Ray Peat's Newsletter

. . . .the invention of a useful product can only follow the understanding of the relevant underlying science. G. Ling

Natural Order and Gilbert Ling

Two studies have estimated that the annual number of deaths in the US caused by medical errors ranks third, behind heart disease and cancer, with estimates ranging from 250,000 to 440,000 deaths per year (Makary and Daniel, 2016; James, 2013, 2017). Many doctors acknowledge that a failure to report "adverse events" resulting in death is common. Behind these estimates is the fact that those are errors recognized by doctors**;** their validity depends on the quality of medical education, and medical science. The presence of mistaken beliefs in the medical culture could mean that medicine's real effect on life, health, and death is radically underestimated. This is something Gilbert Ling has often spoken about.

I don't think it's possible to think about Gilbert Ling's work (which began in the 1940s) without evaluating the way that the science industry has been working during this period, at least in the US and England. "Science" has its rules, but they don't apply when the ruling ideology or paradigm is challenged. In biology, this paradigm insists that all cells are enclosed in a "semipermeable" membrane that actively maintains concentrations of dissolved substances inside the cell, that are different from the concentrations in the water surrounding the cell. This image of the cell implies many other things, for example that the water inside cells has the same solvent properties as water outside cells, and that something that's true of an enzyme outside a cell must be true of enzymes inside cells.

These assumptions are built into the educational system, and govern the way medicine is practiced, and the way research is done. Soon after beginning graduate study in the US, **Ling developed a new electrode capable of making measurements inside a single cell (the Ling-Gerard glass microelectrode), and his observations using that instrument led him to question the ruling doctrine that bioelectricity was produced by an active membrane on the surface of cells.**

> ***…. I have learnt from Professor Gerard's example the critical importance to seek a broader perspective than the experimental subject being pursued at any one time …*** **G. Ling**

In the early '70s, I saw that Ling's view was misstated in an article by a well known physiologist, citing an article by Ling as his source. Using the *Science Citations Index,* I found that the misstatement had been quoted verbatim by a series of other biologists, as the reason Ling's theory was to be dismissed, and in each case they cited Ling's original article, rather than where they had actually found the misstatement. Not many biologists even mentioned Ling's work, but most of those that I found who did, were lying about having read it.

In 1975, two Cambridge professors wrote a review of the "sodium pump," in which they discussed 245 studies supporting the existence of

the pump, and not a single study questioning its existence. Hundreds of studies, by numerous researchers besides Ling, had been published giving evidence against such a pumping membrane. On many scientific issues it's considered scandalous when only the evidence supporting one side is presented, but in this case the professors could count on the fact that most of their readers didn't know anything that wasn't in their textbooks. The situation in our science culture resembles the Jim Carrey movie, "The Truman Show," except that very few of the participants understand that it's a constructed illusion.

In the 1960s, Gilbert Ling's idea of a "living state" had overtones of holism and self-regulation, but to disciples of the ruling paradigm, one of the most offensive things about it was that it proposed to explain all biological processes in terms of known laws of physics and principles of physical chemistry.

For many years, the science culture of the US has at times denounced holism, intentionality, consciousness, epigenetics, self-organization and self-regulation, along with vitalism, as unscientific and superstitious. In the 1960s, Gilbert Ling's idea of a "living state" had overtones of holism and self-regulation, but one of the most offensive things about it was that it proposed to explain all biological processes in terms of known laws of physics and principles of physical chemistry. While biologists claimed to be defending mechanistic materialist science against vitalism, in fact they were rarely able to think in the physical chemical ways that were the essence of Ling's work. His criticism of the membrane sodium pump made it clear that the pump was just the ghost in the machine that was needed to animate the conventional theory of the living cell.

While US and British biologists were occupied with either ignoring or slandering Ling, Karol Mysels, a leading physical chemist, found that when he was writing about our contemporary understanding of ion exchange resins, such as those used in water softeners, the best physical theory existing to describe their function was the theory that Ling had developed to explain the behavior of ions in living cells. In trying to understand cell function he had used existing laws in ways that hadn't yet occurred to people like Mysels, and that turned out to be useful in their work and to have great generality for explaining the interactions of water, ions, and proteins and other polymers.

The principle of ion exchange has been widely recognized for a long time**;** in Aristotle's time it was known that the salt in sea water could be reduced by passing it through a certain mineral. For hundreds of years it has been known that soils generally retain potassium while allowing sodium to leach away, where it eventually concentrates in the oceans. The water in soil can be absorbed by plants during their growth along with the needed potassium, because most of the potassium in the soil isn't dissolved in the water. If all the potassium needed were in solution the concentration would be osmotically too high, and would dehydrate the roots. As the plant removes potassium from the ground water, solids in the soil release more potassium into solution. Water held in clay and similar materials in the soil is in an unusual state, with physical properties different from those of bulk liquid water**;** there is no dispute about that, and there is general agreement that these unusual properties of water in clay are involved in its ion exchange functions.

Although the special properties of water in clay are calmly acknowledged, it was Ling's suggestion that water in the living state is not the same as bulk liquid water that caused the most offense, because it directly challenges the assumptions that underly standard physiology and biochemistry, which assume that water is water, inside or outside of cells. Those assumptions (the Gibbs-Donnan equilibrium, the Nernst equation, and the Michaelis-Menten equation) were put into mathematical form more than 100 years ago, long before there were methods such as nuclear magnetic resonance to study the properties of water in different situations.

The property of cells that was most responsible for the invention of the active cell membrane theory was their ability to concentrate potassium and to exclude sodium**;** blood and other fluids in the body contain much more sodium than

potassium, but the water inside cells contains much more potassium than sodium.

Hair is made up of dead cells, but in an experiment hair was washed thoroughly with dilute acid until it was completely free of ions. The hair was dipped into serum containing the normal high concentration of sodium and low concentration of potassium. When the hair was then analyzed, it contained more potassium than sodium (though the gradient was lower than in living cells, which also regulate water content). The membrane theory says that the process of concentrating a substance against its gradient is "active transport," and requires the use of ATP. Experiments by Ling and others showed that the energy metabolism of cells could be poisoned so that no ATP was being produced, but that cells were able to maintain their ionic gradient, although sodium was free to diffuse into the cell, "through the membrane." All the ATP has to do is to be present, passively occupying its place in the cell.

Around 1970, a famous muscle physiologist was visiting the university to give a talk on his famous new theory of how muscles work, using the energy from the "high energy phosphate bond" of ATP, which he said was 14 kcal/mol, a quantity still commonly cited. He showed how that chemical energy might be used to operate the mechanism of muscle contraction, like little oars rowing a boat. Other people referred to that same bond energy when they wanted to explain the electrical, ion-moving work involved in nerve conduction, imagining little arms plucking and flinging the atoms. During the muscle physiologist's visit, I mentioned to my professor, Sidney Bernhard, that I had read his paper clearly showing that the ATP phosphate bond energy isn't especially high, and asked him why "everyone," such as the guest speaker and his audience, kept talking about it as if it were a reality. All he said was "not everyone does." One thing encouraging people to preserve the myth of the high bond energy is its convenience for running their imaginary machines.

In one of Ling's papers, he noted the amount of ATP energy that was, according to various authors, needed to operate the membrane sodium pumps. He used the commonly accepted figure for ATP's energy, and found that a typical cell would need at least 15 times as much energy as could be produced by the cell, just to perform this single essential minimal chore, and much more would be needed to account for all the other substances that are concentrated by cells against their gradient.

Since Ling didn't imagine that ATP bond energy was being consumed constantly to run membrane sodium pumps, he wasn't concerned with any energy that might be released by hydrolyzing that bond. He, like Albert Szent-Gyorgyi, was aware that the ATP molecule adsorbs with considerable energy to protein molecules, and that its presence governs the shape of the protein molecule. In a muscle cell, the presence of ATP stabilizes the muscle in its relaxed state, and in any cell, similar associations between ATP and proteins stabilize the cell in a basic resting condition in which it favors the presence of potassium over sodium.

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Ling wasn't alone in publishing disproofs of the membrane pump theory, but he persisted for many years, repeating important experiments scores of times, and answering even criticisms that hadn't been made. During these decades, condensed matter physics and physical chemistry were continuing to advance their understanding of the nature of matter. **The image of the living state of matter that Ling had sketched out was now being surrounded by a rich landscape of information about colloids, gels, coacervates, liquid crystals, nanoscale surface effects, self-organization, and membraneless organelles.**

Biological and medical education has assumed a reductionism based ultimately on physics, but it has been a rudimentary physics in which there are three phases of matter, solid, liquid, and gas, and organisms have been seen exclusively in terms of those states of matter**;** if water isn't in the gaseous or solid state, then it has to be in the liquid state.

By 1970, anyone who was interested in the subject could see, using a nuclear magnetic resonance (NMR) apparatus, that cell water isn't the same as bulk water. In connection with my dissertation work, I found that the water in uterine tissue was affected both by estrogen and by aging. **Raymond Damadian, recognizing from Ling's work that the water in cancer tissue is different from the water in the related healthy tissue**, and that the difference can be shown by NMR, built a magnetic resonance scanning apparatus that produced an image of a tumor in a mouse in 1976. **Normally, a person would assume that such an accomplishment would merit a Nobel Prize at least for Damadian, for designing the first MRI instrument, and also for Ling, whose theory led to the production of the instrument, but it didn't.**

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When something is about to change its physical state, as when water boils or freezes, it will sometimes persist in its present state long past the time that conditions had become right for the new state to come into being, like supercooled or superheated water. Reductionist biology has long outlived any conditions that justified its existence. Everything around it in the world of knowledge is now showing the impossibility of its mechanistic models of cell structure.

In 1960, the painter David Alfaro Siqueiros said that the Rockefellers and the US Government had created "ghost art," abstract expressionism, to destroy society's consciousness. **Much of contemporary science has been a ghost science, a mental impediment imposed on society, limiting our ability to perceive the nature of our problems and possibilities.**

When the more objective holistic understanding of the organism becomes acceptable, nearly every part of physiology and biochemistry will be reinterpreted.

The first chemicals produced by animals to be chemically identified, in the late 18th century, were urea and carbon dioxide. For thousands of years before their chemical natures were known, both of them were used therapeutically, in the form of urine therapy and bathing in carbonated mineral springs, then in the 19th century the pure substances began to be used by doctors.

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Carbon dioxide had once been seen as a hormone, and it had been used medically for ulcers, arthritis, cancer, and mental problems, and Yandell Henderson's work had led to its use as "carbogen" (5% CO2, 95% O2) for resuscitation, but by the middle of the century most therapeutic uses had been stopped, and hospitals had been taught to use pure oxygen instead of carbogen, and patients with brain swelling were being hyperventilated with oxygen to lower their blood carbon dioxide.

Oral urea had been used to treat ulcers, heart failure, sickle cell anemia, glaucoma and Meniere's disease, etc., intravenous urea had been used to treat brain swelling, and topical urea had been used to treat wounds. As recently as the 1950s urea was recognized as the most effective treatment for brain swelling, but the "science based" membrane theory reasoned that the removal of water from cells was always governed by osmosis, and since urea could remove water from cells, it must be osmotically active. As an osmolyte, it was added to distilled water for intravenous use, and the red blood cells behaved as they would in distilled water, dissolving. The report that urea causes hemolysis led to general discontinuation of its use for treating brain injury. It is still common to refer to its "osmotic" effects on water. As urea is ubiquitous, the dangerous confusion caused by the membrane theory is ubiquitous. People who die because they don't

receive urea therapy are among the casualties of the membrane theory.

In the 1950s, Gilbert Ling noticed that in the presence of increased carbon dioxide, a given stimulus produces less contraction of a muscle than with a lower concentration of carbon dioxide. Around the same time, Russian physiologists found that the CO2 produced by active brain cells relaxes brain blood vessels, including capillaries, increasing the flow of blood in proportion to the increasing metabolic needs.

Hemoglobin's ability to transport carbon dioxide and oxygen has been studied as an example of how changes in a protein's structure affects its functions. When CO2 associates with an amino (-NH2) group on the protein (forming a carbamino compound), hemoglobin's properties are altered, causing it to release the oxygen that had been bound.

Although this form-changing property of proteins ("allostery") is well recognized (Monod, et al., 1963; Abdel-Magid, 2015), nearly all biologists that I have known have been unaware of the fact that CO2's ability to form carbamino compounds with hemoglobin extends to other proteins, including those that are called "specific receptors." For several decades high altitude physiologists have been perplexed by what they call the "lactate paradox," the fact that exercise at high altitude, with less oxygen, produces less increase in lactic acid in the blood than it does at sea level, allowing quicker recovery, since it is understood that it is oxidative metabolism that prevents the formation of lactic acid—the lower oxygen availability should lead to a higher lactate content at high altitude, and slower recovery.

They consistently neglect to think of CO2's influence on everything in every cell, not just on hemoglobin. The organism is reorganized when there is less oxygen to displace CO2 from the proteins to which it is adsorbed. The principle of induction, central to Ling's view of cell structure and function, is something every student hears about early in the study of chemistry, the transmission of the electron withdrawing properties of various atoms and groups through connected atoms. Carbon dioxide, a Lewis acid, strongly withdraws electrons from the proteins on which it is adsorbed, increasing their acidity. This affects properties such as contraction and nerve activation, as well as oxygen binding and enzyme action.

Everything that associates with a protein, such as potassium or ammonium, has an inductive effect on the protein's structure and interactions with its surroundings, and substances that adsorb powerfully, especially ATP and steroids, have powerful influences on the properties of the system. Molecules that bind powerfully to proteins change the ways the proteins influence the properties of water, and the properties of water govern cells' metabolism and their interactions with each other and with the environment. Ling called these influential binding molecules "cardinal adsorbents."

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Besides this fundamental stabilizing, regulatory function of carbon dioxide, it combines with ammonia to form urea. Urea, like carbon dioxide, powerfully contributes to the regulation of water, modifying its properties. The elimination of ammonia protects against its toxic effects, which include creating pseudohypoxia, increasing the hypoxia inducible factor, HIF, and aerobic glycolysis, the characteristic cancer metabolism and the associated proliferation of cells, while blocking renewal of nerve cells. Reduced availability of CO2 leads to the failure to detoxify ammonia.

Stresses activate the enzyme carbonic anhydrase, which converts the gaseous CO2 (the form that binds to protein and favors "structured" surface or vicinal water) into the ionizable carbonic acid/bicarbonate, which leaves cells. Activating this enzyme raises the intracellular pH, tending to excite cells, and inhibiting it lowers the intracellular pH, quieting cells, saving energy. The activity of carbonic anhydrase, needed for short term survival, exemplified by wound healing (Barker, et al., 2017), disrupts the

fundamental organizing processes of carbon dioxide if it is chronically activated.

Seeing hormones and drugs in terms of the carbon dioxide system, rather than the reductionist system of cascades of receptors and messengers, makes the organism intelligible as a single system. The oxidative processes that support purposive, creative functioning of the organism, optimize CO2 by inhibiting carbonic anhydrase**;** this enzyme is inhibited by thyroid hormone T3, progesterone, urea, caffeine, antipsychotic drugs, and aspirin. Agents that tend to cause reversion to the primitive anaerobic energy production activate the enzyme—serotonin, tryptophan, cysteine, histamine, estrogen, aldosterone, HIF, SSRIs, angiotensin, and parathyroid hormone, for example.

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When the opposing aerobic energy processes are debilitated, more and more tissues fail to resolve the short term restorative, "wound healing," processes. These barely surviving cells spread the stress signals to adjoining tissues, modifying their metabolism and creating inflammation, fibrosis, atrophy, and tumefaction.

In the 1960s, at the peak of the membrane craze, when Otto Warburg, Albert Szent-Gyorgyi, and Gilbert Ling talked about the difference between health and cancer in terms of holistic metabolic energy-structure interactions, their ideas were ridiculed. Many of their basic discoveries are now individually accepted, but seen in terms of the mechanical membrane/pump/receptor doctrine, their meaning isn't accessible.

The implication of Gilbert Ling's revolution in cell physiology is that a new way of thinking is needed. If life is spontaneously ordered even on the molecular level, the ordering process has to be taken into account when trying to correct health problems.

A medical approach that thinks in terms of cardinal adsorbents, induction, association and cooperative phase transitions, is using mental processes analogous to Norbert Wiener's conception of cybernetics, thinking in terms of observably responding wholes, rather than the Shannon-Weaver model of information and control systems—sender, encoder, channel, noise, decoder, and receiver—which is implicit in the drug-receptor-gene-enzyme paradigm, and suitable only for an authoritarian system.

The diseases that are becoming epidemic—hypertension, diabetes, autoimmune inflammatory diseases, mental and neurological diseases—are seen by the drug industry as an exciting new market. **An alternative future would involve a rethinking of biomedical doctrines and education, focusing on the environmental changes needed to support the body's restorative processes.** Like intracellular ATP, an appropriate amount of progesterone, T3, urea and carbon dioxide each has an infinity of beneficial effects, individually and in combination, and with their synergizing nutritional, botanical and pharmaceutical substances their use could transform the nature of health care.

Combinations of substances such as CO2, progesterone, angiotensin receptor blockers, acetazolamide and aspirin that affect fundamental properties of the organism are appropriate for use in a great range of problems now treated with drugs considered to be "specific" for particular ailments. **The purpose should be to support the patient's recovery, not to "eliminate a disease."**

In the past, when doctors in a region have gone on strike, the death rate fell sharply for the duration of the strike. If it becomes possible to stop all medical practices based on the irrational membrane theory, a similar or greater decrease of mortality is likely to become permanent.

REFERENCES

ACS Med Chem Lett. 2015 Feb 12; 6(2): 104–107. **Allosteric Modulators: An Emerging Concept in Drug Discovery.** Abdel-Magid AF.

J Enzyme Inhib Med Chem. 2015 Jun;30(3):420-9. **Chromatographic evaluation and QSAR optimization for benzoic acid analogues against carbonic anhydrase III.** Alzweiri M, Al-Balas Q, Al-Hiari Y.

Exp Mol Med. 2017 May 19;49(5):e334. **Role of carbonic anhydrases in skin wound healing.** Barker H, Aaltonen M, Pan P, Vähätupa M, Kaipiainen P, May U, Prince S, Uusitalo-Järvinen H, Waheed A, Pastoreková S, Sly WS, Parkkila S, Järvinen TA.

Bioorg Med Chem. 2008 Oct 15;16(20):9101-5. **In vitro inhibition of salicylic acid derivatives on human cytosolic carbonic anhydrase isozymes I and II.** Bayram E, Senturk M, Kufrevioglu OI, Supuran CT.

Drug Chem Toxicol. 2005;28(4):409-21. **Combined treatment potentiates the developmental toxicity of ibuprofen and acetazolamide in rats.** Cappon GD, Fleeman TL, Cook JC, Hurtt ME.

Proc Natl Acad Sci U S A. 1980 Sep;77(9):5562-6. **Mitochondrial carbonic anhydrase.** Dodgson SJ, Forster RE 2nd, Storey BT, Mela L.

J Am Soc Nephrol. 2016 Jul;27(7):2082-91. **Acetazolamide Attenuates Lithium-Induced Nephrogenic Diabetes Insipidus.** de Groot T, Sinke AP, Kortenoeven ML, Alsady M, Baumgarten R, Devuyst O, Loffing J, Wetzels JF, Deen PM.

J Appl Physiol (1985). 2004 Aug;97(2):515-21. **Acetazolamide prevents hypoxic pulmonary vasoconstriction in conscious dogs.** Höhne C(1), Krebs MO, Seiferheld M, Boemke W, Kaczmarczyk G, Swenson ER.

Journal of Patient Safety 2013 Sept; 9(3) 2013 122-128. **A New, Evidence-based Estimate of Patient Harms Associated with Hospital Care.** James JT.

Afr Health Sci. 2018 Dec;18(4):1303-1310. **Inhibition of cell proliferation, migration and colony formation of LS174T Cells by carbonic anhydrase inhibitor.** Karakuþ F, Eyol E, Yýlmaz K, Ünüvar S.

Am J Surg. 1982 Nov;144(5):554-7. **Inhibition of gastric mucosal carbonic anhydrase by taurocholic acid and other ulcerogenic agents.** Kivilaakso E.

Physiol Chem Phys Med NMR. 1983;15(2):137-54. **Studies on the physical state of water in living cells and model systems. II. NMR relaxation times of water protons in aqueous solutions of gelatin and oxygen-containing polymers which reduce the solvency of water for NA+, sugars, and free amino acids.** Ling GN, Murphy RC.

BMJ. 2016 May 3;353:i2139. **Medical error—the third leading cause of death in the US.** Makary MA, Daniel M.

J Mol Biol. 1963 Apr;6:306-29. **Allosteric proteins and cellular control systems.** Monod J, Changeux JP, Jacob F.

Biochem Int. 1991 Mar;23(4):779-89. **Changes in carbonic anhydrase may be the initial step of altered metabolism in hypertension.** Parui R, Gambhir KK, Mehrotra PP.

Int J Clin Lab Res. 2000;30(3):119-25. **The mechanism of action of angiotensin II is dependent on direct activation of vascular smooth muscle carbonic anhydrase I.** Puscas I, Coltau M, Gilau L, Baican M, Pasca R, Domuta G, Hecht A.

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