannot be considered large, nor was the elimination of nitrogen excessive. On creatin-free food the excretion of total creatinin fell, both creatinin and creatin being diminished in amount. With a return to diabetic diet these values both became higher.

TABLE XI.—Male aet. 23. Weight, 7 st. 8½ lbs.

Date	Amt. Urine c.c.	Sp. gr.	React.	Sugar grams.	Total Nitro- gen grams.	Total Creati- nin grams.	Creati- nin grams.	Creatin grams.	Remarks
Jan. 28 ...	7,000	1038	Acid	140	27.3	1.484	0.714	0.770	Ordinary diet, carbohydrate limited
„ 29 ...	6,000	1035	„	150	24.0	1.512	0.672	0.840	„ „
„ 30 ...	6,000	1036	„	204	18.0	1.260	0.588	0.672	Creatin-free diet
„ 31 ...	5,500	1037	„	191.4	19.2	1.072	0.566	0.506	„ „
Feb. 1 ...	6,500	1036	„	208	19.8	1.084	0.576	0.508	„ „ Weight 7 st. 7½ lbs.

NOTES ON CASE XI

Although this man had only been in hospital for a week, he refused further treatment, and a more extended examination was impossible.

Like the previous case, he was a poorly nourished man, with a history of about two years' duration. He passed a large amount of urine, and the glycosuria was also great.

On ordinary diet the total nitrogen excretion was large, but the total creatinin output was not high. The large proportion of creatin is noticeable. On creatin-free diet the output of total nitrogen diminished, and the creatinin and creatin values were also reduced.

The patient was losing weight, and the prognosis was considered unfavourable.

The above tables represent the majority of the cases examined for this investigation. It will at once be seen that creatin was always present—sometimes to a considerable extent—when sugar occurred in the urine. The fact that creatin was found even after a patient had been on a creatin-free diet for some days is sufficient indication that it must be under these conditions derived from the tissues and not from the food ingested.

The effect of a creatin-free diet was generally to decrease the output of both creatinin and creatin, but the latter was sometimes increased. This is probably due to the fact that a suitable creatin-free diet is (as has already been noted) of necessity rather rich in carbohydrate, and tends to increase the glycosuria, and in some instances upset the patient.

With the exception of the case of acromegaly diabetes, the total creatinin eliminated by these patients cannot be considered high; even on strict diabetic diet these cases did not eliminate an excessive amount of creatinin.

The case of acromegaly diabetes must be taken separately; the figures in this case reached great heights; but it is reasonable to suppose that the diseased pituitary gland contributed to this great increase in

metabolism, either of itself or in association with a morbid condition of the pancreas.

As a result of this investigation the following conclusions may be drawn.

1. Creatin is constantly found in the urine of diabetics.
2. The presence of creatin in diabetic urine on a creatin-free diet is an expression of increased endogenous protein catabolism due to inability on the part of the tissues to burn sugar. Or it may be due to the non-conversion of creatin into something else, just as β -oxybutyric acid is improperly converted in certain abnormal states of metabolism.
3. Total creatinin excretion is not abnormally increased in diabetes even when a diet rich in flesh diet is being ingested.
4. The amount of creatinin excreted, even on a creatin-creatinin-free diet, varies to a certain extent with the nitrogen intake.

NOTE.—Since this paper was sent in for publication there has appeared in the *Quarterly Journal of Experimental Physiology* a paper by Krause on the presence of creatine in the urine of patients suffering from diabetes mellitus.

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