Resistance of the Heart

by Ray Peat, Ph.D.

The heart gives us some clues to our general resistance to stress, aging, disease, and death. The heart and the brain are the most stress-resistant organs, and while moderate stress and malnutrition can cause the skin and thymus gland to lose more than 90% of their substance, only the most prolonged and intense stress can cause the heart and brain to lose more than a fourth of their substance. In fact, a moderate stress that causes the thymus to shrink by more than 90% can cause the heart to increase its mass by 80%. When we are able to respond adequately and adaptively to stress, there is a transfer of substance from the lower-functioning organs (usually the skin and thymus) to the organs that are bearing the greatest burden, usually the heart and the brain.

The glucocorticoid hormones of stress play the important catabolic role of mobilizing substances from the "idle" organs to support the working organs. The many ways in which the heart is able to resist stress, and even to thrive on it can be generalized to develop ways to protect other organs, and the whole body, from the chronic and cumulative stresses that lead to generalized atrophy, declining function, and aging.

During stress, the heart and other working organs become resistant to the glucocorticoid hormones. When a person is given radioactive testosterone, it can be seen to reach the highest concentration in the heart. It is testosterone's anti-glucocorticoid effect which causes it to enlarge skeletal muscles, when exercise is moderate. Its parallel effects on skeletal muscle and heart muscle can be seen in highly adapted (stressed) long-distance runners, since the walls of their hearts become thinner as their skeletal muscles become slimmer. The other anti-catabolic steroids, pregnenolone, progesterone, and dehydroepiandrosterone (DHEA), are present in larger amounts, and are of more general importance, than testosterone, especially in the brain, where their concentration is very high. Albert Szent-Györgyi showed that the heart responds to progesterone, and more recently other researchers have presented evidence that DHEA is our "endogenous digitalis."

During moderate exercise, adrenalin causes increased blood flow to both the heart and the skeletal muscles, while decreasing the flow of blood to other organs. The increased circulation carries extra oxygen and nutrients to the working organs, while the deprivation of oxygen and glucose pushes the other organs toward a catabolic balance. This simple circulatory pattern achieves to some extent the same kind of redistribution of resources, acutely, that is achieved in more prolonged stress by the actions of the glucocorticoids and their antagonists.

Stress - a need for adaptation - can be seen as an "information gap" between the need and the possibility of meeting the need. Appropriate modification of the organism's structure closes that information gap. The new "structural trace," or memory, can develop as either a phenotypic or genotypic change. "Mutations" are important for bacterial adaptation, and learning is important for mammalian adaptation.

Stress physiology is now recognized as a universal and basic part of life, for plants and micro-organisms, as well as for vertebrates. Our brains are the newest and most powerful organs of adaptation and resistance to stress, allowing the simpler systems of circulation and metabolism to orient themselves appropriately to achieve the most benefit with the least damage. Just as there are pro- and anti-catabolic hormones and circulatory patterns, the brain has stress-promoting and stress-limiting systems. When perception and orientation govern the stress reaction, the ability to suppress certain parts of the reaction permits fine coordination and high efficiency. Sleep is a generalized stress-limiting function of the brain. Another example of how the brain governs the energy mobilizing system in stress was demonstrated by Seligman: Rats that experienced "capitulation stress," being held still until they quit struggling, drowned in a few minutes when they were put into a tank of water. But a single experience of successfully struggling to freedom caused rats to swim for many hours before becoming exhausted.

A single experience, an insight, has tremendous power to shape the way in which a rat deals with stress. Insights and ideas can be gained through practice, but they can also be passed on culturally. We can learn how to prepare ourselves to respond optimally to stress, while also trying to keep the environment from becoming too stressful.

Blue-collar workers have more heart attacks than do sedentary workers, and the "biosocial" stress of low status can be seen as a powerful factor in mortality from heart attacks. The helpless feeling of low status is analogous to capitulation stress. When stress is strong enough and long enough to overcome the multiple protective systems of the heart, the heart fails in certain well-defined ways, both functionally and structurally. But before injury occurs, the stress-limiting "self-restraint" systems of the heart, of the endocrine system, and of the brain, will have to fail. Considering some problems of blood circulation will help to see the integral nature of adaptation, when it succeeds and when it fails.

Pregnant women sometimes develop very high blood pressure. In the 1950s, when new diuretics were being promoted by the drug companies, it became standard practice to give pregnant women diuretics and a low-salt diet to control their blood pressure. It should have been obvious (and it was obvious to people like Tom Brewer who thought physiologically, rather than mechanically) that the increase in pressure was the body's response to an increased need for circulation. As the fetus grows, the blood volume must expand, to meet the increased circulatory needs of the uterus, placenta, and fetus. Two research projects showed that very large supplements of salt reliably normalized the high blood pressure in women with "toxemia" of pregnancy. Other studies showed similar results with a supplement of progesterone. When the blood volume is able to expand as needed, circulation is adequate at normal pressure. When blood pressure is forced down by administering a diuretic to further diminish an already inadequate blood volume, the circulation of oxygen and nutrients to the fetus is seriously impaired, and a huge epidemic of mental retardation and hyperactivity, associated with low birthweight, began in the 1950s, and continued until eventually the fear of malpractice suits stopped the absurd practice.

A few years ago I asked a recently graduated physician what things he would want to consider in a patient with high blood pressure. Some of his suggestions for therapy were very reasonable, but his approach made it clear that he was

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thinking of circulation in a mechanical way, exactly as a skilled plumber would go about normalizing the circulation of water, without caring very much about what the water was being used for. The circulation of blood is nicely adjusted to meet the demands of the tissues. Blood pressure increases gradually with age, and individuals whose blood pressure stops increasing with age have been found to have a shorter life-expectancy than normal. Apparently, aged tissue is less efficient, and needs a more strongly pumped stream of blood.

When I found, around 1970, that the pressure of oxygen was low in old animals and in animals that had been treated with estrogen, I tried to determine the reason for the oxygen deficiency in each case. I found that in old individuals (hamsters or humans) the blood was only about 50% oxygenated as it passed through the lungs, as if diffusion into the capillaries was impaired. Estrogen treatment (rats and humans) does the same, apparently by causing a sort of edema that thickens the lung tissue through which the oxygen has to diffuse. Both estrogen treatment and age cause other inefficiencies in oxygen transport and inefficient use in the tissues, further exacerbating the shortage of oxygen. Interestingly, recent studies show that "capitulation stress" causes the same variety of problems in oxygenation, transport, and use. In stress, even the respiratory center of the brain becomes under-active, tolerating the state of hypoxia. Since progesterone activates the respiratory center, the depressed respiration of stress is consistent with a deficiency of progesterone. (See note at end.)

When tissue oxygenation is inadequate, glucose is depleted quickly. In prolonged stress, the liver's gluconeogenic response to the glucocorticoids is depressed, as is its ability to form and store glycogen. As glucose is less available, the amount of adrenalin in the blood rises, and fat is mobilized from storage as a substitute source of energy. Free fatty acids, especially unsaturated fats, are toxic to the mitochondrial respiratory system, blocking both the ability to use oxygen and the ability to produce energy. The increased use of fats, instead of glucose, causes lipid peroxidation to increase, and promotes the release of lysosomal enzymes, the accumulation of calcium in mitochondria, the depletion of ATP and creatine phosphate, and a failure to "pump" calcium out of the cells, causing incomplete relaxation and rigidity of the heart muscle cells.

This complex of effects can be called "catecholamine toxicity." Rona, *et al.*, using isoproteronol in 1959, clearly established the existence of this toxicity. Several years ago, it was noticed that mortality in the U.S. from asthma increased greatly in the years since catecholamine therapy became common, without a corresponding increase in the incidence of asthma. It is now widely accepted that the therapy caused the increased mortality. Following Rona's work as it did, this large medical experiment can be taken as strong confirmation of the idea of catecholamine toxicity, and as a step in understanding stress sickness. Glucose depletion leads to adrenalin secretion, which causes fat mobilization, calcium-activated over-stimulation of cells, with impairment of the energy production which is necessary for recovery (by way of muscle relaxation and calcium excretion, etc.).

Broda Barnes showed that hypothyroidism causes heart disease, and also causes a tendency toward hypoglycemia. Low thyroid people compensate for the deficiency of energy and glucose (and of oxygen, for reasons similar to those mentioned above) by secreting an excess of adrenalin. Their 24-hour urine metabolites of adrenalin sometimes are 30 or 40 times normal. Recent studies that show that a moderate dose of thyroxin lowers lipid peroxidation confirm that thyroid has an anti-stress effect. The "conduction block" which occurs in hypothyroidism seems to be the same as the conduction block which develops in stress and predisposes to fibrillation. The electrical instability of the heart produced by excessive adrenergic stimulation can also make the sinus pacemaker more susceptible to vagal inhibition. (I think this effect can be observed in the skipped beats often experienced by hypothyroid people during stress or fatigue. In other situations, of long and intense stress, vagal stimulation protects against fibrillation.) In hypothyroidism, there is impaired relaxation of muscles, as seen in the Achilles reflex, or in the T wave of the electrocardiogram. This is similar to the contractural rigidity which develops in the stressed heart.

When stress is severe and prolonged, the liver loses enzymes of the detoxifying system, and also of the system that forms bile acids, causing a tendency toward abnormal lipid metabolism, including hypercholesterolemia. Thyroid deficiency limits the consumption of circulating cholesterol for steroid hormone synthesis, and both stress and hypothyroidism are associated with elevated blood cholesterol. Considering the clear and well defined toxicity of adrenalin and free fatty acids, the role of cholesterol in heart disease begins to look sort of epiphenomenal.

Fats enter and damage cells that are over-stimulated and de-energized. Calcium is a universal activator, but excess calcium is the central link in most types of cell damage. Calcium uptake and retention are promoted by adrenalin, histamine, vasopressin, energy depletion, and lipid peroxidation and by the activity of phospholipases; since calcium can activate phospholipases and lipid peroxidation, and interferes with energy production, vicious circles can develop. Excessive adrenalin and calcium also promote clotting, and - as the beta-adrenergic receptors become desensitized - spasms in the coronary arteries. Altered blood vessel tone, which can be produced by serious stress, can cause venous pooling of blood, which synergizes with the impaired relaxation of the heart to cause cardiogenic shock.

There are several systems that oppose the toxic effects of adrenalin. GABA, dopamine, and adenosine have multiple anti-adrenergic effects. In many situations, the parasympathetic system is protective against adrenalin. The protective steroids also act at many levels. Magnesium, retained in the cell largely under the influence of ATP and thyroid, is our basic "calcium blocker," or calcium antagonist. GABA and dopamine inhibit the ACTH-glucocorticoid system, and shift the steroid balance toward the protective anti-glucocorticoids, progesterone, testosterone, pregnenolone, and DHEA.

Adequate glucose and oxygen are the most important anti-stress substances. "Overload" of an organ means that the blood isn't delivering enough oxygen and glucose to sustain the needed level of functioning. Thyroid and progesterone

tend to prevent overload by increasing respiratory efficiency, and by increasing the liver's glycogen storage.

Uridine, a co-factor in glycogen synthesis, can also prevent stress by improving glycogen storage.

Anti-oxidants, especially vitamin E, prevent tissue damage by promoting normal oxidation.

Selye's demonstration of corn oil's toxicity to the heart is an important link in the general picture of stress injury and adrenalin toxicity. The protective effects of saturated fats are not surprising when seen against the background of the toxic effects of adrenalin, causing the mobilization of fatty acids and the resulting lipid peroxidation.

Meerson's demonstration that gentle adaptation to hypoxia (similar to treatment with thyroid hormone) can prevent heart damage from subsequent intense and prolonged stress, is similar to Seligman's discovery that rats can be protected against stress by an experience of escape, but Meerson has surveyed a great range of protective processes, ranging from the subcellular level to the most highly evolved brain systems. In thinking about Meerson's achievements in protecting the heart against stress, it is important to remember that the heart is our most stress-resistant organ, and that the things that protect the heart from deadly stress will also protect the other organs from the everyday stresses, which accumulate to cause the problems of general aging. Liver, lungs, pancreas and other essential organs are susceptible to the same kinds of damage as the heart, but under conditions that are relatively mild and ordinary.

The resistance of the heart and liver can be compared in several ways. For example, DNA replication is more easily suppressed by stress in the liver, than in the heart, but DNA repair is not affected in the same way by stress. Hyperfunction of the heart stabilizes DNA against injury, so DNA repair is greater in the liver than in the heart, and is least in the brain.

Meerson's laboratory has studied the anti-stress and anti-adrenalin effects of GABA and its metabolite, gamma-hydroxy butyrate, especially in the form of the lithium salt. (Lithium seems to have its own anti-stress effect, probably partly as a sodium agonist, and partly through its ability to complex with the ammonium which is produced in the brain in fatigue, which is exactly when the GABA system becomes active.) GHB is protective against stress damage to many tissues. It prevents stress-induced enzyme leakage from tissues, ulceration of the gastric mucosa, lipid peroxidation, epileptic seizure, damaged contractile function of the heart, and cardiac arrhythmias produced by stress or ischemia.

Meerson's group has also studied the protective effects of the gamma-butyrobetaine derivatives of the sort that are normally produced in the brain and heart, or that have been synthesized or extracted from plants. These substances stabilize the heart rhythm in acute

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myocardial infarction, and also in postinfarction cardiosclerosis (page 173, *Adaptive Protection of the Heart*, F.Z. Meerson, CRC Press, Boca Raton, 1991). They have a protective action against both adrenalin and calcium. Interestingly, atropine potentiates the protective effect of the butyrobetaine against calcium toxicity.

A complete list of protective nutritional chemicals and natural drugs or analogs to our endogenous protective factors would be very long, but we should give special thought to certain ones, including succinic acid, which stimulates respiration and protective steroid synthesis; thyroid and vitamin E, which promote normal oxidation while preventing abnormal oxidation; magnesium; sodium and lithium, which help us to retain magnesium; tropical fruits, which contain GHB; coconut oil, which protects against cardiac necrosis, lipid peroxidation, hypothyroidism, hypoglycemia, and histamine damage; valium agonists, natural anti-histamines; adenosine and uridine. Visits to higher elevations, and exposure to bright, long-wave light, can cause the body to optimize its own anti-stress chemistry. Avoiding the sense of being trapped is a high-level adaptive factor.

Note: The consistency with which oxygen becomes deficient in aging, stress, and estrogen excess suggests that a basic coordination mechanism may be involved, in which there is a shift toward the conditions which will activate the expression of certain genes - possibly the hypoglycemia-stress-heat-shock proteins, or possibly simply the proteins of cell division and growth.

The life-span of cell organelles, DNA, and essential enzymes, is extended by adaptation. The cellular (membrane phospholipid) composition adjusts toward a lower content of unsaturated fatty acids. (S. Gudbjarnasson, et al., "Modification of cardiac phospholipids and catecholamines in stress tolerance," in *Alpha-tocopherol, Oxygen, and Biomembranes*, C. DeDuve and O. Hayashi, Eds., Elsevier/North Holland Biomed. Pr., Amsterdam, 1978, p. 297.) Diacylglycerol causes activation of transcription, cell growth, and proliferation. (G.L. Hammond, et al., "Diverse forms of stress lead to a new pattern of gene expression through a common and essential metabolic pathway," P.N.A.S. 79, 3485, 1982.) Stabilization of mRNA splicing and protein synthesis (H.G. Yost and S. Lindquist, "RNA splicing is interrupted by heat shock and is protected by heat shock protein synthesis," Cell 45, 185, 1986) suggests the possibility that this system might also be important in viral immunity.

Reference

G. Rona, et al. "An infarct-like myocardial lesion and other toxic manifestations produced by isoproteronal in the rat," *Arch. Pathol.* 67, 443, 1959.

P.S.: Pavlov's turn-of-the-century work on the heart's "trophic nerves" should be re-examined in the light of this new information on the trophic effects of adaptation.

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