Ray Peat's Newsletter

A dry soul is wisest and best. **Heraclitus**

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Shock, inflammation, resistance, epigenetics

Septic shock is a major cause of death, and other types of shock (for example traumatic, hemorrhagic, and cardiogenic) often lead to septic shock, when toxic material from the bowel enters the bloodstream as the intestine's barrier function is damaged. Bacterial endotoxin is the main trigger for the reactions of septic shock. Paul Ehrlich's idea of using chemicals to inactivate bacterial toxins dominated 20th century ideas about the nature of "the immune system," a body system that supposedly evolved to destroy alien pathogenic organisms and their toxins, but after more than 100 years there is no generally recognized way to neutralize endotoxin after it has entered the blood.

Elie Mechnikov, who shared the 1908 Nobel Prize with Ehrlich, was an embryologist whose discovery of phagocytosis has been interpreted mainly as a factor in "innate" immunity, that appeared prior to the evolution of "acquired" immunity and the production of specific defensive antibodies. Around 1990, his view of immunity as part of a developmental process was revived, in relation to a view that's now called the "danger theory" of immunity, mainly by Jamie Cunliffe (who calls it the damage, or morphostasis, theory of immunity) and Polly Matzinger. In their view, it isn't the "otherness" of a substance that causes a biological reaction, but only signs that "self" is being damaged. Bacterial endotoxin, mainly by causing cells to release ATP, is one of the most common "danger signals." A complex of DNA and its associated histones from the cell nucleus is a very powerful activator of the biological reactions.

Although ideas about sickness and the recovery of health are fundamental to medicine, the idea of an organism defending itself from genetically distinct pathogens has changed very little since Ehrlich's time, with his idea of chemical "magic bullets" being profitably applied to the treatment of nearly all diseases, including even a degenerative disease such as cancer, with the reasoning that genetic mutations have converted human cells into immunologically alien pathogens.

It was this culture of magic bullet specificity, and of the idea that each hormone has a single purpose, that caused Hans Selye's stress research to be ignored by mainstream medicine for about 50 years. In 1936, his professor J.B. Collip tried to dissuade him from spending his life "studying the pharmacology of dirt." 70 years later, many researchers began to see the importance of studying the pharmacology of fecal matter and bacterial endotoxin, but even now, investigators of the physiology of shock are ignoring the holistic meaning of Selye's General Adaptation Syndrome.

In Selye's analysis of the stress reaction, the process begins with an alarm reaction, divided into a shock phase, lasting from a few minutes to a day, and a counter-shock phase, leading to a state of resistance, in which the organism has adapted to the stressor. The success of the transition from shock to resistance depends on a finite amount of "adaptation energy," which Selye never defined. The shock phase that he described involved a decrease in blood pressure and body temperature, increased permeability of capillaries (and other cells) with the blood becoming more concentrated as water moved from the blood stream into the tissues, a brief increase in blood sugar followed by hypoglycemia, and an imbalance of minerals, as sodium and calcium

enter tissues and potassium and magnesium leave them.

Selye showed that the degree of stress damage could be judged by the amount of shrinkage of the thymus gland after two days of exposure to stressors such as fasting, immobilization, formaldehyde, morphine, adrenaline, or estrogen. Although he described the stress reaction as involving the nervous system and the endocrine system, it was only the sympathetic side of the autonomic nervous system, Walter Cannon's "fight or flight" sympatho-adrenal system, that he saw activating the endocrine stress reactions. Work that had been done several decades earlier, showing different kinds of involvement of the nervous system in stressful situations, was largely ignored. Walter Cannon was one of the people responsible for the disappearance of the preceding knowledge about shock.

During the first World War Cannon, a Harvard professor, was asked by the National Research Council to lead a committee to study the health of soldiers, primarily "shell shock," although he had never seen a patient in shock. In England, a similar committee (Medical Research Committee of the Privy Council) was set up in 1915 in reaction to the very large number of soldiers who were suffering from shock.

Many of the men had no visible injury to explain their disability, but some of these "uninjured" men were dying from shock. Early in 1916, as the increasing number of casualties caused military and economic concern, the British committee instructed military doctors to identify their patients who suffered from distinct wounds with a "W," signifying a war-derived disability and eligibility for a pension, and those without visible wounds with an "S," indicating shell shock, and ineligibility for a pension. Later, after the battle of the Somme with 60,000 casualties, the committee ordered doctors to stop diagnosing shell shock, and to stop evacuating so many men from the front.

In both the US and Britain, a mechanical view of shock, as circulatory collapse, replaced a psychological-neurological view. Walter Cannon's simplistic interpretation was that excessive stimulation of the sympathetic nervous system caused blood pooling and decreased blood volume, interfering with the circulation of blood. Since that war, "circulatory collapse" has been the basic understanding of physiological shock.

The French word *choc* (collision or jolt) is the origin of the English word. From early in the 18th century until the end of the 19th century, the idea of "concussion" from a bullet wound creating a "commotion" in the organism, interrupting the circulation of blood, was a common description of shock. But around 1850, coherent research began to form clear ideas about the interactions of biochemical and nervous interactions with the circulatory system.

In 1785, John Hunter had noticed during treatment of a patient by bleeding, that when the patient was about to faint from the loss of blood, the normally dark venous blood became bright red, showing that the tissues had stopped using oxygen. In the 1850s, Claude Bernard saw the same immediate brightening of the venous blood of animals in a state of shock. Charles-Edward Brown-Sequard did many experiments which showed that a shock to an animal's nervous system immediately prevented the removal of oxygen from blood, causing it to remain bright red in the veins. Even when the animal stopped breathing as it went into shock, the venous blood didn't darken, as it normally does when the lungs aren't functioning.

Brown-Sequard found that strong electrical stimulation of the vagus nerves caused immediate death of an animal, and that milder stimulation induced shock. When the heart was stopped by vagal shock, it was relaxed and full of blood--diastolic. Abdominal surgery, or manipulation of the abdominal organs, could produce different degrees of shock.

When death was caused by stimulating the vagus nerves, the temperature fell rapidly, but the sensitivity of the nerves and muscles remained for an unusually long time, the venous blood wasn't darkened, and rigor mortis and putrefaction were delayed. Brown-Sequard found that intense irritation of the spinal cord near the brain, by stretching it or bending it sharply, produced the phenomenon of the oxygenated venous blood. He found that during this phenomenon, there was contraction of

the blood vessels, showing that "circulatory collapse" wasn't responsible. When he severed one half of the spinal cord, the phenomenon didn't occur in the parts of the body separated from the brain. He also showed that a severed hand was able to darken blood circulated through it 24 hours after its removal from the body, demonstrating that the metabolic arrest of tissues seen in shock was produced by the action of the brain.

Following demonstrations that stimulation of the vagus nerves could stop the heart, and Sechenov's 1862 demonstration of inhibitory influences of stimulation in the brain, there was general recognition of the existence of nerves with an inhibitory function, and in 1886 W.H. Gaskell described the existence of two antagonistic systems. Early in the 20th century many chronic health problems were blamed on an imbalance between the antagonistic systems, and (Eppinger and Hess, 1920) that diseases and individuals could be classified as either "sympatheticotonic" or "vagotonic." Pavlov and his followers clearly established that the body's various organs are reflected in the cerebral cortex, where an equilibrium is maintained between the organism's inner and outer experiences.

George W. Crile was an Ohio surgeon who was interested in improving survival by reducing shock. During the years that he worked at the Lakeside Hospital in Cleveland, the surgical mortality rate fell from over 4% in 1904 to 1.8% in 1910. More than 100 years later, the development of antibiotics, blood transfusions, electronic monitors and other innovations have eliminated some of the risks of surgery, but shock is usually considered to be just a problem of the circulation. A recent study found that the average surgical mortality rate in Europe was about 4%, and in the US about 2%.

Crile knew that ether and chloroform were toxic to the brain (lowering its energy), and that morphine tended to promote shock (histamine hadn't been identified yet, but he later showed that morphine releases histamine, and campaigned against its use because of its contribution to shock and inflammation), so he used a combination of scopolamine and morphine instead of a general anesthetic (scopolamine is now recognized to have antihistamine effects). He later used nitrous oxide as a general anesthetic.

He knew, partly from his own research, that the brain was involved in the production of shock, so he used suggestion and reassurance to reduce the patients' fear, and he used a local anesthetic in the area to be operated on, sometimes starting it a day or two before surgery, to allow the brain to adapt to an absence of sensation from that area. As the operation began, each layer of tissue was locally anesthetized, recognizing that the brain, even under the influence of general anesthesia, was still receiving impulses from the operated areas.

To illustrate that, he described a case in which a leg was being amputated, with the patient under a general anesthetic. The skin, muscles and bone had been cut using local anesthetic, when an assistant holding the leg slipped and let the leg fall, jerking on the sciatic nerve. The patient immediately died.

Crile believed that the brain's energy reserve was depleted in shock, and showed that circulating the blood of a healthy animal into the carotid artery of the injured animal prevented shock. He later studied the contributions of the thyroid gland, adrenal glands, and liver to the brain's energy capacity.

During the time that Crile was developing and demonstrating his ideas, Yandell Henderson, a Yale physiology professor, was studying the effects of carbon dioxide on the circulatory system, and he argued that shock was caused by a lack of carbon dioxide, and that hyperventilation contributed to its development. His work complemented the preceding work demonstrating the brain's role in arresting oxidative metabolism. A deficiency of carbon dioxide reduces blood volume, causes sodium loss, decreases the heart's output and lowers blood pressure, but increases peripheral resistance. Increasing carbon dioxide reverses those changes, and increases the tone of the capacitance vessels, increasing return of venous blood to the heart (Rothe, et al., 1990; Karlsson, et al., 1994; Okazaki, et al, 1989; Olsen, et al., 1988; Fujita, et al., 1989; Buhre, et al., 1998). A deficiency of carbon dioxide impairs the splanchnic circulation and organ function, but

tends to shift blood flow to the large skeletal muscles (similar to the effect of the "fight or flight" nerve activity).

Seen in the context of Brown-Sequard's description of shock as metabolic arrest, these effects of carbon dioxide should have reordered contemporary thinking about shock, giving priority to the nervous system and metabolism, rather than to the circulatory collapse that they produce. Along with the recognition of the protective properties of carbon dioxide, there is some evidence of a movement away from the mechanical circulatory conception of shock (Magder, 2014; Dunser, et al. 2013: "permissive hypotension"; Eastwood, et al., 2014: "... mild hypercapnia may increase the likelihood of discharge home amongst survivors.")

The experiments (beginning in the 1950s) with inescapable stress, producing "learned helplessness," showed that even a single, fairly brief experience of being unable to escape from a stressful situation (pain, fear, or immobilization) could drastically reduce an animal's ability to survive a stress that ordinarily could be survived, and that the hearts of animals that died from learned helplessness had stopped in a relaxed state, filled with blood. This is the state of the heart under the influence of excessive vagal stimulation, one of the things that led so many researchers in the 19th century to describe shock as a vagotonic state. Several experimenters have found that the state of learned helplessness could be cured by treating the animals with scopolamine, opposing vagal effects, or with thyroid hormone or caffeine, which counteract some of the vagal effects, such as increased nitric oxide production and decreased oxygen consumption. "Danger" or damage signals are involved in establishing learned helplessness and shock, as well as in activating the restorative and defensive "immune" functions. Threats that are perceived in the environment can cause the brain to release nitric oxide (Saul'skaia, et al., 2009) and other damage signals, while injured tissues release them in "damage cascades," with one, such as nitric oxide, causing the release of others, including adenosine, heat shock proteins, and histones.

When a tourniquet has stopped the circulation to an animal's leg long enough to deplete its energy reserves, damage signals from the leg enter the general circulation when the tourniquet is removed. These affect every organ, especially the brain, activating defense systems. The autonomic nervous systems are activated, leading to hormonal and metabolic changes, but the signals also act directly on other tissues, and can cause cells to release enzymes (such as acid phosphatase and beta-glucuronidase) from lysosomes, which contribute to weakening of the heart beat and other organ damage (Vornovitskii, et al., 1984; Janson, et al., 1975). Aspirin and glucocortical hormones and other things that stabilize lysosomes protect against shock (Halushka, et al., 1981). The systemic effects include weakening of the intestinal barrier function, with increased absorption of endotoxin and other material from the intestine.

The parasympathetic nervous system is one of the body's stress-limiting factors. Darkness, by its effect on mitochondrial respiration, is a stress, and the parasympathetic system's increased activity at night is generally protective, but when the body's resources are limited (for example because of hypothyroidism), increasing parasympathetic activity can produce symptoms such as nocturnal asthma, sleep apnea, or other sleep disturbances.

In the short days of winter, when some animals hibernate, many people feel the increased activity of the parasympathetic system with decreased body temperature, increased appetite and weight gain, and sometimes a "seasonal affective disorder" (Austen and Wilson, 2001). Activation of the parasympathetic system lowers body temperature by reducing energy production, with the involvement of serotonin and nitric oxide (Lin, et al., 1984, 1979; Szekely, 2000). Drugs, such as atropine and cyproheptadine, which limit the reduction of body temperature, are also protective against shock (Irwin, et al., 1999; Fuentes, et al., 2006; Zhang, et al., 1992). The Flinders strain of rats was bred to be hypersensitive to parasympathetic cholinergic stimulation, becoming more hypothermic than normal rats to a cholinergic drug. They are also highly susceptible to anaphylactic shock.

Inflammation and other stresses activate histone changes that can produce counter-productive loss of function (Liu, et al., 2012). Stress, especially early in life, can methylate certain genes, resulting in increased activity of the parasympathetic system relative to the sympathetic system, leading to asthma, allergies (Wright, 2012), and other traits that have been identified as "vagotonic." Butyric acid (Sailaja, et al., 2012) and other inhibitors of histone de-acetylation can protect against those effects. Other protective agents include emodin, caffeine, niacinamide, and progesterone. A product called Carbogen, 5% CO2 and 95% oxygen, is available to hospitals, and should be generally used instead of oxygen, while other concentrations are investigated. I think carbon dioxide, progesterone, and the other protective substances, act as cardinal adsorbents in Gilbert Ling's sense, reducing signals of danger and damage. Carbon dioxide, even applied topically, seems to restrain the local damage signals, allowing simple healing to progress without counter-productive inflammation.

The brain evaluates the meaning of signals from the environment and the body, in a process of triage, deciding whether to continue on the present course, or to activate the fight or flight sympathetic system, or to activate the dormancy process, with the parasympathetic system. The first time an animal experiences inescapable stress, the learned helplessness can make it very susceptible to a quick death, but a single experience of escape creates the perception of possibility, allowing it to mobilize all its resources for survival.

A common treatment for a minor burn is to immediately put the area into cold water. The idea is to stop the spreading release of histamine, and the associated danger signals; local anesthetics have a similar function (Dear, et al., 1996; Ohishi, et al., 1985; Fisher, 1971). Since the parasympathetic nervous system has direct connections to mast cells throughout the body, signals of various sorts that affect the brain's evaluation of the situation, can either increase or decrease the release of histamine.

The present medical culture supports mental processes analogous to learned helplessness. Beyond the placebo effects of the various mechanistic treatments that it provides, there is the fundamental negative placebo effect of the mechanical doctrine of biology and physiology that is taught at all levels.

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