

Ray Peat's Newsletter

Inheritance must be looked at as merely a form of growth. Charles Darwin, 1868

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Epigenetics, sickness-aging, and changing science

"All journals are bought—or at least cleverly used—by the pharmaceutical industry," says Richard Smith, former editor of the British Medical Journal, who now sits on the board of Public Library of Science (PLoS), a nonprofit open-access group publishing scientific journals that eschew corporate financing and are freely available online to the public. <http://theamericanscholar.org/flacking-for-big-pharma/#.UqKDuvYVz-U>

The recent announcement by the journal Food and Chemical Toxicology of the retraction of a 2012 article on the effects of Roundup and GMO corn on the health of rats, illustrates the growing boldness of the corporate powers in controlling culture and defining the opinions that are permissible.

The editorial process, using anonymous referees, has previously been sufficient to eliminate research that reached undesirable conclusions, despite the prior control exercised by those who control research funding and science training. Now publishers are retroactively correcting the judgments of the original editors and referees. The older generation of gate-keepers has occasionally allowed some inconvenient information to be published, but that can be remedied by the publishers, now that so many people rely on digital publication, which can easily be deleted.

The "advance of science" has consisted largely of an expansion of the number of things which are to be considered as proven, and made part of the educational curriculum. From the conservation of mass and energy to the existence of lock-and-key-like signal substances and receptors in organisms, and now the safety of industrialized foods, proper science consists of things which must not be questioned. This is part of the rhetoric of science, and it works best when it's invisible. Science

journals have usually managed to keep the corruption invisible.

In politics and common culture, discussing the existence of a ruling class had been unacceptable until recent years, but recently several politicians have denounced labor union activism as incitement of "class warfare," acknowledging the existence of classes. The Taft-Hartley Act, automation, and offshoring were clearly processes in a class war, but it was impolite to describe them as such. Rhetoric, silence, and censorship keep dissent nearly invisible.

The corruption of science by commercial interests has become increasingly visible, especially in pharmacology, medicine, and nutrition research, but class interests have been recognizable in science at least since the renaissance. The philosophy that was allowed to be taught and published had to support the status quo, and the natural sciences developed under those conditions of censorship, in the culture shaped by centuries of strict control.

Modern philosophy has been dominated by rationalistic doubting of the senses, with Descartes' and the neo-Kantians' ideas being very influential in the philosophy of science taught in European and US universities. The idea that "the senses mislead" justifies deference to the judgment of the learned authorities. The medieval Great Chain of Being of the neoplatonists obviously served the purpose of the ruling classes, and it was only in the 20th century (after it had been expressed in the 19th century ideas of evolution and racism) that the Great Chain of Being receded into the cultural background. The Platonic essences were replaced by the reductionist explanation of organisms in terms of cells and genes, of chemical substances in terms of atoms, and of atoms in terms of subatomic particles.

Reasoning about the essences, according to this attitude, can discover things that the senses can't discover, and might even contradict the impressions gained from the senses. Heisenberg's uncertainty principle justifies a statistical "quantum mechanical" approach to reality. Noam Chomsky, denying that learning from the senses could explain the learning of language, describes himself as a Cartesian in treating the mind as a "black box," with the language function to be explained by reasoning (dismissing introspective data), concluding that a certain "language acquisition device" exists in the brain, as a result of genetic mutations. At least some of his contemporaries apparently took Descartes' bizarre verbalizations seriously, and the academic world, starting with MIT, has taken Chomsky's absurdly antiscientific assertions seriously.

He who Doubts from what he sees.
Will neer Believe do what you Please.
If the Sun & Moon should Doubt.
Theyd immediately Go out. W. Blake

Konrad Lorenz, nazi theorist of racial hygiene and later Nobel Prize winner, believed that genes for language, art, crime, for every specific kind of behavior, could be inferred from facial features and other individual traits, and that elimination of defective forms of those genes would improve society. His essentialist kind of thinking has thoroughly dominated biology and medicine.

Something analogous to Chomsky's "discovery" of a gene-based language acquisition device has happened in the lie-detector culture. By analyzing external biological signs, the researchers hope to be able to know a person's inner state, a consciousness of lying or telling the truth. By mathematical processing, analysis of the entropy of changes in the heart rhythm for example, they believe they can draw conclusions about deep changes in the physiology of the nervous system, and from that can make inferences about what the person is experiencing. A significant part of the medical culture has made "heart rate variability" an important health status indicator, which could have some value (for example in triage), but

inferences about the nervous system and biochemistry are being based on it, which can lead to inappropriate treatments. The culture of science has made it possible for every science to be tainted with speculation posing as discovery.

The science establishment is like the political establishment, in treating its critics as dangerous barbarians who must be suppressed. The establishment of the medical profession by government has defined the opinions of physicians as authoritative knowledge, so it's good to remember what C.S. Burwell, a former Harvard dean, told his medical students, that half of what they would be taught was false, but that the teachers didn't know which half. Since he said that, specialization has taken over U.S. medicine, and it might be argued that practically everything the specialist knows is false, because of its remoteness from real experience and from meaningful criticism.

When a doctor prescribes the newest, most advertised but least researched, drug, rather than an old product with the most evidence of safety and effectiveness, I think he should be willing to tell the customer the basis for his choice. A customer can treat the doctor as a contract employee, who will be retained only if he can justify his approach.

In recent years, well documented studies have shown that between 200,000 and 400,000 people die annually as the result of recognizable avoidable errors in hospitals (<http://patientsafetyamerica.com/>), making errors in hospitals the third largest cause of death. Other studies, including out-patients, showed much larger numbers of avoidable deaths, making medical error the largest cause of death in the U.S. People are often willing to make an effort to avoid cancer and heart disease, and developing a critical attitude toward medicine might be the single most important thing people can do to protect their health.

To recognize the uniqueness of an individual is to threaten authoritative knowledge, since newness requires openness to learning and reinterpretation of, potentially, everything. Diagnosis, the recognition of a disease, is looking for the familiar, rather than the novel.

A characteristic feature of standard medicine in the US is the diagnostic algorithm or decision

tree, which focuses on identifying a disease. This habit of mind leads many doctors to insist vehemently that a disease such as cancer isn't a systemic disease, and to think of a disease as something troublesome in an otherwise healthy normal body. The term "comorbidity," the simultaneous but independent existence of two or more diseases, makes it clear that the concept of disease is something that can be compartmentalized.

A common result of this approach is the prescription of drugs for each diagnosed condition (with additional drugs for the drugs' side effects). I have known people who were taking more than 20 drugs every day, who recovered when they stopped taking all or most of them. The approach can sometimes result in a person receiving a very appropriate prescription, but such successes don't demonstrate that "scientific knowledge" has been appropriately used.

Without rejecting the achievements of reductionist science, it's now becoming possible to integrate those achievements into a holistic understanding of the individual's problems, in terms of the person's unique adaptive responses to a unique history and situation. Elements of the reductionist system can serve as tools of perception, leading to an inductive generalization that simply ignores the reified metaphors of contemporary biology, such as membrane pumps.

The idea of a comprehensive appreciation of a person's individuality was central to European and American medicine in the 19th century, until it was displaced by the movement that called itself "scientific medicine." The main limitation of that more holistic approach, which identified a person's "constitution," "diathesis," or "miasm," was that, having seen the problem in a unified way, the treatment was likely to be similarly simplified, for example with a homeopathic remedy that had been statistically, scientifically, identified as appropriate for that diathesis. Over-simplified, stereotyped treatment is seen in the contemporary dosage of drugs, and the instructions for their use.

As medicine is institutionalized in the US and Europe, when a customer insists on seeing the evidence justifying a certain treatment rather than another treatment or no treatment, it's natural for

the physician to see it as an inappropriate disruption of his practice. The system is designed to impose its authority, while extracting money, as smoothly and automatically as possible. Learning to see their patients with real objectivity would be to start a revolution in medicine. (The industry is moving effectively to control this threat.)

Without evidence to the contrary, any health problem should be thought of as systemic, and, if the problem hasn't been present since birth, it should be assumed that it isn't "genetically determined," and even congenital problems shouldn't be explained away as necessarily the result of mutant genes.

Genetic faddism in medicine has been increasing because of advertising for genetic tests sold directly to the public. Many people have been disturbed to learn that they have a "mutation" in a gene called MTHFR. This is an extremely common variation in a gene that relates to the activity of an enzyme that regulates methylation, i.e., the attachment of single carbon atoms to a great variety of molecules in the body. A year ago, the American College of Medical Genetics published its recommendation regarding testing for the MTHFR variation: "Recent meta-analyses have disproven an association between hyperhomocysteinemia and risk for coronary heart disease and between MTHFR polymorphism status and risk for venous thromboembolism. There is growing evidence that MTHFR polymorphism testing has minimal clinical utility and, therefore should not be ordered as a part of a routine evaluation for thrombophilia."

People who have the less active form of that enzyme have a slightly higher requirement for one of the B vitamins, folate (which is found in fruits, vegetables, milk, cheese, eggs, liver, etc.). Several other nutrients, vitamins B2, B6, and B12, are involved in the regulation of folate and methylation. Large numbers of people have begun using a variety of supplements that are supposed to increase the body's methylation capacity. Oddly, it seems that the testing companies, as well as of most of the doctors talking about the methylation system, haven't been talking about the association of that "mutant gene" with a much lower risk of cancer. In recent years, excess methylation of

DNA has been associated with stress, cancer, and aging. Choline, an important methyl donor, has been associated with prostate cancer risk (Awwad, et al., 2012).

Identical twins, besides sharing practically identical DNA patterns, also shared very similar intrauterine conditions, yet they differ greatly in their susceptibility to disease; for example, if one twin has rheumatoid arthritis, there's only a 12% chance that the other one will have it. Considering the influence of intrauterine environment and later influences that twins share, such as socioeconomic status, that's a very small concordance. By the age of 18 months, there are considerable differences in the DNA methylation of human twins (Martino, et al., 2013).

The individuation of genetically identical mice sharing an environment shows that subtle differences in experience can lead to distinct developmental differences (Freund, et al., 2013). Developed differences in physiology lead to different ways of using an environment, different needs, and transmissible biological changes: "... recent studies suggest that the epigenetic modulation of gene transcription and translation, epigenetic memory, and epigenetic inheritance are by far the most frequent reliable sources of transgenerational variability among viable individuals within and across organismal species." (Ayala-Garcia, et al., 2013).

The word epigenetic refers to changes in gene expression that persist after cell division, and it can be applied to the inheritance of an acquired trait by following generations, or simply to the state in a cell that could persist through divisions of that cell. The idea allows for the possibility of reversion to an earlier state, as well as conversions to other states. It is a negation of the idea that inherited sickness is irreversible, which has been a basic feature of biology and medicine for a century.

In early transgenerational nutrition studies, it was found that reduction in brain size produced by intrauterine deprivation was transmissible across several generations. The brain is metabolically an expensive organ, and small brained, relatively hypometabolic, animals are better able to survive prolonged famine conditions. Cephalization, the

proportion of the brain to the body, is our most human feature and it's universally useful, across species, when the energy is abundant in the environment, since the quality of the brain governs the scope of our life. Environments vary in the extent to which they support expansive individuation, or encourage retreat and mere survival.

Animals require oxygen for energy production, and its scarcity prevents expansive individuation, leading to the activation of protective measures, and often contributing to tissue degeneration. In the heart and lung, hypoxia causes hypermethylation of DNA, leading to the replacement of the normal cells by fibrotic tissue (Robinson, et al., 2012; Watson, et al., 2013). Fibrotic tissue has a lower metabolic rate, so in a sense is adaptive, although it limits the organism's functions, and eventually can kill it.

Other types of stress can also silence genes, probably selectively silencing those related to high energy functions first. For example, when an animal enters hibernation there is increased inactivation of many genes (Morin and Storey, 2009, 2006) In some organisms, stress-induced sporulation increases gene methylation (Hildebrandt, 1986). From conception to early childhood, the average DNA methylation increases (Herbstman, et al., 2013), and in some DNA regions there is a progressive increase in methylation with age (Schroeder, et al., 2011; Hernandez, et al., 2011), but in old age many other genes become hypomethylated, possibly corresponding to the loss of tissue organization. The hypermethylation of certain locations with aging is consistent enough that it might be used for forensic purposes (Koch and Wagner, 2011). The changes in different tissues are affected similarly enough by aging that blood cells could be used as an indicator of the condition of genes that are partially silenced in Alzheimer's disease (Horvath, et al., 2012).

The attachment of methyl (a single carbon, with hydrogens) groups to DNA is just one of the chemical changes involved in the process of individuation. The proteins (histones) that surround and regulate the availability of the DNA strands are modified by adding or removing several different kinds of chemical, including

acetic acid, methyl groups, and phosphate. When enzymes remove acetate from the histones, gene function is suppressed. Gene suppression by histone deacetylation is involved in aging, rheumatoid arthritis, cancer, and dementia, and substances that preserve or restore gene activity by inhibiting those enzymes (histone deacetylase inhibitors, HDAC-I) are being investigated for the cure and prevention of many diseases that have traditionally been thought to be mainly "genetic" diseases.

During the development of an organism, the chromosome-regulating enzymes in immature cells adopt a new pattern according to the organ that is beginning to form, and even after an organ has developed, its cells will continue to differentiate, according to their place in the organ and the conditions that they encounter. Cells that have been removed from a certain area of the skin retain even during growth *in vitro* their epigenetic features distinguishing them from cells that originated in another area of the skin, their "positional memory" (Koch, et al., 2011). The epigenetic state makes a particular cell specifically adapted to its niche in the organism; individuation is very detailed and complex.

Although every organ seems to be renewed (more or less regularly) by the maturation of stem cells, the lining of the uterus is interesting because it has a monthly cycle, in which stem cells multiply actively during part of the month, and then enter a phase of maturation, with the ability to support a pregnancy. In the proliferative phase, cells are dominated by estrogen, and in the maturation phase, by progesterone. During the estrogen phase genes are massively silenced by the HDAC enzymes, and during the progesterone phase, those HDAC enzymes are inhibited.

Prolonged excessive exposure to estrogen with deficient influence of progesterone can lead to the development of endometriosis and endometrial cancer. The combination of progesterone and other HDAC inhibitors is effective in treating endometriosis and endometrial cancer, and probably in other tumors, such as neuroblastomas (Atif, et al., 2011) and lymphomas. Cyproheptadine, known mainly as an antiserotonergic antihistamine, is also an HDAC inhibitor, helpful in

treating mantle cell lymphoma (Paoluzzi, et al., 2009). Aspirin, with an acetylating effect that has been considered to be harmful, appears to activate a histone, synergizing with a variety of HDAC inhibitors to improve the effectiveness of cancer treatments.

An epigenetic point of view suggests that a generalized view of beneficial synergistic effects should be considered--things that fundamentally support the organism's full development activate genes, and are antagonistic to things which fundamentally interfere with that development. Under harmful conditions, genes are being silenced in the organism's defense, in an organized way, and by understanding the nature of that organization, more coherent interventions to protect the organism will be possible.

Radiation, heavy metals, hypoxia, and estrogen excess tend to create excess gene silencing, and what they have in common is the creation of over-excitable electrons, a reductive and nucleophilic state. The opposing electronic state, electron-withdrawing, typically with one or more ketone groups in resonance with one or more double bonds as in naphthoquinones (e.g., Inks, et al., 2012) characterizes many of the protective substances, for example emodin (found in cascara and aloe), curcumin, progesterone, caffeine and theophylline. (Marcaurelle, et al., 2009; Mukwewho, et al., 2011; Ito, et al., 2002). Some chemicals known to have protective effects on oxidative metabolism, such as short chain saturated fatty acids and procaine and procainamide, are also HDAC inhibitors with a broad range of protective effects. Niacinamide (vitamin B3) is a powerful HDAC inhibitor; vitamins A and D have some synergistic interactions with HDAC inhibitors.

One of the implications of the deep interactive plasticity of the organism in its environment is that it's important to identify and minimize the harmful factors, while optimizing the supportive factors. Toxins that interfere with oxidative metabolism (heavy metals, carbon monoxide, and dioxins, for example), ionizing radiation, bacterial endotoxin, prostaglandins and the unstable polyunsaturated fats that they are derived from,

are burdens that reduce our potential for constructive development.

An optimal air pressure, or balance between oxygen and carbon dioxide, regular exposure to bright light, and foods that supply an appropriate balance of amino acids, minerals, vitamins, glucose and protective substances, such as HDAC inhibitors, would help to support developmental plasticity.

Many commonly used drugs have unexpected harmful epigenetic (degenerative) side-effects. Csoka and Szyf have said (2009) "We propose that epigenetic side-effects of pharmaceuticals may be involved in the etiology of heart disease, cancer, neurological and cognitive disorders, obesity, diabetes, infertility, and sexual dysfunction." Although many researchers are now interested in an epigenetic approach, there is no assurance that the medical and pharmaceutical industry will ever make the adjustment, because the most basic assumptions of their science are challenged.

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