THE EXCRETION OF CREATININ IN A CASE OF PSEUDO-HYPERTROPHIC MUSCULAR DYSTROPHY

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Although creatinin has long been regarded as a product of the metabolism of muscle, comparatively little information is available as to its excretion in diseases involving the muscles. In 1870 a diminution of creatinin in the urine was observed by Rosenthal in three cases of progressive muscular atrophy.¹ In 1877 Weiss² investigated two cases of pseudo-hypertrophic muscular dystrophy. One of these was a boy of seventeen with the disease well marked; in one day less than a decigramme, '08 gramme, of creatinin was found in the 1900 cubic centimetres of urine passed, the normal being taken at '9 gramme. The other was a strongly built male of nineteen years, less severely affected, and from the urine of a day '59 gramme of creatinin was recovered. In a third case, published in 1883, Weiss³ found '63 gramme per day, the patient being a poorly nourished girl of twenty, who had suffered from the disease for four years. In 1883 Langer,⁴ in an advanced case in a boy of eighteen with secondary lordosis, reported that the amount of creatinin never exceeded '122 gramme. Jakubowitsch,⁵ in 1884, found a low excretion of creatinin, urea, uric acid, and

1. *Handb. d. Diagn. u. Therap. d. Nervenkrankh.* Erlangen, 1870, quoted by Langer, loc. cit. *infra*.

2. *Wien. med. Wochenschr.*, 1877, p. 701.

3. *Ibid*, 1883, p. 613.

4. *Deutsch. Arch. f. klin. Med.*, Vol. XXXII, p. 395, 1883.

5. *Diss. St. Petersburg*, 1884, Russ., reported in *Neurol. Centralbl.*, 1884, p. 279. No figures are given in the abstract

sodium chloride in two cases of the disease in children of two and a half and four years old. MacLeod,¹ on the contrary, in 1900, found no diminution in muscular atrophy.

In these cases the creatinin was estimated by precipitating the zinc chloride compound according to Neubauer's method, with or without Salkowski's modification. In none of them is the weight of the patient given, and, with the exception of MacLeod's cases, none are stated to have been upon a creatin-free diet. In the account of Weiss's second case it is stated that the patient took much meat, and this probably formed a part of the dietary of his third case, for the quantity of urine passed in the day was 2810 cubic centimetres; such an amount is usually associated with the metabolism of a fair quantity of proteid, and in the absence of any statement to the contrary, it is probable that some of this was taken in the form of meat.

Recent work appears to show that if creatin be given by the mouth it is not excreted in the urine as creatinin. Klercker found that the creatinin in the urine was not necessarily affected by giving meat, although the creatin was always increased in amount, and this has since been confirmed by Folin.² Meat extracts, however, contain creatinin as well as creatin, and their administration is followed by the appearance of a large proportion of the creatinin given in the urine. Since in the operations of cooking it is likely that some creatinin may be formed from the creatin in meat it is clear that any observations upon the production of creatinin in the body itself should be carried on while the patient is upon a diet containing neither meat nor its extracts.

In 1905 Folin³ described a simple and rapid method of estimating creatinin by means of the colour which it strikes with picric acid in an alkaline solution, and showed that this substance is excreted in almost constant amount in the urine of any given healthy individual, the amount being independent of the total quantity of proteid metabolised. On a diet free from creatin or creatinin he found the

1. *Proc. Physiol. Soc., Journ. of Physiol.*, Vol. XXVI, p. vii, 1900.

2. *Vide Lancet*, September 15th, 1906, p. 738.

3. *Amer. Journ. of Physiol.*, Vol. XIII, p. 45, 1905.

excretion to be about 25 milligrammes per kilogramme body weight for a lean person, and 20 milligrammes for a fat one. These results have been confirmed and amplified by van Hoogenhuyze and Verploegh,¹ Closson,² Klercker,³ and others. Closson found the daily excretion upon a vegetable diet to be 15 to 19 milligrammes per kilogramme.

The results in the cases of muscular affections above referred to were obtained for isolated days only, by the Neubauer or Neubauer-Salkowski method. Now, however, the simplicity and rapidity of Folin's method makes it easy to estimate the creatinin in the urine daily. When, therefore, a patient presented himself in the out-patient department of the hospital suffering from pseudo-hypertrophic muscular dystrophy the opportunity was taken of investigating the excretion of creatinin in this disease, and of comparing it with the published results obtained by the same method of estimation in normal individuals.

The following account of the case is founded upon the notes taken by Mr. R. F. V. Hodge, M.B., B.C., at that time House Physician at St. George's Hospital :—

The patient was a thin man of medium height, weighing 50 kilogrammes, or 7 stone 12 pounds, and by occupation a miner. His age was 29 years. His mother died of consumption when he was five years old. His three sisters and two brothers all died in infancy from causes unknown to him. The patient himself had had influenza twice, the last time six years ago. His present illness began eight years ago with pain in the back occurring in the evening occasionally after the day's work. A year later he noticed that he was getting weaker. Since then both the pain and the weakness have gradually increased, and for two years he has not been able to work. His appetite and general health in other respects have been good, but in the last six months he has lost five pounds in weight.

On admission the patient was weak but could walk. On stooping down he raised himself characteristically by 'climbing up his legs.'

The muscular system was found to be affected as follows :—The pectoralis major, especially the lower half, the trapezius, supraspinatus, latissimus dorsi, and the biceps were wasted on each side. The deltoid and the triceps were comparatively large and

1. *Zeitschr. f. physiol. Chem.*, Vol. XLVI, p. 415, 1906.
2. *Amer. Journ. of Physiol.*, Vol. XVI, p. 252, 1906.
3. *Hofmeister's Beiträge*, Vol. VIII, p. 59, 1906.

rounded, and of a harder consistency than normal resting muscle. The erector spinae, the quadratus lumborum, and the muscles of the forearm appeared normal. In the leg the thigh muscles were wasted and flabby. The anterior tibial and the calf muscles were larger and harder than normal.

Sensation was unaffected. The knee-jerks were absent. No abnormal signs were found in the thoracic and abdominal viscera.

During his stay he received a mixture containing 6 minims of liquor strychninae three times daily, and the affected muscles were galvanised and massaged. The massage was omitted, however, before the commencement of the experimental period. In two months' residence in the hospital he put on 7 pounds in weight.

For the purpose of this investigation the diet of the patient was specially controlled for ten days, and its composition calculated, the urine being collected for the same period. The patient remained in bed.

THE DIET

For the first four days of the experimental period, July 2nd to 5th inclusive, the patient was upon the ordinary diet of the hospital, including meat; on the 4th and 5th each article of food was weighed or measured. For the next four days, July 6th to 9th inclusive, he was placed upon a diet of starch and cream as described by Folin. This contained less than 20 grammes per day of proteid, but supplied a sufficient heat value, and enabled the excretion of creatinin to be determined with a minimum amount of proteid in the food. The source of the starch is arrowroot which is partially digested with diastase and made into a kind of blancmange, and eaten with abundance of cream, and sugar to taste. On the first day the diastatic action was too feeble and the blancmange rather hard, but afterwards it was more successful. On the fourth day, although the patient took a fair quantity, it was with but little relish, and the diet was discontinued. For the next three days the food supplied contained proteid in the form of milk and eggs, but no meat or meat extracts which would contain creatin and possibly creatinin.

In Table I the quantities of proteid, carbohydrate, and fat ingested are set forth, together with the caloric value of the food and the variations in weight of the patient.

The details of the diet for each day will be found in the appendix.

TABLE I—SHOWING WEIGHT AND DAILY FOOD

Date July, 1906	Diet	Weight kilog.	Proteid	N	Carbo- hydrate	Fat	Water	Calories per day	Calories per kilo. per day
2 3	Mixed, with meat. Not weighed	{ —	{ —	{ —	{ —	{ —	{ —	{ —	{ —
4 5	Mixed, with meat. Weighed	{ 50.3	{ 54 90	{ 8.6 15.9	{ 152 385	{ 54 67	{ 1424 1558	{ 1348 2277	{ 27 45
6 7 8 9	Starch and cream	{ 50.3 50.3 50.6 50.8	{ 19 19 19 13	{ 3.0 3.0 3.0 2.1	{ 405 405 379 277	{ 106 106 106 71	{ 2124 2124 2014 1750	{ 2726 2726 2615 1849	{ 54 54 52 36
10 11 12	Mixed with proteid. No meat	{ 50.6 50.7 50.7	{ 74 92 141	{ 11.9 14.7 22.5	{ 246 204 282	{ 121 175 223	{ 1131 2195 3290	{ 2436 2837 2803	{ 48 56 55

APPENDIX—DIETARY

June 9th to July 3rd, inclusive. Hospital 'ordinary' diet, consisting of bread, butter, meat, potatoes, pudding, tea, soup, and a pint of milk.

July 4th. Bread 113 g., butter 28 g., pudding 113 g. (the pudding was made of 565 c.c. of milk, 57 g. of rice, and 10 g. of sugar; each pudding contained proteid 20 g., carbohydrate 78 g., and fat 16 g.), beef 113 g., potatoes 227 g., milk 565 c.c., tea 565 c.c.

July 5th. Bread 538 g., butter 28 g., pudding 113 g., mutton 113 g., potatoes 227 g., milk 565 c.c., tea 565 c.c.

July 6th. Arrowroot mixture (containing 18.2 per cent. of starch, and 77.8 per cent. of water) 1823 g., sugar 57 g., cream 425 g., salt 3 g.

July 7th. Arrowroot mixture 1823 g., sugar 57 g., cream 425 g., salt 3 g.

July 8th. Arrowroot mixture 1681 g., sugar 57 g., cream 425 g., salt 3 g.

July 9th. Arrowroot mixture 1462 g., cream 283 g., salt 3 g.

On the 6th, 7th, 8th, and 9th, 425 c.c. of water was drunk in addition to that contained in the arrowroot mixture.

July 10th. Bread 339 g., butter 57 g., milk 425 c.c., eggs 227 g., sugar 21 g., cream 142 g., Horlick's malted milk 283 c.c., water 128 c.c.

July 11th. Bread 170 g., butter 57 g., milk 425 c.c., eggs 439 g., sugar 21 g., cream 283 g., Horlick's malted milk 283 c.c., potatoes 227 g., water 847 c.c.

July 12th. Bread 170 g., butter 57 g., milk 2,000 c.c., eggs 481 g., sugar 21 g., cream 283 g., Horlick's malted milk 283 c.c., potatoes 227 g., water 565 c.c.

The food value of this dietary was calculated from published analyses for the construction of Table I. The nitrogen content of Horlick's malted milk was determined by Kjeldahl's method, from a specimen prepared as directed on the bottle, one tablespoonful being made up to half a pint with warm water. The nitrogen content of the mixture was low, being from duplicate analyses .182 per cent., or 1.14 per cent. of proteid.

THE URINE

The urine was collected for the twenty-four hours from 8 a.m. to 8 a.m., for which period the diet of the corresponding day was calculated. The total nitrogen was estimated in duplicate by Kjeldahl's method, copper sulphate being used as an oxidising agent, and alizarin red as an indicator in the titration. The creatinin was estimated by Folin's method. Table II shows the figures obtained from these analyses on the different diets.

TABLE II—SHOWING TOTAL NITROGEN AND CREATININ IN THE URINE

Date July, 1906	Diet	Quantity c.c.	Total N	N per kilog.	N + —	CREATININ			
						Grammes	Creat. mg. per kilo.	Expressed as N	Creatinin N % of Total N
2 }	Mixed, with meat. {	860	13·8	·274	—	·663	13·2	·246	1·8
3 }	Not weighed {	1190	15·0	·297	—	·853	17·0	·317	2·1
4 ¹ }	Mixed, with meat. {	(1436)	(16·3)	(·324)	—	(·930)	(18·5)	(·346)	2·1
5 }	Weighed {	850	13·2	·262	+ 2·7	·703	14·0	·261	2·0
6 }	Starch and cream {	530	7·2	·143	- 4·2	·511	10·2	·190	2·6
7 }		350	3·6	·071	- ·6	·584	11·6	·217	6·0
8 }		510	2·5	·049	+ ·5	·607	12·0	·226	9·1
9 }		510	2·0	·039	+ ·1	·566	11·1	·210	10·6
10 }	Mixed, with pro- teid. No meat {	460	3·3	·065	+ 8·6	·454	9·0	·169	5·1
11 }		1190	7·8	·154	+ 6·9	·545	10·7	·202	2·6
12 }		2560	14·1	·279	+ 8·4	·470	9·3	·175	1·2

1. On July 4th a quantity of urine estimated by the nurse at 12 oz. was thrown away by mistake. The figures obtained for that day are calculated from the analyses of the remainder, and are included in brackets. They are evidently too high.

RESULTS

On examining column five in Table II it is seen that the amount of creatinin passed per day upon an ordinary diet was from ·66 to ·85 grammes, while upon a creatin and creatinin free diet, such as that given from July 6th until the end of the observations, ·45 to ·6 grammes was excreted per day. In Folin's normal urines the quantity per day varied from 1·22 to 1·88 grammes, and in a man of 56·6 kilogrammes, a body weight approaching that of this patient, the amount was from 1·22 to 1·50 grammes upon a creatin free diet.¹ We see therefore, that the excretion of the creatinin was lower than normal

1. Loc. cit., p. 60.

though no values were obtained comparable to the extremely low ones of a decigramme, or thereabouts, found by Weiss and Langer.

The significance of the figures can be best appreciated if we consider the milligrammes of creatinin excreted for each kilogramme of body weight. The normal proportion, according to Folin, for a healthy lean man on a diet free from creatin or creatinin, is 25 milligrammes per kilogramme, or 20 for a corpulent man. Closson gives rather lower figures, 17 milligrammes per kilogramme in a man of 70 kilogrammes, and 19 in men of 57 and 61 kilogrammes, and in one subject, whose nitrogen intake was, however, exceptionally low, 15 to 16 milligrammes. In this patient, who was very thin, the excretion of creatinin upon a flesh free diet was lower than in any of the above cases, being 10 to 12 milligrammes per kilogramme on the starch and cream, and rather less, 9 to 10 milligrammes per kilogramme, on the proteid diet without meat. On an ordinary diet with meat the quantity did not exceed 13 to 17 milligrammes per kilogramme. If we take Folin's figures for a normal healthy man as a guide, we see that this patient, in proportion to his weight, was excreting less than half the normal amount. If we take Closson's estimate from three of Chittenden's subjects on a creatin free diet, 17 to 19 milligrammes per kilogramme, then this patient with 9 to 12 milligrammes was excreting less than two-thirds the normal.

Two possible explanations of this low output of creatinin suggest themselves. One is that some tissue specially connected with the metabolism of creatinin, such as muscle has been regarded, is diminished in bulk or activity, or both, relatively to the total bulk of proteid tissues. In this case the total nitrogenous metabolism would be low but the creatinin still lower, and this would be shown in the diminished percentage of the total nitrogen excreted as creatinin. Such a relative diminution of creatinin would appear to indicate that it was specially derived from the tissue known to be diminished by disease. The other possibility is that the general proteid metabolism is lessened and the creatinin proportionately with it. In this case, although the quantity would be less so would be, to an equivalent degree, the total nitrogen, and the percentage of the total nitrogen excreted as creatinin would

be the same as in a healthy person, and the conclusion would be reached that creatinin was derived from other proteid tissues to the same extent as from the wasted tissue. In columns two and three of Table II are given the total nitrogen per day and the nitrogen per kilogramme, and in the last column the percentage of the total nitrogen excreted as creatinin.

That the endogenous nitrogen excretion as a whole was diminished in this patient is shown by the figures in column two, Table II, for July 6th to 9th, when the patient was upon the starch and cream diet. On the third and fourth day of this diet, that is on July 8th and 9th, the very small quantity of 2·5 and 2·0 grammes of nitrogen was excreted, whilst Folin's subject of 55·6 kilogrammes, upon a diet identical in composition and not inferior in caloric value, excreted 5·3 and 4·4 grammes.

The four days on the low proteid diet, however, though furnishing valuable information as to the amount of 'endogenous' creatinin, do not give us the evidence we want as to the percentage of creatinin nitrogen, for this is rapidly rising owing to the fall in the so-called exogenous proteid metabolism, and, although lower to start with, by the fourth day the figures have reached the same level as in Folin's normal individuals, about 10 per cent. It was not possible to continue the diet any longer in order to see how much higher the proportion of creatinin nitrogen might have become. Also, an argument as to the source of creatinin drawn from the period during which this patient was upon such a diet might be fallacious. For in a condition of proteid starvation the tissues are not drawn upon equally to provide the nitrogen excreted, and if a creatinin furnishing tissue were called upon, and other tissues relatively spared, the percentage of creatinin nitrogen would tend to approach that of a normal individual under similar circumstances. Such a supposition would also explain why the total amount of creatinin was slightly higher on the proteid poor diet than on the liberal diet of the following three days when, as is shown in Table II, column four, nitrogen was being retained.

But when the figures from this patient upon a normal diet are

compared with those from Folin's subjects, it appears that the proportion of nitrogen excreted as creatinin is definitely diminished, as is illustrated by the following figures :—

	Folin's subjects on meat-free diet Per cent.		This patient on ordinary diet Per cent.
Proportion of total nitrogen as creatinin ...	3·2—4·5 ¹	...	1·8—2·1

And on the third day after the starch and cream was discontinued, the percentage of creatinin nitrogen sank as low as 1·2 per cent.

A comparison would only hold if the different individuals compared were excreting about the same amount of nitrogen per kilogramme. It is known that the quantity of proteid metabolised may vary within wide limits and is dependent in the main upon the amount in the food. If this patient were taking a great deal of proteid free from creatinin the excretion of this exogenous nitrogen would depress the proportion of creatinin nitrogen when expressed as a percentage of the whole. Column two in Table II shows that this was not the case. Both on the ordinary diet and on July 12, the third day of the proteid diet, he was not excreting more nitrogen than an ordinary individual or than men of rather greater weight, 56 kilogrammes, reported in Folin's paper.²

It appears, therefore, that in this case of pseudo-hypertrophic muscular dystrophy the creatinin excretion was diminished in greater proportion than that of the total nitrogen, and this is in harmony with the usual view that this substance is specially derived from muscle. In this disease, although some of the muscles are large, the hypertrophy is only apparent, for the actual muscular tissue is enormously diminished in amount, the bulk being made up by fatty and fibrous tissue. Even in the apparently atrophied muscles the wasting is greater than it appears for the same reason.

Creatinin has been usually regarded as a direct derivative of the creatin of muscle. Some of the facts upon which this view was founded have, however, been called into question of late, notably

1. Loc. cit., p. 62.

2. Loc. cit., pp. 60, 78.

the statement that creatin given by the mouth appears as creatinin in the urine, for Klercker, as mentioned above, states that this is not so, and has been confirmed by other workers.¹ Koch,² on account of the presence of the methyl group in creatinin, suggests that its likely precursors are lecithin and cephaelin in the food, though he also points out that as methylation can take place in the body, creatinin may be derived from such bodies as arginin. Gregor³ concludes that it is a specific product of muscle and of other tissues. Van Hoogenhuyze and Verploegh also believe that it is formed in nonmuscular as well as in muscular tissues.⁴

The observations here recorded are compatible with the view that other tissues than muscle share in the production of creatinin. The association, however, of such a great diminution in the bulk of muscle fibres, and in the excretion of creatinin, together with the fact that on an ordinary diet the creatinin is also diminished relatively to the total nitrogen, appear to indicate that this substance is specially connected with the metabolism of muscle.

OTHER POINTS ILLUSTRATED BY THE TABLES

Table II shows well the independence of the creatinin excretion of the excretion of nitrogen, to which Folin has drawn attention. On the low proteid diet the nitrogen fell as low as 2 grammes per day, but the creatinin remained at above half a gramme. Closson⁵ found also that there was no direct time relation between the excretion of creatinin and that of the total nitrogen, and in a recent paper Leathes⁶ shows that upon a constant diet the rate of excretion of creatinin, like that of uric acid, is at its highest in the active hours of the day, between ten and four o'clock, sinking to a minimum at about midnight. The rate of excretion of nitrogen, on the contrary, is highest at night.

1. Czernecki, *Z. f. Physiol. Chem.*, Vol. XLIV, p. 294, 1905.
2. Koch, *Amer. Journ. of Physiol.*, Vol. XV, p. 15, 1905.
3. Gregor, *Zeitschr d. Physiol. Chem.*, Vol. XXXI, p. 98, 1900.
4. Van Hoogenhuyze and Verploegh, loc. cit.
5. Closson, loc. cit.
6. Leathes, *Journ. of Physiol.*, Vol. XXXV, p. 125, 1906.

On the low proteid diet the fall in the amount of urine to 500 cubic centimetres, or less, as shown in Table II, column one, is striking. Column six in Table I shows that the intake of fluid was rather greater than before.

The last two columns in Table I show that a high caloric value was attained with the arrowroot and cream, over 50 calories per kilogramme on the first three days, sinking on the fourth day to 36 calories per kilogramme, owing to the patient's distaste for this somewhat monotonous regimen. The body weight, as shown in column one, Table I, increased by half a kilogramme in the four days. Column four, Table II, shows that on the fourth day of the starch and cream, July 9th, the nitrogen passed out had sunk so low as to bring the patient into equilibrium. On passing to a more liberal proteid diet a large retention of nitrogen took place, amounting to 7-8 grammes, or 50 grammes of proteid, equivalent to 200 grammes of flesh per day. The quantity of urine again increased, the caloric value of the food and the patient's weight remaining about the same.

CONCLUSIONS

1. In a case of pseudo-hypertrophic muscular dystrophy the amount of creatinin passed out in the urine upon a diet free from meat and meat extracts was found to be about half that in normal individuals of the same weight.
2. The proportion of nitrogen excreted in the form of creatinin on an ordinary diet was less than normal.
3. Since in this case the muscular tissues had suffered much reduction, these results are in agreement with the prevailing view that creatinin is derived from muscular tissues to a greater degree than from other proteid tissues.
4. On a diet of sufficient caloric value but containing hardly any proteid, the elimination of nitrogen sank in four days to 2 grammes per day, or '039 grammes per kilogramme. Under these circumstances the proportion of nitrogen excreted as creatinin approached that found in normal individuals upon such a diet.