Ray Peat's Newsletter

"The whole is more than the sum of its parts." **Aristotle**

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Urea, coherent life and forgotten or unrealized therapies.

"Vitalism: the idea that living organisms and inanimate things are governed by different principles."

The history of urea helps to understand some of the important questions about the nature of life.

Chemists and biologists typically describe "the first synthesis of an organic chemical," urea, in 1828, as the historic moment when vitalism was disproved, justifying a reductionist-mechanistic approach to understanding life. The date of urea's first synthesis by a chemist is right, but its meaning is very different. Another organic compound, oxalic acid, had been synthesized more than 50 years earlier, and neither of these events had much effect on the idea that living organisms and inanimate things are governed by different principles.

It was during these years that steam engines, and the machines they drove, were becoming very important economically, and that fact was the background for those who adopted Descartes' "animal-machine" philosophy as a way of understanding physiology and biochemistry. In this view of mechanism, causality implied that each effect was determined by a preceding cause, the way the gears in a clock are driven by the force stored in a spring. The parts of a machine, or the atoms in an organism, were supposedly obliged to act in a certain way by the pre-existing natural laws, which were understood to be God's will. Descartes was rejecting Aristotle's view of "becoming" as a process expressing a thing's purpose or "final cause." Self-determination was implicit in Aristotle's view of an organism, and this is what was being rejected by those who were determined to eliminate "vitalism" from science.

The understanding of "substance" is where the crucial difference is between the two views. For reductionism, an atom is always just an atom, existing in itself; its history makes no difference. A certain kind of atom is always the same, whether it's in a rock or a person. Somehow, this idea can be held even by people who recognize that the spins of protons and electrons interact with each other and with their surrounding fields. The alternative view simply omits that unfactual belief about the non-interactive nature of substance.

In 1828, Friedrich Wohler was intending to synthesize a salt, ammonium cyanate, and he was surprised to find that the same atoms in the same proportion had instead become urea. He learned that atoms weren't as simple as he had thought--an ensemble of atoms was in some way self-determining. Since then, "proton spin" and "electron spin" and their interactions with each other and with their environments have been recognized, and used in technologies such as MRI, and the state of an atom is seen to reflect its environment.

Despite the fundamental changes occurring in the understanding of matter and energy, the "mechanistic," "anti-vitalist" doctrine was aggressively enforced in academic science for most of the 20th century, and dominated most departments of philosophy in universities in the U.S. and England. In the background, holistic philosophies of organism continued to develop in the Aristotelian tradition--Alfred North Whitehead, Henri Bergson, V.I. Vernadsky, and Ludwig von Bertalanffy for example. Ecology, cybernetics, and a recognition of epigenetic development, incorporating the principles of holism and self-determination, came into existence despite the ruling dogma of mechanistic reductionism.

Medicine has come to be dominated by the myth or metaphysics of mechanism. Steam engines required fuel, usually wood or coal, and burning the fuel produced the waste materials carbon dioxide and ashes. Urea was seen as a waste material. Around 1850, it was noticed that the blood of people with kidney failure contained an increased amount of urea, and the condition was named uremia. Now physicians (thinking of urea as a toxic waste material) regularly measure the amount of urea in the blood, and treat uremia by dialysis, with an "artificial kidney."

The idea of osmotic pressure grew up in the early 19th century, just as the theory of thermodynamics was being formalized. Osmotic pressure depends on the function of a membrane that allows a solvent to pass through freely, while it excludes a solute. This property of semipermeability wasn't understood at all, but the function could be described in mechanical terms--an osmotic force can do work. The unequal distribution of solvents in different parts of the body came to be interpreted in terms of the abstract and mechanical idea of osmosis and semipermeable membranes.

People began speaking of urea as an "osmolyte," among other osmolytes such as sodium and glucose, and that idea still permeates the practice of medicine, despite the clear evidence that has accumulated over the last century showing that urea is not an osmolyte.

In 1917, Thomas Addis wrote that "urea can increase five or six times normal without disturbance of the osmotic balance." In the 1950s, E.L. Opie at the Rockefeller Institute tested the effects of many substances at different concentrations on the water content of cells. He found that liver cells seem to be in balance with a salt solution that's twice as concentrated as the blood. A solution of some amino acids had to be even more concentrated to be in apparent osmotic balance with the cells, and a solution of urea about 5 or 6 times the normal seemed to be in balance with them. Obviously, he was seeing something other than an "osmotic" function of the cells, and urea was unique in its (non-osmotic) action. According to Mairose (1976), "The real and present osmotic condition can only be calculated when the blood urea concentration is no longer considered."

According to the membrane theory, cells are "osmometers," that respond to the concentration of solutes in the water surrounding them, shrinking when the outer solute concentration is higher, swelling when it's lower. According to the theory, the water inside the cell has to contain the same concentration of solute particles as the water outside, to maintain a constant volume. The movement of water into or out of a cell is considered to be passive, simply moving in response to the osmotic pressure created by the concentration of solute.

When the amount of urea in serum is changed, the amount of urea in red blood cells suspended in the serum changes in response, so the expectation has been that the percentage of urea would be the same in the water both inside and outside the cells. In fact, the water inside the cells stably retains a higher concentration than the water of the serum (Ralls, 1943).

Urea appears to be more soluble in the water inside a cell than it is in the water outside a cell. Water is an unusual solvent in the ways that it interacts with solutes. Potassium and sodium ions, having the same single positive electrical charge, interact very differently with water. In an electrical field, potassium moves freely and quickly towards a negative pole, but sodium moves slowly, because it drags a large amount of water along as it moves. The state of the solvent water also affects the things that are dissolved in it; this is very clear in the case of large molecules such as proteins. When many substances are mixed together, as in cells, the results are often surprising, as in the way urea is taken up by cells.

In physics, the complexity of the "three body problem," in which only the gravitational field (the "law of gravity") is considered, is well known. In a mixture of solutes in a solvent, there are overlapping fields, with substances influencing their environment while being influenced by their environments. Even in the simple three body problem, the motion of the bodies is considered to be non-repeating. The interactions of solutes and solvents in living cells, of cells in organs, of organs in organisms, of organisms in ecosystems, expose the irrelevance of the doctrine of local cause and effect interactions as a basis for understanding living things. Instead of the fields or "laws" that are imagined to govern "simple particles," each organism's ensemble of fields and particles no longer has the properties that were seen when the parts were studied individually, that is, it must be thought of as a new unique substance, with its own "laws" of functioning.

The nature of this self-determining organism is to perceive possibilities and to make choices. A cell makes solubility choices, a kidney chooses how much of each substance it will retain or excrete, and these choices are limited by availability of energy, and by the nature of its environment.

The fact that urine had been used medically since ancient times probably led to the occasional trial of purified urea for some of the conditions that had been treated with urine. A publication in 1892 described its use as a diuretic, and in 1925 Crawford and McIntosh described its use orally as a diuretic to treat heart failure. The idea of using urea therapeutically wasn't derived from mechanistic medical theory, but the reasoning about what was happening when excess water was removed from the tissues occurred within that framework.

When explaining physiological functions in terms of osmotic forces, water is considered to be a simple solvent, passively following solutes moved by

(theoretical) "membrane pumps." To understand the unequal distribution of substances inside and outside of cells, the idea of mutual solvents or cosolvents, in which one substance modifies the solubility of other substances, is helpful. All of the parts of a cell have some cosolvent function, and urea is an extremely important cosolvent.

Excess water in cells is a central feature of the major degenerative diseases--heart failure, dementia, and cancer--as well as of acute inflammatory conditions. It is gradually being recognized that inflammation is a factor in the degenerative diseases, and metabolic explanations are starting to replace genetic and immunological explanations for those chronic diseases. Ammonia produced metabolically can be recycled in various ways, including its combination with carbon dioxide, to produce urea. An excess of ammonia is excitatory, intensifying the action of the excitatory amino acids, increasing the formation of nitric oxide, decreasing cell energy, and causing cell swelling.

All types of cell (skin, brain, eye, intestine, kidney, breast, even red blood cells) contain the enzymes of the urea cycle, and whether or not they synthesize urea depends on their situation. Because of the liver's ability to produce large amounts of urea, it's generally believed that it's the source of most of the urea in the various tissues. When arginine is converted to urea, its availability to make nitric oxide is reduced (and nitric oxide contributes to cell swelling).

Another way that urea is involved in the prevention of cell swelling (and other malfunctions) is that it, like uric acid, inhibits the enzyme that synthesizes nitric oxide. The cytoskeletal actin filaments regulate nitric oxide synthesis (Searle, et al., 2004; Zharikov, et al., 2001), with the polymerized, stiffened state of the cytoskeleton activating the enzyme. Urea's cosolvent function stabilizes actin in its globular, depolymerized state, which is associated with the inactivate state of nitric oxide synthesis. The filament form of actin has a powerful effect on cell water, increasing the cell's water content, and causing the water molecules to have an unusually high mobility; in the globular form, the water mobility and content are lower. Globular actin, urea, and the relatively quiescent form of water can be thought of as cosolvents, affecting the state of the cell as a whole.

In the degenerative diseases, tissues become harder while they bind more water. The hardness is produced by the tension of the actin filaments, and their interaction with hardened (cross-linked) collagen in the extracellular matrix around the cells. Urea not only softens tissue by supporting the depolymerized state of actin, but it also loosens the structure of collagen.

In the whole organism, chronic stress can interfere with the retention and excretion of water in several ways. Loss of salt with retention of water, causing hyponatremia and hypoosmolarity, frequently occurs after surgery, with reduced heart function, with cancer, and in AIDS patients. Sometimes the problem is called the "Inappropriate Secretion of Antidiuretic Hormone" syndrome, but it can occur without an abnormal increase of that hormone, supposedly because of increased sensitivity of the hormone receptors. The cells that secrete the antidiuretic hormone are activated by actin polymerization; this process seems to be activated by a variety of stress signals relating to lower cell energy. The polymerization involves a shift from ATP-binding to phosphate-ADP binding, a lower energy state.

The antidiuretic hormone increases the excretion of sodium in the urine, while increasing the retention of water. Hypothyroidism and excess estrogen both have the same effect on the sodium-water balance, and estrogen doesn't increase production of the antidiuretic hormone, so it is thought to increase the kidney's sensitivity to it (Stachenfeld, et al., 2003). Progesterone opposes estrogen's effects, supporting thyroid's effects (Watanabe, et al., 1997).

The autonomic nervous system contributes to the balance of water and sodium, with the cholinergic, parasympathetic system increasing the antidiuretic hormone, and water retention, sodium loss. Histamine, serotonin, and prostaglandins also activate its secretion. All of these nervous and hormonal effects are likely to be involved in the stress-induced water retention, sodium loss.

A class of drugs that antagonize the antidiuretic hormone, called "vaptans," has been approved for treating hyponatremia, and is used for reducing brain swelling. The vaptans are extremely expensive, and have serious side effects. Urea reduces the antidiuretic hormone effect, is very effective for reducing brain swelling, doesn't have harmful side effects (Gankam-Kengne, et al, 2015), and is very cheap. In one case, a boy with a brain injury wasn't improving with the use of a vaptan, and when dialysis brought his urea down to a normal level his brain function deteriorated quickly; with intravenous urea (90 grams in 20 minutes) his BUN increased to 260 mg/100 ml, and his calculated osmolarity was 385 mosm/L (both far above normal), and his brain functions gradually returned, allowing him to return to school several weeks later. An "excess" of urea protects against hyponatremia (Soupart, et al., 2000; Oo, et al., 2003).

In the 1950s, urea was very commonly used for treating brain swelling. Following some publications reporting that an "isotonic solution" of urea in distilled water caused breakdown of red blood cells, with resulting kidney damage, its use was discontinued, and a hypertonic solution of mannitol came into use, instead. Since urea isn't an "osmolyte," injecting it intravenously dissolved in distilled water has effects similar to using plain water intravenously. Hypertonic mannitol does shrink a swollen brain, but it damages the kidneys (Tsai and Shu, 2010), and probably other organs. In the 1960s and early 1970s urea was used to reduce intraocular pressure in glaucoma, but since then that use has seldom been reported.

Because urea was called a waste material, and the word "uremia" was used to describe the blood changes of kidney disease, when dialysis of the blood was used to treat kidney disease there was no concern with the possible harm that could be done by lowering the plasma urea content. It took many years for the dialysis doctors to realize that hemodialysis increased dementia and cancer mortality. The over-hydration produced by the reduction of urea damages nerve cells, and tests of DNA before and after a single dialysis session showed that it was dialysis itself, rather than chronic kidney disease, that was causing DNA breaks and mutations (Buemi, et al., 2010).

The real "toxins" in uremic blood are just starting to be identified, but ammonia, phosphate, and possibly lactate are involved in the symptoms of kidney disease.

Urea can be used orally, and is very quickly absorbed (Addis, 1917). Descriptions of prolonged use of oral urea for heart failure were published in 1925 (Crawford and McIntosh). When used in heart failure, other diuretics are likely to cause loss of minerals in the urine, but urea, by reducing the effect of antidiuretic hormone, has a sodium-sparing effect, similar to that of thyroid and progesterone. It has a radical scavenging antioxidant protective effect in the heart (Wang, et al., 1999; Lukash, et al., 1978), and lipid peroxidation in the brain is decreased by urea (Krichevskaia, et al., 1976).

In the early 1970s there were dozens of published reports on the treatment of sickle cell anemia with oral urea. Apparently the misleading information on the "dangers" of urea, and the lack of commercial promotion, discouraged its use, and instead the very toxic (mutagenic, carcinogenic) hydroxyurea came into general use. Urea stabilizes the hemoglobin molecule itself, making the cells more flexible, improving circulation, even in normal blood. In heart surgery, urea has the same effect on cell flexibility; without supplemented urea during surgery mortality was 11.6%, but with urea no patient died (Roberts, et al., 1987). Blood dialysis, by lowering urea, makes red cells more rigid (Inauen, et al., 1982). Research support for sickle cell anemia, which occurs mainly in people of African descent, has been very small compared to support for other inherited diseases such as cystic fibrosis.

In 1939, Holder and MacKay described the use of concentrated or crystalline urea for healing wounds, and emphasized that even in concentrated form it didn't damage tissues, allowing restoration of function to a severely damaged foot, for example.

E. I. Danopoulos and others have published several reports on the use of urea for cancer, both intravenously and orally and by injection directly into, or near, tumors. It was very effective compared to other treatments, without the side effects of chemotherapy and radiation. (Danopoulos and Danopoulos, 1979; Gandhi, et al., 1977).

At present, urea is widely used topically, 3% to 40% in creams. In psoriasis, it slows proliferation and induces normal differentiation of cells (Hagemann and Proksch, 1996). Grether-Beck, et al. (2012) showed that urea regulates gene expression in skin cells. The urea content in aged skin is much lower than in young skin, and added urea restores water content, barrier function, and elasticity. Skin inflammation leading to fibrosis is a serious side-effect of radiation treatment for cancer, and a topical urea lotion is protective (Pardo, et al., 2010). It is also helpful for healing damaged corneas (Charlton, et al., 1996).

Because of its basic role in cell stability, urea will probably be found to have beneficial effects in many other conditions that involve regulation of minerals and water, including psychiatric conditions and inflammatory reactions.

While urea therapy can be valuable in many situations, knowledge of urea's place in physiology can guide everyday decisions, such as food choices. An important reason for including plenty of protein in the diet is that it is necessary for urea production. A high protein diet slightly increases the need for vitamin B6 and zinc. Some proteins such as meat and fish have a very high ratio of phosphate to calcium and magnesium, and excess phosphate contributes to some of the problems of aging and kidney function. Milk contains about 300 mg of urea per liter. Thyroid hormone, progesterone and carbon dioxide are important regulators of tissue water and urea content, and will often correct "kidney disease."

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