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T H E S I S

C R E A T I N U R I A

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CREATINURIA.

INTRODUCTION.

Two conditions - Progressive muscular atrophy and Cancer of the liver have been found to be constantly associated with the appearance of creatine in the urine. Creatine occurs also, but irregularly, in a number of other definite pathological conditions,

The investigations set forth in this thesis were carried out at the King Edward VII' Hospital Cardiff during a period of 17 months residency as House Physician to the Gynecological Wards and House Surgeon. The cases examined were all hospital patients and the results obtained chiefly support the views of previous observers. In this paper I record all the cases of creatinuria seen by me.

GENERAL CONSIDERATIONS.

The exact cause of the occurrence of creatine in the urine is at present unknown. It is clearly not derived directly from any creatine or creatinine taken into the body with the food, since the ingestion of these bodies has little if any, influence on the amount excreted. Experiments recorded by Mackenzie Wallis (1) and others, with different known dietaries, are also in favour of the endogenous origin:



The two most probable sources of the creatine in urine are,

- (a) That it represents the end product of a special group of protein metabolism. Arginine has a composition closely resembling that of creatine and as Arginine exists in the protein molecule, we may have in it the possible precursor of creatine.

Arginine, $\text{NH}_2\text{C}(\text{NH}_2)\text{NH}(\text{CH}_2)_3\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$.

Creatine, $\text{NH}_2\text{C}(\text{NH}_2)\text{N}(\text{CH}_3)_2\text{CH}_2\text{CO}_2\text{H}$.

By the oxidation of protein the methyl group may be formed by the splitting up of the amino-acid united to arginine. We have no proof that arginine is the precursor of creatine, at the present time.

- (b) Creatine may represent ~~synthetic~~ activity on the part of the cell. This view receives support from the observations of feeding experiments with glycoamine (guanidine acetic acid). This substance, when given per os, is excreted as creatine, and owing to its poisonous character has to be given in very small quantities. The glycoamine becomes methylated and in this form is removed from the body as an innocuous compound.

Now, methylation is a very common process in the body when noxious compounds have to be synthesised to innocuous compounds. We have, for example, the methylated bases in nitrogen ring compounds,

and amongst methyl-amine derivatives in the body we may mention choline and its derivatives, and also adrenaline. Also the appearance of methyl mercaptan in the urine after asparagus, and methyl-tellurium after ingestion of tellurous acid are of significance in this respect. Now, creatinine is a strongly basic substance, and since it has a ring structure, it offers greater resistance to oxidation in the body. Creatine, on the other hand, is an innocuous neutral substance. Further, creatine is known to have a marked action on the growth and activity of cellular tissues, and consequently we cannot regard it as entirely functionless. Mellanby (2) has investigated the phylogeny and ontogeny of the muscular system in relation to creatine, and his results clearly point to synthetic activity on the part of the cell, with creatine as an end product. Experimental observations on isolated muscles have shown that creatine, unlike lactic acid and carbon dioxide, is quite independent of muscular activity. This is also in accordance with the absence of effects of exercise on the creatinine output in man.

Reviewing all the evidence which has been adduced in support of the origin of creatine in the muscles, and creatinine in the urine, one is inclined to accept the view that creatine may represent synthetic activity on the part of the cell.

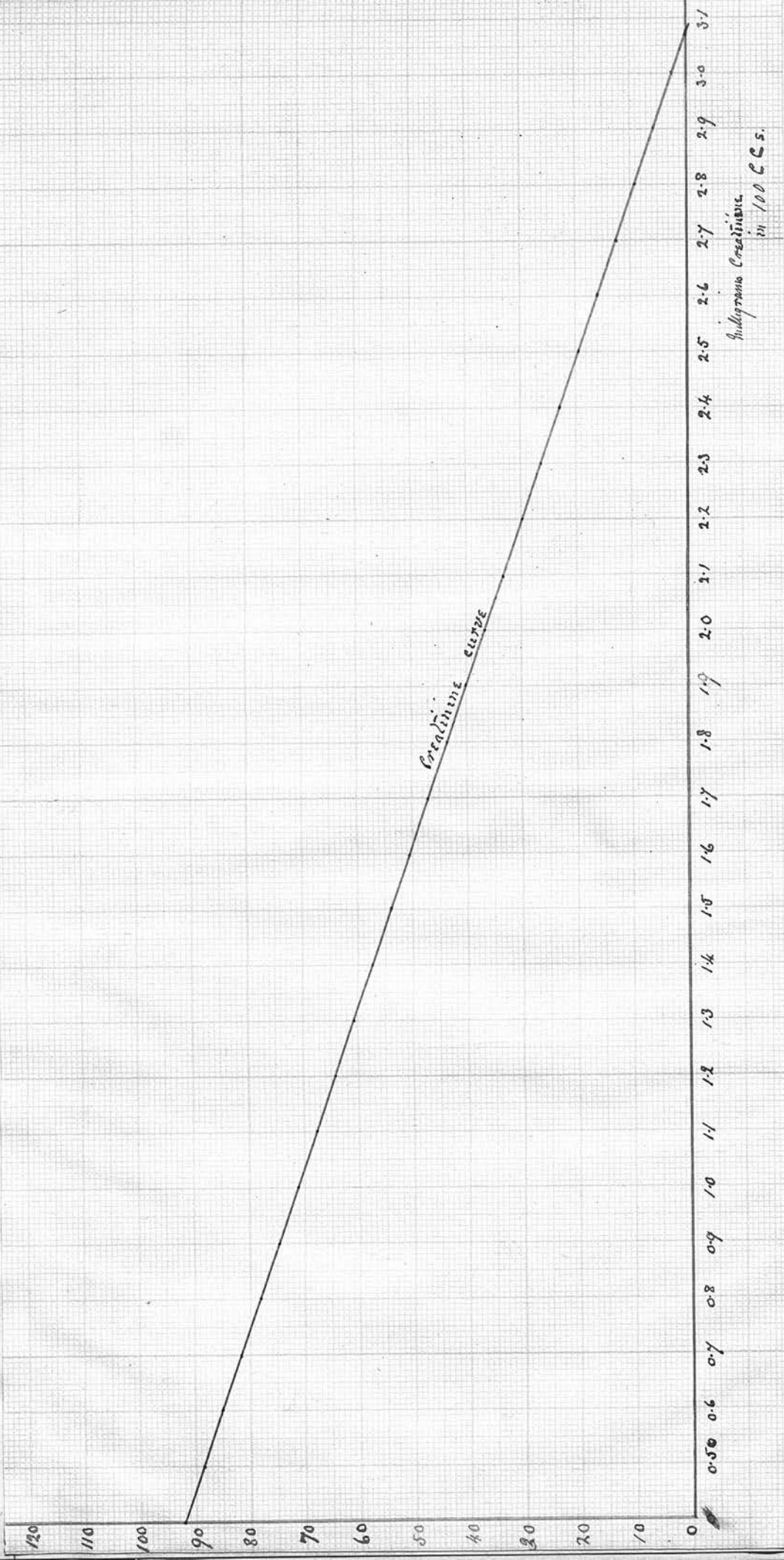
It is probable creatinine is the form, in which this creatine of muscle is excreted. By dehydration of creatine, creatinine is produced, and it is possible, that in the conditions in which creatine is found in the urine, there is some disturbing factor preventing the conversion of creatine into creatinine. It may be that this process goes on in the liver, and that in these conditions the liver is either overtaxed by an increased quantity of creatine to be converted into creatinine, or that the liver itself is diseased and unable to perform this function completely. In support of the first contention, we have the invariable appearance of creatine in urine of cases of progressive muscular atrophy. In support of the second contention we have the fact that creatine is always present in cases of carcinoma of the liver.

Other evidences in support of these contentions are

- (a) Creatinuria in urine during Menstruation and Pregnancy. These two conditions represent increased synthetic activity on the part of certain cells and resultant increase of creatine.
- (b) Diabetic creatinuria, which may be due to some disturbance of the liver function.

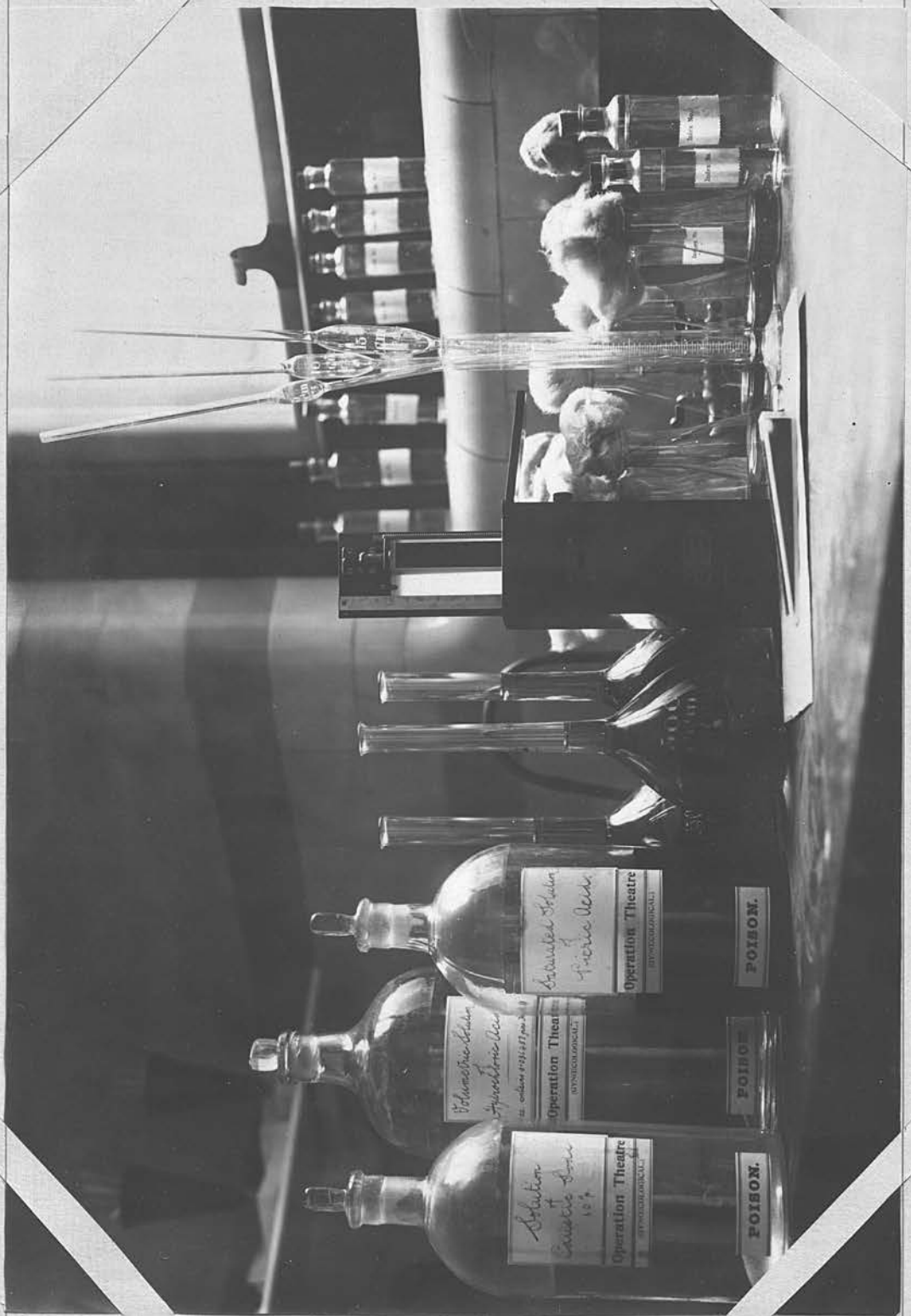
Colorimeter Anterrieth-Koenigsberger.

Creatinine Curve.



Phyllipano Creatinine
in 100 CCs.

The apparatus used in this investigation.



METHOD OF ESTIMATION.

Throughout this investigation the colorimetric method devised by Folin (3) in 1904 has been used, except that a different type of colorimeter was used. The method is based on the colour reaction given by creatinine with picric acid in an alkaline solution. The coloration so produced is compared with a half normal solution of potassium bichromate in a universal Colorimeter as devised by Prof. Dr. W. Antenrieth and Prof. Dr. J. Koenigsberger. This instrument is composed of a wedge which is fixed, with the thick end uppermost, by the side of a sliding trough. The fluid which required testing, is put in the trough and moved upwards and downwards until the correct reading is obtained. By dissolving 24.53 grs of potassium bichromate in a litre of water a half normal solution was formed. This was placed in the wedge and used as the standard. This wedge was calibrated for creatinine, and the curve opposite gives the results obtained. The abscissae represent the number of milli-grams of creatinine dissolved in 100 c.c.s. water, whilst the ordinates give the figures of the scale attached to the wedge. (Diagram of creatinine curve appended)

The apparatus used in this investigation is shown in the appended photograph.

In general, 15 c.c. of a saturated solution of picric

acid and 5.c.c. of a 10 per cent solution of caustic soda were added to 10.c.c. of urine in a 500.c.c. volumetric flask. The volume of urine used had frequently to be varied to ensure more accurate readings. The mixture was allowed to stand for at least five minutes, all due precautions being taken to maintain a constant temperature throughout. The contents of the flask were then diluted up to the 500 c.c. mark, and two or three readings taken immediately on the colorimeter, and the average result recorded. This result gives the amount of creatinine present in 10.c.c. of the urine taken. To estimate creatine 10.c.c of urine were placed in a small Erlenmeyer flask, and to it 10.c.c. of a normal solution of Hydrochloric acid were added, a well fitting wool plug was put in the neck, and the flask heated in an autoclave at a temperature of not less than 120.C for not less than 15 minutes. By this process the creatine present was hydrolysed into creatinine. After allowing to cool 5.c.c. of a 10 per cent solution of caustic soda were added to neutralize the hydrochloric acid present. Next the creatinine was estimated by adding 15.c.c. of a saturated picric acid solution, and 5 c.c. of a 10 per cent solution of caustic soda. After allowing to stand five minutes, and diluting up to 500.C. the result was read off on the scale as before.

This second reading gives the quantity of Creatinine and hydrolysed creatine (in the form of creatinine) present. If creatine be present the difference in the two observations will give the actual amount present, calculated as creatinine.

Example:-

Reading 1.(before Hydrolysis) - 70 - 1.05 milligrams creatinine in 10.c.c.s urine.

Reading 2.(after Hydrolysis) - 50 - 1.62 milligrams Creatinine & hydrolysed creatine in 10.c.c.urine.
'57 mgms Creatine in 10.c.c.Urine.

Readings were taken by several observers in many cases, in order to eliminate as far as possible the personal equation.

GENERAL PROCEDURE.

It was found best to examine the urine within an hour or two of obtaining the specimen, as the creatinine diminished if left. Similarly, best results were got at the second reading when it was done soon after cooling. Many of my earlier results had to be discarded owing to the specimens being allowed to stand, too long. By leaving the hydrolysed specimen for 24 hours exposed to light I once had a second reading recording exactly half the first reading.

All urines examined were subjected to the usual ward

testings, and any abnormality noted. Every Patient mentioned, with the exception of six of the Pregnancy cases, were examined by me at the King Edward VII' Hospital Cardiff. Most of them were directly under my care. The six pregnancy cases were in the Workhouse Infirmary. Whenever possible a 24 hour specimen of urine was obtained. At first measurements were kept but as these were of no value in this paper, they are not quoted. Specimens on a creatine free, and also on an ordinary meat diet, were got when possible.

The head-lines represent the conditions in which the urine was examined for Creatine, In each section a short summary of the literature on the subject is given. Creatinine and creatine are expressed in milligrams per 10.c.c. of urine

NORMAL INDIVIDUALS.

Folin (4) came to the following conclusions:

- (a) The amount of creatinine in urine is independent of the amount of protein in the food, or the total nitrogen in the urine.
- (b) The amount of creatinine excreted is a constant quantity for each individual.
- (c) Creatine is not present in normal urine, and occurs only in minimal quantities after injection of this substance.

Creatinine is therefore a product of endogenous metabolism. The chief factors which regulate the excretion of creatinine are body-weight, age, and sex.

Case 1. age 30. male. suffering from displaced cartilage of knee, awaiting operation. A strong healthy goods porter. No creatine present on creatine or creatine free diet.

Case 2. age 21. male. accidentally shot in chest by a toy pistol. Urine examined whenh was quite healthy walking about the wards. No creatine on creatine or creatine free diet.

Case 3. age 24. male. Healthy coal hewer:urine examined whilst awaiting operation. Four samples on full diet showed no creatine.

Case 4. Age 35. male. Inguinal Hernia. Patient was a labourer awaiting operation, meat diet. Two

TABLE 1.

7 Cases of Normal Individuals.

No of Case,	Age.	Sex.	Disease,	Diet Creatinine, M. grms	Creatine, per 10.c.c urine	Date.
1.	30.	Male	Deranged Knee, Knee,	2.8 2.6.	0 0	16.2.12. 18.2.12.
2.	21.	Male.	Bullet in chest.	1.8, 1.6,	0 0	15.2.12. 17.2.12.
3.	24.	Male,	Varicocele.	1.92, 1.9 1.9.	0 0 0	20.1.12. 20.1.12. 21.3.12.
4.	35.	Male.	Inguinal Hernia,	2.1, 2.4.	0 0	22.3.12. 19.3.12.
5.	31.	Female.	Femoral Hernia.	2.1. 1.6, 1.4.	0 0 0	20.3.12. 16.3.12. 18.3.12.
6.	44.	Female	Endocarditis,	1.4, 1.5, 1.4 Milk	0 0, 0	16.3.12. 17.3.12. 20.3.12.
7.	30.	Male,	Hæmorrhoids.	2.2, 2.4, 2.1.	0 0 0	25.1.12. 26.1.12. 27.1.12.

specimens of urine examined. No creatine.

Case 5. age 31. female. Femoral Hernia. Patient was awaiting operation and had menstruated 2 weeks previously. Meat diet. No Creatine found in 2 specimens.

Case 6. age 44. Female. Endocarditis (1st stage). Menopause 1 year ago. 3 specimens examined one on milk diet and two on meat diet. No Creatine.

Case 7. age 30. Male. Collier. Awaiting operation for haemorrhoids. Meat diet. No creatine in three samples of urine.

The seven cases above are typical examples of the twenty five normal cases examined, These results confirm the view of Folin that Creatine is not an excretory product of the normal individual.

(See Table ¹ appended).

MENSTRUATION & PREGNANCY.

Cramer and Krause (5) pointed out the presence of creatine in the urine of women during pregnancy. These investigations were confirmed by Van Hoogenhuyze and ten Doeschate (6) Later Krause (7) as a result of a large number of analyses of urine obtained during different phases of the sexual cycle came to the following conclusions:-

(a) That in women creatine is not an abnormal constituent since it occurs after menstruation and sometimes during the intermenstrual period.

- (b) Creatine is present in the urine of women during pregnancy.
- (c) There is an intimate association between creatinuria and the female sexual cycle.

Case 1. Female age 34. Early malignant disease of breast.

Urine examined whilst awaiting operation. Creatine from .2-4 found in urine on three consecutive days before menstruation. No Creatine was found 14 days after menstruation three months later. There was a possibility that the creatine present might be due to carcinoma of the liver, so a longitudinal incision was made over the liver. The liver was found to be perfectly healthy.

Case 2. age 23. Convalescent from radical maxillary antrum operation. Three specimens examined one was the urine of the day before menstruation, and the other two were obtained during menstruation. Creatine .1-3 m.grms. per 10cc. was present in all specimens.

Case 3. age 30. Convalescent from mild attack of pleurisy. Two specimens examined, of urine obtained on two consecutive days 2 weeks after last menstrual period. No Creatine present.

Case 4. age 35. Gastritis. Specimens of Dec. 1st 2nd & 3rd obtained. No Creatine was present in the first two but .8 in the third. Menstruation came on on the 5th Dec. i.e. within 2 days

TABLE 2.

MENSTRUATION.

No of Case.	Age.	Date of Menstruation.	Creatinine, M. Grms,	Creatinine, per 10.c.c.c urine	Date.
1.	34.	Dec 20-27.	1.6.	.3 ₄	16.12.11.
			1.3.	.2	17.12.11.
			1.5.	.4	18.12.11.
		Feb 19 - 25.	1.5.	0	8.3.12.
2.	23.	Mar 20 - 25.	1.9.	.2	19.3.12.
			1.3.	.3	20.3.12.
			1.6.	.3	22.3.12.
3.	30.	Mar 4 - 7	1.5	0	20.3.12
		(2 weeks before.)	1.7.	0	21.3.12.
4.	35.	Dec 5 - 9.	1.0	0	1.12.11.
			1.6.	0	2.12.11
			2.38.	.8 ₄	3.12.11.
5.	28.	Mar 12 - 17.	1.7.	.7	18.3.12.
			1.18.	.5	19.3.12.
			2.0.	0	21.3.12.
			.9	0	23.3.12.
6.	21.	Mar 17 - 21.	2.8	.4	22.3.12.
			1.9.	.3	23.3.12.
			2.2.	.3.	24.3.12.

of the appearance of Creatine.

Case 5. age 28. Mitral regurgitation. Menstruated March 12-17. Urine examined on March 18th 19th 21st & 23rd. Creatine was present in first two specimens but absent in other two.

Case 6. age 21. Stenosis of Cervix. Awaiting operation. Menstruation March 17-21st. Creatine present on March 22, 23, & 24.

Creatine was found to be present immediately before and after menstruation as well as during menstruation in all these cases. Creatine was not present in two cases during the intermenstrual period. (See Table 2) Eight cases of pregnancy were examined. All were healthy young women.

Case 11. 8 mos. pregnant. age 21. Creatine was present on the three occasions observed.

Case 2. $8\frac{1}{2}$ mos. pregnant. age 27. Three observations made, Creatine present twice.

Case 3. 8 mos. pregnant. age 27. Creatine present on the three occasions observed.

Case 4. $7\frac{3}{4}$ mos. pregnant. age 44. This case had a carcinoma of the cervix also. No Creatine. One specimen.

Case 5. 8 mos. pregnant. age 23. Three specimens examined. Two contained Creatine.

TABLE 3.

PREGNANCY.

No of Case,	Age.	Duration of Pregnancy,	Creatinine, M. Grms	Creatine, per 10.c.c.c urine.	Date.
1.	21,	8 months	2.35,	.25	18.3.12.
			2.1.	.2	19.3.12.
			1.8.	.3	20.3.12.
2.	27,	8½ "	1.28.	.38	18.3.12.
			1.5	.25	19.3.12.
			.8.	0	20.3.12.
3.	27.	8 "	2.6.	.4	18.3.12.
			2.2	.3	19.3.12.
			1.9.	.3	20.3.12.
4.	44,	7¾ "	1.2,	0	18.3.12.
5.	23.	8 "	2.5.	.4	18.3.12.
			2.2.	.25	19.3.12.
			1.9.	0	20.3.12.
6.	29.	4 "	.9,	.15	18.3.12.
			1.0	.2	19.3.12.
			.8.	.1	20.3.12.
7.		8¾ "	1.9.	0	18.3.12.
8.	18.	9 "	1.8	.25	18.3.12.
			2.6.	.15	19.3.12.
			2.4.	.2	20.3.12.

Case 6. 4 mos. Pregnant. age 29. Three specimens
Examined. All contained Creatine.

Case 7. $8\frac{2}{4}$ mos pregnant. One specimen contained no
Creatine.

Case 8. 9 mos. Preg. age 18. Three specimens examined
All contained Creatine.

The observations in Menstruation and Pregnancy cases confirm the results of Cramer and Krause, with the exception that I did not always find Creatine present in pregnant women.

3.
(See Table³ appended).

DIABETES.

The occurrence of Creatine in the urine of patients suffering from diabetes has been demonstrated by Shaffer (8), Krause and Cramer (9) and also by Ross Taylor (10). All these observers agree in the constant occurrence of creatine in this condition. The association of acidosis with Diabetes has to be taken into account when considering this question. Mellanby (11) in a case of cyclic vomiting found Creatine to be constantly present during the attacks and the Creatine was associated with acetone. Further we find Creatine in the urine in starvation, on a restricted carbo-hydrate diet, and in pregnancy. In all these conditions acidosis is usually present. Before mentioning the cases I would draw attention to the interference in the estimation of creatinine and creatine by the presence of acetone bodies. The

precautions laid down by Hoogenhuyze and Verploegh (12) have been observed in the following estimations. In addition to the estimation of Creatinine and Creatine, the percentage amount of glucose was ascertained, and the tests for acetone and diacetic acid applied to the urine in question.

Case 1. Female, age 21. Advanced diabetes. Acetone and diacetic acid in the urine. Sugar 2.8%. Creatine always present. Seven estimations taken, four on diabetic diet and three on milk.

Case 2. Female age 32. Well marked case of Diabetes. Trace of acetone in the urine on one occasion. Sugar 2.5%. Creatine always present. Six estimations performed, three on diabetic diet and three on milk diet.

The results obtained support the conclusions of the above mentioned observers, namely, that creatine is constantly present in the urine of diabetics. The fact that some of the estimations were carried out with the patients on a creatine free diet shows that the creatine excreted was endogenous in origin. Creatinuria and acidosis appear to be so closely associated as to lead one to suppose that the Creatine is functional in this condition. It seems quite possible that in some way Creatine is produced in order to neutralize the toxin effects of the acetone bodies. Further work in cases of acidosis is required to fully

DIABETES.

TABLE 4.

No of Case.	Age.	Sex.	Percentage sugar,	Acetone.	Diacetic acid,	M. Grms	Creatinine.	Creatinine.	Date,	
							per	10. c. c	urine	
1.	21.	Female,		Present,	Absent	2.0)	.4		20.1.12.	
						1.4) Milk,			.5	22.1.12.
						1.8)			.4	23.1.12.
						.74) Dia-			.5	3.2.12.
						1.4) betic			.5	4.3.12.
1.33) diet.	.4	5.3.12.								
						.8)	.4		8.3.12.	
2.	32.	Female,	1.55 1.25 o/o	Present (trace)	Absent.	1.35)	.4		20.1.12.	
						1.92) Milk			.4	22.1.12.
						1.4)			.3	23.1.12.
						1.1)			.3	3.1.12.
						1.13) Dia			.4	4.1.12.
						1.0) bet	.3		5.1.12.	
						ic.				

demonstrate such a relationship.

(See Table⁴ appended).

MALIGNANT DISEASE.

The excretion of Creatine and Creatinine in malignant disease has been demonstrated by Mellanby (2) Hoogenhuyze and Verploegh and Mackenzie Wallis (13). These observers all agree that Creatine is not present in malignant disease unless the liver is involved. This applies to both carcinoma and sarcoma. The following cases confirm this view.

Case 1. Female age 56. Extensive carcinoma of rectum with secondary malignant disease of Liver. Lower border of Liver could be felt 3 inches below costal margin, and edge was nodular. Two specimens of urine contained very large quantities of Creatine.

Case 2. Male 59. Palpably large liver with nodule on it. Very marked ascites. Primary growth has not been localised. Four specimens all contain large quantities of creatine.

Case.3. Male age 18. Extensive round celled sarcoma involving glands in groins and mesentery. Colostomy has been performed. Over 12 months duration. Original site of disease, was in Ischio-rectal fosse. Liver cannot be palpated. Four specimens of urine examined, all contained copious amounts of Creatine.

Case 4. Male age 60. Had a blow on eye. Developed detached retina and a year later melanotic sarcoma appeared. In spite of excision disease has spread and now there are over a dozen subcutaneous black nodules over the body. One was excised and found to be of typical melanotic sarcoma structure. There is a nodular mass felt below the Liver. Ten specimens of urine examined. All contained Creatine.

Case 5. Male. age 58. Post Mortem showed extensive carcinoma of left kidney. No Liver involvement. Two specimens of urine. No Creatine present.

Case 6. Male age 60. Thought might possibly be malignant glands of neck. Post Mortem showed to be septic glands with very large Cirrhotic liver. Three specimens. No Creatine.

Case 7. Male age 40. Inoperable carcinoma of stomach. Diagnosis confirmed by Laparotomy; liver was examined during operation and found to be not involved. Three specimens. No Creatine.

Case 8. Female 45. Inoperable carcinoma of cervix. No liver enlargement made out. Three specimens. No creatine.

Case 9. Female 42. Follicular erosion simulating malignant disease. Three specimens. No Creatine.

Case 10. Female 50. Carcinoma of Pyloras. Palpable
Refused Laporotomy. Two specimens No Creatine

Case 11. Male 21. Sarcoma of upper jaw. (early).
No liver increase. One specimen. No Creatine.

Case 12. Male 55. Post Mortem showed large
carcinoms of Rectum and a nodule size of a pea
of malignant disease in liver, Four specimens.
Two contained Creatine. This case shows a
transition to creatinuria.

Case 13. Male 28. Post Mortem showed generalised
Round celled sarcoma with liver extensively
involved. Wassermann reaction was negative
in this case. One specimen. Creatine present.

Case 14. Male 50. Carcinoma of glands of groin secondary
ary to epithetioma of scrotum, Over 12 months
duration. No liver difference discernible,
but probably present. Two specimens. Both
contain Creatine.

Case 15. Male 35. Gastric ulcer. Thought to be carcinoma
before operation. One specimen. No Creatine.

Case 16. Female. 65. Operation showed carcinoma of
stomach with a nodule on liver (in the
transverse fissure). Two specimens. Both
contained Creatine.

Case 17. Female 50. Case of repeated attacks of
Jaundice due to gall stones. One specimen.

No Creatine.

TABLE V.

1. MALIGNANT DISEASE.

No of Case.	Age.	Sex.	Diagnosis.	Creatinine, M. Grms in 10.c.c urine.	Creatine.	Date.
1.	56.	Female.	Carcinoma of Rectum & Liver.	1.5.	1.2	17.3.12.
				2	.9	18.3.12.
2.	59.	Male.	Carcinoma of Liver.	2.6	1.8	14.3.12.
				3.8.	1.6	18.3.12.
				2.6.	.9	20.3.12.
3.	18.	Male.	Extensive Round celled Sarcoma.	2.2.	1.2	29.1.12.
				2.4.	1.6	30.1.12.
				2.	1.5	12.3.12.
				1.9	1.6	13.3.12.
4.	60.	Male.	Melanotic Sarcoma of eye Nodule felt on under surface of Liver,	1.05	1.5	15.1.12.
				2.15.	.63	16.1.12.
				1.62.	.6	17.1.12.
				2	.5	18.1.12.
				1.8	.3	15.3.12.
				2.6	1.0	16.3.12.
				2.9	1.1	17.3.12.
				1.9	.4	18.3.12.
				1.3	.8	19.3.12.
			(Post mortem showed)	2.2	1.1	20.3.12.
5.	58.	Male.	Carcinoma of Kidney No Liver involve- ment.	1.6.	0	29.2.12.
				1.55.	0	30.2.12.
6.	60.	Male.	Post Mortem septic glands & Cerrhotic Liver.	.6	0	17.1.12.
				.6	0	18.1.12.
				.6	0	19.1.12.

TABLE V contd.

No of Case.	Age.	Sex.	Diagnosis.	Creatinine, M.Grms per	Creatine, 10.c,C urine.	Date.
7.	40,	Male,	Operation showed	1.1,	0	2.12.11.
			Malignant stomach,	.7	0	3.12.11.
			No Liver involvement	.8	0	4.12.11
8.	45.	Female,	Inoperable Carcinoma of cervix.	1.8	0	9.12.11.
			No Liver enlargement.	1.6	0	10.12.11.
				1.8	0	11.12.11
9.	42.	Female,	Follicular erosion simulating.	1.1	0	9.12.11.
			Malignant disease of cervix.	1.05	0	10.12.11.
				1.2	0	11.12.11.
10.	50.	Female,	Carcinoma of Pylorus.	1.6	0	8. 9.11.
				1.6	0	9. 9.11.
11.	21.	Male.	Sarcoma of Upper Jaw.	.6	0	7. 11.
12.	55.	Male,	Post mortem Malignant Rectum with a small nodule in the Liver.	.75	0	10.1.12.
				.75	0	11.1.12.
				1.0	.8	12.1.12.
				1.05	.3	13. 1.12.
13.	28.	Male.	Post mortem. Generalised round celled sarcoma, with extensive involvement of Liver.	2.6	.9	6. 8.11.
14.	50.	Male,	Carcinoma of groin glands. Secondary to epithetiona of scrotum. Over 12 mos duration.	2.32.	1.68	17.3 .12.
				2.5	1.2	18. 3.12
15.	35.	Male.	Gastric Ulcer,	1.7	0	10. 1.12.
16.	65.	Female.	Operation Carcinoma of stomach with Nodule in transverse fissure of liver	2.4	.8	25. 3.12.
				.5	.7	26. 3.12.

TABLE V. contd.

No of Case.	Age,	Sex.	Diagnosis.	Creatinine. M:GRMS per	Creatine. 10.c,c,urine	Date.
17.	50.	Female,	Gall stones.	1.08,	0	12. 3.12.
18.	45.	Female,	Carcinoma of the Cervix	.9	0	12.2. 12.
19.	35.	Female,	Carcinoma of stomach.	1.0	0	2.12.11.
20.	34.	Female,	Carcinoma of Breast, Liver not in- volved, Examined at Operation.	1.6	.3	16.12.11.
				1.3	{ .2	17.12.11.
				1.5	{ .4	18.12.11
				1.3	{ 0	8. 3.12.

Due to
Menstruation.

See Case 1. Menstruation.

Case 18. Female 45. Carcinoma of cervix. No enlargement of liver. One specimen. No Creatine.

Case 19. Female 35. Carcinoma of pylorus. No liver enlargement. Two specimens Both negative.

Case 20. Female age 34. Carcinoma of Breast. Liver examined at operation and found healthy. Creatine present on three occasions due to Menstruation. (see Case 1 Menstruation.)

The most remarkable point in these observations is the very large quantity of Creatine often equalling, and sometimes exceeding, the quantity of Creatinine. This Creatinuria is evidently quite distinct from that occurring in the other diseases mentioned in this paper. The relationship of the liver to this change is emphasised by these cases. In creatinuria we thus have a very important diagnostic sign of malignant disease of the liver.

(See Table ^v₁ appended).

ACUTE FEBRILE CONDITIONS.

The effects of febrile conditions on the excretion of creatinine and creatine has been studied by Leathes (14) Hoogenhuyze and Verploegh (12) and also Shaffer. Creatine has been found in most acute Febrile conditions and is probably due to the breaking down of tissue since with the disappearance of the fever Creatine is absent.

Case 1' Female age 13. Appendix abscess. Three specimens of urine examined when temperature

and pulse were high and abscess was developing. Creatine found in all. Eight weeks later when temperature and pulse were normal and patient was convalescent, one specimen examined showed no creatine.

Case 2. Male 35. Acute abscess of subgluteal region due to Bacillus Coli infection. Two specimens examined, when Temperature was over 102. Both contained Creatine.

Case 3. Male 40. Large suppurating hydatid cyst extending from Right iliae fossa upwards into the liver. Three specimens examined when temperature was above 101. All contained Creatine.

Case 4. Boy age 13. Acute Brights. Temperature between 101 and 104 when three specimens were examined. All contained Creatine.

Case 5. Female age 44. Suppurating ruptured ovarian cyst. Two specimens examined when awaiting operation. Temperature 101.

Case 6. Male age 37. Stricture of Urethra with acute cystitis. Temperature between 101-3. Creatine found in three specimens of urine examined.

Case 7. Female 28. Acute pleurisy with collection of fluid in one pleural cavity. Two specimens of urine examined. Both contained small quantity of Creatine

These cases tend to support the view that creatine is present in urine of acute febrile conditions. The amount of Creatine present seemed to vary directly as the resistance of the individual. If it was a very acute condition of sudden onset, Creatine was usually present if the individual showed a strong resistance, as evidenced by the pulse, temperature, and Leucocytes. If the resistance was low the Creatine excretion was low. From this one might deduce that cellular activity had an active part to play in Creatine excretion.

(See Table appended). VI.

ANAESTHETICS.

Very few observations have been made on the influence of anaesthetics and drugs in general on Creatine and creatinine metabolism. That these do play a part is shown by the following observations, which, though somewhat scanty, seem to be of sufficient interest to warrant inclusion in this paper.

Case 1. Male 56. Urine examined on two days following his operation. Anaesthetic used was a mixture of Chloroform (1 part) & ether (3 parts) followed by open ether. Both specimens contained Creatine.

Case 2. Female 35. Operation Hysterectomy for Fibroids. Anaesthetic Chloroform & ether. Urine examined on the two days following operation. Both contained Creatine.

TABLE VII.

ANAESTHETICS.

No of Case,	Age	Sex.	Date of on. Operation.	Creatinine. M.Grms in	Creatine. 10.c.c urine	Date.
1.	56.	Male	Inguinal Hernia Radical cure 19.3.12.	4.4 3.8	.4 .3	20.3.12. 21.3.12.
2.	35.	Female,	Hysterectomy for Febroids. 13.3.12.	2.24 3.0	.3	14.3.12. 15.3.12.
3.	36.	Male.	Foreign Body in Knee. Removal 2.3.12.	2.8	.3	20.3.12.

Anaesthetic used in all above Cases
was Chloroform and Open Ether.

Case 3. Male 36. Foreign Body in knee. Urine was examined on the day following operation. Chloroform and ether were used as anaesthetics. Creatine was present.

The cause of creatine in the urine in these post-mortem anaesthetic cases is probably explained by a temporary acidosis being produced by the anaesthetic. It has been mentioned before in this paper that in all conditions of acidosis as in cyclic vomiting creatine is always present in the urine. In the case cited by Mellanby (11) creatine only appeared in the urine during the vomiting and was accompanied by acetones. In delayed Chloroform poisoning we get marked acedosis and similarly probably after chloroform and ether we get a certain amount of acidosis.

(See Table 7)

SOME OBSERVATIONS ON BODY FLUIDS.

A series of Body Fluids other than urine was examined to ascertain the value of the presence of creatine and Creatinine in diagnosis. A careful analysis of the following fluids was made with negative results:-

- Results:- (a) Ascitic fluid.
(b) Pleuritic
(c) Fluid from various kinds of cysts
including several types of ovarian cysts.

The faeces showed absence of Creatinine and Creatine also.

There was a trace of Creatinine present in amniotic fluid, but I must obtain a larger amount than obtained, before a quantitative estimation can be made.

The presence of Creatinine in amniotic fluid is readily explained owing to it containing the urine of the foetus in utero. During these investigations I had the good fortune to have a case of accidental rupture of the ureter. A large collection of fluid collected intra-abdominally, when this was incised I had no difficulty in proving it to be urine, owing to the creatinine it contained. Thus the presence of Creatinine or Creatine in any body fluid determines the presence of urine in that fluid.

CONCLUSIONS.

- (1). Creatine is not a normal urinary constituent in men.
- (2). In women Creatine is present, immediately before, during, and after menstruation. It may or may not be present during pregnancy.
- (3). Creatine is always present in the urine of cases of Diabetes mellitus.
- (4). Creatine is always present in the urine of cases of Carcinoma or sarcoma of the liver. The quantity of Creatine in these cases is very high.
- (5). In acute febrile conditions Creatine is present in the urine. The quantity varies directly as the resistance of the individual.
- (6). Creatine is present for several days in the urine, immediately following chloroform and ether anaesthesia.
- (7). The only body-fluid containing Creatinine or Creatine, is urine.

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