the unmasking of the Piltdown fraud in 1953 served to remove what increasingly had been an awkward piece of evidence and underlined the embarrassing fact that, as Washburn put it, "the most highly regarded scientists had been unable to tell a modern jaw from a fossil for over 30 years."

Zuckerman made much of this latter fact, and from the 1950's onward he and his students strove to show that, as always, paleoanthropologists see in the fossils only what they want to see. Proper examination with metrical analysis fails to classify the australopithecines as especially human, concluded Zuckerman, a view he still holds and is championed too by his most prominent student, Charles Oxnard of the University of Southern California.

Zuckerman once said, "It is something of a record for an active team of research workers whose strength has seldom been below four, never to have produced an acceptable finding in some 15 years of assiduous study." Which observation must mean either that the entire profession of paleoanthropology is wearing blinders, focusing only on what they wish to believe; or that Zuckerman and his co-workers are wrong.

Not that Washburn is any great champion of conventional comparative anatomy. "It is regarded by some as a major science," he says, and yet continuing controversies through the years—excluding Zuckerman—"shows that well trained anatomists could reach diametrically opposed conclusions."

These controversies have included the supposed hominid status of the Miocene fossil *Ramapithecus*; the question of whether *Homo habilis* is indeed a true species, and if so, which specimens should be assigned to it; whether the fossils from the Hadar, Ethiopia, which Don Johanson and Tim White have named as *Australopithecus afarensis*, are ancestral to all other hominids; and whether *Australopithecus afarensis* is in fact merely a geographical variant of *Australopithecus africanus*. Serious practioners hold very different opinions.

Washburn has, of course, long been a proponent of the efficacy of molecular biology in addressing issues of paleoanthropology, and was instrumental in encouraging Vincent Sarich to pursue this line of investigation at Berkeley, in company with Allan Wilson. The problem they addressed was the branching order and times of the great apes and humans, and in 1967 they came up with an answer that was as acceptable to paleoanthropologists then as the Taung skull had been to the adherents of Piltdown. In contrast with paleoanthropological opinion, which put human origins some 15 to 25 million years ago, the molecular biologists said humans split away from apes a mere 5 million years ago. This meant that *Ramapithecus*, every major anthropologist's candidate as the first hominid, could not be one, as it was too old.

More than a decade was to pass before the anthropologists were to admit that Sarich and Wilson were more right than wrong (some still don't), which spurred Washburn to suggest that "To some, a well guarded intellectual territory seemed more important than acceptance of an answer to the problems." It was not a popular remark.

Washburn's intention was not to suggest that nothing has changed since the time of the Taung baby. It has, dramatically so. To be sure, elements of emotionalism still color intellectual views, a fact of all scientific life, but perhaps more vigorously so, and certainly more visibly, in paleoanthropology. But, by concentrating on the warts, it is easy to imagine that the whole face is grotesque, which usually is not the case.

Tobias revels in the continuing controversies. "A sign of an intellectually vigorous profession," he says. "And onlookers forget what tremendous agreement there now is in our field, agreement on the most fundamental of questions." Dart, now 92, was on hand to celebrate the strength of the profession. His aside to a colleague earlier in the meeting: "I wish that man Zuckerman could be here to see this."—**ROGER LEWIN**

# The Immune System "Belongs in the Body"

## *Pervasive anatomical and biochemical links between the immune and nervous systems help explain how mood might influence disease susceptibility*

Over the years, a great many reports, some anecdotal but others more rigorous, have suggested that psychological factors such as stress might influence a person's immune response and therefore his susceptibility to infectious diseases and cancer. Largely missing from all this, however, was an explanation of how the nervous and immune systems might communicate.

That situation is now changing. A great deal of evidence shows that the two systems are inextricably interconnected. "The evidence for neuroimmunomodulation is enormous at every level," says N. Herbert Spector of the National Institute of Communicative Diseases and Stroke, who helped to organize a recent workshop* devoted to the topic.

Investigators have shown that stresses, both severe or more mundane, can alter immune responses and that classical Pavlovian conditioning, a form of learning, also influences them. Moreover, there are both anatomical and chemical connections between the immune and nervous systems that may serve to integrate their activities. Not only can the nervous system influence immune responses but, the new work shows, immune responses can alter nerve cell activities. In fact, the cells of the immune system may function in a sensory capacity, relaying signals to the brain about stimuli, such as invading foreign pathogens, which would not be detected by the more classical sensory system.

All this contrasts with previous thinking that the immune system is largely autonomous, a conclusion based on numerous studies showing that immune cells can be activated and make their responses in test-tube systems, away from other bodily influences. These in vitro studies have been highly successful in elucidating many facets of the immune response. However, the picture they present is incomplete, according to a theme echoed by many of the researchers investigating the interactions of the immune and nervous systems. As Karen Bulloch of the State University of New York at Stony Brook says, "It's time to put the immune system back in the body where it belongs."

Some of the recent work that has been attracting interest in the possibility that the brain may be regulating the immune

*The "First International Workshop on Neuroimmunomodulation" was held 27 to 30 November at the Bethesda campus of the National Institutes of Health.

system has focused on the effects of stress on immune responses in human subjects. For example, Marvin Stein and his colleagues at Mt. Sinai School of Medicine in New York have looked at the effects of conjugal bereavement. The study, which was of men whose wives had advanced breast cancer, showed that the ability of the men's lymphocytes to respond to an activating agent declined significantly within a month or two of the deaths of their wives. In some of the men, the responses remained low for a year.

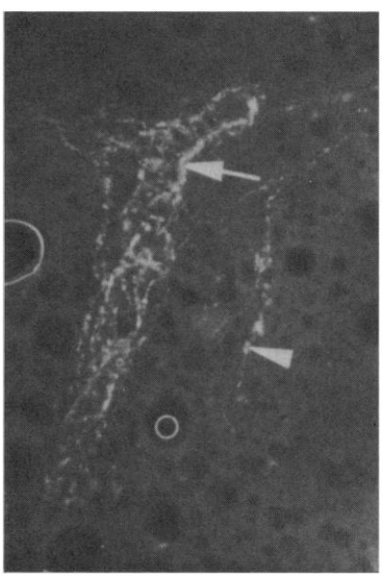
Because depression is one consequence of bereavement, Stein and his coworkers examined the lymphocyte responses in patients hospitalized for severe clinical depression, and also found these to be suppressed. Studies of appropriate controls showed, Stein says, that "the changes seemed to be associated with the severity of the depression and not with hospitalization."

Bereavement is a severe stress, but even milder forms can reduce immune responses, according to Ronald Glaser and Janice Kiecolt-Glaser of Ohio State University School of Medicine. These investigators assessed several forms of cellular immunity in medical students both a month before their final exams and on the exam day itself. "We can show multiple changes in cellular immunity associated with the stress of taking exams," says Glaser, who notes that the alterations were apparent even though medical students are well accustomed to taking tests.

The changes included a reduction in the helper T cells needed to mount many immune responses and a lowered activity of the natural killer cells, a type of immune cell that may help to prevent the development of cancerous tumors. Moreover, these indicators of cellular immunity were depressed even before the exams in those students shown by psychological testing to be experiencing generally higher life stresses or loneliness. One consequence of the depressed cellular immunity may be an activation of the latent herpesviruses that are carried by many individuals, according to the Ohio State workers.

Additional evidence that the brain can influence immune responses comes from Robert Ader and Nicholas Cohen of the University of Rochester School of Medicine and Dentistry. Several years ago, Ader made an unexpected observation while studying conditioned taste aversion in rats. He first gave the animals a saccharin solution (the conditioned stimulus) and then the immunosuppressive drug cyclophosphamide (the unconditioned stimulus), which induces nausea. As expected, the rats learned to avoid drinking the saccharin. During the later phases of the experiment, at a time when the cyclophosphamide was no longer given and the rats were forgetting the taste aversion, Ader was surprised to find that the conditioned animals were dying at an unusually high rate. In particular, the animals that drank the most saccharin were dying. The unconditioned animals, who preferred the saccharin solution to plain water, showed no signs of ill effects.

Ader hypothesized and, with immunologist Cohen, went on to confirm that the rats had been conditioned to associate the taste of the sweetener with immune suppression and were in fact suppressing their own immune responses when they drank the solution. Over the years the Rochester workers have shown that they can condition both cellular and humoral immunity. "It is a small but very highly reproducible phenomenon," Ader concludes. "We can alter immune responses by classical conditioning."



**Nerve net in spleen**

*The individual fiber (arrowhead) extends into the cells of the splenic white pulp.* [*Source: J. M. Williams* et al., Brain Res. Bull. **6**, *83 (1981)*]

If such conditioning is to have any clinical application, it is most likely to be for treating autoimmune diseases in which the immune system goes awry and begins attacking the body's own tissues. As Cohen points out, "It is not in the best interests of an animal to suppress an immune response unless the response is deleterious." The Rochester workers have shown that classical conditioning can reduce by 50 percent the dosage of cyclophosphamide needed to control a mouse version of the human autoimmune disease called systemic lupus erythematosus. So far there have been no attempts to use classical conditioning to reduce the doses of immunosuppressive drugs taken by human patients.

In general, the investigators are very cautious about the clinical implication of their work. They point out, for example, that the studies linking psychological factors such as stress or depression with increased sickness and death are distinct from those linking the factors with depressed immunity. One of the few exceptions to this is a study of breast cancer patients by Sandra Levy of the University of Pittsburgh School of Medicine and her colleagues at the National Cancer Institute. They found that the patients who had higher natural killer cell activity had significantly fewer lymph nodes that were positive for cancer spread, an indicator of a good prognosis for the patient. "The natural killer cells may have been playing a deterrent role in the spread of the cancer," Levy suggests.

In addition, there was a correlation between the patients' responses to their disease and natural killer cell activity. Those who suppressed their anger, lacked good social support, and were apathetic had the lower activities—and more positive lymph nodes. The big question then is whether the psychological factors produced the lowered immune response, which in turn contributed to the spread of the cancer. The decreased immune activity and the disease might be independent consequences of the psychological factors. Or, conceivably, the lowered immunity and progress of the disease might have caused the apathy. About the only way to settle this issue, Levy says, is to do controlled intervention studies to see if the patients' prognoses improve if their behavior is modified so that they respond more aggressively to their disease. Such studies are currently getting under way at Pittsburgh, George Washington University School of Medicine, and other medical centers.

Although the clinical implications of the research into the interactions of the nervous and immune systems may still be uncertain, the evidence for anatomical and chemical connections between the two systems is accumulating rapidly. Investigators have known for many years that stress might produce immune suppression by acting through the hypothalamic-pituitary-adrenal pathway. In response to stress, the hypothalamic region of the brain produces corticotropin-releasing factor, which in turn triggers

the secretion of adrenocorticotropic hormone (ACTH) by the pituitary. The ACTH then acts to stimulate secretion by the adrenal gland of corticosteroid hormones, which include immune suppression among their effects.

The current research shows that interactions between the immune and nervous systems go far beyond this well-established pathway. The two systems may communicate directly through specific nerve connections. Bulloch and her colleagues find that the autonomic nervous system sends fibers to the thymus gland, the immune organ in which T lymphocytes mature. The fibers form a specific innervation pattern, which is similar in organisms as diverse as humans, mice, chickens, and reptiles.

According to Bulloch, proper innervation may be necessary for the development of the thymus. The nerves begin growing into the developing gland even before immature T cells begin to arrive. Moreover, the rudimentary thymus of the nude mouse, which makes very poor T-cell responses, has an abnormally sparse innervation pattern.

The thymus gland is not the only immune system organ to be innervated. David Felten and his colleagues at the University of Rochester School of Medicine and Dentistry have shown that the spleen, lymph nodes, and bone marrow, as well as the thymus, contain specific patterns of nerve fibers. The nerve terminals do not just serve the blood vessels, Felten notes. "We have demonstrated that the innervation follows the blood vessels into the organ and branches out into fields of lymphocytes. It is a very precise innervation." The nerves generally end in regions rich in T cells and avoid the areas that contain the developing B cells.

The ways in which the innervation might affect immune cell function is still incompletely understood. It might help regulate cell movement into and through the various immune organs and tissues. It might also exert direct effects on the cells' activities. There is now much evidence showing that immune cells have receptors that would enable them to respond to a wide range of chemicals that are better known in their guise as transmitters or modulators of nerve signals. These include acetylcholine, norepinephrine, and the endogenous opiates. Investigators have also shown that the neuroactive agents can alter immune cell functions, producing either increases or decreases, depending on the responding cell type and the agent used.

Moreover, immune function can be altered by treatments that destroy specific brain areas. For example, Thomas Roszman of the University of Kentucky College of Medicine has found that lesions in the anterior region of the hypothalamus produce decreases in a variety of immune functions, whereas lesions in the amygdala or hippocampus lead to increases. The immune alterations appear to be mediated, Roszman says, by changes in the activity of a type of immune suppressor cell in the spleen.

Not only can the nervous system regulate the immune system but immune cells and organs also have the potential for influencing neuronal activities. Hugo Besedovsky of the Swiss Research Institute in Davos and his colleagues have shown that the firing rate of brain neurons is altered during immune responses. Besedovsky has proposed that the brain is informed by the immune system about the invasion of foreign antigens.

> "The immune system serves as a sensory organ for stimuli not recognized by the classical sensory system."

The results of the Davos group suggest that the changes in neuronal firing were caused by soluble products released by activated lymphocytes. These products include several agents, such as interferon and the interleukins which regulate immune cell development and function. Investigators from several laboratories are now finding that these agents also have neuronal effects. In fact, Nicholas Hall and Allan Goldstein of the George Washington University School of Medicine propose that these products of the immune system be given the name "immunotransmitter," just as the substances that transmit nerve signals are called neurotransmitters.

Alternatively, immune effects on the nervous system might be mediated by the more typical neurotransmitters, neuromodulators, or hormones. Activated lymphocytes produce a number of these agents. According to J. Edwin Blalock and his colleagues at the University of Texas Medical Branch in Galveston, white blood cells that have been activated by Newcastle disease virus produce ACTH and endogenous opiates. In fact, mice infected with the virus show increased corticosteroid production, a typical stress response, even in the absence of the pituitary gland, which is the more commonly known source of ACTH.

Other immune cell activators can stimulate the release by the cells of different patterns of neurotransmitters or hormones. "The immune system serves as a sensory organ for stimuli not recognized by the classical sensory system," Blalock explains. "Once there is recognition of one of these nonclassical stimuli you get a pattern of hormone production that translates into physiological change."

Finally, Hall and Goldstein have evidence indicating that thymic hormones, which are needed for the normal maturation of T cells, have brain effects. One of these, thymosin $\alpha_1$, acts through the hypothalamus and pituitary gland to increase corticosteroid concentrations. This would seem to be counterproductive because of the immune suppressive effects of the steroids, but the investigators propose that it is part of the normal regulation of immune responses.

Early in the immune response thymosins may protect against the suppressive effects of the steroids by inducing lymphocyte maturation. The mature cells are much less susceptible to the steroids' effects than the immature ones. Thymosin concentrations reach their peak the same time as the antibody concentrations do. What may then happen, Hall and Goldstein suggest, is that the thymosin, by increasing corticosteroid production, helps to damp down the immune response when it gets the foreign invader under control. The suppressive action of the steroid would prevent additional immature lymphocytes from being activated while those already activated would continue to be available.

A great deal remains to be learned about the mutual interactions of the immune and nervous systems. Both are extremely complex, requiring the intricate interplay of networks of cells, and both are incompletely understood. "We're at a stage where it is difficult to say definitively what is happening," Hall explains. "We're putting together two kinds of black boxes and trying to make sense of what happens." Nevertheless, the emerging picture shows that the immune and nervous systems are highly integrated, able to talk back and forth to coordinate their activities.

—JEAN L. MARX

**Additional Reading**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