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Age and Systemic Acid-Base Equilibrium: Analysis of Published Data

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To investigate whether systemic acid-base equilibrium changes with aging in normal adult humans, we reviewed published articles reporting the acid-base composition of arterial, arterialized venous, or capillary blood in age-identified healthy subjects. We extracted or calculated blood hydrogen ion concentration ($[H^+]$), plasma bicarbonate concentration ($[HCO_3^-]$), blood PCO_2, and age, and computed a total of 61 age-group means, distributed among eight 10-year intervals from age 20 to 100 years. Using linear regression analysis, we found that with increasing age, there is a significant increase in the steady-state blood $[H^+]$ ($p < .001$), and reduction in steady-state plasma $[HCO_3^-]$ ($p < .001$), indicative of a progressively worsening low-level metabolic acidosis. Blood PCO_2 decreased with age ($p < .05$), in keeping with the expected respiratory adaptation to metabolic acidosis. Such age-related increasing metabolic acidosis may reflect in part the normal decline of renal function with increasing age. The role of age-related metabolic acidosis in the pathogenesis of the degenerative diseases of aging warrants consideration.

IN normal adult humans eating ordinary American diets, systemic acid-base equilibrium is maintained within narrow limits from day to day, despite a continuing input of fixed acids (e.g., sulfuric acid) generated as end products of the metabolism of neutral precursors in the diet (e.g., sulfur-containing amino acids) (Shock and Hastings, 1934; Moller, 1959; Kurtz et al., 1983). Day-to-day stability of acid-base composition of the systemic circulation is critically dependent on excretion of acid in urine (Schwartz et al., 1959; Widmer et al., 1979), the steady-state rate of which is adjusted by the healthy kidney in keeping with the prevailing rate of endogenous acid production. Considering that renal functional integrity progressively declines with age (Davies, 1950; Rowe et al., 1976; Lindeman et al., 1985), it is conceivable that as an individual ages, blood acidity will be regulated at progressively higher levels and plasma bicarbonate concentration at progressively lower levels. Such progressively worsening metabolic acidosis, however mild, might over time have deleterious effects, perhaps contributing to the pathogenesis of many of the physiologic disturbances and degenerative diseases of aging. Yet, practically no attention has been given to the effect of age on the acid-base composition of the blood in healthy subjects.

One possible deleterious effect of age-related worsening metabolic acidosis is the decline of bone mass that normally occurs in otherwise healthy men and women with advancing age (Riggs et al., 1981; Kurtz et al., 1983; Sebastian et al., 1994), a phenomenon that ultimately manifests as osteoporosis. Preliminary data support the hypothesis that age-related bone mass decline results in part from continual dissolution of bone to release alkaline salts (e.g., calcium carbonate) to titrate a portion of the daily dietary acid load (Wachman and Bernstein, 1968; Bernstein et al., 1970). Even in young healthy subjects, a portion of the daily acid load fails to be excreted by the kidneys and is retained in the body (Lennon et al., 1966; Kurtz et al., 1983), accompanied by a low-level metabolic acidosis whose severity is mitigated by the alkaline salts mobilized from bone. Since renal function declines with advancing age, conceivably an ever increasing fraction of the daily acid load will be retained which can only be compensated for by increased release of bone base (Goodman et al., 1965).

In an attempt to determine whether the acid-base composition of the blood in normal adult humans changes in relation to age, we collected acid-base data in age-specified subjects reported from diverse laboratories and pooled the data into a single cross-sectional data base for statistical analysis.

METHODS

We were unable to find specific reference to the effect of aging on the acid-base composition of the blood in standard textbooks in the fields of gerontology, nutrition, nephrology, respiratory physiology, anesthesiology, and acid-base physiology. Accordingly, we searched for articles reporting data on both the acid-base composition of the blood and the age of the subjects studied, using Medline, references cited by the articles retrieved from Medline, and references cited in handbooks on the values of blood constituents. Medline search terms included: elderly, acid-base, arterial blood gas, acidosis, gerontol#, and geriat#. Original sources were used for the collected data except in one case of data reported in a handbook (Singer and Hastings, 1971) and cited as unpublished data.

More than a hundred articles were scrutinized; from these we selected only articles reporting data on acid-base composition of arterial blood, arterialized venous blood, or capillary blood in healthy subjects. In regard to the healthy status of the subjects, the articles specified that the subjects had no history of medical problems, that they were healthy according to screening examinations, or in the case of some of the younger subjects, that they were healthy medical students. Arterial blood, arterialized venous blood (which is blood drawn from a vein in the dorsum of the hand that has been heated to around 39–43 °C for 15–20 minutes prior to drawing the blood), and capillary blood have nearly the same pH (Gambino, 1959; Paine et al., 1961; Forster et al., 1972).

To be selected for inclusion, the article must have reported, in addition to the age of the subjects, blood pH and at least one of the following: blood or plasma carbon dioxide (CO_2) tension (PCO_2); plasma or serum bicarbonate concentration ($[HCO_3^-]$); plasma or serum total CO_2 (or CO_2 content). We selected only baseline data obtained in the subjects prior to any experimental intervention.

Ultimately, 26 articles published from 1934 through 1982 were used in our analysis (Shock and Hastings, 1934; Hamilton and Shock, 1936; Robinson, 1938; Gibbs et al., 1942; Cournand et al., 1945; Lambertsen et al., 1950; Shock and Yiengst, 1950; Wilson et al., 1950; Scheinberg et al., 1954; Alexander et al., 1955a, 1955b; Hilton, Jr. et al., 1955; Hickam et al., 1956; Holaday et al., 1957; Kennedy and Sokoloff, 1957; Moller, 1959; Manfredi, 1962; Holmgren and McIlroy, 1964; Bouhuys et al., 1966; Ward et al., 1966; Goldring et al., 1968; Singer and Hastings, 1971; Dempsey et al., 1972, 1974; Forster et al., 1975; Gledhill et al., 1975). Cumulatively, those articles report data on 971 normal persons between the ages of 18 and 97 years, 720 of whom were men, 148 women; in 103 subjects the gender was not recorded. The oldest subject known to be female was 77 years old.

Table 1 lists the 26 articles selected, and summarizes the age and sex of the subjects studied and the methods used for determination of blood acid-base composition. Blood pH was usually measured at 37 °C, nearly always using glass electrodes. Three articles cite the use of a colorimetric method for blood pH, which Singer et al. (1955) report gives values differing little from glass electrode values (−.002 to +.007). When measured, PCO_2 was measured by PCO_2 electrode and total CO_2 by volumetric manometry.

In many of the articles, data on blood acid-base composition were not reported for individuals, but only for groups of individuals (mean values) in age-groups by 10-year intervals. For consistency of data representation in articles recording individuals' data, we computed age-group means by decade in the same way. For each acid-base variable, a total of 61 age-group means was collected from the 26 articles and distributed among the following age-groups: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and 90–99 years. Those data constituted our "dataset-1." In dataset-1, within each age-group, the variance will be lower than the among-subject variance would have been had the dataset comprised each subject's individual data point.

To further reduce the variance within age-groups, for each age-group in dataset-1, we calculated an overall age-group mean across all reports. This generated 8 age-group means for each acid-base variable, and those data constituted our "dataset-2."

For statistical analyses, we converted pH to hydrogen ion concentration ($[H^+]$, neq/L), where $[H^+] = 10^{-pH}/10^{-9}$. In cases where the PCO_2 was measured, plasma $[HCO_3^-]$ was calculated from the Henderson-Hasselbalch equation: pH =

Table 1. Summary of Subject Characteristics and Laboratory Methods Used for Analyses

Reference	Total Subjects	Age Range (avg)	No. Men	Male Age Ranges	No. Women	Female Age Ranges	Lab Method Used			Fluid	Posture
							pH	PCO_2	TCO_2		
(Shock and Hastings, 1934)	56	18–28	39		17		B	F	E	cap	NG
(Hamilton and Shock, 1936)	123	17–22	123	17–22			B	F	E	cap	NG
(Robinson, 1938)	49	16–76	49	16–76			A	F	E	art	NG
(Gibbs et al., 1942)	50	18–29	50	18–29			A	F	E	art	supine
(Cournand et al., 1945)	32	21–62	27	21–62	5	22–56	A	NG	E	art	supine
(Shock and Yiengst, 1950)	152	40–89	152	40–89			B	F	E	cap	NG
(Wilson et al., 1950)	11	(31.1)	11	31.1			A	F	E	art	NG
(Lambertsen et al., 1950)	36	18–39	36	18–39			NG	NG	NG	art	NG
(Scheinberg et al., 1954)	13	18–38	12	18–38	1	27	A	F	E	art	supine
(Alexander et al., 1955a)	3	23–24	3	23–24			A	F	NG	art	NG
(Alexander et al., 1955b)	12	17–49	9	17–39	3	20–49	A	F	E	art	NG
(Hilton et al., 1955)	11	17–73	11	17–73			A	F	E	art-v	NG
(Hickam et al., 1956)	14	23–49	14	23–49			A	F	E	art	NG
(Holaday et al., 1957)	5	25–26	5	25–26			A	F	E	art	NG
(Kennedy and Sokoloff, 1957)	12	(24.5)	12	24.5			A	F	E	art	NG
(Moller, 1959)	100	20–60+	50	20–60+	50	20–60+	A	D	E	art	supine
(Manfredi, 1962)	15	20–49	15	20–49			A	F	E	art	supine
(Holmgren and McIlroy, 1964)	10	20–37	10	20–37			A	D	NG	art	supine
(Ward et al., 1966)	100	60–97	NG		NG		A	F	NG	art	seated, supine
(Bouhuys et al., 1966)	73	22–60	73	22–60			A	F	NG	cap	NG
(Goldring et al., 1968)	13	27–40	13	27–40			A	NG	E	art	NG
(Singer and Hastings, 1971)	49	50–81	27	50–81	22	50–77	A	F	E	art	NG
(Dempsey et al., 1972)	10	21–40	10	21–40			A	C	NG	art	supine
(Dempsey et al., 1974)	7	20–49	NG	20–49			A	D	NG	art, art-v	supine
(Gledhill et al., 1975)	8	20–29	8	20–29			A	D	NG	cap	NG
(Forster et al., 1975)	7	20–29	7	20–29			A	D	F	art	NG

Notes. A = pH glass electrode, B = colorimetric technique, C = PCO_2 from Siggard-Anderson nomogram, D = PCO_2 electrode, E = manometric technique, F = calculated from Henderson-Hasselbalch equation, NG = not given, art = arterial blood, art-v = arterialized venous blood, cap = capillary blood.

$pK' + ([HCO_3^-]/0.0301 \cdot PCO_2)$. In cases where PCO_2 was not recorded, but total CO_2 (TCO_2) was recorded, plasma bicarbonate concentration was calculated from the formula: $TCO_2-(TCO_2/[1 + 10^{(pH-6.1)}])$. To avoid potential bias related to the differences in the method for computing plasma bicarbonate concentration, we generated two sets of values for plasma bicarbonate concentration: (a) pbc1, taking plasma bicarbonate concentration preferentially as calculated from pH and PCO_2, secondarily as calculated from pH and TCO_2, and (b) pbc2, taking plasma bicarbonate concentration preferentially as calculated from pH and TCO_2, secondarily as calculated from pH and PCO_2. Statistical analyses were carried out using SigmaStat.

RESULTS

Blood $[H^+]$ correlated positively with age (Table 2, Figures 1 and 2). At age 80 years, blood $[H^+]$ was 6–7% higher than at age 20 years (Table 2). Based on the data from dataset-2, 90% of the variability in blood $[H^+]$ among the 8 age-group means was accounted for by the variability in age (Table 2).

Plasma $[HCO_3^-]$ correlated negatively with age (Table 2, Figures 1 and 2). At age 80 years, plasma $[HCO_3^-]$ was 12–16% lower than at age 20 years (Table 2). Based on the data from dataset-2, 87–88% of the variability in plasma bicarbonate concentration among the 8 age-group means was accounted for by the variability in age (Table 2). The results were similar for the two sets of values of $[HCO_3^-]$ (pbc1, pbc2) (Table 2).

Blood PCO_2 correlated negatively with age (Table 2, Figure 3). At age 80 years, blood PCO_2 was 7–10% lower than at age 20 years (Table 2). Based on the data from dataset-2, 81% of the variability in blood PCO_2 among the 8 age-group means was accounted for by the variability in age (Table 2).

DISCUSSION

Age and Blood Acid-base Composition

The results of the present study suggest that, in aging from young adulthood to old age, otherwise healthy men and women develop a worsening low-level metabolic acidosis. From age 20 to 80 years, the apparent steady-state plasma $[HCO_3^-]$ decreases by about 12–16%, and blood $[H^+]$ increases by about 6–7%. These changes are more than two-fold greater than those occurring in response to the extremes of variation of normal dietary acid loads (Kurtz et al., 1983).

Although the least-squares linear fit of the changes in plasma $[HCO_3^-]$ and blood $[H^+]$ with age was statistically significant, the changes appeared to be less striking in the earlier decades than in the later (Figures 1 and 2). The changes appeared to be most striking starting at about age 50.

From age 20 to 80, blood PCO_2 also decreases (7–10%), as would be expected in response to increased blood acidity (Madias et al., 1979; Kurtz et al., 1983; Cogan et al., 1986). The magnitude of PCO_2 decrease (3.0 mm Hg from age 20 to 80 years) is within the range expected (0.9–1.5 mm Hg PCO_2 reduction per meq/L reduction in plasma $[HCO_3^-]$) for the observed plasma $[HCO_3^-]$ reduction (3.1 meq/L), i.e., within the range of 2.8–4.6 mm Hg (Cogan et al., 1986).

The results of cross-sectional analysis must be interpreted with caution, however. The finding that blood $[H^+]$ is higher in older subjects, and plasma $[HCO_3^-]$ is lower, does not permit one to conclude with certainty that individual subjects increase their blood $[H^+]$ and decrease their plasma $[HCO_3^-]$ as they get older. Age correlation in a cross-sectional study might be due to age-related factors that select against survival of individuals with lower blood $[H^+]$ (i.e., higher blood pH) and higher plasma $[HCO_3^-]$. Although it may seem unlikely that persons with less severe acidosis would be selected against, the findings in this study require confirmation from longitudinal studies of individuals. Nevertheless, without the cross-sectional data reported herein, the need for such studies might not have been appreciated.

Another caveat about cross-sectional studies relates to the potential of procedural bias. An apparent age-related trend in a measurement variable that emerges from pooled data from several laboratories might only reflect differences in procedure among studies, including specimen sampling, processing, and analytical methodology (see section below on potential confounding variables). Few laboratories recorded data from subjects with an age range that spanned young

Table 2. Summary of Linear Regression Analyses of Blood Acid-Base Variables on Age*

	n	y	x	a = Regression Coefficient	b = $y_{@x=0}$	r^2	r	p-value	$y_{@x=20}$	$y_{@x=80}$	% Change (Age 20 to 80 yrs)
	61	pH	age, yr	–0.00042	7.41	.16	.40	<.002	7.40	7.38	
	61	$[H^+]$, neq/l	age, yr	0.040	38.7	.16	.40	<.002	39.5	41.9	+6.1%
Dataset-1	61	pbc1, meq/l	age, yr	–0.051	26.3	.38	.62	<.001	25.3	22.2	–12.1%
	61	pbc2, meq/l	age, yr	–0.054	26.8	.36	.60	<.001	25.7	22.5	–12.6%
	61	PCO_2 mm Hg	age, yr	–0.050	42.8	.13	.36	<.005	41.8	38.8	–7.2%
	8	pH	age, yr	–0.001	7.42	.89	.95	<.001	7.41	7.38	
	8	$[H^+]$, neq/l	age, yr	0.048	38.3	.90	.95	<.001	39.3	42.1	+7.3%
Dataset-2	8	pbc1, meq/l	age, yr	–0.067	27.1	.87	.94	<.001	25.8	21.7	–15.6%
	8	pbc2, meq/l	age, yr	–0.069	27.5	.88	.94	<.001	26.2	22.0	–15.8%
	8	PCO_2 mm Hg	age, yr	–0.071	44.0	.81	.90	<.005	42.5	38.3	–9.9%

Notes. $[H^+]$ blood hydrogen ion concentration; pbc plasma bicarbonate concentration (see Methods section for distinction of pbc1 vs pbc2); PCO_2 = blood carbon dioxide tension; n = number of observations; y = dependent variable; x = independent variable (age); a = regression coefficient; b = y-intercept, or value of y at x = 0 (age = 0); regression equation: $y = ax + b$.

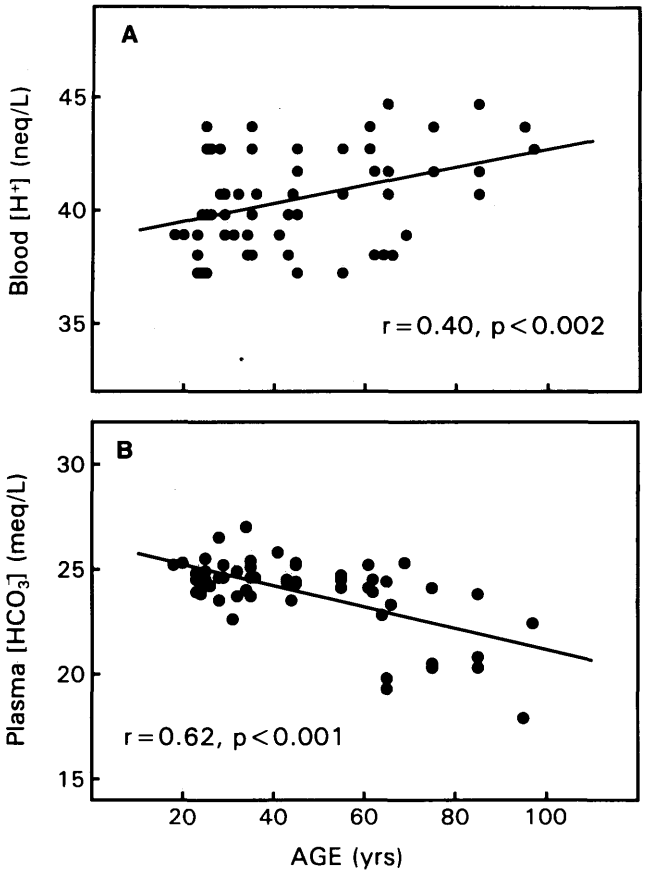

Figure 1. **A** Relation between blood hydrogen ion concentration ([H^+]) and age, and **B** between plasma bicarbonate concentration ([HCO_3^-]) and age, in normal adult men and women: dataset-1. Each data point depicts the means of the paired values (blood [H^+] and age, or plasma [HCO_3^-] and age) for a group of subjects whose ages were in one of the selected 10-year intervals: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and 90–99 years.

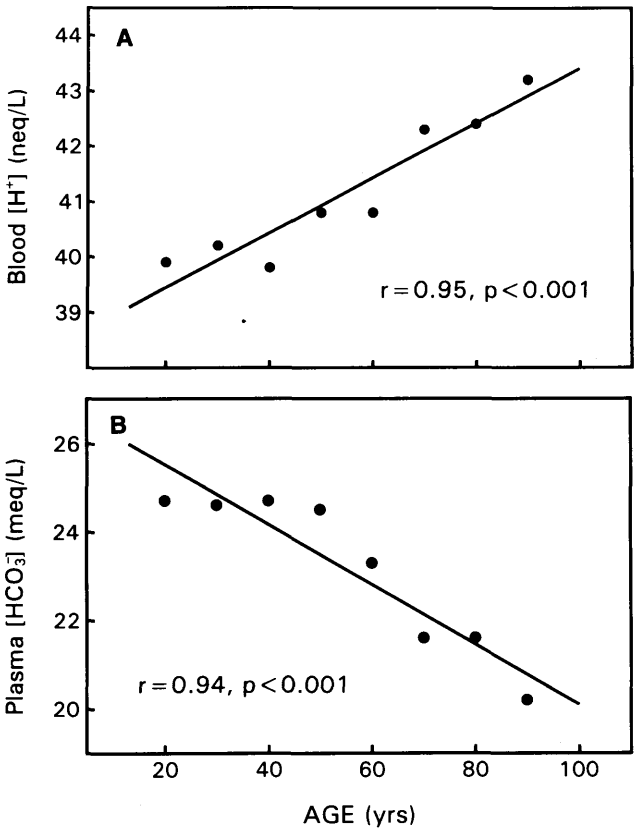

Figure 2. **A** Relation between blood hydrogen ion concentration ([H^+]) and age, and **B** between plasma bicarbonate concentration ([HCO_3^-]) and age, in normal adult men and women: dataset-2. Each data point depicts the mean of the means of the paired values (blood [H^+]) and age, or plasma [HCO_3^-] and age) for all groups of subjects whose ages were in one of the selected 10-year intervals: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and 90–99 years.

adulthood to old age (Cournand et al., 1945; Shock and Yiengst, 1950; Hilton, Jr. et al., 1955; Agarwal and Cabebe, 1980), and in most cases the investigators did not detect an age-related change in systemic acid-base equilibrium. Those usually had too few subjects for meaningful within-laboratory analysis of potential age-related trends. The report by Shock and Yiengst (1950), who studied 152 subjects spanning ages 40 to 89 years, was the only one amenable to such analysis. The findings in that study (Figure 4) are similar to those in the multilaboratory analysis (Figures 1 and 2).

Role of Age-Related Renal Functional Decline

A progressively increasing degree of metabolic acidosis developing with advancing age might be regarded as a predictable finding, inasmuch as renal functional integrity progressively deteriorates with age (Davies and Shock, 1950; Takazakura et al., 1972; Darmady et al., 1973; Kaplan et al., 1975; Rowe et al., 1976; Lindeman, 1986; Rudman, 1988). The kidney is a major determinant of the set-point at which plasma [HCO_3^-] is regulated (Goodman et al., 1965; Lennon et al., 1966). With advancing age, a condition like that of chronic renal insufficiency develops (Davies and Shock, 1950; Takazakura et al., 1972; Darmady et al., 1973; Kaplan et al., 1975; Rowe et al., 1976; Lindeman, 1986; Rudman, 1988). Renal insufficiency impairs systemic acid-base homeostasis, due in variable part to reduced conservation of bicarbonate and decreased excretion of acid (Schwartz et al., 1959; Goodman et al., 1965; Sebastian et al., 1976; Borghetti et al., 1978; Widmer et al., 1979; Schambelan et al., 1980; Madias and Kraut, 1989). In particular, acid-excretory ability in response to acute exogenous acid loading is impaired (Adler et al., 1969; Gonick et al., 1969; Bricker et al., 1971; Agarwal and Cabebe, 1980), and with more prolonged acid loading a more severe degree of metabolic acidosis is sustained compared to that in similarly acid-loaded younger subjects (Hilton, Jr. et al., 1955). It would not be surprising, therefore, to find that elderly persons, like patients with chronic renal insufficiency, regulate their plasma acidity at significantly higher levels, and their plasma bicarbonate concentration at significantly lower levels, than younger persons, i.e., that such individuals have chronic metabolic acidosis (Hilton et al., 1956). A renal mechanism might explain why the rate of change of plasma [HCO_3^-] and blood [H^+] becomes more striking after age 50 years (Figures 2 and 3).

Yet it may be asked whether the degree of renal functional insufficiency that occurs with aging is of sufficient magni-

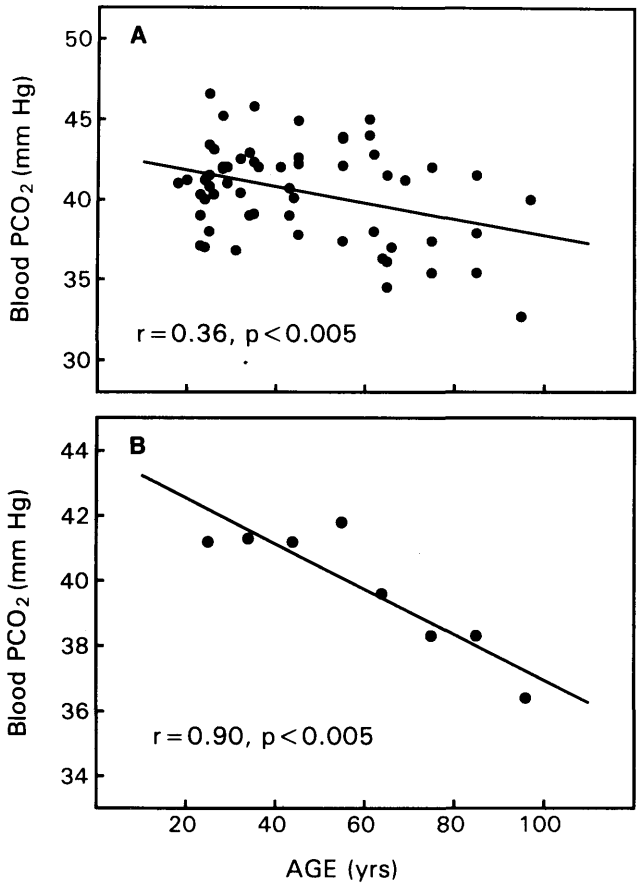

Figure 3. Relation between blood carbon dioxide tension and age, in normal adult men and women: dataset-1 (**A**) and dataset-2 (**B**). Each data point in **A** corresponds to a data point in Figure 1. Each data point in **B** corresponds to a data point in Figure 2.

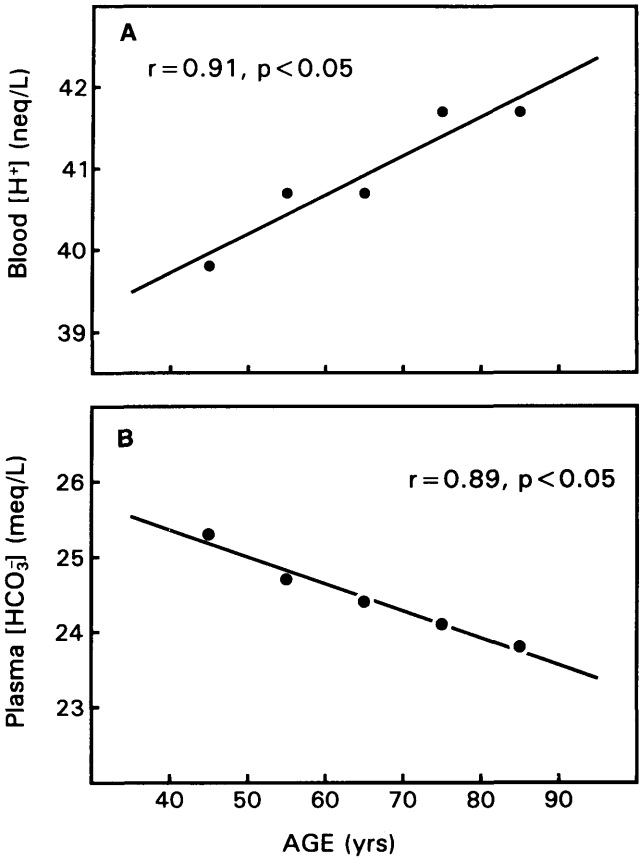

Figure 4. **A** Relation between blood hydrogen ion concentration ($[H^+]$) and age, and (**B**) between plasma bicarbonate concentration ($[HCO_3^-]$) and age, in 152 normal adult men and women: data of Shock and Yiengst (1950). Each data point depicts the means of the paired values (blood $[H^+]$ and age, or plasma $[HCO_3^-]$ and age) for a group of subjects whose ages were in one of the selected 10-year intervals: 40–49, 50–59, 60–69, 70–79, and 80–89 years.

tude to account for the observed age-related change in blood acid-base composition. Glomerular filtration decreases by about 50% from age 20 to 80 years (Davies and Shock, 1950; Rowe et al., 1976). Can that degree of renal insufficiency account for a 12–16% reduction in plasma $[HCO_3^-]$ (Figures 1,2,4)? In patients with chronic renal disease studied by Hakim and Lazarus (1988), serum $[HCO_3^-]$ decreased by about 6% from normal for an estimated 50% reduction in glomerular filtration rate from normal. In a similar study by Widmer et al. (1979), serum $[HCO_3^-]$ decreased by about 15% from normal in those patients whose serum creatinine concentration increased to about 177 μmol/l (2 mg/dl), a value indicative of a reduction in glomerular filtration rate of about 50% of normal. Thus, our observed 12–16% decrease in plasma $[HCO_3^-]$ from age 20 to 80 years is not unequivocally outside the range of reduction of serum bicarbonate that occurs with declining renal function in patients with chronic renal disease. The degree of renal insufficiency that accompanies aging is therefore not so small that renal functional impairment can be excluded unequivocally as a possible mechanism to account for the attendant systemic acid-base changes with aging.

If real, the contribution of the kidney to the development of age-related metabolic acidosis might reflect the pathological changes in the kidney known to occur with age (Davies and Shock, 1950; Kaplan et al., 1975; Lindeman, 1986) and/or the influence of humoral, direct, and indirect modulators of the set-point at which the kidneys regulate plasma $[HCO_3^-]$ (e.g., parathyroid hormone, calcitriol, calcium, phosphorus (Hulter et al., 1982; Hulter, 1985); aldosterone (Hulter et al., 1977; Sebastian et al., 1980), which are known to change with age (Weidmann et al., 1978; Armbrecht et al., 1984; Marcus et al., 1984; Eastell et al., 1989; Marcus et al., 1990; Stim et al., 1994). Furthermore, variability among subjects in the intensity of these humoral influences might act to confound detection of a relationship between blood acid-base composition and degree of renal insufficiency. Unfortunately, data on the levels of these factors and of renal functional status are lacking in nearly all of the articles reviewed for the present meta-analysis.

Role of Age-Related Changes in Diet

In considering age-related decline of renal function as a potential cause of age-related acidosis, one tacitly assumes that there is no counterbalancing reduction in acid load from the diet. Clearly, any reduction in dietary acid load that might occur with age is not sufficient on average to prevent a worsening acidosis with age (Figures 1 and 2). Although it

seems unlikely, it is conceivable that dietary acid load increases with age and contributes to the magnitude of the acid-base changes. As noted above, the magnitude of the observed age-related changes in blood acid-base composition was more than twice that occurring in young subjects with variation in dietary acid load over the extremes of the normal range. Small increases in dietary acid load with age might be expected to have greater impact in older subjects, however, owing to renal functional insufficiency. Little is known about dietary acid production in relation to age.

It is possible that the apparent age-related trend in acid-base equilibrium reflects a lesser acid load in subjects reported on in the older studies (1940–50s) compared to that in subjects of more recent reports. Per capita animal protein intake was about 15% lower in the 1950s than currently (Food and Agriculture Organization, 1991). Whether such small changes are sufficient to explain the apparent trend in acid-base equilibrium remains to be determined. On regression analysis, we found no significant relationship between the age of the subjects and the date the study was done (r^2 = .04), or between blood [H^+] (r^2 = .04) or serum [HCO_3^-] (r^2 = .0008) and date of study.

Potential Confounding Variables

Differences in sex. — Is it possible that the apparent age-related trend in acid-base equilibrium is an artifact of gender-related differences? Women have lower values of serum [HCO_3^-] than men, but they also have *lower* values of blood [H^+] (i.e., higher values of blood pH) than do men (Shock and Hastings, 1934). Such directionally similar changes in [HCO_3^-] and [H^+] indicate that the primary effect of gender difference is on the respiratory component of systemic acid-base equilibrium. Indeed, blood PCO_2 values are lower in women than in men (Shock and Hastings, 1934), and their corresponding directionally similar lower values of blood [H^+] and [HCO_3^-] are those one would expect for the observed PCO_2 decrease (Shock and Hastings, 1934). In our study, the changes in blood [H^+] and [HCO_3^-] with age are in opposite directions, consistent with a primary, age-related change in the metabolic component of systemic acid-base equilibrium. Gender-bias might confound the finding of an age-related primary respiratory acid-base disturbance, which was not observed, but not that of a primary metabolic acid-base disturbance, which was observed.

Differences in posture. — Like differences in gender, differences in posture affect blood acid-base composition by primarily altering blood PCO_2 due to changes in the rate of alveolar ventilation (Ward et al., 1966). Assumption of the supine position elevates the diaphragm, decreasing the functional residual capacity of the lungs, leading to hyperventilation and mild respiratory alkalosis. As in the case of gender bias, posture bias might confound the finding of an age-related primary respiratory acid-base disturbance, which was not observed, but not that of a primary metabolic acid-base disturbance, which was observed.

Age-related endocrine factors. — Additional confounding factors that should be considered are the normally occurring age-related changes in circulating levels of hormones that potentially can directly and/or indirectly influence steady-state blood acid-base composition. Age-related changes have been reported in the levels of parathyroid hormone (PTH) (Endres et al., 1987; Minisola et al., 1993), vitamin D metabolites (Omdahl et al., 1982; Chapuy et al., 1983; Armbrecht et al., 1984), aldosterone (Weidmann et al., 1975), sex hormones, and growth hormone (O'Neill, 1992). The effects and interrelationships among these hormones, the minerals and electrolytes they regulate (viz., calcium, phosphorus, potassium, chloride, sodium, extracellular volume), and acid-base homeostasis are too complex for brief discussion (see Hulter et al., 1982, 1983; Hulter, 1985; Hulter and Peterson, 1985), but are potentially significant mediators or modulators of the observed age-related effects on blood acid-base composition.

Effect of methodological differences. — Although the time span of reports reviewed approximates half a century, similar methods in general were used to measure pH and total CO_2. Both the glass pH electrode (pH) and the manometric CO_2 method were developed in the 1920s and were soon established as standards (Reed and Henry, 1974). Few of the studies we reviewed used other methods (see Table 1), and by inspection no bias appears to have been introduced by their inclusion. By regression analysis there was no trend between blood [H^+] or plasma [HCO_3^-] concentration and the year the study was done.

Significance of Age-Dependent Changes in Acid-Base Homeostasis

Accepting that blood [H^+] increases with age, and plasma [HCO_3^-] decreases, one might question whether the magnitude of the changes is large enough to have pathologic significance. Yet, changes in blood acid-base composition of lesser magnitude are accompanied by persisting retention of acid in the body (Kurtz et al., 1983; Kleinman and Lemann, 1987), and such sequelae of metabolic acidosis as an accelerated rate of bone resorption and reduced rate of bone formation (Sebastian et al., 1994). Moreover, the age-related changes in blood acid-base composition are greater than those occurring in many patients with classic renal tubular acidosis, in particular those with the syndrome of incomplete distal renal tubular acidosis, who have barely discernible metabolic acidosis yet manifest the alkali-reversible sequelae of metabolic acidosis (Konnak et al., 1982; Preminger et al., 1987; Osther et al., 1993).

What are the pathophysiological consequences of diet-dependent extracellular and intracellular increases in acidity and reductions in bicarbonate concentration, and relentless whole-body acid retention, however mild, persisting in otherwise healthy individuals for decades, and increasing in severity with advancing age? We do not know, but several possibilities warrant consideration.

Effect on bone. — Bone mineral base is released into the systemic circulation when exogenous acid is administered (Lemann, Jr. et al., 1965, 1966, 1967; Kleinman and Lemann, 1987; Bushinsky, 1989). When acid loading is continued for several weeks or months, excretion of acid in

urine — quantitatively the major component of the homeostatic response to an exogenous acid load — fails to keep pace with the increased load (Lemann, Jr. et al., 1965, 1966). Release of bone base continues, bone mineral content and bone mass progressively decline (Barzel, 1969, 1976; Barzel and Jowsey, 1969; Burnell, 1971; Delling and Donath, 1973), and osteoporosis occurs (Jaffet et al., 1932; Barzel, 1969, 1976; Barzel and Jowsey, 1969; Delling and Donath, 1973; Schofield and Saith, 1981). Extracellular acidification increases the activity of osteoclasts, the cells that mediate bone resorption (Arnett and Dempster, 1986; Goldhaber and Ribadjija, 1987; Teti et al., 1989; Krieger et al., 1992), and inhibit the activity of osteoblasts, which mediate bone formation (Krieger et al., 1992).

Life-long ingestion of ordinary diets constitutes a less intense, more prolonged variant of the short-term experimental administration of large exogenous acid loads. Typical American diets are net acid-producing in that renal excretion of acid exceeds that of base, and, when measured directly, net endogenous acid production is positive (Lennon et al., 1966; Kleinman and Lemann, 1987). Counterbalancing a normal diet-related endogenous acid production rate with a dietary absorbable base supplement can attenuate or reverse the baseline loss of bone mass that occurs normally (Sebastian et al., 1994).

Effect on skeletal muscle. — Chronic low-level diet-dependent metabolic acidosis might contribute to the progressive diminution of muscle mass characteristic of aging in humans. Metabolic acidosis increases the rate of degradation of skeletal muscle proteins, but not its rate of protein synthesis (May et al., 1986, 1987a, 1987b, 1992; Hara et al., 1987; Mitch et al., 1989a, 1989b, 1993; England et al., 1991; Williams et al., 1991a, 1991b; England et al., 1992; Greiber and Mitch, 1992; Maniar et al., 1992), and as a result, muscle mass decreases. Correction of acidosis by administration of exogenous alkali as the sole experimental maneuver reverses the accelerated proteolysis (Papadoyannakis et al., 1984).

Effect on kidney. — Is it possible that life-long metabolic acidosis consequent to dietary acid loading contributes to the decline of structural and functional integrity of the kidney that typically occurs with aging? If that were the case, age-related worsening acidosis and declining renal function might be mutually exacerbating: a vicious cycle. Perhaps the life-long increased load of skeletal calcium and phosphorus, mobilized in response to the needs of acid-base homeostasis, and delivered to the kidney for excretion, promotes microscopic intrarenal calcification and consequent renal functional abnormalities (Gimenez et al., 1987). Perhaps life-long acid loading lessens the renal production of the calcium-solubilizing factor, citrate, as does acute acid loading (Gordon, 1963), and thereby fosters intrarenal calcification. Are individuals who do not experience an age-related decline in renal functional integrity (Lindeman et al., 1985) those who customarily eat low acid-producing diets, or even base-producing diets, which would minimize or prevent age-related acidogenesis?

No one knows the answers to those questions. But then no one knows what causes the normal age-related decline in renal structural and functional integrity, or why some individuals are spared. The present study suggests that there is a progressively increasing metabolic acidosis occurring in parallel with the renal function decline with age. Considerations of the physiology and pathophysiology of elderly people should take this into account.

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