Ray Peat's Newsletter

"Seek simplicity and distrust it." **A.N. Whitehead**

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Receptors, or Sensitive Substance?

The major science journals avoid publishing things that aren't compatible with the current belief system, so the facts that support the principles taught in the universities are undeniably "cherry picked," first by editors, and then by professors. The journals' editors are hired for their ability to make selections that will add to and expand the established "scientific knowledge," but since they aren't omniscient, their choices sometimes inadvertently provide glimpses of another, more interesting, world of knowledge. The solutions to some of the perennial problems of biology and medicine are taking shape in that other culture. Some of the best known ideas of biology—including genes, membranes and receptors—have blocked, and continue to block, understanding of aging, cancer, stress, shock, epilepsy, regeneration, perception, and thinking.

Mainstream science, the "official" science that is massively financed by government and industry, has been elaborating an ideology based on a metaphysical view of matter, as something known *a priori.* A different, experience-based science, which isn't committed to a particular doctrine about the nature of matter, has barely managed to survive into the present century in the work of a few scattered individuals.

While mainstream science has been committed to a "mechanistic" view of biology (e.g., Francis Crick's "what is there besides atoms?"), the empirical investigators have taken a more global view of living things, recognizing that new properties emerge in new situations, and that these situation-dependent properties can't be understood in terms of the physical principles that were sufficient for understanding steam engines.

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Embryologists began seeing the relevance of principles of long range ordering, as can be seen in liquid crystals and coacervates. In recent times, some of these properties of complex matter have turned out to be useful in new technologies, including electronic displays and drug formulation, and that has to some extent validated their reconsideration in biology. However, the opposing, mechanistic view has been building its doctrines and institutions for more than a century, and they are stabilized by the annual flow of trillions of

dollars—and by controlling the dissemination of information.

Early in his career, Paul Ehrlich observed that certain dyes selectively stained certain types of cell, without coloring other cells, and in the 1890s he related that specificity to Emil Fisher's description of enzyme action on a substrate as a lock and key interaction of specific chemical compounds, and proposed that cells contain chemical "side-chains" that specifically bound the dye. The fact of differing affinities of substances is something that continues to be studied, and that rarely involves anything like Ehrlich's theory, but the spirit of the times, and the power of the German chemical industry, put Ehrlich's idea in the foreground of medical culture.

The assumption of randomness is an integral part of a larger system of interlocking assumptions--genetic determinism, barrier membranes, random diffusion, osmosis, receptors, channels, and pumps. Those are simple concepts to learn, and when they are reinforced by years of "education," they are very hard to question.

In 1900, Ehrlich substituted the word "receptor" for "side-chain." His idea of the side-chain-receptor on cells was that it could be produced in excess, as a defensive antitoxin, neutralizing toxins by binding to them. That part of his theory was a rough but realistic description of the process of natural immunity. He also claimed that his aniline-based dyes were staining and killing microbes because they were a specific chemical match for the microbe; when a dye failed to kill a microbe, he chemically attached the aniline to arsenic, claiming that this would cause the arsenic to be selectively bound to specific receptors on the microbe, sparing the patient's cells. That mistaken belief has continued to exist in popular culture, and still guides the medical approach to cancer treatment.

Ehrlich's newer magic bullet chemotherapy, arsphenamine or Salvarsan, was toxic to human tissue. It was claimed that it caused death only when it was mistakenly injected into muscle rather than into a vein. In Germany there was public hostility toward Ehrlich, the Frankfurt hospital, and the Hoechst company that made Salvarsan. The critics objected to the compulsory administration of the dangerous drug to prostitutes, and claimed that Ehrlich and Hoechst were enriching themselves by charging high prices for a drug developed with government funding. Karl Wassman, the editor of a Frankfurt newspaper making those criticisms, was convicted of insulting Ehrlich and sentenced to a year in prison.

The pharmacologist Walther Straub argued against Ehrlich's specific chemical interactions between receptors and drugs, thinking of the physical properties of drugs and hormones as being able to explain the antagonistic effects and generality of action of a wide range of pharmacologically active substances. Ehrlich believed* that physical chemistry didn't apply to biology, and his attitude, encouraged by the drug industry, has persisted in official science up to the present. Physics and chemistry had become State Sciences by the end of the 18th century, and with Ehrlich, biology became a Commercial Science.

Straub's orientation toward the physical properties of drugs and hormones reflected an important strain of scientific culture of his time, that was widely known because of the famous embryological research of Jacques Loeb. Loeb demonstrated that the specific biological stimulus of a sperm cell, interacting with a "receptor" in the egg, wasn't needed to fertilize an egg; sea water, with added salt or sugar or urea, or acid or alkali, was enough to

trigger the process of embryonic development. The activating signal was non-localized, a pervasive change in the cell water.

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Ehrlich's "lock and key" theory, that all cells are covered with receptors specific for nutrients and toxins, overlaps considerably with the preformationist view that inherited structures in the nucleus are in control of the developmental process. The embryologists who thought in biophysical terms opened the way to the idea of morphogenetic fields and the epigenetic nature of development. Biophysical thinking led them to think in terms of biological "fields," and their lock and key opponents dismissed them as "vitalists."

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From the 1930s to the 1950s, the steroid hormones and their physiological effects were being studied in objective biophysical ways, at the same time that they were being converted into products by the pharmaceutical cartels. Their general properties, including anesthesia, inflammation, and carcinogenesis, were considered in terms of universal, general properties of cells and tissues. Estrogen and the chemicals of soot (polycyclic aromatic hydrocarbons) were known to produce inflammation, atrophy, fibrosis, and cancer, and other steroids, especially progesterone and pregnenolone, were known to protect against those effects.

Alberte and Bernard Pullman were able to demonstrate that it was the electronic properties of the polycyclic molecules that were responsible for their carcinogenicity. They called their work "quantum chemistry" or "quantum biochemistry," but it involved ("holistically") working out the way that the properties of the parts of the molecule were governed by the properties of the whole molecule, its size and shape.

The (electronic) polarizability of a molecule governs its adsorptive properties, the way it interacts with and influences the molecules in its surroundings. The Pullmans' approach to aromatic organic compounds complemented the work of the biophysical ("vitalist") embryologists, who demonstrated that the polarity of an embryo existed in its parts as well as in the whole. This reflection of the whole in the parts is denied by the mechanists, and the denial is built into the basic assumptions of their science.

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One of the arbitrary or metaphysical assumptions of the mechanists is that, in the absence of specifically imposed order, derived from genes, there is random disorder. One of my professors, Sidney Bernhard, simply counted molecules carefully, and found that the metabolism of glucose involved a direct passing of substrate molecules from one enzyme to the next—the cell doesn't contain

enough substrate molecules for it to operate by random diffusion. The historically determined assumption of randomness is an integral part of a larger system of interlocking assumptions—genetic determinism, barrier membranes, random diffusion, osmosis, receptors, channels, and pumps. Those are simple concepts to learn, and when they are reinforced by years of "education," they are very hard to question.

The biophysical approach to cell physiology recognizes that enzymes are sensitive to their surroundings, and that they work in organized systems. The source of that smooth, complex organization is conventionally said to be the result of the natural selection of random variations over a period of a billion years. Experiments by Sidney Fox and others have demonstrated that cell-like structures, composed of protein-like molecules, with enzyme-like catalytic functions, can be produced from amino acids in a school laboratory in an afternoon, because of the spontaneous self-organizing tendency of matter.

Coacervates, formed by mixtures of polymers, spontaneously form structures; electron micrographs have shown that the separate phases contain fine-textured, fibrous internal structures. "Stress granules," that form in the cytoplasm under stress, are now known to be coacervates, formed by the interaction of RNA and protein. Other cell organelles have the properties of spontaneously formed phases, and are sometimes called "membraneless organelles."

The structure of a coacervate is sensitive to small amounts of solutes in the water. The well known effects of ions on the structure of water govern its relative lipophilicity or lipophobicity, the energy involved in its interfaces with lipids and lipid-like parts of proteins and other macromolecules, and so govern the structures of the macromolecules. The solutes in coacervates are analogous to the "dopants" in semiconductor materials—small amounts of a substance that change the electronic properties of an otherwise insulating substance. Electromagnetic fields, affecting the charged materials, significantly affect cellular coacervates, whether the fields are internally or externally produced. The constant energy flow produced by oxidation and reduction is one of the cell's important formative influences.

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In oxygen deprivation, cells take up water, and the "estrogen receptors" behave as though they had been stimulated by estrogen, *but without the estrogen molecule.*

The energetic processes of cells, governing their form and function, are regulated by enzymes, so it's important to know exactly how enzymes are regulated, especially how they are organized so that each cell has a coordinated metabolic pattern. It was obvious that hormones could modify the catalytic actions of enzymes, so various people investigated their possible roles as catalysts, with direct involvement in the chemical action of enzymes. The active thyroid hormone was observed to almost instantly increase cells' oxygen consumption, and estrogen as quickly increases cells' uptake of sugar and water. These changes are far too quick to be the result of communication with the cell nucleus leading to the synthesis of new proteins.

Evidence for a catalytic function of estrogen was produced by a group at the University of Chicago (Talalay, et al., 1958) who showed that it acts in a "transhydrogenase"

process that can increase the cell's reductive and synthetic capacity, allowing reductive equivalents to flow from NADH to NADP, which can support cell growth and replication processes. The reductive balance is an important cell organizing factor, for example governing the conversion of the relatively inactive estrone into the powerful estradiol. (This is where a vicious circle of excitation, fatigue, and degeneration often starts, that requires the intervention of stabilizing substances, such as carbon dioxide, thyroid hormone, sugar, and progesterone.)

However, soon after that demonstration, Elwood Jensen (1962), who had been working on poison gases, began promoting the doctrine that hormones work only by activating genes, after binding to a receptor protein. The US Atomic Energy Commission provided him with tritium, to radioactively label estrogen for his studies, something which other researchers didn't have access to at the time. He claimed that his radioactive estrogen was not metabolized in the uterus, and claimed that he had demonstrated the "nonmetabolic nature of estrogen action," simply contradicting the work of the enzymologists.

The shift of interest from direct effects on enzymes to action on genes by way of receptor proteins doesn't seem logical, because no one had repeated Jensen's experiment, and several different groups were describing estrogen's metabolic changes in the uterus. In 1965, Jensen did another experiment, again using a newly synthesized substance, the antiestrogen, nafoxidine, which wasn't generally available, and which hadn't been studied enough to understand the mechanisms of its actions. Referring to his work, he said**:**

> ***"These results caused the demise of the transhydrogenation hypothesis and convinced all but the most diehard enzymologists that estradiol binds to a characteristic component of target cells to exert its physiological effect without itself being chemically altered."***

I think it's more likely that government funding was shifted away from research showing catalytic and enzyme-modifying effects of hormones, to their preferred explanation in terms of receptor-controlled genes. The line of research that had been fruitful for several years quickly disappeared, and by the late 1960s the receptor doctrine was being taught as the official doctrine.

"The history of the great events of this world is the history of crime." Voltaire.

Jensen's claim that estrogen isn't metabolized in the uterus served to create the receptor dogma, but no one repeats that claim now, because it would seem ridiculous. His results and his claim are anomalies. Besides being metabolized in the uterus and other "target" tissues, estrogen and other hormones are now well known to be able to modify the activity of enzymes, without directly participating in the reaction as a catalyst, and without acting first in the nucleus.

Enzymes' functions are affected by the adjoining water, and that water is affected by dissolved substances. In a coacervate, as in a semiconductor, the properties of the whole can be modified by the presence of a very small amount of a particular substance, the "dopant." While I was in graduate school, I frequently baked bread, and I began thinking of the way water interacted with the wheat flour, as a parallel to the changes that the physical-chemical embryologists had produced with various chemicals. I noticed that the consistency of the dough changed oddly when I added a variety of biologically active chemicals; it would feel wetter with a small amount of one substance, and drier with a similar amount of a different substance; sedatives and stimulants affected it in

opposite ways. The same amount of water can feel very different, in slightly changed conditions.

The effects of estrogen can be produced in a variety of ways, without the estrogen molecule itself. An excess of intracellular water, similar to the water that cells take up immediately when stimulated by estrogen, is enough to imitate its effects. In oxygen deprivation, cells take up water, and the "estrogen receptors" behave as though they had been stimulated by estrogen, but without the estrogen molecule. Many different factors—x-rays, hypoglycemia, excess alkalinity, cyanide, cholera toxin—synergize with estrogen; they obviously aren't acting just upon the estrogen receptors.

A "receptor" is a way to imagine order being introduced into an otherwise supposedly random system of diffusing molecules. The behavior of the receptor proteins may be parallel to, and crucial for, some of the events in a cell, but even then, rather than explaining what's happening in the cell, attention to the receptors is distracting attention from the real processes that should be understood.

Luca Turin's work on olfaction and pharmacology, the detection of and response to molecular resonance, should be a model for thinking about the way cells and organisms are.

The mechanist's tendency is to see the life of a cell in terms of information, digital on-off signals, whether a protein receptor is phosphorylated or not, reduced or oxidized, etc., and to visualize it as atoms arranged in space. That imagined cell may "perceive," but it perceives the way a logician thinks—without melody or aroma or erotic meaning. We accept that we have several distinct kinds of sense (taste, smell, sight, sound, pressure, temperature, vibration, pain, pleasure), but for the cell, the stimuli are transduced, reduced to generic, sometimes "digital," signals. Luca Turin's work on olfaction and pharmacology, the detection of and response to molecular resonance, should be a model for thinking about the way cells and organisms are. Responsiveness or sensitivity is a property of the living substance that needs to be explored without preconceptions, along with the other properties such as polarity and intentionality that guided the best research of the past.

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