The Effects of Diet and Stool Composition on the Net External Acid Balance of Normal Subjects *

EDWARD J. LENNON, JACOB LEMANN, JR.,† AND JOHN R. LITZOW ‡

(*From the Department of Internal Medicine and the Clinical Research Center, Marquette University School of Medicine and Milwaukee County Hospital, Milwaukee, Wisc.*)

In 1961, Relman, Lennon, and Lemann (1) reported an experimental technique that permitted independent measurement of the net production of fixed endogenous acid. When compared with the simultaneous rate of renal acid excretion, external acid balance could be calculated. This technique depended upon the use of a liquid formula diet prepared so that it contained no potential sources of alkali. The only possible sources of fixed acid production in subjects eating the diet were from the oxidation of organic sulfur in the diet to inorganic sulfate and from the urinary losses of organic acid anions generated as free organic acids during the combustion of neutral foodstuffs. Hence, production of fixed endogenous acid could be measured as the sum of urinary inorganic sulfate and organic acid salts.

Although this diet greatly simplified the measurement of endogenous production of fixed acid, its limited palatability and low calcium content were unsuitable for the prolonged studies that we wished to carry out to examine the relationship between acid balance and calcium balance.

The present studies were undertaken to see if a more general approach to the measurement of endogenous acid production could be devised that would be applicable to whole food diets. Three different types of diets were used, two consisting of whole foods and one a new liquid formula diet, each of which contained different amounts of potential alkali. With these diets, no correlation between the sum of urinary inorganic sulfate plus organic acid salts and renal acid excretion was found. However, when gains of potential alkali from the diet and losses of potential alkali in the stool were included in the calculation of total effective acid production, good correlation between acid production and renal acid excretion was found.

Methods

Sixteen metabolic balance studies were carried out on 14 healthy men in the Clinical Research Center, Marquette University School of Medicine.

Each subject's diet was constant throughout his balance study. Three general types of diets were used. Two were whole food diets, and one was a liquid formula. The type A whole food diets were designed to contain more inorganic cations than inorganic anions, as in average American diets. The type B diets were designed to provide more inorganic anions than inorganic cations through unusual intakes of phosphorus in egg yolk. Representative sample menus of type A and type B diets are shown in Table I. In the liquid formula diet used, a purified soy phosphoprotein [1] served as the sole nitrogen source, and inorganic cations and anions were approximately equal. The protein contained very small quantities of inorganic electrolytes except for phosphorus, as shown in Table II. As previously described (2), we added equimolar quantities of $Ca(OH)_2$ and $Mg(OH)_2$ in amounts theoretically sufficient to titrate all of the protein phosphorus as phosphate to pH 7.4, arbitrarily assuming that no other cations were present in the protein.

Each subject was allowed 3 to 6 days to adjust to his constant diet before observations began. Thereafter, each metabolic period lasted 6 days. The number of subjects studied on each type of diet and the number of metabolic periods observed for each subjects were as follows: whole food type A, 7 subjects, 2 to 4 periods each; whole food type B, 2 subjects for 2 periods each; and the liquid formula diet, 7 subjects for 1 period each.

Collection of specimens. Venous blood for measurement of carbon dioxide content and electrolytes was drawn without stasis into syringes rinsed with mineral

[1] Edi-Pro-A, Ralston Purina Co., St. Louis, Mo.

Type A		Type B	
Calories	2,620	Calories	2,210
Protein	78 g	Protein	79 g
Fat	140 g	Fat	118 g
Carbohydrate	262 g	Carbohydrate	208 g
Breakfast	*g*		*g*
Orange juice	100	Grape juice	50
Cereal*	15	Cereal*	20
Egg (whole)	50	Egg (yolk)	125
Toast*	50	Toast*	25
Butter*	15	Butter*	15
Milk	100	Milk	100
Coffee	200	Coffee	100
Sugar	15	Sugar	15
Lunch			
Meat (beef)	90	Meat (turkey)	90
Potato or substitute	80	Noodles	100
Vegetable*	80	Vegetable*	80
Fruit	100	Fruit	100
Bread*	25	Bread*	25
Butter*	20	Butter*	20
Milk	240	Milk	10
Coffee	200	Coffee	100
Sugar	5	Sugar	5
Supper			
Meat (turkey)	60	Meat (beef)	60
Potato or substitute	80	Rice	100
Vegetable*	80	Vegetable*	70
Fruit	100	Fruit	100
Bread*	25	Bread*	25
Butter*	20	Butter*	20
Milk	240	Milk	10
Coffee	200	Coffee	100
Sugar	5	Sugar	5
9 p.m. snack			
Bread*	25	Bread*	25
Butter*	10	Butter*	10
Fruit	100	Milk	80

* Salt-free; constant daily quantities of dry NaCl were provided.

oil. At the same time, specimens of whole blood for estimation of pH were drawn into syringes rinsed with heparin and 1 N sodium fluoride. Twenty-four–hour urine specimens were collected in bottles containing thymol and phenyl mercuric nitrate and a layer of mineral oil and refrigerated during collection. Carmine was administered with breakfast on the morning of the first day of each balance period; it served as a marker to separate stool collections for each period. Stools were collected in stainless steel cans and frozen immediately. All stools for each period were quantitatively transferred to a large blender, brought to a measured volume with distilled water, thoroughly homogenized, and analyzed in triplicate. Whole foods were weighed into a large blender, brought to a measured volume with distilled water, and thoroughly homogenized. Duplicate trays of each subject's

constant diet were analyzed on 4 to 6 days of each study. The coefficient of variation for the determination of each diet constituent averaged the following: Na $\pm$ 3.6%, K $\pm$ 3.3%, Ca $\pm$ 4.1%, Mg $\pm$ 5.2%, Cl $\pm$ 3.4%, and P $\pm$ 3.5%. Samples of the diet and stool homogenates were frozen until analysis.

Analytical methods. Blood and urine pH were estimated at 37° C with a Radiometer pH meter and Astrup capillary glass electrode. Total CO_2 content of serum and urine was measured manometrically with either the Van Slyke-Neill apparatus or the Natelson microgasometer. Chloride in serum, urine, and nitric acid digests of diet and stool homogenates was measured with the Cotlove apparatus. Sodium and potassium in serum, urine, and nitric acid digests of diet and stool homogenates were determined with the Autoanalyzer flame spectrophotometer. Phosphorus in serum, urine, and samples of diet and stool homogenate digested with sulfuric acid and hydrogen peroxide was determined with the Autoanalyzer. Creatinine in serum and urine and ammonium in urine were also measured with the Autoanalyzer. Calcium and magnesium in serum, urine, and samples of diet and stool homogenates ashed at 600° C for 8 hours were determined by atomic absorption spectrophotometry. Urinary inorganic sulfate was measured gravimetrically as barium sulfate.

Organic acid salts in urine were measured by the Van Slyke and Palmer method (3) with the following modifications. Phosphate was removed by mechanical shaking for 30 minutes with added $Ca(OH)_2$ powder, and the suspension was filtered. Portions of the filtrate were brought to pH 2.7 at 37° C with approximately 1 N HCl, with a Radiometer pH meter and automatic titrator. The solution was then titrated with 0.1 N NaOH to the original pH of the urine to estimate organic acid salts. The organic acid salt measurement was corrected for titration of creatinine. In previous studies of acid-base balance (1, 2) all organic acids titratable between pH 2.7 and 7.4 (corrected for creatinine) were considered to represent acid production. This was required because urinary titratable acid was measured by direct titration and included as acid excretion those organic acids titrated between urine pH and pH 7.4. Organic acids produced in the body from neutral foods and excreted as the acid in urine have no net effect on acid balance. In the present studies the calculation of titratable acid (see below) does not include the organic acids; therefore, only the organic acid salts are measured as acid production.

Electrolyte		
Na	1.5	*mEq*
K	2.3	*mEq*
Ca	3.0	*mEq*
Mg	0.5	*mEq*
Cl	2.3	*mEq*
P	26	*mmoles*

Calculations. Bicarbonate and carbon dioxide pressure (Pco_2) in serum and urine were calculated from total CO_2 content and pH.

Titratable acid (TA) was calculated because varying concentrations of calcium and ammonium in the urine may lead to spurious overestimation of TA by direct titration (4). Urinary excretion of titratable acid with phosphate (TA_{PO_4}) was calculated from urinary phosphate and urine pH, assuming $pk_s' = 6.8$ for phosphate. Urinary excretion of titratable acid with creatinine ($TA_{creatinine}$) was calculated from urinary creatinine and urine pH, with $pk' = 4.92$ for creatinine. Net acid excretion in the urine was then calculated as: $(TA_{PO_4} + TA_{creatinine} + NH_4^+) - HCO_3^-$.

Net production of fixed endogenous acid was calculated as the sum of urinary inorganic sulfate + organic acid salts — the difference between diet and stool unmeasured anion content. The unmeasured anion content of diet and stool was taken as $(Na^+ + K^+ + Ca^{++} + Mg^{++}) - [Cl^- + 1.8\ P\ (mmoles)]$. (See Discussion.)

Results

We studied all subjects when their serum bicarbonate concentration and blood pH were normal and stable and body weight was steady.

Table III presents the mean daily urinary inorganic sulfate plus organic acid salt excretion for the subjects eating each type of experimental diet and compares this with the mean urinary net acid excretion. If the differences between urinary inorganic sulfate and organic acid salts minus net acid excretion had been taken as the actual acid balance, shown in the lowest line of Table III as "Δ," small but significant differences from zero would have been found in the subjects fed the liquid diet. Furthermore, on whole food diets of usual composition (type A), an apparent positive acid balance of + 27 ± 9 mEq per day would have been found, whereas the two subjects eating an unusual diet (type B) would have had an apparent negative acid balance of − 20 and − 21 mEq per day. Since the subjects had normal stable serum bicarbonate levels and were in a steady state, an actual acid balance of zero would be expected.

The effect of diet composition on acid production is considered in Table IV, which presents the average daily intakes of measured inorganic constituents for the subjects eating each type of diet. The type A diets had the highest inorganic cation content because of a higher content of potassium and calcium. The type B diets had the highest inorganic anion content because of a higher phosphorus content. If the phosphorus in each diet is assigned a valence of 1.8 (see Discussion), the difference between measured inorganic cations and anions can be taken as an estimate of excess combustible anions, and hence potential alkali in each diet. Thus, as shown in the bottom line of Table IV, the liquid formula contained a small amount of potential alkali,[2] whereas type A diets contained a large quantity of potential alkali. Type B diets, on the other hand, appeared to contain a small amount of organic cation, which would yield acid if combusted.

Table V shows the average stool weight and composition for all subjects. In each group, the stool content of sodium and chloride was close to zero, which indicated that the stools were normally formed. In general, the stools were of similar composition. The stool calcium and magnesium content appeared to vary with dietary intake (Ta-

TABLE III

Urinary sulfate plus organic acid salts compared with urinary net acid excretion

Type of diet		Liquid formula	Whole food, type A	Whole food, type B
Number of studies		7	7	2
Urinary SO_4^-+organic acid salts	mEq/day	64	74	81
Urinary net acid excretion	mEq/day	70	47	102
Δ	mEq/day	−6±5*	+27±9*	−21
p†	mEq/day	<0.025	<0.001	

* Mean ± standard deviation.
† Probability that the mean does not differ from zero.

TABLE IV

Average daily diet composition

Type of diet		Liquid formula	Whole food, type A	Whole food, type B
Number of studies		7	7	2
Na	mEq	123	152	154
K	mEq	60	75	40
Ca	mEq	23	42	27
Mg	mEq	20	22	20
Sum of cations	mEq	226	291	241
Cl	mEq	172	149	155
P	mmoles	26	39	53
P ×1.8	mEq	46	71	95
Sum of anions	mEq	218	220	250
Cations minus anions	mEq	+8±7*	+71±20*	−9

* Mean ±standard deviation.

[2] This occurred because the inorganic cation in the protein had been neglected in calculating the amount of $Ca(OH)_2$ and $Mg(OH)_2$ required to neutralize the protein phosphate groups.

TABLE V

Average daily stool composition

Type of diet		Liquid formula	Whole food, type A	Whole food, type B
Number of studies		7	7	2
Weight	*g*	58	58	82
Na	*mEq*	1	1	2
K	*mEq*	5	7	12
Ca	*mEq*	22	37	26
Mg	*mEq*	13	13	11
Sum of cations	*mEq*	41	58	51
Cl	*mEq*	0	1	1
P	*mmoles*	14	12	15
P ×1.8	*mEq*	25	21	27
Sum of anions	*mEq*	25	22	28
Cations minus anions	*mEq*	+16 ±9*	+36 ±20*	+23

* Mean ±standard deviation.

ble IV), whereas stool phosphorus appeared to be relatively independent of dietary intake and approximately equal in all groups. The stool potassium content was higher in the subjects eating type B diets, who had somewhat bulkier stools. In the bottom line of Table V the differences between measured cations and anions in the three diets are shown; the valence of phosphorus in the feces was assumed to be 1.8. The stool contained unmeasured anion in all studies, even when the diet contained none.

Table VI presents the constituents of acid production, renal acid excretion, and the mean daily

acid balance for each subject when the apparent balance of combustible anions (diet minus stool unmeasured anions) is included in the calculation of total acid production. The acid balance calculated in this way for the subjects on the liquid diet averaged + 2 ± 1 mEq per day; this was not statistically significant from zero balance (p > 0.50). Similarly, the acid balances of subjects on type A diets averaged − 8 ± 13 mEq per day when diet and stool unmeasured anions were taken into consideration. This also was not significantly different from zero balance (p > 0.10).

As shown in the last column of Table VI the mean acid balance calculated in this way for all subjects was − 1 ± 12 mEq per day, which is not significantly different from zero (p > 0.70). It is clear that the correlation between acid production and renal acid excretion is less precise on whole food diets than on the liquid formula, even if gain or loss of combustible anion in the calculation of net acid production is taken into account.

Figure 1 shows the relationship between renal acid excretion and acid production calculated in three ways for the present studies. At the top, acid excretion is compared with the sum of urinary inorganic sulfate and organic acid salts for all subjects. The correlation of this estimate of acid pro-

TABLE VI

The parameters of acid balance

	Patient	Diet combustible anion	Stool combustible anion	Urinary SO₄⁻+ OA⁻*	Total acid production†	Renal acid excretion	Acid balance	Mean acid balance
					mEq/day			
Formula diet	R.S.	10	14	61	65	63	+2	
	E.B.	2	11	60	69	68	+1	
	J.D.	−5	14	56	75	71	+4	
	W.K.	13	35	84	106	90	+16	
	J.B.	12	9	58	55	56	−1	
	D.L.	15	14	59	58	66	−8	
	R.P.	10	17	67	74	74	0	
								+2 ± 7 (p >0.50)‡
Type A diet	C.S.	88	53	102	67	63	+4	
	R.P.	88	52	83	47	52	−5	
	A.H.	66	24	63	21	46	−25	
	J.P.	53	22	76	45	39	+6	
	B.I.	74	29	72	27	54	−27	
	L.K.	89	66	73	50	49	+1	
	A.S.	38	12	48	22	29	−7	
								−8 ± 13 (p >0.1)‡
Type B diet	A.H.	−15	22	72	109	92	+17	
	H.C.	−4	25	91	120	112	+8	
								+12
All studies								−1 ± 12 (p >0.70)‡

* OA⁻ = organic acid salts.
† (Urinary SO₄⁻ + OA⁻) − (diet combustible anions − stool combustible anions).
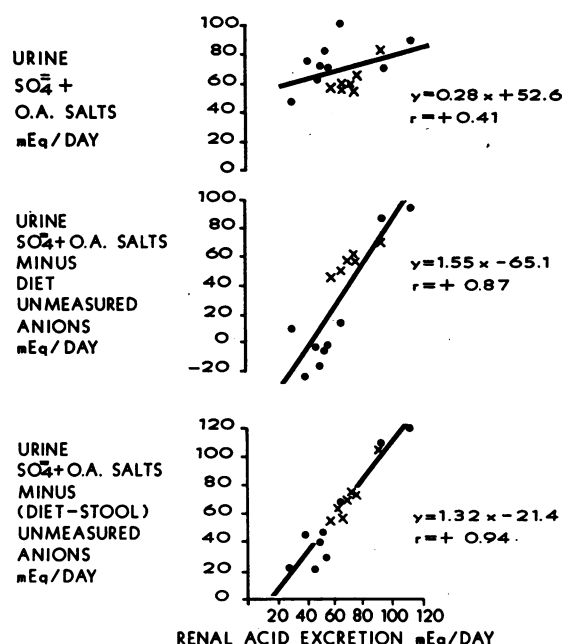‡ Probability that the mean is not different from zero.

FIG. 1. CORRELATION OF FIXED ACID PRODUCTION CALCU-
LATED IN THREE WAYS WITH RENAL ACID EXCRETION. The
circles indicate subjects eating whole food diets, and the
crosses indicate subjects eating a formula diet. OA =
organic acid.

duction and renal acid excretion was poor, as de-
scribed in Table III, which suggested that other
sources of acid, alkali, or both had been omitted in
estimating the acid balance. In the middle of Fig-
ure 1, the ingestion of potential alkali in the diet
("unmeasured anions") was subtracted from uri-
nary inorganic sulfate plus organic acid salts, and
an estimate of fixed acid production that signifi-
cantly correlated with renal acid excretion was
obtained. In the bottom section of Figure 1,
loss of potential alkali in the stool, in addition to
gain of potential alkali from the diet, is taken into
consideration in the calculation of acid production.
The calculation of total effective fixed acid produc-
tion in this way correlates even more closely with
renal acid excretion, which re-emphasizes the ne-
cessity of considering loss of potential alkali in the
feces. The regression equation for this final re-
lationship states that total effective acid produc-
tion in milliequivalents per day = 1.32 (renal acid
excretion, mEq per day) − 21.4. Theoretically,
this line should have a slope of one and an inter-
cept of zero. In fact, statistical testing indicated
that these data would fit the equation equally well:

total effective acid production = renal acid excre-
tion (probability of equally good fit > 0.80).

Discussion

The metabolic reactions that yield or consume
hydrogen ions within the body are summarized in
Table VII and have been discussed in detail previ-
ously (1, 2, 5). In these earlier studies the diet
contained no excess combustible organic cations
or anions, and thus reactions 5 and 6 (Table VII)
were eliminated as factors in acid production.
However, when whole food diets are eaten, all of
the reactions may contribute to effective acid
production.

No direct method is available for identifying and
quantitating the individual organic cations and
anions in food and feces. The net content of or-
ganic anion in excess of organic cation, or the con-
verse, can be estimated by comparing the sum of
the measured inorganic cations ($Na^+ + K^+ + Ca^{++}$
$+ Mg^{++}$) with the sum of the measured inorganic
anions ($Cl^- + P$). Sulfur is not an anion in foods
or feces, since it exists almost entirely in organic
compounds in both (5, 6).

The valence of phosphorus is obviously impor-
tant in making an estimate of the quantity of excess
organic ions. We have assumed that the mean
valence of phosphorus is 1.8 in both natural foods
and feces in the absence of precise information
about the chemical states of phosphorus in these
biological materials. If the actual average valence
of phosphorus is significantly different from 1.8,
the calculation of excess organic ions will be in-
correct.

Assigning phosphorus a valence of 1.8 auto-
matically takes into account reactions 3 and 4 (Ta-
ble VII), since if the two negative changes of the
orthophosphate ester shown in the first equation
of reaction 3 were covered by hydrogen ions, the
organic anion calculation would be reduced by 1.8,
whereas if these changes were covered by potas-
sium, as shown in reaction 4, organic anions would
be increased by 0.2.

By such calculations two of the diets (type A
and liquid formula) used in the present studies
contained excess organic anions, whereas the third
(type B) contained excess organic cations. These
are included in the calculation of acid production
as sources of potential alkali or acid, respectively.

TABLE VII

Metabolic reactions that yield or consume hydrogen ions

Reaction no.

1. Oxidation of organic sulfur to inorganic sulfate

$$\text{Methionine} \xrightarrow{O_2} \text{urea} + CO_2 + H_2O + SO_4^- + 2\,H^+$$
or
cysteine

2. Oxidation of neutral foods to organic acids

$$\text{Glucose} \xrightarrow{O_2} 2\ \text{lactate}^- + 2\,H^+$$

$$\text{Triglyceride} \xrightarrow{O_2} \text{acetoacetate}^- + H^+$$

$$\text{Nucleoprotein} \xrightarrow{O_2} \text{urate}^- + 2\,H^+$$

3. Hydrolysis of phosphoester acids

$$R{-}O{-}\overset{\displaystyle O}{\underset{\displaystyle O^-\,H^+}{\overset{\|}{P}}}{-}O^-\,H^+ \xrightarrow[\text{at pH 7.4}]{H_2O} ROH + \frac{0.8\ HPO_4^-}{0.2\ H_2PO_4^-} + 1.8\,H^+$$

$$R{-}O{-}\overset{\displaystyle O}{\underset{\displaystyle O^-\,H^+}{\overset{\|}{P}}}{-}O{-}R' \xrightarrow[\text{at pH 7.4}]{2\ H_2O} ROH + R'OH + \frac{0.8\ HPO_4^-}{0.2\ H_2PO_4^-} + 1.8\,H^+$$

$$R{-}O{-}\overset{\displaystyle O}{\underset{\displaystyle O^-\,H^+}{\overset{\|}{P}}}{-}O{-}\overset{\displaystyle O}{\underset{\displaystyle O^-\,H^+}{\overset{\|}{P}}}{-}O^-\,H^+ \xrightarrow[\text{at pH 7.4}]{2\ H_2O} ROH + \frac{1.6\ HPO_4^-}{0.4\ H_2PO_4^-} + 3.6\,H^+$$

4. Hydrolysis of phosphoester salts

$$R{-}O{-}\overset{\displaystyle O}{\underset{\displaystyle O^-\,K^+}{\overset{\|}{P}}}{-}O^-\,K^+ + 0.2\,H^+ \xrightarrow[\text{at pH 7.4}]{H_2O} ROH + \frac{0.8\ HPO_4^-}{0.2\ H_2PO_4^-} + 2\,K^+$$

5. Oxidation of organic cations

$$R{-}NH_3^+\ Cl^- \xrightarrow{O_2} \text{urea} + CO_2 + H_2O + Cl^- + H^+$$

6. Oxidation of organic anions

$$R{-}COO^-\ K^+ + H^+ \xrightarrow{O_2} \text{urea} + CO_2 + H_2O + K^+$$

The feces contained organic anions in all studies, and these are also included as loss of potential alkali. Thus, when the dietary gains and fecal losses of organic ions are calculated and the urinary excretion of inorganic sulfate and organic acid salts is measured, an estimate of the net production of fixed acid can be made. Acid production calculated in this way and compared with simultaneously measured renal acid excretion allows determination of net external acid balance.

The nature of the organic ions of the urine and feces suggests that these are largely produced in the body, not derived directly from organic ions of the diet (6, 7). Any dietary organic ion that was unmetabolizable or that escaped combustion would be excreted in the urine or feces in the steady state. Because such ions would then be measured both as gain from the diet and loss in the excreta, the calculation of acid balance would not be affected. Consider, for example, the possible fates of ingested sodium hippurate, identified in the diet as potential alkali. If excreted in the urine or

feces as sodium hippurate, it would be measured again as either endogenous acid production in the urine or potential alkali loss in the stool. In either case the calculation of total acid production would be unaffected. If the hippurate were excreted in the urine or feces as hippuric acid, it would not be measured by our technique. Hence, acid production would be underestimated if the hippurate in the diet were considered potential alkali, but acid excretion from the body would also be underestimated by exactly the same amount and the calculated acid balance would not be altered.

Induced changes in acid balance have previously been related to measured changes in renal acid excretion to allow calculation of a change in acid balance from an assumed zero control balance. If a constant diet is fed, the method described here has the advantage of detecting any changes from the control rate of endogenous acid production in terms of possible variations in the amount of diet sulfur oxidized to sulfate, the loss of organic acid salts in the urine, and the loss of organic anions in the stool.

Summary

The purpose of this study was to determine whether total effective fixed acid production could be measured in subjects eating whole food diets. We carried out sixteen metabolic balance studies using three types of diets during periods when blood pH and serum bicarbonate were normal and stable. As in previous studies, urinary inorganic sulfate and organic acid salts were measured as indexes of acid production. In addition, organic anions in excess of organic cations, or the converse, in both the diet and the feces were estimated as the difference between the sum of inorganic cation $(Na^+ + K^+ + Ca^{++} + Mg^{++})$ and the sum of inorganic anion $[Cl^- + 1.8 \, P \text{ (mmoles)}]$. Excess organic anions or cations in the diet were assumed to represent potential alkali or acid, respectively. The excess organic anions present in all stools were assumed to represent loss of potential alkali. Total effective acid production was calculated as the sum of urinary inorganic sulfate and organic acid salts minus diet organic anions less fecal organic anions. Good agreement was found when acid production calculated in this way was compared with the quantity of acid simultaneously excreted by the kidney, measured as urinary titratable acid plus ammonium minus bicarbonate.

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