

Friedrich Manz

History of nutrition and acid-base physiology

■ **Summary** In the 17th century the notion of nutrition and diet changed in northern European countries. First chemical experiments fostered the idea that salts resulted from a union of acids and bases. Digestion was no more regarded as a process of cooking but a succession of fermentations controlled by a balanced production of acids and alkali. Life seemed to depend on the equilibrium of acids and alkalis.

In the 19th century food was systematically analysed for the content of energy and macronutrients and first scientifically based nutritional

standards were formulated. The preferred use of processed food from the new food industry resulted in epidemics of nutritional disorders. Acidosis seemed to be a plausible pathogenic factor. Practitioners (S Ishizuka, H Hay, FX Mayr) formulated holistic doctrines integrating the concept of balance of acids and bases and recommending food with an excess of alkali.

New micromethods to determine the concentration of electrolytes and blood acid-base status promoted physiological and clinical research into acid-base metabolism in the 1960s. In the new physiologically based terminology of systemic acid-base status, the relationship between blood acid-base status and net acid intake or excretion was, however, incorrectly simplified. In the 1970s metabolic acidosis was observed in patients on chemically defined diets and par-

enteral nutrition. Based on the data of comprehensive acid-base balance studies, calculation models were used to estimate renal net acid excretion from nutrient intake and to predict the potential renal acid load of single foods.

Extrapolating current trends to the future, one can say that acid-base physiology will probably remain a challenge in nutrition and functional medicine over the next few years. The challenge will include new concepts for the manipulation of nutritional acid load in sports, dietetics and preventive medicine as well as new definitions of the upper intake level of potential renal acid load in functional foods and the monitoring of renal net acid excretion in populations.

■ **Key words** History – Nutrition – Acid-base physiology – Acid-base balance – Renal net acid excretion

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Prof. Dr. med. Friedrich Manz (✉)
Research Institute of Child Nutrition
Heinstück 11
44225 Dortmund, Germany
E-Mail: manz@fke-do.de

Acids and alkali in alchemy

Several substances now called acids and bases were already known in antiquity. In the medieval period alchemists searching for the secret of how to make gold were highly interested in strong acids. The dissolution of metals in nitric or sulphuric acid seemed to be the first step to convert a metal into gold [1, 2]. The term acid is probably derived from the sour taste. The term alkali hints at its origin, the ash of vegetables. “Al qali” is the Arabian term of ash.

The change from medieval to modern diet in the 17th century

Up to the 17th century the elite classes of the Islamic and Christian world shared pretty much the same diet: thick purees with lots of spices, sweet and sour sauces, cooked vegetables and warmed wines [3]. The Islamic world and Spanish America continued this tradition. Modern curries in India and moles in Mexico are examples of this. The notion of this diet and nutrition can be traced to Greco-Roman times [3]. Digestion was assumed to be a

form of cooking. A suitable diet supported the equilibrium of the four bodily fluids – blood, phlegm, yellow bile and black bile – corresponding to the four elements – air, water, fire and earth. Food was assigned according to differences in dryness and heat. For example, pepper and beef were dry and hot and affiliated to yellow bile and fire, whereas milk was said to be wet and hot corresponding to blood and air.

In the middle of the 17th century the elite class of northern Europe began to change its diet. Taking experience from distillation in alchemy Paracelsus classified matter at the beginning of the 16th century not into four but into three elements [3]. The volatile part containing the essence, the smell or the aroma was called mercury. The oily substance carrying the moistness and sweetness was termed sulphur. The solid residue of food responsible for taste and consistency was termed salt. These terms have very little in common with modern chemical terms. Digestion was assumed to be succession of fermentations. Vegetables and fruits spoil rapidly. So, there was no need for pre-digestion by cooking. Thus, fresh greens and vegetables were welcomed. Fat-based sauces and oil-based salad dressings became fashionable. Butter or vegetable oils, the components of sulphur were combined with flour and salt, the components of salt, as well as with vine or bouillon, the components of mercury. Sugar and sweets moved to the periphery of the menu as the dessert. In some foods the essence showed up as gas bubbles. So, sparkling mineral waters gained popularity and sparkling champagne was produced for the first time.

"Salt" – a compound of acid and alkali

In the 17th century the investigation of the nature of gases and "salts" were preferred topics in natural sciences. Rudolph Glauber (1627–1691) mixed table salt with sulphuric acid and produced sodium sulphate (Glauber's salt), a wondrous laxative, profitably sold under the brand name "sal mirabile" [2]. His investigations fostered the idea that salts resulted from a union of acids and alkali.

Life – an equilibrium of "acids and alkali"

Francis de la Boé Sylvius (1614–1672) believed that the breakdown of food in the alimentary canal effected by a succession of fermentations was controlled by a balanced production of acids and alkalis. A Dutch scientist Jan Baptista van Helmont (1577–1644) had demonstrated that gastric juice and normal urine were acidic. He visualised acids as sharp rodlets dissolving substances that resisted all other liquids and alkalis as rings blocking the sharpness of rodlets (Fig. 1) [4]. Diseases

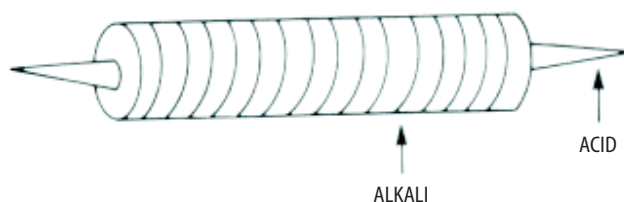


Fig. 1 Structure of salt as a compound of acid and alkali according to Jan Baptista van Helmont (1577–1644) [1, 4].

were assumed to be the result of an abnormal fermentation leading to the development of an acid or alkaline excess in body fluids. In order to maintain a balance, a surplus of acids should be treated with alkali and vice versa. This highly speculative holistic concept of life as an equilibrium of acids and alkalis had a profound influence on European history of the mind.

Landmarks of acid-base chemistry in the 18th century

Joseph Black (1728–1799) searching for a way to dissolve bladder stones demonstrated that chalk (calcium carbonate) lost weight during calcination and simultaneously released a gas today called CO₂, which was also present in expired air and in the smoke of fire. Antoine Laurent Lavoisier (1743–1794) described that ordinary air contained another gas which was respirable, nourished combustion and combined with metals. He called it "oxygène" from the Greek words of "acid" and "to form", as in his view the new gas constituted the principle of acidity common to all acids. He also showed that water was not a basic element but composed of hydrogen and oxygen. In his new chemical terminology mineral alkali were termed "la soude", vegetable alkali "la potasse" and volatile alkali "l' ammoniaque".

Organic chemistry and the relation of nutrition and acid-base metabolism in the 19th century

Based on the accumulating knowledge in inorganic chemistry, Jöns Jacob Berzelius (1779–1848) focused on chemical composition and processes in animals and Justus von Liebig (1803–1873) in plants. Studying the composition of organic acids Liebig defined acids as substances whose content of hydrogen could be replaced by a metal. William Prout (1785–1850) discovered free acid in rabbit gastric juice with about one third of the chloride content. Henry Bence Jones (1813–1878) observed in detail the variations in the acidity of urine in relation to food consumption. He speculated that conversion of oxygen leads to the formation of an acid in the body and, therefore, recom-

mended alkaline waters. Liebig showed that herbivores excreted an alkaline urine.

Heroic treatment of cholera patients

In the 19th century balneology and dietetics were most respected medical therapies. In 1832 the first successful and most spectacular treatment of a mineral imbalance and an acid-base disturbance was the intravenous administration of a 10 l solution containing 0.5 % sodium chloride and 0.2 % sodium bicarbonate to a 50 year old woman with cholera by Thomas Aitchison Latta (-1833), a young unknown Scottish practitioner [5]. Despite further positive experiences by other physicians, Latta's therapeutic concept was not accepted. It was in opposition to the dominant therapeutic principle of Galen, who expelled "the evil" with blood-letting or powerful emetics as mineral acids, calomel and antimony. There were only a few inaccurate data on the sodium and chloride content of body fluids and no basic physiological understanding. Highly varying concentrations of sodium chloride and sodium bicarbonate and usually with volumes estimated too low brought the concept in disrepute.

The detection of the ionic structure of salts and water

The ion concept profoundly transformed the understanding of acid-base physiology. Svante August Arrhenius (1859–1927) observed a correlation between conductivity and chemical reactivity in various salt solutions and outlined the dissociation theory. Wilhelm Ostwald (1853–1932) described the ability of water to dissociate generating H⁺ and OH⁻ ions. Soren Peter Lauritz Sorensen (1868–1939) introduced the pH value and demonstrated its vital importance for the control of enzyme activity [6]. Lawrence Joseph Henderson (1878–1942) and Karl Albert Hasselbalch (1874–1962) investigated buffer systems in biological fluids especially the carbonic acid/bicarbonate system and formulated the "Henderson-Hasselbalch equation" [7, 8].

The beginning of nutritional science in the 19th century

In a patient with a gastric fistula from a gunshot wound, William Beaumont (1785–1853) observed that the digestion of various foods always resulted in an acidic chyme. He assumed that all food contained only one nutrient or "aliment", which is dissolved in the stomach and absorbed later on. In the second half of the 19th century nutrition became a topic of the new sciences of physiology

and biochemistry. Food was systematically analysed for its content of energy and macronutrients and nutritional standards were formulated. An adult men between 70–75 kg should, e. g. receive 3000 kcal, 118 g protein, 56 g fat and 500 g carbohydrates (Karl von Voit 1831–1908; Max Rubner 1854–1932). The new knowledge was the basis of a rapidly expanding food industry which introduced a new category of food, the processed food.

Clinical research of acid-base metabolism from 1850–1950

Up to 1950 clinical research in acid-base metabolism was hampered by delicate and time consuming analytical procedures and the need for large amounts of biological material, e. g. one blood analysis required more than 20 ml of blood. Emil Heinrich du Bois-Reymond (1818–1896) observed the formation of lactic acid during muscle contraction. This was the beginning of intensive studies on the relation between oxygen supply, carbohydrate conversion, lactic acid formation and a decreased blood alkalinity. In patients in diabetic comas, Adolf Kussmaul (1822–1902) called attention to the heavy, deep respiration and Bernhard Naunyn (1839–1925) to large amounts of beta-oxybutyric acid and acidosis in the blood and a high ammonium excretion in urine. Rudolph von Jaksch (1855–1947) assumed that uremic acidosis was due to poisoning by organic acids owing to the retention of urea. Thus, acidosis could be fatal. In 1897 Adalbert Marianus Czerny (1863–1941) presented arguments that acidosis might also be involved in infantile diarrhoea. This was directly shown by John Howland (1873–1936) and Williams McKim Marriott (1885–1936) in 1916 [9]. They used new expensive analytical methods with blood samples of 1–2 ml. With these methods a few paediatricians such as James Lawder Gamble (1883–1959) and Daniel Cade Darrow (1895–1965) systematically analysed the principle physiological and pathophysiological mechanisms of water, electrolyte and acid-base metabolism and introduced experimentally based parenteral therapeutic regimens using firstly subcutaneous, later on intraperitoneal and finally intravenous access [10, 11].

Processed food as a source of nutritional deficiencies disorders

In the industrialising countries, the preferred use of inexpensive non-perishable processed food products, such as superfine flour, resulted in epidemics of nutritional disorders at the beginning of the 20th century [12]. In retrospect, the new epidemics were due to vitamin or trace element deficiencies or food intoxication. They

were a major challenge to public health and set off various reactions.

Composition of food beyond energy and macronutrients

Based on experimental and clinical data with polished rice as the cause of beriberi in pigeons and man, von Funk (1884–1967) presented in 1910 his concept of nutritional deficiency disorders due to the lack of special nutrients which he called vitamins. In the 1950s it was shown that the biological quality of proteins was based on different amounts of essential amino acids. Finally between 1955 and 1975 several trace element deficiency disorders were published. We are witnesses to an expanding knowledge of the biological effects of non-nutritive substances [13].

First quantification of nutritional acid load

In 1912, Sherman published his data on the effects of an isocaloric exchange of single foods with a different estimated acid intake on urinary excretion of titratable acidity and ammonium in an adult man on a constant basal diet [14]. The estimated excess of acid intake corresponded to the difference in the acid-forming elements ($\text{PO}_4 + \text{SO}_4 + \text{Cl}$) and the base forming elements ($\text{Na} + \text{K} + \text{Ca} + \text{Mg}$). Na, K, Cl were calculated in the form of 1 meq/mmol and Ca, Mg, PO_4 , SO_4 were attributed with 2 meq/mmol. There was a rough agreement between the estimated values of the excess of acid-forming elements and the measured data of urinary ammonium and titratable acidity.

Non-academic doctrines of nutrition and lifestyle integrating the concept of an equilibrium of acids and bases

Several practitioners observed that they or their patients were cured by a diet consisting of a large variety of unprocessed vegetables and fruits instead of a uniform diet of processed food products. This was in contrast to the contemporary scientific concepts. They, therefore, developed new holistic health and life-style doctrines which went far beyond the ideas of nutrition and integrated the idea of the 17th century – that life is an equilibrium of acids and alkalis. Sagen Ishizuka (1851–1910), the founder of the macrobiotic doctrine combined the European thinking of equilibrium of acids and alkalis with the Chinese ideas of Yin and Yang [15]. Howard Hay (1866–1940) advocated a diet with an excess of alkali and a separate intake of carbohydrates and proteins [16]. Franz Xaver Mayr (1875–1965) favouring an alkali

predominant vegetable diet formulated his idea of intestinal autointoxication [17].

The contemporary physiological knowledge supported the hypothesis that the new nutritional epidemics were caused by an acidification of the body. The high alkali excess of vegetables and fruits compared, e. g. to meat was well known. However, academic nutritional advice and the food industry neglected differences in mineral content. In food tables, minerals were not specified. Predominant consumption of greens resulted in an alkaline urine and that of meat in an acid urine. Finally, carbohydrate metabolism was accompanied by the production of high amounts of organic acids and diabetic ketoacidosis, whose aetiology was still unknown, was a lethal disorder. The apocalyptic vision of some proselytes of these authors can be demonstrated by the retranslated German title “Cultural sickness and death of acidosis, healthy nutrition a fateful question for the white race” of the American book “The science of eating” by Alfred McCann [18].

Acidified formulas in infant nutrition

In 1919 Mariott observed an improved growth in infants fed acidified compared to non-acidified cow's milk preparations [19]. Acidification with ammonium chloride, calcium chloride or hydrochloric acid proved to be an effective treatment in infants with hypocalcemic tetany [20–22]. In the following years cow's milk preparations acidified with lactic or citric acid became very popular due to the antibacterial effect and an assumed improvement of bioavailability of several nutrients. In the 1960s the improved bioavailability could not be verified [23]. Furthermore, routine clinical control of blood acid-base status revealed late metabolic acidosis in some newborns and infants due to an imbalance between a high renal acid load in nutrition with acidified cow's milk formulas and the age specific low renal capacity for net acid excretion [24]. At the end of the 1960s, acidified cow's milk formulas were replaced by humanised formulas.

Routine micromethods for the analysis of serum electrolytes and blood acid-base status

Two new analytical techniques opened the door for routine evaluation of acid-base metabolism in clinical medicine in the 1950s and 1960s. Flame photometry allowed quick, inexpensive, and precise routine determination of sodium and potassium in small volumes of biological material [25, 26]. In 1952 in Copenhagen a polio epidemic with a high incidence of patients needing artificial respiration demonstrated the primary importance of accurate pH regulation in artificial respiration [1, 2].

Poul Astrup, a young doctor, therefore developed a micromethod to determine acid-base status in the blood. It was based on three measured values of blood pH, one before and two after equilibration at two different CO₂ tensions. The new micromethod was soon accepted as a routine clinical method and induced a boom in clinical research of acid-base metabolism.

In 1964 a common terminology of blood acid-base status was accepted at a consensus conference [27]. Preferring a physiological interpretation a deviation of blood pH value of 7.4 was designated either “acidosis” or “alkalosis”. Two factors may be responsible: the respiratory factor represented by pCO₂ and an unspecific metabolic factor represented either by plasma bicarbonate concentration (preferentially used in the USA) or standard base excess (preferentially used in Europe). In simple disturbances the terms acidosis or alkalosis can be modified with the adjectives “respiratory” or “metabolic” in order to characterise the effect of the primary aetiological factor and with the further adjectives “secondary” or “compensated” if there was enough time for a compensatory response of the other factor. In retrospect, this terminology showed two principal limitations: Firstly, pH 7.4 is not the desired reference signal of the controller of the body to characterise the physiologic optimum hydrogen ion concentration. Secondly, pH, pCO₂ and base excess are concentrations. They can but must not be correlated to turnover rates.

The unifying concept of acid-base regulation

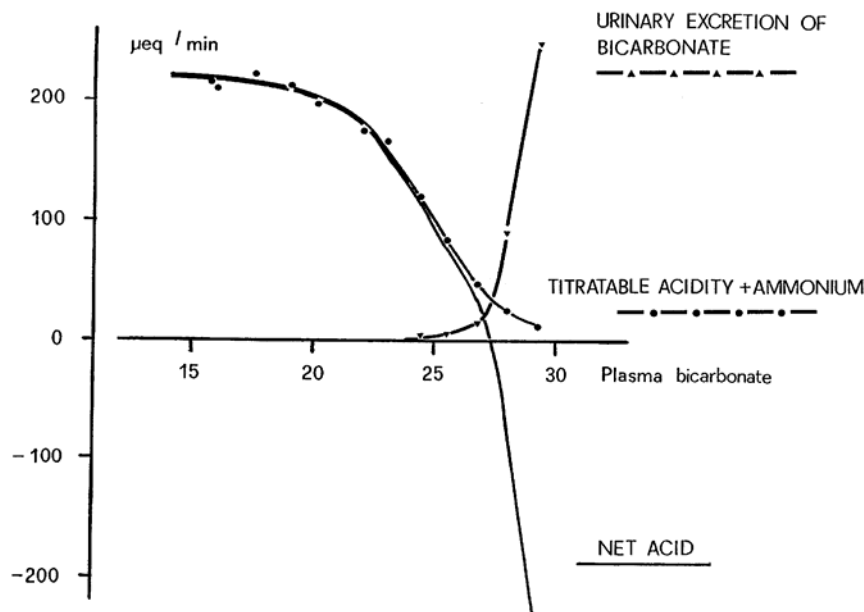
In poikilotherm animals, such as the bullfrog, blood and intracellular pH varies with body temperature [28]. At

10 °C blood pH is about 7.8 and at 30 °C about 7.4 [29]. The slope of the regression line of temperature and blood pH is parallel to the slope of the lines of temperature on one side and pK values of water or histidine imidazole on the other [30]. The fractional dissociation of histidine imidazole is the major determinant of electrochemical charges and therefore of the structural and functional integrity of a protein. Changes of ionic strength and osmolality have similar effects as temperature. Thus, blood pH of 7.4 is not the desired homeostatic control signal of acid-base metabolism of the body. The unifying concept of acid-base regulation reads as follows: The evolution of acid-base equilibrium is geared to maintain the structural and functional integrity of proteins in the presence of unavoidable changes in body temperature, osmolality and ionic strength [28].

Relationship between blood acid-base status and renal net acid excretion

In the 1940s and 1950s acid and bicarbonate loading tests were performed (Fig. 2) [31]. In subjects with a western style diet, renal net acid excretion was about 40% of acute maximum renal net acid excretion at a plasma bicarbonate level of about 25 mmol/l. Maximum renal acid stimulation levelled off at about 18 mmol/l. This is about 9 mmol/l below the plasma bicarbonate level at a renal net acid excretion of zero or – in another term – at a plasma bicarbonate level at the acid-base equilibrium of the kidney. There is no physiological maximum of renal bicarbonate excretion. It is limited by intestinal absorption and production.

Fig. 2 Relationship between renal net acid excretion and plasma bicarbonate level in an adult [31].



Despite these data, a linear relationship between renal net acid excretion and blood base excess was assumed in a group of infants with either acute gastroenteritis or pyloric stenosis [32]. This is an example of the suggestive power of the definitions and interpretations of the consensus conference in 1964 connecting acidosis of the blood with the notion of a net acid load of the body and alkalosis with the notion of a net base load. Some patients with pyloric stenosis showed an acidic urine pH in the presence of a pronounced metabolic alkalosis [32]. According to the consensus conference this seemed to be an incompatible combination of data and, therefore, was called "paradoxical aciduria".

In 1970 Dumas presented the results of 3 bicarbonate loading tests in a seven year old child with congenital chloride diarrhoea at 3 levels of sodium chloride intake, intestinal chloride loss and extracellular volume (Fig. 3) [33]. At the lowest chloride intake of 0.2 mmol per kg per day and the lowest extracellular volume, the plasma bicarbonate level at the renal acid-base equilibrium was 49 mmol/l. At plasma bicarbonate levels just below this value there was a positive renal net acid excretion in the presence of a systemic alkalosis. At a high sodium chloride intake of 10 mmol/kg · d, plasma bicarbonate at the renal acid-base equilibrium was just below normal at about 25 mmol/l. Thus, based on the data of blood acid-base status, a rough estimation of actual renal net acid excretion is only possible if plasma bicarbonate (base excess) at the renal acid-base equilibrium is taken into account.

Plasma bicarbonate level at the renal acid-base equilibrium is not only modulated by extracellular volume but also by blood pCO₂ and serum potassium, parathormone and Ca [34].

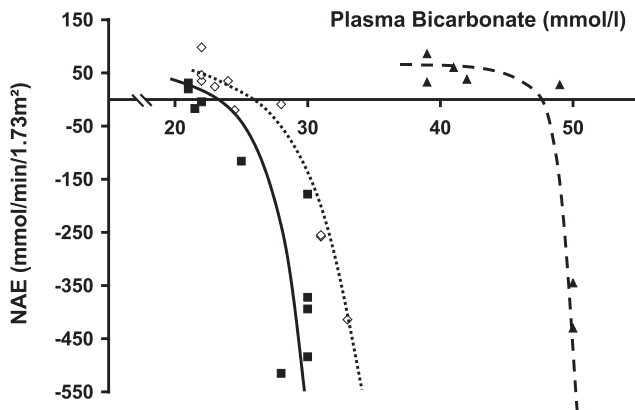


Fig. 3 Relationship between renal net acid excretion and plasma bicarbonate in a patient with congenital chloride deficiency at a dietary intake of chloride of 0.2 mmol/kg · d (▲), 3.5 mmol/kg · d (◇) and 10 mmol/kg · d (■) [33].

Classic input-output acid-base balance studies

In the 1960s classic input-output acid-base balance studies were performed for the first time in healthy adults and patients with chronic renal acidosis [35, 36]. Balance data comprised four non-metabolisable cations (Na + K + Ca + Mg) and two non-metabolisable anions (Cl + PO₄) of intake, stool and urine, urinary data of two metabolic endproducts (sulphate, organic acids) and the three renal metabolites of renal net acid excretion (titratable acidity, ammonium, bicarbonate). If individual retention rates of the major nutritional ions are known and urinary excretion of sulphate, organic acids and net acid excretion are taken into account, net hydrogen balance of the body can be calculated. In healthy adults hydrogen retention was zero [36]. In patients with chronic renal failure with metabolic acidosis daily net acid retention was about 50 % of daily renal net acid excretion [35].

Potential renal acid load

During the last 30 years the contribution of the gut, the liver and growth to acid-base metabolism has been repeatedly controversially debated. Kildeberg assumed an overall active regulation of intestinal ion absorption sustaining a high excess of absorbed cations [37]. However, there is no need for an overall regulation process if individual absorption rates of all major ions are considered. Bourke and Häussinger postulated that the liver plays a role focussing on an isolated segment of acid-base metabolism [38]. During growth a large alkali pool is accumulated in the skeleton. Many authors assumed that skeletal growth is accompanied by an increased renal acid load. An increased intestinal Ca absorption is usually accompanied by an increased absorption of organic acids. For each mmol of Ca laid down in hydroxyapatite, 0.92 mmol of nonmetabolisable base is bound and 0.92 mmol of protons are released into the extracellular fluid. These protons are virtually metabolised by organic acids. The intestinal net gain of nonmetabolisable cations is shifted to a net gain of alkali in the skeleton without altering renal net acid excretion [34]. In contrast, growth of extracellular volume results in an increased renal acid load. Sodium and chloride intake are very similar. Both ions are almost completely absorbed. If more sodium is retained, an unchanged urinary chloride excretion results in a higher renal acid load.

A physiologically based calculation model to yield an appropriate estimate of renal net acid excretion has been recently validated [39]. The calculation model took into account the mineral and protein composition of foods, the average intestinal absorption rates of the respective nutrients, sulfur metabolism and urinary ex-

cretion of organic acids. The portion of urinary net acid excretion that was independent of endogenous organic acid excretion related to body surface area was used to calculate the potential renal acid load of foods.

Metabolic acidosis in chemically defined diets and parenteral nutrition

In normal subjects maximum renal net acid excretion is usually higher than nutritional renal acid load. In the 1960s the chemical industry was able to produce all amino acids at low costs. So, low quality protein hydrolysates were replaced by specifically designed amino acid mixtures or chemically defined diets. Surprisingly, many patients with parenteral nutrition, chronic renal failure or inherited metabolic diseases developed metabolic acidosis [40–42]. Several factors added up to this high renal acid load. The basic amino acids were given as chloride salts [40]. Hydrolysis of phospholipids was another source [43]. Egg protein with a high content of methionine and cystine was used as the reference protein, leading to a high production and urinary excretion of sulphate [41]. Some amino acid mixtures were offered as nitrogen supplements neglecting the mineral content [41]. As the basic low protein diet sometimes also showed a low mineral content the major cation surplus of the basic diet ($\text{Na} + \text{K} - \text{Cl}$) was low [41].

Long-term effects of a nutritional chronic high acid load

A girl with phenylketonuria received unintentionally a highly acidic, low phenylalanine diet for 29 months [44]. Temporary growth retardation, and urolithiasis were the direct effects of chronic acid loading and severe caries a late consequence. Thus, chronic dietary acid loading can cause serious side effects.

Long-term effects of dietary chloride deficiency syndrome with metabolic alkalosis

At the end of the 1970s in the United States two batches of a soya-based infant formula and in Spain one batch of a cow's milk formula were sold with unintentionally very low chloride contents [45, 46]. Infants exclusively fed these formulas for several weeks showed growth failure, psychomotor retardation, hypochloremic metabolic alkalosis, hypokalemia, hypercalciuria and microhematuria. At 2 to 4 years a negative dose-response relationship between former formula intake and developmental outcome was observed. At 7 to 10 years of age the children showed catch-up growth. There was however a remarkable risk of deficits in learning and language skills [47].

Benefits of a historical approach?

This historical review might be helpful to understand concepts and inconsistencies in terminology. Physiology of acid-base metabolism seems to be one of the most unpopular topics of medicine due to its complexity and the horrible simultaneous use of different concepts and nomenclatures. The “so-called” great transatlantic acid-base debate is now 37 years old, but is it really finished [48]?

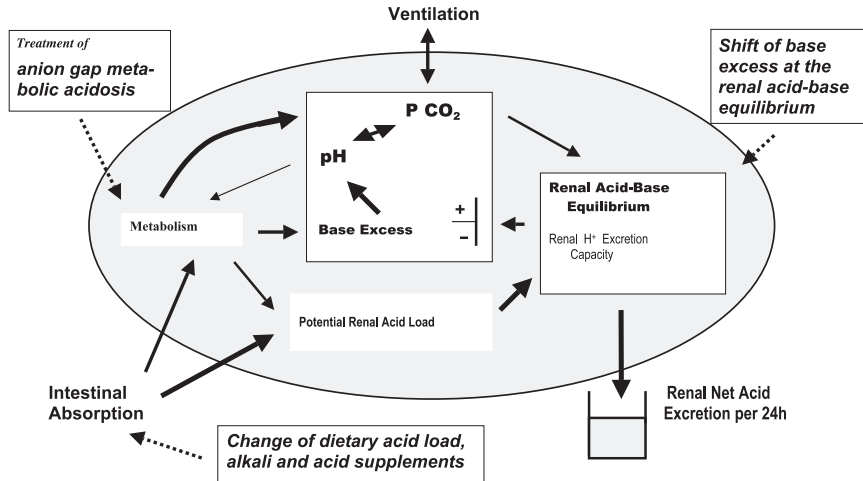
In the non-academic society in Germany there is huge interest in the relationship between nutrition and acid-base metabolism. For instance 750 000 copies of the nutritional advice by Hay have been sold in Germany, Switzerland and Austria in the last 40 years [16]. The original meaning of the word diet the antique term *di-aita* recommending, e. g. adequate eating and drinking, balance of activity and passivity, healthy rhythm of sleeping and wakefulness has lost nothing in its attractiveness. It gives orientation, inner meaning and a feeling of security. For many people the word acid-base equilibrium is a modern scientifically styled functional synonym of the old word *di-aita*. The commercial success of many alkalisating measures may perhaps depend more on the hope of the consumer to feed his insatiable craving for inner meaning and security than the relief of a defined clinical problem.

Finally, extrapolation allows speculation of future trends in nutrition and acid-base metabolism.

Elements of regulation of blood acid-base status and renal net acid excretion

In Fig. 4 the elements of regulation of blood acid-base status and renal net acid excretion are depicted. In a steady state there are three sources of renal net acid excretion: 1) the excess of the absorbed non-metabolisable cations on the non-metabolisable anions in the gut, 2) sulphate production and 3) urinary excretion of organic acids [34]. If blood base excess is just below the level of blood base excess at the acid-base equilibrium of the kidney a decrease in base excess stimulates renal hydrogen excretion. Delta base excess depends both on renal handling of hydrogen ion excretion and on actual renal acid load. Excess production of high amounts of a metabolisable organic acid with almost complete tubular absorption at physiological serum levels, as lactic acid, temporarily decreases the level of blood base excess without altering renal net acid excretion. Finally blood base excess at the acid-base equilibrium of the kidney is modulated by extracellular volume, pCO_2 , and the serum levels of potassium, parathormone and Ca [34].

Fig. 4 Schematic diagram of regulation of blood acid-base status, net acid in- and output and points of voluntary and/or therapeutic measures to manipulate blood base excess and renal net acid excretion.



Functional medicine in nutrition and acid-base metabolism

Functional medicine will perhaps be the preferred topic of nutrition and acid-base metabolism in the next few years. In the following, several concepts to manipulate acid-base status of the body or to treat disorders of acid-base metabolism are presented (Table 1).

During high intensity activities acidosis is thought to be responsible for fatigue and exhaustion in working muscles. Pre-exercise administration of a bicarbonate supplement improved the performance in interval swimming delaying the onset of fatigue [49, 50]. Thus, an *increased buffer capacity of the body* improves muscular performance. In addition, alkali supplements as an adjuvant therapy may be integrated in the treatment of other organs with a risk of local metabolic acidosis, e. g. in skeletal mineralisation [51, 52] or the treatment of pain [53] or angina pectoris? Large *extrarenal bicarbonate losses* in patients with intestinal malabsorption, diarrhoea or urinary diversion [54] must be compensated by alkali supplements.

In several tubulopathies or inherited metabolic disorders a *pathologic urinary excretion of amino acids and/ or organic acids* increases renal net acid excretion. Alkali therapy should be considered in metabolic acidosis or if urine pH values are constantly below 5.4 indicating maximum renal net acid excretion. In children with refractory seizure disorders, a ketogenic diet usually accompanied by metabolic acidosis reduces the risk of seizures [55]. Anticonvulsant action seems to be caused by an increased cerebral metabolism of ketoacids. As acidosis increases the risk of urolithiasis and decreases the production and blood levels of ketone bodies, in patients with refractory seizure disorders on a ketogenic diet the optimum acids-base status remains to be elucidated [56, 57]. In the future, the acid-base sta-

Table 1 Concepts to manipulate blood acid-base status and/ or renal net acid excretion by changes in dietary acid load, alkalinising or acidifying supplements or other specific therapeutic measures

Change of dietary acid load, alkalinising or acidifying supplements
• Increase of acute buffer capacity of the body in sports medicine, mineralisation of the bone, pain therapy
• Compensation of extrarenal bicarbonate losses in intestinal malabsorption, diarrhoea, urinary diversion
• Compensation of an increased urinary excretion of organic acids in inherited metabolic disorders with hyperorganicaciduria, several tubulopathies, increased urinary excretion of ketoacids in diabetes or when fasting
• Modification of urine pH in urolithiasis, catheter incrustation, pyelonephritis
• Compensation of a low maximum renal net acid excretion in premature infants, elderly, chronic renal failure, distal renal tubular acidosis type 1, 3, 4
• Upper tolerance level of potential renal acid load in food, upper tolerance level of daily acid intake, upper limit of potential renal acid load in chemically defined diets or functional food
Treatment of anion gap metabolic acidosis by
• insulin in diabetic ketoacidosis,
• higher energy intake in fasting ketosis
Shifting of blood base excess at the renal acid-base equilibrium by
• compensation of extracellular volume contraction or expansion,
• treatment of hyper- or hypocapnia, hyper- or hypokalemia, hyperparathyroidism and hypercalcemia

tus in patients who are fasting will perhaps also attract more attention.

In patients with a catheter in the bladder or infection stones (magnesium-ammonium-phosphate, calcium-phosphate, ammonium-hydrogen-urate) low *urine pH values* due to acid loading decrease the risk of catheter incrustation or recurrence of urolithiasis [58]. In pa-

tients with uric acid stones a urine pH level above 6.5 inhibits the formation of new stones.

Premature infants, seniors, patients with chronic renal failure and patients with renal tubular acidosis type 1, 3 and 4 show a *low renal hydrogen ion excretion capacity*. In these patients the usual Western-style of diet results in relatively high or even maximum renal acid stimulation without or with metabolic acidosis [34, 59, 60]. In subjects of these groups a diet with a low acid renal acid load is recommendable or mandatory.

In the 1970s metabolic acidosis was observed in patients receiving parenteral nutrition with synthetic amino acids solutions or chemically defined diets [40–42]. This secondary effect demonstrated the necessity for an *upper limit of potential renal acid load* in these products. In 1983 a directive of the German government defining the composition of chemically defined diets stated that the content of minerals must consider the overall effect on renal net acid excretion [61]. In 1995, the European Union limited the content of ammonium chloride in confectionery products to 5% [62]. This is the first example of an upper tolerance level for potential renal acid load in functional food. There are no epidemiological data of the distribution of renal net acid excretion in healthy populations. Therefore we are not aware of the percentages of healthy adults with maximum renal acid stimulation characterised by urine pH values below 5.4 in 24 h urine samples. The much lower renal net acid load in human ancestral diets [63, 64] and the age related trend to metabolic acidosis in populations consuming a Western style of diet [59] are arguments to assume that the mean and the 97.5% percentile of renal net acid excretion in a population could become important data in the valuation of the quality of a diet.

Acute maximum exercise results in transiently high serum levels of lactic acid and metabolic acidosis. This form of *acute anion gap metabolic acidosis* needs no therapeutic intervention as lactic acid is almost quanti-

tatively reabsorbed in the proximal tubules and avidly metabolised in the liver synthesising glucose. Metabolic acidosis in diabetic ketoacidosis is a combination of retention acidosis due to high renal losses of ketoacids and alkali and anion gap acidosis due to high serum levels of metabolisable ketoacids. Retention acidosis needs alkali therapy and anion gap metabolic acidosis insulin to normalise glucose metabolism.

Blood base excess at the acid-base equilibrium of the kidney is shifted to higher (positive) values by volume contraction, hypercapnia, hypokalemia, and hypercalcemia [34]. It is shifted to lower (negative) values by volume expansion, hypocapnia, hyperkalemia, hyperparathyroidism and proximal renal tubular acidosis [34]. Therapeutic measures must specifically correct the cause of the shift. In preterm infants several causes often act simultaneously. Blood base excess may even be normal as a result of two opposite shifts, e.g. hypercapnia and volume expansion. In patients with complex renal tubular disorders including proximal renal tubular acidosis, by way of exception, the pathologic shift to lower blood base excess values may be partly compensated by volume contraction prescribing hydrochlorothiazide [65]. In patients with complex disturbances of acid-base metabolism the effect of dietary acid load is frequently neglected. In preterm infants with a low maximum renal hydrogen ion excretion capacity fed a preterm formula with a high renal acid load, urinary net acid excretion is frequently near the maximum. If these children develop hypercapnia due to bronchopulmonary dysplasia blood base excess does not increase concomitantly, as the kidney is not able to excrete an additional acid load necessary to increase the extracellular bicarbonate pool. These children characteristically show urine pH levels below 5.4. Alkali therapy is needed to relieve the preterm babies from the stress of the functional state of an incipient late metabolic acidosis.

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