# Water: swelling, tension, pain, fatigue, aging

From the original article in 2009. Author: Ray Peat.

I have spoken to many people who believe they should drink "8 glasses of water every day," in addition to their normal foods, even if they don't feel thirsty. Many doctors still recite this dangerous slogan, but the addition of the qualifying phrase, "or other liquids," has become common.

The amount of water a person needs is extremely variable, depending on things such as metabolic rate, activity, and the temperature and humidity of the air. Working hard in hot, dry weather, it's possible to drink more than two quarts per hour for more than eight hours, without forming any urine, because all of the water is lost by evaporation. But in very hot, humid weather, a person with a low metabolic rate can be endangered by the smallest amount of water (e.g., "Meteorological relations of eclampsia in Lagos, Nigeria," Agobe, et al., 1981).

Most foods contain a considerable amount of water, usually more than 70% of their weight, and some water is produced in cells by metabolism. The function of water in the organism has been mystified and neglected because of some deeply rooted cultural images of the nature of organisms and their cellular make-up.

One silly image that has been perpetuated by schools and textbooks is that biochemistry consists of chemical reactions that occur in substances dissolved in water, and that the water is retained by cells because they are enclosed by an oily membrane, and because of the osmotic forces produced by the dissolved substances. Most grade school kids have seen an osmometer made from an egg, in which the egg causes a column of water to rise, and have heard the explanation that this has something to do with the way cells work. Membrane pumps are invoked to explain the differences in solute concentrations and "osmotic pressure" inside and outside cells. The story is that invisible things on the surface of a cell (in its "membrane") force dissolved molecules to move in ways that they wouldn't move spontaneously by diffusion, and that water passively follows the "actively transported" solutes. But the evidence shows that both water and its solutes are regulated by the bulk phase of the cell, not its surface.

In some cultural settings, animism has a kind of charm (water sprites, and such), but in the culture of medicine and biology, the animistic conceptualization of cells and their mechanisms has been very destructive, because it gets in the way of coherent understanding of physiology. Practically every disease would be approached differently if the physiology of water and ions were allowed to advance beyond the animistic doctrines of mainstream medicine, such as the "membrane pumps." If all the substances that are said to be "actively transported" by pumps into, or out of, cells are considered, the amount of energy required to operate the pumps is at least 15 times larger than the total energy available to cells. "Specific" pumps are commonly invoked even for novel synthetic chemicals, to explain their unequal distribution, inside and outside cells. In many biological situations water is ignored, but when it becomes an issue, its distribution is usually mechanistically subordinated to the solutes that are actively "pumped."

Cells aren't osmometers, in the sense the textbooks say. They do control their water content, but no "membrane pumps" are needed. It's more accurate to think of the water of cells as being "dissolved in cells," somewhat the way water is contained in jello or boiled eggs. The cell controls its hydration by the processes that control its structure, its metabolism, and movements, because water is part of its deepest structures and essential functions. The cell's adjustments to changes of hydration and volume appear to be regulated by contractile proteins and energy metabolism (Minkoff and Damadian, 1976).

Any stress or energy deficit that disturbs cellular structure or function disturbs the interactions among water, proteins, and other components of the cell. Excitation causes a cell to take up extra water, not by osmosis resulting from an increase in the concentration of solutes in the cell, or because the membrane has become porous, but because the structural proteins of the cell have momentarily increased their affinity for water.

This increased affinity is similar to the process that causes a gel to swell in the presence of alkalinity, and it is related to the process called electroosmosis, in which water moves toward a higher negative charge. Intense excitation or stress increases the cell's electrically negative charges, and causes it to become more alkaline and to swell. Swelling and alkalinity cause the cell to begin the synthesis of DNA, in preparation for cell division. Mitogens and carcinogens, including estrogen, cause cells to become alkaline and to swell, and substances that block the cell's alkalinization (such as the diuretics acetazolamide and amiloride) inhibit cell division. Prolonged alkaline stress alone can cause malignant transformation of kidney cells (Oberleithner, et al., 1991).

The general idea of "stress" is useful, because it includes processes such as fatigue, osmotic pressure changes, disturbed pH, and the enzyme changes that follow, producing substances such as lactic acid, nitric oxide, polyamines, estrogen, serotonin, and many more specific mediators. But paying attention to the physical factors involved in a stress reaction is important, if we are to see the organism integrally, rather than as a collection of "specific biological mechanisms," involving things like the pixie-powered "membrane pumps."

When a cell shrinks under hyperosmolar conditions, its metabolism becomes catabolic, breaking down proteins and glycogen, and sometimes producing lactic acid, which results in an alkaline shift, increasing the cell's affinity for water, and causing it to return to normal size. A slight degree of hyperosmolarity increases the cell's metabolic rate.

Swelling in hypo-osmolar conditions, i.e,, with an excess of water, is anabolic, leading to cellular proliferation, and inhibiting the breakdown of protein and glycogen.

Respiring cells are always producing some water, by transferring hydrogen from fuel molecules to oxygen. Respiration also produces carbon dioxide, which in itself is a Lewis acid (meaning that it binds electrons, rather than releasing protons), that

associates with cellular proteins, acidifying them in the process. A large amount of carbon dioxide can exist inside cells in the bound form. Acidified cytoplasm (like any other mostly acidic polymer-gel) releases water and sodium. (This process is physically analogous to the process of flushing a water softener with salt, or a demineralizer with acid, to reactivate it.)

Besides binding with the cytoplasm, the carbon dioxide can be changed into carbonic acid, by chemically combining with water. Carbonic acid is hydrophilic, and so it quickly leaves the cell, taking with it some of the oppositely charged ions, such as calcium and sodium. The formation of carbonic acid, which is constantly streaming out of the respiring cell, causes some water and some positively ionized metals to leave the cell, in an "active" process, that doesn't require any mysterious pumps.

As the blood passes through the lungs, carbon dioxide leaves the system, and as carbonic acid is converted to carbon dioxide, water is left behind in the blood, along with the counterions (of alkaline metals or earths), accounting for slight differences in pH and osmolarity between the bloodstream and the tissue cells. Some experiments suggest that the normal osmolarity of various tissues is 2 or 3 times higher than that of the blood, which is called "isosmolar" or isotonic.

The kidneys adjust the osmolarity of the blood by allowing water and solutes to leave the bloodstream, in proportions that usually keep the body fluids in balance with cells. The kidneys are able to compensate for many of the imbalances produced by stress and inappropriate diets, for example by forming ammonia and carbon dioxide, to compensate for imbalances in the alkalis and acids that are being delivered to the blood by other organs. Because of the kidneys' great ability to regulate the flow of solutes between the blood and the forming urine, the "membrane pumps" have great importance for medical nephrologists. But the more extreme the "active transport" is, the more obvious it becomes that processes other than "membrane pumps" are responsible.

Some lizards and sea birds have glands near their noses that are called salt glands, because of their ability to secrete salt. The salt gland is probably the most extreme case of active transport, but its physiology is very similar to the physiology of any other secretory gland or membrane, such as tear glands and sweat glands. The mechanism of salt excretion in these glands should really settle the issue of how active transport works, but most nephrologists, oculists, and medical researchers in general aren't interested in salt glands.

Carbon dioxide is the driving force in the salt gland. The constant formation of $CO_2$, and its loss into the air, allows a high concentration of salt to be excreted. Blocking the interchange of $CO_2$ and carbonic acid, with acetazolamide, or inhibiting the formation of $CO_2$, prevents the excretion of salt.

Since respiratory metabolism, governed by the thyroid hormone, is our main source of carbon dioxide, it's obvious that thyroid deficiency should impair our ability to regulate water and solutes, such as salt. An organism that illustrates this function of thyroid is the young salmon, when it leaves a freshwater river to begin its life in the ocean. As it converts its physiology to tolerate the salty environment, its thyroid hormone surges. When it's mature, and returns to the fresh water to spawn, its prolactin rises sharply. In experiments with rodents, it has been found that drinking a large amount of water increases their prolactin, but the same amount of water, with added salt, doesn't.

Hypothyroidism is typically associated with increased prolactin secretion. Hypothyroid people typically retain water, while losing salt, so the hypothyroid state is analogous to the salmon that has returned to the river, and to the mice that drink too much salt-free water.

The typical hypothyroid person loses salt rapidly in the urine (and probably in the sweat, too, though that is usually diagnosed as cystic fibrosis), and retains water, diluting the urine less than normal. The reduced production of carbon dioxide, with increased susceptibility to producing lactate and ammonium, causes the cells to be more alkaline than normal, increasing their affinity for water. The rise of estrogen that usually accompanies hypothyroidism also increases intracellular pH, loss of sodium, and over-hydration of the blood.

Hypothyroid muscles typically retain excess water, and fatigue easily, taking up more water than normal during exertion. In childhood, mild hypothyroidism often causes the leg muscles to swell and ache in the evenings, with what have been called "growing pains." When the problem is more extreme, all the skeletal muscles can become very large (Hoffman syndrome), because of the anabolic effect of over-hydration. Enlargement of any muscle can result from the excessive hydration produced by thyroid deficiency, but when it happens to the muscles behind the eyes (Itabashi, et al., 1988), it often leads to a diagnosis of hyperthyroidism, rather than hypothyroidism.

The little kids with the Hoffman syndrome don't have the bloated myxedematous appearance that's often associated with hypothyroidism. They look athletic to a ridiculous degree, like miniature body-builders. But after a few weeks of treatment with thyroid, they regain the slender appearance that's normal for their age. The swollen state actually supports enlargement of the muscle, and the cellular processes are probably closely related to the muscle swelling and growth produced by exercise. The growth of the muscle cell during swelling seems to be the result of normal repair processes, in a context of reduced turnover of cellular proteins.

The people who believe in membrane pumps that maintain normal solute distributions by active transport know that the pumps would require energy (far more than the cell can produce, but they don't confront that issue), and so their view requires that they assign a great part of the cell's resources just to maintaining ionic homeostasis, and the result of that is that they tend to neglect the actual energy economy of the cell, which is primarily devoted to the adaptive renewal of the cell structure and enzyme systems, not to driving the systems that don't exist.

The "anabolic" balance of the swollen cell is the result of decreased turnover of the cell's components. The higher rate of metabolism produced by adequate thyroid function maintains a high rate of renewal of the cell's systems, keeping the cell constantly adjusted to slight changes in the organism's needs. The evidence of a high rate of bone turnover is sometimes taken as evidence that thyroid can cause osteoporosis.

Later, in a more mature person, chronically fatigued and painful muscles that at one time would have been diagnosed as rheumatism, may be diagnosed as fibromyalgia. Most doctors are reluctant to prescribe thyroid supplements for the problem, but the association of elevated prolactin with the muscle disorder is now generally recognized.

The hypo-osmolar blood of hypothyroidism, increasing the excitability of vascular endothelium and smooth muscle, is probably a mechanism contributing to the high blood pressure of hypothyroidism. The swelling produced in vascular endothelium by hypo-osmotic plasma causes these cells to take up fats, contributing to the development of atherosclerosis. The generalized leakiness affects all cells (see "Leakiness" newsletter), and can contribute to reduced blood volume, and problems such as orthostatic hypotension. The swollen endothelium is stickier, and this is suspected to support the metastasis of cancer cells. Inflammation-related proteins, including CRP, are increased by the hypothyroid hyperhydration. The heart muscle itself can swell, leading to congestive heart failure.

Some of the nerve problems associated with hypothyroidism (e.g., carpal tunnel syndrome and "foot drop") are blamed on compression of the nerves, from swelling of surrounding tissues, but the evidence is clear that hypothyroidism causes swelling in the nerve cells themselves. For example, in hypothyroidism, nerves are slow to respond to stimulation, and their conduction of the impulse is slow. These changes are the same as those produced by hyper-hydration caused by other means. Hypothyroid nerves are easily fatigued, and fatigued nerves take up a large amount of water. Swelling of the spinal cord is probably responsible for the "spinal stenosis" commonly seen in domestic animals and people; the mobility of intracellular water molecules is distinctly increased in patients with compression of the spinal cord (Tsuchiya, et al., 2003; Ries, et al., 2001).

The hyperhydration of hypothyroidism has been known to cause swelling and softening of cartilage, with deformation of joints, but somehow it has never dawned on surgeons that this process would lead to deformation of intervertebral disks.

It has been known for a long time that hyperhydration can produce seizures; at one time, neurologists would test for epilepsy by having the patient drink a pint of water. Although there are many reasons to think that the hyperhydration produced by hypothyroidism is a factor in epilepsy, physicians have been very reluctant to consider the possibility, because they generally think of thyroid hormone as a stimulant, and believe that "stimulants" are necessarily inappropriate for people with epilepsy.

While it's true that the thyroid hormone increases sensitivity to adrenaline, its most noticeable effect is in improving the ability to relax, including the ability to sleep soundly and restfully. And it happens that increasing norepinephrine (the brain's locally produced form of adrenaline) helps to prevent seizures (Giorgi, et al., 2004).

Cell swelling increases the sensitivity of nerves, and hyperosmotic shrinkage lowers their sensitivity. Increasing carbon dioxide helps to reduce the hydration of tissue (for example, the hydration and thickness of the cornea are decreased when carbon dioxide is increased), and increasing carbon dioxide is known to inhibit epileptic seizures. Another diagnostic trick of neurologists was to have the patient hyperventilate; it would often bring on a seizure. The diuretic acetazolamide, which increases the body's carbon dioxide and reduces water retention, is very effective for preventing seizures.

The sleep-inducing effect of salty food is probably related to the anti-excitatory effects of hyperosmolarity, of adequate thyroid function, and of carbon dioxide.

Degenerative diseases, especially cancer, heart disease, and brain diseases, are less prevalent in populations that live at a high altitude. When oxygen pressure is low, the lungs lose carbon dioxide more slowly, and so the amount of carbon dioxide retained in the body is greater. If the basic problem in hypothyroidism is the deficient production of carbon dioxide causing excessive loss of salt and retention of water, resulting in hypo-osmotic body fluids, then we would expect people at high altitude to have better retention of salt, more loss of water, and more hypertonic body fluids. That has been observed in many studies. The increased rate of metabolism at altitude would be consistent with the relatively active "catabolism" of the slightly hyperosmotic condition.

After the drug companies began, in the late 1950s, marketing some newly discovered (thiazide) diuretics, which cause sodium to be lost in the urine, their advertising campaigns created a cultish belief that salt caused hypertension. They convinced a whole generation of physicians that pregnant women should limit salt in their diet, take a diuretic preventively, and restrict calories to prevent "excessive" weight gain. Millions of women and their babies were harmed by that cult.

Pre-eclampsia and pregnancy toxemia have been corrected (Shanklin and Hodin, 1979) by both increased dietary protein and increased salt, which improve circulation, lower blood pressure, and prevent seizures, while reducing vascular leakiness. The effectiveness of increased salt in pre-eclampsia led me to suggest it for women with premenstrual edema, because both conditions typically involve high estrogen, hyponatremia, and a tendency toward hypo-osmolarity. Estrogen itself causes sodium loss, reduced osmolarity, and increased capillary leakiness. Combined with a high protein diet, eating a little extra salt usually helps to correct a variety of problems involving edema, poor circulation, and high blood pressure.

The danger of salt restriction in pregnancy has hardly been recognized by most physicians, and its danger in analogous physiological situations is much farther from their consideration.

One of the things that happen when there isn't enough sodium in the diet is that more aldosterone is synthesized. Aldosterone causes less sodium to be lost in the urine and sweat, but it achieves that at the expense of the increased loss of potassium, magnesium, and probably calcium. The loss of potassium leads to vasoconstriction, which contributes to heart and kidney failure and high blood pressure. The loss of magnesium contributes to vasoconstriction, inflammation, and bone loss. Magnesium deficiency is extremely common, but a little extra salt in the diet makes it easier to retain the magnesium in our foods.

Darkness and hypothyroidism both reduce the activity of cytochrome oxidase, making cells more susceptible to stress. A promoter of excitotoxicity, ouabain, or a lack of salt, can function as the equivalent of darkness, in resetting the biological

rhythms (Zatz, 1989, 1991).

Bone loss occurs almost entirely during the night, and the nocturnal rise in cortisol and prolactin has strongly catabolic effects, but many other pro-inflammatory substances also rise during the night, and are probably the basic cause of the increased catabolism. Increased salt in the diet appears to improve some aspects of calcium metabolism, such as reducing parathyroid hormone and increasing ionized calcium, when the diet is deficient in calcium (Tordoff, 1997).

The kidneys can produce large amounts of carbon dioxide and ammonia, in the process of preventing the loss of electrolytes, while allowing acid to be lost in the urine. The ammonia is produced by the breakdown of protein. During stress or fasting, the loss of tissue protein can be minimized by supplementing the minerals, potassium, sodium, magnesium, and calcium. Salt restriction can cause aldosterone to increase, and excess aldosterone causes potassium loss, and increases the use of protein to form ammonia (Norby, et al., 1976; Snart and Taylor, 1978; Welbourne and Francoeur, 1977).

Aldosterone secretion increases during the night, and its rise is greater in depressed and stressed people. It inhibits energy metabolism, increases insulin resistance, and increases the formation of proinflammatory substances in fat cells (Kraus, et al., 2005). During aging, salt restriction can produce an exaggerated nocturnal rise in aldosterone.

During the night, there are many changes that suggest that the thyroid functions are being blocked, for example a surge in the thyroid stimulating hormone, with T4 and T3 being lowest between 11 PM and 3 AM (Lucke, et al., 1977), while temperature and energy production are at their lowest. This suggests that the problems of hypothyroidism will be most noticeable during the night.

Rheumatoid arthritis and asthma are two inflammatory conditions that are notoriously worse during the night. Melatonin has been reported to be higher in patients with severe asthma and rheumatoid arthritis, and to promote the secretion of a variety of other pro-inflammatory substances. The peak of melatonin secretion is followed by the peak of aldosterone, and a little later by the peak of cortisol.

The use of bright light (which suppresses melatonin) to treat depression probably helps to inhibit the production of aldosterone, which is strongly associated with depression.

Both aldosterone and melatonin can contribute to the contraction of smooth muscle in blood vessels. Constriction of blood vessels in the kidneys helps to conserve water, which is adaptive if blood volume has been reduced because of a sodium deficiency. When blood vessels are inappropriately constricted, the blood pressure rises, while organs don't receive as much blood circulation as they need. This impaired circulation seems to be what causes the kidney damage associated with high blood pressure, which can eventually lead to heart failure and multiple organ failure.

Progesterone, which helps to maintain blood volume (partly by preventing vascular leakiness, preventing excessive sodium loss and by supporting albumin synthesis) antagonizes aldosterone. Aldosterone antagonists are now being recognized as effective treatments for hypertension, water retention, congestive heart failure, arrhythmia, diabetes, kidney disease, and a great variety of inflammatory problems. (Synthetic drugs to antagonize aldosterone are most effective when they are most like natural progesterone.) Since aldosterone contributes to fibrosis of the heart and kidneys (nephrosclerosis), progesterone, the "antifibromatogenic steroid," should be helpful for those problems that have been considered irreversible. Aldosterone appears to contribute to the hyperglycemia of diabetes itself, and not just to its complications, by interfering with the interactions of insulin and cortisol (Yamashita, et al., 2004).

One of progesterone's fundamental actions is to cause estrogen "receptors" to disintegrate; hypertonicity has this effect in some situations. Estrogen's effects are largely produced by increased tissue hydration.

Aldosterone causes cells to take up sodium, while increasing their pH, i.e., raising their alkalinity (Mihailidou and Funder, 2005). Intracellular sodium has long been known to be a factor, along with swelling and alkalinity, in stimulating cell division (Cone and Tongier, 1971). A lack of salt stimulates the formation of serotonin, which in turn stimulates aldosterone synthesis--that is, a sodium restricted diet activates processes that cause cells to take up sodium inappropriately, in a situation reminiscent of the calcium deficient diet causing inappropriate calcification.

Aldosterone, like stress or hypo-osmolarity, activates the enzyme (ODC) which produces the polyamines, that promote cell division, and that can probably account for some of the harmful effects of excessive aldosterone.

Eating salty food around bedtime usually has a sleep-inducing effect, and it helps to maintain blood volume (which tends to decrease during the night), and to restrain the nocturnal rise of aldosterone, and other indicators of stress or inflammation. Eating gelatin, which lacks tryptophan, will reduce the formation of serotonin, and is likely to limit the formation of aldosterone.

Pregnenolone can sometimes very quickly allow swollen tissues to release their water. This function is probably closely related to its antifibromatogenic function, since swelling and leaking set the stage for fibrosis.

Hyperosmotic sodium chloride solutions (e.g., 7.5%) are being used more often for treating trauma and shock, because the concentrated solution increases blood volume by removing water from the extravascular spaces, unlike the "isotonic" saline (0.9% sodium chloride), which usually adds to the edema by leaking out of the blood vessels.

A 5% sodium chloride solution is effective for promoting healing of damaged corneas, and solutions of 5% to 10% sodium chloride are effective for accelerating the healing of wounds and ulcers. Other hypertonic solutions, for example glucose or urea, have been used therapeutically, but sodium chloride seems to be the most effective in a variety of situations.

Thyroid hormone, by maintaining oxidative metabolism with the production of carbon dioxide, is highly protective against

excessive water retention and loss of sodium and magnesium.

Sometimes doctors recommend that constipated people should drink extra water, "to soften the stool." The colon is where water is removed from the intestinal contents, and when it is inflamed, it removes too much water. Several decades ago, it was recognized (Orr, et al., 1931) that hypertonic saline, given intravenously, would stimulate intestinal peristalsis, and could be used to treat paralytic ileus and intestinal obstruction.

When water is taken orally, it is absorbed high in the intestine, long before it reaches the colon, so the recommendation to drink water for constipation can produce a situation that's the opposite of intravenous hypertonic saline, by diluting the blood. Using a hypertonic salt solution as an enema can have the same beneficial effect on the intestine as the intravenous treatment.

Constipation physiology is probably analogous to the physiology of congestive heart failure, in which muscles are weakened and fatigued by swelling.

In recent decades, the prevalence of congestive heart failure has increased tremendously, so that it is now often called an epidemic. Hyponatremia (too little salt, or too much water) is a recognized "risk factor" for congestive heart failure. In the failing heart, the muscle cells are swollen, causing the heart wall to stiffen, weakening its ability to pump. Osmotically shrinking the cells can restore their function.

The swollen heart, like any muscle, loses the ability to quickly and completely relax, and so it doesn't fill adequately between contractions. Elastic tissues, such as arteries and lungs, stiffen when they are over-hydrated, losing their normal functions. In small blood vessels, swelling narrows the channel, increasing resistance to the flow of blood.

When people force themselves to drink a certain amount of water every day, even when they don't feel thirsty, they are activating complex adaptive processes unnecessarily. Thirst is the best guide to the amount of fluid needed.

When extra water consumption is combined with a low salt diet--as physicians have so often recommended--a healthy person can adapt easily, but for a hypothyroid person it can have disastrous effects.

## References


Br J Obstet Gynaecol. 1981 Jul;88(7):706-10. **Meteorological relations of eclampsia in Lagos, Nigeria.** Agobe JT, Good W, Hancock KW. A retrospective study of the meteorological relations of eclampsia in Lagos, Nigeria supports other observations that the incidence of this disease varies significantly with the weather**. Protective action by arid conditions is consistent with the known effect of dehydration on convulsions of differing aetiologies and is attributable to increased pulmonary transpirational water loss. Exacerbation of eclampsia by cool, humid conditions** may therefore reflect excessive water retention, due partly to suppressed pulmonary transpiration and partly to kidney malfunction in those women.

Neuroendocrinology. 2001 Mar;73(3):185-93. **Hypothalamo-pituitary-adrenal axis sensitization after chronic salt loading.** Amaya F, Tanaka M, Hayashi S, Tanaka Y, Ibata Y.

Neuroscience. 1994 Sep;62(2):371-83. **Imaging cell volume changes and neuronal excitation in the hippocampal slice.** Andrew RD, MacVicar BA. **"Brain cell swelling is a consequence of seizure, ischemia or excitotoxicity."**

Probl Endokrinol (Mosk). 1981 Sep-Oct;27(5):42-5. **[Sex and age differences in the peripheral blood aldosterone levels]** Bekker VI, Svechnikova NV. **"An increase in the blood aldosterone content in menopause appears to be due to the hyperestrogenic phase (the first menopausal phase in women) and estrogen-stimulated aldosterone synthesis.** Sexual differences in aldosterone secretion disappear with age. Aldosterone content is significantly lower in males and females, age over 80 years, than that in younger subjects, and sexual differences are absent."

J Appl Physiol. 2002 May;92(5):1911-22. **Prolonged hypobaric hypoxemia attenuates vasopressin secretion and renal response to osmostimulation in men.** Bestle MH, Olsen NV, Poulsen TD, Roach R, Fogh-Andersen N, Bie P. "In conclusion, chronic hypobaric hypoxemia **1) elevates the set point of plasma osmolality-to-plasma vasopressin relationship, possibly because of concurrent hypertension, thereby causing hypovolemia and hyperosmolality, and 2) blunts the natriuretic response to hypertonic volume expansion . . . ."**

Metabolism. 1999 Apr;48(4):472-6. **Effects of hypoosmolality on whole-body lipolysis in man.** Bilz S, Ninnis R, Keller U.

JAMA. 1984 Jul 27;252(4):524-6. **Impaired osmoregulation at high altitude. Studies on Mt Everest.** Blume FD, Boyer SJ, Braverman LE, Cohen A, Dirkse J, Mordes JP.

Gerontology. 1996;42(4):229-34. **Effect of aging and sodium deprivation on plasma concentration of aldosterone and on plasma renin activity in the rat.** Brudieux R, Rakotondrazafy J.

Endocr Res. 1996 Nov;22(4):577-8. **The role of L-aromatic amino acid decarboxylase in serotonin-stimulated aldosterone secretion in response to salt intake.** Burns N, Brett L, Olverman HJ, Nagatsu T, Lee MR, Williams BC.

Curr Drug Targets Immune Endocr Metabol Disord. 2004 Mar;4(1):1-10. **Melatonin role in experimental arthritis.** Cardinali DP, Garcia AP, Cano P, Esquifino AI.

J Lipid Res. 2003 Apr;44(4):727-32. Epub 2003 Jan 16. **Dietary sodium chloride restriction enhances aortic wall lipid storage and raises plasma lipid concentration in LDL receptor knockout mice.** Catanozi S, Rocha JC, Passarelli M, Guzzo ML, Alves C, Furukawa LN, Nunes VS, Nakandakare ER, Heimann JC, Quintao EC. **"Arterial fat storage correlated with NEFA concentrations in the LDLR KO mice alone (n = 14, P = 0.0065). Thus, dietary sodium chloride restriction enhances aortic wall lipid storage in moderately hyperlipidemic mice."**

Am J Physiol. 1978 Mar;234(3):F235-7. **Acetazolamide and renal ammoniagenesis.** Chapman SK, Hoover MS.

Early Hum Dev. 1989 Jun;19(3):191-8. **Muscle cell potassium, RNA and hydration in pregnancy and pre-eclampsia.** Cheek DB,

Petrucco OM, Gillespie A, Green RC, Ness D, Dalton M. "Thirty four pregnant women from 26 to 38 weeks gestation and 24 pregnant women with pre-eclampsia gave samples of muscle (rectus abdominis) at caesarean section.""**From 26 to 38 weeks gestation the concentration of K+ per litre of cell water ([Ki]) slowly declined.**" "Since other cations per litre of muscle cell water did not change, questions are raised. is the cation gap filled by amino acids or does vascular spasm cause a leakage of K+ from muscle cells? **Does hypotonicity eventually develop leading to water intoxication? The low oncotic pressure in pre-eclampsia (shown here), the negative free water clearance could all favour increased cell hydration (some evidence for this is presented here towards term).** Assessment of available information concerning creatinine excretion . . . **leads us to believe that a significant increase in muscle mass occurs...."**

Autoimmun Rev. 2005 Nov;4(8):497-502. **Altered circadian rhythms in rheumatoid arthritis patients play a role in the disease's symptoms.** Cutolo M, Villaggio B, Otsa K, Aakre O, Sulli A, Seriolo B.

Eur J Pharmacol. 1979 Oct 15;58(4):425-31. **Antiulcer activity of hypertonic solutions in the rat: possible role of prostaglandins.** Danon A, Assouline G.

Peptides. 1990 Jan-Feb;11(1):59-63. **Long-term salt loading impairs pituitary responsiveness to ACTH secretagogues and stress in rats.** Dohanics J, Kovacs KJ, Folly G, Makara GB.

Can J Physiol Pharmacol. 1982 Mar;60(3):331-4. **Role of acidosis in the protein wasting of fasting in the rat and the rabbit.** Hannaford MC, Goldstein MB, Josse RG, Halperin ML. "Therefore, it appears that if more nitrogen is excreted as ammonium, net protein breakdown increases to furnish the substrate for ammoniagenesis...."

Neurosci Biobehav Rev. 2004 Sep;28(5):507-24. **The role of norepinephrine in epilepsy: from the bench to the bedside.** Giorgi FS, Pizzanelli C, Biagioni F, Murri L, Fornai F.

Can J Physiol Pharmacol. 1998 Dec;76(12):1120-31. **Bulbospinal serotonergic activity during changes in thyroid status.** Henley WN, Bellush LL, Tressler M.

Brain Res Mol Brain Res. 1991 Jun;10(3):251-8. **Benzamide derivatives provide evidence for the involvement of a 5-HT4 receptor type in the mechanism of action of serotonin in frog adrenocortical cells.** Idres S, Delarue C, Lefebvre H, Vaudry H. "We have previously shown that **serotonin (5-HT) is a potent stimulator of corticosterone and aldosterone secretion by frog adrenocortical cells and we have demonstrated that the action of 5-HT is not mediated by the classical 5-HT receptor subtypes i.e. 5-HT1, 5-HT2 and 5-HT3."**

Nippon Rinsho. 1992 Sep;50(9):2124-8. **[Effects of pH on the endocrine system and metabolism]** [Article in Japanese] Inoue Y, Kaneko T. "6-phosphofructo-1-kinase, a rate limiting enzyme in glycolysis, seems to be activated directly by a rise in pH. Alkalosis stimulates the production of pyruvic acid and lactic acid."

Am J Physiol. 1997 Jul;273(1 Pt 2):H104-12. **Endothelial ATP-sensitive potassium channels mediate coronary microvascular dilation to hyperosmolarity.** Ishizaka H, Kuo L.

Am J Physiol Cell Physiol. 2001 Oct;281(4):C1403-7. **Hypotonicity induces L-selectin shedding in human neutrophils.** Kaba NK, Knauf PA.

Ross Fiziol Zh Im I M Sechenova. 2003 Feb;89(2):146-53. [**Effect of melatonin on neurogenic vasoreactivity: formation and modulation of the vessel response]** Karachentseva OV, Iartsev VN, Dvoretskii DP, Zhdanova IV.

J Investig Med. 2002 Mar;50(2):101-9. **Stimulatory effects of hyperprolactinemia on aldosterone secretion in ovariectomized rats.** Kau MM, Chang LL, Kan SF, Ho LT, Wang PS.

Biochim Biophys Acta. 1999 Jan 4;1426(1):17-31. **Effect of electric field on physical states of cell-associated water in germinating morning glory seeds observed by 1H-NMR.** Isobe S, Ishida N, Koizumi M, Kano H, Hazlewood CF.

Eur J Clin Nutr. 2003 Dec;57 Suppl 2:S69-74. **Effects of changes in hydration on protein, glucose and lipid metabolism in man: impact on health.** Keller U, Szinnai G, Bilz S, Berneis K. Alterations of cell volume induced by changes of extracellular osmolality have been reported to regulate intracellular metabolic pathways. Hypo-osmotic cell swelling counteracts proteolysis and glycogen breakdown in the liver, whereas hyperosmotic cell shrinkage promotes protein breakdown, glycolysis and glycogenolysis.

Ann Ophthalmol. 1977 Nov;9(11):1383-7. **The effect of hypertonic ointments on corneal alkali burns.** Korey M, Peyman GA, Berkowitz R.

Horm Metab Res. 2005 Jul;37(7):455-9. **Aldosterone inhibits uncoupling protein-1, induces insulin resistance, and stimulates proinflammatory adipokines in adipocytes.** Kraus D, Jager J, Meier B, Fasshauer M, Klein J.

J Cell Physiol. 2003 Apr;195(1):61-9. **Control of hepatocyte DNA synthesis by intracellular pH and its role in the action of tumor promoters.** Lee CH, Cragoe EJ Jr, Edwards AM.

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Acta Endocrinol (Copenh). 1977 Sep;86(1):81-8. **Studies on circadian variations of plasma TSH, thyroxine and triiodothyronine in man.** Lucke C, Hehrmann R, von Mayersbach K, von zur Muhlen A.

Adv Neurol. 1986;44:619-39. **Ionic changes and alterations in the size of the extracellular space during epileptic activity.** Lux HD, Heinemann U, Dietzel I.

J Pediatr. 2002 Oct;141(4):587-92. **The most essential nutrient: defining the adequate intake of water.** Manz F, Wentz A, Sichert-Hellert W.

Semin Arthritis Rheum. 1995 Feb;24(4):282-90. **Bone and joint manifestations of hypothyroidism.** McLean RM, Podell DN.

Clin Invest Med. 1997 Feb;20(1):16-24. **Effective water clearance and tonicity balance: the excretion of water revisited.** Mallie JP, Bichet DG, Halperin ML. "OBJECTIVE: To demonstrate (1) **that hyponatremia is usually due to an inappropriately low rate of excretion of electrolyte-free water and (2) that the measure "effective water clearance" (EWC**) provides better information about renal defence of the body tonicity than does the classic measure free-water clearance, and to provide the rationale for calculating a "tonicity balance," which involves using water and sodium plus potassium intakes and their renal excretion to reveal the basis for changes in body tonicity.""The water load was excreted rapidly by normals, more slowly by patients with CHF, and not at all by patients with SIADH."

FEBS Lett. 2000 Jan 7;465(1):64-8. **Hypoosmolarity influences the activity of transcription factor NF-kappaB in rat H4IIE hepatoma cells.** Michalke M, Cariers A, Schliess F, Haussinger D.

Steroids. 2005 May-Jun;70(5-7):347-51. **Nongenomic effects of mineralocorticoid receptor activation in the cardiovascular system.** Mihailidou AS, Funder JW. "Alzamora et al. showed 11beta-hydroxysteroid denydrogenase 1 and 2 (11betaHSD1, 11betaHSD2) expression in human vascular **smooth muscle cells, and that aldosterone rapidly raises intracellular pH via sodium-hydrogen exchange; cortisol is without effect and spironolactone does not block the aldosterone response."**

Epilepsy Res. 1988 Mar-Apr;2(2):102-10. **Evidence of hypothyroidism in the genetically epilepsy-prone rat.** Mills SA, Savage DD.

Cell Biol Int. 2005 Apr;29(4):261-8. **Down-regulation of immediate early gene egr-1 expression in rat C6 glioma cells by short-term exposure to high salt culture medium.** Morita K, Arimochi H, Yoshida S.

BMC Psychiatry. 2003 Oct 29;3:15. **The renin-angiotensin-aldosterone system in patients with depression compared to controls--a sleep endocrine study.** Murck H, Held K, Ziegenbein M, Kunzel H, Koch K, Steiger A.

Physiol Behav. 1996 Jan;59(1):133-9. **Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans.** Murphy PJ, Myers BL, Badia P.

Probl Endokrinol (Mosk). 1987 Jan-Feb;33(1):18-21. **[Characteristics of the hydration status of patients with hypothyroidism**] Nazarov AN, Lobachik VI, Zhidkov VV, Borisov GI, Abrosimov SV.

Pflugers Arch. 1991 Oct;419(3-4):418-20. **Alkaline stress transforms Madin-Darby canine kidney cells.** Oberleithner H, Westphale HJ, Gassner B. "Similar to growth factors aldosterone stimulates Na+/H+ exchange in renal target cells leading to cytoplasmic alkalinization. An alkaline intracellular pH reduces the H+ bonds between repressor proteins and DNA leading to the destabilization of the nuclear chromatin. **We observed that sustained alkaline stress "per se" can lead to malignant transformation of Madin-Darby canine kidney (MDCK) cells."**

Clin Nephrol. 1976 Sep;6(3):404-13. **On the pathogenesis of Bartter's syndrome: report of studies in a patient with this disorder.** Norby L, Mark AL, Kaloyanides GJ. "During aminoglutethimide inhibition of aldosterone synthesis the subject was able to maintain potassium balance at a normal serum potassium concentration on a potassium intake of 130 mEq/day which suggests that aldosterone is the major cause of the potassium wasting...."

Am J Vet Res. 1978 Jan;39(1):159-61. **Effect of thyroid state on magnesium concentration of rat tissues.** Oliver JW.

Surg. Gynec. Obst. 52, 941 (May), 1931. **[Hypertonic saline and peristalsis]** Orr, FG, Johnstone, PN, and Haden, RL.

Metabolism. 2004 Mar;53(3):278-9. **Treating hypothyroidism improves endothelial function.** Papaioannou GI, Lagasse M, Mather JF, Thompson PD.

Am J Hypertens. 1999 Dec;12(12 Pt 1-2):1217-24. **Modification of intracellular calcium and plasma renin by dietary calcium in men.** Petrov V, Lijnen P.

J Biol Chem. 1991 Apr 5;266(10):6142-51. **An early enlargement of the putrescine pool is required for growth in L1210 mouse leukemia cells under hypoosmotic stress.** Poulin R, Wechter RS, Pegg AE.

J Exp Zool. 1985 Aug;235(2):187-96. **Plasma and pituitary prolactin levels in rainbow trout during adaptation to different salinities.** Prunet P, Boeuf G, Houdebine LM.

J Physiol. 1975 Jan;244(2):303-12. **The relationship between elevated water intake and oedema associated with congestive cardiac failure in the dog.** Ramsay DJ, Rolls BJ, Wood RJ. "**These results suggest that increased fluid intake is probably important in the aetiology of the oedema associated with congestive cardiac failure,** probably through the renin-angiotensin system."

Br J Pharmacol. 1999 Aug;127(7):1666-70. **Effects of melatonin on rat pial arteriolar diameter in vivo.** Regrigny O, Delagrange P, Scalbert E, Lartaud-Idjouadiene I, Atkinson J, Chillon JM. "Based on our finding that melatonin decreased the lower limit of cerebral blood flow autoregulation in rat, we previously suggested that melatonin constricts cerebral arterioles." "Melatonin induced a dose-dependent constriction with an EC50 of 3.0+/-0.1 nM and a maximal constriction of -15+/(-1%)." "Melatonin directly constricts small diameter cerebral arterioles in rats. This vasoconstrictor effect is mediated by inhibition of BKCa channels following activation of mt1 and/or MT2 receptors."

Magn Reson Med. 2000 Dec;44(6):884-92. **Diffusion tensor MRI of the spinal cord.** Ries M, Jones RA, Dousset V, Moonen CT.

Am J Med Sci. 2005 Jul;330(1):1-7. **Bone loss in rats with aldosteronism.** Runyan AL, Chhokar VS, Sun Y, Bhattacharya SK, Runyan JW, Weber KT. "We hypothesized that aldosteronism is accompanied by hypercalciuria and hypermagnesuria that lead to bone loss, which could be rescued by hydrochlorothiazide and spironolactone."

Gen Comp Endocrinol. 1991 May;82(2):184-91. **Kinetic studies of growth hormone and prolactin during adaptation of coho salmon, Oncorhynchus kisutch, to different salinities.** Sakamoto T, Iwata M, Hirano T.

Am J Hypertens. 2005 Jan;18(1):44-9. **Antiproteinuric effects of mineralocorticoid receptor blockade in patients with chronic renal disease.** Sato A, Hayashi K, Saruta T.

Int Rev Cytol. 2003;225:187-228. **Call volume and insulin signaling.** Schliess F, Haussinger D. "**In general an increase in cell hydration stimulates anabolic metabolism and proliferation** and provides cytoprotection, whereas cellular dehydration leads to a catabolic situation and sensitizes cells to apoptotic stimuli."

Med Klin (Munich). 2002 Aug 15;97(8):484-7. **[Hypo-osmolar hyponatremia as the chief symptom in hypothyroidism]** [Article in German] Schmitt R, Dittrich AM, Groneberg D, Griethe W.

Physiol Bohemoslov. 1977;26(5):385-95. **Antioestrogenic action of the aldosterone antagonist canrenoate K in the rat (adenohypophysis, ceruloplasmin).** Schreiber V, Pribyl T.

Epilepsy Res. 1998 Sep;32(1-2):275-85. **Osmolarity, ionic flux, and changes in brain excitability.** Schwartzkroin PA, Baraban SC, Hochman DW.

D. Shanklin and J. Hodin, ***Maternal Nutrition and Child Health,*** **CC** Thomas, 1979.

Zh Nevrol Psikhiatr Im S S Korsakova. 2000;100(8):4-9.**[On myotonia doctrine. Myotonia in myxedema patients.** 1903] Shmidt AN.

Pathol Microbiol (Basel). 1974;41(1):11-25. **Response of vertebral cartilage and bone to hormonal imbalances produced by anterior hypophyseal hormones and hypothyroidism.** Silberberg R.

J Physiol. 1978 Jan;274:447-54. **Aldosterone effects on renal metabolism.** Snart RS, Taylor E.

J Neuroendocrinol. 2004 May;16(5):472-82. **Modulation of oestrogen receptor-beta mRNA expression in rat paraventricular and supraoptic nucleus neurones following adrenal steroid manipulation and hyperosmotic stimulation.** Somponpun SJ, Holmes MC, Seckl JR, Russell JA.

**J Membr Biol. 1985;83(1-2):25-37. Cellular mechanism of HCO-3 and Cl- transport in insect salt gland.** Strange K, Phillips JE.

J Allergy Clin Immunol. 2003 Sep;112(3):513-7. **Elevated serum melatonin is associated with the nocturnal worsening of asthma.** Sutherland ER, Ellison MC, Kraft M, Martin RJ.

Am J Physiol. 1997 Jul;273(1 Pt 2):R423-32. **NaCl ingestion ameliorates plasma indexes of calcium deficiency.** Tordoff MG.

J Neurophysiol. 1989 May;61(5):927-38. **Role of extracellular space in hyperosmotic suppression of potassium-induced electrographic seizures.** Traynelis SF, Dingledine R.

Neuroradiology. 2003 Feb;45(2):90-4. Epub 2003 Jan 15. **Diffusion-weighted MRI of the cervical spinal cord using a single-shot fast spin-echo technique: findings in normal subjects and in myelomalacia.** Tsuchiya K, Katase S, Fujikawa A, Hachiya J, Kanazawa H, Yodo K.

Am J Physiol Heart Circ Physiol. 2001 Jan;280(1):H420-5. **Melatonin potentiates NE-induced vasoconstriction without augmenting cytosolic calcium concentration.** Vandeputte C, Giummelly P, Atkinson J, Delagrange P, Scalbert E, Capdeville-Atkinson C.

Curr Heart Fail Rep. 2004 Jul;1(2):51-6. **Efficacy of aldosterone receptor antagonism in heart failure: potential mechanisms.** Weber KT. "As a circulating hormone, aldosterone has well-known endocrine properties that contribute to the pathophysiology of congestive heart failure. This includes Na+ resorption at the expense of K+ excretion in such tissues as kidneys, colon, sweat, and salivary glands. Mg2+ excretion at these sites is likewise enhanced by aldosterone, whereas adrenal aldosterone secretion is regulated by extracellular Mg2+." **"De novo generation of aldosterone within the cardiovasculature is recognized** and findings suggest its auto/paracrine properties contribute to tissue repair. Each of these actions is interrupted by aldosterone receptor antagonism and therefore may contribute to its salutary response in heart failure."

Am J Physiol. 1977 Jul;233(1):E56-60. **Influence of aldosterone on renal ammonia production.** Welbourne TC, Francoeur D.

Endocr J. 2004 Apr;51(2):243-51. **Aldosterone stimulates gene expression of hepatic gluconeogenic enzymes through the glucocorticoid receptor in a manner independent of the protein kinase B cascade.** Yamashita R, Kikuchi T, Mori Y, Aoki K, Kaburagi Y, Yasuda K, Sekihara H. "Primary aldosteronism is associated with glucose intolerance and diabetes, which is due in part to impaired insulin release caused by reduction of potassium, although other possibilities remain to be elucidated."

Hypertens Res. 2005 May;28(5):447-55. **Excess aldosterone under normal salt diet induces cardiac hypertrophy and infiltration via oxidative stress.** Yoshida K, Kim-Mitsuyama S, Wake R, Izumiya Y, Izumi Y, Yukimura T, Ueda M, Yoshiyama M, Iwao H.

Cytobios. 1986;45(180):25-34. **Regulation of ODC activity in the thymus and liver of rats by adrenal hormones.** Zahner SL, Prahlad KV, Mitchell JL.

J Clin Lab Anal 1998;12(3):145-9. **A proposal for standardizing urine collections for bone resorption markers measurement.** Zaninotto M, Bernardi D, Ujka F, Bonato P, Plebani M

1991 Dec;261(6 Pt 2):R1424-30. **Low salt mimics effects of dark pulses on circadian pacemaker in cultured chick pineal cells.** Zatz M,

Am J Physiol. 1991 Dec;261(6 Pt 2):R1424-30. **Low salt mimics effects of dark pulses on circadian pacemaker in cultured chick pineal cells.** Zatz M, Wang HM.

Brain Res. 1989 Oct 30;501(1):37-45. **Ouabain (or salt solution lacking potassium) mimics the effects of dark pulses on the circadian pacemaker in cultured chick pineal cells.** Zatz M, Mullen DA.