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STRESS, HYPERTENSION AND THE METABOLIC SYNDROME

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Distinguishing The Difference Between Treating A Disease And A Description

What we refer to as "essential" or "primary" hypertension is generally viewed and often treated as if it were a distinct disease. However, it is merely the observation of consistent blood pressure measurements that exceed arbitrary values for which there is no obvious explanation. Like fever, hypertension is really a description rather than a diagnosis. As with an elevated temperature, it may have many varied causes that require very different treatments. This helps to explain why so many diverse and seemingly discrepant drugs and other antihypertensive therapies are available. The cause of fever can usually be determined so that proper specific treatment can be reasonably expected to be effective.

Therefore, while antipyretic drugs like aspirin or sponge baths can lower an elevated temperature, the goal is not to treat the fever but its cause. Large doses of prednisone might be appropriate for a fever of 103° caused by lupus. However, if the identical elevated temperature was due to tuberculosis, administering the same dose of prednisone could be dangerous or lethal. We don't have the same degree of confidence as to which drug will work best in a patient with an elevated blood pressure because of uncertainty about what is causing the problem. Some drugs do tend to be more or less effective in specific demographic groups. Renin level measurements may also be helpful but there is no algorithm or template to follow that will guarantee optimal treatment for any given patient

As a consequence, therapy is often a hit or miss trial and error exercise or a buckshot approach consisting of a combination of drugs designed to lower an elevated blood pressure irrespective of its cause. This is quite understandable since unlike fever, which is

usually self limited and can actually be beneficial in some situations; essential hypertension is a chronic condition that can cause stroke and other complications if not corrected. The downside is that although some antihypertensive drugs are effective in lowering blood pressure they can cause other problems, especially with long-term use. Similarly, the ingredients in some combination products in addition to providing no benefit can have serious side effects. Other "one size fits all" blanket recommendations can also backfire. One of the first things all hypertensives are advised is to avoid salt, dairy products and other foods with a high sodium content. However, sodium restriction has little or no effect in most patients and a subset that improve with calcium supplementation could suffer because milk and cheeses are also a major source of calcium. These various discrepancies illustrate the difficulties in evaluating studies that purport to show a specific cause of hypertension, or the benefits of some therapeutic intervention.

This is a particular problem when considering the role of "stress" which also has multiple causes as well as varied symptoms and signs. The dilemma deepens when attempting to assess whether the results of animal studies designed to delineate the role of stress in experimentally induced hypertension apply to essential hypertension in humans. In some instances, there may be difficulties in extrapolating results in rodents because of genetic differences in various strains that have been bred to be salt sensitive or develop spontaneous hypertension. While blood pressure responses to acute and severe stress are comparable and it is possible to produce pain and frustration in animals, it is difficult to duplicate depression, hostility, Type A traits and other stressful states and behaviors that are more common in people and may be relevant.

Despite these drawbacks, animal studies have contributed enormously to our understanding of the role of stress in cardiovascular and other diseases. During the early part of the last century, Walter Cannon described the "fight or "flight reactions in dogs subjected to sudden and severe stress. These automatic and immediate sympathico-adrenal medullary responses have been exquisitely honed over the lengthy course of human evolution as life saving measures for our primitive ancestors but are no longer appropriate for modern man. Several decades later, Hans Selye, who coined the term stress as it is currently used, demonstrated that intense stress could cause pathologic changes in rats similar to those seen in patients with gastric ulcerations, nephrosclerosis, myocardial infarction, rheumatoid arthritis and other conditions that he viewed as "Diseases of Adaptation". He also showed in his "Alarm Reaction" how this was mediated by stimulation of the hypothalamic-pituitary-adrenocortical axis as opposed to the mechanisms proposed by Cannon. Many of these experiments could not be conducted today since they bordered on torture. Thus, despite Selye's ability to produce pathology that mimicked human diseases, the clinical relevance of such studies has been questioned.

More pertinent advances stem from the research of Jim Henry, who delineated the aggressive defense and passive defeat reactions to psychosocial stress and their associated activation of sympathetic-adrenal medullary or pituitary-adrenocortical activities and other endocrine responses. Jim's rat studies stimulated other leading investigators including Björn Folkow, Chairman of the Department of Physiology at the University of Göteborg and the recipient of numerous awards and honors for his contributions to our understanding of the pathogenesis of hypertension. Björn's exploration of the characteristic "upward structural resetting" of systemic resistance that occurs in primary hypertension had suggested that this was often initiated by the neurohormonal responses to psychosocial stress that Jim Henry described in his defense reaction. Björn was our 1989 Hans Selye Award recipient and Jim was our honoree in 1991. Their close friendship dates back to the early 60's and Jim visited and stayed with the Folkows so frequently that Björn described him to me as our children's "Favourite Uncle". On one of these visits, he introduced Jim to another old friend and Göteborg

colleague, Per Björntorp. They also had much in common since Björntorp's superb studies had shown how abdominal obesity, insulin resistance, lipid disturbances and other manifestations of metabolic syndrome were due to stress-related increases in glucocorticoid secretion that were reminiscent of Henry's defeat response. Both Björn and Per were fascinated by Jim's "mouse-city" experiments and the relevance of rodent responses to psychosocial stress to their own research. It became increasingly apparent that there were several links including shared features between essential hypertension and metabolic syndrome. In a landmark paper, they postulated that such similarities were due to the fact that both these "disorders of civilization" had a "closely related central origin". (1) The source for both appeared to be the type of mental or psychosocial stress that Jim Henry had found could elicit either a defense or defeat reaction in his rat "microsocieties".

My plans to interview both Jim and Per Björntorp were thwarted by their untimely passing. Fortunately, Björn Folkow, a very close friend and colleague of these other two giants in stress research has kindly consented to comment on their contributions. I have also asked him to discuss his thoughts about the role of stress in essential hypertension and the growing problem of metabolic syndrome, both of which he views as interrelated "diseases of civilization".

AN INTERVIEW WITH BJÖRN FOLKOW, M.D., Ph.D.

PJR: Many physicians tend to view essential hypertension primarily as a plumbing problem due to increased cardiac output or increased peripheral resistance or some combination of both. What causes these derangements is not clear but hypertension is often linked with insulin resistance, and other manifestations of metabolic syndrome. You and Per Björntorp have proposed that both essential hypertension and metabolic syndrome share a similar central origin as suggested by animal studies. However, I suspect that proving this in humans would require very long-term studies. What is the evidence to support this hypothesis?

BF: Primary (essential) hypertension (PH) and the metabolic syndrome (MS) have much in common because their multifactorial backgrounds include several shared elements. In both conditions, a polygenetic predisposition interacts with environmental factors that overlap. Increased insulin resistance, which is considered to be the hallmark of MS is common in PH, and conversely, an elevated blood pressure is frequently found in MS. A third important component in chronic hypertension is the gradual "upward structural setting" or remodeling of blood vessels and the heart that reinforces interactions between hereditary and environmental influences. This same phenomenon is also seen in metabolic syndrome. (1)

Genes alone are hardly sufficient to produce the clinical picture of either PH or MS since these disorders are almost absent in hunter-gatherer or small agricultural groups that have retained their traditional lifestyles for centuries. It is only when such rural enclaves are forced to follow the hectic and competitive lifestyles of modern society that rely on technologies rather than physical exercise that these leading "Diseases of Civilization" start to surface. For example, a recent survey in Spain (2) showed that 45% of people aged 34 to 64 were hypertensive. Actually, genetic constellations predisposing to PH may even encompass most people in populations, as other studies show their presence in siblings who were still normotensive. (3) Björntorp and coworkers found that over a third of 51-year-old men in our home town of Göteborg had all the cardinal characteristics of metabolic syndrome. (1,3,4) Moreover, in this third of MS affected men, the incidence of mood disturbances such as frustration, anxiety and depression was surprisingly high. (1) The advent of the genome project has accelerated the current trend to search for a specific

"one and only" genetic cause for human disease. However, the above and other studies tend to confirm a polygenetic basis for both PH and MS. From a biological perspective, a rise in blood pressure and blood sugar, enhanced alertness and other "fight or flight" responses to physical threats would have had survival value for our primitive ancestors. Unfortunately, they are now inappropriate for the mental and emotional stresses that modern man may encounter several times daily rather than once or twice a month. Repeatedly invoked, it is not hard to understand how they could contribute to hypertension, metabolic syndrome, peptic ulcers and other diseases depending on the interaction between genetic and environmental factors.

Do Conclusions Derived From Animal Experiments Apply To Humans?

As to the applicability of animal experiments to man, over a century of research has demonstrated their ability to elucidate the mechanisms responsible for numerous clinical disorders. When it comes to mind/body relationships it is true that the human neocortex is more advanced than in other animals, although dolphins do come close. However the myriad involuntary and immediate responses to stress originate in the limbic system, hypothalamus and other paleocortical structures that comprise what has been called the "emotional brain". This phylogenetically ancient but integrated system activates autonomic nervous system and humoral pathways that have been exquisitely honed over millions of years of evolution to insure survival. These routes and responses, which are the same in mammals from mouse to man, differ from those activated by neocortical cognitive processes.

An excellent illustration of this relevance can be found in the superb studies of Jim Henry and coworkers in "microsocieties" of rodents subjected to psychosocial threats. (4,5) They showed how **stimuli that were designed to range in severity from mere challenges to the complete loss of control could lead to cardiovascular and metabolic changes similar to those seen in hypertension and metabolic syndrome in man**. They also demonstrated how genetic factors influenced the resultant pathology. Thus, some strains of mice exhibited increased or decreased sensitivity to developing cardiovascular damage while others were more predisposed to gastrointestinal disturbances, just as the response to stress varies in humans.

Challenges that represented threats to control tended to induce a Defense Reaction that was mainly manifested by activation of Cannon's sympatho-adrenal medullary axis. Loss of control resulted in a Defeat Reaction that evoked Selye's hypothalamic-pituitary-adrenal cortical axis along with signs of depression. **Both the Defense and Defeat Reactions are identical down to the last detail in mice, rats, dogs, cats, monkeys and man.** (3,4) **As in humans, depending on how the animal interprets the severity of the threat, mixtures or shifts between these two reactions are common and can result in a relative preponderance of either PH or MS elements.**

Kaplan, et al. used monkeys for similar group studies and also demonstrated that prolonged loss of control as well as social support elicited a Defeat Reaction with all the characteristics of metabolic syndrome seen in man. (6,7) As might be anticipated, males were more severely affected than females. However, following removal of the ovaries, females were treated like outcasts and fared even worse with respect to coronary artery disease, possibly because they lacked the protective effect that female hormones may provide. All of the mentally induced and neurohormonally mediated damage to coronary arteries could also be aggravated by placing the animals on atherogenic diets. This illustrates that, as is frequently seen in biomedical research, it is not a question of "either-or", but rather of "both-and" in various combinations. This is also true in humans, where stress induced effects are often modified by diet, exercise, smoking and other lifestyle habits.

Finally, these experiments on the effects of psychosocial interventions in the group life of rodents and primates illustrate that the development of PH or MS depends on how threats are perceived. **A preponderance of the Defense Reaction predisposes to hypertension while a predominant Defeat Reaction is more apt to be manifested by metabolic disturbances.** As previously noted, mixtures or shifts between the two in different degrees are not uncommon. This is what Björntorp and I had in mind when we discussed how various facets of limbic-hypothalamic interactions contribute to hypertension as well as metabolic syndrome so that we frequently see a mixed picture that contains elements of both. (1,3)

Lundberg and Frankenhaeuser have shown this in humans (8), and similar studies in man are well covered in a recent "State of the Art Reviews" book (9). Catecholamine release was used as a marker of the defense response and glucocorticoid secretion as a marker for defeat when subjecting students to mental testing. If an important exam was so simple that most were quite confident about their ability to succeed only catecholamines were increased. However, if it proved to be so difficult that it induced anxiety because of fear of failure, glucocorticoids were also released - in other words, there was evidence of both defense and defeat responses. **It is likely that in daily life, similar dual activations are continually taking place because of psychosocial stressors that vary with respect to their nature, intensity and significance to the individual.** The ultimate development of hypertension or metabolic syndrome also depends on genetic factors, prior exposure, as well as differences in how such threats are interpreted or experienced. It should not be surprising, therefore, that these disorders and especially their interrelationships often seem ambiguous and confusing - because they are. This is a lot different than the "one cause - one disease" pattern of infectious diseases where the etiology can be confirmed by satisfying Koch's postulates. You might argue that in some respects it is reminiscent of Selye's multifactorial concept of "non-specific" stress, which posits that many different stressors can cause the same pathology.

The Significance Of Status And Rank In A Social Hierarchy

PJR: Jim Henry's "defense" and "defeat" reactions in his rat "microsocieties" help to explain **why people respond differently to the same stressor**. Genetic factors undoubtedly play a role but **one's status in a social hierarchy also seems to have a significant influence and perhaps you could expand on this**. You have proposed that hypertension is primarily a defense response whereas metabolic syndrome more often results from the defeat response and that mixtures of both are common. This seems quite plausible since the same hypothalamic and limbic centers that respond to acute mental as well as chronic psychosocial stress regulate both circulatory and metabolic activities via hyperactive hypothalamic-pituitary and sympathetic-adrenal medullary mechanisms. In differentiating the two, Jim has shown that the Defense Reaction is associated with an increase in renin, which is often seen in hypertension. Is this also true in humans and are there other clinical correlations with his biopsychosocial research in rats?

BF: Individual differences in the response to an identical single stimulus or situation are common in Henry's mice and Kaplan, Manuck and Clarkson's monkeys, just as we see in people. A good example that you have often cited is a steep roller coaster ride, where some elated passengers are exhilarated and laughing, some are scared and shaking while others seem to have an air of nonchalance that borders on boredom. These variations are largely due to differences in the feeling of control over the event, which in turn is influenced by genetics, gender, prior experience, social status and other environmental factors.

In all these animal studies, rank in a hierarchical society is an extremely important determinant, as is often seen in humans. **When rank is threatened, a Defense Reaction is elicited and attempts are made to maintain the status quo. However, if this is**

unsuccessful and there is loss of control and social status a Defeat Reaction predominates. Such perturbations and shifts that continually recur in daily life are quite normal and harmless if they are mild or transient. However, when mental challenges become prolonged the resultant defense and defeat neurohumoral responses start to cause disturbances that eventually lead to manifestations of primary hypertension and/or metabolic syndrome as well as other causes of premature death.

With respect to renin, it is important to remember that the Defense Reaction sympatho-adrenomedullary stimulation results in a β_1-receptor-mediated activation of renin production. Thus, the renin-angiotensin-aldosterone axis comes into play when the Defense Reaction predominates and we start to see associated effects on kidney function, positive feedback action on sympathetic tone and perhaps even on "salt appetite".(3,4) These and other far-reaching defense responses, that are controlled by the nervous system are often not fully appreciated or may be overlooked by researchers whose focus is entirely on the role of renin. While obviously significant, in this particular case, renin is only one of many links to other important neurohormonal responses that have widespread effects.

Of course, the renin-angiotensin-aldosterone axis is involved in primary hypertension in other ways, particularly in the late stages of the disease. Here, concerning structural adaptation of small resistance arteries, the preglomerular arterioles being especially susceptible to remodeling changes that lead to luminal narrowing. The resultant restricted blood flow to the kidneys produces a superimposed Goldblatt type of hypertension that may ultimately predominate. Since genetic constellations that predispose to hypertension differ in people and populations, variations in renal function and/or volume regulation are apt to be common. Superimposed on this is the Defeat Reaction activation of ACTH-glucocorticoid responses that introduce a mixture of metabolic syndrome related elements. This seems to be true in humans as well as rodents although the latter provide more information on heritable influences. For example, the effects of stress-related defense responses are apt to differ considerably if they are studied in spontaneously hypertensive rats or Dahl's salt sensitive strain.

In a "one-cause-one-disorder" such as an infection the etiology can be clearly identified. The *causa vera* of tuberculosis is the tubercle bacillus. While it is true that not all people who are infected develop clinical tuberculosis and that crowded, unsanitary conditions and impaired immune system function can influence this, the disease will not occur in the absence of the tubercle bacillus. However, like fever, there is no *causa vera* for primary hypertension or metabolic syndrome since both have multifactorial origins that are further modified by myriad influences to produce either disorder or a mixture of elements of both. This is understandably frustrating and confusing to reductionistically oriented researchers searching for a single "one and only" cause, but given our present state of knowledge, we must learn to live with these complexities.

PJR: Hans Selye, who initially classified adrenal cortical hormones as having primarily glucocorticoid, mineralocorticoid or testoid effects believed that glucocorticoids and mineralocorticoids had certain antagonistic activities. In particular, glucocorticoids like cortisone had anti-inflammatory effects while desoxycorticosterone, the best mineralocorticoid that we had promoted inflammation, at least in rats. It was therefore very disappointing that when aldosterone later became available no such prophlogistic activities could be demonstrated despite its powerful effects on mineral metabolism. Subsequent studies now support Selye's hypothesis. Researchers have demonstrated that aldosterone can contribute to cardiovascular and renal pathology (fibrosis and collagen formation) by promoting sodium influx and hypertrophy in vascular smooth muscle cells, generation of oxygen free radicals, stimulation of growth factors and potentiating the pressor effects of angiotensin II. (10) While primary aldosteronism with low potassium due to an adrenal

adenoma is still a rare cause of hypertension, adrenal cortical hyperplasia with normal potassium is much more common and may account for 10% of all cases. Aldosterone also decreases the activity of glucose-6-dehydrogenase, an antioxidant that blocks free radical damage to small blood vessels. A deficiency of this enzyme is seen in 10-15% of blacks, which may explain their increased prevalence of hypertension. (11) Blocking aldosterone receptors not only lowers blood pressure but has been shown to improve survival and decrease morbidity in patients with severe heart failure. (12)

Selye's arbitrary categorizations were somewhat deceptive. Because of the close structural similarity of all adrenal cortical steroids it might be expected that certain activities would overlap. Thus, glucocorticoids had sodium retention and androgenic properties and mineralocorticoids could mimic certain glucocorticoid effects. This is somewhat reminiscent of the overlaps between primary hypertension and metabolic syndrome. Similarly, polycystic ovary syndrome, which is characterized by increased androgen levels often includes insulin resistance, Type 2 diabetes, obesity and other manifestations of metabolic syndrome. We also see that antihypertensive drugs that affect the renin-angiotensin-aldosterone axis may have unsuspected metabolic activities. Angiotensin II receptor antagonists can reduce the pro-inflammatory and thrombogenic effects of hypercholesterolemia. (13) These and other drugs like ACE inhibitors that inhibit the renin-angiotensin system have also been shown to significantly reduce the incidence of Type 2 diabetes in patients with hypertension and congestive failure. (14) Drugs that selectively block the vasoconstrictor effect of Angiotensin II not only lower blood pressure but also reduce renovascular resistance resulting in increased renal blood flow in patients with Type 2 diabetes, which may explain why they slow or prevent the development of diabetic nephropathy and have been approved for treating this disorder. (15) Adding an aldosterone blocker may provide additional synergistic benefits. (16)

The above observations support your view that the renin-angiotensin-aldosterone system has unappreciated widespread effects. These include not only those related to electrolyte and water balance but also your remodeling changes in small blood vessels in the kidney and elsewhere and the production of fibrosis that can result in sustained hypertension. In addition, blockade of this system may have favorable effects on carbohydrate metabolism in patients with diabetes. There are similarities between essential hypertension and metabolic syndrome because both have multifactorial origins, some of which are shared. The most important appears to be psychosocial stress, which may elicit a defense response with increased renin and hypertension or a defeat reaction that is characterized more by insulin resistance, dyslipidemia abdominal obesity and other manifestations of metabolic syndrome. **However, vacillation between the two and blends of both are probably much more common.** Since essential hypertension and metabolic syndrome are not distinct diseases and can have multiple causes or contributing influences it is not likely that either will respond to monotherapy, such as insulin for diabetes. This re-emphasizes the need to treat hypertensive patients on an individual basis rather than in a cookbook fashion where the goal is simply to lower an elevated blood pressure to arbitrarily set levels. For example, the current push to start all hypertensives on thiazide therapy will undoubtedly lead to an increase in diabetes and possibly interstitial nephritis. Although thiazides should never be given to patients in renal failure, neither diabetes nor impaired kidney function is listed as a contraindication in the latest JNC recommendations.

The Cortisol-Abdominal Fat Connection

The problem is much more cloudy and complex when it comes to treating metabolic syndrome since there is even more confusion as to how this evolves. Trying to lower an elevated blood sugar makes no more sense to me than treating other measurements, like fever or blood pressure, unless you address the cause of the problem. Many people believe that Type 2 diabetes and hypertension are often due to obesity per se rather than increased visceral fat. Yet, active Sumo wrestlers who are extremely obese rarely have these problems because

most of this is due to subcutaneous fat, which may actually have protective anti-atherogenic benefits. The major culprit appears to be cortisol, since conditions that cause chronic cortisol elevations, like Cushing's syndrome, exhibit abdominal obesity and all the characteristics of metabolic syndrome. Moreover, when a pituitary tumor or other cause of the problem is removed, these abnormalities disappear. Administration of prednisone and other synthetic glucocorticoids produces the same picture that is also reversed with cessation of therapy. Jim Henry showed that the defeat response was associated with increased abdominal fat in rats and studies in primates and humans subjected to stress who have elevated cortisols demonstrate similar results. As Per Björntorp has suggested, the sequence of events here seems to be that activation of the hypothalamic-pituitary-adrenal axis results in increased cortisol and other hormones that cause insulin resistance as well as visceral fat deposits that release free fatty acids which further decrease sensitivity to insulin in muscle and liver. These responses may have been useful for our primitive ancestors who required temporary increases in fuel for energy to respond to acute physical threats. However, the chronic elevation of sympathetic activity and stress hormones due to contemporary competitive and hectic lifestyles not only provides few benefits but can prove deadly. As you know from prior Newsletters, Cortislim and numerous other non-prescription products that claim to reduce weight as well as stress by blocking cortisol (now referred to as "the fat hormone") have raked in hundreds of millions of dollars in the U.S. Unfortunately, because these are classified as nutritional supplements they are not under the jurisdiction of the FDA and since they do not have to show any evidence of efficacy or safety, have filled a huge void in the weight loss industry. This is especially true for millions who are convinced they are overweight because they are under stress since manufacturers can cite Bjorntorp's and other legitimate studies for support, even though they have nothing to do with their spurious products.

The critical question is what advice can be given to prevent or reduce the development of hypertension and metabolic syndrome? Is there a way to identify individuals at particular risk other than a family history? Hyperactive blood pressure responses to physical threats (cold pressor test) or emotional stress ("white coat hypertension") do not appear to predict a significantly increased likelihood of developing sustained hypertension. Nor does adherence to any specific diet seem to have protective value, although artificial trans-fats and high fructose corn syrup sweeteners should be avoided, as well as excessive salt intake for certain individuals. The best recommendation appears to be regular physical exercise, which can provide significant benefits in both primary hypertension and metabolic syndrome and is further proof that these are linked. Of course, reducing psychosocial stress would help to prevent these and other "Diseases of Civilization" but cultural and commercial influences seem to preclude such a possibility. I am not sure that all of these opinions are consonant with your own and would welcome your comments on any that should be corrected or expanded on.

Hyperactive Cardiovascular Reactivity, Salt Intake, Stress And Exercise

BF: Let me start by stating that I share your views and especially the need to address the important issues of prevention and treatment. The prognostic significance of exaggerated cardiovascular responses to stress has been a controversial issue for well over a half century. However, immersing a hand or foot in ice water for a minute or two in the cold pressor test causes a transient rise in blood pressure primarily because of bulbo-spinal reflex sympathetic activities. Subjects with spikes that are much higher and/or more sustained than average would not necessarily show a similar enhanced reactivity to the psychosocial challenges that seem to contribute to sustained hypertension via limbic and hypothalamic activities. With respect to "white coat" hypertension, Sir George Pickering's group showed several decades ago the tremendous blood pressure variations that can occur in normotensive individuals during daily activities ranging from sleep to physical activity and strong emotional excitement. (17) Nevertheless, it is not the magnitude of such sporadic short bursts of blood pressure elevation that causes problems. The structural upwards resetting of the cardiovascular system

responsible for chronic hypertension depends more on the extent and duration of the average pressure load for long periods of time. These result from relatively mild but frequent daily psychosocial challenges that elicit defense responses with widespread neurohormonal excitatory influences. Mental stress tests like Brod's forced mental arithmetic can stimulate the "emotional brain" to produce mild defense (or defeat) reactions but this is different than the daily life situations of chronic worries, frustration, challenges that people face in their daily lives. (18-20) Permanent hypertension from these types of psychosocial threat can be demonstrated in rodents in months or even weeks. Similar studies in man might require measuring blood pressure, heart rate, hormone levels, emotional status etc. for years rather than months, which would be prohibitively expensive. Nonetheless, excellent ambulatory monitoring studies of workers during daily activities by Thomas Pickering and others have already provided important and supportive information. (9,21,22,23)

The importance of salt intake is also a subject of considerable controversy. As you have pointed out in previous Newsletters official recommendations for all Americans to sharply restrict salt seem unwarranted. This is supported by Graudal's very thorough meta-analysis of almost 60 well-controlled low-salt studies in normotensives, which found an average fall in mean arterial pressure of only a meager 0.6 mm Hg. (24) However, renin and catecholamine release was increased three or four fold and heart rate also rose in the majority of patients. As explained elsewhere, this could lead to an increased load on the left ventricle in addition to other undesirable consequences. (25, 26) That is not to deny that some groups, and especially Afro-Americans who are salt sensitive should restrict sodium intake. However, for the majority, as Sir George Pickering questioned, why take away from meals one of the really pleasant 'spices' when its absence takes away from meals one of its greatest pleasures? Why not trust our 'salt receptors' in the hypothalamus, like we trust the feedback mechanisms that determine thirst or temperature? In addition, 80% of the sodium in U.S. diets comes from processed foods, not salt shakers.

You have summarized elsewhere the various ways stress can contribute to hypertension (26) and its important role is illustrated by a 30-year follow-up study of Italian nuns in a closed order who pursued a peaceful lifestyle characterized by silence, meditation, regular work activities and isolation from society.(28) Their blood pressures at age 65-70 were only a few mm Hg. different than when initially recorded 3 decades earlier in contrast to a carefully matched group of women exposed to urban Italian lifestyles who showed the usual progressive rise with age seen in most Western countries. The incidence of cardiovascular disease and death was also twice as high in this control group compared to the nuns although there was no difference in family history of hypertension or salt intake. Cholesterol levels and body weight were actually higher in the nuns and **the authors concluded that it was primarily their stress free cooperative rather than competitive environment that provided these cardioprotective effects**.

Regular exercise would also be at the top of my list for prevention and treatment. Low salt diets do not benefit most hypertensive patients but only the minority who are salt sensitive. In contrast, Paul Korner's group at the Baker Institute in Australia has shown that **regular exercise can significantly lower blood pressure in everyone**. In one study, just 40 minutes of bicycling three times a week for a month lowered mean arterial blood pressure in normotensive fairly young sedentary males 7 mm Hg. (ten times more than a low sodium diet). (29) With respect to hypertension, **2 to 3 hours of rhythmic exercise three times weekly can lower elevated blood pressures in patients to the same degree as ordinary antihypertensive drugs**. (30,31) In addition to being safer and much cheaper than drugs, regular exercise provides other benefits such as improved immune system function and reduction of the abnormalities that are seen in metabolic syndrome. (3) More extensive research is required to explore the additional health rewards of exercise and to determine the mechanisms responsible for mediating these effects.

Are Diseases Of Civilization Due To Maladaptive Responses?

PJR: Studies do show that in addition to the benefits you noted, regular exercise reduces the risk of developing diabetes, colon cancer, obesity and osteoporosis. It can also relieve feelings of depression and anxiety and promote a sense of psychological well being. It has even been proposed that essential hypertension is largely due to physical inactivity and could be prevented by promoting regular exercise programs starting shortly after puberty and that the same might hold true for metabolic syndrome. (32) Support comes from studies showing a decline in physical activity during the past five decades that correlates with the progressive increase in these disorders. Since hypertension and obesity are rarely seen in primitive groups or peoples insulated from the stresses of modern society and are absent in wild animals who must constantly forage for food, describing them as "Diseases of Civilization" seems appropriate. This is somewhat reminiscent of Selye's "Diseases of Adaptation", which were various disorders that could be induced in laboratory animals subjected to prolonged stress. (33) In retrospect, "Diseases of Maladaptation" would have been more accurate. **"Diseases of Civilization" may similarly represent maladaptive responses to subtle psychosocial stressors and sedentary lifestyle changes that have occurred over the many millennia of man's evolution.**

BF: Laziness and lack of exercise could certainly be a factor, along with other deleterious lifestyle changes our bodies have not had time to adapt to. Although blessed with a remarkable neocortex, *Homo sapiens* has the same "emotional brain'" designed for preservation of self and species in a primitive world that exists in all other mammals. It was the remarkable efficiency of these limbic-hypothalamic mechanisms that made it possible for our ancestors to survive physical threats for millions of years of evolution. While appropriate for a hunter gatherer's existence and small group enclaves, contemporary man faces a barrage of hectic and competitive challenges and daily stresses that are bound to arouse such protective mechanisms that are no longer appropriate but have boomeranged to produce deadly diseases. With respect to not enough time having elapsed for us to adapt to these changes in our psychosocial environment, I am reminded of a metaphor from my friend and "exercise" professor P.O. Ästrand. He compared man's evolution with a 42,195 meter long marathon run. If this run began some 2 million years ago when the first primitive tools came into use, we gradually spread from Africa around the globe as small groups of hunter gatherers during the first 42,000 meters and it is only during the last 150 meters of the run some 7500 years ago that a gradual shift to agriculture started. The "Machine Age" started only 10 - 12 generations ago when less than 5 meters of the run remained and the past three decades of our computer driven culture are the last few centimeters of the marathon. Computerization is only a few inches old.

As I have also indicated in a discussion of this issue (34), Paul MacLean's metaphor is equally to the point. MacLean, who coined the term limbic system to describe the "emotional brain" considered mans neocortex and its relation to our mammalian or premammalian emotional brain as analogous to a fairly competent rider on an inherently unruly and instinct-driven horse. As long as the rider is in control, the two cooperate to provide an efficient and productive unit. But if the rider forces the horse beyond what its instincts will allow, the horse takes over and may even throw its master off the saddle.

Man is a link in a great evolution and it is important for us to recognize how much we have in common with Jim Henry's mice and Kaplan, Manuck and Carlson's monkeys, especially with respect to defense and defeat responses that ultimately lead to disease. The central nervous system mechanisms responsible for this are complex, cause-effect relationships are complicated and the time-course is much more insidious, compared e.g. to infectious diseases. Nevertheless, I suspect we already have enough information to advise regulatory authorities on ways to prevent what are truly "Diseases of Civilization".

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