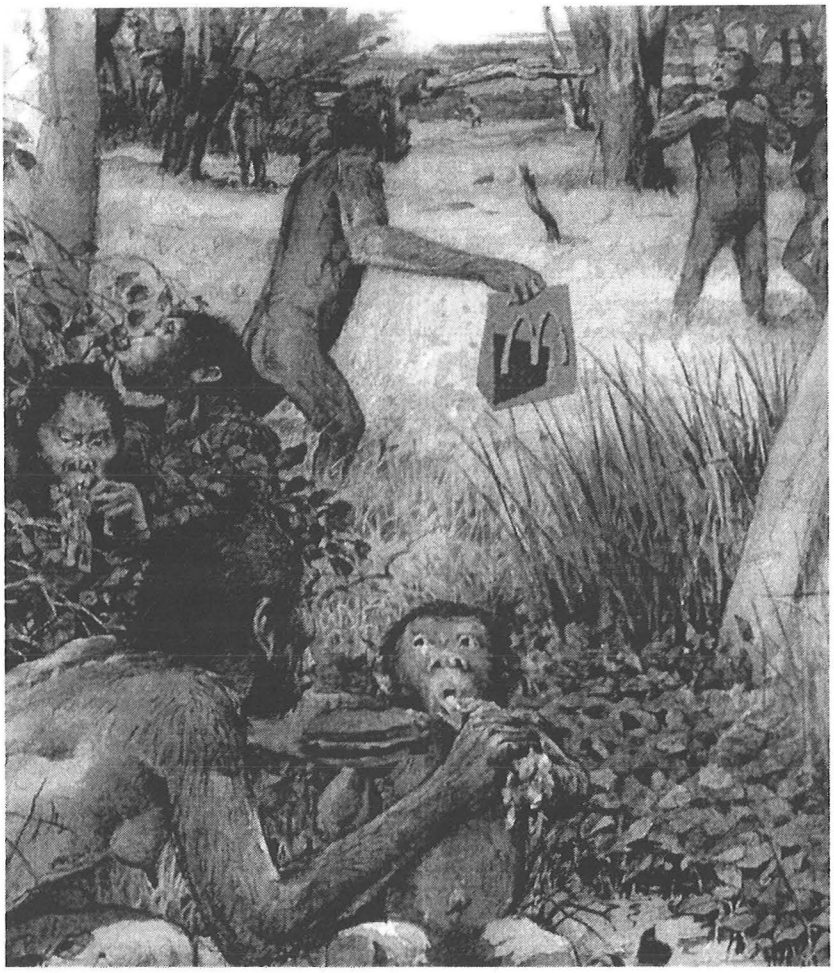
Hypertension and Nephrolithiasis:
Conflicts Between Evolution and Lifestyle



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6. Summary

Using two common conditions in clinical medicine as examples, we shall discuss and speculate on how differences between our biologic constitution and the environment can contribute to human diseases. We will examine some basic tenets of evolution and emphasize that organs and organisms are seldom if ever optimal; they are merely adequate. From this standpoint, conflict between physiology and the environment will always be present. While the current biologic systems in vertebrates evolved over a protracted period of time, human lifestyle changes have occurred very recently at a pace much faster than any evolutionary changes can possibly heed. We will examine some of the evolutionary basis for the current physiologic mechanisms for homeostasis of three cations: Na^+, Ca^{2+}, and H^+. We will conjecture on how the imposition of the modern lifestyle on these archaic systems can contribute to unfavorable phenotypes. Clinical data compatible with this view is presented.

1. Case presentations

Patient 1

A 59 year old black male with a history of hypertension for 10+ years.

He has documented end organ diseases including retinopathy, mild concentric left ventricular hypertrophy by echocardiogram but no history or symproms of heart failure. He has about 1 gm of protein/24 hrs and mild renal insufficiency (Cl_{Cr} 73 ml/min). Previosu evaluation for secondary hypertension has been negative.

Medications: felodipine 20 mg qd, furosemide 20 mg bid, and lisinopril 10 mg qd.

Twenty hr BP monitor (mean sys/dias) before and after dietary NaCl restriction:

	Before	After
24 hr BP monitor (mm Hg)	165/ 98	127/85
24 hr urine Na (mEq)	407	67 mEq

Patient 2

A 36 year old black male with history of nephrolithiasis.

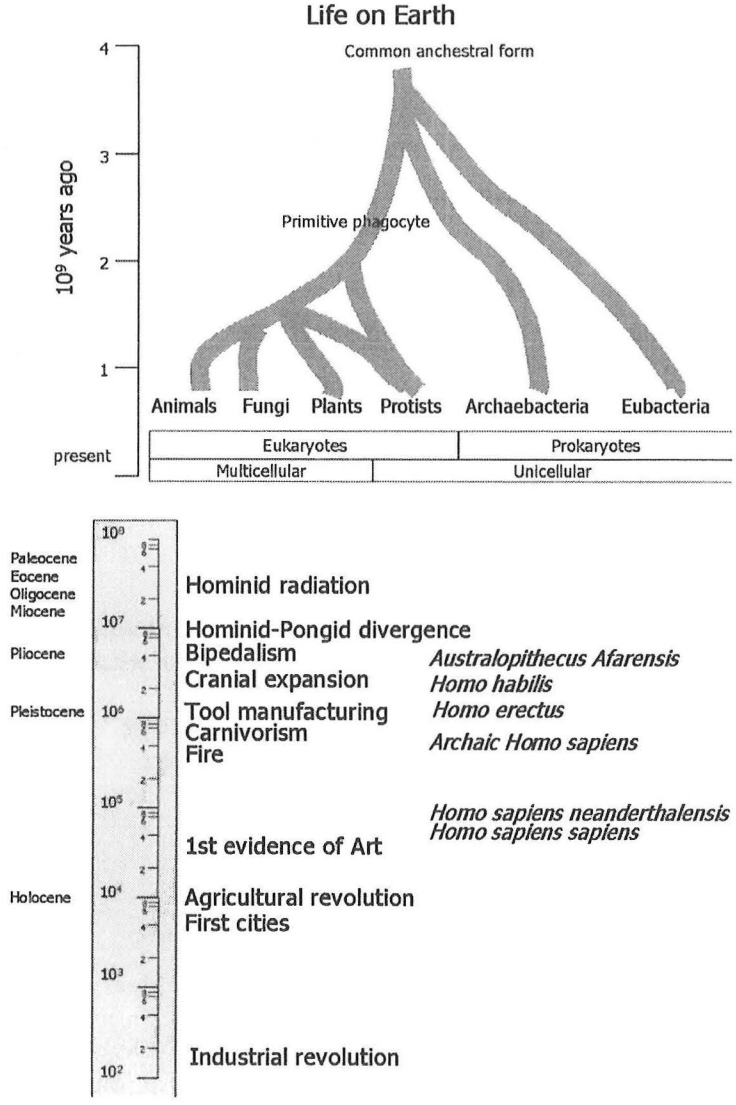
He passed one Ca oxalate stone 6 months ago. A plain KUB showed 3 radio-opaque stones. A renal sonogram showed no obstruction. There no significant pertinent histories. The patient admits to being an enthusiastic body builder who also consumes a high protein and salt diet. Plasma biochemical parameters were normal.

Dietary modification consisting of increase in water intake and protein and salt restriction was prescribed. Twenty four hour urinary biochemical parameters before and after dietary changes:

	Before	After
Ca (mg)	621	400
Oxalate (mg)	65	60
Uric acid (mg)	700	540
Citrate (mg)	100	380
pH	5.8	6.2
Volume (L)	1.7	2.5
Na (mEq)	480	130
Sulphate (mmoles)	55	20
Phosphate (mg)	1100	850
Magnesium (mg)	100	95
Ammonium (mEq)	120	40
Potassium (mEq)	39	80
Creatinine (mg)	1909	1882

2. Evolution of life on the planet

Properties of living organisms today are cumulative results of evolutionary processes. Life originated about 4 billion years ago on this planet with hominids emerging about 350 million years ago. Our earliest bipedal ancestor *Australopithecus afarensis* walked erect on earth only 4 million years ago. Though the archaic form of the *Homo* genus lived 2 million years ago, the earliest modern *Homo sapiens* have been around for no more than 50-70 thousand years. *Homo sapiens* have populated this planet for a relatively short period of time in the context of evolution and "modern" civilization as marked by the dawn of the agricultural revolution is only about 10 thousand years old. Compared to the time frame of primates on earth, even to the existence of our own species, modern civilization is no more than a brief flicker in time. There is no conceivable way that evolution of our species can have adequate number of generations to respond to changes brought about by modern human lifestyles.



Comparative physiologist Malcolm S. Gordon and evolutionary biologist Theodore Garland have written extensively on the basic tenets of evolution. It is clear that organs evolve to be adequate, not optimal. As such, conflicts between our genetic composition which determines organ physiology, and our lifestyle is what is to be expected. There are many reasons why trade-offs are omnipresent in biologic systems.

1. Organisms are not designed. Evolution has neither preconceived direction nor purpose.
2. Evolution is entirely contingent upon existing constraints. Engineers start from scratch but organisms only have what they have inherited.
3. Evolution is a continuous ongoing process: Selection is slow but environmental changes can be fast
4. Behavioral adaptation may occur faster than a physiologic or structural adaptation. A successful behavioral adaption negates the need for structural adaptation.
5. Multiplicity of organ function. Serving two masters means trade-offs and compromises
6. Reproductive selection often does not lead to optimal function. Certain traits are selected purely because they confer reproductive but not necessarily survival advantage.

Organs and organisms are never ideal or optimal. They are merely adequate and they are invariably products from yesteryears. We will examine the regulation of 3 cations in the context of the evolution of their homeostatic mechanisms, the stress placed on these mechanisms by modern lifestyle and the hypothetical phenotypic consequences relevant to clinical medicine.

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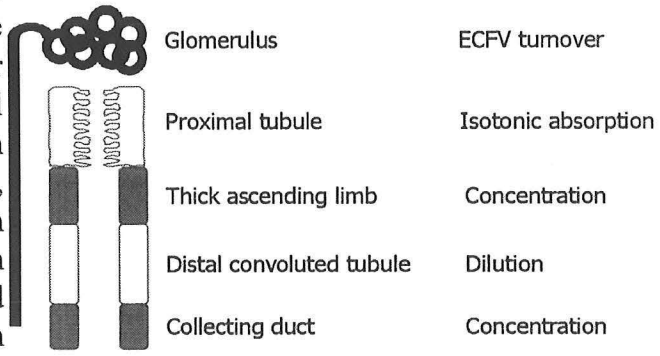
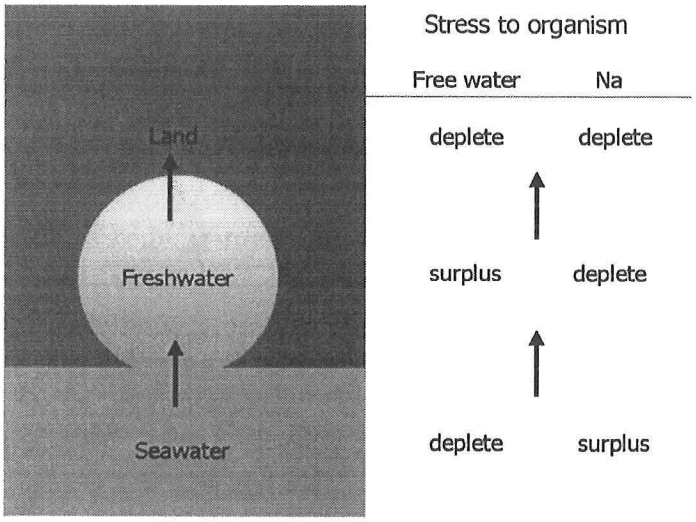
3. Mammalian Na Homeostasis

Evolution of Na homeostasis

If one examines life forms developed over a sufficiently long span of time (about 10-50 million years), the evolution of renal mechanisms for salt and water balance conservation have

paralleled environmental demands. This can be illustrated by the evolution of the nephron in vertebrates. With the exception of the lowest forms of aglomerular or pauciglomerular fish where the proximal tubule functions as a secretory epithelia (akin to the Malpigians tubules in invertebrates), all vertebrates commence their nephrons with the **glomerulus**. The glomerular filtration rate is particularly high in more advanced vertebrates where endothermy mandates high metabolic rates. Humans filter about 150 L/day which is more than 10-fold the total extracellular fluid volume (ECFV). This allows the organism to have enormous clearances of metabolic waste in the ECFV. The **proximal tubule** is probably the oldest part of the nephron serving to retrieval the bulk of the glomerular filtrate minus the waste. In addition, some waste such as creatinine and uric acid are actually secreted into the urine. The water-impermeant **thick ascending limb** transport solutes from the urine to the interstitium which lowers luminal osmolarity dilutes the urine. However, it generates the high medullary interstitial tonicity to concentrate urine passing through **the collecting duct** which is juxtaposed adjacent to the thick ascending limb. In conjunction, the thick ascending limb and the collecting duct can be termed the concentrating segment which is crucial to life forms exposed to dehydrating conditions. In lower vertebrates, an archaic version of the thick limb is present and is called the intermediate segment. The **distal convoluted tubule** absorbs urinary solutes without water and generates a dilute urine. This allows the organism to excrete a water load.

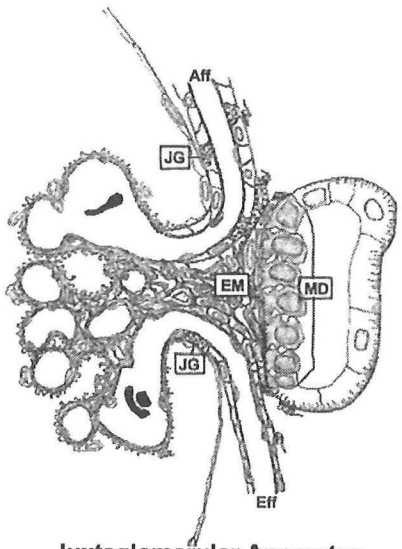




As vertebrates moved from seawater to fresh water and eventually abandoning an aquatic for a terrestrial habitat, different stresses in terms of water and Na homeostasis are placed on the organism. This is summarized in the adjacent figure. The organization of the nephron in various classes within the phyllum *vertebrata* reflects these environmental demands. Examples for each are presented at the talk. The fully developed nephron as we have learned in humans was developed likely during evolution of the class *aves* (birds) with some further modifications later in the class *mammalia* (mammals). Therefore if examined over a long time span, kidney structure and function correlate well with the environment. Although it may not be optimal, nephron structure and function are certainly adequate

for the lifestyle and habitat overall.

The juxtaglomerular apparatus (JGA) is a critical intrarenal structure that controls the endocrine renin-angiotensin-aldosterone axis. It is composed of: 1. Juxtaglomerular cells (JG) which are highly specialized renin containing vascular smooth muscle cells in the afferent and efferent arteriole. 2. Macula densa cells (MD) which are specialized cells of the distal convoluted tubule that loops back and contacts the junction between the afferent and efferent arteriole. 3. The extraglomerular mesangium (EM) containing polkissen cells of Goormaghtigh

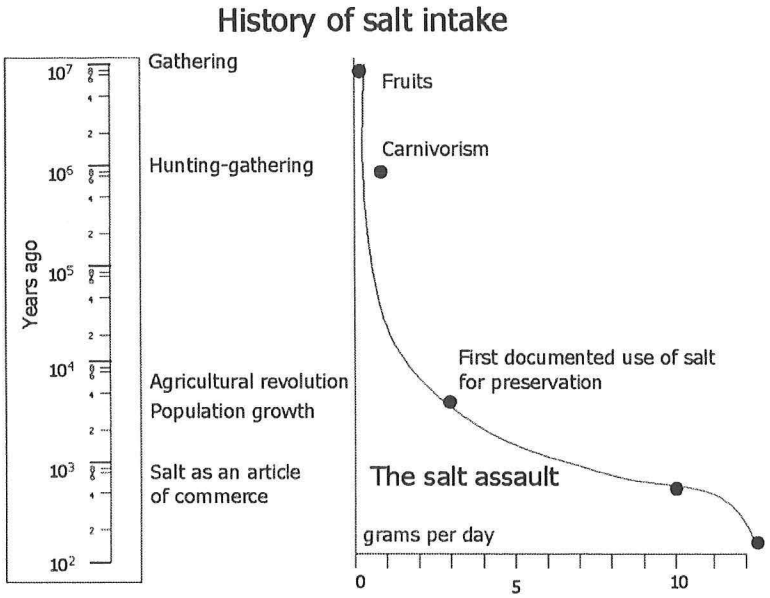


Juxtaglomerular Apperatus

This endocrine system is geared towards a terrestrial subsistence. The renin-angiotensin system defends the organism against a compromised circulation by sustaining vascular tone and modulating epithelial Na balance via peptides and steroid hormones. In addition, the JGA supports the physiologic process of tubuloglomerular feedback that allows the organism to sustain its renal plasma flow and glomerular filtration rate despite fluctuations in extracellular fluid

	Juxtaglomerular apparatus			*Renin-Angiotensin function*			
	Juxta glomerular cells	Macula densa	Extra glomerular mesangium	Pressor	Osmotic	Na transport	Aldosterone
Jawless fish	-	-	-	-	-	-	-
Cartilaginous fish elasmobranch	-	-	-	-	-	-	-
Cartilaginous fish holocaphalian	**granules**	-	-	+/-	-	-	-
Bony fish seawater	**granules**	-	-	+	-	-	-
Bony fish freshwater	**granules**	-	-	+	+	-	-
Amphibians	**yes**	**yes**	-	+	-	+	-
Reptiles	**yes**	**yes**	-	+	-	+	-
Birds	**yes**	**yes**	**yes**	+	-	+	+/-
Mammals	**yes**	**yes**	**yes**	+	-	+	+

volume. This intrarenal autoregulation is a vital process that allows terrestrial vertebrates to maintain a high metabolic rate despite periodic salt and volume depletion which was a way of life in the African Savannah.. As shown in the accompanying table, the structure of the JGA and the fully developed renin-angiotensin-aldosterone axis is present only in the higher terrestrial vertebrates.

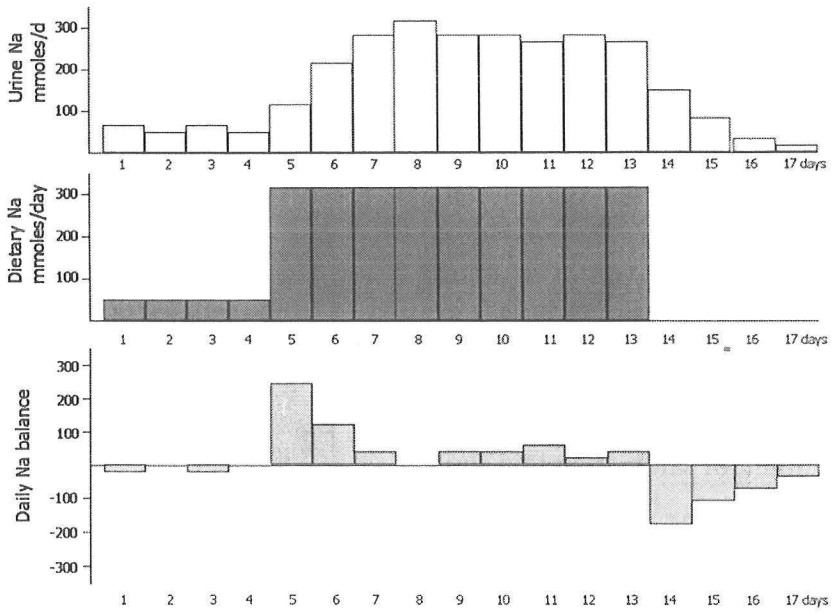


While the Na-retaining physiology of the terrestrial vertebrate evolved over almost 100 million years, primates are relatively new comers. In the evolution of mammals, the body has adapted to relying on a small amount of salt to maintain fluid. The first bipedal hominid *Australopithecus afarensis* started out as gatherers and for over 5 million years our ancestors ate a diet which contained a very small amount of salt. Even with the introduction of carnivorism, the amount of salt that was present in the residual blood of the hunted was still quite minimal. Languages before Sanskrit and Greek had no word for salt. While nomadic hunter-gatherers usually consumed their kill even hours, salt addition likely started with the agricultural revolution when a geographically-restricted lifestyle mandated food preservation. First documentation of salt preservation was in ancient Egypt. When salt became a commercial commodity, its usage soared. The 5000 years of high salt intake is brief compared to the millenia that it took for mammals to evolve a salt-conserving phenotype.

What is normal salt intake and extracellular fluid volume

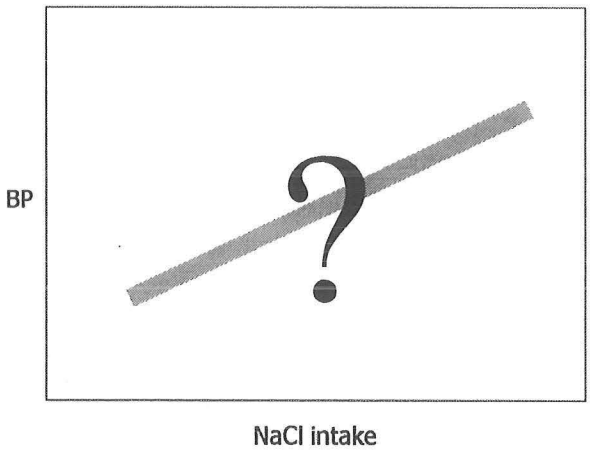
Most homeostatically regulated physiology parameters a normal range above or below which corrective feedback measures will be activated. For instance, pCO_2, pO_2, plasma glucose, plasma osmolarity etc. are all maintained within very tight limits. There is no clear evidence for such limits in Na homeostasis. This concept has generated much controversy and discussion but the data is very clear and reproducible. It is universally observed and agreed that there is a minimal ECFV below which, the kidney will stop excreting sodium. This has been called "the state between surfeit and deficit" by Strauss, "basal state or threshold" by O'Conner, and "set-point" by Hollenberg. Although the data is unequivocal on this lower limit, it is uncertain whether there is an upper limit for ECFV. With a sustained increase in dietary salt intake, the organism enters a state of positive balance transiently before the renal excretion matches intake and zero balance is once again established.

Now this new steady state is characterized by weight gain and expanded ECFV. With further increments in salt intake, the ECFV will increase further but zero balance and a steady state will always be maintained. Conversely, when switched to a low salt diet, the excess surfeit will be excreted by the kidney. The fall in urinary sodium excretion classically assumes an exponential pattern. This results in Na loss and contraction of ECFV until balance and a new steady state is established. These findings have been remarkably reproducible. The peculiar lack of an upper limit for this physiologic parameter may be advantages when considered in the light of the habitat where our species evolved. Since salt was scarce, an opportunity to increase salt intake should be accompanied by the ability to "bank" this extra NaCl which may be life saving imminently in the event of injury. This type of homeostatic mechanism is actually quite sensible for a biome with a prevailing feast-or-famine patterns. Body fat for instance, also follows this pattern because body fat stores were life saving. However, when this feast-or-famine physiology is challenged with a feast-or-feast lifestyle, undesirable traits may emerge.



Salt and hypertension

Theoretically, the excess salt can be sequestered in the extravascular space, the venous circulation, or even in the arterial circulation with a commensurate fall in vascular tone. Whichever way, the extra fluid volume can be secured without a change in blood pressure. Does this happen? This brings us to a most controversial topic. A lot has been written about "salt sensitivity". There is no uniformity of definition of salt sensitivity. Some define it as the magnitude of natriuresis for a given salt load, the ability for salt to suppress neurohumoral indicators of effective arterial volume, or the rise blood pressure for a given



salt load. Perhaps the best approach is not to try to rigidly define salt sensitivity but rather think of it as a general concept. If blood pressure were plotted against salt intake with most other factors being roughly equal, does one observe a positive slope?

Salt sensitivity as a variable no doubt exists. One of the best example is in the Akita region in Northern Japan where dietary Na can reach 600 or even 1000 mEq per day. The regional incidence of hypertension has been noted to be in excess of 60%. However, the most intriguing part of this observation is the 40% of individuals who maintains a normal blood pressure while ingesting 1000 mEq of Na per day. It is clear that salt sensitivity is a very complex trait which is determined by a large number of factors including renal retention of the volume, partition of the extra volume, sensing mechanisms for the existence of this volume, sensitivity of vascular tone due to central and peripheral neural as well as local endothelial and smooth muscle factors, and cardiac output responses to the increased volume. Each of these determinant is in turn governed by multiple factors (genetic and environmental) many of which are quantitative in nature with continuous rather than on/off effects. Most of the genetic loci that contributes to salt sensitivity are likely polymorphic in the population.

The clinical literature addressing the link between salt and hypertension is immense. An attempt to summarize them in totality will be ludicrous. The clinical data stems from several forms of settings.

1. In isolated small number patients, the use of drastic salt restriction have been reported in numerous instances to be effective in lowering blood pressure. The rice diet prescribed by Kempner is a classic example. There are numerous anecdotes such as the first patient presented in this Grand Round that can all be labeled "clear-cut" cases of success. If our patient #1 is representative of the general population, there should be no problems in demonstrating the relationship between salt and blood pressure.

2. These anecdotal reports were reinforced by a large number of epidemiologic observational studies. A large number of these were conducted in primitive societies with low salt intake and low incidence of hypertension. These included the Yanomano indians from Brazil and Venezuela, the Solomon islanders, and the Qash'qai in Iran. On the other end are the high salt consumption societies in Japan and Portugal. These across population studies have largely been positive in showing a linear relationship between salt intake and blood pressure. Some were followed by migration studies that eliminated the genetic differences. The best documented one was a carefully controlled study from Kenya. However, in addition to salt, intake, there must be countless number of variables that differ between populations. The largest one of these conducted to date was Intersalt which showed only very weak correlation and a positive finding that indicated lower salt intake is associated with a lesser rise in blood pressure with age. This is indeed a very weak result. Moreover, a large number of intra-population studies failed to show a relationship between salt intake and blood pressure. This constitute one of the strongest evidence against the salt-hypertension link.

3. A large number of interventional trials have been included numerous times in multiple

combination in metanalyses. The results range from strongly positive, to very weakly positive, or negative. It seems that a metanalysis showing the "desired result" is available to all.

Amongst this tangle of controversy, two points are evident. First, the advocates of opposing camps are emotional and at times even evangelical in their tone of arguments. The exact same set of data can spark completely opposite conclusions. Facts are often screened if not twisted and one sided arguments are common. The second point is that if dietary salt does increase blood pressure, why is it so hard to show? This is not due to lack of effort, motivation, or bias. Establishing the role of salt in the genesis of hypertension in hyperaldosteronism or bilateral renal artery stenosis was not this agonizing. It may be true that dietary sodium, at the population level, indeed has a very small effect on blood pressure. Given the variation of blood pressure measurement and inaccuracy of urine collection, and all the other variable determinants of blood pressure, the very weak relationship between salt and blood pressure simply does not surface. Within any population, there may be and will be a few individuals who display the characteristic linear relationships of blood pressure to dietary salt. But these effects will never show through the entire population of predominantly flat curves.

The political ramifications of this debate was well described in the 1998 *Science* article. It is probably true that we do not have convincing data to warrant population-wide salt restriction. Having stated that, it is also true that in certain individuals (not all) with hypertension, salt restriction can be very effective. Since we do not know this fact *a priori*, a trial of low salt diet is perfectly reasonable. Lastly, the evidence for the ill effects of salt restriction is even weaker than that supporting salt and hypertension.

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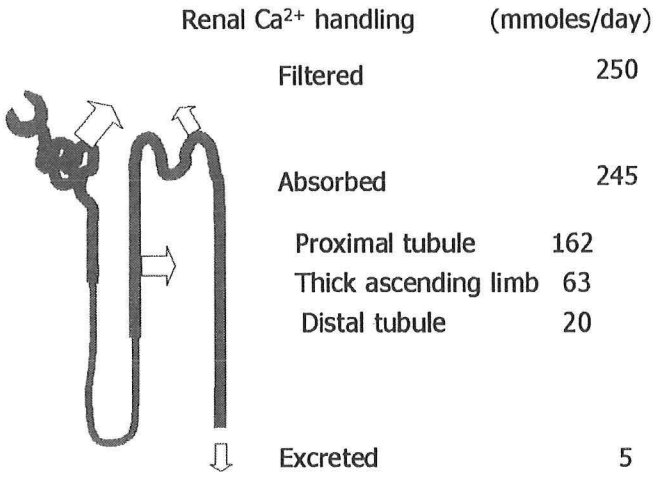
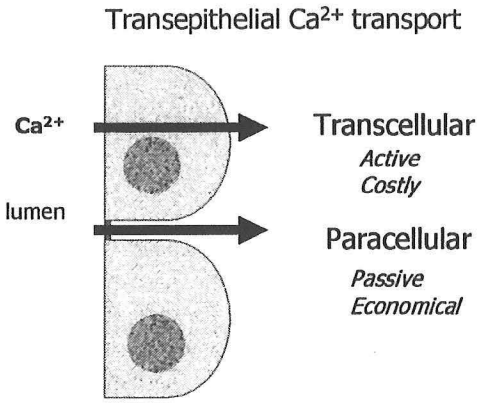
4. Mammalian calcium homeostasis

Calcium homeostasis is coordinated by flux between three organs: kidney, bone, and gastrointestinal tract and are regulated by several peptide and steroid hormones throughout the animal kingdom. We will focus on one particular aspect of Ca^{2+} handling by the kidney. Because of the need for a high GFR, the kidney filters nearly 100 times more calcium than it usually excrete. Renal calcium balances is maintained by reabsorbing 99% of the filtered Ca^{2+}. The labor is partitioned into 3 parts of the nephron. The proximal tubule, the thick ascending limb, and the distal convoluted tubule. Note that absorption by the proximal tubule and the thick limb comprises over 90% of the filtered Ca^{2+}.

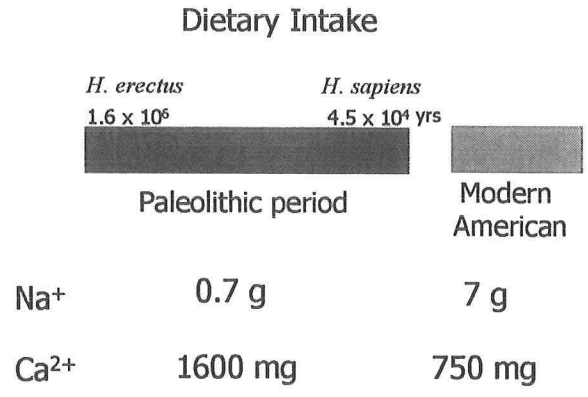




Like all solutes, transepithelial Ca^{2+} transport can proceed by one of two routes: *Transcellular* or *paracellular*. The transcellular route has the advantage of providing exquisite control. If all things are perfect and there is no restriction in terms of cell economy, transcellular Ca^{2+} transport is preferred. However there are good reasons for using paracellular pathways. First, the paracellular pathway is economical. Here one utilizes passive driving forces that has already been set-up. Simply by having the right kind of junction, one can send the Ca^{2+} to the other side. There is

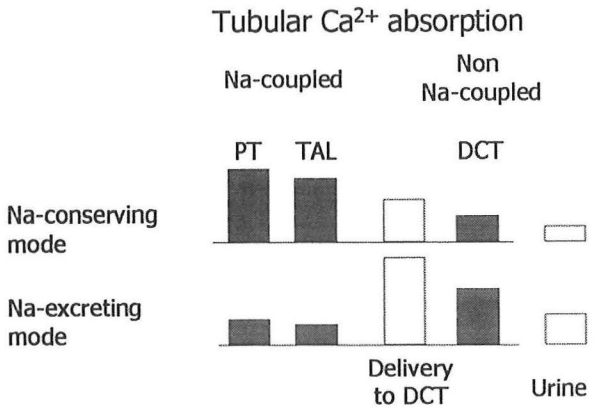
another reason why the paracellular route is preferred. Free ionized Ca^{2+} concentrations in the extracellular and intracellular compartments differ by 4 orders of magnitude. It is rather difficult to have millimole quantities of Ca^{2+} sauntering through an area where Ca^{2+} concentration need to be kept at nanomolar concentrations without killing the cell. This predicament is by no means unique for humans. It is pervasive throughout all biology. No cell can tolerate millimolar amounts of Ca^{2+}. This has been elegantly studied in crustaceans where molting cycles mandate enormous amount of Ca^{2+} flux between the body fluids, the exoskeleton, and the environment. Paracellular transport plays a crucial role in effecting these large fluxes. In the mammalian kidney, similar principles apply. In the proximal tubule and the thick ascending limb where large fluxes of Ca^{2+} are required, Ca^{2+} travels predominantly paracellularly. The benefits are two fold. It circumvents cellular toxicity and it exploits the gradients already established by the Na^+ transporters essentially sending Ca^{2+} on a "free-ride". The sole by the proximal tubule for Ca^{2+} transport is a Ca^{2+} -permeable tight junction. A similar model operates at the thick ascending limb except instead of convection, the flux is via electrochemical diffusion. Although this is highly efficient and economical, the "price" to pay with this mode of transport is that Ca^{2+} absorption is at the mercy of Na^+ transport. This is consistent with two of the basic evolution concepts wė raised earlier. First, single structures (in this case, proteins serving Na^+ absorption) frequently have multiple functions. Second, it is clearly not ideal to have Ca^{2+} transport dependent on Na^+ homeostasis. However, it is quite adequate. Again, the "good enough" principle at work.

In the distal convoluted tubule, Ca^{2+} transport is transcellular and is completely dissociated from Na^+ transport. In fact, Ca^{2+} absorption is regulated in opposite direction to Na^+ transport. Clinicians are aware of the fact that conditions that lead to natriuresis and hypocalciuria (thiazides, amiloride, Gitelman's syndrome) can have their pathophysiologic origin traced to this segment. As minute amounts of $Ca^{2+}$is absorbed pass the distal convoluted tubule, this segment s the final arbiter of urinary Ca^{2+} absorption and excretion. This is an exquisitely well controlled process. The price to pay is that it is very costly for the the cell's economy. A multitude of proteins are required to control and co-ordinate fluxes across the two tandem membrane. Complex mechanisms are also necessary to buffer and/or sequester the Ca^{2+} in transit from causing toxicity. In sum, the mammalian kidney has a high flux, economical but slightly compromised system followed by a low flux expensive sophisticated system to absorb the filtered Ca^{2+}.Can this with axial dual design work? It did for millions of years and it still does most of the time. However, modern compared to paleolithic has dramatically diminished Ca^{2+} along with the aforementioned higher Na^+content. Our system is likely operating at its "adequacy"limits.



This system evolved at a time when organisms were perpetually in a salt-conserving mode. With Na^+ stimulated in the proximal

tubule and thick limb, the amount of paracellular Ca^{2+} absorption was quite adequate. However, when the Na^+ transport mechanisms has to deal with their primary function of Na^+ homeostasis and engage in a Na^+-excretion mode, the "hitchhiker", namely Ca^{2+}, suffers. It turns out that the distal convoluted tubule has a load-dependent transport rate of considerable capacity that will maintain a fairly constant fractional absorption. However, since the Ca^{2+} load delivered out of the thick ascending limb is so high, hypercalciuria occurs almost invariably with high salt diet.

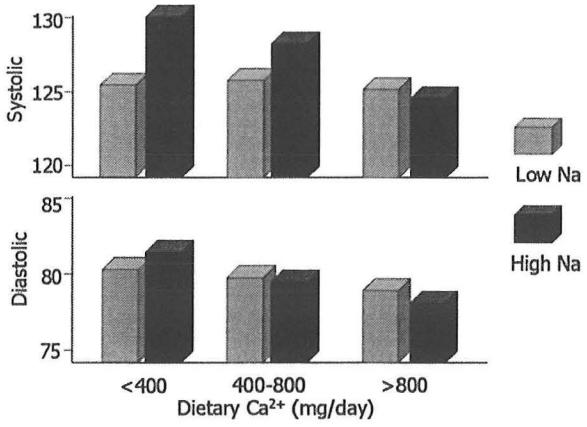


The negative impact of hypercalciuria includes osteoporosis and nephrolithiasis. Certainly in our patient, the hypercalciuria was much improved after restriction in salt intake. In addition to these two maladies, Ca^{2+} deficiency has now been linked to primary hypertension.

Link between Ca^{2+} and hypertension

Although a number of postulates have been raised as to how abundant Ca^{2+} stores can lower blood pressure via modulation of vascular smooth muscle tone, there is no convincing data showing the mechanism. Despite the empirical nature, there are clinical findings in support of a role for Ca^{2+} in the genesis of primary hypertension.

MaCarron and collegues analyzed the National Health and Nutrition examination Survey (NHANES I) data and noted an inverse relationship between blood pressure and dietary Ca^{2+} intake. Gruchow and coworkers independently analyzed the same database and found a similar trend. In addition, they found that the effect of salt on hypertension was only evident when the subjects were on a low Ca^{2+} intake. When dietary $Ca^{2+}$is high, dietary salt had no effect, or if anything, actually lowered blood pressure. A most recent large scale study was the Dietary Approaches to Stop Hypertension trial (DASH). In persons whose intake of dairy products were below the recommended level, increasing Ca^{2+} intake with no change in salt intake, dramatically improved blood pressure control.



Although the mechanism of action is still elusive, there is mounting empirical evidence that the Ca^{2+} status of the subject can

independently affect blood pressure and likely also interact to influence salt sensitivity.

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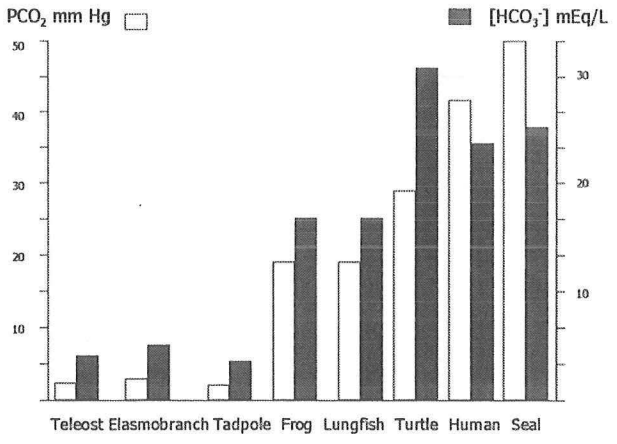
5. Mammalian acid-base homeostasis

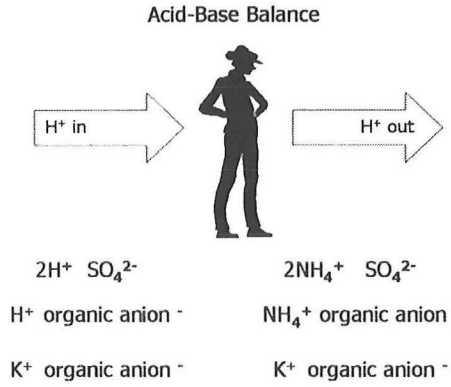
Evolution of H+ homeostasis

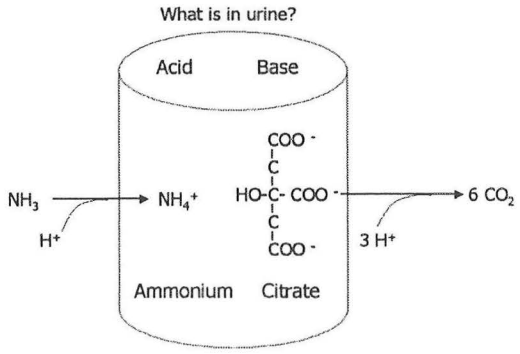
The last cation (or anion) that we will consider is H^+ (or OH^-). Organisms stay in external acid base balance by virtue of the fact that the kidney can adjust acid or base excretion that is commensurate to that of the rate of their addition to body fluids. It is important to note that a steady state can be attained, i.e. constant ECFV $[H^+]$ and $[HCO_3^-]$, and maintained without establishing external balance by using buffers outside the ECFV. The use of skeletal buffers are common throughout the animal kingdom. Since all proteins and hence all cellular processes function on fairly narrow pH ranges, acid-base homeostasis at the level of the organism, the cell, and cellular organelles has been in place since the first cells appeared several billion years ago. Whether it is a cell or an organism, acid-base balance involves two general overlapping steps: 1. The invading H^+ or OH^- is immediately sequestered from where it may do harm. 2. Elimination of the invading H^+ or OH^- from the cell or the organism. A critical buffer system in mammalian ECFV is the CO_2/HCO_3^- system. This system did not evolve from original lifeforms. A high CO_2 tension in the ECFV is unique to air-breathers as a high gradient is required to allow CO_2 to diffuse into the low flux medium (ventilated air as opposed to water through gills). The CO_2/HCO_3^- buffer system



appeared in the amphibians. The most remarkable example is the emergence of CO_2/HCO_3^- buffer system as tadpoles mature into frogs.

External balance is established by excretion of acid or base from the organism. The mechanisms of acid/base excretion has been established in higher vertebrates over the last 100 million years. In mammals, acid in the urine is carried by buffers. Quantitatively NH_4^+ constitutes

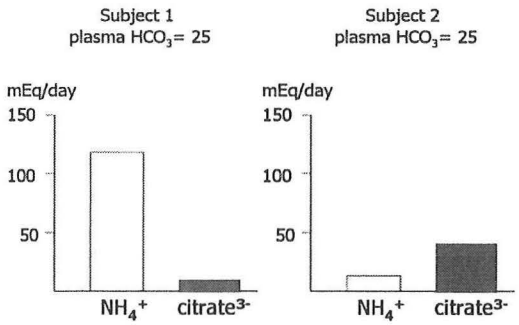


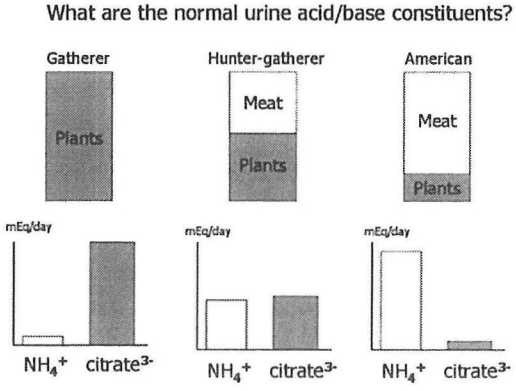


the major form of H^+ excreted. The accompanying anion depends on the species of the invading acid. Base expulsion is achieved by either excreting HCO_3^- or an organic anion that is a HCO_3^- equivalent. Quantitatively the most abundant organic anion base equivalent if citrate. The relative quantities of these acid/base components in the urine depends on the diet of the individual. Both NH_4^+ and HCO_3^- /citrate^{3-} are regulated to establish external acid-base balance. When acid intake is increased, NH_4^+ excretion rises and HCO_3^-/citrate^{3-} decreases. The opposite occurs for alkaline ingestion.

A number of investigators have indicated that citrate^{3-} is not an important acid-base component in human urine based on relative rates of "normal" citrate excretion. For example:

0.3 μEq/g BW/day	human
1-2 μEq/g BW/day	rat
3-4 μEq/g BW/day	rabbit

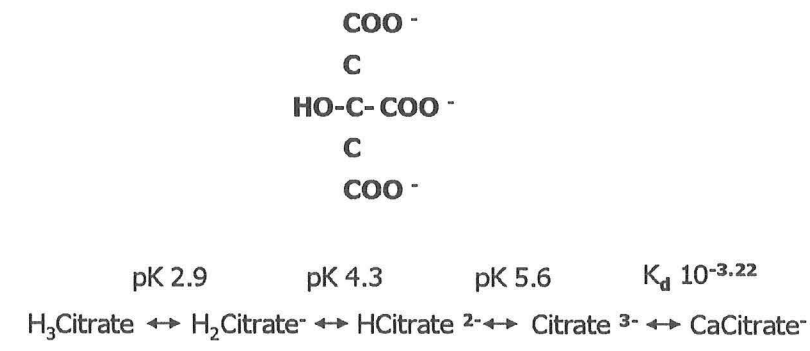




This has led efforts in studying acid-base balance to skew to the NH_4^+ system. In fact, we even ignore $citrate^{3-}$ in our calculation of net acid excretion in clinical practice . However, the concept of "normal" urinary $citrate^{3-}$ has no real foundation. Urine parameters are "normal" only if one considers the current diet as "normal". For that matter, the laboratory rat chow is not normal for he rat. The normal diet for a modern urban cosmopolitan rat is whatever is in the alley trash can. Instead of a statistical definition of a normal diet, an evolutionary definition may be more appropriate. Then the normal diet should be what the organism was eating when it evolved. Therefore, the typically low urinary $citrate^{3-}$ seen in North Americans does not reflect human renal physiology but rather our current diet. An examination of the diet of our ancestors will reveal that urinary $citrate^{3-}$ should play an equally important role as NH_4^+.

As we mentioned earlier, organs frequently serve multiple functions. This is also true of metabolites. In addition to serving as a base equivalent in urine, $citrate^{3-}$ plays the important role in prevent stone formation. The following functions has been shown although the most important one is likely forming a soluble complex with Ca^{2+} as the Kd suggests that nearly $citrate^{3-}$ are complexed with Ca^{2+}.

Dual role of citrate in urine



Citrate inhibits stone formation in several ways:

1. Complex with Ca^{2+}
2. Inhibits agglomeration of Ca oxalate
3. Decreases spontaneous nucleation of calcium oxalate and uaret
4. Decrease crystal growth of Ca oxalate

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6. Summary (take home messages)

1. Organisms are evolved to be adequate, not optimal. Conflict between the biologic constitution and the environment is the rule rather than the exception. Most of the time, the conflicts can be dealt with adequately.

2. Evolution occurs over time spans that are many orders of magnitude greater than changes in our lifestyle. Today's human physiology developed eons before we were exposed to modern lifestyle.

Life on the planet	$\sim 4 \times 10^9$
Vertebrates	$\sim 2 \times 10^8$
Hominids	$\sim 6 \times 10^7$
Humans	$\sim 10^5$
Modern lifestyle	$< 10^4$

3. The mammalian kidney has evolved to conserve Na^+. This type of physiology was advantageous when the organ evolved under feast-or-famine conditions so ECFV would be maximally defended. Today, there is no particular need for this defense mechanism and this outdated system probably puts ECFV constantly in surplus. However, it is unclear whether this is actually an undesirable phenotype or whether it is merely neutral. In certain individuals, high salt intake results in elevation of arterial blood pressure and in others high salt intake aggravates underlying hypertension. In the entire population, manipulations of salt intake has minimal if any effect on blood pressure.

4. Like sodium, calcium homeostasis also evolved a long time ago. In the kidney, the majority of calcium transport is coupled to sodium transport for the sake of cell economy. The trade-off is that calcium transport is at the mercy of sodium transport. The system is not ideal, but it is sufficient. When our diet switched from high calcium/low sodium to high sodium/low calcium, this ancient system began to reach its limits. High sodium intake coupled with low calcium intake predisposes humans to hypercalciuria which contributes to kidney stones, osteoporosis, and primary hypertension.

5. Acid-base balance is achieved by renal excretion of acid (mainly ammonium) or base (mainly trivalent citrate). Normal urinary parameters defined by statistics overemphasize ammonium as the sole player in acid-base balance. This definition is misconstrued and simply reflects the dietary habits of our immediate population. An evolutionary definition of the urinary acid-base parameters would place equal emphasis on ammonium and trivalent citrate. Citrate has more than one role in the urine. In addition to being a base equivalent, citrate is pivotal in preventing nephrolithiasis. Whereas hypocitraturia is appropriate from an acid-base standpoint under the acid burden of a modern North American, an unintentional by product of this acid-excreting physiology is renal stones.

6. The morbid conditions mentioned is very unlikely to exert selection pressure to effect evolution of new cation homeostatic mechanisms for several reasons. a. The changes are too fast. b. The morbidity is mild and post-reproductive. c. Medical intervention can largely though not entirely eliminate natural selection.