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Effect of diet on plasma acid-base composition in normal humans

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Effect of diet on plasma acid-base composition in normal humans. Steady-state plasma and urine acid-base composition was assessed in 19 studies of 16 normal subjects who ingested constant amounts of one of three diets that resulted in different rates of endogenous noncarbonic acid production (EAP) within the normal range. Renal net acid excretion (NAE) was used to quantify EAP since the two variables are positively correlated in normal subjects. A significant positive correlation was observed between plasma $[H^+]$ and plasma P_{CO_2}, and between plasma $[HCO_3^-]$ and plasma P_{CO_2}, among the subjects. Multiple correlation analysis revealed a significant interrelationship among plasma $[H^+]$, plasma P_{CO_2}, and NAE ($r = 0.71$, $P < 0.001$), and among plasma $[HCO_3^-]$, plasma P_{CO_2}, and NAE ($r = 0.77$, $P < 0.001$). The partial correlation coefficients indicated a significant positive correlation between plasma $[H^+]$ and NAE, and a significant negative correlation between plasma $[HCO_3^-]$ and NAE, when plasma P_{CO_2} was held constant. These findings indicate that two factors influence the level at which plasma $[H^+]$ is maintained in normal subjects: *(1)* the steady-state rate of endogenous noncarbonic acid production, and *(2)* the set-point at which plasma P_{CO_2} is regulated by the respiratory system. Plasma $[HCO_3^-]$ is also co-determined by these two factors. In disease states, therefore, both factors must be known before a disturbance in acid-base homeostasis can be excluded.

Effet du régime sur la composition acido-basique plasmatique chez des sujets humains normaux. La composition acido-basique plasmatique et urinaire à l'équilibre a été déterminée dans 19 études de 16 sujets normaux qui ingéraient des quantités constantes de l'un de trois régimes aboutissant à différents taux de production endogène d'acides non carboniques (EAP) à l'intérieur de la normale. L'excrétion rénale nette d'acides (NAE) a été utilisée pour quantifier l'EAP puisque les deux variables sont positivement corrélées chez des sujets normaux. Une corrélation significative positive a été observée entre le $[H^+]$ plasmatique et la P_{CO_2} plasmatique, et entre le $[HCO_3^-]$ plasmatique et P_{CO_2} plasmatique, parmi ces sujets. Une analyse par corrélations multiples a révélé une interrelation significative entre $[H^+]$ plasmatique, P_{CO_2} plasmatique et NAE ($r = 0{,}71$, $P < 0{,}001$), et entre $[HCO_3^-]$ plasmatique, P_{CO_2} plasmatique et NAE ($r = 0{,}77$, $P < 0{,}001$). Les coefficients de corrélation partielle ont indiqué une corrélation significative positive entre $[H^+]$ plasmatique et NAE, et une corrélation significative négative entre $[HCO_3^-]$ plasmatique et NAE, lorsque P_{CO_2} plasmatique était maintenue constante. Ces résultats indiquent que deux facteurs influencent le niveau auqeal $[H^+]$ plasmatique est maintenu chez des sujets normaux: *(1)* le taux de production à l'équilibre d'acides non carboniques endogènes, et *(2)* le point d'équilibre auquel P_{CO_2} plasmatique est régulée par le système respiratoire. $[HCO_3^-]$ plasmatique est également codéterminé par ces deux facteurs. Ainsi, dans les états pathologiques, les deux facteurs doivent être connus avant de pouvoir exclure une perturbation de l'homéostasie acido-basique.

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In normal subjects ingesting self-selected diets, the differences among individuals in steady-state plasma hydrogen ion concentration and plasma bicarbonate concentration are determined to a large extent by corresponding differences in the set-point at which the plasma carbon dioxide tension is regulated by the respiratory system in response to factors other than plasma acidity ("respiratory factors") [1]. Plasma hydrogen ion concentration correlates positively and linearly with plasma carbon dioxide tension, as does plasma bicarbonate concentration. Approximately 50% of the interindividual variance in plasma bicarbonate concentration and 35% of the interindividual variance in plasma hydrogen ion concentration are accounted for by the variance in plasma carbon dioxide tension.

It may be considered that in addition to respiratory factors, metabolic factors contribute to the interindividual differences in steady-state plasma hydrogen ion and bicarbonate concentration. The present study considers whether one such factor is the rate of endogenous acid production. Endogenous acid production in normal subjects eating ordinary diets may differ among individuals by nearly tenfold [2], and it is conceivable that the differences in acid production are accompanied by corresponding differences in the extent of titration of body buffers and therefore in the acidity of cellular and extracellular fluid. To investigate the acid-base consequences of differing normal rates of endogenous acid production among healthy subjects, we assessed plasma and urine acid-base composition under steady-state conditions in normal subjects ingesting one of three different diets that provided a tenfold difference in acid production within the previously defined normal range [2]. We utilized renal net acid excretion as an index of endogenous acid production in these studies since under steady-state conditions there is a strong positive correlation between the rate of endogenous acid production and the rate of renal net acid excretion, and since the latter is more readily and accurately determinable than the former [2, 3]. The results indicate that normal values of plasma bicarbonate concentration and plasma hydrogen ion concentration are dependent on the rate of

Table 1. Comparison of nutrient composition of diets ingested by normal subjects (quantities per 70 kg body weight/24 hr[a])

	Diet		
	A	B	C
Calories	2452.1	2421.4	2258.0
Nitrogen, *g*	13.2	15.7	15.9
Fat, *g*	64.2	105.5	112.5
Carbohydrate, *g*	409.1	277.6	249.2
Sodium, *mEq*	126.0	126.0	126.0
Potassium, *mEq*	109.3	84.2	104.9
Calcium, *mg*	376.4	1101.3	1297.0
Phosphorus, *mg*	950.4	1595.8	3801.0

[a] The quantities in the table are estimated from [4, 5].

endogenous acid production as well as on plasma carbon dioxide tension, hence that both "metabolic" and "respiratory" factors contribute to the interindividual variation in plasma acid-base composition in normal subjects.

Methods

Nineteen chronic balance studies were carried out in 16 normal subjects (14 men, 2 women), whose ages ranged from 22 to 44 years and whose body weights ranged from 55 to 79 kg. All studies were carried out while the patients were hospitalized on the Metabolic Ward of the General Clinical Research Center at Moffitt Hospital, San Francisco, California. Each subject ingested a constant amount of one of three diets (diet A, B, or C), the nutrient composition of which is summarized in Table 1 [4, 5]. Three subjects who had ingested diet A also ingested diet B in a second study after an interval of at least 1 month during which time a self-selected diet was ingested. Diet A (N = 5 studies) and diet B (N = 6 studies) were whole-food diets; diet C (N = 8 studies) was a liquid formula diet. The subjects ingested the diets for an average of 5 days (range, 3 to 9 days) before collection of specimens for measurements of plasma and urine acid-base and electrolyte composition was initiated; this equilibration period permitted establishment of a steady-state (see **Results**). During the steady-state period, an average of six consecutive 24-hr urine collections were obtained and at least three consecutive collections were obtained in all studies but one. An average of five blood collections were obtained, and at least three were obtained in all studies but one.

The original purpose of the study for each of the three separate diet groups was not the same. The differences in study purpose are reflected in experimental maneuvers (not described) carried out during periods subsequent to the above described steady-state period that was utilized for the present analysis of the effect of diet on plasma acid-base composition. The present study thus constitutes a retrospective analysis of data obtained for differing reasons. But, except for the variable of diet, the experimental conditions prior to and during the steady-state period selected for retrospective analysis were identical among the three diet groups.

Blood specimens were obtained anaerobically at approximately 10 A.M., before the subjects ate breakfast, from a superficial vein on the back of the hand that had been heated by immersion for 10 to 15 min in a thermoregulated (44°C) water bath. Blood specimens with values of oxygen tension less than 60 mm Hg were not accepted. Spontaneously voided urine specimens were kept refrigerated and collected in 24-hr pools in plastic vessels containing thymol and mineral oil as preservatives. The pH of blood and urine, and the oxygen tension of blood, were measured at 37°C utilizing a Radiometer BMS-3 blood gas analyzer. Plasma and urine total carbon dioxide content were determined either by manometry (utilizing the Natelson microgasometer) or by thermal conductivity (utilizing the Ericson CO_2 analyzer); the two methods have similar precision (Natelson, CV = 1.2%; Ericson, CV = 0.7%) and, within an examined range of values of total carbon dioxide content from 22 to 33 mmoles per liter, yield nearly identical values ($\overline{\Delta X}$ = 0.1 ± 0.5 [SD] mmoles/liter, N = 27). Plasma bicarbonate concentration and carbon dioxide tension were calculated from the measured values of blood pH and plasma carbon dioxide content utilizing the Henderson-Hasselbalch equation, where pK′ (6.1, 37°C) was corrected for pH and body temperature [6], and the solubility coefficient of carbon dioxide in plasma (0.0301, 37°C) was corrected for body temperature [7]. Blood pH values were also corrected for body temperature [8]. Urine bicarbonate concentration was calculated from the measured values of urine pH and carbon dioxide content utilizing the Henderson-Hasselbalch equation, where the solubility coefficient of carbon dioxide was taken as 0.0309 and pK′ corrected for ionic strength was calculated as follows: $pK' = 6.33 - 0.5([Na^+]+[K^+])^{1/2}$, where sodium and potassium concentrations are expressed in eq/liter. Net acid excretion was calculated as the sum of the excretion rates of titratable acid and ammonium minus the excretion rate of bicarbonate. Urine titratable acid concentration was determined by titration, and urine ammonia concentration was determined either by the microdiffusion method of Conway [9] or by the phenol method [10]. Plasma and urine sodium concentrations were determined by flame photometry and chloride by potentiometric titration. Urine aldosterone concentration was measured by radioimmunoassay.

Values are reported as mean ± SEM. Statistical analyses comprise Student's t test for paired and unpaired variables and simple and multiple linear regression and correlation analysis [11, 12].

Results[1]

Criteria employed to certify presence of steady-state. The following analyses were carried out to ascertain whether the subjects were in a steady-state with respect to plasma and urine acid-base composition during the study period: *(1)* the daily differences in the value of each acid-base variable from the value obtained on the first day of the study period was calculated for each subject; *(2)* for each diet group, the average

[1] Because under ordinary clinical circumstances, blood pH and CO_2 solubility are not corrected for body temperature, and the value of the pK′ of the $CO_2/H_2CO_3/HCO_3^-$ buffer system is not corrected for blood pH and body temperature, the results were also analyzed using uncorrected values for blood pH, CO_2 solubility, and pK′. The results were nearly identical to those obtained when the corrected values of blood pH and pK′ were used, including nearly identical values of the regression coefficients reported. The only noteworthy differences were higher values for certain of the correlation coefficients, as notated in the legend to Fig. 4, and higher values for certain of the partial correlation coefficients, as notated in the footnote to Table 4.

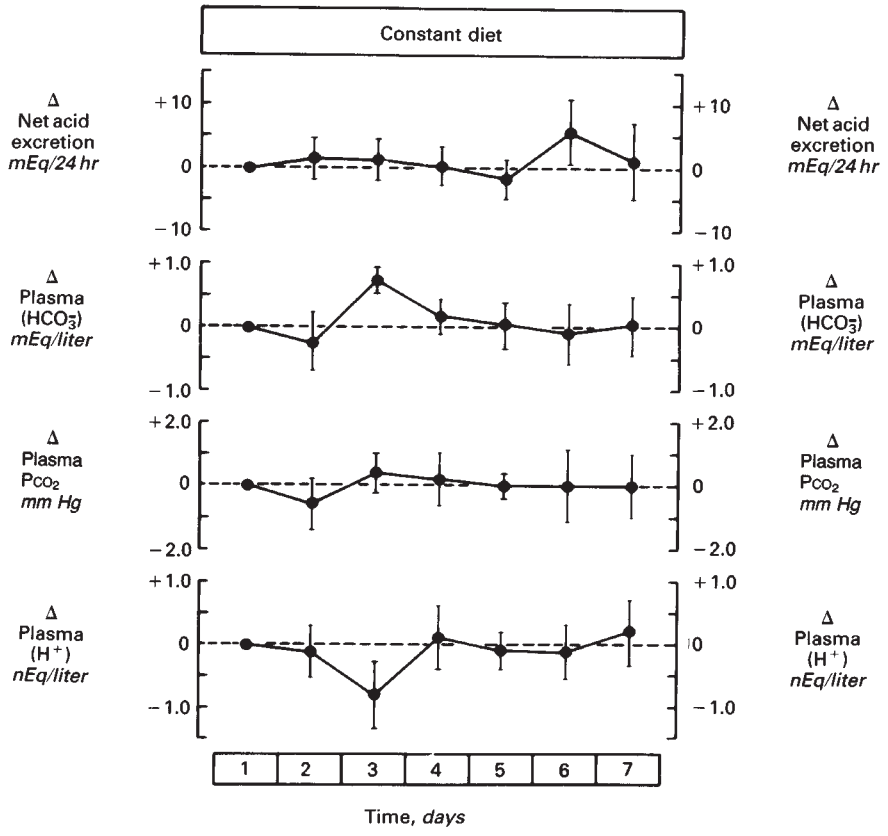

Fig. 1. *Plasma and urine acid-base composition in 19 studies of 16 normal subjects ingesting a constant diet (diet A, B or C; see Table 1).* The figure depicts the time-course of the daily differences in the value of each plasma and urine acid-base variable from the value obtained on the first day of the study period. Each *data point* plotted represents the mean ± SEM for all 19 studies, where for each variable each day's difference from day 1 is calculated for each study prior to calculation of the mean difference for all studies. The subjects ingested the diet for an average of 5 days (range, 3 to 9 days) before collection of specimens for measurements of plasma and urine acid-base composition was initiated. The findings indicate that there is no significant trend during the period of observation in the values of the selected components of plasma and urine acid-base composition in the 19 studies.

Table 2. Plasma and urine acid-base composition: Comparison of initial and final values during the study period[a]

	Plasma			Urine net acid excretion
	H^+ *nEq/liter*	P_{CO_2} *mm Hg*	HCO_3^- *mEq/liter*	*mEq/24 hr*
First day	38.5 ± 0.4	37.7 ± 0.6	24.5 ± 0.3	88 ± 11
Last day	38.5 ± 0.3	37.8 ± 0.6	24.5 ± 0.3	84 ± 11
Mean difference[b]	0.0 ± 0.2	0.1 ± 0.4	0.0 ± 0.2	−4 ± 3
P value[c]	> 0.95	> 0.70	> 0.95	> 0.20

[a] The average duration of the study period was 6 days.
[b] The values were calculated as the average of the differences between the last and the first day of each study.
[c] The *P* values were calculated with the Student's *t* test for paired values.

of these daily differences was calculated for each day, and these average daily differences were examined to determine the maximal difference from day 1 of the study, and also to determine whether there was a significant trend as reflected by analysis of the simple linear correlation between the average daily differences and the duration of the study performed; *(3)* for all three diet groups and all 19 studies taken together, the time-course of the daily differences in the value of each acid-base variable from the value obtained on the first day of the study period was examined as plotted in Figure 1; *(4)* for all 19 studies, the values of each acid-base variable on the first and last day of observation in each subject were compared utilizing Student's paired *t* test (Table 2). For each of the diet groups considered separately, none of the daily differences exceeded 1.1 mEq/liter for plasma bicarbonate concentration, 10 mEq/24 hr for net acid excretion, and 3.4 mm Hg for plasma P_{CO_2}; these differences are well within the limits employed by other investigators to certify the presence of steady-state conditions prerequisite to analysis of the determinants of interindividual variation in plasma acid-base composition [1]. The results of these analyses indicate that there was no significant variation or trend during the period of observation in the values of the selected components of plasma and urine acid-base composition either in the 19 studies taken as a whole or in each of the diet groups considered separately.

Effect of diet on urine net acid excretion and plasma acid-base composition. The mean value of urine net acid excretion (NAE) for each subject, and the mean NAE for all subjects within each diet group, are shown on Table 3. There was no overlap of the range of NAE among diet groups: diet A, 14 to 40 mEq/24 hr; diet B, 53 to 76 mEq 24 hr; diet C 111 to 154 mEq/24 hr. The mean value of NAE for each diet group was highly significantly different ($P < 0.001$) from that of each of the other diet groups. Table 3 also summarizes the mean values of plasma hydrogen ion concentration ($[H^+]$), carbon dioxide tension (P_{CO_2}), and bicarbonate concentration ($[HCO_3^-]$) for each subject, and the mean of each parameter for all subjects within each diet group. For each diet group, the mean value of each of these components of plasma acid-base composition was not significantly different from that of either of the other diet groups.

Interrelation between plasma $[H^+]$ and P_{CO_2}, and between

Table 3. Effect of diet on plasma acid-base composition and urine net acid excretion: Steady-state values in normal subjects (N = 19)

Patient no.	Weight *kg*	Plasma			Urine net acid *mEq/24 hr*	Plasma[a,b]	
		H^+ *nEq/liter*	P_{CO_2} *mm Hg*	HCO_3^- *mEq/liter*		H^+ at P_{CO_2} = 38 mm Hg *nEq/liter*	HCO_3^- at P_{CO_2} = 38 mm Hg *mEq/liter*
Diet A							
1	67	37.2	37.3	25.0	40	37.5	25.3
2	75	38.4	38.9	25.2	37	38.1	24.9
3	64	38.0	39.3	25.9	14	37.5	25.4
4	76	38.0	38.4	25.3	20	37.8	25.2
5	59	35.4	35.9	25.6	26	36.2	26.4
$\bar{X}$	68	37.4	38.0	25.4	27	37.4	25.4
±SEM	±3	±0.5	±0.6	±0.2	±5	±0.3	±0.2
Diet B							
6	75	38.9	40.7	26.2	76	37.9	25.2
7	73	39.1	39.0	24.5	70	38.7	24.1
8	75	40.5	38.4	23.6	61	40.4	23.4
9	67	38.2	38.4	25.1	59	38.0	25.0
10	66	36.1	34.7	24.2	53	37.4	25.4
11	65	38.9	37.4	23.9	67	39.1	24.1
$\bar{X}$	70	38.6	38.1	24.6	64	38.6	24.5
±SEM	±2	±0.6	±0.8	±0.4	±3	±0.4	±0.3
Diet C							
12	55	38.9	40.2	25.7	111	38.1	24.9
13	79	40.2	39.8	24.8	154	39.5	24.1
14	76	39.6	36.2	22.9	142	40.3	23.6
15	68	39.3	36.7	23.4	129	39.8	23.9
16	68	38.0	37.9	25.0	138	38.0	25.0
17	74	37.5	37.9	25.4	150	37.5	25.4
18	65	39.4	37.5	23.7	136	39.6	23.9
19	61	36.8	32.7	22.5	112	38.8	24.5
$\bar{X}$	68	38.7	37.4	24.2	134	39.0	24.4
±SEM	±3	±0.4	±0.8	±0.4	±6	±0.4	±0.2
Comparisons among groups (P < values shown below)							
B vs. A	NS	NS	NS	NS	0.001	NS	NS
C vs. B	NS	NS	NS	NS	0.001	NS	NS
C vs. A	NS	NS	NS	NS	0.001	0.02	0.02

[a] Determinations were made on arterialized venous blood pH and plasma total CO_2; P_{CO_2} and HCO_3^- calculated from the Henderson-Hasselbalch equation (see **Methods**).

[b] For each subject, plasma $[HCO_3^-]$ at P_{CO_2} = 38 mm Hg ($[HCO_3^-]_{P_{CO_2}=38}$) was calculated as follows: $[HCO_3^-]_{P_{CO_2}=38} = [HCO_3]_{observed} + \beta_1 \cdot (38 - P_{CO_2,observed})$, where β_1 is the slope of the linear regression equation of $[HCO_3^-]_{observed}$ on $[P_{CO_2}]_{observed}$ for the group as a whole (N = 19, see Fig. 2). For each patient, blood $[H^+]$ at P_{CO_2} = 38 was calculated in a similar manner from the observed value of blood $[H^+]$ and P_{CO_2} for each subject and the slope of the linear regression equation of blood $[H^+]$ on P_{CO_2} for the group as a whole (N = 19, see Fig. 2).

plasma $[HCO_3^-]$ and P_{CO_2}. Utilizing the mean values of plasma $[H^+]$ and plasma P_{CO_2} for each of the 19 studies, there was a significant positive linear correlation between the two variables. $[H^+] = 0.38 \cdot P_{CO_2} + 24.2$, r = 0.55, $P < 0.02$ (Fig. 2). Similarly, there was a significant positive linear correlation between plasma $[HCO_3^-]$ and plasma P_{CO_2}: $[HCO_3^-] = 0.37 \cdot P_{CO_2} + 10.7$, r = 0.68, $P < 0.005$ (Fig. 2). These findings are nearly identical to those reported by Madias et al [1] in a study of 25 normal subjects: $[H^+] = 0.41 \cdot P_{CO_2} + 24.0$, r = 0.63, $P < 0.01$; $[HCO_3^-] = 0.36 \cdot P_{CO_2} + 10.4$, r = 0.73, $P < 0.01$. As discussed by Madias et al [1], the finding of a significant positive correlation between plasma $[H^+]$ and plasma P_{CO_2} indicates that plasma P_{CO_2} must be the independent variable, and that at least a part of the observed interindividual differences in steady-state plasma $[H^+]$ and plasma $[HCO_3^-]$ can be accounted for by corresponding interindividual differences in the set-point at which plasma P_{CO_2} is regulated by factors other than plasma acidity.

Interrelation between plasma $[H^+]$ and urine NAE, and between plasma $[HCO_3^-]$ and urine NAE. Utilizing the mean values for each of the 19 studies, there was no significant linear correlation between either plasma $[H^+]$ or plasma $[HCO_3^-]$ and urine NAE: $[H^+]$ versus NAE, r = 0.41, $P > 0.05$; $[HCO_3^-]$ versus NAE, r = 0.40, $P > 0.05$.

Interrelation between plasma $[H^+]$ and urine NAE, and between plasma $[HCO_3^-]$ and urine NAE, at constant plasma P_{CO_2}: Multiple linear regression analysis. Multiple linear regression analysis with plasma $[H^+]$ as the dependent variable and both urine NAE and plasma P_{CO_2} as independent variables revealed that there was a significant interrelation among the three variables $[H^+] = 22.4 \pm 0.40 \cdot P_{CO_2} + 0.01$ NAE, r = 0.71, $P < 0.001$) (Table 4). The multiple correlation coefficient

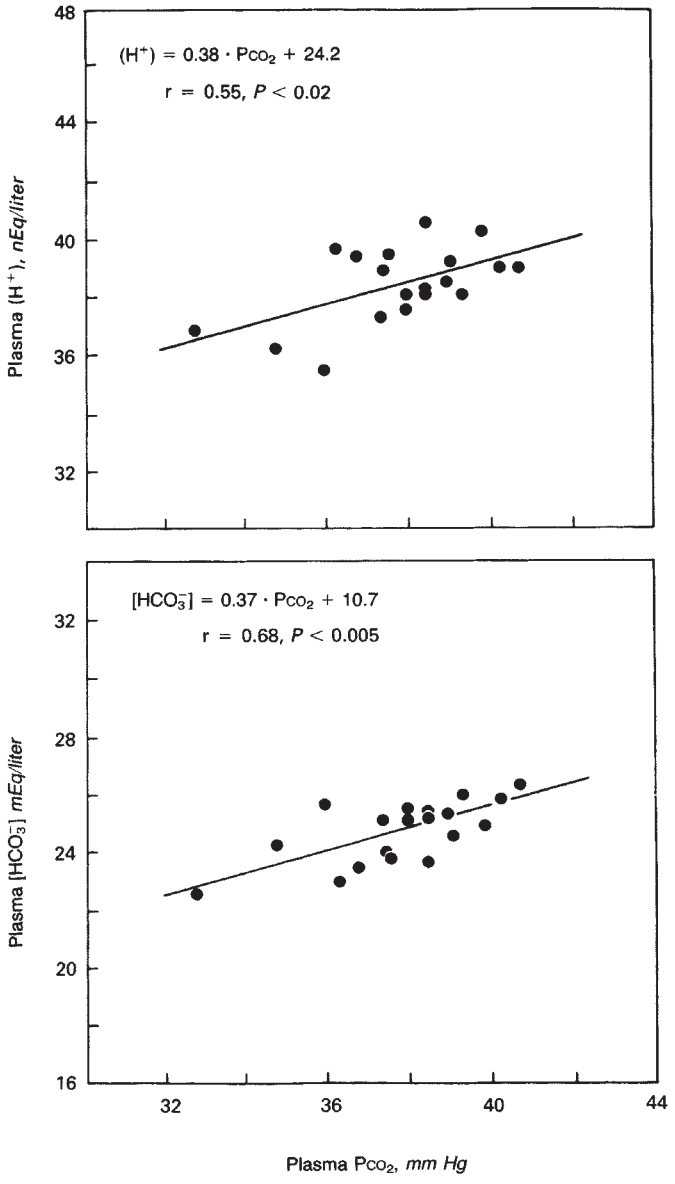

Fig. 2. *Relation between plasma hydrogen ion concentration and plasma carbon dioxide tension, and between plasma bicarbonate concentration and plasma carbon dioxide tension, in 19 studies of 16 normal subjects who ingested a constant diet (diet A, B or C; see Table 1).* Each *data point* plotted represents the mean steady-state values in one individual.

of 0.71 among these three variables ([H^+], P_{CO_2} and NAE) (Table 4) was greater than the simple correlation coefficient of 0.55 between plasma [H^+] and plasma P_{CO_2} (Fig. 2). Furthermore, in the multiple linear regression equation, the partial regression coefficients of both plasma P_{CO_2} (+0.40) and urine NAE (+0.01) were significantly different from zero (Table 4), indicating that interindividual differences in both plasma P_{CO_2} and urine NAE contributed to the observed interindividual differences in plasma [H^+] among the 19 studies. The partial correlation coefficient of plasma [H^+] on plasma P_{CO_2} (urine NAE held constant) ($r = 0.64$, $P < 0.005$), and the partial correlation coefficient of plasma [H^+] on urine NAE (plasma P_{CO_2} held constant) ($r = 0.53$, $P < 0.05$), were significantly

Table 4. Interrelationship of plasma acid-base composition and urine net acid excretion in normal subjects ($N = 19$); multiple linear regression

$$Y = B_0 + B_1X_1 + B_2X_2$$

$[H^+] = 22.4 + 0.40 \cdot P_{CO_2} + 0.01 \cdot NAE$, $r = 0.71$, $P < 0.001$
t test of null hypothesis (H_0)
H_0: $B_1 = 0$, $t = 3.257$, $P < 0.005$
H_0: $B_2 = 0$, $t = 2.503$, $P < 0.025$
Partial correlation coefficient[a]
[H^+] on P_{CO_2} at constant NAE
$r = 0.64$, $P < 0.005$
[H^+] on NAE at constant P_{CO_2}
$r = 0.53$, $P < 0.05$

$[HCO_3^-] = 11.9 + 0.35 \cdot P_{CO_2} - 0.01 \cdot NAE$, $r = 0.77$, $P < 0.001$
t test of null hypothesis (H_0)
H_0: $B_1 = 0$, $t = 4.117$, $P < 0.001$
H_0: $B_2 = 0$, $t = 2.309$, $P < 0.05$
Partial correlation coefficient[a]
[HCO_3^-] on P_{CO_2} at constant NAE
$r = 0.72$, $P < 0.001$
[HCO_3^-] on NAE at constant P_{CO_2}
$r = 0.50$, $P < 0.05$

[a] When the data are reanalyzed utilizing blood pH and CO_2 solubility uncorrected for temperature, and values of pK′ for the $CO_2/H_2CO_3/HCO_3^-$ buffer system uncorrected for blood pH and body temperature, the following values were obtained for the partial correlation coefficients: [H^+] on P_{CO_2} at constant NAE, $r = 0.59$, $P < 0.01$; [H^+] on NAE at constant P_{CO_2}, $r = 0.54$, $P < 0.025$; [HCO_3^-] on P_{CO_2} at constant NAE, $r = 0.74$, $P < 0.001$; [HCO_3^-] on NAE at constant P_{CO_2}, $r = 0.54$, $P < 0.02$.

different from zero (Table 4), further indicating a significant contribution of both plasma P_{CO_2} and urine NAE to the observed interindividual differences in plasma [H^+].

Similarly, by multiple linear regression analysis, there was a significant interrelation among plasma [HCO_3^-], plasma P_{CO_2} and urine NAE (plasma $[HCO_3^-] = 11.9 + 0.35 \cdot P_{CO_2} - 0.01 \cdot NAE$, $r = 0.77$, $P < 0.001$) (Table 4), and the multiple correlation coefficient of 0.77 among the three variables was greater than the simple correlation coefficient of 0.68 between plasma [HCO_3^-] and plasma P_{CO_2} (Fig. 2). In the multiple linear regression equation, the partial regression coefficients of both plasma P_{CO_2} (+0.35) and urine NAE (−0.01) were significantly different from zero. The partial correlation coefficient of plasma [HCO_3^-] on plasma P_{CO_2} (urine NAE held constant) ($r = 0.72$, $P < 0.001$), and the partial correlation coefficient of plasma [HCO_3^-] on urine NAE (plasma P_{CO_2} held constant) ($r = 50$, $P < 0.05$), were significantly different from zero.

Interrelation between plasma [H^+] and urine NAE, and between plasma [HCO_3^-] and urine NAE, at constant plasma P_{CO_2}: Normalization of plasma [H^+] and [HCO_3^-] to a common plasma P_{CO_2}. For each of the 19 studies, the mean value of plasma [H^+] and plasma [HCO_3^-] was normalized to a common value of plasma P_{CO_2}, 38 mm Hg, which was the mean plasma P_{CO_2} for the 19 studies (Table 3). The rationale for the method of normalization of the values of plasma [H^+] is based on the following considerations: *(1)* the finding that there is a significant correlation between plasma [H^+] and plasma P_{CO_2}, wherein the plasma P_{CO_2} is inferred to be the independent variable; *(2)* the assumption that in the normal range, the quantitative influence of differences in chronic steady-state values of plasma P_{CO_2} on plasma [H^+] among subjects (Fig. 2) predicts the quantitative influence of chronic steady-state P_{CO_2} differences

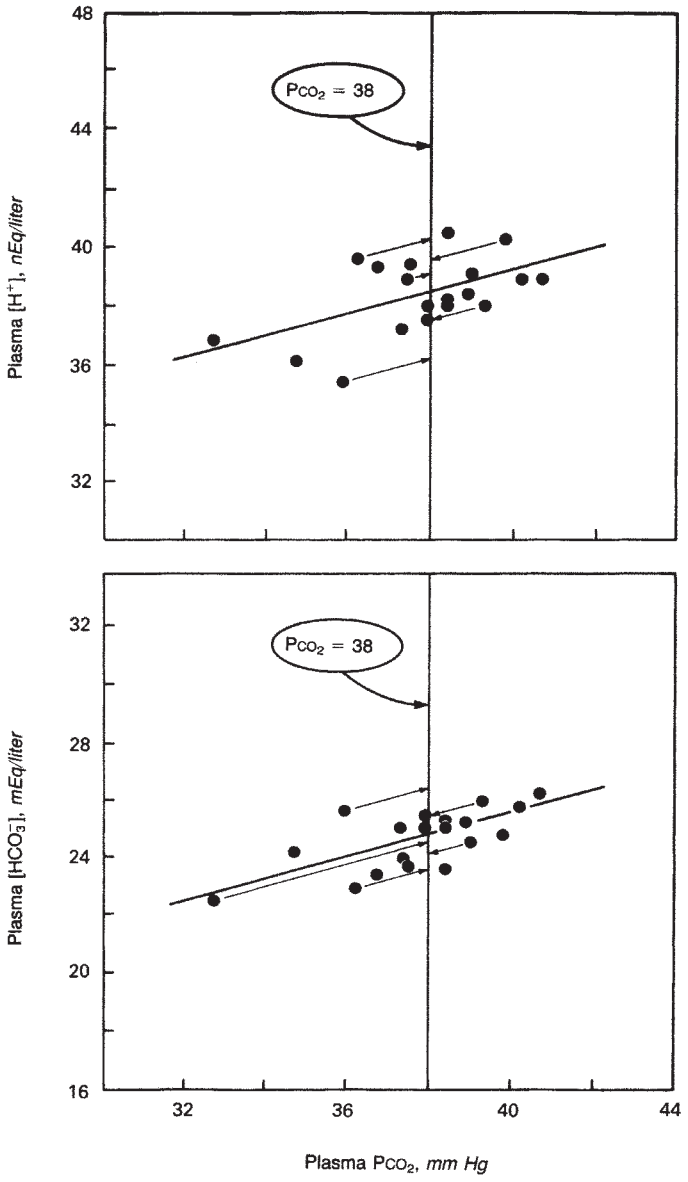

Fig. 3. *Graphical representation of the procedure utilized to normalize the mean steady-state values of plasma hydrogen ion concentration and bicarbonate concentration to a common value of plasma carbon dioxide tension, namely* P_{CO_2} *= 38 mm Hg, the mean plasma carbon dioxide tension for all 19 studies.* The individual steady-state values of plasma hydrogen ion concentration are extrapolated to P_{CO_2} = 38 mm Hg by transposition along a *line* that is parallel to the *slope* of the linear regression equation relating plasma hydrogen ion concentration and plasma carbon dioxide tension for the group (see Fig. 2). Similarly, the individual steady-state values of plasma bicarbonate concentration are extrapolated to P_{CO_2} = 38 mm Hg by transposition along a *line* that is parallel to the *slope* of the regression equation relating plasma bicarbonate concentration and plasma carbon dioxide tension for the group (see Fig. 2).

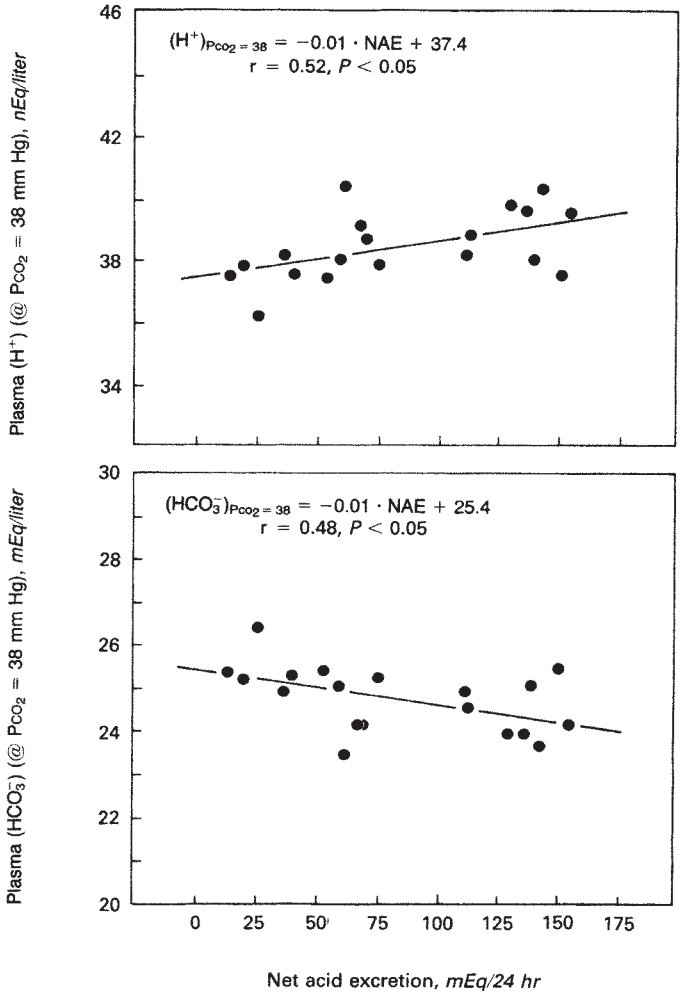

Fig. 4. *Relation between plasma hydrogen ion concentration (at* P_{CO_2} *= 38 mm Hg) and net acid excretion, and between plasma bicarbonate concentration* (at P_{CO_2} *= 38 mm Hg) and net acid excretion, in the steady-state in 19 studies of 16 normal subjects ingesting one of three different diets.* Each *data point* plotted represents the mean steady-state value observed in one individual. (When the data were re-analyzed utilizing blood pH and CO_2 solubility uncorrected for temperature, and values of pK′ uncorrected for blood pH and body temperature, the mean value of plasma P_{CO_2} for the group was found to be 41 mm Hg, and the following correlations were observed: $[H^+]_{P_{CO_2}=41}$ = +0.01 NAE + 38.4, r = 0.53, $P < 0.02$; $[HCO_3^-]_{P_{CO_2}=41}$ = −0.01 NAE + 25.5, r = 0.55, $P < 0.02$).

within subjects. Figure 3 provides a graphical representation of how the individual values of plasma $[H^+]$ are normalized to a common plasma P_{CO_2} utilizing a common slope equal to the slope of the linear regression line of plasma $[H^+]$ on plasma P_{CO_2}; the footnotes to Table 3 provide the algebraic formulas used for precise calculation of the normalized values. The values of plasma $[HCO_3^-]$ were normalized analogously, as indicated (Fig. 3, Table 3).

There was no significant difference in the mean normalized values of plasma $[H^+]$ or plasma $[HCO_3^-]$ between diet groups A and B or between B and C, but there was a significant difference in both ($P < 0.02$) between diet groups A and C, that is, between the diet groups with the lowest and highest values of urine NAE. When all 19 of the normalized values of plasma $[H^+]$ and plasma $[HCO_3^-]$ were plotted against the corresponding values of urine NAE, there was a significant positive linear correlation between plasma $[H^+]_{P_{CO_2}=38}$ and urine NAE (r = 0.52, $P < 0.05$) and a significant negative linear correlation between plasma $[HCO_3^-]_{P_{CO_2}=38}$ and urine NAE (r = 0.48, $P < 0.05$) (Fig. 4).

Table 5. Effect of diet on plasma and urine electrolyte composition: Steady-state values in normal subjects (N = 19)

	Plasma			Urine			
	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	
	mEq/liter			*mEq/24 hr per 70 kg*			Aldosterone *μg/24 hr*
Diet A (N = 5)							
$\bar{X}$	138	4.1	106	106	89	115	11.7[a]
±SEM	±1	±0.1	±1	±6	±2	±5	±3.1
Diet B (N = 6)							
$\bar{X}$	139	4.1	107[b]	104	68	118[b]	16.0[b]
±SEM	±1	±0.1	±1	±6	±2	±8	±2.4
Diet C (N = 8)							
$\bar{X}$	141	4.0	106	110	87	113	16.7
±SEM	±1	±0.1	±1	±3	±3	±3	±2.3
Comparison among groups (P < values shown below)							
B vs. A	NS	NS	NS	NS	0.001	NS	NS
C vs. B	NS	NS	NS	NS	0.001	NS	NS
C vs. A	0.02	NS	NS	NS	NS	NS	NS

[a] N = 4.
[b] N = 5.

Effect of diet on plasma and urine electrolyte composition and urine aldosterone excretion. Table 5 summarizes the mean steady-state values of plasma and urine electrolyte composition for the three diet groups. The only notable significant differences were those in urine potassium excretion between diet groups A and B and between C and B in keeping with corresponding differences in dietary intake of potassium (Table 1). There was no significant difference in urine aldosterone excretion among diet groups.

Discussion

In normal subjects ingesting self-selected diets, plasma $[H^+]$ differs among individuals by as much as 10 nEq/liter, which is 25% of the mean value (40 nEq/liter) [1]. Previous studies have defined homeostatic mechanisms that minimize deviations in plasma acidity within an individual during disturbances of acid-base balance [13–17]. The factors that account for the differences in plasma acidity among normal individuals under ordinary physiological conditions have not been extensively investigated.

Madias et al [1] proposed that the interindividual differences in plasma acidity in normal subjects are accounted for in part by corresponding differences in the level at which plasma P_{CO_2} is regulated. This proposal was based on studies, carried out under steady-state conditions in 25 normal subjects, that demonstrated a positive correlation between plasma $[H^+]$ and plasma P_{CO_2} among the subjects, using the mean value of each variable in each subject. Assuming a causal relationship between the two variables, Madias et al inferred that the set-point at which plasma P_{CO_2} is regulated in an individual determines the plasma acidity in that individual, at least in part. The possibility that plasma acidity rather than carbon dioxide tension is the independent variable was excluded on the basis of the consideration that primary differences in plasma acidity would be expected to correlate negatively rather than positively with plasma P_{CO_2}, inasmuch as acidemia is known to stimulate alveolar ventilation and alkalemia to suppress it. In the Madias et al study, the interindividual differences in steady-state plasma P_{CO_2} accounted for approximately 35% of the interindividual differences in plasma $[H^+]$.

Prior to the Madias et al study in normal subjects [1], a positive correlation between steady-state plasma $[H^+]$ and plasma P_{CO_2} was demonstrated in normal dogs and dogs with induced states both of chronic hypercapnia and hypocapnia, wherein plasma P_{CO_2} was specifically altered as the sole experimental maneuver [18].

The results of the present study confirm the findings of Madias et al in normal subjects. In addition, the results of the present study confirm the finding of Madias et al of a significant positive correlation between plasma $[HCO_3^-]$ and P_{CO_2} among normal subjects. We concur with the analysis of Madias et al that the most likely interpretation of these findings is that interindividual differences in both plasma acidity and $[HCO_3^-]$ are determined to a significant extent by differences in the set-point at which plasma P_{CO_2} is regulated by factors other than blood acidity (that is, by "respiratory" factors).

It may be considered whether "metabolic" factors also play a role in determining the interindividual differences in plasma acidity and plasma $[HCO_3^-]$ in normal subjects. Conceivably, differences in such factors as plasma potassium concentration, dietary chloride intake, plasma aldosterone concentration, and the rate of endogenous noncarbonic acid production alter the steady-state plasma acidity in normal subjects independent of carbon dioxide tension. The present study considers the role of interindividual differences in the rate of endogenous acid production.

Endogenous noncarbonic acid production in normal subjects eating self-selected diets may differ by nearly tenfold, with a range of approximately 20 to 120 mEq/24 hr [2]. These differences reflect to a considerable extent differences in the composition of the diet. The effect of such interindividual differences in endogenous acid production on steady-state plasma acidity has not been previously studied, to our knowledge, and it has been presumed that such differences are without significant effect. Yet, it is well known that plasma acidity is maintained at an increased level both in clinical conditions that result in a sustained pathological increase in endogenous acid production [19–21], and experimental conditions in which the net systemic acid load is maintained at an increased level by exogenous acid loading [13]. It is reasonable to consider whether increases in endogenous acid production secondary to normal diet differences might also appreciably increase plasma acidity in the steady-state.

It is possible to quantify endogenous noncarbonic acid production in normal subjects ingesting whole food diets by measurements of the quantity of the inorganic constituents of diet, urine and stool, and of the total organic anion content of the urine [2]. However, in the present studies we utilized renal net acid excretion as a quantitative index of endogenous noncarbonic acid production, since under steady-state conditions there is a predictable relation between these two variables [2, 3], and since net acid excretion is more readily measured. The high degree of predictability of endogenous acid production from measurements of net acid excretion in the steady-state is evident in Figure 5, which shows the relation between the two variables, determined independently, in 16 normal subjects studied by Lennon, Lemann, and Litzow [2]. Nearly 90% of the

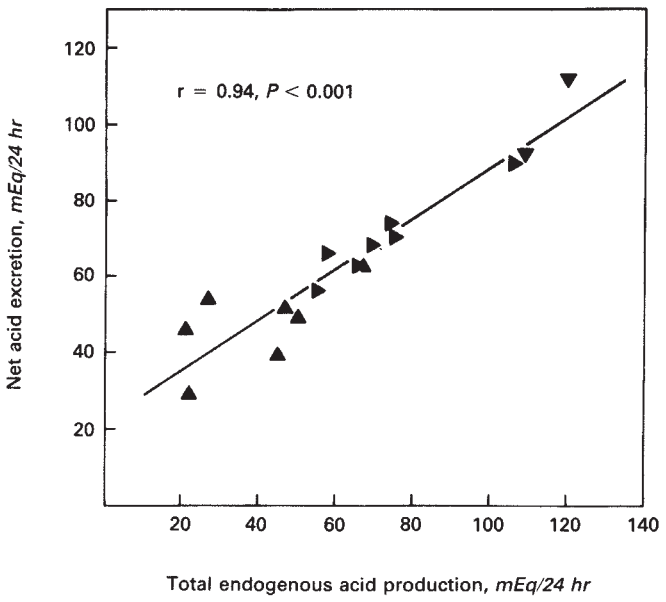

Fig. 5. *Relation between renal net acid excretion and total endogenous acid production in the steady-state in normal subjects ingesting one of three different diets.* Each *data point* plotted represents the mean steady-state value observed in one individual. Endogenous acid production was estimated as the sum of urinary sulphate plus organic anion excretion less the difference between diet and stool combustible anion excretion. Data are plotted from tabular data taken from [2]. Symbols are: ▶, formula diet; ▲, whole food, type A; ▼, whole food, type B.

variance in net acid excretion among the subjects was accounted for by differences in endogenous acid production.

The three diets used in the present study resulted in steady-state net acid excretion rates that ranged from low-normal to high-normal by comparison with the result of the studies by Lennon, Lemann, and Litzow (Table 3). Despite the marked and statistically significant differences in net acid excretion among the three diet groups, however, no significant differences were observed in the mean values of either plasma $[H^+]$ or plasma $[HCO_3^-]$ among the groups (Table 3). Furthermore, among all 19 studies taken together, there was no significant correlation either between plasma $[H^+]$ and net acid excretion or between plasma $[HCO_3^-]$ and net acid excretion. These results provide no evidence to support the hypothesis that interindividual differences in the rate of endogenous acid production influence plasma acid-base composition in normal humans.

However, the possibility must be considered that an influence of endogenous acid production on plasma acidity might not be readily appreciated owing to the wide variation of values of plasma P_{CO_2} among the subjects studied, given the major impact that differences in plasma P_{CO_2} has on plasma acidity (Fig. 2). A significant relationship between plasma acidity and net acid excretion might be discernible only among those subjects in whom plasma P_{CO_2} is identical or nearly so. Because the number of individuals within any narrow range of values of P_{CO_2} (for example, 1 to 2 mm Hg) was small in this study, we utilized the statistical technique of multiple linear regression and correlation analysis to ascertain whether, in addition to plasma P_{CO_2}, a second independent variable, namely net acid excretion (index of endogenous acid production), might also influence plasma acidity in the subjects studied. This technique yields an equation wherein the numerical coefficients of the plasma P_{CO_2} term and the net acid excretion term, the so-called partial regression coefficients, quantify the influence of the two variables on plasma hydrogen ion concentration (Table 4). These partial regression coefficients both were significantly different from zero, indicating that plasma P_{CO_2} and net acid excretion each has a significant quantitative influence on the value of plasma $[H^+]$. Furthermore, in both cases the sign of the partial regression coefficient was positive, indicating that higher steady-state values both of P_{CO_2} and net acid excretion are associated with higher steady-state values of plasma $[H^+]$. Assuming that net acid excretion reflects endogenous acid production, this finding agrees with the hypothesis that increases in endogenous acid production within the normal range result in an increase in plasma acidity. Using correlation analysis on the same data, it is possible to assess the degree of correlaton between plasma acidity and plasma P_{CO_2} when net acid excretion is held constant, and the degree of correlation between plasma acidity and net acid excretion when plasma P_{CO_2} is held constant. This requires computation of the so-called partial correlation coefficient between the dependent variable (plasma $[H^+]$) and each independent variable (plasma P_{CO_2}, net acid excretion) in the multiple regression equation. In both cases, the partial correlation coefficients were significantly different from zero, indicating that there is a significant correlation between plasma acidity and plasma P_{CO_2} when net acid excretion is held constant, and between plasma acidity and net acid excretion when plasma P_{CO_2} is held constant (Table 4). Taken together, these findings are interpreted as indicating that there is a significant effect of interindividual differences in endogenous acid production on plasma acidity in normal subjects, and that this relationship is obscured when tested for by considering only the simple correlation between the two variables, owing to the extent and impact of interindividual differences in plasma P_{CO_2} on plasma acidity.

Similarly, by multiple linear regression and correlation analysis, we infer that for plasma $[HCO_3^-]$ a significant proportion of the interindividual differences among normal subjects can be accounted for by corresponding interindividual differences in endogenous acid production as reflected by net acid excretion in the steady-state (Table 4). The negative sign of the partial regression coefficient of the net acid excretion term is consistent with the interpretation that endogenous acid production has a physiological impact on plasma $[HCO_3^-]$ in the normal range: Activation of extrarenal buffer mechanisms that limit the degree of acidemia caused by higher levels of endogenous acid production predictably would result in reduced buffer base concentration in blood, hence a lower plasma $[HCO_3^-]$.

Given the extent and impact of the differences in plasma P_{CO_2} on plasma acidity, another way to assess the independent influence of differences in endogenous acid production on plasma acidity might be to experimentally alter plasma P_{CO_2} in each subject such that all subjects regulated plasma P_{CO_2} at the same level. More expediently, the individual values of plasma P_{CO_2} may be normalized to a common value utilizing the known relationship between plasma acidity and plasma P_{CO_2} for the group as a whole (Fig. 2). A graphical representation of the normalization technique is depicted in Figure 3, in which the common value of carbon dioxide tension is 38 mm Hg, the

Table 6. Comparison of the impact of the observed maximal interindividual differences in plasma carbon dioxide tension versus the observed maximal interindividual differences in net acid excretion on plasma acidity and bicarbonate concentration[a]

$$[H^+] = 22.4 + 0.40 \cdot P_{CO_2} + 0.01\ NAE$$

(A) Impact of observed maximal interindividual differences in plasma P_{CO_2} on plasma acidity at an assumed constant value of net acid excretion equal to the average net acid excretion for the group (84 mEq/24 hr, $N = 19$):
Minimum P_{CO_2} = 32.7; calculated $[H^+]$ = 36.5
Maximum P_{CO_2} = 40.7; calculated $[H^+]$ = 39.7
ΔP_{CO_2} = 8.0; $\Delta[H^+]$ = 3.2

(B) Impact of observed maximal interindividual differences in net acid excretion on plasma acidity at an assumed constant value of plasma P_{CO_2} equal to the average P_{CO_2} for the group (37.8 mm Hg, $N = 19$):
Minimum NAE = 14; calculated $[H^+]$ = 37.7
Maximum NAE = 154; calculated $[H^+]$ = 39.1
ΔNAE = 140; $\Delta[H^+]$ = 1.4

(C) Comparison of A vs. B:

$$\frac{\Delta[H^+]\ (P_{CO_2}\ \text{impact @ constant NAE})}{\Delta[H^+]\ (\text{NAE impact @ constant } P_{CO_2})} = \frac{3.2}{1.4} = 2.3^b$$

[a] Units of plasma $[H^+]$, nEq/liter; P_{CO_2}, mm Hg; $[HCO_3^-]$, mEq/liter; NAE, mEq/24 hr.

[b] By similar calculation:

$$\frac{\Delta[HCO_3^-]\ (P_{CO_2}\ \text{impact @ constant NAE})}{\Delta[HCO_3^-]\ (\text{NAE impact @ constant } P_{CO_2})} = \frac{2.8}{1.1} = 2.5$$

average carbon dioxide tension for the group. The isocapnic values so obtained are summarized on Table 3. The results indicate that the mean isocapnic (P_{CO_2} = 38 mm Hg) plasma $[H^+]$ is significantly different in the subjects ingesting diet A compared to those ingesting diet C, the two diets that produced the extreme values of endogenous acid production. Furthermore, utilizing the data obtained from all 19 studies, there was a significant positive correlation between the isocapnic plasma $[H^+]$ and net acid excretion (Fig. 4). Taken together, these findings provide further evidence to support the hypothesis that interindividual differences in steady-state endogenous acid production significantly influence the level at which plasma $[H^+]$ is regulated, and that the effect is independent of the influence of interindividual differences in plasma P_{CO_2} on plasma acidity.

Utilizing the same technique (Fig. 3), normalization of the values of plasma $[HCO_3^-]$ in the 19 studies yield isocapnic values of plasma $[HCO_3^-]$ that significantly differ in the subjects ingesting diet A compared to those ingesting diet C (Table 3), and that correlate significantly (negatively) with net acid excretion (Fig. 4). As noted previously, the finding that higher values of net acid excretion are associated with both lower values of plasma $[HCO_3^-]$ and higher values of plasma $[H^+]$ is consistent with the expected directional effect of variation in endogenous acid production on the titration of body buffers.

It is possible from these data to compare the impact on plasma acidity of the observed interindividual differences in plasma P_{CO_2} with the impact of the observed interindividual differences in endogenous acid production (Table 6). The results indicate that the impact of observed differences in plasma P_{CO_2} on plasma acidity exceeds by a factor of two that due to observed differences in endogenous acid production (Table 6). Utilizing a similar analysis, it may be concluded that differences in plasma P_{CO_2} have twice the effect on plasma $[HCO_3^-]$ than do differences in acid production (Table 6).

Another method to estimate the relative impact of differences in P_{CO_2} tension versus acid production differences on plasma acidity utilizes the results of the multiple correlation analysis summarized on Table 4. Using the partial correlation coefficient of the regression of plasma acidity on P_{CO_2} at constant net acid excretion ($r = 0.64$), and that of plasma acidity on net acid excretion at a constant P_{CO_2} ($r = 0.53$), differences in P_{CO_2} account for about 40% ($r^2 = 0.41$) of the interindividual differences in plasma acidity, and differences in endogenous acid production account for about 30% ($r^2 = 0.28$) (Table 4). Correspondingly, differences in plasma P_{CO_2} account for about 50% of the interindividual variation in plasma $[HCO_3^-]$, and acid production differences account for about 25% (Table 4). Taken together, these estimations suggest that the relative quantitative impact of interindividual differences in endogenous acid production on plasma acid-base composition is of the same order of magnitude but only about one-half as important as that of plasma P_{CO_2}.

Characteristics of the diet other than that which determines the rate of endogenous acid production might also influence the level at which plasma acidity is regulated. During mineral acid administration in dogs, it has been demonstrated that the steady-state level of plasma acidity during chronic acid loading is influenced by the nature of the anion accompanying the acid [22]. Conceivably, differences in the anion species released with endogenous acid might explain part of the interindividual differences in plasma acid-base composition not accounted for by differences in plasma P_{CO_2} and rate of endogenous acid production. The extent to which differences in the content of other dietary constituents (for example, fat, carbohydrate, calcium, and phosphorus) (Table 1) influence plasma acid-base composition also remains to be investigated.

By indicating that dietary and respiratory factors co-determine the normal level of plasma acidity in healthy individuals, the present results imply that recognition of disturbances in plasma acid-base composition requires a consideration of these two factors. Metabolic acid-base disturbances become recognizable when plasma acidity is observed to be outside the range of values expected for the prevailing rate of endogenous acid production and plasma P_{CO_2}. In patients with suspected disorders of acid-base metabolism, clinical determinations of plasma acid-base composition may yield values well within the broad range of normal values undefined in relation to these two modulating factors, yet a significant degree of metabolic acidosis or metabolic alkalosis might be present. The "normal" range of plasma acidity for a given rate of endogenous acid production and plasma P_{CO_2} will be smaller than the range defined by the observed maximal differences in plasma acidity among normal individuals, and such a restricted normal range would therefore permit the recognition of metabolic acid-base disturbances that might otherwise be overlooked. The results of the present study do not establish definitive criteria for the normal range of plasma $[H^+]$ and $[HCO_3^-]$ in relation to the rate of endogenous acid production and the plasma P_{CO_2} because the number of individuals studied and the number of diets utilized was relatively small. Further investigations are required for this purpose, as well as to investigate the acid-base impact

of normal diet variations in relation to age, sex, and renal functional integrity.

If normal differences in the rate of diet-modulated endogenous acid production compel corresponding differences, however, small, in plasma acid-base composition, then the potential physiological consequences of small differences in plasma acid-base composition of lifelong duration require consideration. A persisting increase in plasma [H^+] concentration of even 1 to 2 nEq/liter, or reduction in plasma [HCO_3^-] of even 1 to 2 nEq/liter, cannot be dismissed as pathophysiologically insignificant or benign since the deleterious consequences of chronic metabolic acidosis remain to be completely defined and may not be inconsequential [23–39]. Chronic metabolic acidosis has been implicated as a factor in the pathogenesis of metabolic bone disease, nephrocalcinosis, and nephrolithiasis [26–28]. Chronic metabolic acidosis induced experimentally by exogenous acid loading characteristically results in persisting hypercalciuria [29–31] and negative calcium balance [29, 30], and as found by some investigators [31] but not others [29], a persisting increase in plasma parathyroid hormone concentration. The circulating levels of parathyroid hormone are supernormal in patients with renal tubular acidosis, and the levels can be normalized by administration of exogenous alkali in amounts sufficient to sustain correction of metabolic acidosis [32, 33]. Acutely induced metabolic acidosis enhances the ability of parathyroid hormone to mobilize calcium salts from bone [34], and experimentally induced chronic acidosis is accompanied by losses of both organic and inorganic phases of bone [35, 36]. Metabolic acidosis reduces the rate of urinary excretion of citrate [37, 38], an organic anion that functions normally to inhibit precipitation of calcium salts in the urinary tract [40]. A reduced rate of urinary citrate excretion has been implicated as a factor in the pathogenesis of nephrocalcinosis and nephrolithiasis in patients with renal tubular acidosis [28] and those with recurrent nephrolithiasis of unknown cause [39]. These findings raise the possibility that major organ damage can occur in states of mild chronic metabolic acidosis. In this context, the findings of the present study compel consideration of the role of diet-determined rates of endogenous acid production and plasma acid-base composition in the pathogenesis of idiopathic metabolic bone disease, nephrocalcinosis, and nephrolithiasis.

Though it may be conceded that a persisting state of mild metabolic acidosis exists in some normal subjects, it might be argued that such acidosis is not likely to be associated with deleterious consequences inasmuch as external hydrogen ion balance is not positive in normal subjects, in contrast to patients with renal acidosis [41] and normal subjects receiving a chronic exogenous acid load [13]. Computing external hydrogen ion balance as the difference between the rate of endogenous acid production and the rate of renal net acid excretion in the steady-state, Lennon, Lemann, and Litzow [2] reported that, on the average, external hydrogen ion balance was not significantly different from zero in normal subjects ingesting diets yielding endogenous acid production rates ranging from 20 to 120 mEq/day, a range similar to that observed in the subjects of the present investigation. However, on closer inspection of the data reported by Lennon, Lemann, and Litzow [2], it is evident that external hydrogen ion balance was substantially positive in those patients with the highest rates of endogenous acid production of the group. Indeed, utilizing the tabular data in their paper, we noted a significant positive correlation between external hydrogen ion balance and the rate of endogenous acid production (Fig. 6), and that a positive value of hydrogen ion balance is expected when endogenous acid production exceeds about 70 mEq/day (Fig. 6), which is close to the average value of endogenous acid production for the group. These findings and those of the present investigation taken together permit the inference that when the steady-state rate of endogenous acid production exceeds about 1 mEq/kg body weight per day in normal subjects ingesting normal acid-producing diets, external hydrogen ion balance will be persistently positive and a relative state of mild metabolic acidosis will exist.

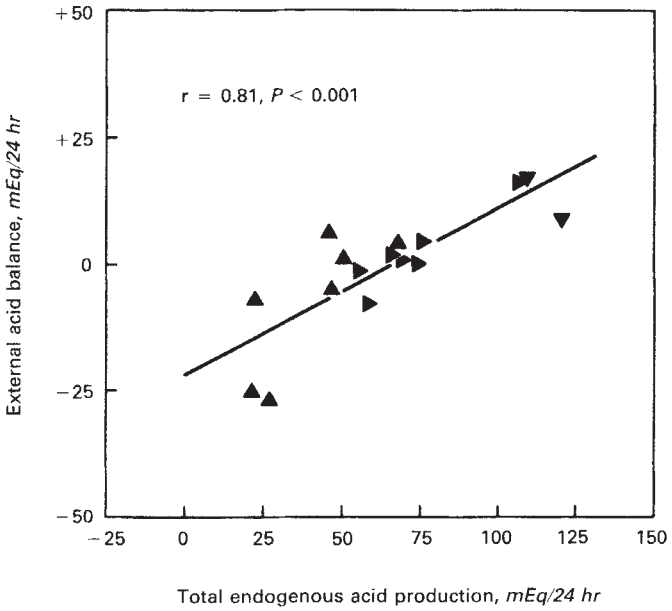

Fig. 6. *Relation between external acid-balance and total endogenous acid production in the steady-state in normal subjects ingesting one of three different diets.* Each *data point* plotted represents the mean steady-state value observed in one individual. Endogenous acid production was estimated as the sum of urinary sulfate plus organic anion excretion less the difference between diet and stool combustible anion excretion. Data are plotted from tabular data taken from [2]. Symbols are: ▶, formula diet; ▲, whole food, type A; ▼, whole food, type B.

The findings in this study may also have implications relating to the pathophysiology of metabolic acidosis in patients with chronic renal insufficiency. In these patients, diet-modulated differences in the rate of endogenous acid production might have a magnified effect on plasma acid-base composition inasmuch as renal acid excretory ability is impaired. Metabolic acidosis in patients with chronic renal insufficiency, is associated with continuing positive external hydrogen ion balance [41]. The substantial variability of plasma bicarbonate concentration for a given degree of glomerular insufficiency observed in such patients [42] might be accounted for in part by consideration of the prevailing rate of endogenous acid production.

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