circus movements of the heart. Such changes in impulse formation or conduction probably represent an imbalance between the various substrates and enzymes implicated in the release of energy through glycolysis, which is known to proceed over an intricate chemical pathway involving numerous stages. High concentrations of the effective sulfa drug may alter impulse initiation or propagation within the reticular gray matter of the medulla by disturbing the enzyme-substrate relationship in one or more stages, and in this way modify the development of the unstable chemical-nervous state necessary for "toppling."[5]

It is not clear why the drugs increase the anaerobic survival. It is possible that depression of certain enzymes diminishes the rate of release of anaerobic energy and thus permits continued utilization of a limited amount of available fuel. However, the apparent increase in overall energy liberation would seem to speak for an enhancing action of certain enzyme systems and an increase in utilizable fuel.

Nor is it clear why sulfanilamide and sodium sulfathiazole were effective in producing the results described while equivalent amounts of sodium sulfadiazine and sodium sulfamerazine were not.

Summary. Sulfanilamide and sodium sulfathiazole in non-toxic doses prolonged the survival of the anaerobic activity of the respiratory center of young rats and increased the overall energy release. Neither sodium sulfadiazine nor sodium sulfamerazine acted similarly.

[5] Bard, P., *Macleod's Physiology in Modern Medicine*, C. V. Mosby Co., St. Louis, 1941, p. 555.

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Recovery of Creatinine After Ingestion and After Intravenous Injection in Man.

RAFAEL DOMINGUEZ AND ELIZABETH POMERENE.

From the Department of Pathology, St. Luke's Hospital, Cleveland, Ohio.

It is a known fact that not all the creatinine administered by mouth is excreted in the urine.[1] The amount so excreted is at most 80% of the quantity ingested and is usually less. Although no satisfactory explanation has been offered for this incomplete recovery, creatinine is regarded by many as a waste product of metabolism.[1,2] The possibility that a small amount of creatinine may be destroyed by intestinal bacteria has been mentioned by some investigators.[3] From the fact that creatinine is not stored in the tissues, these same investigators conclude that such creatinine as is not excreted undergoes some transformation in the body.[3] This conclusion, however, is not valid unless it is proved that creatinine is completely absorbed by the intestine. The possibility that part of the ingested creatinine may not be absorbed has received practically no consideration.

We have studied the recovery of administered creatinine in several human subjects. One of these subjects (G.N.B.), as treatment for a chronic ulcerative colitis complicated by hemorrhages, had a permanent ileostomy near the cecum. This operation severed the continuity of the intestine. At the time of the experiments, the fistula was working well, hemorrhages had ceased and the man was in apparent health. Another subject (W.K.) was studied on 3 occasions. At the time of the first 2 experiments he was in good health, but at the time of the last experiment he was greatly emaciated because of a carcinoma of the esophagus. The other subjects were either volunteers in perfect health or ambulatory

[1] Hunter, A., *Physiol. Rev.*, 1922, **2**, 586.

[2] Bloch, K., and Schoenheimer, R., *J. Biol. Chem.*, 1939, **131**, 111.

[3] Beard, H. H., *Creatine and Creatinine Metabolism*, Chemical Publishing Company, Inc., Brooklyn, N.Y., 1943.

TABLE I.
Recovery of Creatinine Administered to Normal Subjects and to One with an Ileal Fistula.

Subject	Sex	Age yr	Creatinine given by mouth (M) or by vein (V) g	Creatinine excreted in stated time: From fistula g	From urine: Total g	From urine: Endogenous* g	From urine: Exogenous g	% recovered
M.B.	F	25	6.0 M		5.[illegible] (23.1 hr)	1.2	3.8	63
S.S.B.	M	35	8.0 M		6.[illegible] (25.2 '')	1.9	4.8	60
A.P.	F	27	8.0 M		6.[illegible] (23.6 '')	1.7	4.9	61
B.G.	M	31	10.0 M		9.[illegible] (24.4 '')	1.9	7.3	73
W.K.	M	55	12.0 M		8.[illegible] (24.5 '')	1.0†	7.1	59
		50	15.0 M		9.[illegible] (24.5 '')	1.7	7.5	50
			4.8 V		6.[illegible] (25.6 '')	1.7	4.5	94
V.R.	F	26	9.5 V		11.[illegible] (27.9 '')	1.7	10.0	105
			20.7 V		22.[illegible] (26.4 '')	1.6	20.4	98
			23.3 V		22.7 (27.7 '')	1.7	21.0	90
H.G.	M	56	12.6 V		13.[illegible] (27.7 '')	1.6	11.8	94
J.J.	M	53	16.2 V		17.[illegible] (24.1 '')	1.6	15.4	95
G.N.B.§	M	24	4.0 M	1.0 (6.4 hr)	2.4 (6.4 '')	.38	2.0	94‡
			8.0 M	1.9 (10.0 '')	8.[illegible] (24.0 '')	1.4	6.6	106

* The rates of the endogenous creatinine output of these subjects, in the same order of the table, are: 50, 74, 73, 78, 68, 61, 59, 66 and 60 mg/hr. The mean of these rates is 65.4 and the standard error of the mean is 2.94. Three times this standard error represents 13.4% of the mean. We have verified that a variation of this magnitude in the outputs of endogenous creatinine in these experiments changes by 3.8 the average % recovered after ingestion and by 2.2 the average % recovered after intravenous injection.

† At the time of this experiment on W.K. the excretion of endogenous creatinine had fallen to 43 mg per hr. This subject was then suffering from a carcinoma of the esophagus and was considerably emaciated.

‡ We do not have a 24-hr collection in this experiment because the subject failed to follow instructions. An estimate of the amount of exogenous creatinine recovered in 24 hr can be obtained as follows. The amount recovered in about 6 hr (from 6.0 to 6.3 hr) in the other ingestion experiments was, in the order of the table, 2.9, 3.9, 3.3, 5.3, 4.9, and 5.5 g and in the second experiment on G.N.B., 4.3 g. The ratio of each of these figures to the corresponding exogenous amount excreted in about 24 hr (column headed ''Exogenous'') is, in the same order, .763, .812, .67[illegible], .726, .690, .733, and .652. The mean of these ratios is 0.721. Applying this mean to the data of the first experiment on G.N.B., we get for the amount recovered in 24 hr, 2.0/.721 = 2.77 g. This amount added to the amount from the fistula gives 3.77 g, or 94% of the quantity ingested. This is the % shown in the table.

§ These experiments could not be repeated because this subject developed a fatal subacute bacterial endocarditis.

patients with minor ailments. None had any evidence of renal disease.

The endogenous excretion of creatinine was examined at irregular intervals of time on different days and in different parts of the day and night, and the average hourly rate computed. The creatinine concentration in the urine was determined by the method of Folin.[4] During the control periods and during the experiments, the subjects were up and about in the laboratory and followed their customary diets.

The age, sex, quantity of creatinine given, mode of administration and amount excreted in the urine are shown in Table I. The rates of endogenous creatinine excretion are given in a footnote of Table I. For the estimation of the endogenous amounts excreted during the experiments these rates were treated as constants.

Corroborating previous workers, we found that the amount of creatinine recovered in the urine within 24 hours after ingestion varies between 50 and 73% of the quantity ingested (Table I). In our other experiments in which the collection of urine was not carried out for 24 hours, the amount recovered in 24 hours was calculated by fitting exponentials to the latter part of the data and integrating. In 13 of the latter experiments in 10 subjects, the amount actually recovered in 6.5 hours was 44% and the average 24-hour total calculated by integration was almost 60% of the quantity

[4] Folin, O., *J. Biol. Chem.*, 1914, **17**, 469.

ingested. In 6 other experiments in one subject,[5] the average amount actually recovered in 8.1 hours was 60% and the average 24-hour total calculated, 70% of the quantity ingested.

When creatinine was injected intravenously the results were entirely different. On an average, 96% of the quantity injected was recovered in about 24 hours (Table I). Incidentally, this percentage in human experiments is about equal to the percentage obtained after intravenous injection in the dog.[6] In intravenous experiments, therefore, there is no evidence of creatinine transformation.

In order to ascertain whether the smaller percentage of the creatinine excreted in oral experiments was the result of incomplete absorption, we gave creatinine to the subject with the fistula (G.N.B.) and determined both the amount of creatinine collected from the fistula and the amount excreted in the urine. The experiments were carried out after we had convinced ourselves that creatinine added to the material from the fistula could be recovered quantitatively by the method of Folin.[4] Blank analysis of this material gave a color development equivalent to a creatinine concentration of 2 to 7 mg per 100 cc. Expressed in terms of creatinine, the rate at which these chromogenic substances were collected from the fistula was, on an average, 5 mg per hour. This small amount was subtracted from the total amount collected in actual experiment.

The results of 2 experiments after ingestion of 4 and 8 g, respectively, are given in Table I (subject G.N.B.). Creatinine began to appear in the fluid from the fistula during the second hour after ingestion and continued to appear from the second to the fifth hour, with a peak during the third hour. The total amount of creatinine collected from the fistula represents 24 to 25% of the quantity ingested (Table I).

In oral experiments, therefore, creatinine is not completely absorbed by the small intestine. That it is probably not absorbed by the colon follows from the fact that, although in subject G.N.B. the ingested creatinine could not reach the colon, this subject excreted in the urine 81% of the quantity ingested, an amount of creatinine which is as large as the largest to be expected in normal subjects.

Within the limits of experimental error, the amount of creatinine excreted in the urine was equal to the difference between the quantity ingested and the amount collected from the fistula. Hence, the amount excreted in the urine represents the amount actually absorbed. There is no need for assuming a transformation of creatinine to account for the whole quantity ingested.

The recovery of creatinine after administration by routes other than oral and intravenous deserves re-investigation.

Summary and Conclusions. In a patient with an ileal fistula it was shown that about 25% of ingested creatinine was expelled unabsorbed from the fistula. The amount of creatinine excreted in the urine was equal to the amount absorbed. The evidence suggests that, in oral experiments, no creatinine is absorbed by the large intestine. When injected intravenously, creatinine is virtually all excreted in the urine. These results are at variance with the hypothesis of creatinine transformation in the human body.

[5] Dominguez, R., and Pomerene, E., *J. Biol. Chem.*, 1934, **104**, 449.

[6] Dominguez, R., Goldblatt, H., and Pomerene, E., *Am. J. Physiol.*, 1935, **114**, 240.