The Correlation between Excess Calories and Excess Urinary Nitrogen in the Specific Dynamic Action of Protein in Animals

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Notes:

nor 3 could be fitted so closely to this type of equation; nor could the average of the three experiments. For these reasons we prefer not to emphasize the fit in the one case.

Summary.—When the rate of entrance of guanidine is plotted against the external concentration of guanidine, a curve which is concave to the horizontal axis is obtained. This is explainable on the assumption that the entrance is preceded by a reversible action between the penetrating base and one or more acidic constituents of the protoplasm.

[1] Osterhout, W. J. V., *Proc. Nat. Acad. Sci.*, **21**, 127 (1935).

[2] Jacques, A. G., and Osterhout, W. J. V., *Proc. Soc. Exptl. Biol. Med.*, **31**, 1121 (1933–34).

[3] Cooper, W. C., Jr., Dorcas, M. J., and Osterhout, W. J. V., *Jour. Gen. Physiol.*, **12**, 427 (1928–29).

[4] Davis, T. L., and Elderfield, R. C., *Jour. Am. Chem. Soc.*, **54**, 1499 (1932).

[5] Marston, H. R., *Austral. Jour. Exp. Biol. and Med. Sci.*, **1**, 99 (1924); **2**, 57 (1925).

[6] Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry*, Baltimore, Williams and Wilkins, **2**, 23 (1932).

[7] Cooper, W. C., Jr., and Osterhout, W. J. V., *Jour. Gen. Physiol.*, **14**, 117 (1930–31).

[8] Teorell, T., *Biochem. Zeit.*, **248**, 246 (1932).

[9] Nessler's reagent according to Folin and Wu (Folin, O., and Wu, H., *Jour. Biol. Chem.*, **38**, 81 (1919)). Two drops of gum ghatti was added to each 50 cc. of the mixture before the addition of the Nessler reagent according to the advice of Folin and Svedberg (Folin, O., and Svedberg, A., *Jour. Biol. Chem.*, **88**, 77 (1930)). Urbach (Urbach, C., *Mikrochemie*, **11**, 37 (1932)) has shown that a linear relationship between the extended coefficient and concentration with the purple filter of the Zeiss photometer can be obtained under the best conditions. In our work the calibration curve was not quite linear, but had so little curvature that no serious error was introduced.

THE CORRELATION BETWEEN EXCESS CALORIES AND EXCESS URINARY NITROGEN IN THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN ANIMALS

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Several years ago it was pointed out that after the ingestion of proteins or amino acids a definite correlation existed between the calories and urinary nitrogen in excess of the basal.[1] The data used were those obtained by Rapport,[2] Weiss and Rapport[3] and Rapport and Beard.[4] Aubel and Schaeffer[5] were of the opinion that this correlation bears no relation to the specific dynamic action of protein and amino acids. Their main reason was that the curves of extra calories and extra nitrogen are not

synchronous; that the curve of caloric metabolism returns to the basal level before that of the nitrogen. They maintained that no correlation is to be found between excess calories and excess nitrogen in any one experiment; and cited data from the experiments of Rapport and Beard[4] which they maintained show that very large differences in specific dynamic action of individual amino acids occur which bear no relation to the extra nitrogen excreted.

This criticism is rooted in the refusal of Aubel and Schaeffer, in accord with the views of the Lusk School, to ascribe any significant fraction of the specific dynamic action to the heat evolved in the metabolism and excretion of the nitrogen. Yet both Lusk and Aubel agreed that the specific dynamic action of an amino acid is to be correlated with the amount metabolized. The most obvious measure of this quantity is the urinary nitrogen. Because the nitrogen excretion lags behind the increase in metabolism Lusk preferred to use the extra glucose excreted in a phlorhizinized animal. The choice between these two indices of the quantity of amino acid metabolized rests on the accuracy with which they may represent this quantity, and it is quite immaterial if there is any increased expenditure of energy in the metabolism of the nitrogen or not.

The use of the extra glucose stands and falls on the assumption that the rate of metabolism is the same in the phlorhizinized and normal animal. Examination of the data on nitrogen excretion in the experiments of Lusk[6] and of Csonka[7] which form the basis of Lusk's method show that the rate of nitrogen metabolism was not the same in the two conditions. Furthermore the increase in metabolism lagged behind the glucose excretion. This method breaks down entirely with ketogenic amino acids such as phenylalanine and tyrosine which yield no glucose and yet exert a larger specific dynamic action than glucose forming amino acids.

The nitrogen excretion is obviously a more direct index. The difficulty that the nitrogen excretion lags behind the increase in metabolism can be circumvented by giving most weight to the data during the approximate steady state when the nitrogen is excreted as fast as it is metabolized. It was for this reason that the increase in heat production (or oxygen consumption) and nitrogen excretion during the first four to six hours were used, and indeed could be used, to show the correlation between increase in calories and nitrogen excretion. The curves of energy metabolism and nitrogen excretion are not widely divergent; they cover nearly the same area (with appropriate units) and the quantity of nitrogen whose excretion is really delayed represents a small fraction of the total quantity excreted by the time the descending arm of the nitrogen curve begins to flatten out. It appears to have been tacitly assumed by Lusk and by Aubel that all of the ingested nitrogen, being exogenous, is quickly metabolized. This is not the case. In man in nitrogen balance at a moderate

TABLE 1

The Steady State between Excess Caloric Metabolism and Urinary Nitrogen Excretion after the Ingestion of Protein

HOURS	EXCESS CALORIES PER CENT OF BASAL	EXCESS NITROGEN PER CENT OF BASAL	EXCESS CALORIES EXCESS NITROGEN % OF BASAL × 100	OBSERVER
1	61	128	48	
2	87	385	23	
3	85	465	18	
4	79	495	16	
5	82	525	16	
6	98	505	19	
7	79	500	16	
8	89	500	17	Dog, 1200 gm. meat.
9	83	500	16	Williams, Riche and
10	71	450	16	Lusk[9]
11	69	450	15	
12	61	450	14	
13	65	487	13	
14	31	400	8	
15	38	400	10	
16	42	304	14	
17	39	238	16	
18	17	194	9	
19	23	141	16	
20	12	100	12	
1	11.7	85	13	
2	21.5	190	11	
3	26.5	255	9	
4	19.8	330	6	Man, 69 gm. gelatine.
5	19.6	315	6	Borsook and Keigh-
6	9.6	290	3	ley[10]
7	11.8	214	6	
8	9.6	190	5	
9	11.6	206	6	
10	13.6	170	8	
1	17.5	0	∞	
2	16.9	37	46	
3	27.6	76	36	Man, 630 gm. meat.
4	16.3	85	19	Borsook and Keigh-
5	17.8	130	14	ley[10]
6	23.8	137	17	
7	28.4	180	16	
8	23.0	142	17	

level of nitrogen intake the urinary nitrogen excreted in 24 hours is not more than fifty per cent of exogenous origin.[8]

Table 1 contains a summary of one experiment of Williams, Riche and Lusk[9] and of two typical examples of our own[10] showing the attainment of a steady relation between increase in energy metabolism and urinary nitrogen excretion. This steady state in our experiments appeared in most cases after the fourth hour.

The same phenomenon is shown in another form in table 2. This form permits (on account of space limitations) the presentation of more experiments than table 1. The ratio of excess calories to excess nitrogen is, except where a very large quantity of meat was ingested, nearly the same over the first four hours as over a much longer period. Even though the

TABLE 2

RELATION BETWEEN EXCESS CALORIES AND URINARY NITROGEN IN EXCESS OF THE
BASAL AFTER THE INGESTION OF PROTEIN

SUBJECT OF EXPERIMENT; SUBSTANCE AND QUANTITY INGESTED	OBSERVER	TOTAL PERIOD OF OBSERVATION, HRS.	EXCESS CALORIES EXCESS NITROGEN FOR	
			TOTAL PERIOD	FIRST FOUR HRS.
Dog, 1200 gm. meat	Williams, Riche & Lusk[9]	20	11.0	10
Dog, 700 gm. meat	Williams, Riche & Lusk[9]	7	13.0	13
Man, 69 gm. gelatine	Borsook & Keighley[10]	10	31	30
Man, 69 gm. gelatine	Borsook & Keighley[10]	10	18	16
Man, 69 gm. gelatine	Borsook & Keighley[10]	10	18	21
Man, 69 gm. gelatine	Borsook & Keighley[10]	10	20	24
Man, 32.8 gm. gelatine	Borsook & Keighley[10]	10	28	31
Man, 315 gm. meat	Borsook & Keighley[10]	10	38	38
Man, 315 gm. meat	Borsook & Keighley[10]	10	18	25
Man, 630 gm. meat	Borsook & Keighley[10]	10	21	45
Man, 150 gm. meat	Borsook & Keighley[10]	10	29	21
Man, 315 gm. meat	Borsook & Keighley[10]	10	25	27
Man, 450 gm. meat	Borsook & Keighley[10]	10	28	38

nitrogen excretion lags behind the energy metabolism in the first two hours it represents only a small quantity of nitrogen. Hence the ratio is not seriously disturbed by this lag.

Data suitable for such a compilation as in tables 1 and 2 is limited because relatively few experiments have been reported which were carried out over a sufficiently long period to make such comparisons possible; in even fewer cases are the hourly urinary nitrogen as well as metabolic data given.

Aubel and Schaeffer, in criticizing the use of four to six hour averages in our original demonstration of the correlation between excess calories and excess nitrogen apparently attach more weight to the hourly data in individual experiments. Our reason for preferring averages to indi-

vidual hourly values was that the hour to hour caloric values are as irregular as the urinary nitrogen excretion. It is obvious, however, that if the averages from different experiments group themselves about a smooth curve the individual values from which these averages were obtained will also do so. It was pointed out that the deviations of any individual value from the smooth curve are within the extremes of variation of the basal metabolism values.

It is this irregularity in the metabolic data that makes it extremely difficult in the terminal stages of an experiment to determine the increase in metabolism to be attributed solely to increased renal work. At this time the increased excretion of nitrogen is not, expressed in absolute quantities, greatly in excess of the basal. Any possible increases in metabolism are well within the variations in the basal metabolism values.

Aubel and Schaeffer referred to the observations of Gigon,[11] and stated that the energy metabolism had returned to the basal level long before the nitrogen excretion. Examination of Gigon's data shows that this is

TABLE 3

EXCESS CALORIES AND URINARY NITROGEN AFTER THE INGESTION OF VARYING AMOUNTS
OF CASEIN[11]

AMOUNT OF CASEIN INGESTED, GM.	PERIOD OF OBSERVATION, HRS.	AMOUNT OF CASEIN N RECOVERED IN URINE, PER CENT	EXCESS CALORIES, CAL.	EXCESS NITROGEN, GM.	EXCESS CALORIES / EXCESS NITROGEN
50 (6.4 g. N)	3.5	17	19	1.1	17
100 (12.8 g. N)	5.75	30	53	3.8	14
150 (19.2 g. N)	7	30	118	5.7	21
200 (25.6 g. N)	10	35	171	9.0	19

not the case. In the experiment where 50 gm. of casein were ingested, which Aubel and Schaeffer selected for citation, the nitrogen excretion from the fifth to the tenth hours was below the basal, 2.5 gm. as against 2.95 gm. Table 3 is a summary of the data in Gigon's experiments, with varying amounts of casein. The ratio of excess calories to excess nitrogen is not widely different through a fourfold variation in the amount of protein ingested, and a threefold difference in the period of observation. These data confirm the usefulness of the correlation of excess calories to excess nitrogen.

Aubel and Schaeffer referred to the data of Rapport and Beard which they maintained showed no relation between the specific dynamic action and the excretion of nitrogen. The data of Rapport and Beard are summarized in table 4. In interpreting these data the varying mode of metabolism of the individual amino acids must be taken into account. The specific dynamic action is a composite of two quotas, one nearly constant representing the metabolism and excretion of the nitrogen, and another

variable quota, the metabolism of the deaminized residues.[8] When nitrogen is released by hydrolytic processes the energy change will be less than in the case of oxidative deamination. In the case of arginine, urea arises directly by hydrolysis; hence the increased oxygen consumption attending deamination and urea synthesis will not occur here. With histidine ammonia arises by splitting of the imidazole ring; the energy of oxidative deamination again will be missing. The metabolism of the deaminized residues in the case of tyrosine and phenylalanine, splitting of the benzene ring, etc., will lead to a greater specific dynamic action than with alanine or glycine. The same applies to glutamic and aspartic

TABLE 4

RELATION BETWEEN EXCESS NITROGEN AND EXCESS CALORIES AFTER THE ADMINISTRA-
TION OF DIFFERENT AMINO ACIDS TO DOGS[4]

AMINO ACID KIND	AMOUNT, GM.	NITROGEN EXCRETION IN EXCESS OF BASAL PER HOUR, GM.	CALCULATED INCREASE IN METABOLISM DUE TO WORK OF EXCRETION OF N, 5 CAL./GM. OF N CALORIES	OBSERVED INCREASE IN METABOLISM CALORIES	FRACTION OF N ADMINISTERED RECOVERED IN URINE, PER CENT
Glutamic acid	10	0.048	0.24	1.55	16
	10	0.044	0.22	1.22	16
	10	0.027	0.14	1.36	16
	20	0.033	0.17	1.32	6
Aspartic acid	10	0.032	0.16	1.09	11
	10	0.028	0.14	0.93	11
	20	0.043	0.21	1.17	6
Histidine dichloride	5	0.034	0.17	0.27	15
Cystine	10	0.024	0.12	1.23	7
Valine	10	0.11	0.55	0.47	21
Tyrosine	10	0.037	0.19	2.7	19
	10	0.033	0.16	2.1	17
Phenylalanine	10	0.10	0.51	5.0	47
	8.5	0.11	0.57	4.6	62
Arginine carbonate	5	0.038	0.19	0.65	12

acids. The data show that though Rapport and Beard, and Aubel and Schaeffer assigned no specific dynamic action to histidine and valine, the increases in metabolism observed were in every case sufficient to account for the cost of excreting the nitrogen; and in every case except valine the increased metabolism was much greater than this figure. Until more is known of the intermediary metabolism of valine it is unprofitable to speculate on the small increase in metabolism observed. Small as it was, this increase was sufficient for the excretion of the nitrogen. Further, in the case of valine, the observations were terminated at a time (the third hour) when the increase in metabolism was at its peak for the period, 0.99 calories per hour above the basal. It seems that more extended observa-

tions may have given a value for the ratio of excess calories to excess nitrogen more in accord with those of other amino acids.

Summary.—1. When protein is ingested a steady state is attained after four hours between the increase in energy metabolism and urinary nitrogen.

2. The ratio of total excess calories to total excess nitrogen is nearly the same after four hours as after ten to twenty hours.

3. These results confirm the usefulness and significance of the correlation previously demonstrated between excess calories and excess nitrogen in the specific dynamic action of protein in animals.

4. Analysis of the data upon which Aubel and Schaeffer based their criticism of the significance of this correlation shows that this criticism is invalid.

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[3] Weiss, R., and Rapport, D., *Ibid.*, 60, 513 (1924).

[4] Rapport, D., and Beard, H. H., *Ibid.*, 73, 299 (1927); 80, 413 (1928).

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RELATION OF THE REGULATORY MECHANISM OF RESPIRATION TO CLINICAL DYSPNEA

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According to classical theory, respiration is regulated by impulses which are automatically generated within and which emanate from the "respiratory center" situated in the medulla. Recent work (Lumsden,[1] Hess,[2] Heymans,[3] Gesell[4]) has shown that this concept must be broadened, and that the regulation of respiration is a mechanism of wide extent, mediated through many "centers," in brain, spinal cord, carotid sinuses, sympathetic and para-sympathetic nervous systems, as well as in the "respiratory center" in the medulla. Both somatic and vegetative periph-