

CREATININE IN MENTALLY DEFECTIVE PATIENTS.

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INTRODUCTION.

THE influence of the endocrines on the excretion of creatine and on the urinary creatinine level has become increasingly recognized of recent years. It has, of course, long been known that hyperthyroidism is accompanied by creatine excretion. A recent investigation by Sohval, King and Reiner (1938) found that the creatine tolerance test was positive in 90% of patients with active Graves' disease, but only in 10-18% of controls. Shelton and Tager (1937) showed that four out of five slightly hypothyroid children had an increased creatine tolerance.

Schrire and Zwarenstein have investigated the relationship of the gonads to creatinine and creatine excretion. Castration causes a rise in creatinine level (Schrire and Zwarenstein, 1932). They further showed that this effect was due to the pituitary (Schrire and Zwarenstein, 1933). Injection of anterior pituitary extracts raises the urinary creatinine in normals, while it has no effect on the high creatinine of castrated rabbits. Castration also causes low tolerance to creatine. Pugsley, Anderson and Collip (1934) discovered that, in experimental animals, the thyrotropic hormone of the pituitary has almost the same effect as thyroid extract in causing creatinuria. Schrire (1937), using human subjects, showed that it is the thyrotropic extract of the pituitary which is responsible for the creatinuria, creatinine being unaffected, while with antuitrin, creatinine rose, creatine remaining absent from the urine. Schrire and Sharpey-Schafer (1938) have recently further established that it is the gonadotropic pituitary extract which increases creatinine excretion without affecting creatine, while the thyrotropic extract causes creatinuria by stimulating the thyroid to increased activity.

On an ordinary diet normal men are said not to excrete creatine, while women frequently do so, though not regularly (Hunter, 1928). This has usually been ascribed to the lesser muscular development of women, which results in the creatine being less efficiently taken up. In the light of present knowledge of the effect of the endocrines on creatine metabolism, however, it

seems possible rather that the lesser muscular efficiency of women may be attributable to the greater instability in a woman's endocrine balance. Hodgson and Lewis (1928), who reported creatinuria in 14% of female subjects, found that it was related neither to menstruation nor to lack of muscular development, being found in women athletes; in these, however, creatinine excretion is high.

Creatinine is regularly excreted as a product of muscular metabolism, the amount depending on the quantity of muscle in functioning condition, and is remarkably constant for any given individual. In the muscles it is present as creatine: 98% of the creatine of the body is found in the muscles. In nearly all muscular dystrophies and in conditions of the nervous system affecting the muscles creatine is excreted, sometimes in enormous quantities and associated with a fall in creatinine excretion (Hunter, 1928). Children constantly excrete creatine.

On the one hand, endocrines exert so important an influence on development and mentality and, on the other hand, abnormal conditions affecting muscular development are so often found among mental defectives, that it was thought that a survey of the excretion of creatine and creatinine in mental defectives would be of value. This has therefore been carried out.

EXPERIMENTAL.

The most obvious difficulty of the survey lay in the impracticability of regulating the diet of the hundreds of patients to be examined. Normal men, however, can consume between 1 and 5 grm. of creatine without any appearing in the urine (Hunter, 1928) as it is taken up by the muscles. Nitzescu and Gontzea (1937) found that creatinuria is produced in 20% of normals only when 1.5 grm. or more is given. One gramme is equivalent to about half a pound of meat. It was therefore assumed that, on an institution diet, and particularly for comparative purposes, any marked and persistent creatine excretion would denote an abnormally low tolerance.

Creatinine excretion, while remarkably constant day by day, is not at the same rate throughout the twenty-four hours, and therefore 24-hour specimens are desirable. Under institution conditions again, particularly in dealing with mental defectives, and for hundreds of specimens, this was out of the question.

Early morning specimens were therefore used throughout the investigation as providing the most significant and comparable results. The specimens were obtained in batches on a similar diet and any marked deviation from normal was confirmed, or its temporary nature indicated, by obtaining a second specimen. Finally the results were considered statistically as well as individually. Patients of each of the definite clinical types—such as mongols, diplegics, muscular dystrophies—were grouped separately, and the residual cases, showing no known syndrome of significance, were used as the controls.

For the estimation of creatinine and creatine, the micro-method of Folin was used and an autoclave was available for the hydrolysis. Bichromate standard was used in the colorimeter in view of the very large number of estimations and the relative nature of the results. Every estimation was carried out in duplicate, the readings agreeing closely, and the mean taken. Creatine is throughout expressed as creatinine. The results are given in mgrm. per 100 ml. urine.

In calculating *A*, a measure of creatinine excretion, account has been taken only of the dilution of the sample of urine. *A* is mgrm. creatinine per ml. urine divided by the last two figures of the specific gravity and multiplied by 10. This gives a rough measure of the ratio of creatinine to total metabolites. The main factor influencing the actual quantity of creatinine excreted is the quantity of muscle or, roughly, the weight of the patient. The calculation of *A* only partly eliminates this factor. The presence of some substance in the urine in excessive quantity, affecting the specific gravity, as in glycosuria, fictitiously brings down the figure.

Creatine is expressed in *B* as its ratio to creatinine multiplied by 100. Creatinine is the most constant of normal metabolites, being purely of endogenous origin, so, in a normal case, excessive (exogenous) creatine would appear simply in relation to a normal metabolite. In the event of high creatine excretion, with lowered creatinine, the effect would appear enhanced. In the event of high creatine with high creatinine, however, it might be that only the high creatinine would be apparent, but statistical analysis would reveal the facts.

RESULTS.

In the following tables, the results are presented in statistical form where there was no individual variation of significance; the results, however, are given in full where variation between cases under one heading is of interest.

Non-specific Cases of Mental Defect.

	Males.*	Females.*
Number of cases	134	26
„ tests	158	36
Mean specific gravity	1018.5	1019.0
„ creatinine	114.2 (±58.8)	98.5 (±49.5)
„ creatine	4.9 (± 5.5)	4.6 (± 5.2)
„ value of <i>A</i>	60.3 (±16.5)	51.1 (±11.9)
„ „ <i>B</i>	4.9 (± 4.7)	5.6 (±5.3)

(Figures in brackets give the standard deviation.)

* Females and males were all 16 years or over.

Non-specific Cases—Females under the Age of 16.

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.	Age.
3	1019	104	5	55	5	13
6	1023	109	8	47	7	14
7	1022	65	9	30	14	12
9	1024	92	12	38	13	14
10	1026	55	9	21	16	8
16	1021	83	1	40	1	15
18*	1035	84	31	24	37	8
27	1032	226	24	71	11	14
29	1029	93	6	32	6	13

* Clinically a possible diplegic.

Myopathy.

	Males.	Females.
Number of cases	2	..
„ tests	5	..
Mean specific gravity	1023·0	..
„ creatinine	76·0	..
„ creatine	131·6	..
„ value of A	27·0	..
„ „ B	253·6	..

*Neurological Cases.**(a) Cerebral Diplegia—Bilateral Pyramidal Lesion.*

	Males.	Females.
Number of cases	21	8
„ tests	34	19
Mean specific gravity	1019·0	1018·7
„ creatinine	107·0	97·1
„ creatine	16·7	13·5
„ value of A	56·0	51·4
„ „ B	18·6	14·7

*(b) Bilateral Extra-pyramidal Lesion.**Males.*

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.
158	1,028	176	8	63	5
159	1011	70	13	64	18
	1021	117	30	56	26

Female (aged 14).

44	1023	147	5	64	3
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(c) *Hemiplegia—Unilateral Pyramidal Lesion.*

Males.

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.
160	1026	101	7	39	7
161	1014	92	3	66	3
162	1022	114	4	52	3
163	1009	48	2	53	4
	1030	202	3	67	1
164	1032	172	17	54	10
	1015	100	7	67	7
165*	1032	213	23	67	11
166	1010	64	1	67	2
167*	1007	21	4	30	19
	1005	12	7	24	58
168	1016	121	2	76	2
169	1024	119	5	50	5
170	1012	92	7	77	8
171	1022	159	9	72	6
172*	1024	151	6	63	4

* Congenital syphilis.

	Females.
Number of cases	4
„ tests	7
Mean specific gravity	1018.6
„ creatinine	127.4
„ creatine	1.9
„ value of A	64.7
„ „ B	2.4

(d) *Cerebellar Ataxia.*

	Males.	Females.
Number of cases	3	..
„ tests	8	..
Mean specific gravity	1024.5	..
„ creatinine	188.1	..
„ creatine	5.4	..
„ value of A	80.9	..
„ „ B	2.5	..

(e) *Post-encephalitis.**Males.*

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.
176	1015	171	4	114	2
	1021	212	4	101	2

Females.

49*	1026	101	10	39	10
50	1019	208	8	110	4
	1022	216	8	98	4
51	1026	210	6	81	3

* Encephalitis following measles; the others are cases of encephalitis lethargica.

Congenital Syphilis.

	Males.	Females.
Number of cases	6	3
„ tests	7	5
Mean specific gravity	1018·4	1024·2
„ creatinine	98·0	123·2
„ creatine	10·1	8·2
„ value of A	57·3	50·2
„ „ B	9·9	6·0

Mongolism.(a) *Typical Cases.*

	Males.
Number of cases	12
„ tests	12
Mean specific gravity	1012·5
„ creatinine	78·9
„ creatine	3·2
„ value of A	62·9
„ „ B	4·9

Females.

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.
55	I017	III	5	53	5
56	I019	60	2	32	3
57	I022	I29	II	59	9
	I016	68	I	42	I
58*	I018	I45	I4	81	10
	I022	I32	I5	60	II
	I018	III	4	62	4
	I006	35	5	58	14
59	I031	202	6	65	3
	I021	I64	0	78	0
	I031	I09	26	35	24
	I022	I24	3	56	2
60	I018	88	I2	49	I3
	I016	42	I	26	2
	I020	92	8	46	9
	I024	I07	0	45	0
61†	I023	I47	I5	64	10
	I009	44	I	49	2
	I028	I16	2I	4I	18
	I027	I40	10	52	7

* Feverish ; died.
 † Under thyroid therapy.

(b) *Doubtful Cases.*

	Males.	Females.
Number of cases	5	I
„ tests	8	I
Mean specific gravity	1015·6	1020·0
„ creatinine	110·4	124·0
„ creatine	5·2	0·0
„ value of A	66·2	62·0
„ „ B	7·7	0·0

*Endocrine Dystrophies.**Males.*

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.
200	1018	114	5	63	4
	(1025	284	2	114	1
201	1013	67	1	51	2
	(1023	134	3	58	3
	(1016	82	21	51	26
202	1014	93	5	67	6
	(1014	102	3	73	3
203*	1014	50	0	36	0
204†	(1016	62	1	39	2
	(1011	46	0	42	0
205	1015	92	10	61	11
206	1020	117	2	58	2
207‡	1023	141	17	61	12
208‡	1023	88	7	38	12
209	(1029	125	0	43	0
	(1029	183	4	63	2
210	1017	108	6	64	6
211	1029	187	9	65	5
212§	1010	72	4	72	6
213	1010	64	4	64	7
	(1025	253	47	101	19
214	(1021	85	1	40	1
	(1026	170	0	65	0
215	1028	20	4	72	2
216	1017	96	5	57	6
217	(1020	53	6	27	12
	(1017	42	5	25	12
218	1016	79	6	50	8

* Dwarf.

† Cretin—no treatment.

‡ Cretin under thyroid treatment.

§ Tall and fat.

|| Hyperthyroidism and glycosuria.

Females.

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.	Age.
63	1023	128	3	56	2	35
64*	1016	84	5	52	6	31
	1023	102	4	44	4	..
65†	1011	34	2	31	6	..
	1024	168	10	70	6	39
66*	1018	84	10	47	12	16
	1013	32	9	25	19	..
	1015	60	1	40	2	..
67*	1016	46	4	29	9	..
	1025	67	4	27	6	10
68	1011	83	11	75	14	36
	1021	161	25	77	15	..
69	1013	63	6	49	10	35
70	1029	136	11	47	8	19
71	1020	110	6	55	5	24
72	1022	101	10	46	10	18
73*	1015	74	3	49	4	20
74*	1020	126	9	63	7	25
75	1027	117	8	43	7	37
76	1024	92	1	38	1	19
77*	1028	180	34	64	19	17
78	1011	92	14	84	15	11
	1009	59	8	66	14	..
79*	1017	70	1	41	1	30
	1018	53	5	29	9	..
	1016	61	4	38	3	..

* Under thyroid therapy ; all cretins except Case No. 77.
 † Large and fat.

Psychosis.

	Males.	Females.
Number of cases	28	4
„ tests	28	4
Mean specific gravity	1016·2	1018·2
„ creatinine	116·9	88·0
„ creatine	5·1	4·5
„ value of A	59·5	50·5
„ „ B	4·5	5·5

		<i>Epilepsy.</i>	
		Males.	Females.
Number of cases	41	14
„ tests	44	15
Mean specific gravity	1017·4	1021·8
„ creatinine	107·0	119·3
„ creatine	4·5	4·6
„ value of A	59·9	55·7
„ „ B	4·3	4·2

Dermatitis under Thyroid Therapy—Female.

No. of case	Specific gravity.	Creatinine.	Creatine.	A.	B.
98	1023	147	15	64	10
	1030	108	30	36	28
	1022	114	32	52	28
	1021	70	12	33	17

Glycosuria—Male.

No. of case.	Specific gravity.	Creatinine.	Creatine.	A.	B.
288	1043	33	3	8	9

DISCUSSION.

The results quoted with regard to males refer to adults over the age of 16 years. Among the females were a number of adolescent age and a few children. If, however, creatinine and creatine excretion are considered in relation to age, the cases who deviate markedly from the normal for that age are apparent.

For non-specific cases, the average creatinine figure is higher for males than for females owing, doubtless, to the greater average size of males. The average creatine excretion shows no significant difference from that for females provided only females over 16 years are taken into account. In both sexes there is a slight creatinuria, although determined in early morning specimens and on a diet containing almost certainly less per day than the usual test dose of creatine.

Certain clinical types show obvious marked deviations. The myopathies, as is well known, are most outstanding. They show an enormously increased creatine excretion and a correspondingly low creatinine rate. Diplegias also show distinct abnormality, as is, again, well known; the creatine excretion is significantly high. The existence of the same phenomenon in cases of extra-pyramidal lesion is doubtful. In marked contrast are the hemiplegias,

which give normal results except for a few syphilitic cases. There is a slight but probably significant increase in creatine excretion in congenital syphilis.

In cerebellar ataxia, and also in post-encephalitic cases (except one due to measles) there is a significantly high excretion of creatinine. Porta and Pelliocioli (1936) reported creatinuria in post-encephalitic Parkinsonism and Vianello-Pierguidi (1935) found marked fluctuations in creatine and creatinine.

In mongols, there is no significant deviation from normal, except that in the male patients the specific gravity average is low. Among psychotics the creatinine-creatinine picture is normal (except in post-encephalitis lethargica). The normality of creatinine and creatine excretion in psychotics supports the view that psychosis is not in general associated with endocrine disorder. In the epileptic group nothing abnormal has been found.

Among endocrine dystrophies wide variation is noted, according to the type of the disorder. There is an obvious difference between a dwarf and a tall, fat patient and between a cretin and the same under thyroid treatment. In hyperthyroidism, creatine excretion is high and in cases under thyroid therapy higher than it would be without such treatment.

SUMMARY.

A survey of over 500 estimations in duplicate of creatinine, and of creatine, excretion in early morning specimens of urine from nearly 300 male and 100 female mental defectives has been made. The patients were purposely kept on ordinary institution diet. The results were expressed as (*A*) creatinine level, taking into account the specific gravity of the sample, and (*B*) ratio of creatine to creatinine; they were also worked out statistically.

Using this simple procedure, it was found that the following well-established observations were readily apparent:

- (1) In muscular dystrophy creatine excretion is greatly increased at the expense of creatinine.
- (2) In diplegia, similarly. (In hemiplegia, by contrast, results were normal.)
- (3) High creatine was found in patients suffering from hyperthyroidism and relatively high in patients under thyroid therapy.
- (4) In children high creatine and low creatinine were found.

The method was therefore regarded as qualitatively reliable and the following further observations were noted:

- (1) In cerebellar ataxia and in post-encephalitis lethargica creatinine excretion was found to be high.
- (2) Apart from post-encephalitis, no abnormality of creatinine-creatinine excretion was apparent in psychosis in mental defect.
- (3) There appeared to be a slight increase in creatine excretion in congenital syphilis.

(4) Results were normal with mongols and with epileptics.

(5) Among endocrine dystrophies results were irregular and in accordance with the nature of each case.

It was further noted that :

(1) Slight creatinuria is normal on a diet containing probably less per day than the usual test dose of creatine, even when the estimation is made on an early morning specimen.

(2) There is no significant difference between average creatine excretion of men and women patients.

(3) Owing probably to their greater average size and consequently greater muscle bulk, the average creatinine excretion of men is greater than that of women.

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