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STRESS AND MULTIPLE SCLEROSIS

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As noted in prior Newsletters, stress can have important influences on the course of multiple sclerosis (MS). Charcot noted that emotional distress was often a precipitating factor in his initial description of the disease, and subsequent investigators have corroborated this. Similarly, many patients link the development of disabling symptoms to some distressful event or a period of prolonged stress. Others believe that stress is responsible for causing their condition to rapidly deteriorate, or to recur after having been quiescent for months or even years.

The disease often begins with the fairly abrupt onset of neurologic symptoms such as numbness and tingling, marked weakness or paralysis, double vision or loss of vision in one eye, brief but excruciating episodes of facial pain, dizziness and difficulty in maintaining balance, or problems with bladder control. This may progress to severe vertigo and incoordination, spasticity or paralysis of one or more extremities, various speech difficulties, bladder and bowel incontinence, marked fatigue, depression, and emotional lability.

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The course of the illness and the nature and severity of complaints varies tremendously. Some individuals may experience a transient episode of loss of vision, disturbed speech, or unilateral facial pain in their twenties, with no recurrence for months or years, and no apparent permanent neurologic damage. Others pursue a progressive downhill course that confines them to wheelchairs, and require constant assistance to perform daily functions.

MS is believed to be due to a disturbance in immune system function, in which normal tissues are perceived as being foreign invaders. This leads to an attack by the body's defense mechanisms that result in destruction of myelin, the lipid substance that surrounds nerve fibers to protect them from damage. A specific cause for MS has not been identified, but heredity, infections, stress, and other environmental factors seem to play a role in certain patients.

The deterioration and loss of myelin hinders the ability of nerves to relay information. Since the distribution of these lesions is patchy, signs and symptoms are erratic and unpredictable, but are apt to be most severe when the transmission of nerve signals is disrupted in the spinal cord and brain. These can cause speech and visual disturbances, motor dysfunction that makes it difficult to walk or maintain balance, and various cognitive and emotional deficits. The diagnosis for years depended on finding the "Charcot triad" of tremor, nystagmus, and erratic speech. However, it is now apparent that these signs are absent in many patients, or may not appear for years.

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Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief
home page: www.stress.org
e-mail: stress124@earthlink.net

Making The Diagnosis

Establishing the diagnosis of MS can therefore be extremely difficult, especially when it first starts. The abrupt onset of unexplained, excruciating facial pain that lasts for a few hours or days in a young woman is often assumed to be trigeminal neuralgia, until other neurologic complaints surface months or years later. Symptoms and signs can be similar to those seen in other demyelinating diseases of the nervous system, like the encephalomyelitis that often follows viral infections. They may also resemble immune-mediated or deficiency diseases that affect the nervous system, such as lupus and sarcoidosis, or Vitamin B-12 deficiency.

Unlike the above disorders, there are no blood tests, x-rays or other diagnostic procedures that are definitive. Spinal fluid examination may reveal increased amounts of certain immunoglobulins resulting from chronic immune system stimulation in well established cases. Lesions in the brain can often be detected by special sensory-evoked potentials, but both of these are complex research procedure that are still not specific. The most useful technique is magnetic resonance imaging (MRI) of the brain, which can display many of the areas of demyelinization. Serial studies are able to show how these increase over time, and using a contrast agent like gadolinium, will identify recent damage.

What Causes Multiple Sclerosis?

As with Parkinson's and Alzheimer's disease, which are also neurodegenerative disorders, it seems likely that MS may result from more than one cause. There is some evidence that it may have a genetic component, since in some instances, more than one close relative may be affected. Sixty years ago, one investigator was able to collect 84 references in the literature to support a familial tendency. It is estimated that up to 10 percent of patients have a near relative with the disease. This is much lower than is seen with other heritable disorders, and its occurrence in successive generations is uncommon. However, in one study, the parents, siblings, nephews and nieces of MS patients had a much higher incidence of other nervous and mental disorders compared to the relatives of a control group admitted for fractures. Perhaps MS is simply one manifestation of some familial neuropathic disorder that is expressed in different ways, depending on the genes that are involved.

Some research studies support the theory that multiple sclerosis can be linked to several genes. In one recent study of 75 families with at least two MS members, American and French researchers identified 19 chromosome locations believed to house the genes that determine who will develop MS and who will not. As the lead author commented "This study demonstrates that there is no one gene responsible for causing multiple sclerosis . . . . . We believe it is the interaction of several genes, potentially triggered by an environmental stimulus." As occurs in many other disorders, that stimulus could be emotional stress, which pulls the trigger of a loaded gun.

However, it might also be an infection, and there is good evidence that a herpes virus may be responsible for some cases. In 1995, researchers first identified traces of herpesvirus 6 (HHV-6) in the genetic material of brain tissue from MS patients. Since then, traces of the active human virus have been found in the spinal fluid of three out of seven patients in one study, and in the lymph nodes of three of four in another. Further support comes from a very recent NIH report showing that 73 percent of patients with chronic MS had an increased antibody response to HHV-6 antigen, compared to only 18 percent of matched controls.

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About 30 percent of these MS patients had active virus particles in their blood, while none was found in the other participants. Traces of HHV-6 were detected in the diseased brain plaques of a cadaver with MS, but not in normal (non-diseased) brain tissue. Since experimental HHV-6 infections of the central nervous system have been shown to damage the myelin sheath, there is good reason to suspect a causal relationship.

Herpes infections are extremely common, but these viruses characteristically lie dormant in the cell, and produce no signs or symptoms unless triggered by some stress that lowers the body's resistance. Common examples of this are seen in patients with recurrent herpes of the lips or genitalia. It is estimated that nine out of ten American adults harbor the HHV-6 virus, suggesting that many MS cases could be due to infection with this organism. This might also explain why emotional stress and depression can precipitate or aggravate the disease, since both have been shown to lower immune defenses. HHV-6 infection responds to antiviral medications like acyclovir, and trials are under way to determine whether a course of therapy might result in clinical improvement. If results are positive, a vaccine might be considered.

The participation of the immune system seems clear from microscopic and other studies of MS lesions. They show macrophages, plasma cells, T-lymphocytes, and other immune components in fresh plaque lesions. These characteristics suggest a cell-mediated immune response directed against some protein component of myelin. What initiates this, and why it is not prevented or held in check by suppressor cell activity, or other normal balancing mechanisms remains to be determined. The specific antigen against which the immune response is directed has not yet been identified. In addition, it is not clear whether most or any of these immunological responses are the cause of the damage to myelin or the result of it. Attempts have therefore been made to try to develop an animal model of MS that might clarify these relationships, as has been possible with disseminated lupus erythematous. The difficulty is that it would be extremely difficult to replicate the wide variation in signs and symptoms seen in MS. And drugs that might help some complaints, could aggravate others.

Is There An Animal Model Of MS?

Experimental allergic or autoimmune encephalomyelitis (EAE) is an acute disease of the central nervous system that can be induced in susceptible animals by the injection of certain nervous system tissues. Researchers hit on this method over 60 years ago, following the observation that humans who received rabies vaccine often developed a condition known as acute disseminated encephalomyelitis. This appeared to be an "allergic" response to certain nervous system components in the preparation rather than anything to do with the rabies virus. However, affected individuals often had some signs and symptoms reminiscent of those seen in multiple sclerosis.

In 1933, Rivers produced a similar disorder in monkeys by repeatedly injecting them with normal rabbit spinal cord tissue. This was an acute illness characterized by a loss of tail tone, an ascending paralysis of the hind legs that progressed to quadriplegia, urinary incontinence, and fecal impaction. The onset of symptoms usually started within two weeks, although microscopic lesions could be detected much sooner. The animals either subsequently died or made a spontaneous recovery, depending on a several factors. Since then, various refinements have led to a chronic model of EAE which has a much longer incubation period of up to 6 months. It is characterized by relapses and remissions that more closely resemble the clinical course of MS, and is generally viewed as its animal equivalent. Numerous T-helper cells are found in infiltrates, and the lesions in this chronic form are also more like those seen in humans.

It is possible to trace out what transpires in the immune system using this model. For example, the disease will not occur if T-lymphocytes are absent either as a result of removal or the thymus or irradiation. Certain antibodies can reverse EAE in rodents, and specific antigens have been shown to prevent or suppress the disease, suggesting that both cell mediated and humoral responses may be involved. It has also been possible to demonstrate the protective benefits of Cytoxan and other immunosuppresant drugs, and study the effects of cortisone, other steroids, and immune system components like interferon, to explore possible applications in humans.

Recent Advances In Treatment

As indicated, evidence that herpes or other infections may trigger MS, raises the possibility that anti-viral drugs might provide benefits for some patients. If successful, then vaccines could be developed for groups at increased risk because of a family history. Several different genes or combinations of genes may be involved, and researchers are zeroing in on these. They are also using genetic approaches to manipulate the immune system's deranged cytokine activities that appear to be responsible for causing the damage to myelin.

Cytokines are hormone-like substances that are released by the immune system's T cells. Some can suppress the inflammatory response, while others promote it. Certain cytokines actually seem to set off little "brushfires" in structures like nerves or joints to which they are attracted. If this inflammatory response is not checked, it will continue to cause damage that can result in the neurologic deficits of MS, or the pain and swelling of rheumatoid arthritis. Under normal circumstances, these smoldering fires are extinguished by cytokines that suppress inflammation. Suppressor cell activity is lowered in MS, so that their anti-inflammatory products are not as available to stop the destruction of myelin.

However, researchers have identified the genetic code responsible for manufacturing the anti-inflammatory cytokines found in suppressor cells. Stanford scientists recently reported that they were able to insert these instructions into other immune system cells that are automatically attracted to areas of inflammation. This was accomplished by the use of specially inactivated retroviruses. Retroviruses permanently integrate themselves into the DNA of host cells, and since they cause no illness, they are ideal delivery vehicles, acting like little Trojan horses. When injected into laboratory animals, immune system defense cells gobble them up, and the command for making inflammation suppressing cytokines now becomes incorporated into their own genetically programmed response activities. As a result, as soon as these immune system cells reach a site of damage to which they are naturally attracted, they begin churning out inflammation fighting proteins .

Results in animals have been so encouraging, that human trials are being considered not only in MS, but also rheumatoid arthritis and diabetes. Most treatments for these and other autoimmune disorders utilize drugs that suppress the immune system in general. This might be dangerous, since it could increase susceptibility to infection and other problems for some patients. This new technique targets specific sites, rather than exerting systemic effects, which has obvious advantages.

There are several other promising approaches that are in progress or on the horizon. These include efforts to bolster the immune system with specific cytokines known as interferons. One such product is beta-interferon-1-b (Betaseron), which patients can give themselves by subcutaneous injection. It has had promising results, but is often associated with annoying flu-like symptoms, depression, and anemia. An interferon-beta-1a product (Avonex) given by intramuscular injection was also approved last year, and while reportedly even more effective, has similar adverse side effects.

These difficulties have apparently been overcome by a new interferon-beta-1a derivative (Rebif), that seems to improve all of the major signs and symptoms of MS without any significant side effects. Researchers recently reported that in a two-year multi-center study of 560 patients with multiple sclerosis, Rebif significantly delayed the progression of disability, decreased the number and severity of exacerbations, and increased the time between onset of relapses as well as the number of patients who remained in remission. Those who received 22 μg subcutaneously three times a week had a 29 percent reduction in relapses over two years, and those receiving 44 μg had 32 percent fewer exacerbations, when compared with placebo treated controls. There were no side effects in any of the treated groups, except for occasional slight skin reactions at site of injection.

The Rebif study included data from 22 centers in Canada, Europe, and Australia. The manufacturer has reportedly been considering applying for FDA approval, but no human trials have been conducted in the U.S. This may seem strange since it is apparently a superior product, but it would not be terribly surprising if these never took place.

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Obtaining FDA approval is a costly, time consuming, and arduous process In addition to having to demonstrate that a medication or therapy is effective, it is also necessary to prove within the shadow of a doubt that there are no adverse side or long term effects by completing expensive and lengthy animal studies and human trials. Although such tremendous outlays can be justified when the potential profit is enormous, as with obesity and cold medications, there is little payback from drugs designed to treat relatively rare disorders like MS.

Rigorous FDA requirements are justified to protect the public, but there is no guarantee of this. As indicated in a previous Newsletter, the manufacturers of dexfenfluramine (Redux) pulled out all the stops to get it approved as a safe and effective appetite suppressant. This included pressure on the FDA advisory panel members, as well as obtaining written support from members of the Editorial Board of the pristine *New England Journal of Medicine*, some of whom were later found to have serious and unethical conflicts of interest. Sales went through the roof until it was found, as some critics had predicted, that like fenfluramine, it caused fatal pulmonary hypertension and valvular damage, and it was immediately recalled.

In other instances, despite the fact that an FDA advisory panel approves a drug, there is no guarantee that the Agency will go along with its recommendations. A good example of this is Copaxone, an entirely new approach to treating MS. It is composed of four naturally occurring amino acids that are chemically similar to those components of myelin that seem to attract inflammatory cytokines. Copaxone appears to act as a molecular decoy to divert these damaging agents away from their myelin targets, A two year trial at 11 U.S. medical centers in over 250 patients, found that those receiving the drug were one-third less likely to have a relapse than those receiving placebos. In 1996, a Food and Drug Administration advisory panel voted 7 to 0 that it was effective in delaying relapses of multiple sclerosis, and 6 to 0 with one abstention that Copaxone was safe. There were few side effects except for minor local skin irritation at injection sites. About one in ten patients reported either a mild flush or slight chest tightness that might last for a few minutes after the injection.

Despite the advisory panel's approval, the FDA expressed concerns about the chest complaints, even though it had been shown these were not of cardiac origin. They also wanted more animal studies to demonstrate there was no risk for cancer. This seems highly unlikely, since Copaxone consists of naturally occurring amino acids, and was developed by scientists at the Weizmann Institute of Science in Israel who had already conducted extensive safety studies. However, FDA approval will not be granted until these concerns are satisfied.

Many feel that this is both unfortunate and unfair, and will lead to a black market or cause patients to go to Canada to get it. The two drugs currently available in the U.S. each cost approximately $10,000 a year, and Copaxone should be much less expensive. In addition, it represents not only another treatment option, but since its mechanism of action is different, there is a good possibility that combining it with one of the interferon derivatives might have synergistic and superior results.

Immunologists at Georgetown University are investigating another lead based on reports of remarkable improvement in MS following bee stings. Benefits are apparently so impressive, that some patients have arranged to be stung by honey bees periodically, and in some instances, several times a week. Scientists were originally quite skeptical, but subsequently discovered that bee venom had unusual effects on certain immune system components that might support these claims.

The Multiple Sclerosis Association of America recently awarded a grant of $250,000 to Georgetown researchers to evaluate the therapeutic potential of bee venom. Since the course of the disease can vary so much, eight patients with "chronic progressive MS" will be carefully followed for one year. To insure standardization, they will be injected with a specific amount of bee venom twice a week, rather than simply allowing them to be stung, and will be on no other medication. Critics point out that the number of patients is too small, and that this group is not representative of the majority of MS patients. However, if results seem promising, it could lead to larger trials, and also further research to determine whether other chemical products found in nature that are similar to bee venom might be superior.

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Other alternative medicine approaches such as acupuncture, homeopathy, and nutritional interventions are available, but few have been studied scientifically. Antioxidants have been found to be effective in preventing the free radical damage that contributes to Parkinson's and Alzheimer's disease, and should theoretically provide benefits in other neurodegenerative disorders that are mediated by disturbances in immune system activities. Vitamins C and E, melatonin and ginkgolides have been found to be helpful in the above disorders, but there has been little published research in MS.

Regular exercise was demonstrated to increase lung capacity and otherwise improve both the physical condition and quality of life for MS sufferers in a recent study of over 50 patients. About 10 percent of the National Multiple Scerosis Society chapters now sponsor tai chi classes because of similar benefits. A researcher at the University of Minnesota Medical school is investigating the role of distant prayer in MS based on anecdotal reports and results obtained in patients with other autoimmune disorders like lupus and rheumatoid arthritis. Any therapy is likely to help if patients have a strong faith that it will work, because it reduces their stress.

It is well known that stress stimulates the hypothalamic-pituitary adrenal axis (HPA), which results in an increased secretion of pituitary and adrenal hormones. However, one of the other effects of HPA stimulation that is not as well appreciated, is to increase the metabolism of serotonin in the brain. The synthesis of serotonin is dependent upon the availability of its precursor tryptophan, and tryptophan levels fall during stress as they are used up depleted to manufacture more serotonin. Both blood and spinal fluid tryptophan levels have been shown to be diminished in chronic MS, and might be expected to be even lower in those subjected to chronic stress. Sandyk believes that raising tryptophan levels through diet and supplements, could correct this and improve their clinical status. Low serotonin might also be responsible for depression in some patients, and cranioelectrical stimulation has been shown to raise serotonin and relieve depression. Sandyk has reported improvement in symptoms in patients with MS as well as Parkinson's disease using picotesla magnetic fields, and this approach has exciting potential.

Stress And MS In Animals

Since EAE produces disseminated lesions of demyelinization in animals, it is viewed as a counterpart of multiple sclerosis in humans. A few words about nomenclature. Many neurologists and researchers, particularly those in England, refer to this disorder as "disseminated", rather than "multiple" sclerosis, which is probably more accurate and descriptive. EAE was originally an acronym for experimental *allergic* encephalomyelitis, because little was known about the immune system sixty years ago. It now stands for experimental *autoimmune* encephalomyelitis, which is also probably more precise with respect to the mechanisms of action that are involved.

This animal model has facilitated the study of various chemicals and drugs that might have implications for patients. The question is whether it can also shed some light on the role of stress in MS? Meaningful studies would obviously be difficult for several reasons. It is impossible to reduplicate in animals the threat of bereavement, divorce, or poverty, which are so commonly encountered. In addition, the acute, physical stressors used in animal research differ from the chronic emotional complaints that characterize contemporary human stress. It is unlikely that the psychophysiologic responses to both are the same or even similar.

The effect of stress on EAE was investigated as early as 1962, when it was found that physical restraint could be effective in suppressing the disease in rats if it was repeatedly applied before or soon after sensitization. Injecting adrenal hormones at these same times had a similar effect. Adrenalectomy, loud noises, electric shocks to the tail, have also been studied, but as might be expected, results can differ considerably depending on timing and other factors.

There are no clear conclusions, but in general, most of these effects are protective. For example, spontaneous remission in animals has been attributed to the stress of paralysis, which causes an outpouring of adrenal steroids with powerful anti-inflammatory effects. However, the response to stress in humans is modified by factors not present in experimental animals. Anecdotal reports and clinical studies suggest that stress has a deleterious effect on the clinical course of MS.

Stress And MS In Humans

In his initial description of MS in 1868, Charcot noted that stress, and particularly the trauma of grief, seemed to precipitate the disease. However, a 22 year old Englishman named Augustus D'Este may have been the first to describe this. On December 13, 1822, he experienced the sudden onset of a severe disturbance in vision shortly after attending the unexpected funeral of a close relative and friend. As he wrote in his diary, "I was obliged to have my letters read to me, and their answers written for me, as my eyes were so attacked, that when fixed on minute objects, indistinctness of vision was the consequence. Soon after, they completely recovered their strength and distinctness of vision." Although he made an initial recovery, subsequent diary entries leave little doubt that this was the onset of MS, which later progressed.

Around the middle of the present century, separate investigators reported that a significant number of MS patients had experienced a relapse or worsening of their symptoms during or immediately after some severe stress. A controlled study was designed to investigate this in 100 MS patients and an equal number of others with neurologic and non neurologic diseases. It found no difference in the incidence of emotional stress in the month prior to the onset of symptoms between the two groups, although some MS patients described a worsening of symptoms immediately following some stressful event.

However, the time interval may have been too short, based on a controlled study done two decades later in 100 MS patients and 73 controls with neurological and non-neurological diagnoses. These two groups differed significantly with respect to the degree of stress they had been subjected to in the 2 years prior to the onset of symptoms. Four out of five MS patients reported high degrees of stress during this interval, compared to little more than half for the other group. In a more recent study of MS patients, no difference was again found in life change event stress rating scores in the month prior to a relapse, compared to baseline values or other periods. However, when these patients were interviewed two years later, 60 percent believed that stress had adversely affected their condition, and almost half felt that stress had been responsible for a relapse. Another study of relapsing-remitting MS showed that those reporting more stress were at greater risk for an attack.

Researchers from the Mount Zion Multiple Sclerosis Center in San Francisco just confirmed that high levels of daily stress were positively associated with the development of new brain lesions. About 50 patients were rated monthly for levels of stress, anxiety, and depression as well as clinical status and evidence of brain lesions with gadolinium enhanced MRI scans. All of the patients, average age 44, had either relapsing-remitting or progressive MS. When the results of all these findings were analyzed, it was found that there was a clear correlation between the development of new brain lesions, with increased stress as assessed by both major life change events and daily hassle scores. There was also an association between new lesions and levels of depression, but this was not as statistically significant. The researchers suggest that stress and depression may worsen MS because of their effects on immune system function, which have been well documented in other studies.

Not everyone agrees with this interpretation. One authority suggests that stress, depression, and other psychological problems may result from a worsening of MS, rather than being responsible for this. However, the sequence of events in this study so strongly support a causal relationship, that the lead author urged physicians to be more aware of how stress could make their MS patients worse, In addition, he said his findings underscore the usefulness of "...behavioral ways to reduce stress levels in MS patients."

That's a lot easier said than done. It's comparatively easy to blame stress as the cause of most anything - after all, very few of us have a stress free day. And even if we could clearly show that stress was really responsible for a worsening of MS, or cancer, it does not follow that meditation, jogging, or following some stress reduction strategy enthusiastically espoused by others, will work for you. There are clearly many more questions than answers, but exciting new discoveries are starting to tip the balance the other way. The ability to deliver tailor made magnetic fields to specific sites appears particularly promising, so stay tuned.

Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief

BOOK REVIEW: *A Commotion in the Blood: life, death, and the immune system.*

Stephen S. Hall, Henry Holt, New York, 1997.544 pages, $30.00

The nature and function of the immune system has been pretty much of a mystery. Up until several decades ago, there was relatively little appreciation of the wide clinical repercussions of disturbed immune system function. It was apparent that some people had "hay fever" and other allergic reactions to things they breathed in, or certain things they ate, or could have an unusual sensitivity to a drug like penicillin that could be fatal. Such tendencies could be detected by skin tests, which could also be used to demonstrate a prior exposure to tuberculosis, or some other infectious agent. It was also well established that following an infection, there was usually strong resistance to further attacks because of protective antibodies made by the immune system. This was particularly evident in viral infections, and especially those commonly seen in children, which led to the development of various vaccines that could have the same effect. When interest heightened in organ and tissue transplantation, the problem of rejection required intervention with drugs to dampen immune system responses, which, although successful, increased the risk for subsequent cancers.

Interest in the relationship between immune system function malignant growth has increased in recent years, largely due to advances in the field of psychoneuroimmunology. A link between emotional stress and cancer had been known since antiquity. Evidence that stress could depress immune system components responsible for resistance to cancer seemed to tie things up in a nice little package. Further support came from studies showing that strong social support and other stress reduction strategies increased longevity and had other salubrious rewards in cancer victims. The increased incidence of cancer in AIDS, and the role of stress in accelerating the clinical expression of HIV infection have also been established. Yet, we really don't know very much about how to manipulate the immune system on a long term basis. All the strategies we use to cure cancer, like irradiation and chemotherapy, cause cancer. It is not clear why the immune system suddenly goes awry, and starts to attack normal tissues in multiple sclerosis, rheumatoid arthritis, and systemic lupus. Nor is it possible to explain either the adverse or beneficial influences stress can exert on these and other autoimmune diseases.

This book explains these and other issues that are in the forefront of current immunologic research . It also provides a fascinating account of the history of immunotherapy, including the contributions of Pasteur, Metchnikoff, and other pioneers. The influence of politics and commercial interests in shaping research efforts and public opinion is vividly illustrated by Coley's toxins, a cancer cure and vaccine developed in the early part of this century, which is again attracting increased attention. Clinical results were extremely impressive, and the preparation was distributed by Parke-Davis, until political machinations effectively discredited it. Other compelling historical vignettes are included in this highly recommended compendium of how doctors have learned to use the immune system, and its various "commotions". as one put it.

Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief

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