By Stephen S. Hall

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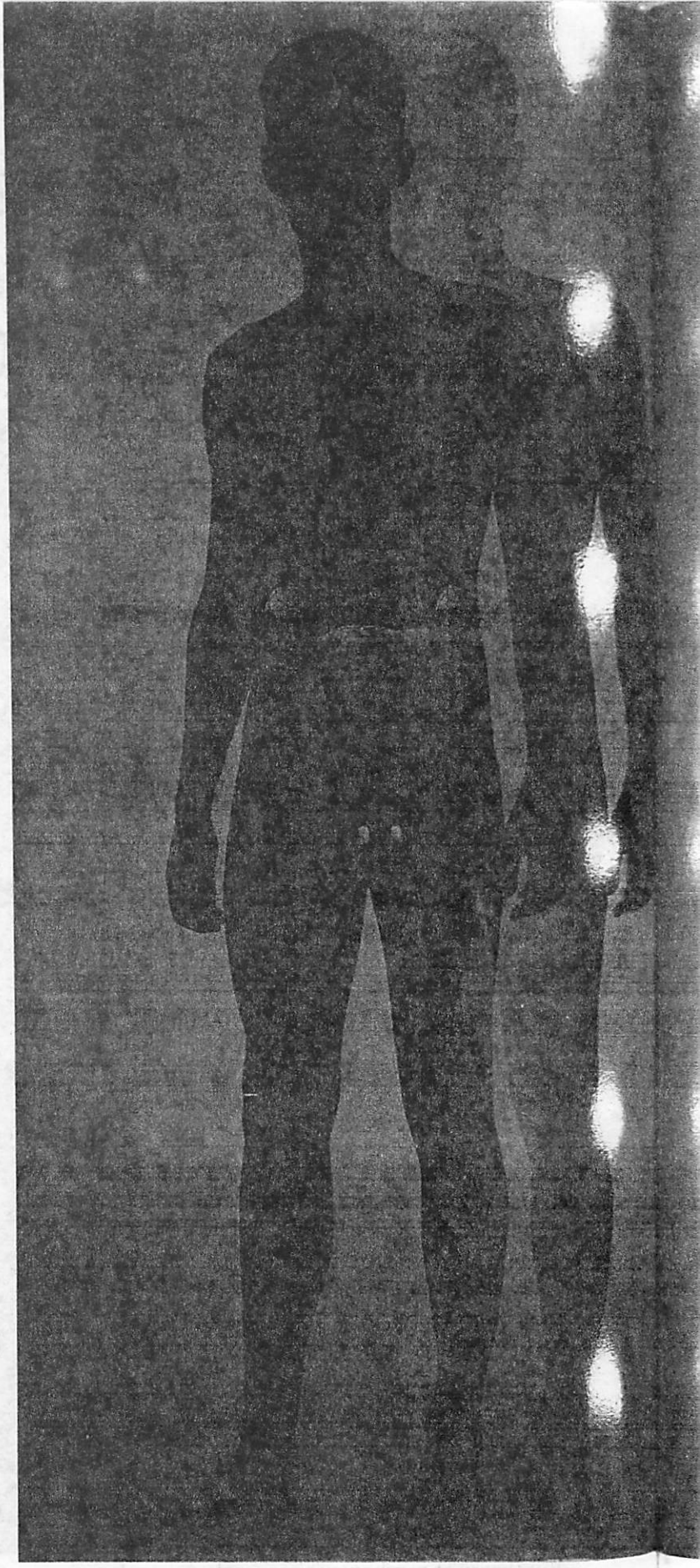
A molecular code links emotions, mind and health

The classic view of the body as three separate systems is challenged as research points the way to the new medicine of the 21st century

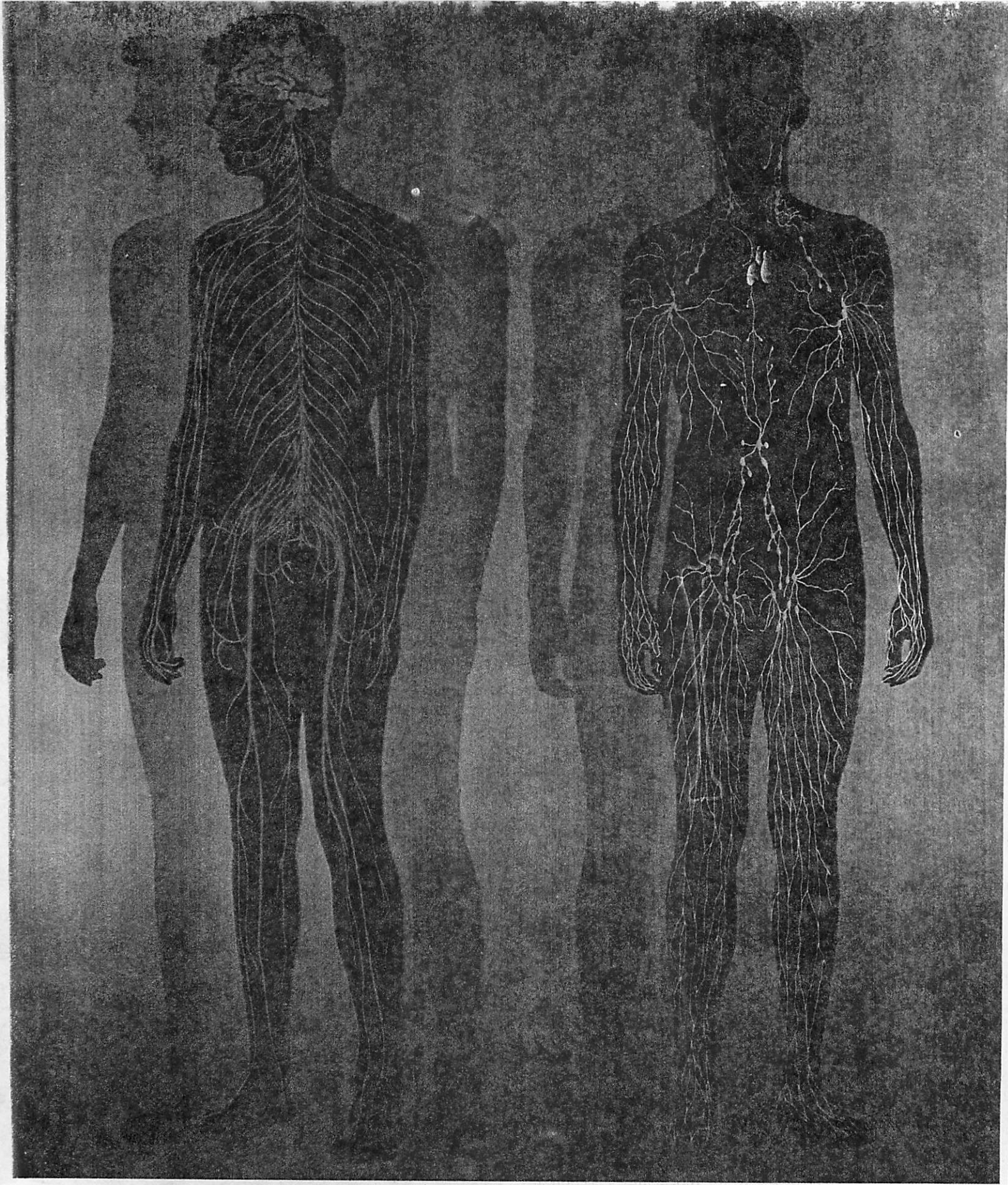
Scientists tend to remember the day they arrive at a conclusion they are certain no one else is going to believe. For J. Edwin Blalock, that day came in 1981, when his research group at the University of Texas Medical Branch at Galveston found a biological molecule where it wasn't supposed to be. The molecule was a hormone called ACTH (short for adrenocorticotropic hormone); according to every medical textbook of the time, this hormone was made exclusively by the pituitary gland in the brain and "belonged" to the endocrine system. Blalock, working with his collaborator Eric Smith, kept finding it in the wrong place. They kept finding it in a laboratory flask filled only with human cells belonging to the immune system. In fact, they began to make the unbelievable suggestion that ACTH, a hormone, was made by white blood cells.

The scientific community politely cleared its collective throat in public and not so politely cast aspersions on the work in private. A commentary in the British journal *Nature* harrumphed about "radical psychoimmunologists" and went on to imply that Blalock's work lay beyond even that suspect fringe. "That was not a whole lot of fun," Blalock says now.

Before she joined the ranks of radical psychoimmunologists, Candace Pert was a doubter, too. When researchers suggested around the same time that white blood cells had qualities in common with brain cells, Pert—then chief of the Brain Biochemistry section at the National Institute of Mental Health (NIMH) in Bethesda, Maryland—reacted the way scientists often

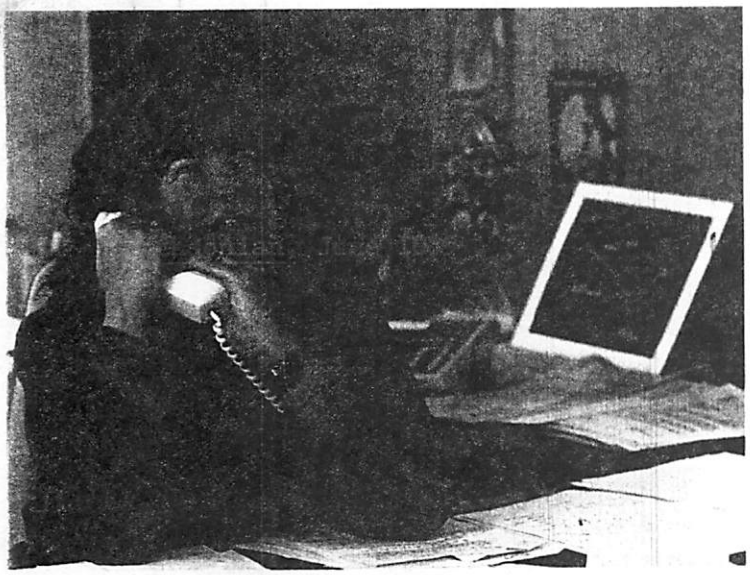


Traditional view holds that endocrine (red), central nervous (gold), lymphatic (blue) systems are discrete.

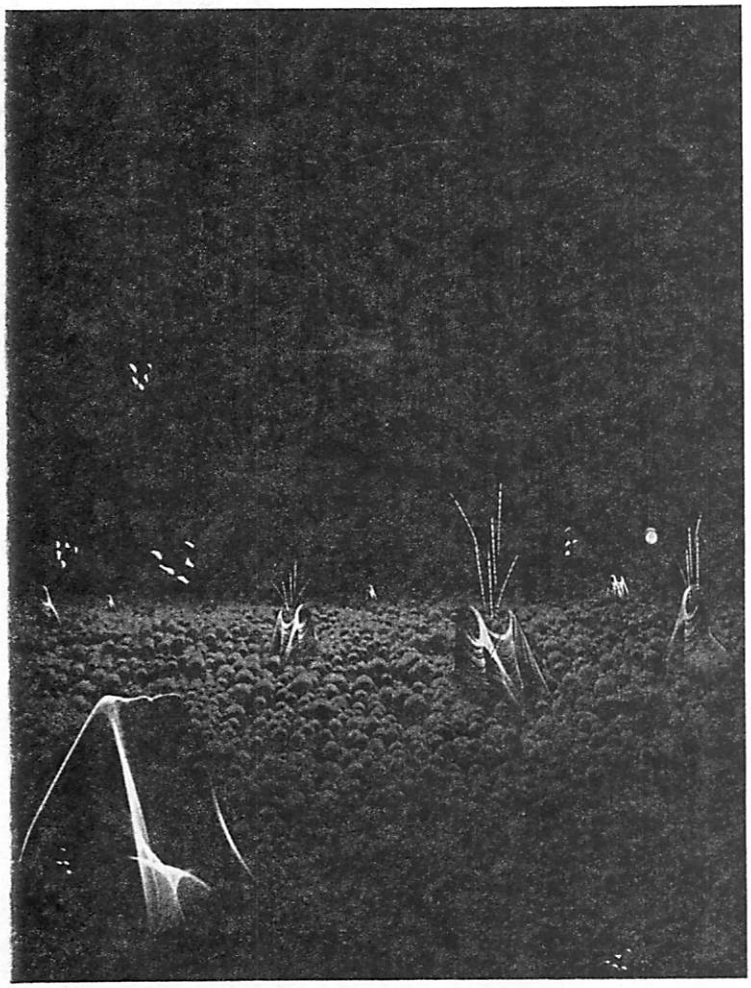


But theory of psychoneuroimmunology says that they are tied closely together via messenger molecules.

Photographs by Michael Freeman



Peptide researcher Candace Pert, a main proponent of psychoneuroimmunology, is working on AIDS cure.



Under branches of a distant neuron, the surface of a brain cell is studded with peaked peptide receptors. Like locks, the receptors "open" only with a specific key, in this case peptide molecules (flying V's). Once unlocked, receptors change shape, allowing other chemicals (dashed streaks) to flow in and out of cell.

do when things don't fit: they question the rigor of other people's science. "I thought perhaps the work was sloppy, shoddy, didn't have the right controls," she admits. "When you can't fit it into your cosmos, it's a lot easier to think someone else is a slob." Then Pert and her NIMH collaborator, Michael Ruff, began to find the same thing: certain white blood cells were equipped with the molecular equivalent of antennas tuned specifically to receive messages from the brain.

Getting set to tear down the barricades

As more and more of these "misfit" molecules turn up in unexpected places, some biologists believe we need to rethink some long-cherished principles, beginning with medicine's traditional separation of the central nervous system (the seat of thought, memory and emotion) from the endocrine system (which secretes powerful hormones) and the immune system (which defends the body from microbial invasions). To be sure, many other scientists argue that these misfit molecules are, at best, not well understood and, at worst, the product of unfit science. But scientists like Blalock, Pert and Ruff are prepared to declare a revolution. The barricades they seek to tear down separate nothing less than the mind and the body.

Bit by bit, these and other scientists are assembling a mosaic of data suggesting that our anatomical systems, separated by 19th-century tradition, routinely communicate with one another. Carrying the messages back and forth, moreover, are small, go-between molecules. There may be from 60 to 100 of these powerful biochemicals; traditionally known as neurotransmitters, hormones, neuropeptides, growth factors and lymphokines, these chemicals are now seen by some as a related family of biochemical words, essential turns of phrase in the vocabulary of life. Francis O. Schmitt, a neuroscientist at MIT, refers to them as "informational substances." As they are better understood, some researchers believe, they may assemble into the intercellular equivalent of the genetic code and may influence medicine in the 21st century the way research on DNA has influenced 20th-century biology.

Research on informational substances forms the molecular avant-garde of a relatively young scientific discipline that holds enormous promise. The discipline travels under various aliases—"psychoneuroimmunology" is perhaps the best known of several tongue-tying alternatives. The informational substances, many of which are known to have a powerful effect on mood and emotion, provide a molecular way to understand the long-suspected connection between state of mind and state of health.

How interconnected are mind and body? Ed Blalock, now at the University of Alabama at Birmingham,

believes the immune system functions as a sensory organ, just like the eyes or nose: white blood cells recognize what he calls "noncognitive stimuli," such as bacteria and viruses, and these immune system cells influence behavior by unleashing a gush of powerful biochemicals. In a similar vein, Pert, Ruff and their colleagues, then of NIMH, theorized about a "neuropeptide and psychosomatic network," where the mind and body constantly chatter back and forth using a vocabulary of biochemicals, the detectable result of which is the full range of human emotions. In their scenario, white blood cells are "bits of the brain floating around the body." They make and discharge hormones. They receive messages directly from the brain. They may even send messages to the brain that affect behavior, too.

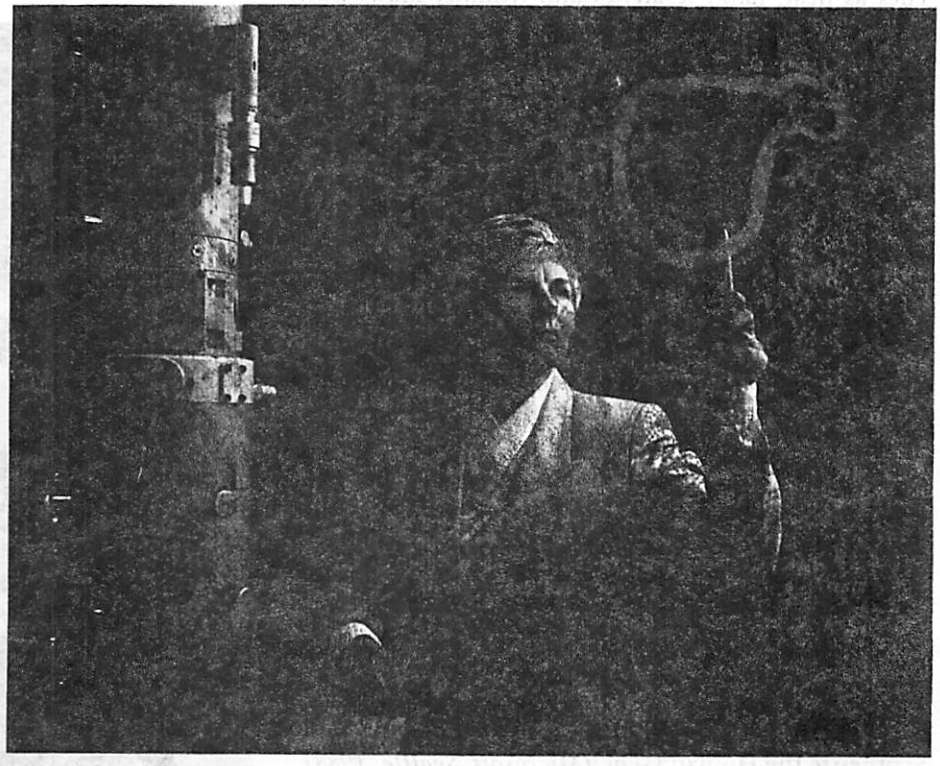
What all this means is unclear, but some researchers are not bashful about speculating. "Just as there are only a finite number [of nucleic bases] that code for all forms of life, whether it be viral or human," says Pert, "there's going to be a finite number of information molecules that code for intercellular communication, whether we're talking about communication between two separate organisms or we're talking about intercommunication between the cells of your gut and the immune system and your glands and your brain."

It is not an easy scientific leap to make, as Pert herself acknowledges. At a meeting last year sponsored by the UCLA School of Medicine at Lake Arrowhead, California, she described a recurring dream about a giant chasm that separated the "old medicine" from the "new medicine." "And there's a guy on the other side who is telling me to jump," she told her colleagues, "and I'm scared to jump."

In truth, Pert's group has helped define the field in theoretical leaps and is taking a running start at the far side of that chasm, where the mind resides in the body as well as in the brain, and where emotions play an important role in disease and health. That world lies somewhere in the 21st century, but Pert is confident we are going to get there. "It's going to be so quickly forgotten," she predicts, "how controversial this all was."

It was another dream—possibly the most important and most debated dream in the history of philosophy—that helped build the walls that have so recently been set atremble by molecular biology. More than three centuries ago, on the morning of November 10, 1619, the French philosopher René Descartes awoke from a dream that, he revealed later, inspired him to embark on a lifelong philosophic mission. That metaphysical journey culminated in his most famous assertion—that the mind and the body are segregated into two separate branches of worldly existence.

Not that everyone subscribed to the idea, before or since. Aristotle was among the first to suggest the connection between mood and health ("Soul and body, I suggest, react sympathetically upon each other," he



Photomicrograph of cross section of mouse thymus enmeshes Karen Bulloch, who points out protective sheath (mauve) surrounding nerve fiber. The thymus, transplanted into a mouse without one, grew nerve fibers, showing importance of nerves to immune system.

once noted). Charles Darwin, too, believed the connection was important; it was a major premise of his largely overlooked book, *The Expression of the Emotions in Man and Animals.* And no less revered a practitioner than Sir William Osler, the turn-of-the-century physician described as the "father of modern medicine," once remarked, "The care of tuberculosis depends more on what the patient has in his head than what he has in his chest."

Aristotle, Darwin and Osler form an impressive trio of observers; all were struck by the apparent connection between mind and body, emotions and health. Yet all, too, were essentially powerless to sketch out that connection in anything but the broadest and fuzziest of strokes. The tools they brought to the task—dissection, microscopes, x rays and the like—simply were not powerful enough to discern the links. Only with the convergence of molecular biology, immunology and neuroscience have scientists begun to span the huge gap between emotions, mental processes and molecules.

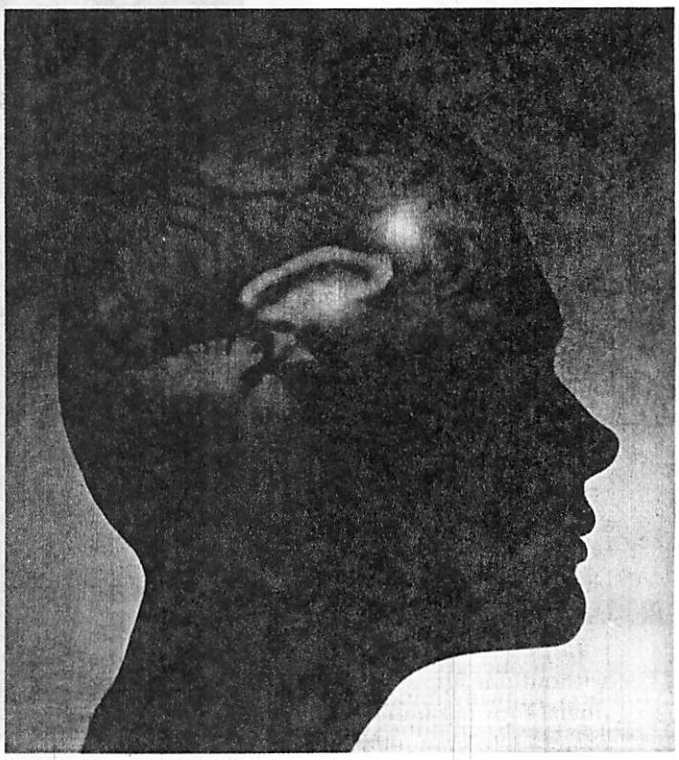
One remarkable pioneer was Russian émigré S. I. Metal'nikov. Working at the Pasteur Institute in Paris with V. Chorine in the 1920s and '30s, Metal'nikov showed that classical (Pavlovian) conditioning could both suppress and enhance the immune response. At the turn of the century, Pavlov had shown that if you rang a bell shortly before presenting dogs with meat powder, the dogs mentally associated the bell with food and, after many repetitions, began to salivate solely at the sound of the bell. Metal'nikov paired such cues as heat, hand scratches and trumpet blasts with injections of bacteria that stimulated the immune systems of guinea pigs and rabbits. After repeated trials, the animals in effect "learned" to rev up their immune systems with a horn, suggesting that the central nervous system communicated with the immune system.

Two Americans stand out both as pioneer researchers in the field and as major figures in establishing its credibility. Psychiatrist George F. Solomon and colleague Rudolf Moos of Stanford University, in a landmark study of women published in 1964, demonstrated a link between emotional conflict and the onset and course of rheumatoid arthritis. Despite a genetic predisposition, certain women remained free of disease. "They were all emotionally healthy," Solomon recalls of the disease-free group. "They were not depressed. They were not alienated. They had good marriages. We felt that emotional health protected them from rheumatoid arthritis." The study, not surprisingly, provoked great skepticism in the scientific community.

The other historical giant in the field is psychologist Robert Ader of the University of Rochester School of Medicine. Ader is credited by some with putting psychoneuroimmunology (he coined the term) on the map in the 1970s in a series of groundbreaking experiments with Nicholas Cohen. Ader's rats were trained to associate an initial stimulus with a subsequent event. In this case, they "learned" to depress their immune system when given sweetened water. In other words, mere mental association could put a damper on the immune system—supporting Metal'nikov's precept that the central nervous system could influence the vigor of the immune system.

Connections, however, demanded mechanisms—demanded, literally, to be fleshed out, and at about the same time, links between the central nervous and immune systems began to provide some anatomical answers. Karen Bulloch, now of the University of California, San Diego, and David Felten of the University of Rochester medical school both have done pioneering work tracing nerve threads that run, like wires, from the central nervous system to two key immune organs, the thymus (Bulloch) and the spleen (Felten).

So the early research provided a rough anatomical sketch, suggesting areas where mind and body intersected. But all these links begged several fundamental questions. How could the central nervous system influence the immune system? Moreover, shouldn't there be two-way communication, with the immune system



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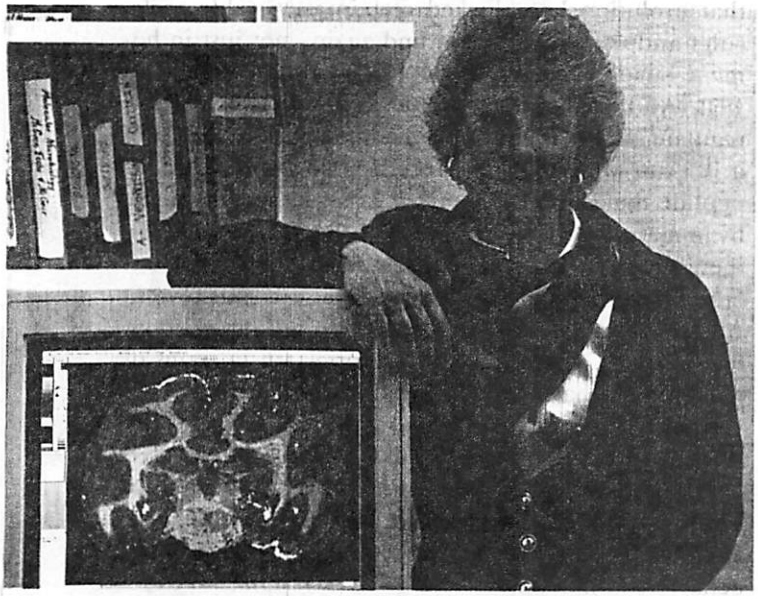
talking back, as it were, to the central nervous system as well? And by what means did they communicate with each other?

At this point, the questions of psychoneuroimmunology began to overlap some longstanding puzzles of brain research, and that is where Candace Pert comes in. Although she set out to be an English literature major when she went to college in the mid-1960s, it was the precise science of psychopharmacology—studying the effect of drugs on the brain and behavior—that ultimately hooked Pert on the neurosciences. She went on to the Johns Hopkins School of Medicine for graduate studies. Trained there in the powerful techniques of modern biology, she began research that led to a bold new theory—that a relatively small family of molecules could be identified as the biochemical basis of emotions.

Working with Solomon Snyder, Pert in 1973 discovered an important biological landmark called the opiate receptor. Psychopharmacologists had assumed that in order to have an effect on the brain, natural pain-killing substances such as morphine and other opium-derivatives (known collectively as opiates) needed some specific way of interacting with brain cells. What Pert found was a molecule on the surface of the cell that accommodated the drug like a keyhole accepts the notches of a particular key. That cellular keyhole became known as a "receptor."



Opposite: White "hot spots" in brain image, dense with peptide receptors, occur where human emotions originate. Researcher Joanna Hill (above), using "tagged" molecules, found AIDS virus also attaches to receptors at similar sites (yellow) in monkey's brain.

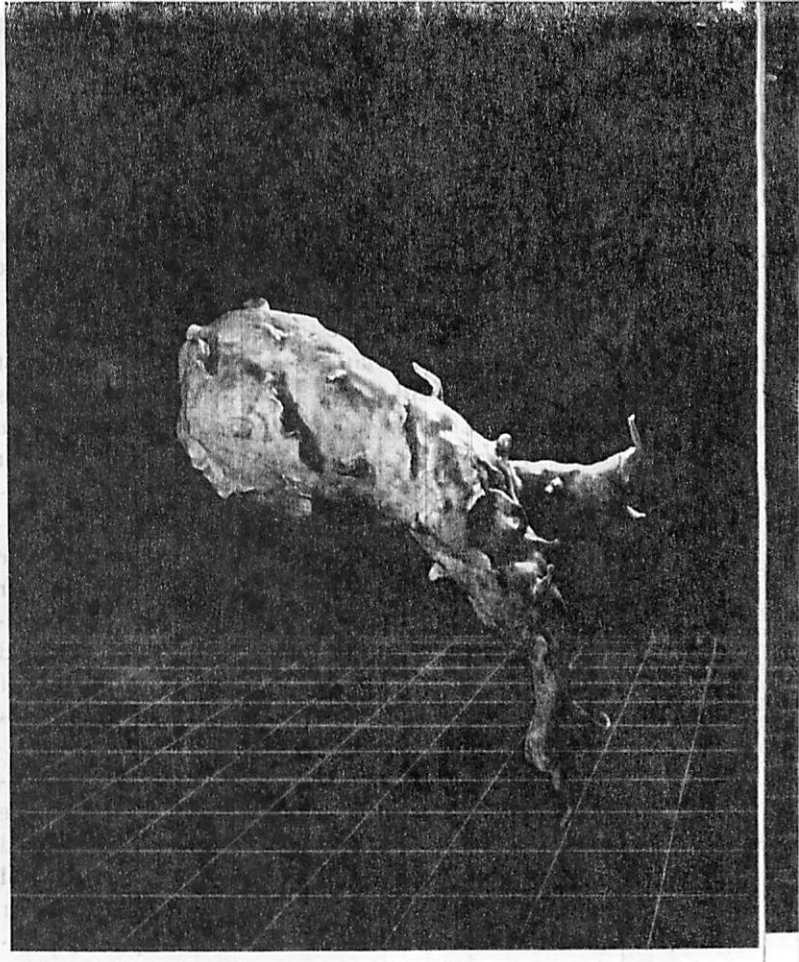
As Pert later put it, "God presumably did not put an opiate receptor in our brains so that we could eventually discover how to get high with opium." If the body naturally made opiate receptors, the inescapable implication was that the body made opiates, too—natural "in-house," pain-killing molecules that resembled "foreign" molecules like opium, morphine and heroin. Implication became reality in 1975 with the discovery of the first in-house, or endogenous, opiate.

"The key thing about the opiate receptor discovery," Pert says now, "is that it pointed the way." As evidence accumulated, it indeed became clear that the human body is an impressive pharmacological factory. Since the early 1970s, beginning with the isolation of a pain-inducing peptide called substance P, about 50 similar molecules have been discovered. These peptides are formed by strings of amino acids—joined "like popette beads," Pert says—and like all proteins, each of these molecules folds into a unique three-dimensional shape that can be likened to the unique grooves and notches on a key. It interacts with a specific type of receptor just as a particular key, for example, engages only the tumblers of a particular lock. As with a lock, a small event such as the insertion and turning of the key leads to big changes—the biochemical equivalent of throwing a deadbolt—inside the cell. Here then were the elements of Pert's theory: these peptides and their receptors, she proposed, are the biochemistry of emotions.

The hormone insulin provides a good example of how these molecules work. Secreted by the pancreas into the bloodstream, insulin affects metabolism by allowing cells throughout the body to use glucose as a fuel. In the early 1980s, a group at the National Institutes of Health headed by Jesse Roth discovered insulin receptors on brain cells. Later they found that some brain cells *make* insulin and that, in the brain, insulin performs different tasks: by promoting cell growth, it acts as a growth factor instead of as a hormone, and by suppressing appetite, it also functions as a neuropeptide.

A molecular map of emotions

Peptides, like keys, are portable and they can move around; receptors, like door locks, are stationary, rooted to one spot. Candace Pert and her NIMH colleagues, principally Miles Herkenham and Joanna Hill, began surveying neighborhoods of the brain for specific receptors. They took very thin slices of rat brains and, using radioactively tagged molecules, created maps of specific receptors localized in the brain. Pert began to see these maps as a kind of molecular atlas of emotions, because certain dense clusters of receptors appeared in parts of the brain long associated with emotional processes (opposite).



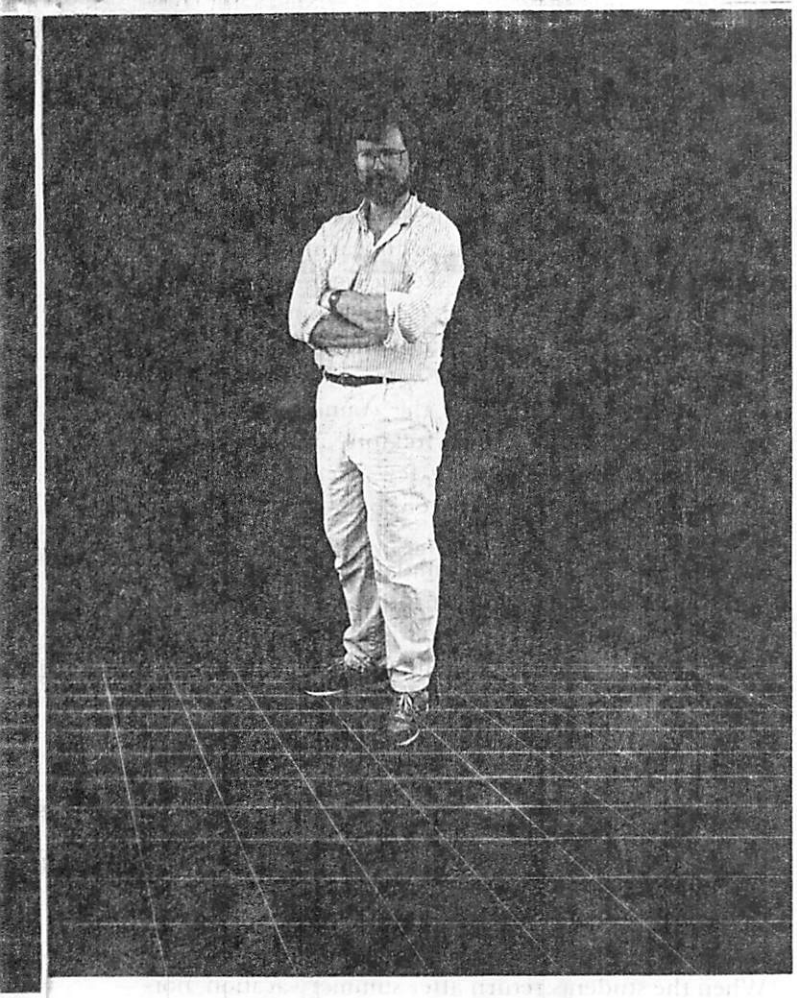
Pert refers to these "hot spots" as nodal points that seem to correlate with emotions. Three key neighborhoods of the brain—the frontal cortex, the hypocampus and the amygdala—are especially dense with many peptide receptors, as is a part of the spinal cord known as the dorsal horn, which runs from the neck to the tailbone and is a major point of convergence for sensory information. The nodal point that lies in the frontal cortex is not only rich in peptide receptors but is heavily threaded with specialized neurons associated with touch, smell, sight, sound and taste. In Pert's view, nodal points mark junctions where information molecules commingle and influence behavior. Indeed, she argues that some of the figures of speech we use out of habit have molecular underpinnings.

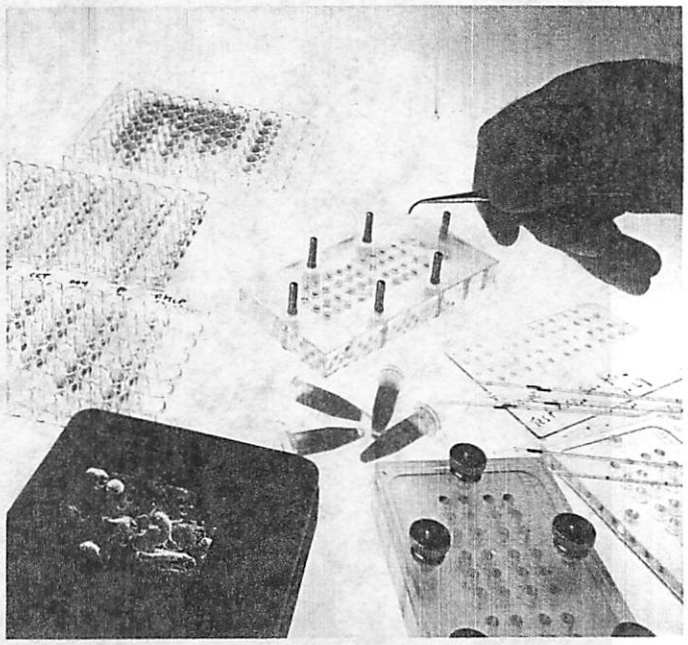
"Take a deep breath" is an injunction to calm down. Breathing is controlled in the brain stem, and research shows this region is saturated with opiate receptors; Pert even argues that changes in breathing—like those experienced by athletes and yogis—can alter the flow and concentration of peptides. Or consider "gut feelings." The stomach and gut are heavily wired with nerves and with receptors to many peptides. A pain-killing peptide, CCK, is released in the gut after a meal. Not only does it tell the brain to shut down appetite, but it also contributes to a feeling of well-being. "No wonder we feel so good after a great meal," Pert observes.

Even more surprisingly, researchers have found the same—or very similar—substances in other animals, in higher plants and even in single-celled organisms. Investigators were astounded recently to find that a substance virtually identical to insulin is made by a primitive unicellular protozoan called tetrahymena. The peptide that tickles yeast cells into mating seems to be a cousin of human gonadotropin releasing factor, which controls the release of human sex hormones. Prolactin, the hormone that stimulates the development of mammary glands in mammals, allowed fish to adapt to a saline environment in an earlier stage of evolution. The same powerful neurochemicals that alter mood in the human brain have been found on the skin of frogs.

What does this mean? It means, according to Pert, that evolution has plucked certain serviceable molecules and used them again and again—not just in humans but in all living creatures—to do what they do well. And what these molecules seem to do well is regulate, modulate and convey information. Whether it is a hormone that influences sexual urges, a neuropeptide that elevates mood, or even a chemical made by immune cells like interleukin-1 that can spur fevers, these substances clearly allow cells to talk to one another, and the cumulative din of those chemical conversations can make us feel frisky or euphoric or feverishly ill. "Emotions are so important in terms of regulating behavior, and regulating survival, that the very first successful evolution in that direction would be preserved," Pert believes. "It would tend to be used over and over again. After all, the great pleasures of life—eating and sex—are both necessary for survival, and there's tons of emotional wiring around those behaviors in humans."

Perhaps the most important mechanism for survival is the way the body preserves health and fends off disease, which is the province of the immune system.





Michael Ruff (left) studies model of macrophage, a white blood cell that relays chemical messages between brain and immune system. In a more conventional setting (above), he prepares an experiment to show how macrophages detect peptides, migrate toward them.

And that is where the misfit molecules really began to confound conventional thought.

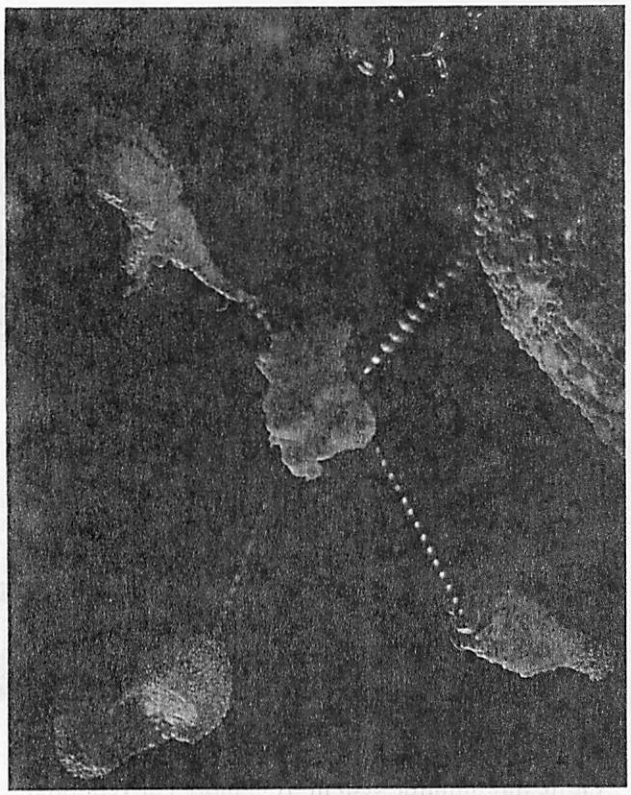
The immune system is extraordinarily complex and fluid. Like branches of the armed services, it maintains a varied corps of task-specific cells in a perpetual state of vigilance and readiness. Some cells (monocytes) act as sentinels, others (antibodies, and natural killer and cytotoxic T cells) as infantry and artillery; some (helper and suppressor T cells) rouse or mute the general alarm, and others (macrophages) come around to clean up the battlefield and cart off the results of the carnage. Humans can generate up to one billion different antibody molecules to attack foreign invaders. The system is sophisticated enough to "remember" any invader, which is why vaccination works—it gives the immune system something to lodge in its memory cells. And it is amazingly self-preservative—when an individual suffers a severe, hemorrhaging injury leading to massive blood loss, these crucial memory cells know enough to seek refuge in the bone marrow, so they won't bleed out onto the street.

How do these cells coordinate this flurry of activity? The answer is that they send messages to one another. A cell will send a message by squirting one of those very small, short-lived molecules known as peptides. And in order to receive those messages immune cells also need to have receptors. Back in 1976, Nicholas Plotnikoff of Oral Roberts University first reported that immune cells possessed, of all things, the opiate receptor (in other words, immune cells theoretically received messages from the brain).

In his work at the University of Alabama, Blalock, coming from the other direction, has reported that immune cells can make the mood-altering brain peptides known as endorphins.

One of the most intriguing networks has been worked out by Michael Ruff at NIMH. His work has concentrated on macrophages, once derided as the "garbage collectors" of the immune system. When first formed in the bone marrow, macrophages enter the bloodstream as nomadic adolescent cells called monocytes. Monocytes are among the first cells to spot a foreign intruder and raise the alarm. Later on, monocytes can settle down in the skin, lungs or brain and take up permanent residence as macrophages.

Ruff's research shows that these cells, in motion or at rest, have enormous potential for sending and receiving biochemical messages. Macrophagelike cells in the brain (called glia) possess receptors to powerful molecules made by the immune system; both monocytes and macrophages have receptors on their surface that accommodate virtually every neuropeptide known. Because of these cells' movement and informational dexterity, Pert and Ruff call them "mobile synapses."



Helper T cell (center) coordinates other immune cells, including macrophage (top left), a mobile link to brain.

What all this work has established is that there are the molecular equivalent of telephone lines between the brain and immune system. "What we have done, with the help of others, is maybe pointed out the molecular basis for the communication between these systems, but that's all," says Joanna Hill of the Pert lab. "You don't know if it is being used, and you don't know what's being said." One obvious—and difficult—next step in research is to eavesdrop on those conversations; a more distant goal is to enter into the dialogue pharmacologically to aid healing.

The mere existence of those lines of communication, however, convinces Ed Blalock that the immune system is a sensory organ as much as the eyes or ears. "The immune system serves to recognize and sense those things you can't hear or taste or touch or smell or feel, things that are not recognized by any of the other senses," he says. "If you came into contact with a grizzly bear, for example, the visual recognition would evoke the production of stress hormones, which would change your physiology in a way that would help you deal with the situation. If your body comes into contact with a virus, you can't see it or smell it or touch it. But your physiology needs to change nonetheless. Well, our argument is that your physiology changes when your immune system senses it and produces the hormones that change physiology."

It bears repeating at this point that many—perhaps the majority—in the scientific and medical communities view these developments with wariness, if not outright disbelief. Part of this skepticism is the legacy of overblown, unsubstantiated claims connecting stress with illness or certain personality traits with cancer. In a 1985 editorial in the *New England Journal of Medicine*, Marcia Angell called the connection between emotions and health "largely folklore" and argued that the "literature contains very few scientifically sound studies of the relation, if there is one, between mental state and disease."

Nonetheless, as data accumulate, that vast gulf between molecules and state of mind is being gradually closed. "I used to say we were at square one," says Robert Ader. "Now I think we're at about square three."

Ronald Glaser and Janice Kiecolt-Glaser, both of Ohio State University, have done studies of first-year medical students showing that during periods of academic stress (just before or during exam week), the immune function suffers both in numbers of cells and in the ability of cells to perform. "It suggests," says Kiecolt-Glaser, "that even commonplace events that we associate with emotional arousal or discomfort can be associated with [decreases] in immune functions." When the students return after summer vacation, normal vigor has returned to the immune system.

Trying to track the signals

Robert Ader's recent work with rats suggests that behavior may somehow be influenced by the immune system—more evidence pointing toward the long-sought feedback mechanism where the immune system affects the central nervous system. He has shown that a special breed of laboratory rat defies the normal aversion to water laced with the nausea-inducing drug cyclophosphamide. When the drug is paired with sweetened water, rats with systemic lupus erythematosus—a disease caused by an overly aggressive immune system—ignore the unpleasant side effects and continue to drink. Cyclophosphamide also depresses immune function, but that is beneficial for lupus-prone animals and their hyperactive immune systems. "The animals know it's 'good' for them, as it were," says Ader. "Signals generated by the immune system are being read by the central nervous system. What that signal is and where it is going—that I don't know."

Even AIDS can be viewed through the prism of psychoneuroimmunology. Candace Pert and her NIMH colleagues have advanced a hypothesis that AIDS is a disease rooted in the disruption of peptide communication. Specifically, her group argues that a

portion of the AIDS virus' external spike, used to gain entry to cells through a particular receptor, actually mimics a ubiquitous neuropeptide known as vasoactive intestinal peptide (VIP). This molecule is active not only in the gut, but also in the brain, where it apparently promotes the growth and health of neurons. When the AIDS virus attaches to the VIP receptor, it preempts the activity of VIP, and neurons die. Pert believes this is the cause of the dementia that afflicts many AIDS patients.

Viewing the disease as a peptide disorder, the NIMH group has gone on to design a protective peptide that covers the receptors of neurons like a cap and prevents the AIDS virus from attaching (below). Called peptide T, in small-scale clinical trials its use has been accompanied by significant physical and neurological improvement. Whether peptide T works or not—and there is considerable skepticism in the scientific community about it—it represents a novel departure from traditional disease treatments, such as vaccines and antibiotics. So optimistic about the possibilities is Pert, she and Ruff have formed a biotechnology company called Peptide Design L.P.

There is a sign in Pert's new office that reads: "If you are being run out of town, get out in front of the crowd and make it look like you're leading a parade." There are still a lot of people raining on this particular scientific parade, but Pert and her allies are convinced they are on the right track. "I've got the goods, the little nuts and bolts, the peptides," she likes to say. "Our work is just beginning to prove some of this. A lot of this has been my interpretation of the significance of my lab's work. But I know it's right." Scientists don't often talk that way, at least for public consumption. Revolutionaries do, however, and as far as Candace Pert is concerned, we're in the midst of a revolution.

Pert believes an AIDS virus (top) infects cell when one of its protein spikes binds to peptide receptor on cell's surface. Peptide T molecules (flying V's) block access of virus' spikes by occupying all receptor sites.