

Body Heat and Chronic Disease

In 1832, as the Beagle lay anchored near Cape Horn, Charles Darwin stared dumbfounded at what appeared in the mists before his eyes. In a heavy bone-numbing rainfall, naked Indians in canoes drew alongside the ship to observe the strange sight. In one canoe, wrote Darwin, sat a woman, nursing a recently born child, gazing curiously, 'whilst the sleet fell and thawed on her naked bosom, and on the skin of her naked baby!' Later, on the beach, Darwin and members of the crew, heavily clothed and huddled around a blazing fire, looked with great surprise at the natives, who, though at a distance from the flames, were 'streaming with perspiration at undergoing such a roasting.'

These Yaghan Indians, now nearly extinct, live at the southernmost tip of South America on the island of Tierra del Fuego. Its climate, which Darwin described as 'wretched,' is cool and rainy throughout the year. Even during the summer, when temperatures average only about 50°F, snowfall is common. The Indians' only clothing, used mainly during extremes of temperature, was a small sealskin or otter cape, worn about the shoulders. They otherwise remained naked to the elements. Throughout the year they swam in frigid ocean water to harvest mussels, kelp and fish. They slept on the ground in flimsy straw huts and used occasional small fires for heat.

The Yaghans and Australian aboriginals exhibited one of the most remarkable adaptations to cold that science has yet encountered. Other indigenous cultures, the Inuit, Lapps, Eskimos, Alaskan natives, and even the more temperate native peoples of North America, also developed exceptional hardiness to climatic conditions that white people find intolerable. Unfortunately, the native people's hardiness began to disappear once they adopted the white man's lifestyle. They now have among the highest rates of obesity, diabetes, and heart disease in the world. This tragic collision of cultures has threatened some indigenous peoples to the point of extinction.

In the 1940s, anthropologist J. M. Cooper noted that 'the clothing of the Yaghan seems to us utterly inadequate, given the climatic conditions. . . but in view of the seeming role played in their decline by introduced European clothing and their relative good health prior thereto, perhaps their clothing was reasonably well adapted to the environment.' The deterioration of the world's native peoples' health is an omen, a thundercloud on the horizon, of an evolving global catastrophe of unparalleled

magnitude. The lifestyle that the white man unleashed upon the world is eroding the health of nations.

For centuries, 'innate heat,' what we now call the metabolism, was considered to be the source of all bodily functions. Sickness was said to originate from disturbances in the movement of heat throughout the body. But as the science of chemistry came into favor and cellular theories were advanced in the 19th century this traditional knowledge was overturned. It isn't so surprising then that modern science is thoroughly baffled by a phenomenon known as 'thermogenesis,' the release of heat from living bodies that none of their chemical theories satisfactorily explains. Intriguingly, most of the chronic diseases that plague modern civilization involve a deterioration of thermogenesis and the body's heat rhythm.

Thermogenesis signals that the body is increasing its energy production. It occurs throughout the day as bursts of heat related to different activities such as exercise, meals or even during states of intense emotion. The blushing of the cheeks and the feeling of facial warmth during states of shame, embarrassment, or anger are common everyday examples. Thermogenesis also occurs in healthy people when they are exposed to the cold. Their metabolism increases and they produce more heat to offset what is being lost to the colder environment.

We have another all too common phenomenon that medical science has been unable to easily explain. Why is it that some individuals can consume large amounts of food and not gain weight while other individuals need to restrict their caloric intake just to maintain an even weight? An experiment involving two groups of lean men draws attention to this discrepancy. One group habitually consumed large amounts of food and did not constrict caloric intake, while the second group restricted food and caloric intake. When these two groups consumed identical meals, there were marked differences in thermogenesis between them. The high energy intake group showed, on average, almost a two-fold greater thermogenesis. Why would this be the case?

The apparent relationship between thermogenesis and obesity is equally mystifying. During exercise, following a meal, or during exposure to the cold, obese individuals have diminished ability to generate body heat; they have what researchers call a 'thermogenic defect.' Moreover, this defect,

present from the onset of obesity, worsens as obesity progresses. Defective thermogenesis may also explain other puzzling aspects of obesity.

Many obese people who lose weight subsequently regain it during the next several years. Some studies find that after people successfully diet to lose weight, they still have defective thermogenesis and, in some, it actually worsens. This incongruity, which scientists are at a loss to explain, suggests a link between obesity and body heat. As a consequence, some researchers now propose to use drugs that promote thermogenesis as a strategy in the treatment of obesity.

Thermogenesis, it seems, has an inverse relationship to the amount of body fat; as obesity increases, thermogenesis decreases. This appears to be the case regardless of whether thermogenesis is stimulated by a meal, exercise, drugs, or from exposure to the cold. Some researchers now wonder if thermogenesis may be essential for the control of body weight. As obesity progresses, for example, thermogenesis becomes even more impaired and linear. When obesity evolves into diabetes, as it often does, thermogenesis is reduced even further or disappears altogether. Numerous other abnormalities in the blood, like elevated cholesterol and triglycerides, are associated with obesity and diabetes.

Consider this experiment: When healthy lean women are exposed to mildly cool temperatures, their metabolism increases by about 4 percent. But when obese women with diabetes are exposed to the same conditions, their metabolism decreases by nearly the same amount—they lose body heat. At the same time, their release of thyroid hormone into the blood is diminished and their cold-induced thermogenesis (heat production) is markedly impaired. What does this suggest?

People who develop obesity have decreased thermogenesis compared to lean individuals. As obesity progresses, their thermogenesis continues to decline. As the duration of a person's obesity lengthens, even in the absence of significant weight gain, his or her likelihood of developing diabetes increases. By the time diabetes develops, thermogenesis is severely impaired. Many diabetics have no thermogenic response to cold exposure or after meals. These findings suggest that obesity and diabetes are part of a continuum in the deterioration of the body's heat rhythm. But the source of thermogenesis and body heat remains shrouded in a mystery that none of the modern chemical and

cellular theories is able to explain. A large body of accumulated evidence over the past 25 years points to the heart.

Heat, Heart & Health

For centuries physicians used the pulse as a means of diagnosing sickness. The Eber's Papyrus, dating from about 1550 BC, describes the pulse as 'the beginning of the physician's secret knowledge of the heart's movement.' The ancient Egyptian word for heart, *ib*, meant 'dancer.' An early Chinese pulse master declared that 'nothing surpasses the examination of the pulse, for with it errors cannot be committed.' Al Majusi, 10th century Arab physician wrote that 'the pulse is a messenger that does not lie and a mute announcer that tells of secret things by its movement.' Pulse diagnosis was the common thread that held together all the healing traditions of the ancient world.

The heart's rhythms change throughout the day as the body's activities and functions change. When you awake in the morning, even before getting out of bed heart rate begins to increase, reflecting the activities of the sympathetic nervous system and brain. Once you jump out of bed it may increase even further, up to 10-15 beats per minute. Throughout the day the heart's activity accelerates and decelerates according to your activities. When you begin to exercise the heart responds dramatically often increasing by 80-100 beats per minute. And during the deepest phase of sleep the heart rate may drop as many as 20 beats per minute. Heart patterns continue to change throughout life as well.

If we were to graph the variations in the heart rate of an individual over the course of a day or week we would observe wavelike patterns of periodic crests and troughs with the span between the highest peak and the lowest trough indicating what is called the 'dynamic range.' In the last few decades of the 20th century the heart's dynamic patterns caught the eye of medical researchers and what they found led to many new insights into the heart's relationship to health and sickness.

In 1963 a report in the obstetrical literature by two physicians, E. H. Hon and S. T. Lee, described abnormal heart patterns containing 'specific lethal changes' in fetuses that were about to die. As death approached the heart patterns became more linear and invariant, like the beats of a metronome. At the time it was believed to be a curious behavior of newborns. Fifteen years later a

report in an Australian medical journal reported an association between decreased rhythmical variability of the heart, loss of dynamic range, and the development of cardiac electrical disturbances, known as arrhythmias. Among people with recent heart attacks those whose heart rhythms had the least amount of variation had a fivefold greater risk of death.

Since then thousands of studies have appeared in the medical literature supporting these findings. Abnormal heart rate patterns are associated with virtually every imaginable illness, vascular diseases such as stroke, heart attack, heart failure, and hypertension as well as diabetes, asthma, cancers, and autoimmune disorders. In fact, heart rate variability (HRV), the rhythmical fluctuation of heart rate patterns in time, is now recognized as the single leading predictor of all causes of mortality. When the heart patterns of patients admitted to the hospital for stroke or heart attack are examined there is a clear distinction in survival rate based on HRV patterns: patients who recovered showed a parallel recovery of heart rhythmicity.

Scientists later realized that the fluctuations in rate and rhythm of the heart were largely a function of what is now called 'autonomic balance,' the activities of the two branches of the autonomic nervous system (ANS), the sympathetic and parasympathetic. All the activities and functions of every bodily organ are determined by the rate and amount of blood flow into that organ, and bodily blood flow patterns are determined by the sympathetic and parasympathetic systems.

The activities of the ANS are reflected in the heart rhythms. As the activities and functions of the body's organs change throughout the day and night they change the dynamics of the heart's rhythms. Ancient Roman physician Galen not only used the pulse to diagnose disease but was able to determine on the basis of the pulse which organs were not properly functioning. There are prominent day-night variations in heart patterns: the higher heart rate during the day reflects the activities of the sympathetic nervous system while during nighttime sleep when the parasympathetic system is active the pulse is slower. But scientists have never figured out how these patterns play into the development of disease.

A curious pattern emerges when one examines the HRV patterns of the most common chronic diseases of modernity. Coronary artery disease (CAD), hypertension (HT), stroke, diabetes, cancers,

and autoimmune disorders all have one common feature: increased sympathetic and diminished parasympathetic activity. What could this mean?

The answer becomes obvious once one realizes that the heart does more than just pump blood around the body. Through its cycles of contraction and dilation it generates a large electromagnetic (em) field within the arterial blood that not only influences the activity of every cell in the body but serves as the source of the electrical currents that course through the brain and nervous system—including sympathetic and parasympathetic nerves. The ECG tracings used to diagnose cardiac disorders are direct evidence of this strong pulsating em field that, with appropriate technology, can be detected many feet outside the body. And here is where the connection to disease begins.

The sympathetic nervous system is more active during waking hours because it functions in support of the brain and waking consciousness. And as conscious related activities increase more energy is drawn into the brain and the nervous system. In periods of intense fear, anxiety, anger, or in chronic stress, heart rate increases dramatically due to sympathetic hyperactivity. What has been called the 'fight or flight response,' is orchestrated by the sympathetic nervous system. Large amounts of glucose and other chemical metabolites are released from the liver to supply the energy needs of the nervous system and muscles. Inflammatory pathways and the immune system are activated. Blood pressure skyrockets as the heart pumps more blood into the brain and muscles and the arteries become constricted. Because of its relation to the waking state we call the sympathetic system the light physiology. Ancient physicians knew when the pulse became taut, wiry, and fast that the body was under stress. Stress is OK in short bursts but when prolonged then problems begin to arise. And here is where the parasympathetic system plays its role.

The parasympathetic system is the recovery system. Because of its increased activity during the night hours we call it the dark physiology. It is responsible for all the up-building and restorative activities of the body and when impaired the whole body is affected. In states of chronic sympathetic hyperactivity like stress and anxiety the actions of the parasympathetic system are weakened. The dark physiology controls not only the digestive system but all processes concerned with the formation of blood and the generation of the electromagnetic field by the heart. And this developing imbalance

can be traced directly back to the cycles of contraction and dilation, known as systole and diastole, of the heart.

When William Harvey published his groundbreaking work *On the Motions of the Heart* in 1628 detailing his discovery of the circulation of the blood he introduced a grave error that persisted in medical science for over 350 years until the 1990s. Observing the rhythmic contraction and dilation of the beating heart in a living animal, he claimed that the forward movement of blood through the arteries was caused by the contraction of the heart during systole and likened the actions of the heart to a mechanical pump. He emphatically claimed that dilation, the outward movement or diastole, was entirely passive. This contradicted how physicians for centuries had conceived the nature of the heart's function.

In the 2nd century CE, Roman physician Galen, first to describe the actions of the heart and its role in the generation of an em field, claimed that diastole was the most important part of the cardiac cycle. He argued the heart moved the blood mainly through suction. He likened its functions to a set of bellows that moves air in both phases of its movement. In the early 1990s medical researchers discovered a vacuum effect in the ventricle of the heart in early diastole indicating that it indeed moves blood through the arteries and veins by suction. MRI studies later showed spiral flow patterns in the arteries, which could only develop through a suction force, as when a toilet is flushed. Dilation of the heart is not passive as Harvey claimed but is an active movement.

One of the earliest and most consistent findings in HT and CAD, restriction of the outward movement, known as 'diastolic dysfunction,' is seen not only in the motions of the heart but in the quality of the arterial pulse. Diastolic dysfunction, simply, is incomplete relaxation of the ventricular wall. As the ventricle's dilation becomes progressively impaired, its wall develops stiffness and blood flow into the ventricular chamber during diastole is impeded. The arterial pulse, likewise, feels hardened and tight, its tempo accelerated, indicative of excessive sympathetic influence.

With chronically elevated heart rate due to excessive sympathetic activity there is progressive shortening of the diastolic recovery period compared to the systolic contraction phase, creating an asymmetry between energy expenditure and generation. This forms the basis of autonomic

imbalance. As this condition progresses not only is the contraction and dilation of the heart affected but the generation of the metabolic energy field.

Unfortunately, medical science formulated all of its strategies for treating CAD and HT based upon blocking excessive sympathetic activity and never considered the possibility that diastolic impairment was the main problem. But simply lowering blood pressure does not correct the underlying disturbance. Even when blood pressure is reduced into an acceptable range affected individuals are more prone to develop blood clots, rhythmic disturbances, diabetes, heart attacks, and kidney problems, the now ubiquitous constellation of disturbances known as the 'metabolic syndrome' first described by endocrinologist Gerald Reaven in the late 1980s.

In the late 1990s the World Health Organization warned of an emerging global epidemic of chronic heart failure, now a leading cause of hospital admissions in people over sixty years of age. And what are the main causes of chronic heart failure? CAD, HT, and diabetes, the same disorders that medical science claimed to have been successfully treating in the previous decades. All current medical treatments for the rapidly spreading metabolic syndrome are aimed at blocking the effects of excessive sympathetic activity but do nothing to correct the diastolic dysfunction. To understand how diastolic impairment plays such a key role in the evolution of so many chronic diseases, we need to reexamine the role of the heart in the generation of body heat. This, in turn, helps us understand why hot tub therapies play an important role in the reversal of the various disease conditions.

The Metabolic Field & Thermogenesis

For over two millennia body heat was considered to be the single most important phenomenon of living bodies, a fundamental energetic force from which all functions, including thought and movement, were made possible. Physicians of antiquity taught that the preservation of vital heat was essential for the continuance of life and that when heat was extinguished or exhausted, death ensued. They associated body heat with hardiness and vitality, when strong it could overcome

opposing forces. They recognized that as a person aged the capacity to generate innate heat gradually diminished. Coldness of the breath meant that death hovered nearby.

Early physicians observed that during states of exertion or with fever the most striking changes appeared in the circulation. The motions of the heart became stronger and more rapid. The pulse became swollen and more forceful. They ascribed these changes to the release of heat into the arterial blood by the heart. Early healing traditions attached great significance to protecting and sustaining innate heat. It had to be carefully moderated and periodically cooled to prevent it from burning itself to exhaustion. Numerous sicknesses arose due to an obscure condition described as 'insufficient cooling.' Once the Yaghan Indians began wearing clothing the outward movement and release of body heat between the cardiovascular system and the skin was impaired. This forms the basis of insufficient cooling.

Galen claimed that the heart not only caused the forward movement of blood but was the body's main source of heat production. He likened it to a furnace. Even Harvey recognized the relation between the heart and body heat. Calling the heart 'the sun of the microcosm,' he viewed it as a radiant energy source that through its actions brought about the transformation of arterial blood. All the parts of the body, he told his readers, are fed and warmed by the movement of 'more perfect, more spirituous, and hotter' arterial blood. And once in the tissues blood loses its heat and must return to its source, the heart, to recover its virtue.

We see, as well, in the medical traditions of antiquity the recognition of a close relation between emotions, body heat, and the cardiovascular system. Emotions, the very word meaning 'outward movement,' were considered to be a form of energy like heat. Originating in the upper abdomen and chest area, they first become manifest in the rhythmic motions of the heart and pulse, the patterns of breathing, and the distribution of blood flow around the body.

We unconsciously employ metaphors relating to warmth and cold to describe the content of emotional experiences. Emotions erupt during the 'heat of passion' when the 'heart is aroused.' In these states, we 'see red,' are 'on fire,' 'burn with desire,' or are overcome with 'feelings of warmth.' During states of anger, when we reach our 'boiling point,' the face reddens with rushing blood, nostrils

flare, veins engorge, as we 'lose our cool' and get 'hot-headed.' Emotions are a response from the deepest place of self and, when unleashed, the entire body moves in unison.

As the heart pumps blood throughout the body, it generates large amounts of heat, so much in fact that one is drawn to question its primary role. Researchers found that only about 10-20% of the heart's chemical energy is used for the mechanical pumping of blood. But since scientists conceive the heart's function on that basis, they conclude that its ability to convert chemical into mechanical energy is highly inefficient and wasteful.

A prime source of the heart's 'inefficiency' is the release of heat into the bloodstream during its cycles of contraction and dilation. A large heat pulse, referred to as 'recovery heat,' is infused into the ventricle at the beginning of diastole. The magnitude of the heat pulse varies with the activities of the heart, increasing during periods of exercise or in states of emotional arousal. The heat pulse plays a key role in the outward diastolic movement. These arterial heat pulses have profound effects on cellular metabolism throughout the body.

As we have seen, modern science has been unable to offer a compelling explanation for thermogenesis, the production and release of innate heat, related to a host of different bodily states such as exercise, food intake, intense emotional experiences, even during the menstrual cycle. We can also observe the dynamics of thermogenesis at play in the daily internal heat cycle initiated by the actions of thyroid hormone (TH).

When TH enters the bloodstream the metabolism increases promptly. The heart beats faster and stronger. The pulse swells and becomes more forceful. Researchers are uncertain how TH influences the heart and circulation. Because there is marked increase in heat release by the heart, some speculate that TH induces 'inefficiencies' in its function. But the notion that one of the body's key hormones, one that regulates metabolic energy flow in nearly all tissues, would mediate its effects by creating inefficiencies and increasing the wastage of energy, seems ridiculous.

The heat-producing effects of TH are similar to exercise or fever. They occur almost immediately after the hormone is released into the bloodstream: body heat rises, mimicking a low-grade fever;

respiration increases as tissues consume more oxygen; more blood flows to the skin, muscles, kidneys, and heart as body functions are accelerated under the active mediation of heat.

There are two elemental rhythms of the body's heat field. The first, mediated by the release of TH, involves the passage of heat from the circulation into the tissues throughout the body. This is the daily internal heat cycle that manifests in the circadian body temperature rhythm. Heat pulses released by the heart into the blood pass throughout the body and alter cellular metabolism.

The second movement of heat, the central-peripheral heat rhythm, takes place between the interior of the body and the outer environment. It oscillates between the center of the vascular system in the chest, the heart, and peripheral blood vessels in the skin. The skin capillaries rhythmically constrict and dilate in relationship to conditions in the outer environment. When temperatures outside are cold the vessels constrict and blood flow is forced into the deep tissues of the body in order to preserve heat. When outside conditions are warmer capillaries dilate to release excess body heat.

When the body generates increased heat, after the release of TH into the blood or through exercise or fever, the heat produces active dilation of skin capillaries and is then released to the outside. Galen claimed that when heat is not properly vented to the outside it gradually produces deterioration in the quality of the blood. Obviously in states of chronic increased sympathetic activity like stress, anxiety, HT, CAD, or the metabolic syndrome, the outward movement of body heat is disturbed.

We can see the relation between TH and body heat in various thyroid disorders. When excessive TH is released into the blood, a condition called hyperthyroidism, it accelerates the metabolism, and heat production by the heart increases. An individual's daily caloric requirements may increase dramatically. People with longstanding hyperthyroidism may appear emaciated despite normal or increased food consumption.

TH acts directly on the heart by enhancing every aspect of its function. The heart's motions may become so powerful as to lift the chest wall during its cycles of contraction and dilation, a condition physicians call a hyperdynamic precordium. TH increases the force and speed of both systole and diastole. The work done by the heart may double despite only a modest increase in heart rate.

Through the agency of innate heat, TH alters the dynamics of the blood. With more powerful active dilation of the right ventricle, increased fluid is pulled from the tissues into the veins. The volume of blood within the arteries and veins may expand by as much as 20-25 percent. Blood vessels dilate widely and offer less resistance to blood flow. The pulse, bounding and rapid, feels energized. For this reason, early physicians believed that hyperthyroidism originated in the heart. If doubts remain concerning the agency of innate heat, or its relation to the cardiovascular system, we need only examine the effects of insufficient TH and the opposite condition of hypothyroidism.

Hypothyroidism is a common condition characterized by impairment of cellular metabolism and decreased body temperature, which in advanced cases may lead to life-threatening coma. The loss of body heat and reduction of cellular metabolism have dramatic effects in the soft tissues: coarse, at times grotesque, puffy features; dry, cold, scaly skin; lethargic molasses-in-winter movements, slowed speech often hampered by a thick, swollen tongue. It is a metabolism in slow motion.

Those with hypothyroidism often complain of intolerance to the cold. Indeed, their skin is often cool to touch and may be thickened by an accumulation of fluid, known as 'myxedema.' They experience drowsiness and fatigue. Depression is a common accompaniment. And while their appetites may be blunted, they easily gain weight.

The most striking changes can be found in the cardiovascular system. Heart rate slows. The dynamic range of its rhythm is reduced. The heart is sapped of strength and ability to contract. Diastole is impaired, its expansion incomplete. Blood volume contracts, often by as much as 50 percent, as fluid in the tissues can no longer be efficiently drawn back into the veins by right ventricular dilation. And in the arterial system, heightened constriction increases resistance to blood flow further impairing the heart's capacity to circulate blood. The volume of blood pumped by the heart may decrease by up to half.

In hyperthyroidism and hypothyroidism we recognize yet another paradox. Many of the signs and symptoms of the hyperthyroid state—increased heart rate, tremor, anxiety, agitation—mimic states of high sympathetic discharge. Meanwhile the clinical features of hypothyroidism—low heart rate, somnolence, lethargy—suggest a withdrawal of sympathetic activity. And yet the opposite actually

holds true. In hyperthyroidism sympathetic activity is usually normal or decreased while in hypothyroidism it is usually markedly elevated. How to explain this paradox?

It is the sympathetic system that mediates the release of thyroid hormone and thermogenesis. Only sympathetic nerves innervate the thyroid gland. Over a long period of time increased sympathetic activity causes deterioration of thermogenesis and once this happens sympathetic activity into the thyroid increases even more, releasing more and more TH into the blood in an attempt to stimulate thermogenesis by the heart. In the process it causes the thyroid to burn out and fail. And as this deterioration proceeds active dilation in the heart and vascular system progressively worsens.

Thus hypothyroidism, with increased sympathetic activity and impaired thermogenesis is a strong risk factor for CAD. Found in association with elevated cholesterol and other blood lipids, it increases the likelihood for heart attack and accelerates the evolution of atherosclerosis. Like the ubiquitous metabolic syndrome described by Reaven, hypothyroidism has its origins in the deterioration of the metabolic field.

In the Heat of a Run

The paradoxes that confound medical scientists are resolved once we examine the relationship between the heart and body heat. But this still does not give us a complete picture of how heart, heat, and the parasympathetic system are related. Put differently, why are conditions such as CAD, hypothyroidism, and the metabolic syndrome all associated with increased sympathetic and decreased parasympathetic activity?

Intriguingly, modern research suggests that all the different conditions of the metabolic syndrome—obesity, hypertension, diabetes, and heart disease—are preventable or reversible by regular exercise. What happens in the body during exercise that exerts such a profound influence on these conditions, and how is this related to autonomic balance? Let's go for a run.

At the beginning sympathetic nerves and chemical messengers from the pituitary gland activate the entire body. The adrenal glands churn out stress hormones like cortisol and epinephrine. Nerves send electrical impulses to skeletal muscles in the arms and legs to produce their contraction. Exercise presents researchers with another dilemma. Since sympathetic nerves, which fire during muscle contraction, cause constriction of blood vessels, how does blood flow into muscles increase so rapidly in the early moments of exercise? And as the intensity of exercise increases, so does sympathetic activity. This surge of sympathetic electrical activity should diminish blood flow into the muscles but quite the opposite actually occurs. The active dilation of blood vessels throughout the body caused by thermogenesis and the release of heat pulses into the blood by the heart.

As you begin to run, blood vessels in your skin constrict under the influence of the sympathetic system and skin temperature drops, most noticeably in your hands and fingers. Depending upon the intensity with which you start running, skin blood flow may decrease by as much as two-thirds. Blood flow to internal organs like the kidneys and intestines also decreases sharply. These reflexes, orchestrated by the heart, redistribute the flow of blood and heat into active muscle tissue. As muscles work harder they too generate and release more heat into the circulation.

Within less than a minute, the dynamics of the heart and circulation change dramatically. Your heart rate may double. Both contraction and dilation are enhanced; contraction, stronger and quicker, followed by an equally forceful dilation. Each heart cycle may pump twice the blood volume as when you are at rest; and considering the increase in heart rate, cardiac output of blood each minute may actually increase by fivefold. Blood flow into exercising muscles may increase by up to 25-fold. With your arms and legs churning, pumping back and forth, your breathing rapidly increases in depth and frequency as the lungs draw inward the qualities of air. The amount of air moved during breathing may increase up to 20-fold. Heat production in your body rises in direct proportion to your breathing.

In the first few minutes of exercise, as skin vessels remain constricted, only small amounts of heat are given off to the outside, usually less than when you are at rest. As you continue, however, your central core body temperature rises and heat begins its outward motion, moving from the body's center toward the periphery. As heat moves into skin arterioles it overcomes sympathetic constriction and blood vessels actively dilate.

As you continue to run, you feel increasing warmth, your skin becomes reddened, and you begin to sweat. During a long run, when environmental temperatures are around 70°F, body temperature may increase as high as 102°-103°F, while on hot and humid days it can reach even higher levels. Throughout exercise, skin vessels remain dilated to release heat back into the environment. During intense exercise, blood flow to the skin may increase by as much as eight-fold because of this vasodilation and account for over half the body's total blood flow.

As body heat increases, your performance improves. Your muscles now contract with more power and efficiency. Running is easier and smoother. Peak performance times for many athletes occur in the mid- to late-afternoon and early evening, when the internal heat rhythm is in full bloom and body temperature is highest. Heat enhances exercise, exercise enhances heat. For the remainder of your run you will be able to maintain a comfortable stride.

After your run, the pendular motions of the heart and circulation move in the opposing direction as the recovery physiology kicks into high gear. Sympathetic discharge wanes while parasympathetic activity surges. Heart rate, breathing, and blood pressure decrease, often dropping below pre-exercise levels. There is profound dilation of blood vessels in the muscles and skin to release body heat and, consequently, blood pressure may be decreased for up to 2 or 3 hours after exercise. And during this time, as the body gradually cools, blood sugar levels plummet as the body's sensitivity to the effects of insulin increases dramatically. The functions of the immune system is qualitatively enhanced. These effects occur to greater or lesser extent every time you exercise.

Regular exercise increases heart rate variability, parasympathetic tone, thermogenesis, and restores balance between the light and dark rhythms. Along with this, a gradual lowering of resting heart rate and blood pressure occurs over a period of weeks to months. Blood levels of light hormones in the blood such as epinephrine, norepinephrine, and cortisol gradually decrease, while dark hormones such as melatonin and bilirubin increase. Lipid patterns in the blood change as good cholesterol, HDL, increases and bad cholesterol, LDL, decreases. All mediated through the agency of body heat.

The period of exercise does not have to be prolonged to achieve these results. In fact, people with various chronic conditions may experience beneficial effects to brief pulses of exercise, as with

interval training, in which several minutes of intense exercise alternate with periods of rest. And behind this surprising effect lies a remarkable phenomenon discovered by medical scientists several decades ago.

The Warm-up Phenomenon

Legend has it that during the 1st century BC King Mithradates of Pontus, fearing that assassins would poison him, consumed daily small doses of poison to gain protection. He lived to a ripe old age and, ironically, when he attempted to end his own life through poisoning, failed miserably. The moral of the story is that which doesn't kill you makes you stronger. Mithradates' tale takes on a strange twist in the field of cardiology.

In the 1960s cardiologists described a previously unknown phenomenon in persons with CAD who experience chest pain during physical activity, what is called effort related angina. The pain is caused by decreased blood flow beyond the area of arterial narrowing, what scientists call ischemia. Typically occurring while performing strenuous activities like shoveling snow, the individual, overcome with chest pain, is forced to rest for several minutes in order to gain relief. Upon resumption of the activity, they often observe that they can exert themselves longer and with greater intensity than on the original attempt.

When cardiologists subjected such individuals to stress testing on the treadmill, they too found increased duration of activity with improved performance during the second period of exercise. Calling it the warm-up phenomenon, they observed that the key ingredient is one or more brief intervals of intense activity interposed by short periods of rest. But to this day they remain uncertain how the phenomenon is mediated or what exactly happens in the cells and tissues.

Given the fact that the coronary arteries of individuals with CAD are narrowed by plaques, cardiologists were hard pressed to explain the warm-up phenomenon on the basis of increased blood flow into the heart muscle. Indeed, recent studies found that flow across the narrowed segment of artery doesn't change dramatically. Some argued that the period of ischemia caused the heart muscle to decrease its metabolism so that oxygen demand decreases. But the enhanced

performance on stress tests suggests otherwise and research evidence has shown improved contractility of the heart muscle. This led others to argue that the heart works harder and more efficiently due to better coupling, a 'synergistic adaptation,' between blood flow and muscle fiber function. As we will see, this improved performance can only be explained through the actions of heat.

More recent studies found that during the second bout of exercise when the period of enhanced protection is observed, there is decreased vascular resistance in the tiny arterioles of the heart, associated with increased blood vessel dilation, a more powerful suction wave, and enhanced relaxation of the left ventricle beyond the level of the area of stenosis. When vascular surgeons studied tiny skin arterioles and capillaries through a microscope immediately after the pulsed preconditioning sequence they observe striking changes. Blood surges through widely dilated vessels; constriction of blood vessels is inhibited; blood flows faster; blood cells are less likely to clump together and adhere to the blood vessel wall; blood clotting is impaired. All of these effects are attributable to increased body heat, the same effects that occur in fever.

In the 1980s a group of researchers opened the chests of anesthetized dogs and occluded the coronary arteries for five minutes after which they reopened them for five minutes. This cycle of ischemia and reperfusion, called ischemic preconditioning, was repeated four times at which point the coronary arteries were then occluded for forty minutes. The results stunned researchers. Animals who underwent the preconditioning (PC) sequence had markedly smaller areas of infarction, muscle cell death, compared to control animals that did not.

The PC phenomenon is now recognized as the most powerful protective mechanism ever discovered. Short periods of ischemia interposed with recovery periods make the heart muscle more resistant to subsequent injury. The effects are time dependent with the period of protection diminishing after several hours. We see that this period corresponds nicely with the recovery period of exercise. Exercise induces the PC phenomenon.

In the mid-90s researchers discovered that while the initial period of protection dissipates within several hours, it returns 24 hours later, a phenomenon known as the second window of protection

(SWOP), and persists up to 72 hours. When the coronary arteries of lab animals were occluded during the SWOP the extent of damage was markedly decreased compared with animals not receiving the PC cycles. Researchers remain at a loss to explain how this occurs. The SWOP is an echo effect mediated through the agency of body heat.

Around the same time the SWOP was recognized, other researchers stumbled upon another linchpin discovery concerning the PC phenomenon. PC cycles were applied to arteries within the abdominal cavity of experimental animals and then their coronary arteries were occluded for an extended period. The results were the same as before: animals receiving the PC stimulus had far less ischemic damage to heart muscle. This phenomenon is called remote preconditioning.

Remote PC tells us that the effects of preconditioning in a single blood vessel are realized throughout the entire body. And these effects can only originate in the vascular system and the blood. Brief and repetitive periods of ischemia in one vascular territory confer protection against subsequent prolonged ischemia in tissues throughout the body. Remote PC can be induced throughout the body, the brain, lungs, heart, kidneys, intestines, even the extremities with the same results. Surgeons now use remote PC in the forearms prior to cardiac surgery to protect the heart from surgical injury.

Early on it was recognized that the PC effect could be induced through means other than ischemia. Various chemical mediators, including alcohol, have been shown experimentally to induce the PC effect. Researchers now believe that the beneficial protective effects of exercise are mediated through the PC phenomenon. Whole body hyperthermia, as in fever or through sauna and hot tub immersion, confers similar protection. Researchers even induced the protective effects in animals by simply raising the heart rate for several minutes with a pacemaker device! PC thus represents a stabilizing force that confers hardiness and resistance on the body's tissues by transiently strengthening the metabolism. It is hardly surprising that many scientists have heralded the discovery of preconditioning as a harbinger of a new era in medicine.

Body Heat and Immunity

In the spring of 1891, a young American surgeon, William B. Coley, spent weeks searching in the tenement neighborhoods of New York's Lower East Side for a German immigrant named Fred K. Stein. Six years earlier, Stein had been released by doctors at New York Hospital after an inexplicable recovery from cancer, and had not been heard from since. Coley's sleuthwork sought to answer a lingering question: was Stein still alive? When Coley finally stood before the man with a long jagged scar running down the left side of his neck, a remarkable chapter in medicine commenced.

In the earlier years of Coley's surgery practice, a young woman with a rare sarcoma tumor came to him for treatment. He excised the tumor, but following surgery it spread rapidly and she died. Distraught, Coley was determined to learn more about this kind of tumor so that, as he wrote, 'some little light' might be shed on its treatment. He searched through the medical records of the New York Hospital to review all its cases of sarcoma and crossed paths with Fred K. Stein.

In 1885, Stein was diagnosed with an advanced sarcoma involving the left side of his neck and face. Surgical removal was attempted, but the tumor had already spread into the surrounding tissues. The surgery left a gaping crater in the left side of his neck that resisted all healing attempts by the body. Stein languished in the hospital for months as his disease progressed. His prognosis was absolutely hopeless. Then chance, or perhaps destiny, intervened, for in those days hospitals were repositories of pestilence.

Stein developed a violent fever and severe skin inflammation that spread rapidly over his neck and face. He had contracted erysipelas, a highly contagious skin infection caused by the bacteria *Streptococcus pyogenes*. He was placed in isolation and the staff awaited his death. Fever raged for days and then subsided. But Stein was then overcome by a second wave of skin inflammation and fever, which he also miraculously survived. To the amazement of his doctors and nurses, the tumors shrank like snowballs and disappeared altogether. The wound rapidly healed. Seizing this unanticipated twist of fate, Stein's doctor declared victory and discharged him to an uncertain future.

The relationship between Stein's infection and the spontaneous resolution of his tumor intrigued Coley. If unintended infection cured a sarcoma, he reasoned, perhaps the same effect could be

achieved when infection was deliberately introduced. Coley reviewed the medical literature and found other reports of tumor regression following skin infection with *Streptococcus pyogenes*. He deliberately introduced the bacterium under the skin of a patient with sarcoma; the patient survived more than eight years following treatment.

Over the years, Coley used his bacterial suspension, known as 'Coley's toxin,' to obtain beneficial results in various kinds of cancer. He published reports that piqued the interest of the medical community. Numerous physicians replicated his results but unfortunately most could not. By the mid-1890s Coley's method was under attack and he was labeled as a sensation monger who deluded the sick with false hope. Physicians eventually condemned his therapy and abandoned the practice. Coley and his toxin fell victim to the times, swept aside by changing ideas about the nature of inflammation. But as evidence continues to emerge, it appears that Coley was onto something.

Roman poet Marcus Lucanus coined the term 'immunis', meaning exemption in Roman law, to describe the legendary resistance among a certain North African tribe to the effects of snakebite. It has long been known that repeated exposure by the body to a wide range of stressful conditions such as physical trauma, extreme heat or cold, bacterial toxins, as well as various drugs and poisons confers hardiness and resistance to what would otherwise have been a lethal injury.

It now appears that the recurring high fevers in Fred K. Stein were preconditioning pulses of body heat that set into motion processes in the tissues that led to the disappearance of his tumor. Earlier in the 19th century, physicians observed dramatic recoveries from cancer following bacterial infections or high fevers they ascribed to spontaneous regression. French physicians Tanchou and Vautier described spontaneous regression in breast cancer after deliberate introduction of infection. Reports such as these led physicians to use 'laudable pus' in the treatment of advanced breast cancers. Women were inoculated with material from infected wounds, gangrenous tissues, and even syphilitic chancres. This practice stirred up controversy and was eventually abandoned. Modern physicians have never been able to explain the basis for such spontaneous regressions.

Coley himself failed to recognize the importance of fever and the qualitative aspects of the inflammatory response. In his patients with sarcoma, for example, a favorable response was more

likely to occur when their fevers reached temperatures above 102°F. The ability of the blood to initiate a robust fever or to release heat into the tissues determined the strength of the subsequent immune response. Besides conditioning the immune system, fever and heat pulses from the blood stabilized and conferred hardiness in body tissues just like the PC phenomenon we described above.

The other amazing side of the preconditioning story concerns the immune system. If a blood vessel in which no preconditioning sequence has been performed is occluded for an hour or so, when it is reopened a pattern of irreversible tissue damage known as reperfusion injury occurs that provides insight into the behaviors of the immune system. Within the injured tissues many cells have died due to the stress of blood flow deprivation, ischemia, but many that remain alive will soon die as a result of the subsequent immune response.

As blood flow suddenly returns to the stressed tissues, T-lymphocytes, a type of white blood cell, release chemical substances that trigger inflammation. Other immune cells migrate into the area, congregate along the walls of tiny veins just beyond the capillaries and cross through into the injured tissues. These cells release chemical substances and as a result many seemingly intact cells swell up and die. Apparently many cells that did not die from ischemia were injured and so became targets of the immune system. The activation of the immune system as a result of the PC phenomenon raises a paradox.

In healthy tissues when PC is performed the immune response and cellular injury is prevented, and high states of resistance to further injury are generated. In diseased or injured tissues, inflammation and fever, as preconditioning pulses, strengthen the immune system, as William Coley discovered when he introduced his bacterial toxin under the skin of his cancer patients.

Since ancient times physicians recognized inflammation through its symptoms: rubor (redness), dolor (pain), calor (heat), and tumor (swelling). Nowadays when physicians encounter fever they assume it is due to infection or internal inflammation and often attempt to quell the fever with antibiotics or anti-inflammatory drugs. Ancient Greek physicians, however, regarded fever as an indication that the body was attempting to correct an internal problem. 'I think that you cannot find

another drug which heats in a more penetrating manner than fever,' wrote physician Rufus of Ephesus. He called fever a good remedy.

Preconditioning, through the agency of body heat, represents a physiologic response originating in the blood and cardiovascular system that organizes all adaptive attempts in living bodies. The PC phenomenon consists of three interwoven strands that flow in sequence: an encounter with a specific or general stress engages the sympathetic system or light processes within cells and tissues or at a whole-body level; blood flow and heat then surge into the affected tissues or body region thereby stimulating the heat-related metabolic phase of activity; the period of heat-induced change recedes and is followed by the parasympathetic or dark phase during which the restorative or adaptive response ensues. This process of transformation involves three distinct aspects of the physiology, what we have called light, heat, and dark. The same process occurs during the hot soak.

Hot Soak and Cold Plunge

[CLEAN THIS SECTION UP. STILL DOESN'T FLOW SMOOTHLY.]

We've now seen how heart, heat and health are vitally related. The health benefits of hot tub therapies obviously occur through induction of the PC phenomenon. Almost immediately upon immersing in hot water you begin to feel the penetrating effects of heat moving into the skin tissues. Instead of occurring from the inside-out as in exercise, immersion therapies act from the outside-in. The process works in the opposite direction but the end result is the same. As heat penetrates the skin it dissipates sympathetic constriction and blood vessels actively dilate. The skin becomes flushed and reddened. Blood vessels of the fingers and toes dilate widely producing a throbbing sensation.

As in exercise skin blood flow increases dramatically. As blood surges through the dilated arterioles it absorbs heat, carrying it throughout the body and causing the core temperature to rise. You begin to feel a general sense of warmth, relaxation and well-being. Just as with exercise or after the release of thyroid hormone, the dynamics of the heart and circulation respond dramatically to increased heat in the blood. Heart rate quickens and the pulse grows stronger. Contraction and

dilation becomes more forceful, and each heart cycle pumps greater blood volume. Your muscles loosen up, and tension disappears. As you sit for longer periods you may start to feel overheated as the core body temperature continues to climb, often up to 102°-103°F, mimicking fever. Your face becomes reddened and sweat appears on your cheeks and forehead.

After finishing the hot soak, the pendular motions of the heart and circulation move in the opposite direction and the entire physiology changes. Sympathetic tone diminishes as the strength of the parasympathetic field surges. Heart rate and blood pressure drop below pre-soak levels. Blood vessels in the muscles and skin remain dilated to release body heat and, consequently, there may be hypotension for a period after your soak. During this time, as the body temperature gradually drops, the body's sensitivity to the effects of insulin improves dramatically, causing blood sugar levels to plummet. The activity of the immune system is greatly enhanced. You experience these effects after each hot soak.

The recovery period from hot soaks, lasting about 2 or 3 hours, corresponds to the period of protection following the PC phenomenon. And based on what the medical literature tells us, these effects must occur throughout the entire body and recur the next day as an echo: the 'second window of protection'. Regular hot soaks help restore balance between constriction and dilation in the cardiovascular system, increase parasympathetic tone, and gradually improve heart rate variability. Resting heart rate and blood pressure gradually decrease. Hot soaks help restore the central-peripheral heat rhythm and the elimination of excess heat and metabolic wastes from the blood through the skin.

And like the Yaghan Indians and aboriginals we encountered in the beginning section, thermogenesis can be stimulated and enhanced through the opposite means, by deliberate exposure to the cold. Take the cold plunge. The effects of the cold are diametrically opposed to the hot soak. The immediate experience of cold immersion takes your breath away. As skin vessels constrict, your skin tightens up and pales from diminished blood flow. As the skin cools and loses color, the small arterioles at the skin's surface constrict while the activity of the sympathetic nerves and adrenals increase. The body limits blood flow to the surface in an effort to preserve body heat. But as you sit for a longer period the cold gradually penetrates more deeply toward the core and your internal

temperature starts to drop. As the cold sinks in deeper you begin to feel chilly and shiver just a bit. This is a sign that the body is starting to produce its own heat.

You then notice your heart rate accelerates in an attempt to stimulate thermogenesis. The heart begins to release more heat into circulation to overcome the invasion of cold. It is this cold-induced thermogenesis that gives rise to so many of the beneficial effects--you are teaching the heart to regenerate thermogenesis. The longer you stay in the cold the more the cardiovascular system will build up its capacity to stimulate thermogenesis, just like the Yagghans did when they were exposed to environmental cold. As you develop the capacity to withstand the cold you will be able to remain in the cold tub for as long as you please without experiencing discomfort. But, like exercise, you don't have to stay forever to reap the benefits.

Hot and cold immersion therapies, through the preconditioning effect and thermogenesis, represent innovative dynamic means to restore cardiovascular dynamics and impaired body heat rhythms.

Hydrotherapy & Health

[Combine a brief review on the historical aspects of heat therapies and the few medical research papers we quote below. This section doesn't need to be more than 1-2 pages.]

For centuries, cultures throughout the world have used various heat therapies to promote good health and reap the dramatic benefits. Heat plays a central role in many cultures, and has been transformed in various ways to fit their customs- for example- the Finnish sauna, Japanese hot baths, Russian banya, Native American sweat lodges and Turkish steam bath. Modern Western traditions have not adopted the everyday use of heat therapy and treat 'hot-tubbing' as a recreational treat.

The Finnish word for sauna- loyly- translates to 'life' or 'spirit'

Wherever there are hot springs

For centuries traditional cultures throughout the world recognized the beneficial effects of heat therapies. The Finnish sauna, Russian banya, Japanese onsen, and Turkish hammam all enlisted the medicinal properties of heat to prevent and treat sicknesses. Using heat therapies Japanese

researchers observed dramatic benefits in people with heart failure. Warm water immersion and sauna treatments produced thermal vasodilation along with improvements in heart function along with lower blood pressure. Blood flow throughout the body increased.

Up until the early 1990s, medical science advised limited activity or bed rest for patients with CAD or chronic heart failure even though such recommendations were never shown to have any benefit. Immersion in hot water or sauna therapies were believed to be harmful, although this had never been established by clinical studies. But new studies are changing ideas about the treatment of heart failure..

Sitting in water heated to 41° C for ten minutes, or in a sauna heated to 61° C for fifteen minutes, once or twice a day for four weeks, led to significant improvement in symptoms. Their repeated thermal therapy promoted mental and physical relaxation. Quality of life, as gauged by appetite, sleep habits, and general well-being, improved as well. And not surprisingly, people with the greatest improvement in symptoms had the greatest increases in active dilation. The Japanese scientists observed that this non-pharmacological treatment produced results rivaling drug therapies. Moreover treatment was inexpensive, readily available, and had no adverse side effects.

The same beneficial effects were found in asymptomatic individuals with coronary risk factors like high cholesterol. Repeated sauna treatment improved active dilation in blood vessels and lowered fasting blood sugar levels. Other studies also found that hot tub therapies beneficially affected blood sugar levels. The Japanese researchers concluded that such thermal treatments have a therapeutic role in people with risk factors for CAD and the cluster of conditions associated with the metabolic syndrome.

In a study aimed at showing the effects of hyperthermia and the immune system (1), 50 participants were tested. For six months, Group 1 took sauna baths once or twice a week, while Group 2 abstained from sauna baths or any hyperthermic treatment. The frequency of colds in the control group was 28% higher than that of the bathing group

Product/Introduction

[This section needs a lot of work, text is copied from various sources from James. Will integrate and combine.]

Our Japanese style hot tubs, called Furo®, offer water temperatures between 108° and 115° degrees Fahrenheit. There is no required temperature and every bather can set it where they feel most comfortable. In time, almost everyone is surprised at the increased temperatures they become accustomed to and enjoy. The health benefits and pain relief of a Furo® become more pronounced and faster to achieve with higher temperatures.

The Furo® experience differs significantly from a jetted or aerated spa. The human body's internal temperature increases more over a shorter period of time in a Furo® than in a jetted spa. The reasoning and research show that elevated body temperatures kill viruses and bacterial agents that can cause infection, inflammation, pain and other problems.

The skin is of great importance because it is the body's largest organ, as big as a double sized bed sheet, in an average adult. The average human body has 2.3 million sweat glands. A hot bath stimulates every single one of them. Skin has a variety of functions ranging from regulation of body temperature and blood pressure, to acting as an immunological defense to disease, and aids in the removal of toxins from the body. A Furo® stimulates the sweat glands thoroughly and allows them to function much more efficiently. The water in a Furo® cleans the body in a way not possible with conventional American bathing, leaving the bather cleaned from the inside out.

The skin is also heavily supplied with blood vessels. Through increased blood flow while soaking, vessels dilate allowing more blood to pass through them. The skin's blood vessels get a real workout. Imagine how alive and revitalized this largest organ feels after such an experience!

FURO® Japanese Soaking Tubs by FUROHEALTH® deliver an old world relaxing experience with the modern cutting edge technology. The art of the Japanese bath is preserved by keeping the water hot, pure, chemical-free and clean for an extended period of time - years if maintained correctly (which takes a combined total of about 15 minutes per month)! Extremely easy to own. FURO®

Japanese Soaking Tubs are the world's simplest and most user-friendly tubs in existence! Our soaking tub prices are affordable and available in a variety of sizes to fit your needs perfectly.

The FURO® Hot Soaking Tub offers deep-healing relaxation and reduces pain, aiding a myriad of health conditions: autoimmune diseases such as arthritis, lupus, and fibromyalgia, as well as athletic & non-athletic stress, inflammation, sleep-related problems, and more.

The FUROHEALTH® Water Purification System maintains pure, chemical-free, clean water for an extended period of time. It allows chemical-free use of the tub, and rejuvenates the water with our PUREHEAT System. Your water stays fresh, clean and hot for many, many months automatically for only a few dollars total cost per month. The health benefits are in the clean, chemical free hot water...so set the temperature and enjoy!

FUROHEALTH® tubs are self-contained, space saving and use standard 110-volt 15 amp household electricity. They can also be integrated into your existing standard plumbing to be enjoyed in the privacy of your own bathroom with or without the pure heat system! Hot therapy, cold plunge, steam, or a dual tub of hot and cold are all available by simply adding the proper FUROHEALTH® equipment.

HYOGA™ Cold Plunge Tub by FUROHEALTH® is a cold therapy unit designed specifically for maintaining optimum health. Plunging into cold water at temperatures between 48-50 degrees Fahrenheit has been practiced for hundreds of years. It improves circulation, relieves depression, keeps your skin and hair healthy, strengthens your immune system, increases testosterone levels, increases energy levels, promotes better sleep, and invigorates your spirit.

Cold plunge therapy has also become an invaluable tool for trainers and coaches. Modern athletes, both professional and amateur, have learned to love the use of cold plunge therapy. The HYOGA Cold Plunge Tub shrinks and constricts stretched and warmed muscles from athletic workouts, game play, or any other strenuous activity. The decreased time it takes to recover from muscle pain and soreness allows a quicker return to full use of muscle groups and range of motion, a key component for any athlete.

Why Soaking Tubs?

Japanese style soaking tubs differ from traditional 'hot tubs' in a number of ways. Unlike traditional hot tubs, having no jets allows the water to reach temperatures between 108° and 115° Fahrenheit and sitting in water up to your chin, internal core body temperature increases over a shorter period of time, essentially forcing a fever. This is something that cannot be accomplished in a conventional hot tub. Alternating between hot and cold soaking increases hardiness and resilience. The health benefits lie in the fact that the water can retain and transmit heat. The increase in the body's core temperature allows for the body to begin the healing process.

REFERENCES

[Will clean and organize this section]

Cardiovascular

1. [Cardiovascular responses to a hot tub bath](#). J Alt Complement Med vol. 5(3): pp. 301-304; June 1999
2. Keast ML, Adamo KB. [The Finnish sauna bath and its use in patients with cardiovascular disease](#). J Cardioplum Rehab vol. 20: pp. 225-230; 1990
3. Tei C, Tanaka N. [Comprehensive therapy for congestive heart failure: a novel approach incorporating thermal vasodilation](#). Int Med vol. 35 (1): pp. 67-69; January 1996
4. Eisalo A, Luurila OJ. [The Finnish sauna and cardiovascular diseases](#). Ann Clin Res vol. 20: pp. 267-270; 1988
5. Leppäluoto J, Tuominen M, Väänänen A, Karpakka J, Vuori J. Some cardiovascular and metabolic effects of repeated sauna bathing. Acta Physiol Scand vol. 128: pp. 77-81; 1986
6. Grant, J. (2007, April 10). Hot Tub Therapy - Can Water Therapy Help You Lower Blood Pressure? Retrieved April 25, 2013, from <http://ezinearticles.com/?Hot--Tub--Therapy-----Can--Water--Therapy--Help--You--Lower--Blood--Pressure?&id=521325>
7. The effects of balneotherapy on blood pressure and pulse in osteoarthritis patients with hypertension [<http://www.ncbi.nlm.nih.gov/pubmed/24254034>]
8. Imamura M, Biro S, Kihara T, et al. [Repeated thermal therapy improves impaired vascular endothelial function in patients with coronary risk factors](#). J Am Coll Cardiol vol. 38(4): pp. 1083-1088; October 2001
9. Kihara T, Biro S, Imamura M, et al. [Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure](#). J Am Coll Cardiol vol. 39 (5): pp. 754-759; 6 March 2002
10. Forestier RJ, Briancon G, Francon A, et al. [Balneohydrotherapy in the treatment of chronic venous insufficiency](#). Vasa 2014 Sep;43(5):365-71
11. Ikeda Y, Biro S, Kamogawa Y, et al. [Repeated thermal therapy upregulates arterial endothelial nitric oxide synthase expression in syrian golden hamsters](#). Jpn Circ J vol. 65: pp. 434-438; 2001
12. Vuori J. Sauna bather's circulation. Ann Clin Res vol. 20: pp. 249-256; 1988
13. Findikoglu G, Cetin EN, Sarsan A, et al. Arterial and intraocular pressure changes after a single-session hot-water immersion. Undersea Hyperb Med. 2015 Jan-Feb. 42(1):65-73.

Pain/Arthritis/Fibro

1. A randomised controlled trial of hot water (45°C) immersion versus ice packs for pain relief in bluebottle stings [,Rheumatol Int](#). 2005 Apr;25(3):220-4. Epub 2004 Jul 15.
2. [Bender T](#), [Karagülle Z](#), [Bálint GP](#), [Gutenbrunner C](#), [Bálint PV](#), [Sukeník S](#), Hydrotherapy, balneotherapy, and spa treatment in pain management.. [Rheumatol Int](#). 2008 Dec;29(2):119-30. doi: 10.1007/s00296-008-0674-9. Epub 2008 Aug 27.
3. [Boyles](#), S., WebMD Health News, June 29, 2011, 100 Million Americans Have Chronic Pain Accessed April 24, 2013 <http://www.webmd.com/pain-management/news/20110629/100-million-americans-have-chronic-pain>

4. Conrad Loten, Barrie Stokes, David Worsley, Jamie E Seymour, Simon Jiang and Geoffrey K Isbister, The effect of combined therapy (spa and physical therapy) on pain in various chronic diseases, *Med J Aust* 2006; 184 (7): 329-333.
5. [McVeigh JG](#), [McGaughey H](#), [Hall M](#), [Kane P.](#), The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: a systematic review. *Rheumatol Int.* 2008 Dec;29(2):119-30. Epub 2008 Aug 27.
6. Wright, Anthony Ph.D.; Sluka, Kathleen A. Ph.D Non-pharmacological Treatments for Musculoskeletal Pain, *Complementary Therapies in Medicine* [Volume 13, Issue 4](#) Pages 244-250, December 2005
7. Ablin JN, Häuser W, Buskila D. [Spa treatment \(balneotherapy\) for fibromyalgia-a qualitative-narrative review and a historical perspective](#). *Evid Based Complement Alternat Med.* 2013 July 31. Epub
8. Bender T, Bálint G, Prohászka Z, et al. [Evidence-based hydro- and balneotherapy in Hungary--a systematic review and meta-analysis](#). *Int J Biometeorol.* 2014 Apr;58(3):311-23
9. Kalunian KC. Non-pharmacologic therapy of osteoarthritis. <http://www.uptodate.com/home/index.html>. Accessed Nov. 18, 2010.
10. Effect of spa therapy after intervertebral disc surgery in the cervical spine. [\[http://www.ncbi.nlm.nih.gov/pubmed/24797600\]](http://www.ncbi.nlm.nih.gov/pubmed/24797600)
11. Isomäki H. The sauna and rheumatic diseases. *Ann Clin Res* vol. 20: pp. 271-275; 1988
12. Forestier R, Genty C, Waller B, et al. [Crenobalneotherapy \(spa therapy\) in patients with knee and generalized osteoarthritis: a post-hoc subgroup analysis of a large multicentre randomized trial](#). *Ann Phys Rehabil Med.* vol. 57(4): 213-27. June 2014
13. Marković M, Majkić-Singh N, Ignjatović S. [Beneficial effects of cellular stress response in traditional spa treatment of rheumatoid arthritis](#). *Clin Lab.* 2009. 55(5-6): 235-41
14. Falagas M. E.: [The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials](#). *International Journal of Clinical Practice* [Volume 63, Issue 7](#), pages 1068–1084, July 2009

Sleep/Insomnia

1. van Straten A, Cuijpers P. Self-help therapy for insomnia: a meta-analysis. *Sleep Med Rev.* 2009 Feb;13 (1):61-71. Epub 2008 Oct 26.

Immune

1. Ernst E, Pecho E, Wirz P, Saradeth T. [Regular sauna bathing and the incidence of common colds](#). *Annals of Medicine* pp. 225-227; 1990
2. Lee YB, Lee JY, Lee HJ, et al. [Immunomodulatory effects of balneotherapy with hae-un-dae thermal water on imiquimod-induced psoriasis-like murine model](#). *Ann Dermatol.* 2014 Apr. 26(2):221-30

3. Leicht CA, Kouda K, Umemoto Y, et al. [Hot water immersion induces an acute cytokine response in cervical spinal cord injury](#). Eur J Appl Physiol. 2015 Nov. 115(11): 2243-52

Cold Soaking

1. The Next Challenge, 05 February 2010 5 Health Benefits of Cold Water Swimming, Accessed April 24, 2013 <http://thenextchallenge.org/2010/02/cold-water-swimming/>

Parkinson's/Neurologic

1. Comparing the effects of hydrotherapy and land-based therapy on balance in patients with Parkinson's disease: a randomized controlled pilot study. [<http://www.ncbi.nlm.nih.gov/pubmed/24895382>]
2. The effect of hydrotherapy treatment on gait characteristics of hereditary spastic paraparesis patients. [<http://www.ncbi.nlm.nih.gov/pubmed/24556467>]

History

1. Butler, Lee, "Washing off the Dust": Baths and Bathing in Late Medieval Japan, Monumenta Nipponica Vol. 60, No. 1 (Spring, 2005), pp. 1-41 Published by: [Sophia University](#) Article Stable URL: <http://www.jstor.org/stable/25066349>
2. Valtakari P. The sauna and bathing in different countries. Ann Clin Res vol. 20: pp. 230-235; 1988
3. Moss, GA. [Water and health: a forgotten connection?](#). Perspect Public Health vol. 130 (5): pp. 227-32
4. Helamaa E, Äikäs E. The secret of good löyly. Ann Clin Res vol. 20: pp. 224-229; 1988

Metabolic Syndrome/Diabetes

1. Hooper PL. [Hot-tub therapy for type 2 diabetes mellitus](#). NEJM vol. 341(12): pp. 924-925; 16 September 1999
2. Gin H, Demeaux JL, Grelaud A, et al. [Observation of the long-term effects of lifestyle intervention during balneotherapy in metabolic syndrome](#). Therapie. 2013 May-Jun; 68(3): 163-7

Stress Management/Quality of Life

1. Stress-relieving effects of short-term balneotherapy - a randomized controlled pilot study in healthy adults. [<http://www.ncbi.nlm.nih.gov/pubmed/24851847>]
2. Hayaska S, Shibata Y, Goto Y, et al. [Bathing in a bathtub and health status: a cross-sectional study](#). Complement Ther Clin Pract. 2010 Nov. 16(4): 219-21

Endocrine

1. Kukkonen-Harjula K, Kauppinen K. [How the sauna affects the endocrine system](#). Ann Clin Res vol. 20: pp. 262-266; 1988
2. Koska J, Rovensky K, Zimanova T, et al. [Growth hormone and prolactin responses during partial and whole body warm-water immersions](#). Acta Physiol Scand. 2003 May. 178(1): 19-23

Exercise

1. Zurawlew MJ, Walsh NP, Fortes MB, et al. Post-exercise hot water immersion induces heat acclimation and improves endurance exercise performance in the heat. Scand J Med Sci Sports. 2015 Dec 9.
- 2.

Scientific evidence-based effects of hydrotherapy on various systems of the body

[\http://www.najms.org/article.asp?issn=1947-

[2714;year=2014;volume=6;issue=5;spage=199;epage=209;aulast=Mooventhan\]](http://www.najms.org/article.asp?issn=1947-2714;year=2014;volume=6;issue=5;spage=199;epage=209;aulast=Mooventhan)

15. Hannuksela MI, Ellahham S. Benefits and risks of sauna bathing. Am J Med vol. 110: pp. 188-126; 2001
16. Leppäluoto J. Human thermoregulation in the sauna. Ann Clin Res vol. 20: pp. 240-243; 1988

Weston M, Taber C, Casagrande L, Cornwall M. [Changes in local blood volume during cold gel pack application to traumatized ankles](#). J Orthop Sports Phys Ther 1994;19:197-9.

Srámek P, Simecková M, Janský L, Savlíková J, Vybíral S. [Human physiological responses to immersion into water of different temperatures](#). Eur J Appl Physiol 2000;81:436-42.

Huttunen P, Kokko L, Ylijukuri V. [Winter swimming improves general well-being](#). Int J Circumpolar Health 2004;63:140-4.

Iiyama J, Matsushita K, Tanaka N, Kawahira K. [Effects of single low-temperature sauna bathing in patients with severe motor and intellectual disabilities](#). Int J Biometeorol 2008;52:431-7.

Ohori T, Nozawa T, Ihori H, Shida T, Sobajima M, Matsuki A, *et al.* [Effect of repeated sauna treatment on exercise tolerance and endothelial function in patients with chronic heart failure.](#) Am J Cardiol 2012;109:100-4.

Sobajima M, Nozawa T, Shida T, Ohori T, Suzuki T, Matsuki A, *et al.* [Repeated sauna therapy attenuates ventricular remodeling after myocardial infarction in rats by increasing coronary vascularity of noninfarcted myocardium.](#) Am J Physiol Heart Circ Physiol 2011;301:H548-54.

Imai Y, Nobuoka S, Nagashima J, Awaya T, Aono J, Miyake F, *et al.* [Acute myocardial infarction induced by alternating exposure to heat in a sauna and rapid cooling in cold water.](#) Cardiology 1998;90:299-301.

Crinnion WJ. [Sauna as a valuable clinical tool for cardiovascular, autoimmune, toxicant- induced and other chronic health problems.](#) Altern Med Rev 2011;16:215-25.

Grüner Sveälv B, Cider A, Täng MS, Angwald E, Kardassis D, Andersson B. [Benefit of warm water immersion on biventricular function in patients with chronic heart failure.](#) Cardiovasc Ultrasound 2009;7:33.

Digiesi V, Cerchiai G, Mannini L, Masi F, Nassi F. [Hemorheologic and blood cell changes in humans during partial immersion with a therapeutic method, in 38 ° C water.](#) Minerva Med 1986;77:1407-11.

Boldt LH, Fraszl W, Röcker L, Schefold JC, Steinach M, Noack T, *et al.* [Changes in the haemostatic system after thermoneutral and hyperthermic water immersion.](#) Eur J Appl Physiol 2008;102:547-54.

Choukroun ML, Varene P. [Adjustments in oxygen transport during head-out immersion in water at different temperatures.](#) J Appl Physiol 1990;68:1475-80.

Dogliotti G, Galliera E, Iorio E, De Bernardi Di Valserra M, Solimene U, Corsi MM. [Effect of immersion in CO₂-enriched water on free radical release and total antioxidant status in peripheral arterial occlusive disease.](#) Int Angiol 2011;30:12-7.

Sato M, Kanikowska D, Iwase S, Nishimura N, Shimizu Y, Belin de Chantemele E, et al. [Effects of immersion in water containing high concentrations of CO2 \(CO2-water\) at thermoneutral on thermoregulation and heart rate variability in humans](#). Int J Biometeorol 2009;53:25-30.

Pagourelas ED, Zorou PG, Tsaligopoulos M, Athyros VG, Karagiannis A, Efthimiadis GK. [Carbon dioxide balneotherapy and cardiovascular disease](#). Int J Biometeorol 2011;55:657-63.

Choukroun ML, Kays C, Varène P. [Effects of water temperature on pulmonary volumes in immersed human subjects](#). Respir Physiol 1989;75:255-65.

Goedsche K, Förster M, Kroegel C, Uhlemann C. [Repeated cold water stimulations \(hydrotherapy according to Kneipp\) in patients with COPD](#). Forsch Komplementmed 2007;14:158-66.

Iarosh AM, Kurch TK. [The effect of cold exposure on the respiratory function in children suffering from inflammatory lung diseases](#). Vopr Kurortol Fizioter Lech Fiz Kult 1995;1:9-11.

Herrera E, Sandoval MC, Camargo DM, Salvini TF. [Motor and sensory nerve conduction are affected differently by ice pack, ice massage, and cold water immersion](#). Phys Ther 2010;90:581-91.

Bender T, Karagülle Z, Bálint GP, Gutenbrunner C, Bálint PV, Sukenik S. [Hydrotherapy, balneotherapy, and spa treatment in pain management](#). Rheumatol Int 2005;25:220-4.

Robiner WN. [Psychological and physical reactions to whirlpool baths](#). J Behav Med 1990;13:157-73.

Shevchuk NA. [Hydrotherapy as a possible neuroleptic and sedative treatment](#). Med Hypotheses 2008;70:230-8.

Shevchuk NA. [Possible use of repeated cold stress for reducing fatigue in chronic fatigue syndrome: A hypothesis](#). Behav Brain Funct 2007;3:55.

Shevchuk NA. [Adapted cold shower as a potential treatment for depression](#). Med Hypotheses 2008;70:995-1001.

Chevutschi A, Lensele G, Vaast D, Thevenon A. [An Electromyographic Study of Human Gait both in Water and on Dry Ground](#). J Physiol Anthropol 2007;26:467-73.

Bleakley C, McDonough S, Gardner E, Baxter GD, Hopkins JT, Davison GW. [Cold-water immersion \(cryotherapy\) for preventing and treating muscle soreness after exercise](#). Cochrane Database Syst Rev 2012;2:CD008262.

Morton RH. [Contrast water immersion hastens plasma lactate decrease after intense anaerobic exercise](#). J Sci Med Sport 2007;10:467-70.

Skurvydas A, Kamandulis S, Stanislovaitis A, Streckis V, Mamkus G, Drazdauskas A. [Leg immersion in warm water, stretch-shortening exercise, and exercise-induced muscle damage](#). J Athl Train 2008;43:592-9.

Versey NG, Halson SL, Dawson BT. [Effect of contrast water therapy duration on recovery of running performance](#). Int J Sports Physiol Perform 2012;7:130-40.

Janssen RG, Schwartz DA, Velleman PF. [A randomized controlled study of contrast baths on patients with carpal tunnel syndrome](#). J Hand Ther 2009;22:200-7.

De Nardi M, La Torre A, Barassi A, Ricci C, Banfi G. [Effects of cold-water immersion and contrast-water therapy after training in young soccer players](#). J Sports Med Phys Fitness 2011;51:609-15.

McVeigh JG, McGaughey H, Hall M, Kane P. [The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: A systematic review](#). Rheumatol Int 2008;29:119-30.

Yurtkuran M, Yurtkuran M, Alp A, Nasircilar A, Bingöl U, Altan L, *et al.* [Balneotherapy and tap water therapy in the treatment of knee osteoarthritis](#). Rheumatol Int 2006;27:19-27.

Altan L, Bingöl U, Aslan M, Yurtkuran M. [The effect of balneotherapy on patients with ankylosing spondylitis](#). Scand J Rheumatol 2006;35:283-9.

Oosterveld FG, Rasker JJ, Floors M, Landkroon R, van Rennes B, Zwijnenberg J, *et al.* [Infrared sauna in patients with rheumatoid arthritis and ankylosing spondylitis. A pilot study showing good tolerance, short-term improvement of pain and stiffness, and a trend towards long-term beneficial effects](#). Clin Rheumatol 2009;28:29-34.

Eversden L, Maggs F, Nightingale P, Jobanputra P. [A pragmatic randomised controlled trial of hydrotherapy and land exercises on overall well being and quality of life in rheumatoid arthritis.](#) *BMC Musculoskelet Disord* 2007;8:23.

Honda T, Kamioka H. [Curative and health enhancement effects of aquatic exercise: Evidence based on interventional studies.](#) *Open Access J Sports Med* 2012;3:27-34.

Silva LE, Valim V, Pessanha AP, Oliveira LM, Myamoto S, Jones A, *et al.* [Hydrotherapy versus conventional land-based exercise for the management of patients with osteoarthritis of the knee: A randomized clinical trial.](#) *Phys Ther* 2008;88:12-21.

Xu XS, Lin WP, Chen JY, Yu LC, Huang ZH. [Efficacy observation on rear thigh muscles strain of athletes treated with surrounding needling of electroacupuncture and hot compress of Chinese medicine.](#) *Zhongguo Zhen Jiu* 2012;32:511-4.

Da Silva FM, de Oliveira SM, Nobre MR. [A randomised controlled trial evaluating the effect of immersion bath on labour pain.](#) *Midwifery* 2009;25:286-94.

Brenner IK, Castellani JW, Gabaree C, Young AJ, Zamecnik J, Shephard RJ, *et al.* [Immune changes in humans during cold exposure: Effects of prior heating and exercise.](#) *J Appl Physiol* 1999;87:699-710.

Shevchuk NA, Radoja S. [Possible stimulation of anti-tumor immunity using repeated cold stress: A hypothesis.](#) *Infect Agent Cancer* 2007;2:20.

Sugahara K, Eguchi M. [The use of warmed water treatment to induce protective immunity against the bacterial cold-water disease pathogen *Flavobacterium psychrophilum* in ayu \(*Plecoglossus altivelis*\).](#) *Fish Shellfish Immunol* 2012;32:489-93.

KauppinenK, Pajari-Backas M, Volin P, Vakkuri O. [Some endocrine responses to sauna, shower and ice water immersion.](#) *Arctic Med Res* 1989;48:131-9.

Mughal MA, Alvi IA, Akhund IA, Ansari AK. The effects of aerobic exercise training on resting blood pressure in hypertensive patients. *J Pak Med Assoc* vol. 51(6): pp. 222-226; June 2001

Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. *Med Sci Sports Exerc* vol. 33(6 Suppl): pp. S484-494; June 2001

Halbert JA, Silagy CA, Finucane P et al The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomized controlled trials of 4 week or longer. *J Hum Hypertens* vol. 11(10): pp. 641-649; October 1997

Fagard RH. The role of exercise in blood pressure control: supportive evidence. *J Hypertens* vol. 13(11): pp. 1223-1227; November 1995

Fagard RH. Physical activity in the prevention and treatment of hypertension in the obese. *Med Sci Sports Exerc* vol. 31(11 Suppl): pp. S624-630; November 1999

Petrella RJ How effective is physical training for the treatment of hypertension?

J Clin Sport Med vol. 8(3): pp. 224-231; July 1998

h) Peirce NS Diabetes and exercise. *Br J Sports Med* vol. 33(3): pp. 161-172; 1999

i) Borghouts LB, Keizer HA Exercise and insulin sensitivity: a review.

Int J Sports Med vol. 21(1): pp. 1-12; January 2000

j) Koivisto VA, Yki-Jarvinen H, DeFronzo RA Physical training and insulin sensitivity.

Diabetes Med vol. 1(4): pp. 445-481

k) DeFronzo RA, Ferrannini E, Sato Y, Felig P, Wahren J Synergistic interaction between exercise and insulin on peripheral glucose. *J Clin Invest* vol. 68(6): pp. 1468-1474; December 1981

l) Helmrich SP, Ragland DR, Paffenbarger RS Prevention of non-insulin-dependent diabetes mellitus with physical activity. *Med Sci Sports Exerc* vol. 26(7): pp. 824-830; 1994

m) McInnis KJ Exercise and obesity. *Coron Art Dis* vol. 11: pp. 111-116; 2000

n) Ericksson BE, Tyni-Lenne R, Svedenhag J et al Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X.

J Am Coll Cardiol vol. 36(5): pp. 1619-1625; November 2000

o) Leaf DA, Goldhaber J Effects of physical exercise training in syndrome x.

Clin Cardiol vol. 16(1): pp. 65-66; January 1993

p) Hubinger LM, Mackinnon LT The acute effect of moderate exercise on high density lipoprotein cholesterol in untrained middle-aged men.

Eur J Appl Physiol Occup Physiol vol. 65(6): pp. 555-560; 1992

q) Tolfrey K, Jones AM, Campbell IG The effect of aerobic exercise training on the lipid-lipoprotein profile of children and adolescents. *Sports Med* vol. 29(2): pp. 99-112; February 2000

r) Coats AJS, Adamopoulos S, Meyer TE, Conway J, Sleight P Effects of physical training in chronic heart failure. *Lancet* vol. 335; pp. 63-66; 1990

s) Coats AJS, Adamopoulos S, Radaelli A et al Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* vol. 85: pp. 2119-2131; June 1992

t) Uren NG, Lipkin DP Exercise training as therapy for chronic heart failure.

- Br Heart J* vol. 67: pp. 430-433; 1992
- u) Tavazzi L, Mortara A Exercise training and the autonomic nervous system in chronic heart failure. *Eur Heart J* vol. 16: pp. 1308-1310; 1995
- v) Sullivan MJ, Higginbotham MB, Cobb FR Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. *Circulation* vol. 78: pp. 506-515; 1988
- w) O'Connor GT, Buring JE, Yusuf S et al An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* vol. 80(2): pp. 234-244; August 1989
- x) Mayer-Davis EJ, D'Agostino R, Karter AJ et al Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* vol. 279(9): pp. 669-674; March 1998
- y) Stratton R, Wilson DP, Endres RK, Goldstein DE Improved glycemic control after supervised 8-wk exercise program in insulin-dependent diabetic adolescents. *Diabetes Care* vol. 19(5): pp. 589-593; Sept-Oct 1987
- z) Amano M, Kanda T, Moritani T et al Exercise training and autonomic nervous system activity in obese individuals. *Med Sci Sports Exerc* vol. 33(8): pp. 1287-1291; August 2001
- aa) Pagani M, Somers V, Furlan R Changes in autonomic regulation induced by physical training in mild hypertension. *Hypertension* vol. 12: pp. 600-610; 1988
- bb) Kiilavuori K, Toivonen L, Näveri H, Leinonen H Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. *Eur Heart J* vol. 16: pp. 490-495; 1995
- cc) Stahle A, Nordlander R, Bergfeldt L Aerobic group training improves exercise capacity and heart rate variability in elderly patients with a recent coronary event. *Eur Heart J* vol. 20(22): pp. 1638-1646; November 1999
- dd) Deligiannis A, Kouidi E, Tourkantonis A Effects of physical training on heart rate variability in patients on hemodialysis. *Am J Cardiol* vol. 84(2): pp. 197-202; 1999
- ee) Coats AJ, Conway J, Isea JE et al Systemic and forearm vascular resistance changes after upright bicycle exercise in man. *J Physiol* vol. 413: pp. 289-298; June 1989
- ff) Pratley RE, Hagberg JM, Dengel DR et al Aerobic exercise training-induced reductions in abdominal fat and glucose-stimulated insulin responses in middle-aged and older men. *J Am Geriatr Soc* vol. 48(9): pp. 1055-1061; September 2000
- gg) Sullivan MJ, Higginbotham MB, Cobb FR Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation* vol. 79(2): pp. 324-329; February 1989
- hh) Blumenthal JA, Emery CF, Madden DJ et al Effects of exercise training on cardiorespiratory function in men and women older than 60 years of age. *Am J Cardiol* vol. 67(7): pp. 633-639; 15 March 1991
- ii) Gielen S, Schuler G, Hambrecht R Exercise training in coronary artery disease and coronary vasomotion. *Circulation* vol. 103(1): pp. E1-6; 2 Jan 2002
- jj) Lakka TA, Laukkanen JA, Rauramaa R et al Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann Intern Med* vol. 134(1): pp. 12-20; 2 January 2001
- kk) Akashi YJ, Koike A, Osada N et al Short-term physical training improves vasodilatory capacity in cardiac patients. *Jpn Heart J* vol. 43: pp. 13-24; 2002
- ll) Hambrecht R, Fiehn E, Weigl C et al Regular physical exercise corrects endothelial

- dysfunction and improves exercise capacity in patients with chronic heart failure.
Circulation vol. 98(24): pp. 2709-2715; 15 December 1998
- mm) Hambrecht R, Wolf A, Gielen S et al Effect of exercise on coronary endothelial function in patients with coronary artery disease. *NEJM* vol. 342: pp. 454-460; 17 February 2000
- nn) Niebauer J, Schuler G The anti-atherogenic mechanism of action of physical training in patients with coronary artery disease. *Z Kardiol* vol. 90(11): pp. 799-806; 2001
- oo) Niebauer J, Hambrecht R, Velich T et al Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. *Circulation* vol. 96(8): pp. 2534-2541; 21 Oct 1997
- pp) Franklin BA, Kahn JK Delayed progression or regression of coronary atherosclerosis with intensive risk factor modification. Effect of diet, drugs, and exercise. *Sports Med* vol. 22(5): pp. 306-320; November 1996
- 19)a) Ray CA, Mark AL Augmentation of muscle sympathetic nerve activity during fatiguing isometric leg exercise. *J Appl Physiol* vol. 75(1): pp. 228-232; 1993
- b) Ray CA, Gracey KH Augmentation of exercise-induced muscle sympathetic nerve activity during muscle heating. *J Appl Physiol* vol. 82(6): pp. 1719-1725; 1997
- c) Saito M, Tsukanaka A, Yanagihara D, Mano T Muscle sympathetic nerve response to graded leg cycling. *J Appl Physiol* vol. 75(2): pp. 663-667; August 1993
- d) Seals DR Sympathetic neural discharge and vascular resistance during exercise in humans. *J Appl Physiol* vol. 66(5): pp.2472_2478; May 1989
- e) Saito M, Watanabe H, Mano T Comparison of muscle sympathetic nerve activity during exercise in dominant and nondominant forearm. *Eur J Appl Physiol Occup Physiol* vol. 66(2): pp. 108-115; 1993
- f) Ray CA Muscle sympathetic nerve responses to prolonged one-legged exercise. *J Appl Physiol* vol. 74(4): pp. 1719-1722; April 1993
- g) Steele SI, Ray CA Comparison of sympathetic nerve responses to neck and forearm isometric exercise. *Med Sci Sports Exerc* vol. 32(6): pp. 1109-1113; June 2000
- h) Saito M, Sone R, Ikeda M, Mano T Sympathetic outflow to the skeletal muscle in humans during prolonged light exercise. *J Appl Physiol* vol. 82(4): pp. 1237-1243; April 1997
- i) Victor RG, Seals DR, Mark AL Differential control of heart rate and sympathetic nerve activity during dynamic exercise. Insight from intraneural recordings in humans. *J Clin Invest* vol. 79(2): pp. 508-516; February 1987
- j) Fadel PJ, Ogoh S, Watenpaugh DE et al Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans. *Am J Physiol* vol. 280(3): pp. H1383-1390
- k) Ray CA, Hume KM, Gracey KH, Mahoney ET Muscle cooling delays activation of the metaboreflex in humans. *Am J Physiol* vol. 273(5 Pt 2): pp. H2436-2441; 1997
- 20) Sheriff DD, Rowell LB, Scher AM Is rapid rise in vascular conductance at onset of dynamic exercise due to muscle pump? *Am J Physiol* vol. 265(34): pp. H1227-1234; 1992
- 21)a) Johnson JM Exercise and the cutaneous circulation. *Exerc Sport Sci Rev*

vol. 20: pp. 59-97; 1992

b) Kenney WL, Johnson JM Control of skin blood flow during exercise.

Med Sci Sports Exerc vol. 24(3): pp. 303-312; 1992

c) Wyss CR, Brengelmann GL, Johnson JM et al Control of skin blood flow, sweating, and heart rate: role of skin vs. core temperature.

J Appl Physiol vol. 36(3): pp. 726-733; June 1974

d) Rowell LB, Murray JA, Brengelmann GL, Kraning KK Human cardiovascular adjustments to rapid changes in skin temperature during exercise.

Circ Res vol. XXIV: pp. 711-724; May 1969

e) Wyss CR, Brengelmann GL, Johnson JM et al Altered control of skin blood flow at high skin and core temperatures.

J Appl Physiol vol. 38(5): pp. 839-845; May 1975

f) Johnson JM, O'Leary DS, Taylor WF, Park MK Reflex regulation of sweat rate by skin temperature in exercising humans.

J Appl Physiol vol. 56(5): pp. 1283-1288; 1984

g) Taylor WF, Johnson JM, O'Leary DS, Park MK Modification of the cutaneous vascular response to exercise by local skin temperature.

J Appl Physiol vol. 57(6): pp. 1878-1884; 1984

h) Johnson JM, Niederberger M, Rowell LB et al Competition between cutaneous vasodilator and vasoconstrictor reflexes in man.

J Appl Physiol vol. 35(6): pp. 798-803; December 1973

i) Brengelmann GL, Wyss C, Rowell LB Control of forearm skin blood flow during periods of steadily increasing skin temperature.

J Appl Physiol vol. 35(1): pp. 77-84; 1973

j) Rowell LB, Brengelmann GL, Detry J-M, Wyss C Venomotor responses to rapid changes in skin temperature in exercising man.

J Appl Physiol vol. 30(1): pp. 64-71; 1971

k) Rowell LB, Brengelmann GL, Detry J-M, Wyss C Venomotor responses to local and remote thermal stimuli to skin in exercising man.

J Appl Physiol vol. 30(1): pp. 72-77; January 1971

l) Nishiyasu T, Shi X, Gillen CM, Mack GW, Nadel ER Comparison of the forearm and calf blood flow response to thermal stress during dynamic exercise.

Med Sci Sports Exerc vol. 24(2): pp. 213-217; 1992

22)a) Brandao MU, Wajngarten M, Rondon E et al Left ventricular function during dynamic exercise in untrained and moderately trained subjects.

J Appl Physiol vol. 75(5): pp. 1989-1995; November 1993

b) Nixon JV, Wright AR, Porter TR, Roy V, Arrowood JA Effects of exercise on left ventricular diastolic performance in trained athletes.

Am J Cardiol vol. 68(9): pp. 945-949; October 1991

c) Di Bello V, Santoro G, Talarico L et al Left ventricular function during exercise in athletes and in sedentary men.

Med Sci Sports Exerc vol. 28(2): pp. 190-196; 1996

d) Huonker M, Konig D, Keul J Assessment of left ventricular dimensions and functions in athletes and sedentary subjects at rest and during exercise using echocardiography.

Doppler sonography and radionuclide ventriculography.

Int J Sports Med vol. 17(Suppl 3): pp. S173-179; November 1996

e) Matsuda M, Sugishita Y, Koseki S et al Effect of exercise on left ventricular diastolic filling in athletes and nonathletes.

J Appl Physiol vol. 55(2): pp. 323-328; August 1983

f) Fagard R, Van den Broeke C, Amery A left ventricular dynamics during exercise in

- elite marathon runners. *Am J Cardiol* vol. 14(1): pp. 112-118; July 1989
- g) Fagard R, Van den Broeke C, Vanhees L et al Noninvasive assessment of systolic and diastolic left ventricular function in female runners. *Eur Heart J* vol. 8(12): pp. 1305-1311; December 1987
- h) Ogawa T, Spina RJ, Martin WH et al Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* vol. 86(2): pp. 494-503; 1992
- 23) *Sports Physiology* In: *Textbook of Medical Physiology* eds. Arthur C. Guyton and John E. Hall Tenth Edition publ. W. B. Saunders Company 2000; pp. 968-978
- 24)a) Halliwill JR, Taylor JA, Eckberg DL Impaired sympathetic vascular regulation in humans after acute dynamic exercise. *J Physiol* vol. 495.1: pp. 279-288; 1996
- b) Halliwill JR, Taylor JA, Hartwig TD, Eckberg DL Augmented baroreflex heart rate gain after moderate-intensity, dynamic exercise. *Am J Physiol* vol. 270(39): pp. R420-426; 1996
- c) Kenny GP, Chen AA, Nurbakhsh BA et al Moderate exercise increases postexercise thresholds for vasoconstriction and shivering. *J Appl Physiol* vol. 85(4): pp. 1357-1361; October 1998
- d) Ray CA, Carrasco DI Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. *Am J Physiol* vol. 279(1): H245-249; July 2000
- e) Smith ML, Hudson DL, Graitzer HM, Raven PB Exercise training bradycardia: the role of autonomic balance. *Med Sci Sports Exerc* vol. 21(1): pp. 40-44; Feb 1989
- f) Ekblom R, Kilbom A, Soltysiak J Physical training, bradycardia, and autonomic nervous system. *Scand J Clin Lab Invest* vol. 32(3): pp. 251-256; Nov 1973
- g) Maciel BC, Gallo Junior L, Marin Neto JA et al Parasympathetic contribution to bradycardia induced by endurance training in man. *Cardiovasc Res* vol. 19(10): pp. 642-648; October 1985
- h) Abete P, Calabrese C, Ferrara N et al Exercise restores ischemic preconditioning in the aging heart. *J Am Coll Cardiol* vol. 36(2): pp. 643-650; August 2000
- i) Borghouts LB, Keizer HA Exercise and insulin sensitivity: a review. *Int J Sports Med* vol. 21(1): pp. 1-12; January 2000
- j) Goodyear LJ, Kahn BR Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med* vol. 49: pp. 235-261; 1998
- k) Hambrecht R, Wolf A, Gielen S et al Effect of exercise on coronary endothelial function in patients with coronary artery disease. *NEJM* vol. 342(7): pp. 454-460; 17 February 2000
- l) Oya M, Itoh H, Kato K, Tanabe K, Murayama M Effects of exercise training on the recovery of the autonomic nervous system and exercise capacity after myocardial infarction. *Jpn Circ J* vol. 63: pp. 843-848; 1999
- m) Nakamura Y, Yamamoto Y, Muraoka I Autonomic control of heart rate during physical exercise and fractal dimension of heart rate variability. *J Appl Physiol* vol. 74(2): pp. 875-881; 1993
- n) Breuer H-WM, Skyschally A, Schulz R et al heart rate variability and circulating catecholamine concentrations during steady state exercise in healthy volunteers. *Br Heart J* vol. 70: pp. 144-149; 1993

- o) Kamath MV, Fallen EL, McKelvie R Effects of steady state exercise on the power spectrum of heart rate variability. *Med Sci Sports Exerc* vol. 23(4): pp. 428-434; 1991
- q) Mackinnon LT, Hooper SL, Jones S et al Hormonal, immunological, and hematological responses to intensified training in elite swimmers. *Med Sci Sports Exerc* vol. 29(12): pp. 1637-1645; Dec 1997
- r) Atkinson G, Drust B, Reilly T, Waterhouse J The relevance of melatonin to sports medicine and exercise. *Sports Med* vol. 33(11): pp. 809-831; 2003
- s) Buxton OM, L'Hermite-Baleriaux M, Hirschfeld U et al Acute and delayed effects of exercise on human melatonin secretion. *J Biol Rhythms* vol. 12(6): pp. 568-574; 1997
- t) Strassman RJ, Appenzeller O, Lewy AJ et al Increase in plasma melatonin, beta-endorphin, and cortisol after a 28.5-mile mountain race: relationship to performance and lack of effect of naltrexone. *J Endocrinol Metab* vol. 69(3): pp. 540-545; Sept 1989
- u) Kraemer RR, Blair S, Kraemer GR et al Effects of treadmill running on plasma beta-endorphin, corticotropin, and cortisol levels in male and female 10K runners. *Eur J Appl Physiol Occup Physiol* vol. 58(8): pp. 845-851; 1989
- v) Theron JJ, Oosthuizen JM, Rautenbach MM Effect of physical exercise on plasma melatonin levels in normal volunteers. *S Afr Med J* vol. 66(22): pp. 838-841; 1984
- w) Skrinar GS, Bullen BA, Reppert SM et al Melatonin response to exercise training in women. *J Pineal Res* vol. 7(2): pp. 185-194; 1989
- x) Nash MS Exercise and immunology. *Med Sci Sports Exerc* vol. 26(2): pp. 125-127; February 1994
- y) Pedersen BK, Ullum H NK cell response to physical activity: possible mechanisms of action. *Med Sci Sports Exerc* vol. 26(2): pp. 140-146; February 1994
- z) La Perriere A, Ironson G, Antoni MH et al Exercise and psychoneuroimmunology. *Med Sci Sports Exerc* vol. 26(2): pp. 182-190; February 1994
- aa) Nieman DC, Pedersen BK Exercise and immune function. Recent developments. *Sports Med* vol. 27(2): pp. 73-80; February 1999
- bb) Pyne DB, Gleeson M Effects of intensive exercise training on immunity in athletes. *Int J Sports Med* vol. 19(Suppl. 3): pp. S183-191; July 1998
- 25)a) Segal KR, Gutin B Thermic effects of food and exercise in lean and obese women. *Metabolism* vol. 32(6): pp. 581-589; June 1983
- b) Segal KR, Gutin B, Albu J, Pi-Sunyer FX Thermic effects of food and exercise in lean and obese men of similar lean body mass. *Am J Physiol* vol. 252(15) pp. E110-E117; 1987
- c) Segal KR, Blando L, Ginsberg-Fellner F, Edaño A Postprandial thermogenesis at rest and postexercise before and after physical training in lean, obese, and mildly diabetic men. *Metabolism* vol. 41(8): pp. 868-878; August 1992
- d) Davis JM, Sargent RG, Brayboy TD, Bartoli WP Thermogenic effects of pre-prandial and postprandial exercise in obese females. *Addict Behav* vol. 17(2): pp. 185-190; 1992
- e) Glesson M, Brown JF, Waring JJ, Stock MJ The effects of physical exercise on metabolic rate and dietary-induced thermogenesis. *Br J Nutr* vol. 47(2): pp. 173-181; March 1982
- f) Nielsen B, Astrup A, Samuelson P, Wengholt H, Christensen NJ Effect of physical

- training on thermogenic responses to cold and ephedrine. *Int J Obes Relat Metab Disord* vol. 17(7): pp. 383-390; July 1993
- g) Savourey G, Bittel J Thermoregulatory changes in the cold induced by physical training in humans. *Eur J Appl Physiol Occup Physiol* vol. 78(5): pp. 379-384; October 1998
- h) Segal KR Exercise and thermogenesis in obesity. *Int J Obes Relat Metab Disord* vol. 19(Suppl 4): pp. S80-87; October 1995
- i) Galassetti P, Mann S, Tate D et al Effects of antecedent prolonged exercise on subsequent counterregulatory responses to hypoglycemia. *Am J Physiol* vol. 280(6): pp. E908-917; June 2001
- j) Stein PK, Ehsani AA, Domitrovitch PP et al Effect of exercise training on heart rate variability in healthy older adults. *Am Heart J* vol. 138: pp. 567-576; 1999
- k) Schuit AJ, Van Amelsvoort LGPM, Verheij TC et al Exercise training and heart rate variability in older people. *Med Sci Sports Exerc* vol. 31(6): pp. 816-821; 1999
- l) Montaurier MB, Pickering G, Ritz P et al Effects of 14 weeks of progressive endurance training on energy expenditure in elderly people. *Br J Nutr* vol. 80(6): pp. 511-519; December 1998
- m) Jensen-Urstad K, Bouvier F, Jensen-Urstad M Preserved vascular reactivity in elderly male athletes. *Scand J Med Sci Sports* vol. 9(2): pp. 88-91; April 1999
- n) Krieger EM, Da Silva GJ, Negrao CE Effects of exercise training on baroreflex control of the cardiovascular system. *Ann NY Acad Sci* vol. 940: pp. 338-347; 2001
- o) DeSouza CA, Shapiro LF, Clevenger CM et al Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation* vol. 102: pp. 1351-1357; 2000
- p) Spina RJ, Ogawa T, Martin WH et al Exercise training prevents decline in stroke volume during exercise in young healthy subjects. *J Appl Physiol* vol. 72(6): pp. 2458-2462; June 1992
- q) Spina RJ, Ogawa T, Coggan AR et al Exercise training improves left ventricular contractile response to beta-adrenergic agonist. *J Appl Physiol* vol. 72(1): pp. 307-311; January 1992
- r) Levy WC, Cerqueira MD, Harp GD Effect of endurance exercise training on heart rate variability at rest in healthy young and older men. *Am J Cardiol* vol. 82: pp. 1236-1241; 1998
- s) Furlan R, Piazza S, Dell'Orto S et al Early and late effects of exercise and athletic training on neural mechanisms controlling heart rate. *Cardiovasc Res* vol. 27: pp. 482-488; 1993
- t) DeMeersman RE Heart rate variability and aerobic fitness. *Am Heart J* vol. 125: pp. 725-730; 1993
- u) Ohuchi H, Suzuki H, Yasuda K et al Heart rate recovery after exercise and cardiac autonomic nervous activity in children. *Ped Res* vol. 47(3): pp. 329-335; 2000
- v) Perini R, Orizio C, Baselli G, Cerutti S, Veicsteinas A The influence of exercise on the power spectrum of heart rate variability. *Eur J Appl Physiol* vol. 61: pp. 143-148; 1990
- w) Yamamoto Y, Hughson RL, Peterson JC Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. *J Appl Physiol*

vol. 71(3): pp. 1136-1142; 1991

- 26) a) Meyer K, Samek L, Schwaibold M et al Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med Sci Sports Exerc* vol. 29(3): pp. 306-312; 1997
- b) Meyer K, Lehmann M, Sunder G, Keul J, Weidemann H Interval versus continuous exercise training after coronary bypass surgery: a comparison of training-induced acute reactions with respect to the effectiveness of the exercise methods. *Clin Cardiol* vol. 13(12): pp. 851-861; December 1990
- c) Capecchi PL, Pasini FL, Cati G et al Experimental model of short-time exercise-induced preconditioning in POAD patients. *Angiology* vol. 48(6): pp. 469-480; 1997
- d) Gardner AW Dissipation of claudication pain after walking: implications for endurance training. *Med Sci Sports Exerc* vol. 25(8): pp. 904-910; August 1993
- e) Coppoolse R, Schols AM, Baarends EM Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J* vol. 14(2): pp. 258-263; August 1999
- f) MacVicar MG, Winningham ML, Nickel JL Effects of aerobic interval training on cancer patients' functional capacity. *Nursing Res* vol. 38(6): pp. 348-351; 1989
- g) Lindsay FH, Hawley JA, Myburgh KH Improved athletic performance in highly trained cyclists after interval training. *Med Sci Sports Exerc* vol. 28(11): pp. 1427-1434; 1996
- h) Babineau C, Léger L Physiological response of 5/1 intermittent aerobic exercise and its relationship to 5km endurance performance. *Int J Sports Med* vol. 18(1): pp. 13-19; 1997
- i) MacDougall D, Sale D Continuous vs. interval training: a review for the athlete and the coach. *Can J Appl Sport Sci* vol. 6(2): pp. 93-97; 1981
-
- 1) *A Commotion in the Blood*, Stephen S. Hall publ. Henry Holt & Co. New York 1997; pp. 21-127
- 2) *ibid.*, pp. 30-42
-
- 3) "The Failure of the Erysipelas Toxins" *JAMA* vol. 23(24): pg. 919; 15 December 1894
-
- 4) a) Murry CE, Jennings RB, Reimer KA, Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* vol. 74(5): pp. 1124-1136; 1986
-
- 5) a) Meldrum D Mechanisms of Cardiac Preconditioning: Ten Years after the Discovery of Ischemic Preconditioning *J Surg Research* vol. 73: pp. 1-13; 1997
- b) Yellon DM, Baxter GF Protecting the ischemic and reperfused myocardium in acute

- myocardial infarction: distant dream or near reality? *Heart* vol. 83(4): pp. 381-387; April 2000
- c) Tomai F, Crea F, Chiariello L, Gioffre PA Ischemic preconditioning in humans: models, mediators, and clinical relevance. *Circulation* vol. 100(5): pp. 559-563; August 1999
- d) Ferrari R, Ceconi C, Curello S, Percoco G, Toselli T, Antonioli G Ischemic preconditioning, myocardial stunning, and hibernation: basic aspects. *Am Heart J* vol. 138(2 Pt 2): pp. 61-68; August 1999
- e) de Zeeuw S, Van den Doel MA, Duncker DJ, Verdouw PD New insights into cardioprotection by ischemic preconditioning and other forms of stress. *Ann NY Acad Sci* vol. 874: pp. 178-191; June 1999
- f) Li G, Vasquez JA, Gallagher KP, Lucchesi BR. Myocardial Protection with Preconditioning. *Circulation* vol. 82: pp. 609-619; 1990
- g) Matsuda M, Catena TG, Vander Heide RS, Jennings RB, Reimer KA. Cardiac protection by ischemic preconditioning is not mediated by myocardial stunning *Cardiovasc Res* vol. 27: pp. 585-592; 1993
- h) Dekker L. Toward the heart of ischemic preconditioning. *Cardiovasc Res* vol. 37: pp. 14-20: 1998
- i) Ikonomidis JS, Tumiati LC, Weisel RD, Mickle DAG, Li RK. Preconditioning human ventricular cardiomyocytes with brief periods of simulated ischemia. *Cardiovasc Res* vol. 28: pp. 1285-1291; 1994
- j) Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. *Lancet* vol. 342: pp. 276-277; 1993
- k) Yellon DM, Pasini E, Cargnoni A, Marber MS, Latchman DS, Ferrari R The protective role of heat stress in the ischemic and reperfused rabbit myocardium. *J Moll Cell Cardiol* vol. 24: pp. 895-907; 1992
- l) Walker DM, Pasini E, Kocukoglu S et al Heat stress limits infarct size in the isolated perfused rabbit heart. *Cardiovasc Res* vol. 27: pp. 962-967; 1993
- o) Miura T, Adachi T, Ogawa T, Iwamoto T, Tsuchida A, Imura O. Myocardial infarct size-limiting effect of ischemic preconditioning: Its natural decay and the effect of repetitive preconditioning. *Cardiovasc Pathol* vol. 1: pp. 147-154; 1992
- m) Kuzuya T, Hoshida S, Yamashita N, Fuji H, Oe H, Hori M, Kamada T, Tada M. Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. *Circ Res* vol. 72: pp. 1293-1299; 1993
- n) Hoshida S, Kuzuya T, Fuji H et al Sublethal ischemia alters myocardial antioxidant activity in canine heart. *Am J Physiol* vol. 264 (*Heart Circ. Physiol* .33): pp. H33-H39; 1993
- o) Ito H, Shimojo T, Fujisaki H et al Thermal preconditioning protects rat cardiac muscle cells from doxorubicin-induced apoptosis. *Life Sci* vol. 64(9): pp. 755-761; 1999
- p) Novalija E, Fujita S, Kampine JP, Stowe DF Sevoflurane mimics ischemic preconditioning effects on coronary flow and nitric oxide release in isolated hearts. *Anesthesiology* vol. 91(3): pp. 701-712; September 1999
- q) Ferrari R, Ceconi C, Curello S et al Ischemic preconditioning, myocardial stunning, and hibernation: basic concepts. *Am Heart J* vol. 138(2 Pt 2): pp. S62-S68; Aug 1998
- r) Leier CV, Huss P, Lewis RP, Unverferth DV Drug-induced conditioning in congestive heart failure. *Circulation* vol. 65(7): pp. 1382-1387; 1982

- s) Bilinska M, Rudnicki S, Beresewicz A Delayed attenuation of myocardial ischemia with repeated exercise in subjects with stable angina: a possible model for the second window of protection? *Basic Res Cardiol* vol. 95(5): pp. 418-423; October 2000
- t) Walker RD, Nawaz S, Wilkinson CH et al Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances with intermittent claudication. *J Vasc Surg* vol. 31(4): pp. 662-669; April 2000
- u) Remijnse-Tamerius HC, Duprez D, De Buyzere M et al Why is training effective in the treatment of patients with intermittent claudication? *Int Angiol* vol. 18(2): pp. 103-112; June 1999
- v) Gibellini R, Fanello M, Bardile AF, Salerno M, Aloï T Exercise training in intermittent claudication. *Int Angiol* vol. 19(1): pp. 8-13; March 2000
- w) Zdrenghen D, Ilea M, Predescu D, Potang E Ischemic preconditioning during successive exercise testing. *Rom J Int Med* vol. 36(3-4): pp. 161-165. 1998
- 6) a) Domenech RJ, Macho P, Vélez D et al Tachycardia preconditions infarct size in dogs. Role of adenosine and protein kinase c. *Circulation* vol. 97:pp. 786-794; 1998
- b) Szekeres L, Papp JG, Szilvássy Z, Udvary E, Vegh A Moderate stress by cardiac pacing may produce both short term and long term cardioprotection. *Cardiovasc Res* vol. 27: pp. 593-596; 1993
- 7) a) Yellon DM, Baxter GF, A "Second Window of Protection" or Delayed Preconditioning Phenomenon: Future Horizons for Myocardial Protection? *J Mol Cell Cardiol* vol. 27: pp. 1023-1043; 1995
- b) Ghosh S, Standen NB, Galinanes M Preconditioning the human myocardium by simulated ischemia: studies on the early and delayed protection. *Cardiovasc Res* vol. 45(2): pp. 339-350; January 2000
- c) Noda T, Minatoguchi S, Fujii K, Hori M et al Evidence for the delayed effect in human ischemic preconditioning: prospective multicenter study for preconditioning in acute myocardial infarction. *J Am Coll Cardiol* vol. 34(7): pp. 1966-1974; Dec 1999
- d) Marber MS, Latchman DS, Walker JM, Yellon DM. Cardiac stress protein elevation 24 hours following brief ischemia or heat stress is associated with resistance to myocardial infarction. *Circulation* vol. 88: pp. 1264-1272; 1993
- e) Bolli R The late phase of preconditioning. *Clin Res* vol. 87(11): pp. 972-983; 24 November 2000
- 8) a) Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Remote Ischemic 'Preconditioning' Protects Remote Virgin Myocardium From Subsequent Sustained Coronary Occlusion. *Circulation* vol. 87: pp. 893-899; 1993
- b) Gho BCG, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial Protection by Brief Ischemia in Noncardiac Tissue. *Circulation* vol. 94: pp. 2193-2200; 1996
- 9) a) Stagliano NE, Perez-Pinzon MA, Moskowitz MA, Huang PL Focal ischemic preconditioning induces rapid tolerance to middle cerebral artery occlusion in mice. *J Cereb Blood Flow Metab* vol. 19(7): pp. 757-761; July 1999

- b) Perez-Pinzon MA, Alonso O, Kraydieh S, Dietrich WD Induction of tolerance against traumatic brain injury by ischemic preconditioning. *Neuroreport* vol. 10(14): pp. 2951-2954; 29 September 1999
- c) Chen J, Simon R Ischemic tolerance in the brain. *Neurology* vol. 48: pp. 306-311; February 1997
- d) Peralta C, Prats N, Xaus C, Gelpi E, Rosello-Catafau J Protective effect of liver ischemic preconditioning on liver and lung injury induced by hepatic ischemia-reperfusion in the rat. *Hepatology* vol. 30(6): pp. 1481-1489; December 1999
- e) Toosy N, McMorris EL, Grace PA, Mathie RT Ischaemic preconditioning protects the rat kidney from reperfusion injury. *BJU Int* vol. 84(4): pp. 489-494; September 1999
- f) Okamura T, Miura T, Iwamoto H et al Ischemic preconditioning attenuates apoptosis through protein kinase C in rat hearts. *Am J Physiol* vol. 277(5 Pt 2): pp. H1997-2001; November 1999
- g) Dickson EW, Reinhardt CP, Renzi FP et al Ischemic preconditioning may be transferrable via whole blood transfusion: preliminary evidence. *J Thrombosis Thrombolysis* vol. 8: pp. 123-129; 1999
- h) Dickson EW, Lorbar M, Porcaro WA et al Rabbit heart can be "preconditioned" via transfer of coronary effluent. *Am J Physiol* vol. 277(6 Pt 2): pp. H2451-2457 December 1999
- i) Dickson EW, Porcaro WA, Fenton RA "Preconditioning at a distance" in the isolated rabbit heart. *Acad Emerg Med* vol. 7(4): pp. 311-317; April 2000
- 10) a) Post H, Heusch G Ischemic preconditioning. Experimental facts and clinical perspective. *Minerva Cardioangiol* vol. 50(6): pp. 569-605; December 2002
- b) Bushell AJ, Klenerman L, Davies H et al Ischaemic preconditioning of skeletal muscle: Investigation of potential mechanisms involved. *J Bone Joint Surg* vol. 84(8): pp. 1189-1193; November 2002
- c) Mubagwa K, Flameng W Adenosine, adenosine receptors and myocardial protection: an updated overview. *Cardiovasc Res* vol. 52(1): pp. 25-39; October 2001
- d) Li W, Jia G, Guo W, Wang H Nitric oxide opens second window of protection in ischemic preconditioning via induction of heat-shock protein 72. *Chin Med J* vol. 116(2): pp. 258-262; February 2002
- 11) a) Akimitsu T, Gute DC, Korthuis RJ Ischemic preconditioning attenuates postischemic leukocyte adhesion and emigration. *Am J Physiol* vol. 271(5 Pt 2): pp. H2052-2059; November 1996
- b) Dammers R, Wehrens XHT, oude Egbrink MGA et al Microcirculatory effects of experimental acute limb ischemia-reperfusion. *Br J Surg* vol. 88: pp. 816-824; 2001
- c) Wang WZ, Anderson G, Maldonado C, Barker J Attenuation of vasospasm and capillary no-reflow by ischemic preconditioning in skeletal muscle. *Microsurgery* vol. 17: pp. 324-329; 1996
- d) Kinnunen I, Laurikainen E, Schrey A et al Effect of acute ischemic preconditioning on blood-flow response in the epigastric pedicled rat flap. *J Reconstr Microsurg* vol. 18(1): pp. 61-68; 2002
- e) Attkiss KJ, Suski M, Hunt TK, Buncke HJ Ischemic preconditioning of skeletal muscle

- improves tissue oxygenation during reperfusion. *J Reconstr Microsurg* vol. 15(3): pp. 223-228; April 1999
- f) Wang WZ, Tsai TM, Anderson GL Late-preconditioning protection is evident in the microcirculation of denervated skeletal muscle. *J Orthop Res* vol. 17(4): pp. 571-577; July 1999
- g) Küntscher MV, Kastell T, Sauerbier M et al Acute remote ischemic preconditioning on a rat cremasteric muscle flap model. *Microsurg* vol. 22(6): pp.221-226; 2002
- h) Banbury J, Siemionow M, Porvasnik S et al Muscle flaps triphasic response to sympathectomy and denervation. *Plast Reconstr Surg* vol. 104(3): pp. 730-737; September 1999
- i) Zahir TM, Zahir K, Syed SA et al Ischemic preconditioning of musculocutaneous flaps: effects of ischemia cycle length and number of cycles. *Ann Plast Surg* vol. 40: pp. 430-435; 1998
- j) Hoffmeister HM, Strobele M, Bassler A et al Preconditioning preserves energy metabolism in prolonged low-flow ischemia. *Basic Res Cardiol* vol. 93(6): pp: 487-496; December 1998
- k) Tanoue Y, Herijgers P, Meuris B et al Ischemic preconditioning reduces unloaded myocardial oxygen consumption in an in-vivo sheep model. *Cardiovasc Res* vol. 55(3): pp. 633-641; August 2002

12) *Breast Cancer: Immunological Factors Affecting Incidence, Prognosis, and Survival*

Helen Coley Nauts publ. Cancer Research Institute, New York 1984; pp. 36-40

- 13) a) Grace PA Ischemia-reperfusion injury. *Br J Surg* vol. 81(5): pp. 637-647; 1994
- b) Zhao ZQ, Nakamura M, Wang NP et al Reperfusion induces myocardial apoptotic cell death. *Cardiovasc Res* vol. 45(3): pp. 651-660; February 2000
- c) Thiagarajan RR, Winn RK, Harlan JM The role of leukocyte and endothelial adhesion molecules in ischemia-reperfusion injury. *Thromb Haemost* vol. 78(1): pp, 310-314; July 1997
- d) Zhao ZQ, Velez DA, Wang NP et al Progressively developed myocardial apoptotic cell death during late phase of reperfusion. *Apoptosis* vol. 6(4): pp. 279-290; 2001
- e) Liu X, Peter FW, Barker JH et al Leukocyte-endothelium interaction in arterioles after ischemia and reperfusion. *J Surg Res* vol. 87(1): pp. 77-84; Nov 1999
- f) Granger DN, Kvietys PR, Perry MA Leukocyte-endothelial cell adhesion induced by ischemia and reperfusion. *Can J Physiol Pharmacol* vol. 71(1): pp. 67-75; 1993
- g) Maroszynska I, Fedor P Leukocytes and endothelium interaction as rate limiting step in the inflammatory response and a key factor in the ischemia-reperfusion injury. *Ann Transplant* vol. 5(4): pp. 5-11; 2000
- h) Anversa P, Cheng W, Liu Y et al Apoptosis and myocardial infarction. *Basic Res Cardiol* vol. 93(Suppl 3): pp. 8-12; 1998
- i) Scarabelli T, Stephanou A, Rayment N et al Apoptosis of endothelial cells precedes myocyte cell apoptosis in ischemia/reperfusion injury. *Circulation* vol. 104(3): pp. 253-256; July 2001
- j) Zhao ZQ, Vinten-Johansen J Myocardial apoptosis and ischemic preconditioning. *Cardiovasc Res* vol. 55(3): pp. 438-455; August 2002
- k) Sheridan FM, Dauber IM, McMurtry IF Role of leukocytes in coronary vascular

endothelial injury due to ischemia and reperfusion. *Circ Res* vol. 69(6):
pp. 1566-1574; December 1991

- 14) *FUO: Fever of Undetermined Origin* ed. Henry W. Murray, M.D.,
publ. Futura Publishing Co., 1983, pp. 9-13
- 15) *A History of Immunology*: Arthur M. Silverstein, publ. Academic Press Inc. San Diego;
1989; pp. 38-159
- 16) *Paul Ehrlich's Receptor Immunology: The Magnificent Obsession* Arthur M. Silverstein
publ. Academic Press, San Diego; 2002; pp. 81-85
- 17) *Milestones in Immunology: A Historical Exploration* Debra Jan Bibel publ.
Springer-Verlag, Berlin. 1988; pp. 7-12
- 18) *ibid.*, pp. 12-15
- 19) *Paul Ehrlich's Receptor Immunology*, pg. 17
- 20) *ibid.*, pg. 18
- 21) *ibid.*, pp. 55-94
- 22) *A History of Immunology*, pp. 87-159
- 23) *ibid.*, pg. 105
- 24) *ibid.*, pp. 107-112
- 25) *ibid.*, pp. 72-83
- 26) *Blood: Pure and Eloquent: A Story of Discovery, of People, and of Ideas*
Maxwell M. Wintrobe, publ. McGraw-Hill Book Co., 1980; pp. 97-138
- 27)a) Knekt P, Adlerkreutz H, Rissanen H et al Does antibacterial treatment for urinary tract
infection contribute to the risk of breast cancer? *Br J Cancer* vol. 82(5):
pp. 1107-1110; March 2000
b) Velicer CM, Lampe JW, Heckbert SR et al Hypothesis: is antibiotic use associated with
breast cancer? *Cancer Causes and Control* vol. 14: pp. 739-747; 2003
- 28) *Milestones in Immunology*, pp. 309-316

- 29)a) Pert CB The wisdom of the receptors: neuropeptides, the emotions, and bodymind.
Adv Mind Body Med vol. 18(1): pp. 30-35; Fall 2002
- b) Pert CB, Dreher HE, Ruff MR The psychosomatic network: foundations of body-mind medicine. *Altern Ther Health Med* vol. 4(4): pp. 30-41; July 1998
- c) Pert C Candace Pert: a molecular Jungian in search of the quantum experiment. Interview with Sheldon Lewis. *Adv Mind Body* vol. 18(1): pp. 36-40; Fall 2002
- d) Ader R, Cohen N Conditioning of the immune response. *Neth J Med* vol. 39(3-4): pp. 263-273; October 1991
- e) Homo-Delarche F, Dardenne M The neuroendocrine-immune axis. *Semin Immunopathol* vol. 14(3): pp. 221-238; 1993
- f) Maier SF, Watkins LR, Fleshner M Psychoneuroimmunology: The interface between behavior, brain, and immunity. *Am Psychol* vol. 49(12): pp. 1004-1017; Dec 1994
- g) Ballieux RE The mind and the immune system. *Theor Med* vol. 15(4): pp. 387-395; December 1994
- h) Brittain RW, Wiener NI Neural and Pavlovian influences on immunity. *Pavlov J Biol Sci* vol. 20(4): pp. 181-194; Oct-Dec 1985
- i) Ader R, Felten D, Cohen N Interactions between the brain and the immune system. *Annu Rev Pharmacol Toxicol* vol. 30: pp. 561-602; 1990
- j) Besedovsky HO, del Ray A Immune-neuroendocrine circuits: integrative role of cytokines. *Front Neuroendocrinol* vol. 13(1): pp. 61-94; January 1992
- k) Petrovsky N Towards a unified model of neuroendocrine-immune interactions. *Immunol Cell Biol* vol. 79(4): pp. 350-357; August 2001
- l) Solomon GF Psychoneuroimmunology: interactions between the central nervous system and immune system. *J Neurosci Res* vol. 18(1): pp. 1-9; 1987
- m) Webster JI, Tonelli L, Sternberg EM Neuroendocrine regulation of immunity. *Annu Review Immunol* vol. 20: pp. 125-163; 2002
- n) Ader R Conditioned immunomodulation: research needs and directions. *Brain Behav Immun* vol 17(Suppl 1): pp. S51-57; Feb 2003
- o) Bowler DF "It's all in your mind": The final common pathway. *Work* vol. 17(3): pp. 167-173; 2001
- p) Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom Med* vol. 64(1): pp. 15-28; Jan-Feb 2002
- q) Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annu Rev Psychol* vol. 53: pp. 83-107; 2002

30) *Psychoneuroendocrinology* eds, Robert Ader, David L. Felten, Nicholas Cohen
 publ. Academic Press, San Diego; 2nd edition, 1991; pp. 3-25, pp. 447-513

- 31)a) Chen CC, David AS, Nunnerley H et al Adverse life events and breast cancer: a case-control study. *BMJ* vol. 311(7019): pp. 1527-1530; December 1995
- b) Forsen A Psychosocial stress as a risk for breast cancer. *Psychother Psychosom* vol. 55(2-4): pp. 176-185; 1991
- c) Ginsberg A, Price S, Ingram D, Nottage E Life events and the risk of breast cancer.

Eur J Cancer vol. 32A(12): pp. 2049-2052; November 1996

d) Butow PN, Hiller JE, Price MA Epidemiological evidence for a relationship between life events, coping style, and personality factors in the development of breast cancer.

J Psychosom Res vol. 49(3): pp. 169-181; September 2000

e) Butler LD, Koopman C, Classen C, Spiegel D Traumatic stress, life events, and emotional support in women with metastatic breast cancer: cancer-related traumatic

stress symptoms associated with past and current stressors. *Health Psychol*

vol. 18(6): pp. 555-560; November 1999

f) Jacobs JR, Bovasso GB Early and chronic stress and their relation to breast cancer.

Psychol Med vol. 30(3): pp. 669-678; May 2000

g) Zisook S, Shuchter SR, Irwin M et al Bereavement, depression, and immune function.

Psychiatry Res vol. 52(1): pp. 1-10; April 1994

h) Spratt ML, Denney DR Immune variables, depression, and plasma cortisol over time in suddenly bereaved patients. *J Neuropsychiatry Clin Neurosci* vol. 3(3): pp. 299-306;

Summer 1991

i) Irwin M, Daniels M, Risch SC, Bloom E, Weiner H Plasma cortisol and natural killer cell activity during bereavement. *Biol Psychiatry* vol. 24(2): pp. 173-178; June 1988

j) Irwin M, Daniels M, Smith TL, Bloom E, Weiner H Impaired natural killer cell activity during bereavement. *Brain Behav Immun* vol. 1(1): pp. 98-104; March 1987

k) Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M Suppression of lymphocyte stimulation following bereavement. *JAMA* vol. 250(3): pp. 374-377; July 1983

32)a) Malone KE, Daling JR, Weiss NS Oral contraceptives in relation to breast cancer.

Epidemiol Rev vol. 15(1): pp. 80-97; 1993

b) Althaus FA, Kaeser L At the pill's 30th birthday, breast cancer question is unresolved.

Fam Plann Perspect vol. 22(4): pp. 173-176; July-Aug 1990

c) Paul C, Skegg DC, Spears GF Oral contraceptives and risk of breast cancer.

Int J Cancer vol. 46(3): pp. 366-373; September 1990

d) Rookus MA, van Leeuwen FE Oral contraceptives and risk of breast cancer in women aged 20-54 years. Netherlands Oral Contraceptives and Breast Cancer Study Group.

Lancet vol. 344(8926): pp. 844-851; September 1994

e) Brinton LA, Brogan DR, Coates RJ et al Breast cancer risk among women 55 years of age by joint effects of usage of oral contraceptives and hormone replacement therapy.

Menopause vol. 5(3): pp. 145-151; Fall 1998

f) White E, Malone KE, Weiss NS, Daling JR Breast cancer among U.S. women in relation to oral contraceptive use. *J Natl Cancer Inst* vol. 86(7): pp. 505-514; April 1994

g) Thomas DB Oral contraceptives and breast cancer: review of the epidemiological literature. *Contraception* vol. 43(6): pp. 597-642; June 1991

h) Brinton LA, Daling JR, Liff JM et al Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst* vol. 87(11): pp. 827-835; June 1995

33) Shakhar G, Bar-Ziv I, Ben-Eliyahu S Diurnal changes in lung tumor clearance and their relation to NK cell cytotoxicity in the blood and spleen. *Int J Cancer* vol. 94(3): pp. 401-406; November 2001

34)a) Nilsson N, Carlsten H Estrogen induces suppression of natural killer cell cytotoxicity

- and augmentation of polyclonal B cell activation. *Cell Immunol* vol. 58(1): pp. 131-139; October 1994
- b) Baker DA, Salvatore W, Milch PO Effect of low-dose oral contraceptives on natural killer cell activity. *Contraception* vol. 39(1): pp. 119-124; Jan 1989
- c) Forsberg JG Short-term and long-term effects of estrogen on lymphoid tissue and lymphoid cells with some remarks on the significance for carcinogenesis. *Arch Toxicol* vol. 55(2): pp. 79-90; July 1984
- d) Shakhar K, Shakhar G, Rosenne E, Ben-Eliyahu S Timing with the menstrual cycle, sex, and the use of oral contraceptives determine adrenergic suppression of NK cell activity. *Br J Cancer* vol. 83(12): pp. 1630-1636; December 2000
- e) Ben-Eliyahu S, Shakhar G, Shakhar K, Melamed R Timing within the oestrus cycle modulates adrenergic suppression of NK activity and resistance to metastasis: possible clinical implications. *Br J Cancer* vol. 83(12): pp. 1747-1754; December 2000
- f) Yovel G, Shakhar K, Ben-Eliyahu S The effects of sex, menstrual cycle, and oral contraceptives on the number and activity of natural killer cells. *Gynecol Oncol* vol. 81(2): pp. 254-262; May 2001
- g) Souza SS, Castro FA, Mendonca HC et al Influence of menstrual cycle on NK activity. *J Reprod Immunol* vol. 50(2): pp. 151-159; May 2001
- h) Trzonkowski P, Mysliwska J, Tukaszuk K et al Luteal phase of the menstrual cycle in young healthy women is associated with decline in interleukin 2 levels. *Horm Metab Res* vol. 33(6): pp. 348-353; June 2001
- i) Garland M, Doherty D, Golden-Mason L et al Stress-related hormonal suppression of natural killer activity does not show menstrual cycle variations: implications for timing of surgery for breast cancer. *Anticancer Res* vol. 23(3B): pp. 2531-2535; 2003
- 35)a) Reiter RJ, Calvo JR, Karbownik M et al Melatonin and its relation to the immune system and inflammation. *Ann NY Acad Sci* vol. 917: pp. 376-386; 2000
- b) Guerrero JM, Reiter RJ Melatonin-immune system relationships. *Curr Top Med Chem* vol. 2(2): pp. 167-179; February 2002
- c) Nelson RJ, Drazen DL Melatonin mediates seasonal adjustment in immune function. *Reprod Nutr Dev* vol. 39(3): pp. 383-398; May-June 1999
- 36)a) Ben-Eliyahu S, Shakhar G, Page GG et al Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors. *Neuroimmunomodulation* vol. 8(3): pp. 154-164; 2000
- b) Ben-Eliyahu S, Yirmiya R, Liebeskind JC et al Stress increases metastatic spread of a mammary gland tumor in rats: evidence for mediation by the immune system. *Brain Behav Immun* vol. 5(2): pp. 193-205; June 1991
- c) Ben-Eliyahu S, Page GG, Shakhar G, Taylor AN Increased susceptibility to metastasis during pro-oestrus/oestrus in rats: possible role of oestradiol and natural killer cells. *Br J Cancer* vol. 74(12): pp. 1900-1907; December 1996
- d) Shakhar G, Ben-Eliyahu S In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. *J Immunol* vol. 160(7): pp. 3251-3258; April 1998
- 37)a) Ben-Eliyahu S, Page GG, Yirmiya R, Shakhar G Evidence that stress and surgical

interventions promote tumor development by suppressing natural killer cell activity.

Int J Cancer vol. 80(6): pp. 880-888; March 1999

b) Yoshihara H, Tanaka N, Orita K Suppression of natural killer cell activity by surgical stress in cancer patients and the underlying mechanisms. *Acta Med Okayama* vol. 40(2): pp. 113-119; April 1986

c) Page GG, Ben-Eliyahu S Increased surgery-induced metastasis and suppressed natural killer cell activity during proestrus/estrus in rats. *Breast Cancer Res Treat* vol. 45(2): pp. 159-167; September 1997

d) Beitsch P, Lotsova E, Hortobagyi G, Pollock R Natural immunity in breast cancer patients during neoadjuvant chemotherapy and after surgery. *Surg Oncol* vol. 3(4): pp. 211-219; August 1994

e) Brenner BG, Margolese RG The relationship of chemotherapeutic and endocrine intervention on natural killer cell activity in human breast cancer. *Cancer* vol. 68(3): pp. 482-488; August 1991

38)a) Nerozzi D, Santoni A, Bersani G et al Reduced natural killer cell activity in major depression: neuroendocrine implications. *Psychoneuroendocrinology* vol. 14(4): pp. 295-301; 1989

b) Irwin M, Lacher U, Caldwell C Depression and reduced natural killer cytotoxicity: a longitudinal study of depressed patients and control subjects. *Psychol Med* vol. 22(4): pp. 1045-1050; November 1992

c) Irwin M, Patterson T, Smith TL et al Reduction of immune function in life stress and depression. *Biol Psychiatry* vol. 27(1): pp. 22-30; January 1990

d) Raison CL, Miller AH The neuroimmunology of stress and depression. *Semin Clin Neuropsychiatry* vol. 6(4): pp. 277-294; October 2001

e) Kiecolt-Glaser JK, Glaser R Depression and immune function: central pathways to morbidity and mortality. *J Psychosom Res* vol. 53(4): pp. 873-876; Oct 2002

f) Jozuka H, Jozuka E, Takeuchi S, Nishikaze O Comparison of immunological and endocrinological markers associated with major depression. *J Int Med Res* vol. 31(1): pp. 36-41; Jan-Feb 2003

g) Evans DL, Folds JD, Petitto JM et al Circulating natural killer cell phenotypes in men and women with major depression. Relation to cytotoxic activity and severity of depression. *Arch Gen Psychiatry* vol. 49(5): pp. 388-395; May 1992

39) Scanlan JM, Werner JJ, Legg RL, Laudenslager ML Natural killer cell activity is reduced in association with oral contraceptive use. *Psychoneuroendocrinology* vol. 20(3): pp. 281-287; 1995

40)a) Garner WL, Minton JP, James AG, Hoffmann CC Human breast cancer and impaired NK cell function. *J Surg Oncol* vol. 24(1): pp. 64-66; September 1983

b) Konjevic G, Spuzic I Stage dependence of NK cell activity and its modulation by interleukin 2 in patients with breast cancer. *Neoplasma* vol. 40(2): pp. 81-85; 1993

c) Konjevic G, Spuzic I Evaluation of different effects of sera of breast cancer patients on the activity of natural killer cells. *J Clin Lab Immunol* vol. 38(2): pp. 83-93; 1992

d) Brenner BG, Benarrosh S, Margolese RG Peripheral blood natural killer cell activity in human breast cancer patients and its modulation by T-cell growth factor and autologous

plasma. *Cancer* vol. 58(4): pp. 895-902; August 1986

- 41)a) Mackay IR, Rosen FS Autoimmune diseases. *NEJM* vol. 345(5): pp. 340-350; 2001
b) Williams JP, Meyers JA Immune-Mediated Inflammatory Disorders (IMIDs): the economic and clinical costs. *Am J Managed Care* vol. 8: S664-681; 2002
- 42) *A History of Immunology*: pp. 160-189
- 43)a) O'Shea JJ, Ma A, Lipsky P Cytokines and autoimmunity. *Nat Immunol* vol. 2: pp. 37-45; 2002
b) Watford WT, O'Shea JJ Autoimmunity: a case of mistaken identity. *Nature* vol. 421(6924): pp. 706-708; February 2003
c) Cope AP Regulation of autoimmunity by proinflammatory cytokines. *Curr Opin Immunol* vol. 10(6): pp. 669-676; December 1998
d) Beutler B, Bazzoni F TNF, apoptosis, and autoimmunity: a common thread? *Blood Cells Mol Dis* vol. 24(2): pp. 216-230; June 1998
e) Revel M, Schattner A Interferons: cytokines in autoimmunity. *Ciba Found Symp* vol. 129: pp. 223-233; 1987
f) Cavallo MG, Pozzilli P, Thorpe R Cytokines and autoimmunity. *Clin Exp Immunol* vol. 96(1): pp. 1-7; April 1994
g) Schattner A Lymphokines in autoimmunity—roles of interferon in systemic lupus erythematosus and other autoimmune disorders. *Isr J Med Sci* vol. 24(12): pp. 728-731; December 1988
h) Brennan FM, Feldmann M Cytokines in autoimmunity. Vol. 4(6): pp. 754-759; 1992
- 44)a) Romanini S The Th1/Th2 paradigm. *Immunol Today* vol. 18(6): pp. 263-266; 1997
b) Druet P, Sheela R, Pelletier L Th1 and Th2 cells in autoimmunity. *Clin Exp Immunol* vol. 101(Suppl 1): pp. 9-12; July 1995
c) Mackay IR, Rosen FS T-cell function and migration. *NEJM* vol. 343(14): pp. 1020-1034; 5 October 2000
d) Santamaria P Effector lymphocytes in autoimmunity. *Curr Opin Immunol* vol. 13(6): pp. 663-669; December 2001
e) Elenkov IJ, Chrousos GP Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann NY Acad Sci* vol. 966: pp. 290-303; June 2002
f) Agnello D, Lankford CS, Bream J et al Cytokines and transcription factors that regulate T helper cell differentiation: new players and new insights. *J Clin Immunol* vol. 23(3): pp. 147-161; May 2003
g) Encinas JA, Kuchroo VK Mapping and identification of autoimmunity genes. *Curr Opin Immunol* vol. 12(6): pp. 691-697; December 2001
- 45)a) Wilder RL Neuroimmunoendocrinology of the rheumatic diseases: past, present, and future. *Ann NY Acad Sci* vol. 966: pp. 13-19; 2002
b) Brennan FM, Maini RN, Feldmann M Role of pro-inflammatory cytokines in rheumatoid arthritis. *Semin Immunopathol* vol. 20(1-2): pp. 133-147; 1998
c) Krogh Rasmussen A, Hartoft-Nielsen ML, Feldt-Rasmussen U Models to study the

- pathogenesis of thyroid autoimmunity. *Biochimie* vol. 81(5): pp. 511-515; 1999
- d) Podolsky DK Inflammatory bowel disease. *NEJM* vol. 347(6): pp. 417-428; 2002
- e) Ogorek CP, Fisher RS Differentiation between Crohn's disease and ulcerative colitis. *Med Clin North Am* vol. 78(4): pp. 1249-1258; November 1994
- f) Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG Multiple sclerosis. *NEJM* vol. 343(13): pp. 938-952; September 2000
- g) Isomaki P, Luukkainen R, Saario R et al Interleukin-10 functions as an anti-inflammatory cytokine in rheumatoid synovium. *Arthritis Rheum* vol. 39: pp. 386-395; 1996
- h) Kurina LM, Goldacre MJ, Yeates D et al Depression and anxiety in people with inflammatory bowel disease. *J Epidemiol Commun Health* vol. 55: pp. 716-720; 2001
- i) Bach JF Insulin-dependent diabetes mellitus as an autoimmune disease. *Endocr Rev* vol. 15: pp. 516-542; 1994
- j) Rabinovitch A An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus. *Diabetes Metab Rev* vol. 14: pp. 129-151; 1998
- k) Rabinovitch A, Suarez-Pinzon WL Cytokines and their roles in pancreatic islet β -cell destruction and insulin-dependent diabetes mellitus. *Biochem Pharmacol* vol. 55: pp. 1139-1149; 1998
- m) Mandrup-Poulsen T The role of interleukin-1 in the pathogenesis of IDDM. *Diabetologia* vol. 39: pp. 1005-1029; 1996

46) *The Birth of the Clinic: An Archeology of Medical Perception* Michel Foucault
publ. Vintage Books, Random House, New York 1994; pg. 182

47) *FUO: Fever of Undetermined Origin*, pp. 49-65, 109-122

48) *A History of Immunology*, pp. 142-145