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REPORT

The Role of Inflammation in Chronic Diseases

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ACAM
Medical Conference Report
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organization dedicated to
supporting research and education
in alternative and complementary
medicine. ACAM was founded in
1973, with a mission to make

by Ivy Greenwell

Other conference highlights:

Men with low insulin live the longest

Updates on testosterone and growth hormone replacement therapy

Nutritional approaches in the treatment of HIV

physicians and other health professionals aware of scientific advances relevant to holistic approaches to health and disease. Speakers at twice-yearly ACAM conventions are recognized experts in their fields. Each convention is an opportunity to gain more understanding about the underlying causes of many chronic disorders and learn about cutting-edge treatments. The October 2000 ACAM conference emphasized the role of chronic inflammation as a causative factor in the development and progression of a host of degenerative diseases.

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Introduction

Several years ago I heard a holistic practitioner say, "If we prevent inflammation, we can prevent Alzheimer's disease." I was stunned. The mainstream view was, "If you live long enough, you will develop Alzheimer's." The same went for cataracts and cardiovascular disease. Then last June Paul Ridker, MD, a Harvard cardiologist, publicly stated, "We have to think of heart disease as an inflammatory disease, just as we think of rheumatoid arthritis as an inflammatory disease." He asserted that it's inflammation that leads to pieces of arterial plaque breaking off and causing heart attacks, even in people with normal or low cholesterol. Recently headlines announced that men regularly taking non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen lowered their risk of prostate cancer by 66%; some risk reduction with NSAID use has also been reported for breast cancer and colon cancer. On a minor but important note, Dr. Nicholas Perricone, an innovative dermatologist, is now saying (or at least implying) that if we prevent inflammation, we can prevent a lot of skin aging.

Because of our new awareness of the importance of inflammation, it is not surprising that the most recent conference of the Academy for the Advancement of Medicine (ACAM) had inflammation and infection as its main theme. Only by understanding the mechanisms involved in the pathogenesis of diseases such as AIDS, cancer or Alzheimer's disease can we develop effective therapies. The growing understanding of the major role that oxidative stress and inflammation play in the development and progression of various pathologies has brought progress in devising more effective treatment protocols. In addition, the conference also included lectures and workshops dealing with updates in hormone replacement. Here are some of the highlights.

"The brain on fire"—Inflammation as the key to neurodegenerative diseases

David Perlmutter, a neurologist and director of the Perlmutter Health Center in Naples, Florida, and the author of BrainRecovery.com — Powerful Therapy for Challenging Brain Disorders, delivered an exciting lecture on the nature, prevention and treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. He concentrated on two factors: inflammation and glutathione depletion. Once we understand the critical importance of inflammation and glutathione depletion in brain diseases, we can take steps to prevent or even reverse the damage.

First, Dr. Perlmutter presented evidence that the current mainstream drugs such as Aricept are “essentially useless” in actually treating Alzheimer's disease. Their effectiveness is minimal at best, while their side effects include vomiting, dizziness and insomnia. These drugs do not correct the underlying inflammation. The brain in a state of chronic inflammation is, in Perlmutter's colorful phrase, “the brain on fire.” Current therapies “treat the smoke, but not the fire.”

The first real breakthrough in the understanding and treatment of Alzheimer's disease has been the discovery that the use of aspirin and NSAIDs such as ibuprofen (Advil) has a very significant protective effect. In one large study of those who used aspirin, NSAIDs or acetaminophen, NSAIDs reduced the risk of Alzheimer's disease to only 40% that of nonusers. Aspirin reduced the risk to 74%. Acetaminophen, however, raised the risk by 35% (this may have something to do with a toxic metabolite of acetaminophen, which depletes glutathione).

This finding is of tremendous importance to arthritis sufferers—they must become aware that their choice of a pain reliever is crucial in determining their risk of developing Alzheimer's disease. The effectiveness of ibuprofen is likely to stem from its superior ability to inhibit Nuclear Factor kappa B (NFkB), a transcription factor that switches on the production of inflammatory cytokines that initiate the process of cell death. It also supports Dr. Perlmutter's thesis that inflammation (“fire”) is at the core of Alzheimer's disease, and may turn out to be far more important than the beta-amyloid plaque.

We need to put out the fire in the brain—that is, reduce inflammation. Fortunately, we have some knowledge about how to accomplish this goal. For instance, we know that simply by taking nonsteroidal anti-inflammatories on a preventive basis, we can cut the risk of developing the disease by as much as 60%.

Can anti-inflammatories be used not only for prevention of neurodegenerative diseases, but also as treatment? Indomethacin, a well-known nonsteroidal anti-inflammatory, has been found to produce improvement in Alzheimer's patients, Perlmutter pointed out. The improvement was modest, but dramatic in the light of the fact that over the six-month course of the study the placebo group continued to deteriorate. Currently there is also great interest in the effect of selective COX-2 inhibitors (Celebrex, Vioxx) on the prevention of Alzheimer's disease, Perlmutter said. A few participants were concerned that “we may discover the price later on,” but for now we simply have to wait for more research findings. The main point is there has been a revolution in medical thinking. The gloomy dogma that nothing can be done to prevent Alzheimer's is giving way to an increasing awareness that reducing inflammation is powerful prevention. And now that we have those expensive COX-2 inhibitors, with more underway, the drug companies are certainly interested.

Pharmacological NSAIDs are not the only way to reduce inflammation. Fish oil has been shown to be an effective natural anti-inflammatory. The consumption of fish oil results in a different composition of cell membranes, with less arachidonic fatty acid available for the production of pro-inflammatory cytokines. Animal studies showed that diets containing fish oil profoundly reduce the levels of pro-inflammatory chemicals such as tumor necrosis factor alpha (TNF alpha) and various interleukins. Flax oil, a rich source of short-chain omega-3 fatty acids, also appears to be anti-inflammatory, though to a lesser degree. Epidemiological studies have amply demonstrated that frequent fish-eaters enjoy much better health, including less cognitive impairment and lower incidence of Alzheimer's disease, than those who eat little or no fish.

In addition, all antioxidants are also anti-inflammatory. Alpha lipoic acid and various flavonoids (such as those found in green tea and blueberries) may be particularly effective. A diet that emphasizes fish and seafood rather than meat, along with antioxidant-rich fruits and vegetables, can be useful in preventing degenerative brain disorders. This type of anti-inflammatory diet can make all the more difference with the right supplementation.

Perlmutter, however, placed special emphasis not on reducing inflammation once it has already started, but on trying to prevent it in the first place. “It's best to prevent inflammation from starting, rather than use drugs to dampen it,” he said. He emphasized that inflammation in the brain is particularly difficult to control. Cerebral inflammation tends to be self-perpetuating. We know that head injury and strokes (including mini-strokes), as well as various toxins and infections, produce inflammation and increase the risk of neurodegenerative disease. But few people know about the role of excess blood sugar in producing inflammation and thus contributing to the death of neurons. Perlmutter observed that Ronald Reagan's notorious sweet tooth might have contributed to the pathogenesis of his Alzheimer's disease.



The brain in a state of chronic inflammation is, in Perlmutter's colorful phrase, “the brain on fire.” Current therapies “treat the smoke, but not the fire.”

Perlmutter cited a Dutch study that found a more than quadruple risk of dementia in type II diabetics who use insulin. On the other hand, calorie restriction, which profoundly reduces blood sugar and insulin, is perhaps the best dietary protection against age-related brain damage. Consuming fewer calories translates into lesser production of free radicals. In addition, glucose can damage proteins, modifying them to pro-inflammatory compounds called AGEs (Advanced Glycosylation End Products). AGE-modulated beta-amyloid is extremely pro-inflammatory. One way or another, Perlmutter kept returning to the theme of reducing inflammation as a means of preventing, and possibly even treating, Alzheimer's disease.

Apart from anti-inflammatory supplements, magnesium may also prove a useful neuroprotector. One cause of neuron death is excess influx of calcium ions. If magnesium is present in sufficient concentration, the resulting "magnesium block" (magnesium is a natural calcium channel blocker) can save the neurons.

People who have suffered head trauma, small strokes or infections affecting the brain are especially likely to have the kind of low-grade cerebral inflammation that makes them more susceptible to developing Alzheimer's disease. These high-risk individuals should be made aware that they can reduce their risk with fish oil, NSAIDs, lipoic acid, flavonoids and through calorie restriction.

Those protective measures should be practiced by all of us. The dismal prediction is that by the year 2030 there will be nine million Alzheimer's victims in the United States. Some even predict that the economic burden of Alzheimer's disease alone will be enough to bankrupt the medical system. Such disaster can be averted through relatively simple means. It is time to educate the public about the prevention of brain diseases.

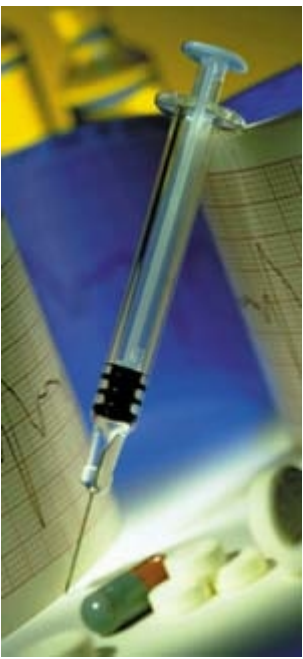
Parkinson's disease and "The glutathione miracle"

Perlmutter went on to discuss his approach to Parkinson's disease. It is more than a brain disease, he said. Parkinson's is a systemic disease as well, with the whole body involved. More specifically, Parkinson's patients tend to be poor detoxifiers. They show low levels of glutathione not only in the brain (especially in the dopamine-producing region of substantia nigra), but also in the liver. This may be why exposure to pesticides and herbicides can be so damaging to individuals with a genetic vulnerability to Parkinson's. We all have to deal with a tremendous toxic burden, but those who happen to be poor detoxifiers are at a special risk.

The central feature of Parkinson's is the progressive destruction of substantia nigra, resulting in a profound deficiency of the neurotransmitter dopamine. Mainstream treatment centers on the use of L-dopa, a precursor of dopamine. This approach to increasing dopamine works for a limited time, though not without severe side effects, including further brain damage. "The very drug that's used to treat the smoke increases the fire," Perlmutter stated. It turns out that L-dopa reduces detoxification. L-dopa also increases the conversion of S-adenosyl-methionine (SAMe) to homocysteine, and thus promotes vascular disease. At the same time, it's sometimes not possible to take patients with advanced Parkinson's off L-dopa. It may be possible, however, to counteract the drug's side effects and increase the patient's motor ability through a relatively simple alternative treatment.



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Within less than an hour of the injection, Parkinson's patients experienced an almost complete restoration of the ability to walk, turn around and move their arms.

Perlmutter's holistic approach is based chiefly on the need to increase detoxification, and thus enhance glutathione levels. The most dramatic part of Perlmutter's presentation consisted of slides showing a profound improvement in Parkinson's symptoms after intravenous glutathione. Within less than an hour of the injection, Parkinson's patients experienced an almost complete restoration of the ability to walk, turn around and move their arms. Perlmutter calls this "the glutathione miracle." He uses 1200 mg of injectable glutathione at first, then lowers the dose to 600 mg per injection. The injections are given two days apart. The effectiveness of the treatment has been validated in a controlled study. Many holistic physicians already use intravenous glutathione as part of their treatment for Parkinson's disease.

If the treatment is discontinued, its benefits last for up to four months after the end of the treatment. Besides acting as a detoxifier and lowering oxidative stress, glutathione may also enhance the sensitivity of dopamine receptors in Parkinson's patients, Perlmutter speculated. He also mentioned that intravenous glutathione is immediately effective against irritable bowel syndrome and diarrhea.

Is there a more convenient way to increase glutathione levels, for longevity in general and as part of a preventive neuroprotective protocol? It turns out that lipoic acid is the most effective supplement for raising glutathione—especially if it is taken together with N-acetyl-cysteine (NAC) and vitamins C and E. In addition, the amino acid glutamine is, like NAC, an important precursor of glutathione. Silymarin (milk thistle extract) has also been shown to increase glutathione in the liver.

In addition, lipoic acid is known to chelate iron. The elevated levels of free iron in Parkinson's patients increase free-radical damage and the destruction of neurons. And, like ibuprofen, lipoic acid inhibits NFkB and thus the production of inflammatory cytokines.

Perlmutter mentioned other helpful supplements, including CoQ10, which enhances mitochondrial function and is known to be low in the cerebral mitochondria of Parkinson's patients (and, interestingly, also of their spouses). Ginkgo biloba was also discussed. Ginkgo has been shown to have many neuroprotective properties, including the protection of brain mitochondrial glutathione against oxidation. Ginkgo also inhibits the enzyme monoamine oxidase B (MAO-B),

and thus helps protect dopamine against quick degradation. The drug selegiline (Deprenyl) also acts as a MAO-B inhibitor.

Predictably, there also arose some controversy over coffee, recently shown to be protective against the development of Parkinson's disease. Raising cyclic adenosine monophosphate (cyclic AMP—a "second messenger" that amplifies the hormonal message) has been shown to protect against Parkinson's.

"Caffeine dramatically increases cyclic AMP and decreases the risk of Parkinson's," Perlmutter said. Caffeine also competes for receptors with adenosine, an inhibitory compound. By displacing adenosine, caffeine indirectly increases the action of dopamine.

Perlmutter condemned the use of long-term antibiotics. Certain antibiotics are mitochondrial inhibitors. "If you increase antioxidants, you don't need long-term antibiotics," he stated. He also suggested that if a patient is put on statins, s/he ought to take supplemental CoQ10 to try to compensate for the CoQ10 deficiency induced by the drug. (Incidentally, a recent British study has found that statins appear to reduce the risk of dementia. As in the case of heart disease and stroke, this may be due to the anti-inflammatory properties of statins.)

One conference participant, an MD from England, suggested that supplementing with Vitamin B12 can be of enormous importance in treating dementia. He described a patient of his whose dementia virtually disappeared after treatment with B12. Many elderly are deficient in this vitamin, crucial for brain function. B12 also increases the oxygen-carrying capacity of red blood cells, and helps lower homocysteine. Dr. Perlmutter agreed that B12 should be an important part of the treatment. He also discussed magnesium as protective against excess calcium ion influx.

In summary, current research findings suggest the following: take lipoic acid and other antioxidants, eat fish and/or take fish oil, drink coffee (unless you can't tolerate it) and be happy. And forget about dessert. Calorie restriction still appears to be the most potent brain saver.

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Oxidative stress and chronic fatigue syndrome

Another speaker, Christian Renna, DO, presented an interesting thesis that without sufficient serotonin and antioxidant defenses, the brain decides that it's not safe to produce dopamine and norepinephrine—hence chronic fatigue and related neurosomatic disorders. A central feature of chronic fatigue-like disorders is a deficiency of norepinephrine. But simply increasing norepinephrine through pharmacological means is not appropriate, since the brain is already overwhelmed with stress, and thus with free radicals. In Renna's view, both stress reduction and antioxidant supplements are absolutely necessary to help the brain produce and maintain inhibitory and excitatory neurotransmitters in proper ratios. This applies not only to those diagnosed with chronic fatigue, but to all of us, especially as we age.

In the presence of excess free radicals, the brain seeks to protect itself by lowering its activity. This means lower production of excitatory neurotransmitters such as dopamine, and less energy production in the mitochondria. Every neuron has an excitatory threshold beyond which it will not fire, Renna explained. Instead, the overstimulated neuron shifts to an “escape pathway,” preventing the synthesis of dopamine and norepinephrine. In chronic fatigue, the neuroexcitatory threshold is set too low. Raising it requires increasing the brain's safety mechanisms: serotonin and antioxidants. “If the cell doesn't need to fear oxidative stress, the mitochondria light up like Las Vegas,” Renna said.

He also pointed out that many chronic fatigue patients responded well to fen/phen, which was a combination of a serotonin-raising drug and an amphetamine analogue. “Overcoming serotonin deficiency allows the brain to tolerate more norepinephrine,” Renna said. He didn't favor long-term use of antidepressants, however. He felt such use prevented the patient from achieving a more complete recovery. The point is to help the brain produce more of its own serotonin. Thus, we need to address the necessity of lowering stress—not only emotional stress, but also stress coming from chronic low-grade infections, toxins (including endotoxins [toxins produced within the body] originating in the gut under conditions of dysbiosis, meaning an overgrowth of harmful intestinal flora), excess calories, insufficient sleep or any other source. “The more gentle the stimulation, the better,” Renna said. “So don't rush.”

In addition, we must make sure the patient's antioxidant defenses are adequate before we use any kind of stimulant. “If a person is not energetic, maybe it's not safe for them to be energetic,” Renna said, again reinforcing the point about low serotonin and depleted antioxidant defenses. Both need to be corrected through stress reduction, diet, the right exercise and supplements. The brain will produce more dopamine when it becomes safe to do so.

Dopamine is a very energizing, feel-good neurotransmitter; in addition, dopamine stimulates the release of nerve growth factors. But dopamine has its dark side. “Dopamine is the most dangerous of all neurotransmitters because the brain needs to defend itself against overstimulation,” Renna explained. When serotonin is low, the threshold for what constitutes overstimulation is also set low. Low serotonin, low dopamine, and low energy production in cerebral mitochondria all lead to a cascade of harmful consequences. Since the brain is in constant chemical communication with the rest of the body, including the endocrine system and the immune system (in fact Renna calls the immune system “morcelized brain”), the whole body suffers. We see this not only in the chronic fatigue syndrome, but above all in aging.

Renna also discussed neuroprotective supplements. His special emphasis was on flavonoids as particularly effective antioxidants and neuroprotectants. Flavonoids (such as those present in blueberries and bilberries, green tea, grape seed extract, and various fruits and vegetables) not only raise glutathione levels, but also help prevent inflammation by inhibiting the enzymes in the lipoxygenase family (LOX), which NSAIDs and COX-2 inhibitors cannot do. Renna added folic acid, SAME and acetyl-L-carnitine to the list of essential neuroprotective supplements. As for the so-called smart drugs, such as deprenyl and piracetam, these too are worth looking into, according to Renna. They increase energy production while reducing oxidative stress (acetyl-L-carnitine works the same way).

Tofu has recently come under suspicion as deleterious to the brain. In an ironic reversal of our previous beliefs, coffee and tea are now seen as neuroprotective, while tofu is increasingly under attack. Renna takes his patients off tofu, at least until there is some solid new evidence of its safety.

Both Perlmutter and Renna covered a huge territory, at times overwhelming the audience. Perlmutter focused on the “anti-inflammatory breakthrough”: preventing and fighting inflammation in the prevention and treatment of Alzheimer’s disease, as well as on the use of intravenous glutathione, the body’s chief detoxifying compound, as a new and potentially revolutionary treatment for Parkinson’s disease. Perlmutter also touched on the production of energy in the cerebral mitochondria, a subject developed more fully by Renna. The main message was clear: we already know a great deal about preventing and treating brain diseases and age-related cognitive and motor dysfunction. Relatively simple measures such as reducing caloric intake and taking fish oil, NSAIDs, lipoic acid and CoQ10 could save millions from terrible brain diseases. It is high time to start implementing this knowledge on a much broader scale.

Antioxidants against vitamins: lipoic acid and selenium improve the survival of AIDS patients

The excitement over the new anti-retroviral drugs designed to fight the AIDS virus is yielding to a sober assessment of their limitations. By now it has been shown that these drugs do not fully restore immune function. They are not the long-awaited cure. Their side effects are so severe that many AIDS patients drop out of treatment. In addition, the majority of the virus is in the latent stage in the nuclei of T cells, and antiviral drugs cannot affect latent viruses.

Are there effective alternative treatments? An affirmative answer was compellingly presented by two speakers: Raxit Jariwalla, PhD, a research scientist at California Institute for Medical Research in San Jose, and Lynn Patrick, ND, medical director of HIV Wellness Program in Tucson, Arizona. The speakers cited study after study showing improved survival rate for AIDS patients who used certain critical supplements known to reduce oxidative stress (a major factor in the progression of the disease) and, in some cases, to significantly suppress viral reproduction.

Both presenters singled out lipoic acid as particularly important. All antioxidants are also anti-inflammatory agents, but lipoic acid is regarded as an especially effective anti-inflammatory.

It has been known for almost a decade that lipoic acid effectively inhibits the replication of the AIDS virus in vitro. This is not surprising in view of our knowledge that lipoic acid inhibits the activation of Nuclear Factor kappa B (NFkB), which is believed to play an important role in the activation of the HIV virus. Essentially, the latent virus is activated by certain inflammatory cytokines that result from the activation of NFkB. These cytokines include Tumor Necrosis Factor alpha (TNF alpha)—hence the goal of reducing TNF alpha, and the similarity between alternative treatments against AIDS and hepatitis, Dr. Patrick pointed out. Both protocols emphasize lipoic acid, selenium and a combination of various other antioxidants. In addition, many AIDS patients are co-infected with Hepatitis C. “All AIDS patients need liver support,” Patrick said. In addition to 500 mg of lipoic acid/day, she also uses silymarin, shown to be remarkably effective in restoring liver health.

Lyn Patrick largely confirmed Dr. Jariwalla’s primary emphasis on lipoic acid, stating that “lipoic acid is of extreme importance for HIV patients.” She reinforced this with some added details. Studies have found that lipoic acid inhibits reverse transcriptase (a viral enzyme needed for replication), and makes AZT significantly more effective.

Another obvious reason for the importance of lipoic acid for HIV patients is its ability to raise glutathione, our chief detoxifier and a crucial endogenous antioxidant. Glutathione is low in all serious illnesses. When the levels of glutathione rise, the result is reduced oxidative stress. The role of oxidative stress has been neglected in the discussion of AIDS, with the public getting the impression



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that the sole factor in the progression of this disease is the presence of AIDS virus, commonly referred to as HIV. Yet oxidative stress and consequent inflammation play a major role in whether symptoms of AIDS will appear at all, and in the rate of progression. Some people who are HIV positive do not show any symptoms of AIDS. Interestingly, this group tends to have a higher intake of antioxidants, from diet or supplements or both. Even merely taking a multivitamin turned out to reduce the risk of developing the symptoms of AIDS by 33% in HIV-positive individuals.

While lipoic acid plays a starring role in the alternative treatment for HIV patients, another thiol (i.e. sulfur-containing) antioxidant, the acetylated form of cysteine known as NAC, appears to be somewhat helpful as well. NAC too helps raise the levels of glutathione, but by itself it is not likely to have enough effect in AIDS patients; lipoic acid is far more efficient at raising glutathione and blocking NFkB. The special effectiveness of lipoic acid may derive from the fact that it's a dithiol (it has two sulfur groups), while NAC is a monothiol.

NAC is more effective when used with other antioxidants. In particular, it synergizes with high-dose ascorbate. High-dose ascorbate, Dr. Jariwalla stated, is unique in that it recycles itself to the reduced state. It also produces "dramatic dose-dependent suppression of viral reproduction." It is believed that high-dose ascorbate suppresses viral replication through a different mechanism than thiol antioxidants (lipoic acid and NAC) and selenium. Some participants suggested that intravenous delivery of ascorbate would be most effective, due to the large dose required (6 to 12 grams if taken orally).

Selenium also plays a starring role in anti-viral regimens. It too inhibits NFkB. But the main reason that selenium is known as "birth control for viruses" derives from the fact that many viruses, including HIV, need selenium to replicate. Interestingly, in a selenium-rich milieu the viral genes that control replication stay turned off. In addition, selenium is required by T cells, and potentiates the action of interleukin-2. An AIDS patient is ten times more likely to die if s/he is selenium-deficient, according to Dr. Patrick. She uses the dose of 400 mcg per day.

Vitamin E is known to play an important part in bolstering immunity and reducing inflammation. Like lipoic acid, vitamin E also inhibits NFkB, essential for viral replication. Dr. Patrick stressed that only the succinate form of vitamin E inhibits both the activation of NFkB and the binding of activated NFkB to DNA, as shown by the research of Dr. Lester Packer in the early nineties. Vitamin E has also been shown to enhance the action of AZT. Thus, the form of vitamin E known as alpha-tocopheryl-succinate ("dry E" in popular parlance) is of crucial importance for HIV patients. It is possible, however, that gamma-tocopherol, being a COX-2 inhibitor, is also of value.

Vitamin A and beta carotene have been found helpful, as has zinc—but only in small doses. Zinc supplements in excess of 10 to 15 mg appear to increase disease progression. We don't know very much about zinc and HIV, but we do know that zinc is important for the immune system. Zinc activates the thymus hormone thymulin, which plays a part in the differentiation of T cells. Zinc is also involved in protease and integrase enzymes. It seems that supplementing with 12 mg of elemental zinc works best, according to Patrick.

HIV infection has also been linked to deficiencies in B6, B12 and folate—the methylating factors. There is a "rampant deficiency" of B12 among AIDS patients, according to Dr. Patrick. Such nutritional deficiencies in patients with full-blown AIDS result mainly from their poor absorption of nutrients due to gut problems, Patrick explained. Thus doses need to be especially large.

Most HIV patients are also glutamine-deficient, Patrick said. This is true of anyone under chronic severe stress, even though glutamine is abundant in any protein-rich diet (interestingly, the immune dysfunction seen in AIDS resembles the symptoms of protein-calorie malnutrition). Glutamine helps stop diarrhea and prevents muscle wasting. Large doses are needed (Patrick uses 40 g/day in four divided doses), but the cost is only \$31 per week versus \$1000 a week it would take for growth hormone treatment, another therapy aimed at preventing wasting.

Patrick mentioned yet another supplement: acetyl-L-carnitine. AZT is a mitochondrial toxin. It turns out that the combination of acetyl-L-carnitine and lipoic acid can reverse this toxicity.

After learning about the effectiveness of lipoic acid, NAC, Vitamin E, high-dose ascorbate and other supplements in fighting the HIV virus and improving the survival rate of AIDS patients, it was sad to hear that AIDS activists have largely lost interest in alternative therapies and are mostly waiting for the next "miracle drug." So far, the drugs have proven highly toxic and not effective in many patients. We need to seriously consider the preventive and therapeutic use of supplements such as lipoic acid. In Dr. Jariwalla's words, "nutrients are compelling candidates for treatment of immune dysfunction underlying AIDS."

Much is to be gained from paying attention to the developments in the alternative treatment for AIDS. Cellular immunity decreases not only in the course of AIDS, but also during aging. It is of utmost importance that we learn how to sustain a healthy immune system that can fight viruses and bacteria. Thus, the results presented in the lectures on AIDS are of special interest for anti-aging medicine. Antioxidants, with special emphasis on lipoic acid and selenium, once again show their amazing potential.

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Lipoic acid, inflammation and skin aging

Dr. Nicholas Perricone is best known as the author of *The Wrinkle Cure*, a cutting-edge book on reversing skin aging. In the book, he announces, "After years of working with antioxidants, I knew I had finally found the ultimate wrinkle cure." What is it? Topical lipoic acid in the right concentration. Why does it work so well? Because it's a superb anti-inflammatory.

"Lipoic acid inhibits Nuclear Factor kappa B (NFkB) better than anything else," Perricone stated. The ability to inhibit NFkB seems a key to anti-inflammatory action, since NFkB is a transcription factor that activates the production of inflammatory cytokines that initiate cellular destruction. And if inflammation plays a central part in skin aging, as Perricone believes, then an effective anti-inflammatory cream makes perfect sense.



Lipoic acid has been found to significantly reduce fine lines and shallow wrinkles. This is far from sensational, since Retin-A, topical vitamin C (Perricone recommends the ascorbyl palmitate form for topical use), CoQ10 and various other antioxidants do the same thing. The surprising discovery made by Dr. Perricone was that lipoic acid can also help heal acne scars. It is generally believed that only aggressive procedures such as laser resurfacing can do anything about acne scars. Needless to say, compared to a laser peel, lipoic acid is much cheaper, not to mention non-traumatic.

How does lipoic acid perform this feat? According to Perricone, lipoic acid activates a transcription factor known as AP-1, which leads to the production of enzymes called metalloproteinases. These enzymes digest the damaged collagen, thus helping erase wrinkles and even scars. At the same time, lipoic acid helps cells produce more energy in the mitochondria, thus making more energy available for healing. Finally, due to its anti-inflammatory effectiveness, lipoic acid makes it easier for patients to tolerate Retin-A. Both Retin-A and lipoic acid inhibit the inflammatory cytokine-induced destruction of normal collagen.

Yet another benefit of topical lipoic acid is diminished puffiness around the eyes. This puffiness, or swelling, is technically called edema, and is one of the visible signs of inflammation (redness is another; since inflammation is pro-aging, beware of products that irritate your skin to the point of redness).

"The effective range for topical lipoic acid is between 3% and 10%. We use mainly 5%. We sell this product to dermatologists," Perricone explained. The bad part is that Perricone's products sold to the public typically contain only 1% lipoic acid, with 3% available, but for over \$100 for a small amount. Fortunately there are compounding pharmacies. You may be surprised how many of them work closely with dermatologists. Many topical products, however, are available to the public without the need for a prescription. This is where having the right knowledge really pays.

Dr. Perricone emphasized that his approach to skin rejuvenation goes far beyond topical anti-inflammatories. "Beauty is the look of health," he said. Good looks serve as a terrific incentive for patients to eat a low-glycemic, anti-inflammatory diet (high in fish oil and flavonoids—instead of meat, think fish and seafood; instead of cake, think strawberries). Perricone also encourages patients to take supplements, exercise, practice meditation and improve their lifestyle in general.

The greatest enemy of youthful skin is probably smoking. "There is a 15 to 20 year difference in appearance between smokers and nonsmokers," Perricone asserted. Speaking of sun exposure, Perricone made the interesting point that we need some sun exposure—fifteen minutes a day is probably enough. He also noted that perhaps as much as 50% of skin damage is due to glycation (the damage to proteins caused by simple sugars such as glucose and fructose). The skin of people whose blood sugar is chronically high can look as old and wrinkled as the skin of smokers. While a low-glycemic diet that excludes refined carbohydrates is the main means to reducing glycation, Dr. Perricone noted that lipoic acid also helps reduce glycation.

Our pursuit of the dazzling dermis has never been more relentless—or more expensive. The old saying, "After 40, you have the

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face you deserve" should be amended to, "After 40, you have the face you can afford." Fortunately there are some topical antioxidant preparations that are both effective and affordable (at least by comparison with laser surfacing). The first breakthrough was Retin-A, a form of vitamin A. Then came the hydroxy acids (including salicylic acids). Hydroxy acids act not only as exfoliants, but also as antioxidants and anti-inflammatories. Then the power of topical vitamin C to increase collagen production was discovered. Now Dr. Perricone has publicized his discovery of the powerful rejuvenating effects of topical lipoic acid. No doubt more discoveries lie ahead. The future looks beautiful.

Of dwarf mice and growth hormone: does growth hormone replacement shorten life expectancy?

The lectures and workshops on hormone replacement showed a remarkable consensus on two points: testosterone and growth hormone have extraordinary health benefits. But while a few years ago the safety of testosterone replacement was being questioned, now the controversy is directed to the impact of growth hormone replacement on longevity.

The news about testosterone couldn't be better. According to the latest findings, testosterone lowers LDL cholesterol and triglycerides, increases insulin sensitivity, strengthens the heart muscle and increases cardiac output, dilates the coronary arteries and alleviates angina.

"Every male cardiovascular patient should be on testosterone," Dr. Neal Rouzier declared. This is a revolutionary reversal of the old dogma that held that testosterone was bad for the heart. Not one person in the audience contested Rouzier's assertion.

Furthermore, testosterone builds muscles and bones, decreases exercise-induced stress, reduces abdominal fat, protects joints, helps prevent cognitive decline and Alzheimer's disease, and is a wonderful antidepressant. One conference participant commented, "Testosterone is a wonderful everything." I think testosterone is fabulous," another physician concurred.

As for the danger of prostate cancer, the new thinking is that the main culprit is estrogen. Consequently we now see a lot of interest in aromatase inhibitors, compounds that decrease the conversion of testosterone to estradiol. Chrysin, a flavonoid, has become particularly popular.

Interestingly, dihydrotestosterone (DHT), once maligned, is now in greater favor, since it can't be converted to estradiol. A DHT patch is in use in Europe, and so far no increase in prostate cancer has been found.

Rouzier favors testosterone for women as well, though of course in gender-appropriate doses. The addition of testosterone appears to further enhance bone density. It also increases a woman's libido and her sense of energy and well-being.

What kind of testosterone replacement is best? The news is that the gel appears to be more effective than the patch (not to mention the fact that if you order testosterone gel or cream from a compounding pharmacy, you are getting a terrific bargain).

Rouzier observed that Prozac and similar drugs work poorly at best. The real improvement in mood and energy comes from increasing the levels of hormones such as testosterone, growth hormone and thyroid. By the way, Rouzier pointed out the little known finding that T3, the most active of the thyroid hormones, enhances cardiac performance; he warned that Synthroid (thyroxine, or T4) may not raise T3.

As for the anti-hormone stance of many conservative mainstream physicians, Rouzier remarked, "Someone out there doesn't want you to feel good." The old attitude is that only specific diseases are to be treated, but not aging as such. The new attitude, represented by Rouzier and many other holistic physicians, is that we should begin safe hormone replacement relatively early in life, before the development of pathological changes (such as insulin resistance, atherosclerosis or cognitive decline) that are related to "natural" hormone deficiencies that progress as we age. Again, there was no disagreement with this still revolutionary notion.

The high drama of the conference began with the first presentation on growth hormone. Actually all three main speakers were in agreement that growth hormone replacement (or enhancement) should be universal, and started as early as mid-thirties. "Everyone over the age of 35 is growth hormone-deficient," Rouzier stated, arguing that we shouldn't wait for symptoms of "somatopause" such as atherosclerosis and osteoporosis before beginning replacement with multiple hormones, definitely including growth hormone. Rouzier stressed that he doesn't believe that "reversing aging" is possible. We can, however, slow down aging by various



"Every male cardiovascular patient should be on testosterone," ... furthermore, testosterone builds muscles and bones, decreases exercise-induced stress, reduces abdominal fat, protects joints, helps prevent cognitive decline and Alzheimer's disease, and is a wonderful antidepressant.

means, including maintaining hormones at youthful levels and in youthful ratios. Hence the urgency about starting hormone therapy early.

If we are serious about anti-aging medicine, sooner or later we have to face the thorny issue of “growth hormone for everyone over 35.” Very likely, growth hormone is the most potent rejuvenating therapy currently available. No other hormone can decrease body fat so dramatically while building muscle. No other hormone can actually cause a regrowth of organs such as the kidneys back to their youthful size. Patients on correct (low-dose) growth hormone replacement appear extremely satisfied with it: their “spare tire” disappears, together with the flab under the chin; their skin thickens and smooths out, their energy, zest for life and libido increase.

No one at the conference questioned the well-documented benefits of growth hormone in terms of its ability to restore a more youthful physiology and enhance the quality of life. The controversy centered on the possibility that maintaining youthful growth hormone levels may actually be harmful in the long run, shortening life span. The conference participants seemed surprisingly familiar with the research on the extraordinary longevity of dwarf mice, which are deficient in growth hormone and IGF-1. IGF-1 stands for insulin-like growth factor 1, and is regarded as the most important metabolite of growth hormone, an anabolic hormone that promotes tissue growth. IGF-1 has a structure similar to insulin, and many of its effects overlap those of insulin. The mainstream view is that growth hormone is “translated” in the liver into IGF-1, and expresses its activity through IGF-1—even though it has been documented that low levels of IGF-1 are not a reliable indicator of growth hormone deficiency.

The uproar began when Dr. Rashid Buttar, who discussed trans-D-tropin (a validated prescription-only growth hormone releaser) announced that his study found that as growth hormone levels go up, IGF-1 levels go down. The mainstream belief is that growth hormone always raises the levels of IGF-1. “The literature is wrong,” Buttar flatly stated. He himself was surprised to find this inverse correlation, but it made sense in the light of his other data: he found that aged, sedentary, obese subjects had very high levels of IGF-1 (250-300), while young athletes had levels as low as 88. The highest IGF-1 in the sedentary group was 304, while the highest IGF-1 among athletes was 196. According to literature, IGF-1 levels below 150 may be a marker of growth hormone deficiency. Buttar reminded the audience that young athletes typically have low insulin, but higher testosterone and higher growth hormone than older, sedentary individuals.

Young athletes differ from obese, sedentary, elderly people in many ways, but levels of insulin and cortisol may be of special importance in regard to IGF-1. We know that high cortisol reduces growth hormone release, but increases somatostatin and IGF-1. Excess insulin likewise inhibits the release of growth hormone, though its effects on the levels of IGF-1 may be a more complex story. Somewhat surprisingly, Buttar's emphasis was on cortisol more so than insulin. “Adrenal stress is a big factor in insulin resistance, high IGF-1 and low growth hormone,” he stated. It is also well known that cortisol rises with age, while the release of growth hormone keeps on declining. IGF-1 levels correlate with stress, while they do not reliably correlate with growth hormone levels. There is also some inverse correlation with amount of exercise. An increase in exercise results in lower IGF-1 levels.

In fact under certain conditions high levels of growth hormone are accompanied by low levels of IGF-1. For instance, when humans or other primates significantly reduce their food intake (thus causing a dramatic decline in the levels of blood sugar and insulin), the levels of growth hormone go up while the levels of IGF-1 drop. On the other hand, type II diabetics, known to have excess insulin and insufficient growth hormone, show high levels of IGF-1. Incidentally, Buttar found diabetics to be nonresponsive to trans-D-tropin. Their growth hormone levels did not go up. Interestingly, however, their glucose levels went down in the course of trans-D-tropin treatment.

Obviously, there are still many things we need to learn about growth hormone and its metabolites. Sex steroids such as estradiol and testosterone, as well as cortisol, insulin and thyroid hormones all interact with growth hormone. Growth hormone in turn affects the release of many other hormones. The more we study these interactions, the more complex everything looks.

The assertion that growth hormone can actually lower IGF-1 upset Dr. Rouzier, who said that his IGF-1 doubled when he started taking growth hormone shots. Rouzier did admit that IGF-1 is not a reliable measure of growth hormone activity, and its levels fluctuate considerably. Asked, “Why test for IGF-1 if it's unreliable?” Rouzier replied, “Because it's a simple test.”

We must note that Dr. Rouzier used growth hormone injections, while Dr. Buttar used a growth hormone releaser, obtaining a more physiological release of growth hormone. Buttar's argument is confined to growth hormone secretagogues. Enhancing growth hormone release with secretagogues is regarded as a more physiological method, less likely to produce side effects. We know that the effects of hormones are extremely dose-dependent. There is no question that high doses of growth hormone are dangerous. The ideal is the physiological pulse.

Richard Walker, PhD, was a more formidable figure, being regarded as being at the top of his field. He too had trouble with the idea of an inverse correlation between growth hormone and IGF-1, but appeared open-minded toward new evidence. Since women on oral estrogens have also been found to have higher growth hormone levels but lower IGF-1 levels, clinicians have assumed that they need to give women higher doses of injectable growth hormone to produce the same levels of IGF-1 as are seen in men. Walker explained that estradiol actually enhances sensitivity to growth hormone, and that women preserve much better growth hormone levels than men until menopause—and this may be a big factor in women's greater longevity. As for IGF-1, Walker admitted that we simply do not know what the optimal range is for either sex.

Still, it was the specter of those long-lived, growth hormone-deficient dwarf mice that haunted all lectures and workshops on hormone replacement. Could it be that growth hormone per se shortens life expectancy, or is it rather a combination of high insulin and high IGF-1? If the answer turns out to be growth hormone, that most dramatically rejuvenating of all hormones, then we may have on our hands the painful choice between quantity and quality of life. On the other hand, the chief culprits are likely to be excess insulin and excess IGF-1— precisely the type of pathological endocrine profile that we see in obese, sedentary individuals.

A massive National Institute of Aging study singled out low insulin as the best predictor of longevity in men. In other words, men with the lowest insulin had the lowest mortality. Also, this reporter contacted Dr. A. Bartke, one of the chief investigators involved in the dwarf mouse research, for comment on high IGF-1 in relation to longevity. His opinion is that it's high IGF-1 that is likely to be harmful. For instance, we know it's linked to higher risk for various common cancers; this is not surprising, since, like insulin, IGF-1 promotes tissue proliferation. When calorie-restricted monkeys are given IGF-1 injections, they lose their resistance to cancer. Buttar pointed out that initial stages of cancer are accompanied by high levels of IGF-1, while treatments that suppress IGF-1 also inhibit cancer.

Low IGF-1 correlates with longevity, according to Bartke. IGF-1 is “virtually absent” from the serum of the long-lived dwarf mice. Thus, aiming at high IGF-1 levels might not be desirable, both in terms of life expectancy and susceptibility to cancer. Bartke warned, however, that at this point we have trouble separating the effects of growth hormone itself from those of its metabolites, chiefly IGF-1. It is an enormously confusing situation.

It is still too early to make clear practical recommendations as to the optimal form of growth hormone therapy for everyone over 35 or 40. Too many questions remain to be answered. Dr. Walker warned that injectable growth hormone should not be used as a short-term treatment for obesity. Obese patients tend to have high blood sugar and high insulin, and need to be monitored more closely than non-obese patients due to the possibility of extremely serious side effects such as the development of diabetes. In the future, growth hormone replacement or enhancement will probably emerge as a universal anti-aging therapy. Currently, the use of growth hormone releasers (secretagogues) rather than injections appears to be the safest route to obtaining the benefits of increased growth hormone release without the risk of raising IGF-1 to potentially excess levels. Restricting calorie intake is another proven way to raise growth hormone. Drugs that raise dopamine (e.g. deprenyl) also increase growth hormone release. Meditation has been shown to increase growth hormone (possibly because it decreases cortisol). Melatonin also slightly raises growth hormone.

Finally, there is also a lot of interest in improving the depth of sleep as another means to safely raise growth hormone release. We know that the length of slow-wave sleep starts decreasing in men as early as age thirty. The deeper the sleep, the greater the release of growth hormone. But how do we counteract the age-related loss of deep sleep? According to Dr. Walker, growth hormone-releasing hormone (GHRH) enhances sleep, but giving growth hormone through injection may cause the side effect of sleep shortening. As we age, we appear to lose sensitivity to GHRH. There seems to be no end of complexity the more we look into any issue pertaining to hormone replacement.

For now, the only answer is “We need more research.”

Overall, in spite of the continued controversy over growth hormone therapy, the recent ACAM conference showed the emergence of a growing consensus that alternative medicine is coming of age, and gaining a respectable scientific base. In all presentations dealing with specific diseases there was an effort to get at the root causes, not just treat the symptoms. One of the root causes in the development and/or progression of a chronic disease is often inflammation. Inflammation has also emerged as one of the most important factors in aging. We do have considerable knowledge about inflammation as well as about anti-inflammatory agents. Simple, inexpensive remedies such as ibuprofen, aspirin, fish oil, lipoic acid or bilberry extract have been validated as powerful preventive medicine. The future should bring even more exciting breakthroughs in this area.

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