Nervous and Immune System Disorders Linked in a Variety of Diseases

Many diseases affecting both the nervous and immune systems seem to strike individuals who are genetically predisposed

RECENT advances in understanding a variety of diseases from myasthenia gravis and measles to asthma and arthritis reveal complex interactions between the nervous system and the immune system. Researchers are also gathering evidence that some individuals may be genetically predisposed to these diseases.

Myasthenia gravis, a crippling neuromuscular disease, is now being treated successfully in some patients by procedures that reduce the immune response, as well as with drugs that enhance nerve-to-muscle communication. Some neurological complications that accompany a measles infection are associated with a breakdown in normal immune system functioning. And current studies suggest that neuropeptides released into respiratory airways or joints exaggerate the underlying abnormal immune response in asthma and arthritis.

Physicians and basic research scientists discussed current findings at a recent meeting on the immune system and neurologic disorders held at the National Academy of Sciences.* According to Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases at NIH, "Scientists have known for a long time that there are nervous system diseases that are mediated by the immune system. And recently it has become clear that the immune system itself may be regulated by the nervous system. So the immune system has an impact on the nervous system and the nervous system has an impact on the immune system."

The evidence points to at least two major groups of diseases. The first is a group of neurological diseases strongly associated with disturbances of the immune system which may occur more often in people who are genetically predisposed to the disorders. This group includes myasthenia gravis and multiple sclerosis, the neurological complications that follow measles and other viral infections, and those that accompany cancer. In the second group are asthma and arthritis. These disorders are characterized by an abnormal immune response that researchers now think becomes exaggerated when nerve cells release certain peptides into respiratory airways or joints.

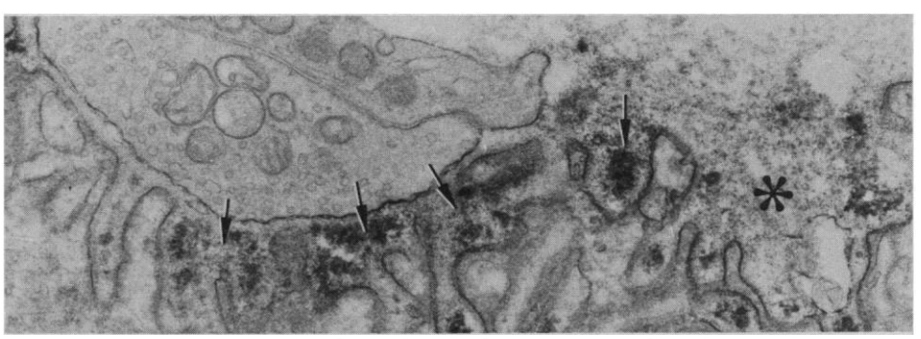
In myasthenia gravis, which Daniel Drachman of the Johns Hopkins School of Medicine characterizes as "the neuroimmunological disease we know most about," antibodies of the immune system attack the synapses where nerve signals reach muscle cells. Most patients with myasthenia gravis produce antibodies against their own receptors for acetylcholine, the neurotransmitter that controls muscle contraction. This autoimmune attack causes serious muscle weakness: myasthenia victims find it difficult to speak, swallow, move their arms and legs, and even breathe, in severe cases.

Many myasthenia patients have abnormally active thymus glands, the tissue in which T lymphocytes mature. Drachman notes that "right there in the thymus you have the makings of an autoimmune response." His working hypothesis is that the thymus is somehow involved in triggering or maintaining the diseases. Treatments that reduce the immune response alleviate the symptoms of myasthenia gravis.

Multiple sclerosis is another disease of unknown origin that seems to involve the immune system as well as the nervous system. Barry Arnason of the University of Chicago thinks "there is a serious derangement of immune function in multiple sclerosis. We think there is an immune attack, but we don't know what it is against. We think it fluctuates, but we don't know why." The immune attack may be against myelin basic protein, a component of the fatty myelin sheath around nerves that is destroyed in multiple sclerosis. As with a growing list of autoimmune disorders, people seem to inherit a predisposition for multiple sclerosis.

In some neuroimmune disorders, the cause of, or at least the trigger for, the disease is known. For example, some children (usually over 5 years of age) who get measles caused by the rubeola virus develop various neurological problems. The most common is post-measles encephalomyelitis, an inflammatory disorder that destroys myelin and can cause paralysis.

Diane Griffin of the Johns Hopkins University School of Medicine described how the nervous system and the immune system both participate in this encephalomyelitis. "The rash signals the onset of the immune response to the measles virus, and it's usually shortly after the rash has appeared that patients begin developing the acute encephalomyelitis. It was postulated some years ago that this may be an autoimmune disease response that has been triggered in some way, as yet not completely clear, by the measles virus infection." Certain aspects of the immune response are depressed while



Damaged neuromuscular junction in human myasthenia gravis. *The nerve terminal is the large pale structure in the upper left region of the micrograph. In contrast to the normal appearance of the nerve ending, the synaptic region of muscle membrane in the lower half of the figure shows extensive damage. The normally occurring finger-like synaptic folds are partially destroyed. The space between the nerve terminal and the muscle is wider than normal and is filled with a darkly staining component of complement (arrows), evidence of the immune attack against muscle synaptic membrane. The asterisk marks a severely damaged region of muscle membrane that is no longer covered by the nerve terminal (×21,250).* [*Reprinted by permission from K. Sahashi, A. G. Engel, E. H. Lambert, F. M. Howard,* J. Neuropathol. Exp. Neurol. *39, 160 (1980)*]

*The symposium on The Immune System and Neurologic Disorders was held 24 and 25 February 1986. It was presented by the National Institute of Neurological and Communicative Disorders and Stroke and the National Institute of Allergy and Infectious Diseases and was sponsored by the National Coalition on Immune System Disorders.

others are enhanced. Griffin thinks "it is very likely that there is a genetic component to explain why only 1 in 1000 patients develops these complications."

In addition to their primary disease, many cancer patients also suffer from a variety of nervous system complications, according to Karl Stefansson of the University of Chicago. These include the degeneration of certain cell populations in the cerebellar region of the brain, an inflammation of the brain's limbic system which causes memory loss, and the death of sensory neurons whose cell bodies lie just outside the spinal cord.

Regarding the formidable list of neurological complications that can occur with cancer, Stefansson says, "Most questions are unanswered. This is a completely heterogeneous group of syndromes. But certain factors make it tempting to postulate that the neurological problems are caused by a common immunological mechanism." Again, the signs of immune involvement are there, including changes in lymphocyte number, antibodies that seem to attack specific neuronal cell types, and a certain amount of therapeutic success in patients treated with drugs that suppress immune responses.

The second group of diseases involving both the nervous and immune systems includes asthma and arthritis. According to Edward Goetzl of the Howard Hughes Medical Institute and the University of California in San Francisco, "there was always a sense that the nervous system is involved in these diseases. So the idea of a link between the nervous and immune systems is not new. What's new is that we are beginning to sort out the molecular mechanisms for these diseases."

Both asthma and arthritis are hypersensitivity diseases. Goetzl says that "instead of protecting the host, the immune system has gone awry in a hypersensitivity response. It is no longer being regulated normally." The nervous system actively participates in and exaggerates this abnormal immune response by secreting peptides into the respiratory tract in asthma and into the joints in arthritis.

The best described culprit seems to be a neuropeptide called substance P. In both asthma and arthritis, sensory nerves that normally end in cells lining the lungs and joints begin to secrete substance P in an abnormal way. In asthma, substance P induces spasms in muscles surrounding the bronchial tubes, closing off the air passages and making it difficult to breathe. The peptide also seems to stimulate a group of T lymphocytes and it promotes mucous secretion in lung airways. The net result is that the original hypersensitivity response is made worse because of the involvement of the nervous system.

But not all of the peptides secreted by sensory nerves aggravate the immune response in asthma and arthritis. Goetzl notes that "there is a balancing action among neuropeptides." Whereas substance P and certain other peptides are generally stimulatory, a peptide called somatostatin is generally inhibitory. So, depending on the mix of secreted neuropeptides, the hypersensitivity reaction can be increased or decreased.

As in the first group of neuroimmunological diseases, a genetic predisposition seems to be important for both asthma and arthritis. More than one gene is probably involved, according to Goetzl, who thinks environmental factors also play a major role. "With asthma," he says, "we're talking about an airway hyperirritability that is reversible." When the triggering environmental factors are absent, many asthmatics can breathe normally.

Dale McFarlin of the National Institute of Neurological and Communicative Disorders and Stroke relates genetics to diseases that affect both the nervous and immune systems. "It has been established in experimental animals that the abnormal immune response is largely under genetic control. When this concept is extrapolated to man, certain genetic backgrounds will probably be found that predispose an individual to a disease. But both a genetic background and environmental factors contribute to many neuroimmunological diseases."

The genes most often implicated in neuroimmunological diseases belong to a group called the major histocompatibility complex (MHC). According to McFarlin, "MHC genes control the expression of proteins that present antigens to immune system cells, particularly T lymphocytes. The proteins coded for by MHC genes are expressed on the surface of macrophages, scavenger cells of the immune system. Their job is to present antigens to T lymphocytes."

Researchers have studied this process in animals and "have tried to extrapolate these ideas into human diseases. In myasthenia gravis and multiple sclerosis patients, genes that regulate histocompatibility proteins have been identified," McFarlin says. In both diseases there may be histocompatibility proteins that direct the abnormal immune response. The individual genes coding for the proteins are different in the two diseases, but they are all part of the same gene family.

McFarlin's hope is that "understanding the nature of the abnormal immune response will help us to correct or modify it." In the future, researchers may use gene probes for patients' DNA to see if it codes for molecules that are involved in the disease. "The idea behind gene probing is that you are going after a single gene that is associated with a particular disease. This is being tested now and is at the leading edge of what people are trying." ■

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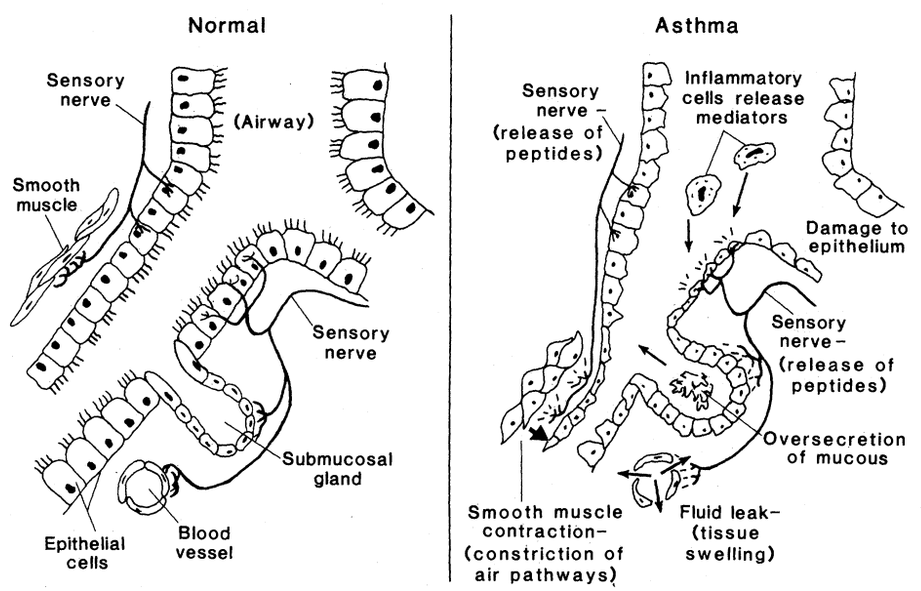

Possible neuronal contributions to lung abnormalities in asthma. *In asthma, sensory nerve endings in epithelial cells that line lung airways become irritated and release substance P and other peptides. Neuropeptide release triggers contraction of smooth muscle cells (which causes constriction of air pathways), leakage of fluid from small blood vessels (which causes tissue swelling), and oversecretion of mucous from submucosal glands and specialized epithelial cells. Together, these effects narrow respiratory airways. Neuropeptides may also stimulate inflammatory cells to release chemical mediators that contribute to epithelial cell damage. [Adapted by D.M.B. from D. G. Payan and E. J. Goetzl,* Eur. J. Resp. Dis., *in press; and P. Barnes,* Lancet *1986-1, 242 (1986)]*