DISCUSSION,

At the Quarterly Meeting of the Medico-Psychological Association, on February 23rd, 1911, at Cardiff.

Dr. COLLINS added: In such an institution as this there must be many women with pelvic disease, but I do not advocate interference with the idea that these women who are insane will be cured of their mind trouble, as some American writers have suggested, by operations. But it is evident that where serious pelvic lesions do exist, and more especially if during the times of menstruation the hallucinations and excitement are increased, one ought to give them the chance afforded by interference if pelvic trouble does exist.

Dr. SAVAGE (who was temporarily in the chair), in thanking Dr. Collins for bringing forward such an important set of cases, expressed regret that the lateness of the hour and the fact that there was another paper yet to be read precluded the possibility of discussion.

Metabolism in the Insane.[1]

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Introductory.

THE investigation of the problems of metabolism has now become almost exclusively the domain of the chemical physiologist. Much valuable information regarding the method of utilisation of the food-stuffs which enter the body has been ascertained by a study of the excretions. The physiological chemist has, however, passed beyond the boundaries connecting the income and output of these substances. He now seeks to trace the different transformations and combinations which take place in the body, and to connect up all the links of the chain. These changes are intimately bound up with the individual cells, and their metabolism. Unfortunately our knowledge of the cell is at present very limited, but it will be seen how important even this scanty information is to the subject under discussion. It becomes more and more evident every day that pathological changes in the tissues and cells of the body must be considered not only from a morphological point of view, but also from the purely metabolic standpoint. A disturbance in the metabolism of the cell may in time make itself evident, but it is quite conceivable that such changes are taking place without any definite anatomical signs. On the other hand, a morphological change

may produce only a very slight derangement of cell metabolism, so slight as to escape recognition. The study, therefore, of pathology with physiological chemistry for its foundation, offers a wide field for further investigation. The object of the present communication is twofold, namely, to correlate the known facts with regard to metabolism in the insane, and to emphasise the importance of studying cellular metabolism in its relation to pathological disturbances.

The Results as Regards the Metabolic Products in the Urine.

Creatinine.—Our present knowledge of metabolism in the insane person is due mainly to the labours of Folin (1) and his co-workers in America, and Hoogenhuyze and Verploegh (2) and also Kauffmann (3) in Europe. Folin has published extensive analyses of the urine in various forms of insanity with particular reference to the nitrogenous component creatinine. This substance is one of the most constant urinary constituents, and is found to show only slight variations in each individual from day to day. As a result of his studies Folin concluded "that mental disorders do not necessarily involve great changes in metabolism sufficient to modify the output of creatinin."

The excretion of creatinine in some forms of insanity has also been investigated by Hoogenhuyze and Verploegh (2), and Benedict and Myers (5). The observations of these authors agree very closely with those of Folin.

In collaboration with Dr. Goodall, the writer (4) has investigated the output of creatinine in the insane, with especial reference to the influence of warm and electric baths. The conclusions arrived at were:

(1) That the excretion of creatinine in the insane is in general subnormal.

(2) That electric bath treatment tends to increase the creatinine in the urine.

(3) That warm bath treatment, on the other hand, has little, if any, effect on the creatinine output.

(4) That variations in the volume of the urine excreted seem to be characteristic of the insane.

The significance of the results so obtained will be referred to later in the present paper. Since creatinine in the urine is constant in amount from day to day for the normal healthy

individual, it may be of interest to consider the excretion of this body in different forms of insanity.

An investigation of the variations in excretion of creatinine in a number of insane patients has been carried out at the Cardiff City Mental Hospital through the kindness of Dr. Goodall, and I would here express my indebtedness to him for much valuable help and assistance.

The same precautions were observed as noted in the previous communication (4), namely, with reference to the diet, the collection of the sample of the twenty-four hours' excretion, and the rapidity of estimation of the contained creatinine. The method used was also the same as therein described.

I would here point out the existence of certain very definite fallacies in the colorimetric method of estimation of creatinine, which may introduce very serious errors into the results. At the present juncture it is advisable to emphasise this point, and to bear this in mind when drawing any definite conclusions.

The results as regards the relation to creatinine excretion are here appended:

CASE I.—J. L—, male, æt. 39; melancholia. Body-weight 54·8 kg.; height 1·62 metres. Patient in bed. Diet of milk and milk foods. The body temperature of this patient, and of all the patients examined, was taken twice daily, and showed no marked variations from that usually considered as normal. The urine, on examination, always appeared deeply pigmented, and invariably showed a dense white deposit consisting mainly of earthy phosphates.

Volume in cc.'s*	350	310	350	490	575	660
Specific gravity	1025	1015	1025	1030	1025	1015
Creatinine	0·707	0·339	0·567	0·264	0·788	0·554

* The figures indicating the volume of urine represent the total twenty-four ours' excretion.

The average excretion for five days was 0·680 grm., and the creatinine coefficient 12 mgrms. The figure for the fourth day has been omitted, since it shows an apparent discrepancy.

A later experiment on the same patient with a change of diet was performed. The nature of the mixed diet, and the actual quantities given, correspond with that already described for the male patients described in a previous paper (*loc. cit.*).

Volume	850	690	790
Specific gravity	1020	1020	1025
Creatinine	0·467	0·772	0·481

This experiment gave an average of 0·573 grm. *per diem*. The small quantity of urine secreted daily is to be partly accounted for by the fact that the patient suffers from ptyalination.

CASE 2.—J. R—, male, æt. 32; subacute melancholia with ideas of unworthiness. Body-weight 55·7 kg.; height 1·7 metres. The patient was kept on a mixed diet similar to that referred to in Case 1, with the addition of slightly more protein. The urine appeared quite clear, and showed no tendency to deposition on standing.

Volume	2500	2890	2095
Specific gravity	1010	1012	1012
Creatinine	1·00	1·38	0·963

The volume of the urine passed is very striking, amounting almost to a condition of polyuria. The experiment, however, was carried out in the month of January. It is of interest to note that the quantity of actual fluid consumed *per diem* amounted to about 1·5 litres, and in spite of the polyuria the patient gained weight. Average excretion 1·114 grms., and the coefficient 21·3 mgrms.

CASE 3.—B. S—, female, æt. 43; subacute melancholia with ideas of unworthiness, and suicidal impulses. Body-weight 55·8 kg.; height 1·54 metres. The diet was the same as that given for all the female patients described in the previous communication. The urine was quite clear on all occasions, and showed no tendency to deposition on standing.

Volume	1010	1220	1620
Specific gravity	1015	1015	1010
Creatinine	0·555	0·451	0·662

The average excretion for the three days was 0·556 grm., and the creatinine coefficient 9·9 mgrms.

CASE 4.—M. T—, female, æt. 37; acute melancholia. Body-weight 54·6 kg.; height 1·67 metres. Diet as in Case 3.

Volume	1040	960	1140
Specific gravity	1020	1020	1020
Creatinine	0·645	0·537	0·752

This gives an average daily excretion of 0·644 grm., and a coefficient 11·7. A month later the patient had increased in weight by 3·4 kg., and an experiment with the same diet gave a similar result.

Volume	1330	750	800
Specific gravity	1015	1025	1025
Creatinine	0·611	0·612	0·712

Average daily excretion of creatinine 0·645 and the coefficient 11·1.

CASE 5.—J. F—, male, æt. 40; acute melancholia. Body-weight 63·9 kg. Diet a mixed one of known composition and similar to previous cases. The urine was in all cases acid in reaction, and quite clear.

Volume	2440	1440	2430
Specific gravity	1010	1010	1010
Creatinine	1·593	0·940	1·035

The average daily excretion 1·189, and the creatinine coefficient 18·5. On another occasion the average creatinine excretion for three days amounted to 1·858 grms., and the quantity of urine secreted was also large.

CASE 6.—C. G. H—, male, æt. 29; acute melancholia. Body-weight 49·3 kg.; height 1·67 metres. Diet—milk, etc.—creatine free. Patient kept in bed.

Volume	720	1070	550	750	1470	950
Specific gravity	1025	1015	1030	1030	1015	1020
Creatinine	0·806	0·832	0·839	0·945	0·654	0·665

The average creatinine excretion for the six days amounted to 0·790 grm., corresponding to a coefficient of 17 mgrms.

A later experiment on a mixed diet yielded similar figures after an interval of one week, sufficient to allow the body to adjust itself to the changed dietary.

Volume	840	1620	1220
Specific gravity	1025	1015	1020
Creatinine	0·829	0·830	0·978

This experiment gave an average value for the creatinine output on the three days of 0·879, corresponding to a creatinine coefficient of 18 mgrms.

CASE 7.—W. A—, male, æt. 38; chronic melancholia.

Body-weight 53·9 kg. Patient very thin and pale, kept in bed. Diet—milk, etc.—creatine free.

Volume	1600	795	735	107	1090
Specific gravity	1020	1015	1025	1020	1017
Creatinine	1·905	2·109	1·553	1·124	0·970

The average excretion of creatinine for the five days of the experiment was 1·552 grms., giving a coefficient of 28·6.

CASE 8.—M. A—, female, æt. 79; senile melancholia. Body-weight 45·9 kg.; height 1·54 metres. Diet—milk, etc.—creatine free.

Volume	890	880	425	1480	450	960
Specific gravity	1015	1010	1015	1010	1015	1020
Creatinine	0·525	0·375	0·442	0·666	0·346	0·691

This experiment illustrates the variations in the amount of creatinine excreted daily, and is in striking contrast to the normal healthy individual. The average for the six days of the experiment was 0·507 grm., and the creatinine co-efficient 11.

CASE 9.—H—, male, æt. 57; melancholia, hypochondriacal. Body-weight 59·0 kg.; height 1·72 metres. Diet—milk, etc.—creatine free.

Volume	1650	845	1350	600	850	625
Specific gravity	1015	1015	1030	1020	1010	1015
Creatinine	0·951	1·536	0·877	0·899	0·592?	0·6378

Average—0·980 grm. for five days of the experiment, giving a coefficient of 16·6.

CASE 10.—A. L. G—, female, æt. 28; melancholia with stupor. Body-weight 50·5 kg.; height 1·62 metres. Diet—milk, etc.—creatine free.

Volume	2620	1480	1540	1290	1150	1070
Specific gravity	1015	1010	1010	1015	1015	1020
Creatinine	1·143	0·768	1·084	0·842	0·802	0·709

The average creatinine excretion for the six days was 0·891 grm., and the coefficient 14 mgrms.

CASE 11.—D. H—, female, æt. 25; melancholia with stupor. Body-weight 49·0 kg.; height 1·67 metres. Diet—mixed, similar to Case 2, but without addition of milk, eggs, and milk puddings.

Volume	890	1180	1700	750	1140	1100
Specific gravity	1015	1015	1015	1015	1018	1020
Creatinine	0·667	0·884	1·105	0·532	0·941	0·679

The average for the six days amounted to 0·801 grm., and the creatinine coefficient 16 mgrms.

CASE 12.—J. O. B—, male, æt. 24; adolescent dementia. Body-weight 60·3 kg.; height 1·67 metres. Mixed diet.

Volume	2940	1055	990	1380	1800	1170	1020	1150	1250	1810
Specific gravity	1015	1023	1020	1020	1015	1015	1015	1025	1018	1010
Creatinine	1·440	1·392	0·881	1·324	1·602	1·067	0·979	1·449	1·250	0·932

The average value for nine days of the experimental period was 1·270, and the coefficient 21.

CASE 13.—M. W—, female, æt. 28.; adolescent dementia. Body-weight 45·9 kg.; height 1·65 metres. Mixed diet.

Volume	880	850	900	1000	1260	820	700
Specific gravity	1020	1010	1015	1020	1015	1020	1015
Creatinine	0·731	0·603	0·892	——	0·642	0·844	0·544

The average value for the six days amounted to 0·659 grm., giving a creatinine coefficient of 14·3 mgrms.

CASE 14.—H—, male, æt. 29; catatonia. Body-weight 75·8 kg.; height 1·79 metres. Diet—milk, etc.—creatine free.

Volume	1430	1540	815	890	1450	1052
Specific gravity	1015	1015	1025	1015	1015	1025
Creatinine	0·993	1·540	1·043	0·998	1·123	1·209

The average value for the six days was 1·136 grms., and the coefficient 14·9.

CASE 15.—E. M—, female, æt. 24; acute mania. Body-weight 53·4 kg.; height 1·60 metres. Diet a mixed one, and similar to preceding cases.

Volume	920	520	790	860
Specific gravity	1025	1025	1020	1015
Creatinine	0·737	0·676	0·995	0·662

The average excretion for the four days amounted to 0·767 grm., and the creatinine coefficient 14 mgrms.

CASE 16.—D—, male, æt. 42; general paralysis, demented, exacerbation. Body-weight 57·8 kg. Diet—milk, etc.—creatine free.

Volume	1370	1440	900	250?	1960	1020	1300
Specific gravity	1015	1015	1020	1020	1015	1015	1015
Creatinine	1·289	1·780	1·121	0·610	1·156	1·397	0·809

Average value for creatinine 1·078 grms., and the creatinine coefficient 18·6.

CASE 17.—M—, male, æt. 45; general paralysis, demented. Body-weight 53·4 kg. The diet consisted entirely of milk, milk puddings, and eggs.

Volume	1920	1370	1200	760	1180	3020	815
Specific gravity	1010	1010	1010	1025	1010	1010	1020
Creatinine	0·893	1·037	0·823	0·927	0·803	0·941	0·794

The average excretion in this case was 0·888 grm., and the creatinine coefficient 16·4.

CASE 18.—M. E. C—, female, æt. 49; general paralysis. Indications of cerebral tumour at the time of the experiment. Body-weight 53·0 kg.; height 1·67 metres. Diet—mixed, and similar in composition and quantity to that already described for female patients (*loc. cit.*). The urine was quite clear, and of a very pale colour, but no sugar or albumen was detected.

Volume	1210	1140	1990	2340	1850
Specific gravity	1015	1015	1010	1010	1010
Creatinine	0·901	0·932	2·507	1·022	1·004

The average daily excretion for the five days of the experiment amounted to 1·271 grms., and the coefficient was 23·9 mgrms. per kilo. The figures given are very striking, and the large increase on the third day of the experiment is difficult to explain. These variations are frequently seen in cases of this nature.

CASE 19.—H—, male, æt. 49; general paralysis, demented, exacerbation. Body-weight 58·0 kg.; height 1·74 metres. The urine of this patient gave an average value of 0·343 grm. on days when it was tolerably certain that all the twenty-four hours' sample had been collected. The difficulty of securing a full daily excretion rendered a series of analyses impossible.

CASE 20.—R. R—, female, æt. 27; acute hallucinations, delusions, secondary depression. Body-weight 42·9 kg.; height 1·54 metres. A mixed diet given of known constitution.

Volume	880	1830	650
Specific gravity	1017	1010	1010
Creatinine	0·519	0·704	0·475

The creatinine excretion in this experiment gave an average for the three days of 0·566 grms., and a coefficient of 13·1.

CASE 21.—R. C—, male, æt. 25; hypochondriacal delusions about gastric region; secondary depression. Body-weight 57·3 kg.; height 1·67 metres. Mixed diet as already described.

Volume	840	650	740	710	680
Specific gravity	1025	1020	1030	1030	1030
Creatinine	0·924	0·605	0·886	0·946	0·999

The average value in this case amounted to 0·872 grm., and the coefficient 14 mgrms. per kilo.

CASE 22.—M. S—, female, æt. 55; acute hallucinations and delusions; secondary depression. Body-weight 36·7 kg.; height 1·39 metres. Diet mixed, with a high protein content. The urine was in all cases acid in reaction, and showed a slight deposit.

Volume	1250	1360	1110
Specific gravity	1015	1015	1010
Creatinine	0·857	0·802	0·840

The average creatinine excretion for the three days of the experiment was 0·833 grms., and the co-efficient 22·6 mgrms.

CASE 23.—M—, male, æt. 21; dementia. Body-weight 57 kg.; height 1·7 metres. A milk diet was prescribed, together with milk puddings and eggs.

Volume	480	610	940	670	500	1125
Specific gravity	1025	1040	1030	1026	1030	1025
Creatinine	1·050	1·171	1·951	1·219	1·038	2·070

The average daily excretion was 1·416 grms. and the co-efficient 24·8 mgrms. At first it appeared that the sample analysed did not represent the twenty-four hours' excretion, but the relatively high excretion of creatinine on these days did not favour this view. A later experiment with the same patient gave similar results, and every possible care in collection of the sample was taken.

Volume	1500	910	900
Specific gravity	1030	1030	1039
Creatinine	1·910	1·619	0·990

TABLE *showing synopsis of recorded Cases of Creatinine Excretion in various Mental Disorders.*

No. of case.	Age in yrs.	Sex.	Nature of psychosis.	Weight in kilos.	Height in metres.	Average daily excretion of creatinine.	Creatinine co-efficient.	Author.
						Grms.		
	23	M	Normal person	62·5	...	1·33	22·7	Wallis.
	...	...	7 normal persons	...	...	1·55	20–25	Folin.
1	68	M	Melancholia	...	...	1·045	...	Folin.
2	64	M	,,	59·7	...	1·09	18·2	,,
3	75	M	,,	61·5	...	0·936–1·106	15·3	Hoogenhuyze and Verploegh.
4	47	M	,,	43·8	1·57	0·823	18·8	Benedict and Myers.
5	59	F	,,	39·9	1·16	0·473	11·9	,, ,,
6	57	F	,,	59·4	1·68	0·676	11·4	,, ,,
7	45	F	,,	47·6	1·50	0·476	10·0	,, ,,
8	39	M	,,	54·8	1·62	0·680, 0·573	12·0	Wallis.
9	32	M	Melancholia, subacute	55·7	1·7	1·114	21·3	,,
10	43	F	,,	55·8	1·54	0·556	9·9	,,
11	37	F	Melancholia, acute	54·6	1·67	0·644, 0·645	11·1, 11·7	,,
12	40	M	,, ,,	63·9	...	1·189	18·5	,,
13	29	M	,, ,,	49·3	1·67	0·790, 0·879	17, 18	,,
14	38	M	,, chronic	53·9	...	1·552	28·6	,,
15	81		,, ,,	32·5	...	0·274	8·4	Hoogenhuyze and Verploegh.
16	79	F	,, senile	45·9	1·54	0·507	11·0	Wallis.
17	57	M	Melancholia, hypochondriacal	59·0	1·72	0·980	16·6	,,
18	28	F	Melancholia, with stupor	50·5	1·62	0·891	14·0	,,
19	25	F	,,	49·0	1·67	0·801	16·0	,,
20	24	M	Adolescent dementia	60·3	1·67	1·270	21·0	,,
21	28	F	,, ,,	45·9	1·65	0·659	14·3	,,
22	85		Senile ,,	39·0	...	0·324, 0·215	8·3	Hoogenhuyze and Verploegh.
23	85	F	,, ,,	39·3	1·65	0·292	7·4	Benedict and Myers.
24	92	F	,, ,,	62·6	1·50	0·464	7·4	,, ,,
25	20	M	Dementia præcox	69·7	...	1·40	20·0	Folin.
26	26	F	,,	52·8	...	0·940	17·7	,,
27	17	M	,,	56·9	...	1·09	19·0	,,
28	29	F	,,	...	...	0·858	...	,,
29	66	F	,,	40·1	1·65	0·505	12·6	Benedict and Myers.
30	45	F	,,	48·3	1·65	0·786	15·8	,,
31	32	F	,,	52·9	1·58	0·732	13·9	,, ,,
32	39	F	,,	61·2	1·65	0·863	14·1	,, ,,
33	30	F	,,	41·7	1·50	0·565	13·5	,, ,,
34	57	F	,,	49·0	1·55	0·627	12·8	,, ,,
35	45	F	,,	42·5	1·49	0·487, 0·447	10·5	,, ,,
36	31	F	,,	51·1	1·60	0·765	15·1	,, ,,
37	51	F	,,	59·0	1·65	0·754	12·8	,, ,,
38	52	F	,,	75·9	1·50	1·153	15·2	,, ,,
39	45	F	,,	49·0	1·59	0·885	21·8	,, ,,
40	18	F	,,	44·0	1·58	0·689	15·6	,, ,,
41	26	F	,,	28·6	1·79	0·324, 0·369	...	,, ,,

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No. of case.	Age in yrs.	Sex.	Nature of psychosis.	Weight in kilos.	Height in metres.	Average daily excretion of creatinine.	Creatinine co efficient.	Author.
						Grms.		
42	16	F	Dementia præcox	43·0	1·55	0·330	7·6	Benedict and Myers.
43	57	F	,,	50·0	1·63	0·559	11·1	,, ,,
44	45	F	Paranoia	42·5	1·49	0·447	10·5	,, ,,
45	29	M	Catatonia	75·8	1·79	1·136	14·9	Wallis.
46	58	F	Manic depressive	40·86	...	0·614	15·0	Folin.
47	52	F	,,	63·78	...	0·814	13·3	,,
48	41	F	,,	50·83	...	1·104	21·7	,,
49	63	M	,,	55·85	...	0·81	14·5	,,
50	47	F	,,	80.3	...	0·75	9·4	,,
51	33	M	,,	67·2	...	1·58	23·3	,,
52	18	M	,,	40·1	...	0·678, 0·679	16·9	,,
53	50		,,	47·0	...	0·991–1·183	...	,,
54	63	F	,,	64·3	1·68	0·748	11·6	Benedict and Myers.
55	50	F	,,	46·5	1·64	0·973	20·9	,, ,,
56	70	F	,,	68.5	1·65	0·963	14·0	,, ,,
57	25	F	,,	85·0	1·51	1·126	13·2	,, ,,
58	19	F	,,	58·0	1·71	0·633	10·9	,, ,,
59	65	F	,,	45·8	1·28	0·620	13·5	,, ,,
60	45		Mania	52·5	...	0·607–2·414	23·9	Hoogenhuyze and Verploegh.
61	61		,,	65·3	...	0·634–1·200	14·1	,,
62	24	F	Mania, acute	53·4	1·60	0·767	14·0	Wallis.
63	36	F	Toxic delirium	49·0	1·65	0·696, 0·722, 0·671	...	Benedict and Myers.
64	49	M	General paralysis	49·7	...	0·75–0·97	...	Folin.
65	42	M	,,	64·75	...	1·485	22·9	,,
66	41	M	,,	85·3	...	1·81	21·2	,,
67	44	F	,,	41·5	...	0·800	19·2	,,
68	35	M	,,	56·6	...	1·38	24·3	,,
69	44	M	,,	70·6	...	1·05	14·8	,,
70	53	M	,,	...	...	0·70	...	,,
71	42	M	,,	57·8	...	1·078	18·6	Wallis.
72	45	M	,,	53·4	...	0·888	16·4	,,
73	49	F	,,	53·0	1·67	1·271	23·9	,,
74	49	M	,,	58·0	1·74	0·343	...	,,
75	53		Cyclic insanity	57·3	...	0·828–1·918	18·6	Hoogenhuyze and Verploegh.
76	37	F	Dementia paralytica	71·6	...	0·934–1·714	18·6	,,
77	51	F	,,	79·3	...	0·936–1·854	16·7	,,
78	19	F	,,	61·0	...	0·947	15·1	,,
79	52	F	,,	64·9	1·45	0·698	10·8	Benedict and Myers.
80	21	M	Dementia	57·0	1·7	1·416, 1·506	24·8, 26·4	Wallis.
81	27	F	Acute hallucinations	42·9	1·54	0·566	13·1	,,
82	25	M	Hypochondriacal delusions	57·3	1·67	0·872	14·0	,,
83	55	F	Acute hallucinations	36·7	1·39	0·833	22·6	,,
84	46	M	Alcoholic delusional insanity	53·0	1·75	0·697	15·0	Benedict and Myers.
85	69	M	,,	58·0	1·65	0·827	14·2	,, ,,
86	56	F	Depression	40·86	...	0·586	14·3	Folin.

Average creatinine excretion 1·506 grms., and the coefficient 26·4 mgrms.

The relatively high excretion of creatinine in this case calls for

some remarks. The variations in the volume of urine passed and the high specific gravity point to very marked metabolic changes. This is further emphasised by the creatinine excretion. The body-weight is quite low considering the height of the patient, and this does not supply any explanation for these results. The only conclusion is that we have here a very marked pathological disturbance, but no definite locus can be assigned from the clinical aspects of the case.

Summary of Results.

An examination of the records of the experiments detailed above reveals the close agreement with those of other writers on the subject. To make this fact clearer a synopsis of all the recorded cases has been compiled, and is included in the accompanying table. My results agree with Folin (1) that mental disorders do not necessarily involve any marked changes in the output of creatinine. The creatinine excretion appears in all the cases to be generally subnormal, as also the creatinine co-efficient, or the relation of creatinine to the body-weight. This, however, is not surprising in view of the fact that a low output of this body is found in a large number of pathological conditions. This low excretion is, therefore, not peculiar to any one disease. The relationship to the body-weight of the patient, or more especially to *the active protoplasmic mass* is emphasised in these experiments, as is also the influence of age and sex. The absence of any differences due to variations in the diet also supports the work of previous investigators.

The results also agree with Folin that the creatinine excreted is independent of the amount of protein in the food, or of the other nitrogenous constituents in the urine. Further, the quantity of creatinine in the urine is not influenced by muscular work.

When, however, we endeavour to verify the statement that the creatinine output is constant for each individual from day to day certain very definite discrepancies are noted. The experiments recorded above all show considerable variations, and these seem to be characteristic of the insane person. The same varietions are also very well seen in the results recorded by Folin (1), Benedict and Myers (5), and Hoogenhuyze and Verploegh (2), for mental disorders. Further, the observable clinical symptoms do not show any coincidence with these

changes. What is the possible significance of this disordered metabolism in the insane person, whereby the excretion of this body is not only subnormal, but at the same time departs considerably from the normal constancy?

In attempting to solve this question one has first to consider the possible origin of creatinine in the urine. 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. The experiments recorded above with different known dietaries are also in favour of its endogenous origin.

There are, then, four possible sources of the creatinine in the urine, assuming that it is not exogenous, namely:

(*a*) From a special part of the tissue-cell, for creatine is found in the muscular system, and it is possible that it may exist in a complex similar to nucleic acid, and thus similar in origin to the purine substances. These substances, however, do not accumulate in the muscle. Further, nucleic acid and other substances share in the breakdown during autolysis, and if creatine exists in a similar form one would expect it to appear on autolysis. Seemann, Gottlieb and others have stated this to be the case, but their results have been disproved by Mellanby (6), who noted the extraordinary rapidity of the action of bacteria on creatine. Again, no nucleic acid or phosphatide has been found to yield creatine on hydrolysis. This mode of origin therefore appears unlikely, but has not been entirely disproved.

(*b*) Creatinine in the urine may represent a phase in the general protein metabolism, either from—

(i) A general nitrogenous breakdown, or—

(ii) A concentration of the nitrogen of the cell-protein before conversion into urea.

Now, creatine is not an *a*-amino-acid, and further, it contains a methyl group in the molecule. Although we do not know of the existence of a methylated amino-acid amongst the breakdown products of proteins, there is a possibility of such a substance being present. If creatine and creatinine originated in this way it would be quite justifiable to assume that pure protein would increase the excretion of creatinine in the urine. This, however, has been disproved above, and also by other observers.

(*c*) Creatinine represents the end-product of a special group of protein metabolism.

Now since arginine has a composition closely resembling that of creatine, and further, that it exists in the protein molecule, we may have in this substance a possible precursor.

Arginine . . $NH : C(NH_2). NH. (CH_2)_3. CHNH_2. CO_2H.$

Creatine . . $NH : C(NH_2). N(CH_3). CH_2. CO_2H.$

In the oxidation of protein the methyl group may arise by the splitting up of the amino-acid united to arginine. At present, however, we have no proof that arginine is a precursor of creatine or creatinine.

(*d*) Creatinine may represent synthetic activity on the part of the cell. This view receives support from the observations of feeding experiments with glycocyamine (guanidine acetic acid). This substance, when given *per os*, is excreted as creatine, and since it is distinctly poisonous it has to be given in very small quantities. The glycocyamine 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 nocuous compounds have to be synthesised to innocuous compounds. We have, for example, the methylated bases in nitrogen ring compounds, and amongst methylamine derivatives in the body mention may be made of choline and its derivatives, and also adrenalin. 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 (*loc. cit.*) 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 last-mentioned as the most probable view.

The creatinine in the urine, owing to its constancy in the normal healthy individual, is therefore the best measure of tissue metabolism that we have at present. Any very marked variations in this urinary constituent will indicate a disorder of metabolism. Now, in all the diet experiments on the insane the creatinine excretion appears to be subnormal, and, further, shows variations from day to day. These daily variations I have so far only found in mental cases, although a large number of pathological conditions have been investigated. The results seem to point to distinct errors of cellular metabolism in these cases, and as such should suggest lines of treatment.

The Presence of Indican and Indigo Derivatives in the Urine of Insane Persons.

A number of estimations were made on the cases described above by the method of comparison of the blue tint obtained from a definite quantity of urine.

The method, of course, is open to many objections, but it may be of interest to make a few observations on the results. The amount of indigo obtained showed very marked variations from day to day. In some cases a small quantity appeared constantly, but in others marked fluctuations were noted. Further, a rise in the output of this substance was found to be followed by a distinct fall. The test was in every case applied to a mixed twenty-four hours' sample, and in consequence the changes observed may possibly be due to destruction of the indigo derivatives by bacterial agency or otherwise. The whole subject of the method of estimation of these indigo derivatives has been investigated by my friend, Dr. R. V. Stanford, and the results recorded in another part of this Journal. My object in this paper is to draw attention to the possible significance of the presence of indigo derivatives in the urine of the insane person. For many years, it has been usual to regard the presence of indican in the urine as an indication of the extent of putrefactive changes in the intestinal tract. There are, however, reasons for thinking that the indol and indol deriva-

tives arise from processes other than putrefaction. The discovery of tryptophane as a characteristic breakdown product of protein substances by Hopkins and Cole (7), and the further work of Ellinger on the constitution and synthesis of this substance, has led to the view that it may be one, or possibly the only precursor of indol in the body, and indican in the urine. We must not, however, regard this statement as in any way dogmatic, since the possibility of a synthesis of the benzene ring in the body must be considered.

If indol is administered to animals whose urine is free from its derivatives the animals still remain free, but if the indol be inserted directly into the cæcum of the animal then the urine is found to be rich in indican. Now, several protein substances are known which do not yield tryptophane on hydrolysis by acids, or ferments; amongst these gelatine and zein (the protein of maize) may be cited. Underhill (8) has carried out feeding experiments on animals with gelatine and zein, and compared the indican excretion with other dietaries. He came to the conclusion that gelatine and zein diets considerably reduce the quantity of indican excreted, but in the latter case the zein was only imperfectly utilised. The results he considers of importance in relation to the treatment of intestinal troubles, where putrefaction is to be counteracted. In the same paper, he has reviewed the evidence of other observers with regard to the origin of indican in the urine. These results, however, are very doubtful in view of the fact that the methods of estimation of this substance are faulty. When a more accurate method has been devised, then, and then only, will it be possible to decide whether the indican in the urine is derived from putrefactive changes in the intestine, or whether it represents an intermediate product in the metabolism of tryptophane and other benzene derivatives. Indol is very rapidly absorbed by the intestinal mucous membrane, and, furthermore, is a toxic substance, and rapidly eliminated by the kidneys.

The importance of tryptophane in the dietary has been especially emphasised by Willcock and Hopkins. They fed young mice on the protein from maize (zein), and found that the animals died in a few days. Examination of the organs *post-mortem* did not reveal any anatomical lesions, and they consequently considered that a supply of tryptophane was in some way essential to the regulation of cell metabolism.

In those animals where tryptophane was added to the diet the survival period was prolonged, and materially added to their well-being. These observations on animals supply a possible explanation of the low physical and mental condition of some of the inhabitants of Northern Italy, whose chief food supply consists of maize.

These experiments are very striking, and suggest the possibility that tryptophane supplies the active principle of an internal secretion to regulate the cycle of events associated with the life of the individual cell. These facts are, however, difficult to correlate with the results already ascertained with regard to indigo derivatives in the urine of the insane. This is not surprising in view of the irregularities described by Dr. Stanford in the paper already referred to. The object of bringing these points forward is to emphasise the importance of work on this subject and the possible pathological significance of indican in the urine, especially when it occurs in large quantities.

The Sulphur Metabolism, with Especial Reference to Neutral Sulphur.

The phases in the metabolism of sulphur in the body can be best followed by studying the variations of the sulphur compounds in the urine. These amount in the normal person to about 3 grms. *per diem*.

Three distinct types of sulphur combination are found, *viz.*:

(*a*) Sulphur as inorganic sulphates, amounting to from 1 to 2 grms. *per diem*.

(*b*) Sulphur as ethereal sulphates, representing about one-tenth of the total sulphur content of a twenty-four hours' excretion.

(*c*) Unoxidised, or neutral sulphur. This is closely related to the sulphur containing amino-acid cystine, and is present in very small amount in normal urine, namely, 0·2 grm. (calculated as SO_3) *per diem*.

The principal source of sulphur in the body is that contained in the protein fractions of the food-stuffs. Now proteins contain 1 to 1·5 *per cent.* of sulphur, and 100 grm. of protein will yield 16 grm. of nitrogen, with 2·5 grm. of sulphur as SO_3. In view of these facts it would be reasonable to assume that with

variations in the protein content of the diet there would be corresponding variations in the sulphur compounds excreted in the urine. Such differences are noticed in the case of the inorganic sulphates and the ethereal sulphates.

The unoxidised or neutral sulphur in the urine is, however, quite independent of the total metabolism of sulphur compounds in the food-stuffs, and therefore of endogenous origin. In this respect the neutral sulphur is similar to creatinine. The normal figure, *viz.*, 0·2 grm. *per diem*, is found to be constant even with an increased protein diet.

The distribution of the sulphur compounds was ascertained in the urine from Cases 1, 6, 7, 9 and 10 above described, by the methods of analysis adopted by Folin. In all these cases the nature of the psychosis was varying forms of melancholia, and consequently no definite conclusions can be drawn as to the influence of different mental disorders on the sulphur metabolism.

The results, though very scanty, seem of sufficient interest to warrant their mention in this communication.

In all the cases the total sulphur excreted varied between 1·3 and 1·5 grms. Of this sulphur, that combined in inorganic form varied from 1 to 1·15 grms., and the ethereal sulphur amounted to 0·06 to 0·1 grm. The diet in all the experimental periods was comparatively rich in sulphur.

The neutral sulphur excretion in these cases showed, on the other hand, a very distinct departure from the amount usually recognised as normal. In the same patient variations were noticed from day to day corresponding almost exactly to the creatinine excretion. The figures varied from 0·09 to 0·15 in the different cases examined.

A consideration of these observations, though they are far from numerous, emphasises the value of neutral sulphur as an index of metabolism. The amount of sulphur excreted in this form appears to indicate the degree of cellular activity, and when taken in conjunction with other products of cell metabolism, *e.g.*, creatinine, affords valuable information as to the pathological condition of the subject.

Finally, I would refer to the detailed work of Koch (10) on the sulphur compounds of the central nervous system. Many interesting points have been elucidated by this observer, which have a direct bearing on the subject under discussion. He

found that the grey matter of the nervous system contains sulphur mainly in the form of neutral sulphur, whilst the white matter contains sulphur in the form of lipine and neurokeratin combinations. Further, Koch emphasised the importance of this element in the processes of oxidation, which are essential to the functional activity of the nervous system. In dementia præcox a diminution of neutral sulphur and a rise in the inorganic sulphur content of the brain was observed. These changes may produce an interference in the utilisation of oxygen by the brain, and explain some of the symptoms of this, and allied mental disorders.

Such internal changes in the distribution of the element sulphur will undoubtedly be reflected in other parts of the body, and finally exert their influence on the output of sulphur compounds in the urine.

Discussion of Results.

The observations recorded above on the metabolism of insane persons deal mainly with the excretion of three urinary constituents, *viz.*, creatinine, indican, and neutral sulphur. The extensive analyses recorded by Folin, Hoogenhuyze and Verploegh, and also Kauffmann, include figures for many of the metabolic products excreted in the urine of the insane, and the original papers or monographs of these authors should be referred to. The figures given all agree in the apparent absence of any marked variations from the normal individual. The excretions of creatinine, indican, and neutral sulphur, have been considered from a different point of view in the present investigation, and the bearing of these results on metabolism in the insane person has now to be discussed. The three constituents under examination have been regarded largely, if not entirely, as products of cellular activity, and as such bear no direct relation to the constituents of the dietary. By the administration of a known dietary and an analysis of the urine, we may gain some insight into the complex processes involved in the metabolism of the normal individual. Similarly, by adopting the same procedure information is obtained of the disturbances associated with pathological conditions. The complex changes occurring in the tissues, involving hydrolytic breakdown, dehydrolytic synthesis, and the extraction of energy we are unable to

follow in detail. Again, complexes may be formed, and as rapidly decomposed, but the products, instead of leaving the organ, may undergo re-synthesis. The kidney, for example, possibly transforms substances which are useful to the organism, and returns them to the circulation. The retention of chlorides, and also the economising action of the body on phosphoric acid, may be cited as examples of such renal activity. Further, we have evidence of the synthesis of hippuric acid from benzoic acid and glycine by the kidney-cells, and it is highly probable that this is not the only synthesis performed by this organ. The instances thus given serve to emphasise the relation of the organs to one another, and the inter-dependence of separate organs. The chemical correlation existing in the body by the presence of certain specific hormones is now well known, owing to the great advancement in recent years of our knowledge in this field of investigation (11). Before the work on this subject, the organs of the body were regarded as being connected together by the nervous system, but we now know that a more intimate relationship exists. The functions of glandular organs, and in particular of the so-called ductless glands, have been studied both from a physiological, and a pathological point of view. From the physiological side, the results of removal of different glands have led observers to seek for some abnormal chemical product in the blood, or the absence of some definite internal secretion. It does not imply, however, that if the removal of a gland from the body is followed by the accumulation of some chemical substance in the blood, this substance is normally formed by the organ. We may with equal justification say that the substance is formed because the organ is not there to destroy it. The observations of pathological changes in these glands have been mainly concerned with morphological changes. These changes do not necessarily imply that the gland is exerting its normal function, since we know of cases of Addison's disease where the suprarenals have been found to be quite normal. If, therefore, we recognise that the ductless glands have different functions to perform, we shall be in a better position to study their influence on metabolism. So far we have obtained much useful information regarding the influence of the sexual organs, the suprarenals, the thyroid, the pituitary, and the thymus glands upon the nervous system, and upon general metabolism.

Besides these organs I am of the opinion that every cell in the body is connected with the regulation of metabolism, and of secretory activity. Just as we find one cell yielding the activator of a ferment, and another cell the ferment itself, so it is possible that the production of internal secretions is a reciprocal action of the different units of the organism. Unfortunately our knowledge of the metabolism of the nerve-cell and of nervous tissue is very limited, and at present we have no information regarding the final products of their activity. By attacking the problem from the two sides, namely, derangement of function and disease of structure, we may arrive at some definite diagnosis. The results recorded above seem to indicate a disturbance of cellular metabolism. The possibility of increasing metabolism in the insane by administering thyroid gland or thyroid extract has already received considerable attention at the hands of Lewis Bruce (12), and his results are very satisfactory. That the ductless glands play a prominent part in diseases of the nervous system is well known, and the symptoms in certain cases of insanity are in accord with these observations. In a recent communication Barton White and Schölberg (13), have recorded details of a case of dementia with a tumour of the pituitary and suprarenals, and their results lend support to this view.

Conclusions.

(1) The excretion of creatinine in the insane is generally subnormal, and the creatinine coefficient is correspondingly low.

(2) The indigo excreted by the insane appears to be derived from sources other than intestinal putrefaction.

(3) The neutral sulphur excretion is low, and points to a diminished cellular activity.

(4) The results indicate a derangement of cell metabolism in certain forms of insanity, and suggest the administration of glandular extracts known to produce an increase in metabolic changes.

References.

(1) Folin.—*Amer. Journ. of Insanity*, vol. lx, 1904–5, p. 732; *ibid.*, vol. lxi, p. 299.

(2) Hoogenhuyze and Verploegh.—*Zeit. f. physiol. Chem.*, Bd. lvii, 1908, p. 161.
(3) Kauffmann.—*Path. d. Stoffwechsels bei Psychosen*, Jena, Fischer, 1908, 3 vols.
(4) Wallis and Goodall.—*Journal of Mental Science*, April, 1910.
(5) Benedict and Myers.—*Amer. Journ. of Physiol.*, vol. xviii, 1907, p. 377.
(6) Mellanby.—*Journ. of Physiol.*, vol. xxxvi, 1908, p. 447.
(7) Hopkins and Cole.—*Ibid.*, vol. xxvii, 1901, p. 418; vol. xxix, 1903, p. 451.
(8) Underhill.—*Amer. Journ. of Physiol.*, vol. xii, 1905, p. 176.
(9) Willcock and Hopkins.—*Journ. of Physiol.*, vol. xxxv, 1906, p. 88.
(10) Koch.—*Mott's Arch. f. Neurol.*, vol. iii, 1907, p. 331.
(11) Starling.—*Croonian Lectures*, London, 1905.
(12) Lewis Bruce.—*Journal of Mental Science*, January, 1895; *Edin. Hosp. Rep.*, vol iii, 1895; *Journal of Mental Science*, October, 1895; *Edin. Hosp. Rep.*, vol. iv, 1896.
(13) Barton White and Schölberg.—*Journal of Mental Science*, January, 1911.

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Clinical Notes and Cases.

Abnormal Mental States Associated with Malignant Disease.

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A RELATIONSHIP between malignant growths and mental disturbance has been established in a variety of ways. Some writers have approached the subject from a purely general standpoint. Thus Knapp has noted an increased liability to cancer in individuals who show signs of mental instability and has suggested a possible correlation between the two disorders which are both associated with grave metabolic changes. (1) Proceeding on similar lines, Snow instituted an inquiry which revealed a considerable difference of opinion as to the incidence of cancer in the insane, and concluded that its occurrence is relatively rare. (2)

A more important aspect of the subject is that bearing on carcinoma of the brain and the mental symptoms associated therewith. It need only be mentioned here, however, as one