There are an estimated 125 million Americans who have at least one chronic condition. By 2020, this number is expected to rise to 157 million. Of these, a substantial number have chronic pain syndromes. Further, there are 60 million Americans who suffer from multiple chronic conditions. Whereas acute conditions have yielded in large part to modern medical interventions, chronic conditions have proved far more resistant. The revolution in molecular biology and genomics, still in its infancy, has given us miraculous new tools with which to approach these challenges.

Unfortunately, 72% of all Americans who suffer from a chronic condition report difficulty in obtaining the needed care from a medical specialist. This is not surprising in view of the complex and multifaceted nature of these conditions. Research continues to identify even deeper complexities and a startling array of interconnections among chronic conditions, treatments, toxins, the environment and individual hereditary variability. Science, which functions by isolating variables, finds these relationships daunting and is challenged to broaden its basis of investigation to include multiple factors that act synergistically, non-linear dose-responses, and isoforms with contrasting properties.

In such a setting, “holistic” approaches are the only rational approach to effective treatment, although they are fraught with uncertainties and test the limits of scientific investigation. Among the methods that have achieved some degree of scientific substantiation, a detoxification regimen to managing chronic conditions appears to have demonstrated considerable success as a foundational approach. In addition, it is not disease-specific, assuming the reasonable hypothesis that chronic conditions share commonalities that are addressed with such a broad-based approach.

Current research data elucidates the effects of exogenous and endogenous toxins on the most prevalent chronic diseases we face today, providing a basis for a comprehensive nutritional and environmental regimen for chronic conditions. The methodology incorporates minimizing exposure to identified and suspected toxins, augmenting intake of foods and nutrients that have demonstrated or suggested beneficial metabolic effects, and altering lifestyle according to the best epidemiologic and physiologic evidence available. Much is already known from such studies. Combining multiple avenues of investigation yields a comprehensive approach that has already shown clear benefits and that is, above all, entirely safe and more than practical in economic terms.

Research is already underway into a revolutionary new approach that individualizes nutritional intervention according to each person’s unique metabolism. The heady requirement for progress in this area, known as nutrigenomics, is to discover through individual genetic mapping how each person responds to proposed regimens. Parallel discoveries are necessary to predict responses to pharmaceuticals, something that is as often as not a trial-and-error procedure, even when treating a condition as seemingly straightforward as hypertension.

This article is divided into two segments. The first covers current understanding of pain and its treatment and the role of toxins in the generation of chronic conditions. The second explores future possibilities including current research into chronic disease and pain mechanisms, the role of environmental and endogenous toxins, and nutrigenomics.

Chronic Pain

It is becoming increasingly evident that low-grade inflammatory processes underlie most, if not all, chronic conditions, including chronic pain. Indeed, understanding of the inflammatory cascade has grown almost exponentially along with the identification of its ubiquitous presence in these conditions.

Chronic pain is entirely different from acute pain. To begin with, from a functional view acute pain is useful, while chronic pain is not only useless but highly detrimental. Chronic pain induces progressive changes in its own pathophysiology so that it can truly be called a malignant disease in its own right, regardless of the initiating cause. The presence of pain over time increases the intensity of the neural response (hyperalgesia), alters the nature of the sensation (allodynia), and expands the area of nociception (recruitment). These changes are due to the continued activity of excess amounts of chemicals both produced locally and circulated systemically, many of which are participants in the inflammatory response.

Because of the progressive nature of chronic pain, intervention at the earliest stage is most likely to be effective. Although the initial insult may not be preventable, the circumstances surrounding it that predispose to chronicity can be substantially improved. The approach is dual in nature – both the internal and the external environment can be optimized to inhibit the progressive advance of what has been called the “sickness response.” Further, to subdivide the approach, the internal mechanisms are both psychologic and physiologic.

Toxins

As mankind continues to alter the environment, exposure to unnatural agents increases. Many of these are toxic. Beginning in 1930 or thereabouts, the release of manmade chemicals into the environment has increased exponentially to over 160 billion kilograms per year. Several surveys have tracked this progression. The National Human Adipose Tissue Survey (NHATS) and the FDA’s Total Diet Survey.

From 1976 to 1987, the Environmental Protection Agency (EPA) ran the National Human Adipose Tissue Survey that provides substantial evidence for the presence of xenoestrogens in the environment and their direct effect on our bodies. This is an annual program whereby the EPA recruited pathologists and medical
Detoxification

Endogenous Factors

Among the endogenous factors, intestinal permeability ranks high as a condition predisposing to immune stimulation and chronic pain. The surface area of the gut at 200 m² exceeds that of the lungs (160 m²) and the skin (<2 m²) as an interface with the environment. Correspondingly, gut-associated lymphoid tissue (GALT) is responsible for 60% of the body's immunity. A careful balance is required between the gut's absorptive and its exclusionary function. Increased permeability of the mucosa allows an excess of antigens to enter the body, generating an immune response that has been correlated with numerous chronic disease conditions, among them malabsorption, enteritis, arthropathies, food allergies, migraine and autoimmune diseases. Causes of increased mucosal permeability include infections, ethanol, NSAIDS, low dietary fiber, cytotoxic drugs, and nutritional deficiencies of zinc, vitamin A and folate.14

Of particular importance to mucosal integrity is the amino acid glutamine. Glutamine's role in detoxification and chronic illness offers a clear example of the relationship between chronic exposure to toxins and chronic pain.

Glutamine, abundant in meat, fish, legumes, dairy products, and raw cabbage and beets, is the most abundant amino acid in the blood stream, comprising 30-35% of amino acid nitrogen in plasma. It is not an "essential" amino acid, but it is vitally important to healthy metabolic function. Glutamine is the main metabolic fuel for lymphocytes, macrophages, enterocytes and fibroblasts, thereby playing a central role in immune functioning.

When bacteria, fungi, and other toxins translocate across a weakened mucosal barrier into the bloodstream, they react with the reticuloendothelial system, stimulating production of cytokines via the hypothalamic-pituitary-adrenal axis.15 Cortisol is subsequently released from the adrenals, which increases glutaminase activity in intestinal enterocytes, thereby increasing breakdown of glutamine in the small intestine. This results in a progressive depletion of glutamine and glutathione (which contains glutamine), leading to oxidative tissue damage, inflammation and chronic pain.

Not surprisingly, glutamine is deficient in many disease states, such as cancer, trauma, excess exercise and other catabolic conditions, and repletion of glutamine has been shown to improve immune function,16-18 particularly in the gut, and in recovery from catastrophic diseases such as major trauma,19 critical illness,20,21 burns,22 and bone marrow transplantation.23

Glutamine is best administered enterally24,25 and, in keeping with the "holistic" approach necessary in these complex conditions, in glutamine-rich foods as part of an otherwise nutritious menu.

Psychologic Factors

One useful construct for understanding chronic illness and pain is the chronic pain/stress interaction. In this paradigm, pain (or

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Detoxification

Disability is the primary problem, not simply a symptom. The individual's response to having a chronic life-altering problem may cause depression, anxiety, deconditioning, cognitive dysfunction, poor sleep, and neuroendocrine changes. It is currently thought that many of these secondary problems result from activation of the limbic system and its sympathetic and neuroendocrine output. This combination of factors generates the progressive pathology of chronic pain through its multiple interactions in a positive feedback cycle.

When pain becomes a disease in its own right it takes firm hold of the emotions, stirring up old experiences and mixing them into the present discomfort. Childhood sexual abuse, a parent with chronic disease, or a host of other unpleasant memories exacerbate the interpretation of present pain. The context of present pain also alters its interpretation. A classic study during wartime compared battlefield injuries with similar civilian auto accidents. Soldiers going home needed far less morphine than their civilian equivalents. From what we now know of the neuroendocrine mechanisms of pain, combined with the resulting sleep deprivation and other life disruptions, we can begin to see how the interface between mind and body becomes an open channel of communication with real chemical determinants.

Medications and Chronic Disease States

Antidepressants
Such a view of chronic pain suggests a different role for antidepressants in its treatment. Antidepressants raise circulating levels of three major neurotransmitters—serotonin, noradrenaline, and dopamine. Rather than simply improving mood, these chemicals can act directly upon nerve tissue to improve its functional integrity. However, it is important to note that because environmental toxins disrupt the natural balance of biogenic amines, further contributing to chronic pain, a more physiologic approach is to minimize toxins entering the system. In this way one can normalize biogenic amine production at its source while preserving the body's innate feedback controls and avoiding the side effects associated with antidepressants.

The role of these neurotransmitters in pain modulation is further discussed in the second part of this article.

Analgesics
There are really only two classes of pharmaceutical pain relievers currently available—NSAIDs and opioids—plus the alternative of acetaminophen. For non-cancerous pain opioids are seldom used for fear of abuse, tachyphylaxis and habituation. Acetaminophen has no anti-inflammatory action, and recent evidence suggests it shares with NSAIDs the potential for adverse gastrointestinal side effects, even at low to moderate doses. These effects led to the development of selective cyclooxygenase-2 inhibitors, but these have proved so dangerous to the vascular system that the leading agent, rofecoxib (Vioxx), was withdrawn from the market. There is no reason to doubt that this is a class effect and that the other two COX-2 inhibitors will eventually follow suit since COX-2 in vascular endothelium is essential for the production of prostacyclin, a vasodilator and anti-thrombotic agent. COX-2 is also abundant in normal brain, kidney and other tissue. One further problem is that the selective COX-2 inhibitors are not exclusive; there is a crossover to COX-1 inhibition.

The problems with NSAIDs do not stop there, however. It has become evident that COX-2 is indispensible for many other physiologic functions. All NSAIDs can block mitochondrial oxidative phosphorylation, uncouple mitochondrial respiration and inhibit substrate oxidation and ATP turnover. This problem is further exacerbated by exposure to toxins, since mitochondria are highly sensitive to the effects of free radicals. The result is reduced production of ATP.

What this suggests is that better approaches to pain may be found upstream from the cyclooxygenase system, perhaps all the way to the genetic expression of the pain response. The second part of this article will discuss current research into pain and inflammation, further explore the role of toxins, both exogenous and endogenous, in pain generation, and introduce the concept of nutrigenomics and detoxification as a treatment modality for chronic pain.

References