The Science of Wellbeing

Addictions, Compulsive Disorders, and The Brain Reward Cascade
Alcohol and Other Drugs are associated with:

- 20-35% Suicides
- 50% Spousal Abuse
- 50% Traffic Fatalities
- 62% Assaults
- 49% Murders
- 52% Rapes
- 88% Menslaughter Charges
- 38% Child Abuse
- 69% Drownings

America Has a Big Problem with Alcohol and Other Drugs
Few know that most residents of Clearview Sanitarium were addicts.

All poisons affect nerves, in an Allopathic sense; but the facts are, as learned by Chiropractors, the mental brain impulses conveyed by nerves tried to eject the intruder; failing to do this, they do the next best; accommodating changes are made by the motor impulses. The continued use of a narcotic becomes a habit, not because of suggestion, but by suitable changes made in the mechanism to adapt itself to the environment. Chiropractors have discovered where and what alterations are made and are able to return the disarranged portions to their natural positions, thereby relieving the body of its noxious habit.”

The Science of Chiropractic, — 1920
B.J. Palmer, D.C., Ph.C.
June 23, 1989

To whom it may concern:

Alan Walden, D.C., C.Ac., has been working in the detox department of the Haight Ashbury Free Clinics. A chiropractor, Dr. Walden is also trained and Board Certified by the American College of Addictionology and Compulsive Disorders. He renders subluxation-based chiropractic care using Dr. Jay Holdar’s Torque Release Technique and protocols.

For many years this clinic has introduced many innovative strategies in addiction treatment. Patients are responding favorably to non-force chiropractic care.

Peace and Health,

David E. Smith, M.D.
President & Founder
President, American Society of Addiction Medicine
DESMed
Addictions

Food
Sex
Gambling
Work
Risk-taking Behavior

Compulsive Disorders

ADD*
ADHD
Autism
Dyslexia (many)
Tourette Syndrome
Asperger’s Disorder

Binging
Smoking Behavior
PTSD
Pathological Gambling Polysubstance Dependence

*not a diagnosis according to DSM IV
PART V. NEUROIMMUNOMODULATORY CONTROL OF ONCOGENESIS AND TUMOR GROWTH

The Neuropeptide Network

CANDACE PERT WITH HARRIS DIENSTFREY

Section on Brain Biochemistry
Clinical Neuroscience Branch
National Institute of Mental Health
Bethesda, Maryland 20892

I am going to discuss my laboratory's work on neuropeptides and outline the reasons why we believe that neuropeptides are the biochemical basis of the emotions. Neuropeptides, as we understand them, are not simply one more item in the increasingly more detailed comprehension of the chemistry of the body. We have shown that neuropeptides can influence the body, and this is crucial to our understanding of neuropeptides. People sometimes say they are overcome with this or that feeling. Biochemically speaking, we would say that they are overcome with this or that neuropeptide. What we are dealing with in neuropeptides, we believe, is a body-wide system, or, to put it differently, a system that simultaneously includes brain and body. Conventional scientific wisdom tends to see a clear, distinct difference between brain and body. When talking of neuropeptides, the distinction, for all practical purposes, virtually disappears. We are talking about something that can "grip" the whole organism.

This is one reason we contend that this "whole body" system—the system of neuropeptides, the system of emotions—can play a critical part in matters of health and disease. In this connection, I will briefly mention, at the end of the paper, the new understandings of AIDS to which our work on neuropeptides has led us.

The story of neuropeptides, which is evolving so rapidly, is taking us into rather strange new areas for science. My background is largely in the field of brain receptors, particularly their biochemistry. That is to say, the original focus of my attention was on the part of an individual that generally was taken to be his command post, the brain. But it soon became clear that what we were learning about brain receptors had some startling implications about what could command what.

Some years ago, during the early stages of the studies demonstrating the existence of brain receptors, I was asked to talk about the work to lay people and to try and explain, if I could, its practical application. I thought about this for quite a while—or, as some people would now say, I expanded my consciousness as much as I could—and my response came in the last word of a subtitle for a National Institutes of Health lecture that I delivered to lay people in 1981. The title was "Brain Receptors for Opiates and Other Psychoactive Drugs," and the subtitle, "Keys to the Biochemistry of Emotion."

The concept of "emotion" took me out on a limb. Even today, the word is slightly disreputable in many scientific quarters; a half dozen years ago, its use smacked of the scandalous. Emotion, at best, lingered on the periphery of science, and was never a bona fide subject for investigation. People like Sigmund Freud used the word, but whatever people like Freud did, their activity certainly was not science. Walter Pier-
Paoli said earlier in this workshop that you cannot teach someone something they think they already know. My own work and efforts to investigate emotion suggest a corollary: that it is impossible to teach somebody something that they think is unknowable. Many people think emotions are unknowable in a scientific sense. Our work on neuropeptides strongly suggests otherwise.

What are neuropeptides? What do they do in the life of the brain and body? There used to be heated arguments about what to call these neurosubstances. Were they neurotransmitters or neuromodulators? The general concept first proposed by F. O. Schmitt and independently outlined in our first full-scale effort to explain neuropeptides, "Neuropeptides and their receptors: a psychosomatic network," is that they are informational substances. This is the key thing that neuropeptides do; they are a vehicle for providing information. Where they provide it is equally important. Specifically, they transmit information throughout the brain and body in a network of communication, thereby integrating at the level of the whole organism. The concept of network as it applies to the organism is extremely important and deserves a discussion in itself. Here I would just say that a network is nonhierarchical, that it is a system in which there is potentially equal access to all the nodal points.

In the category of informational molecules that constitute part of the neuropeptide informational network, we now include not only the classical neuropeptides but also hormones (including classical peptide hormones like insulin), lymphokines, and growth factors. We have done gel work and are certain that many molecules similar to if not identical with molecules on T-cells and B-cells in the immune system are also found in the brain, in a pattern that we call the typical neuropeptide receptor pattern. We have not yet found a single growth factor that does not have a feedback loop and receptors in the emotion-mediating parts of the brain. The growth factors include insulin-like growth factor I and II, epidermal growth factor, transferrin receptor, and the lymphokine, interleukin-1.

What we have, then, are peptides diffusing great distances throughout both the brain (it turns out that most if not all neuropeptides are stored in one part of the brain while the receptors are in another part) and the body, having more of a hormone-like action than a neurotransmitter-like action. In short, the peptides flow. They do not need a neural system to enable them to pass, as in a high-wire act, from one neural platform to another. A word to describe the peptide movement might be neurojuices.

Why is the body not confused by all these oozing chemicals, which flow without the benefit a predetermined road-way system? The answer lies in the exquisite specificity of the receptor recognition molecules. Each type of receptor molecule is different from every other type of receptor molecule, each type has a different molecular weight, and it can be shown that each one recognizes only one class of neuropeptide. Despite the fact that there are sixty well-documented neuropeptides, and more if one counts all of the growth factor substances, the receptor molecules keep all straight. There is no confusion because each class of neuropeptide can come to rest, so to speak, in only one kind of receptor molecule.

What has all this to do with emotions? Why do we consider neuropeptides the biochemicals of emotions?

For some years, my laboratory has been working with a receptor-analyzing technique that Dr. Miles Herkenham and I developed in 1979. We call it chemical or molecular neuroanatomy or autoradiography of receptors. Briefly, unfixed frozen sections are incubated in various radio-labeled ligands. The sections are juxtaposed against a film so that we can study the receptor pattern. We then use a computer to transform the pattern into a color gradient according to density. For example, in a section of a rhesus monkey brain which has been incubated with tritiated naloxone.
the computer color-translation shows red and yellow areas that represent approximately 40 times the density of opiate receptors that occur in “cooler” areas. Now, brain sections repeatedly show the same receptor pattern. The cool areas, where the receptors are least dense, are in the cortex, and the hot areas, where they are the densest, are in the amygdala and the hypothalamus, which are classically considered to be the core of the so-called limbic system, which in turn is classically considered to be the system that is the neurosubstrate of the emotions. The neuropeptide receptors, in other words, cluster in those areas of the brain that are classically considered to be key juncture points in the production of emotions.

But it turns out that the amygdala and the hypothalamus are not the only areas in the brain that are rich in neuropeptide receptors. This finding, which has arisen in our work, led Dr. Joanna Hill and I to an expanded view of the limbic system. We now think that the appropriate way to characterize the limbic system is not simply in terms of the parts of the brain that show connections to the amygdala and hypothalamus but rather in terms of the nodal points at which information about neuropeptide status converges in the brain.4

The amygdala and hypothalamus are two such nodal points, of course. Moreover, they are particularly rich areas, because they contain receptors for essentially every neuropeptide we so far have identified. If our reasoning is correct—that the presence of a heavy density of neuropeptide receptors identifies a part of the limbic system—our research suggests that the usual picture of the limbic system should be extended to include the spinal cord, for a third area enriched with neuropeptide receptors is the dorsal horn of the spinal cord. We have not undertaken a systematic study of the receptors to be found there, but our work, whether on insulin receptors or angiotensin receptors, indicates that it is always the dorsal horn that is enriched.5

Now, the dorsal horn has to do with incoming sensory information and not motor outflow, which is associated with another part of the spinal cord, and this central characteristic of the dorsal horn has led to an important theoretical consideration about which Dr. Morton Mishkin and I have speculated in print.6 We argue that the emotions are very important in determining what an individual pays attention to at any given moment. Put simply, your emotions tell you what to do. At any given moment, you are hearing something, seeing something, feeling something. All of your senses (including what Dr. Edward Blalock calls the sixth sense, which reports on the status of the immune system) are communicating simultaneously, and you need a chemical system to prioritize all of this information. We think it is very interesting that not just the spinal cord with the tactile sense is enriched with neuropeptide receptors. The pathway into the brain of all sensory modality input zones, whether they involve sight, sound, smell, taste, or touch, are marked by neuropeptide receptors.

Above, I spoke of peptides diffusing throughout the body as well as the brain—neurojuices—all connecting at the proper places because of the exquisite sensitivity of the receptor molecules. This picture now needs to be joined to the expanding picture of the emotional network in the body. For it seems to us that the concept of emotions, like the concept of the limbic system, should be defined, in effect, by the presence of neuropeptide receptors.

Angiotensin receptors in the rat provide an example. Angiotensin is a neuropeptide made in the brain and has receptors in the subfornical organ. In a rat, when you inject angiotensin into the subfornical area, within about 30 seconds, the rat, regardless of how water sated he may have been, begins to drink water. Now, the kidney of the rat has the same molecular receptors (the technique of chemical neuroanatomy is also applicable, of course, to the peripheral organs), and when angiotensin occupies those receptors, the kidney works to conserve water. In other words, the chemical angiotensin that makes the rat drink when it is injected into the brain also makes the kidney
conserve water. Thus, angiotension leads to water saving and water seeking, two aspects of the same phenomenon. This example seems to us to illustrate a general principle, that the same general mood is integrating to the whole animal level by means of the particular chemical that is diffusing throughout the brain and body.

Where else in the body can neuropeptide receptors be found? Over the past three or four years, Dr. Michael Ruff has accumulated evidence showing that six neuropeptide receptors that have been well documented in brain exist in very similar molecular form on various monocytes. In a study published several years ago, we found that bombesin and other neuropeptides can mediate chemotaxis not just of human monocytes but also of several human tumor cells.

The presence of neuropeptide receptors on monocytes is supported by on-going work on insulin receptors being done by Dr. Joanna Hill and myself. Dr. Hill and I, with Dr. Jesse Roth, have already published a distribution of insulin receptors in rat brains. The distribution follows the standard neuropeptide pattern: the receptors are rich in amygdala, limbic cortex, and other parts of the limbic system. We now are applying our techniques to the spleen, and our early findings suggest that there are similar insulin receptors on monocytes in the spleen.

The presence of neuropeptide receptors on monocytes is the rule not the exception. We now have enough data on enough neuropeptides (not all of it published) to support this proposition.

Looking at this picture of the body-wide, hormone-like distribution of neuropeptides from another angle, we have also begun to explore growth factors. Dr. Hill, an expert in growth factors, had a great interest in transferrin, which has been appreciated as an iron-binding protein and as a major growth factor for a number of cells. Naturally, Dr. Hill wanted to find receptors for transferrin in the brain, and we recently described the limbic-associated pattern of receptors that we found.

Our “mapping” studies, incidentally, are based on a system of carefully graded controls. We validate radioactive ligand-binding distribution patterns by obtaining a rank order of potency of over 20 peptides previously ranked for eliciting a physiological response. We expect the peptides to have the identical rank order in displacing bindings, which is how we know that it is a specific binding. This approach is excellent for peptides, but for larger molecules, for which there is elegant immunological data but not much short peptide work, we need another approach to prove that we have a genuine binding. And in these situations we use what the immunologists have done so beautifully for us—antibodies raised to receptors. The two approaches give us virtually identical patterns. For example, the pattern of transferrin receptors revealed by using classical monoclonal antibodies is the same pattern revealed using a labeled ligand.

In any event, a portion of the receptors are in areas outside the limbic pattern, but many are in areas within the limbic pattern. This suggests that something as unemotional as transferrin and iron has a neuropeptide-like emotional distribution pattern in the brain. And this in turn suggests a feedback loop between brain and body. Again we see an association, a congruence, between peptides and emotions.

Dr. Hill, in collaboration with Dr. Peter Nisley of the National Institutes of Health, has extended this work to other growth factors. With insulin-like growth factor II, for example, both the labeled-ligand and monoclonal-antibody approaches reveal virtually identical patterns of receptors, a large portion of which are, again, in the limbic portions of the brain.

For a final example of the brain/body/neuropeptide network—and one rather closer to the subject of this conference on aging and cancer—I draw on the work of Dr. George Mark of the Cancer Institute. Dr. Mark is an expert on the raf oncogene. He has raised antibodies to synthetic peptides coded by the raf oncogene sequence.
and when we use our antibody mapping technique on a slice of brain, we can show that there are receptors for this raf antibody and that they form neuropeptide receptor-like patterns. Indeed, we have not found an oncogene product that is not in the brain, which supports our idea that virtually everything in the immune system, in terms of cell-surface communication molecules, can also be found in brain.

The biochemists of emotions, because they are so important, are likely to be highly conserved throughout evolution. We believe that this proposition highlights the significance of some findings concerning peptides in unicellular animals. In work done between our laboratory and the laboratory of Dr. Jesse Roth, we demonstrated that the *Tetrahymena* and *E. coli*, simple cellular animals, contain beta-endorphin and other opiate peptides. Dr. Roth had shown previously that they also contained insulin which was immunologically and bioactively indistinguishable from insulin in humans.

In more recent work by Dr. Blanche O’Neill, to be published in *Brain Research*, we have shown a single opiate receptor recognition molecule in the *Tetrahymena*. This molecule is generally 110 kD, but it likes to fragment along a weak point to produce a molecule with the molecular weight of 58 kD. In the *Tetrahymena*, we have found molecules of these two weights. Protease digests of these bands show that they have the same fragmentation pattern and indistinguishable isoelectric focusing points. These molecules may not be strictly identical. However, they are certainly very similar, and we are awaiting the results of their sequencing in a collaborative venture with Dr. Craig Venter.

It was Freud, of course, who drew our attention to the possibility that the brain has a conscious part and an unconscious or subconscious part. Normally, one thinks of the conscious part on the top and the unconscious part toward the back. But we would go further “back” (or down) and say that the subconscious is in the spinal cord and even “lower.” Psychologists talk about deep subconscious processes. Clearly, the network of chemicals that I have attempted to describe suggests that the subconscious extends to one’s T-cells, to one’s monocytes, and, in a kind of flowing wave, back to one’s brain cells.

Freud also made important observations about how emotional status could contribute to disease status. In this context, it seems to us appropriate to consider that with all the circulating neurojuices—and all the neuropeptides can be found in different proportions in different organs throughout the brain, the glands, and the immune system cells—we are seeing a constant aqueous solution that makes a continuum of the brain and the body.

Such a formulation obviously raises the issue of the blood-brain barrier. This barrier exists for only a limited number of substances. We must stay open to the possibility that cells themselves may cross the barrier, just like the microglial cells that start life as macrophages/monocytes in the bone marrow and then actually travel into the brain where they become glial cells. It is possible that there is more cellular trafficking between these two compartments than is currently appreciated. We have no experimental evidence to support this proposition—but we consider it one worthy of serious investigation.

A brief word, finally, on the significance of neuropeptides to health and disease, specifically with regard to AIDS. Our work on neuropeptides has led us to appreciate the AIDS virus in a neurochemical and neuropeptide context. We have shown that the AIDS virus wreaks its havoc through its envelope, gp 120, which blocks vasoactive intestinal peptide binding throughout the brain and the body. We believe that the capacity of gp 120 to negate the important positive effects of vasoactive intestinal peptide provides the solution to the dilemma of why an organism can be so severely damaged by AIDS even though only a small percentage of cells are actually infected.
The exogenous peptide blocks the endogenous peptide, preventing it from doing its good work.

REFERENCES

Breakthrough Brain Research Links Chiropractic Treatment to Addictive Behaviors
Kenneth Blum, Ph.D., D.A.C.A.C.D.; John G. Cull, Ph.D., FAABM
and Jay Holder, D.C., D.A.C.A.C.D.

A "brain reward cascade" of neurotransmitters, when operating properly, results in feelings of well-being. If an imbalance impede the normal flow of the "cascade", the feelings of well-being are supplanted by anxiety, anger, ... or by craving substances which alleviate the negative emotions. Disruption of the "brain reward cascade" results in Reward Deficiency Syndrome ("RDS").

"RDS" can be manifested in mild forms (such as the chain smoker) or more severe forms as in the chemical addict. A genetic based biochemical inability to derive reward from everyday activity links these extremes in behaviors. Alcohol addiction, obesity (as a result of carbohydrate binging), nicotine addiction, attention-deficit/hyperactivity disorder, cocaine addiction, Tourette's disorder, and post-traumatic stress disorder are centrally mediated "RDS" behaviors. Anomalies of the Dopamine D2, Receptor genes, Dopamine Transporter genes, and Dopamine Beta-Hydroxylase genes predispose individuals to "RDS".

Lack of dopamine receptors results in the inability to cope with stress and causes craving. A number of substances (i.e., alcohol, cocaine, marijuana, nicotine, carbohydrates) that release neuronal dopamine may be taken in the attempt to gain temporary relief of stress and craving. These substances can be used singly, in combination, or to some extent interchangeably (have you noted how often recovering alcoholics crave nicotine and/or sugar?).

In support of a comprehensive treatment regimen for "RDS" behaviors, we must review research establishing the vertebral subluxation complex as a primary issue in the multi-factorial expression of addictions and compulsive disorders. The foundation of chiropractic is neurological; therefore, for our purpose we re-focus on neurophysiology and neuroimmunology.

The state of well-being has not received adequate scientific investigation in chiropractic; nor has vertebral subluxation received due study relative to its ability to interfere with the expression of both function and communication "information". The "Brain Reward Cascade" model is effective in providing a better understanding of one's ability to maintain a state of well-being.

Feelings are mediated in the limbic system and are expressed through the reward cascade of neurochemicals. A number of these neurochemicals including neuropeptides are the biochemical mediators of a state of well being. Using autoradiography science has established opiate receptors are densest in the amygdala and hypothalamus (classically considered the core of the limbic system). Port and Dienstrey (1988) expanded the limbic system (the neurosubstrate of emotions) to include the amygdala, hypothalamus, dorsal roots and dorsal horn of the spinal cord. In this regard a direct connection of the nociceptive reflex at any level of the spine to the limbic system has been established.
Moreover, we suggest it is time to accept that "every level of the spine has an intimate relationship with the limbic system's ability to process and establish a balanced brain reward cascade" (Holder and Blum, 1995). A literature review (Holder and Blum, 1995) revealed only vertebrates have an opiate receptor brain reward cascade mechanism; therefore, inside opioid peptides found in invertebrates, only vertebrates express a well-being state. In this instance the common denominator is the spine and spinal cord. If the spine is allowed to express itself without interference (minus subluxations), the vertebrate can express a state of well-being at its greatest potential. Consequently, the ability of the limbic system to function and express itself without interference requires a subluxation free spine. In 1994 The Holder Research Institute finished a study implicating the vertebral subluxation complex as a primary intervention resource in the treatment of chemical dependency in a residential setting.

Pert and Dienstfrey (1988) state "The sub-conscious is in the spinal cord and even lower" and "the sub-conscious extends to one's T-cells [and] one's monocytes, and, .... back to one's brain cells." The origin of Pert's inference was at the dorsal horn of the spinal cord.

Burstein and Potrebie (1993), Harvard Medical School, provide evidence for direct projection of spinal cord neurons to the amygdala and orbital cortex. Their laminar distribution in the spinal cord and the involvement of the amygdala and orbital cortex in limbic functions suggest these pathways play a role in neuronal circuits that enable somatosensory information, including pain, to effect autonomic, endocrine, and behavioral functions. Giesler, et al. (1994), University of Minnesota, found the spinal pathways to the limbic system for nociceptive information; they describe the pathway to include the hypothalamus bilaterally. Prior to Giesler, et al. nociceptive information was thought to reach the hypothalamic neurons through indirect, multisynaptic pathways.

Raffa, et al. (1993), Robert Wood Johnson Pharmaceutical Research Institute, report evidence linking the immune and opioid systems. Kyles, et al. (1993), University of Bristol, found that when dopaminergic and opioid systems process nociceptive information, it is mediated spinaly.

Chiropractic must be maintained on a broad base, not limited to musculo-skeletal applications. Further evidence supports the connection of a healthy spine in mediating, not just immune system function, but growth factor, chemotaxis of human tumor cells, body temperature, water saving and water seeking behavior, etc. (Pert and Dienstfrey, 1988).

Similarities between the addictive process and subluxation are striking. When one considers these similarities and the connection between the subluxation complex and genetic deficits in the dopaminergic system, it becomes important for the modern chiropractor to consider a total regimen of natural healing including the maximum reduction of the subluxation complex, genetic testing, and the administration of appropriate nutraceuticals.