This proposal may seem far-fetched to some since it implies that heart attacks associated with bacteremia might respond to appropriate antibiotics or that vaccines could be used to retard the development of atherosclerosis. There was similar skepticism two decades ago when it was suggested that peptic ulcers were caused by helicobacter infection, rather than stress. However, the vast majority of patients harboring helicobacter have no gastrointestinal complaints. It is only when stress related hormones or non-steroidal anti-inflammatory drugs impair normal protective defenses that ulcer symptoms start to surface. It is well established that stress reduces immune system resistance to bacterial and viral infections. Stress hormones or the administration of cortisol like steroids can often cause the clinical reappearance of previously quiescent tuberculosis because they impair immune system defenses that normally prevent this. Similarly, when healthy young adults were exposed to rhinoviruses, the frequency as well as the severity of subsequent colds were directly correlated with the magnitude of their stress levels.

**How Does Stress Reduction Prevent Heart Attacks And Atherosclerosis?**
Reducing stress and bolstering immune system function in other ways should help to prevent the development of unstable plaque due to infection. However, coronary atherosclerosis is a multifactorial process and stress also plays a crucial role in the development of metabolic syndrome and its damaging cardiovascular consequences. Stress related cortisol secretion promotes the deposition of deep abdominal fat cells that not only secrete proinflammatory molecules but also stimulate the hypothalamic-pituitary-adrenal axis to produce more cortisol. These visceral fat cells (adipocytes) have increased receptors for cortisol that tend to perpetuate its deposition. Thus, stress-induced increased cortisol contributes to fat cell accumulation and vice versa and both promote insulin resistance and low-grade smoldering inflammation to create another sinister self-perpetuating cycle.

Inflammation appears to be the most important cause of metabolic syndrome based on levels of C reactive protein (CRP). CRP levels in patients with any one of the components of metabolic syndrome (hypertension, lipid disturbances, Type 2 diabetes, increased coagulation etc.) can vary considerably, but a progressive rise in CRP with each additional factor has been clearly demonstrated. It should also be noted that CRP levels correlate very closely with the severity of abdominal obesity, which, as previously emphasized, is largely due to increased cortisol activities that increase fat cell production of inflammatory cytokines.

It has become increasingly clear that heart attacks as well as atherosclerosis are due to inflammation rather than elevated lipid levels. However, this
inflammation is subclinical and can only be detected or measured with crude markers, such as CRP, interleukin-6 and tumor necrosis factor. If stress reduction is effective in preventing heart attacks and atherosclerosis, what evidence is there that it suppresses inflammation? And what is the mechanism of action? Fortunately, Kevin Tracey's ground breaking research on the "anti-inflammatory reflex" have now provided some clues and answers to these questions. It is difficult to explain this in a few paragraphs but key aspects are summarized in the following diagrams and legends.

The Cholinergic Anti-inflammatory Pathway

As illustrated to the left, efferent activity in the vagus nerve leads to the release of acetylcholine (ACH) in compartments of organs of the reticuloendothelial system. ACH interacts with its receptors on tissue macrophages that inhibit the release of tumor necrosis factor (TNF), interleukin 1 (IL-1) and other cytokines. Tracey refers to this as the "cholinergic anti-inflammatory pathway" because acetylcholine is the principle neurotransmitter for parasympathetic nervous system activities. Macrophages that are exposed to acetylcholine are effectively deactivated. In addition to the heart, the vagus nerve (named for its wandering course) also innervates reticuloendothelial sites in the liver, lung, spleen and gut.

The cholinergic anti-inflammatory is only one component of the body's ability to suppress inflammation, as shown below.

Anti-inflammatory Reflex Pathways

Inflammatory products produced in damaged tissues activate afferent signals that are relayed to the nucleus tractus solitarius. This then activates vagus efferent activity that inhibits cytokine synthesis through the cholinergic anti-inflammatory pathway ('the inflammatory reflex'). Information can be relayed to the hypothalamus and the dorsal vagal complex to stimulate ACTH that activates humoral anti-inflammatory pathways. Fight or flight responses that stimulate sympathetic nervous system activities can increase local concentrations of adrenaline and noradrenaline, that further suppress inflammation.
This runs counter to classical teaching that actions of the sympathetic and parasympathetic nervous systems are usually in opposition. But in some situations, as noted above, the two systems function synergistically and their combined action is significantly anti-inflammatory. Similarly, simultaneous stimulation of both sympathetic and vagus nerves produces a higher increase in cardiac output than does isolated stimulation of either alone.

Tracey's research is supported by studies showing that activation of the cholinergic anti-inflammatory pathway by direct electrical stimulation of the efferent vagus nerve inhibits the synthesis of TNF in liver, spleen and heart. Conversely, vagotomy significantly exacerbates TNF responses to inflammatory stimuli and sensitizes animals to the lethal effects of endotoxin. Vagal and parasympathetic nervous system activation blocks stressful fight or flight reactions and produces a "Relaxation Response" that is its antithesis. Heart Rate Variability (HRV) feedback research now confirms this as well as the effect of differing emotions on HRV.

Low HRV is seen in depression, frustration and other stressful states. The reverse is true during relaxation and when feeling positive emotions such as true love and deep appreciation, as shown to the right in this HeartMath study. Low HRV reflects the inability of the heart to adapt to change and a powerful predictor of sudden death. HRV provides the most accurate and objective method of assessing current stress levels.

Heart rate variability can only be measured by complicated ECG analysis but the recent availability of inexpensive hand held devices that convert these ECG patterns to easily understood visual signals. This allows the user to not only immediately get the same information but also to learn how to correct dangerously low levels by altering respiratory patterns to obtain maximal parasympathetic stimulation. In many instances, it is possible to achieve the same degree of relaxation in a week or two that can take months to attain with meditation. In studies of coronary artery disease patients, five or six biofeedback sessions coupled with daily practice resulted in significantly increased heart rate variability, improved symptoms and quality of life. In heart failure patients, eight biofeedback sessions markedly improved performance on a 6-minute walk test and reduced perceived stress levels. There are numerous other examples that could be cited that demonstrate the efficacy of HRV biofeedback in relieving asthma, insomnia and other stress related complaints. HRV biofeedback is also an extremely cost effective way to improve learning skills and various cognitive functions as well as performance and productivity in numerous diverse areas.
The diagram above to the left shows how stress causes inflammation, low HRV and cardiac damage by suppression of vagal activities. Possible therapies that reduce inflammation by cholinergic stimulation and where they operate are shown on the right. Some of these are consistent with an emerging paradigm of unappreciated subtle energy communication pathways in the body that could explain poorly understood phenomena such as the power of placebos, strong faith, prayer, therapeutic touch and acupuncture. Vagal and cranioelectrical stimulation can relieve depression, and anxiety and are also being used to treat obesity, migraine and other pain syndromes. Weak electromagnetic stimulation has been shown to promote healing and reverse metastatic malignancy and terminal cardiomyopathy.

**The heart's electromagnetic field is 6,000 times more powerful than the brain.** Can it be harnessed to provide similar therapeutic benefits? I am looking forward to participating in the Prince Sultan Cardiac Center's "The Heart as King of Organs" conference in Saudi Arabia, where this and relevant topics will be discussed. Few of us aware of the great contributions of Islamic physicians, – so stay tuned for more on this fascinating event!

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