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1. "Magic Bullets"

They were going to be the "magic bullets" of psychopharmacology, miraculous chemical keys to unlock the secrets of pleasure and pain, joy and sorrow, memory, intelligence, and behavior.

They were supposed to explain everything from falling in love to falling asleep, and a full understanding of their actions and effects was going to cure drug addiction and mental illness, regulate mood and appetite, and even heighten creativity and sexual response.

They were the endorphins, the internally-produced morphine-like substances responsible for an array of drug-like effects in the body, and for a while after their 1975 discovery, everyone wanted to speculate about them.

the High

According to some scientists and most reporters, endorphins were clearly the Next Big Thing in the neurosciences, maybe even the Last Big Thing, and the imaginations of headline writers across the country lit up like major league scoreboards on the Fourth of July as they scrambled to encode news reports in hyperbole.

But the euphoria didn't last. Life got complicated. Research findings were confusing, then contradictory. Somebody even changed the name -- as the number of identified internal body chemicals grew from month to month and began to defy simple classification -- and the catchy "endorphins" became the colorless "neuropeptides" or, even worse, the murky "endogenous opioids."

the LOW

And when the scientists who'd started all the buzzing announced that they were settling down for a few decades' basic research into nuts-and-bolts issues of why the compounds worked and how they were going to make every thing better for everybody forever, the entire phenomenon seemed to die an unmourned media death.

Reporters stayed away from the funeral in droves. Research is boring -- or at least not as exciting as science fiction -- and members of the press moved on to more interesting scientific topics -- choosing baby's sex, for example, or pyramid power.

But the investigators who were drawn to the study of the linked amino-acid-chain neuropeptides did not walk away. Instead, they continued to look hard and long at the powerful new body chemicals and quietly went about the difficult work of figuring them out -- or, at least, figuring out a way to figure them out.

In the process, they linked them with a vast array of physical and emotional problems -- as both possible causes and potential cures -- and the prognosis is now good for at least some of the promised early magic bullets to hit their mark.

What those magic bullets could mean in scientific terms is anybody's guess, and some of the scientists currently engaged in neuropeptide research seem as unsure where it will all end as anyone else. But in human terms, for the millions of people afflicted with a wide range of problems -- from alcoholism and obesity to chronic pain and schizophrenia -- the future is looking brighter than many would have dared to hope even a few years ago.

..2. "Walking Chemistry Sets"

At the bottom of the search for biochemical magic bullets is the suddenly wide-open study of the human brain.

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Dr. Steve Henricksen, senior staff scientist at the Salk Institute in La Jolla, California, knows as much about the brain as anybody, and he just shakes his head when he thinks about the complexity of it all. "We're witnessing an exponential growth in our knowledge of the brain," he says. "Our whole conception of how the brain works is changing right now."

A key ingredient in the current revolution in brain research has been the neuropeptides, Henrieksen says. Where prior to the discovery of neuropeptides, the brain was thought to be a complicated enough place -- with a small handful of neurotransmitters and a grab-bag of hormones and enzymes simulating the approximate complexity and organizational efficiency of an advanced digital computer -- today things upstairs are beginning to look positively like a full-scale riot: "Things are incredibly complex in the brain," Henricksen says. "We used to think the brain was like a computer. Now we think each cell is like a computer, a separate computer. And one single cell is like the whole brain."

If the brain is a collection of integrated, high-speed, ultra-tech computers, the neuropeptides may just turn out to be the electrochemical glue that holds them together -- and the communications link that keeps them buzzing and whirring in unison. But if you're thinking that the brain's communications system is the nice, pat, linear axon-dendrite chain you learned about in high school, with individual neurons passing along biochemical signals like so many pails of water along a volunteer fire department bucket brigade, think again. "The old concept that the nervous system communicates with itself from one cell to another by firing a single neurotransmitter across a synapse is obsolete," Henricksen says. "Right now, that's at best a special case."

More likely is a composite of discrete single-cell impulses mingled with and modulated by a variety of enzymatic, hormonal, and neuropeptide signals, according to Henricksen. How big a variety is open to question, but pharmacologist Dr. Thomas Davis of the University of Arizona Neuropeptide Research Group argues that the possible number of potential neuropeptides is staggering. "There are a large number -- I wouldn't know how many millions -- of different permutations of amino acids yielding neuropeptides of different behavioral effects," Davis says, pointing out that some of those effects could involve processes as diverse as appetite, memory, and aging. Factor in the consideration that dozens, hundreds, thousands are working simultaneously in different directions -- interacting with 20 billion or so brain cells in processing thought and emotion and sensation while regulating motor control and body maintenance functions -- and you've got a system that is almost bewildering in its complexity. That the system, the entire amalgamation of chemicals and electricity and blood and tissue, is in operation -- and in perfect balance -- in each one of us at every moment of our lives seems nothing less than miraculous.

The miracle isn't lost on Davis. "We're just a mixture of chemicals," he says. "We're just a chemistry set walking around in total control, most of the time." In total control? You wonder.

In total control. Davis smiles. "All you have to do is trigger a one-part per million concentration change in the brain and you're totally out of control."

..3. "Lock-and-Key" Analogies

To fully appreciate just how far we've come in our current understanding of the brain and neuropeptide systems -- and to fully understand what the systems are and how they affect our lives -- it's first necessary to take a backward look at the general context in which the discovery of the internal chemicals took place.

Neuropeptides were first discovered in 1975 by a pair of drug addiction researchers in Aberdeen, Scotland, named John Hughes and Hans Kosterlitz, who were searching for an internally-produced body chemical similar to opiate drugs that would plug into existing opiate receptor cells and "turn on" the body's own built-in pain-relief system.

The existence of such receptor cells had been suggested in 1972 by Stanford University psychopharmacologist Avram Goldstein and verified in 1973 by John Hopkins University

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researchers Solomon Snyder and Candace Pert. Goldstein, who hypothesized that the brain must contain receptor sites of some type for opiate narcotics for the drugs to exert any effect at all in the brain and central nervous system, even provided a handy analogy to describe the system he envisioned. "The places in the brain cells where morphine and similar molecules combine," he said, "must be shaped to accommodate the morphine exactly as a lock accommodates a particular key."

In seeking out this biochemical lock and key, Hughes and Kosterlitz discovered simple amino-acid chains in a centrifuged extract taken from pigs' brains, which they then exposed to tissues of the vas deferens in mice. The vas deferens, the duct which carries sperm from the testicles to the prostate gland, seemed an ideal location to measure possible opiate response since it contains, for still unknown reasons, a large number of opiate receptor cells.

What Kosterlitz and Hughes discovered was a heretofore unknown substance binding to their vas deferens samples, a substance which they quickly learned could block, like morphine, electrically-stimulated convulsions in the tissue. They dubbed the substance "enkephalin," from the Greek words for "in the head," where it was produced. After analyzing the new enkephalin structurally, they discovered that the substance was actually not one, but two substances, both amino-acid chains, known as peptides.

As research progressed around the world in the years following the Hughes-Kosterlitz discovery, to further test the notion of internal, or endogenous, opiate-like substances and receptors, the potential applications of the new substances (often lumped loosely, if inaccurately, under the generic term "endorphins" after the 1975 discovery of the beta endorphin molecule became more diverse -- and the supporting evidence a lot more compelling.

At the University of California, Dr. Huda Akil discovered increased endorphin levels in rats exposed to electro-acupuncture with a corresponding increase in tolerance to pain. Administration of the narcotic antagonist naloxone, a drug that reverses the effects of narcotics by displacing them at binding sites, immediately reversed that effect.

At John Hopkins University, Solomon Snyder showed that the central periaqueductal gray (PAG) region of the brain is particularly high in opiate receptor sites and that minced extracts of calf-brain PAG tissue blocked electrically-induced contractions of smooth muscle tissue, like morphine. Naloxone again blocked the response.

In 1978, Salk Institute researchers Jean Bossier, Floyd Bloom, and Roger Guillemin found that stimulation of the PAG region in three patients suffering from peripheral pain triggered relief from pain and increases of from 50 to 300 percent in the brain's concentration of beta-endorphin. As in the other experiments, the effects were blocked by naloxone.

Seemingly all at once, evidence began piling up around the world implicating the neuropeptides in a constantly increasing range of activities. From aging to analgesia, tranquility to transformation, it seemed the endogenous opioids had a biochemical hand in all the events that shape our lives -- or at least that shape our feelings about our lives. And it was this sheer accumulation of evidence, and the tantalizing potential benefits described in early media reports about the chemicals, that fueled our imagination -- and sparked increasing scientific curiosity about the substances themselves.

..4. Boxcar Molecules

What Hughes and Kosterlitz found, as did others who followed them, were chains of amino acids, the large organic molecules often called the "building blocks of life."

The amino-acid chains they discovered in the pigs' brains were short, only five acids long, compared to more complex amino-acid groups in the body such as proteins, which can contain over 100 amino acids.

But it is not the number of amino acids in neuropeptides that determines their function, it is their order, according to Davis.

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"Amino acids are in a specific link, a specific pattern. They're like boxcars on a train, but each one of these boxcars is in a specific position on that train because of the activity of the molecule. You can't exchange boxcars. Otherwise you change the activity."

Summary

To the best of our current knowledge, neuropeptides fall into three main categories: enkephalin (two of which, leu-enkephalin and met-enkephalin, were discovered by Hughes and Kosterlitz); beta-endorphin (a large 31-acid molecule that long served as a basic prototype for understanding the neuropeptides); and dynorphin, a substance discovered in 1979 with much more powerful effects than either enkephalin or simple endorphin.

Discovery of the chemicals really amounted to a jarring, wheelspinning detour off the road neuroscience had been travelling up to that time. Prior to the discovery of the neuropeptides, nerve cell transmission was thought to be a fairly straightforward affair, with individual cells believed to communicate exclusively through the release of chemical messengers known as neurotransmitters. These molecular messengers (serotonin, dopamine, acetylcholine, and norepinephrine are the most common) squirt across the two-millionth of a centimeter gap between neurons, urging the connecting nerve cell to turn on or off or fire or not fire, depending on the nature, and specific instructions, of the signal.

Although similar to neurotransmitters in a number of ways, neuropeptides are also different in that they are made up exclusively of amino acids, rather than inorganic chemical compounds. And while neurotransmitters seem largely to researchers to be little more than a transmission medium for neurological messages, neuropeptides, with the preciseness of their fit in the biochemical "locks" Goldstein described and the specificity of their actions, seem increasingly to be no less than the message itself.

..5. "Do-It-Yourself" Drugs

Probably the most commonly-known neuropeptide "message" discovered thus far is contained inside the beta-endorphin molecule. Beta-endorphin, discovered in 1975, was the first superstar neuropeptide, hailed as the body's own "do-it-yourself" drug, a natural, inborn chemical capable of producing high levels of both pain relief and tranquilization and a range of other emotional, behavioral, and physiological effects.

The beta-endorphin molecule itself has long held a special fascination for many researchers. It so effectively quashes pain that it was instantly dubbed endorphin (a contraction for "endogenous morphine") and served as a special focus for much early neuropeptide research. But endorphin is not a simple substance. In fact, researchers know today that it is not even a single substance, but a class of neuropeptides.

The life cycle of the endorphin molecule in the body probably provides the clearest understanding of just how complex the neuropeptide system really is. Produced in the brain and the pituitary gland, the beta-endorphin molecule is active at binding sites in the brain and in locations throughout the body, after being released into the bloodstream. It can also move to the gastrointestinal system, where it is acted on by enzymes which break down the 31-amino-acid molecule into smaller fragments that are active in digestion.

Davis believes the endorphins have "at least a dual function" in the brain and gastrointestinal system, but he isn't willing to stop there. "They could have many functions. They could modulate the function of other neuropeptides and other neurotransmitters as well as have a central effect themselves," he says.

"It's like this damn thing," he says, pulling a Swiss Army knife from his desk drawer. "Like a little knife that has 42 different facets to it. yet it's still a knife. It's a corkscrew, a file, a screwdriver. The endorphin molecule is the basic knife and all the different fragments are all the other parts and their different functions -- one can unlock a door, the other can open a bottle, the other turn a screw. One endorphin fragment may affect behavior, the other one memory, the other one acclimation, the other one heat response and sweating."

"But it's not just one chemical."

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..6. Inner Workings

The neuropeptides themselves are present in great profusion in the brain, particularly in the limbic system, the emotional center of the brain. Although more than 20 separate peptides have been identified thus far, most researchers expect dozens, maybe hundreds, more to be identified before we get a complete handle on their actions and effects.

How the chemicals work exactly is poorly understood, but Professor Goldstein's lock-and-key analogy still seems the best (or at least the most understandable) description of what's going on in there: The neuropeptides are complex chemical "keys" with a high affinity for certain types of receptor "'locks," and seem to fit them perfectly -- or trigger other chemicals that fit them perfectly. Production of the neuropeptides themselves may well be regulated by body enzymes that respond to a bewildering variety of internal and external signals.

Also poorly understood at the moment is the reason that external drugs are able to plug into and turn on various parts of the endogenous neuropeptide system. While at first many believed that drugs work in the body because they have structural similarities to neuropeptides, researchers are less sure today. "Psychoactive drugs may work because of their structural similarity to endogenous chemicals in the brain," Davis explains. "Or they may work because they trigger release of substances that act on receptors in the brain.

"The drug has to lock in or it has to affect the chemical that does the locking in," he says.

But regardless of which chemical key snuggles inside which receptor lock, once the key is turned all sorts of things start to happen. So many, in fact, that the full range of effects associated with various neuropeptides are only vaguely beginning to be understood.

The endorphins probably best demonstrate the complexity of these effects. Beta-endorphin became something of a showcase neuropeptide because of its effects, which closely resembled those of the opiates, and which include the same general feel-good feelings of pleasure and relaxation over which people have risked life and limb for millions of years. As a result, early stories on the neuropeptides focused almost exclusively on beta, and early research linked it to all manner of pursuits, from acupuncture to runner's high. But just as with the other peptides, the longer researchers looked at beta-endorphin, the less it looked like a simple explanation for anything.

One reason for this, according to Davis, is that the peptides continually change in the body: "These things may just break down and break down and exert all sorts of different effects in different parts of the body until you get down to small amino acids" he says. "Then the body does it all over again."

Further complicating matters, Davis points out, is that the effects of the peptides seem to change, sometimes remarkably so, as their structures change. "The same endorphin molecule can have opposite effects once it's cleaved in half," he says. "You break beta-endorphin in half...and it's not beta-endorphin anymore. It can act completely different."

Can it ever. Because a common breakdown product of beta is a 17-amino-acid fragment called gamma-endorphin. Strip away a single amino acid from gamma and you get alpha-endorphin. The effects of both seem far removed from the blissed-out, mellow-fellow effects of beta. And according to Davis, they couldn't be much more different.

"If you had too much alpha-endorphin, you might have an amphetamine-type behavior, because it acts like amphetamines. If you have too little gamma-endorphin, you may lack the neuroleptic action of gamma-endorphin and, therefore, you could have a schizophrenic problem."

And while Davis is quick to point out that all this is still highly speculative, he is willing to

think out loud about potential applications of neuropeptide research: "Someday, we may be able to control consciousness through the homeostatic control of chemicals."

..7. Problems and Potentials

Leaving all other considerations and potential applications aside, the neuropeptides provide, at the very least, built-in circuitry and wiring for the actions of drugs in the body. This being so, it's probably not surprising that pharmaceutical manufacturers have wasted little time in attempting to translate the explosion of neuropeptide research into cold cash and a hot new roster of medications. Within months of the discovery of enkephalin in 1975, dozens of chemical analogues were under patent by pharmaceutical houses on both sides of the Atlantic, in spite of the fact that problems seem to pop up as quickly as new peptide combinations themselves.

For one, there's been a continual problem with the sheer unmanageability of manipulating and evaluating the complex organic molecules that comprise the neuropeptides.

"Peptides are large, and they're susceptible to rapid degradation in the body," says Dr. Robert Frederickson, a research scientist in the central nervous system labs at pharmaceutical giant Eli Lilly and Company.

"They're also not transported against membrane barriers, which represents quite a problem in delivering them to appropriate sites in the brain."

For this reason, much current research has focused more on the development of substances that cause the body to increase its own level of specific neuropeptides than on simply introducing external chemicals that mimic existing endorphins or enkephalins.

Particularly promising, Davis says, are the enzymes that trigger the breakdown of neuropeptides into constituent elements, beta-endorphin into alpha- and gamma-endorphin, for example, or beta-endorphin into met-enkephalin. "We know what some of the enzymes are in the brain and the gut, but we don't know what all of them are," says Davis. "If we could determine what they are, we could model drugs to control that enzymatic process if it was out of control."

Ways that enzymatic processes in the neuropeptide system can manifest their going out of control are legion, but the specific areas that look most interesting -- and most promising -- to researchers today include appetite, addictions, pain relief, memory and learning, and mental illness.

Some of the most interesting neuropeptide research -- and a type that has potential value to millions of Americans -- investigates the possible role of neuropeptides in regulating appetite. Current research underway at a variety of locations around the country is aimed at establishing the neuropeptides' role in regulating appetite. If successful, the research could lead to the development of the first safe and effective diet pills and unlock the secrets of eating disorders such as bulimia, in which victims gorge before forcing themselves to vomit, and anorexia nervosa, in which sufferers are unable to eat -- sometimes to the point of complete starvation.

How are neuropeptides linked to appetite? One theory suggests that food engages the neuropeptide system in a manner very similar to drugs and causes the body literally to become addicted to itself.

The theory, first proposed by British researchers James and R.F. McCloy, suggests that the presence of food in the intestines causes local enkephalin release which, for reasons yet unknown, could have such a strongly reinforcing effect in some individuals that they become addicted to their own body chemicals.

Whether or not the McCloys' "auto-addiction" obesity theory holds, it is widely conceded that endogenous opioid systems are involved in appetite regulation, and various compounds are currently being tested for their effectiveness in blocking and controlling appetite. Potential treatments include:

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- **Naltrexone**, an opiate antagonist which blocks opiate receptor sites and presumably, the sensation of hunger. The drug, which is currently being tested at six medical centers across the country, is a long- lasting (6-8 hour) oral derivative of the opioid-blocker naloxone.
- **CCK**, a newly-discovered neuropeptide called cholecystokinin, which researchers at Cornell University believe may be the brain's own satiation signal. In tests, animal subjects given CCK cut their food consumption by three-fourths, and simply seemed to be not hungry when presented with food. Researchers plan to test the substance on human volunteers in the near future.
- **Butorphanol**, a pain-killing drug, which has been shown to stimulate appetite in animals. University of Minnesota researchers who have studied the drug's effects on appetite hope the compound will be effective in treating anorexia nervosa.

Recent advances in memory and learning have also been spurred by neuropeptide research, and at least six major pharmaceutical firms are betting there's money to be made by the first producer of a reliable memory-boosting, intelligence-raising drug.

One current entry with links to the neuropeptides is the anti-diuretic hormone vasopressin. Secreted by the pituitary gland, vasopressin tripled the memory length of mice in one study and has been shown to improve recall in humans, particularly the recall of longs lists of items.

In addition, other neuropeptides have tentatively been shown to up learning performance. Subjects in tests involving one, DDAVP, showed increases of up to 20 percent in learning and memory tests, while another neurohormone, MSH, has also been shown to increase recall. Scientists believe the substances work by increasing alertness and attention.

Possible connections between emotional illness and endogenous substances has been one of the hottest research topics in the behavioral health field since neuropeptide pioneer Roger Guillemin first theorized that the beta-endorphin system could be a "key mechanism" in sorting out normal and abnormal behavior. If so, Guillemin wondered, shouldn't a drug like naloxone, which blocks endorphin's effects, have some value in reducing symptoms of a major psychiatric illness such as schizophrenia?

Tests run to date have yielded puzzling results, according to the Salk Institute's Steven Henricksen, with both beta-endorphin and its antagonist naloxone proving effective in reducing psychotic symptoms. According to Henricksen, this factor alone -- that both agonists (beta-endorphin-like compounds) and antagonists (which displace beta molecules at binding sites) have been shown to alleviate symptoms of schizophrenia -- points out the difficulty in fully understanding the neuropeptide system, and the nature of the disease. "That should tell us something about the complexity of the problem," Henricksen told *Newservice* in a recent interview, "when both the agonist and the antagonist both seem to be involved in the disease state." In addition, Henricksen adds, it also tells researchers that "we've got more work to do," in clarifying the relationship between neuropeptides and emotional illness.

One research area that has tended to support the notion of a direct connection between the endogenous opiate system and emotional illness has been the study of addictions. In one study involving methadone- stabilized ex-heroin users, it was shown that, when daily dosage of methadone fell below critical levels (20 mg/day),that psychotic symptoms consistently developed in 10-15 percent of the subjects. Symptoms disappeared when daily dosage was increased to 30 mg. As a result of such studies, researchers believe that, for a large percentage of users, drug use and addiction represents an attempt to manage, and self-medicate, symptoms of major emotional illness that can otherwise be disabling.

Investigators hope that current research in the area of addictions will more precisely establish the hows and whys of addiction and lead to the development of non-addictive

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substitutes for narcotics and other drugs. But other investigators aren't so sure.

Dr. David Pickar, chief of the Clinical Studies Section of the National Institute of Mental Health, believes that addiction is an unavoidable byproduct of any substance that affects the endogenous opiate system. "The issue around addiction and withdrawal is, I think, central to the whole pharmacology of opioids and opiates," Pickar says, "I think what you see in heroin, morphine, and codeine (in terms of dependence and addiction) is going to be duplicated in endogenous opiates at some level."

Research into addictions has also fueled the single biggest area of neuropeptide research currently under way: the relationship between the chemicals and the control of pain.

Easily the most interested parties in the study of neuropeptides and pain relief are the major drug companies, who stand to benefit most -- and most immediately from the development of an effective, non-addictive, non- narcotic pain-killer.

One of the most interested among them is Eli Lilly and Co., in Indianapolis, a company that's made untold billions of dollars during the past two decades off its popular prescription pain relievers Darvon and Darvocet.

According to research scientist Robert Frederickson, Lilly is interested "across the board" in potential central nervous system applications of neuropeptide research, although it has concentrated, in its research, on analgesic applications of internal opioid systems.

Frederickson is optimistic about the company's chances of developing -- and marketing -- an effective neuropeptide-derived pain reliever in the near future. And although he says specifics "can't be discussed" at the moment, he will say that Lilly is currently clinically testing a "slightly modified" injectable version of Hughes and Kosterlitz's five-amino-acid met-enkephalin molecule, a version he says contains "specific benefits over existing agents."

And will it match early researchers' hopes for an addiction-free side-effect-free drug? Frederickson isn't sure. "I don't know if it will ever be possible to have a completely side-effect free drug," he says. "That is our hope. Whether we will achieve it or not remains to be seen.

"There's great promise, but there are great problems, too. When you're looking at it from this end, it gets a lot more complicated than just a wish list."

..8. The DNA of Consciousness

Also remaining to be seen is how long it will take to fully uncover the remaining mysteries of the neuropeptides and, through them, learn the secrets of the brain, personality, and consciousness itself.

It's generally conceded that there is simply no way of knowing now what will be known when about neuropeptides, and how soon that knowledge can be translated into technologies and treatments to aid people. One reason that prognostication is such an imperfect art in the neuropeptide field is because data is turning up so fast on so many fronts that the sheer volume is difficult to process and assimilate, much less use to extrapolate what the future may (or may not) look like.

Tom Davis of the University of Arizona puts things into perspective this way: "What we know about receptors today is very different from what we knew six to eight months ago. We have no way of knowing what we'll know six months from now."

One thing that is generally recognized among researchers is the critical importance of their work. As its focus has widened steadily over the years -- beyond analgesia and other drug states to memory, sensation, appetite, and emotion -- researchers have come to grasp the immense significance of the task before them: deciphering the codes of consciousness. And as the neuropeptides have emerged as the neurobiological

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equivalent of DNA, researchers have glimpsed the incredible potential of the corkscrew chains and spirals of amino acid permeating the brain and central nervous system. These chemical clusters are not, the scientists have come to recognize, merely an artifact of thought or sensation or emotion; rather, they are the thought or sensation or emotion -- or all of it our brain ever knows. It's the ultimate reduction or clarification of Descartes' famous argument: My brain is full of neuropeptides; therefore I am.

And regardless of when the breakthroughs come (and some researchers believe they may occur in the next five years), and no matter when neuropeptide research "pays off" in the form of enhanced memory or longer lives or expanded emotional well-being, thus far it has contributed much to the study of who -- and what -- we all are. No less intriguing are the questions it raises about how we will be in the future. "Magic bullets" should have to do no more.

..Sidebar | Mapping the Mind

Just as early phrenologists sought to link specific areas of the brain with individual attitudes and aptitudes, researchers today have become increasingly interested in the overlap between psychology and physiology.

For years, the three-and-a-half pound glob of grayish-pink tissue each of us carries in our heads was regarded as the ultimate unknowable object. And for just as many years, the "science of mind" was more accurately a philosophy of mind, with elaborate (and often unfounded) conceptual systems propounded to describe what no one could explain.

But recent breakthroughs in the study of the brain have revolutionized the way in which people think of themselves.

"We constantly hear about things being "just psychological,' as if they're somehow not real," says Dr. Robert Frederickson of Eli Lilly and Company's central nervous system research labs.

"But when you say something is psychological, what you're really talking about is the physical chemistry in the brain. That's as much physiological as it is psychological."

The solution to the traditional split between the "science of mind" and the rest of science, according to Frederickson and others like him, must involve further research into the tangle of chemical codes that link the brain, its billions of neurons, and their quadrillion connections.

And while no one expects researchers to devise a system soon that comes anywhere near the simplicity of the phrenologists' ancient maps of the mind, scientists do expect to learn much more about the biochemical connections between thought and behavior, and to apply that knowledge to a range of problems that predate even the earliest psychology-physiology debate.

Both sides agree it won't come a minute too soon.

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