

**REVIEW ARTICLE**

Key Words: migraine, limbic system, emotional trauma, pathophysiology, trigeminovascular, transformed migraine, 5-HT, neuropsychiatry

# Migraine and the Limbic System: Closing the Circle

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*ABSTRACT ~ A tremendous gap still exists between the disciplines of psychiatry and neurology, viewed as the study of the mind, and the brain, respectively. While functional neuroimaging has served to blur this separation, many still consider the two mutually exclusive entities. But the study of migraine and limbic pain offers convincing evidence of Viktor Frankl's dichotomous model of the individual yet dependent spheres of psyche and soma. Chronic headache, though biomedical, wrestles with emotional issues, pharmacologic response, and other behavioral occurrences and conditions that confound the headache scientist. Similarly, research has shown that a vulnerable limbic system will perhaps amplify pain after years of sensitization caused by emotional trauma, loss, or abuse. These developments point to the need for a new model that embraces the approach of "one brain, multiple manifestations." Only with a transformed understanding of the integrated psyche and soma can neuroscientists expect to truly understand human pathologies. Psychopharmacology Bulletin. 2007;40(4):12-23.*

## INTRODUCTION

We live in a world divided. There is a "Berlin Wall" of misunderstanding between the disciplines of neurology and psychiatry. The division is artificial and reflects both our ignorance and our dualistic heritage. Neurologists have traditionally taken pride in their field which was clearly distinguished from the psychiatrists. Neurologists deal with structure, the psychiatrists deal with function. Functional neuroimaging has blurred the distinction but neurologists still deal with "brain" while psychiatrists deal with "mind." The dichotomous model was illustrated beautifully by Viktor Frankl (figure 1). His view of human beings is expressed metaphorically. He likens the person to a three dimensional cylindrical object which is illuminated vertically and horizontally. When illuminated vertically, the cylinder reveals a circle. Conversely, when illuminated horizontally, a square appears. However, neither the circle nor the square exists independently or captures the fullness of the cylinder. Neither one really exists; they are shadows without substance. Only the cylinder exists. In our world, the physician takes care of the body and the psychiatrist specifically treats the mind. Hence, the medical versus psychiatric model. To access the medical model, one needs a lesion and a bona fide diagnosis. To have a medical problem is to have a "real" problem. On

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FIGURE 1

## FRANKL'S CYLINDER MODEL



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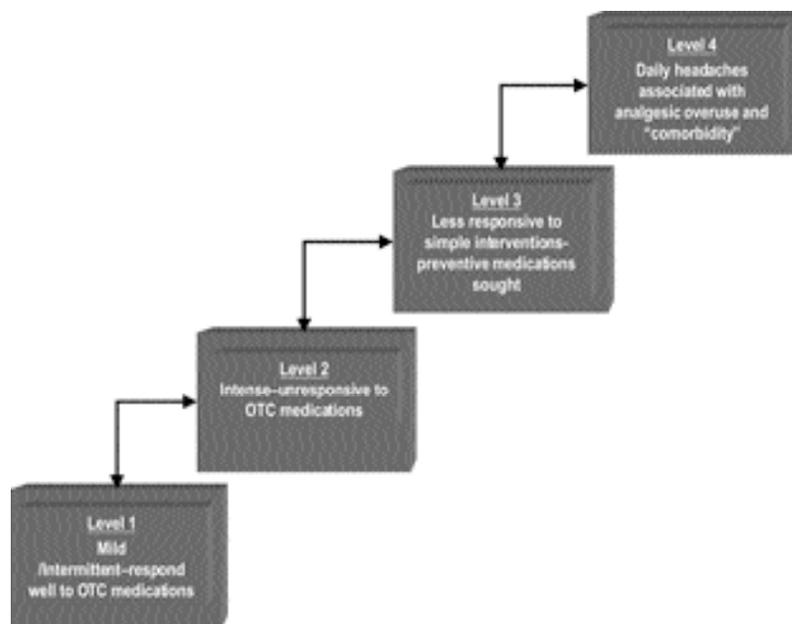
the other hand, behavioral problems do not have obvious pathology and so lack the “dignitas” of the medical model. It is no wonder why the depressed and anxious patient presents with somatic symptoms and why so many spurious and fashionable diagnoses exist (fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivities, etc.). Nobody wants to be told that the problem is “all in their head,” and therefore, these arbitrary diagnoses are well accepted.

Nowhere is the neurological versus psychiatric model as redundant as in the migraine sufferer. Migraine, as a disorder involving the whole person, demands a new approach. There is no other disorder in which biological processes, mood and behavior are so inextricably intertwined. It truly renders the old mind-body dualism obsolete.

Migraine is a continuum ranging from pure cultures to extraordinarily complicated disorders. Within this spectrum, there exists varying levels of complexity (figure 2). At one end of the spectrum, migraine conforms to a biomedical model. In its purest form, migraine is an intermittent, phasic, and episodic disorder. As such, migraine is easily managed and has yielded many of its secrets. We now have a rough idea of the genetic basis of the disorder, an elegant neurovascular model, and some extraordinary pharmacologic antidotes. In its more chronic form, however, migraine continues to bedevil us, as do many other chronic pain disorders. It is clear that chronic ailments, especially chronic pain, do not play to the strengths of technologic medicine. In fact, forms of chronic pain rarely conform to the neat medical model. In this model, the formula pain equals injury applies. Chronic pain disorders, especially chronic headache, defy such neat categorization and can only be understood in a biopsychosocial model.

FIGURE 2

## LEVELS OF DIFFICULTY



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## PATHOPHYSIOLOGY OF MIGRAINE

The early pioneers in headache speculated, often inaccurately, on the structural changes in a migraine brain and blood vessels. However, they never lost sight of the essential dynamic and changeable nature of the disorder. We would do well to remember some of the comments of the father of American headache medicine, Dr. Harold Wolff:

*One must appreciate that elimination of the headache may demand more in personal adjustment than the patient is willing to give. It is the role of the physician to bring clearly into focus the cost to the patient of his manner of life. The subject must then decide whether he prefers to keep his headache or attempt to get rid of it.*

This is certainly a far cry from the mechanistic and deterministic concept of disease. As the years have passed, we have seen veritable explosion in the understanding of what is happening in the brain and blood vessels of a migraine sufferer (although we may have neglected the insights of Wolff). From a naïve and simplistic concept of blood vessels constricting and dilating, we have evolved a polished neuroscience that

has elevated migraine to the exalted status of “disease.” While there are holes, the trigeminovascular model explains a great deal of the epiphenomena of migraine.

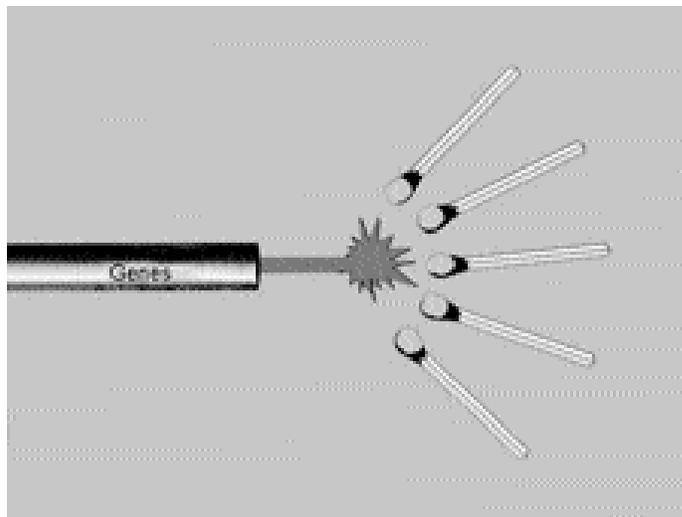
### MODERN MIGRAINE PARADIGM

A genetic predisposition exists which may render cortical neurons hyperexcitable (figure 3).<sup>5</sup> When genetics meets the appropriate environmental stimulus, either internal or external, the fuse is ignited. A wave of excitation, followed by a wave of depression, rolls across the cortex like an electrophysiological tsunami. This activity is responsible for many of the complex neurobehavioral phenomena seen in migraine including the classical aura. In ways still not fully elucidated, this disturbance in cortical function excites trigeminal fibers, triggering the release of neuropeptides from nerve terminals embedded in the blood vessel walls.<sup>2</sup> This inflammatory brew of substance P, neurokinin A, and calcitonin gene-related peptide leads to swelling and dilatation of the blood vessels. This ultimately manifests in the generation of a pain signal (figure 4). Thus, migraine can be thought of as a dual process—cortical factors are responsible for the neurological symptoms and brain stem/trigeminal activation responsible for the pain component.

The cortico/trigeminovascular model (or synonymously, the excitable brain hypothesis) has enormous heuristic value and has led to the

FIGURE 3

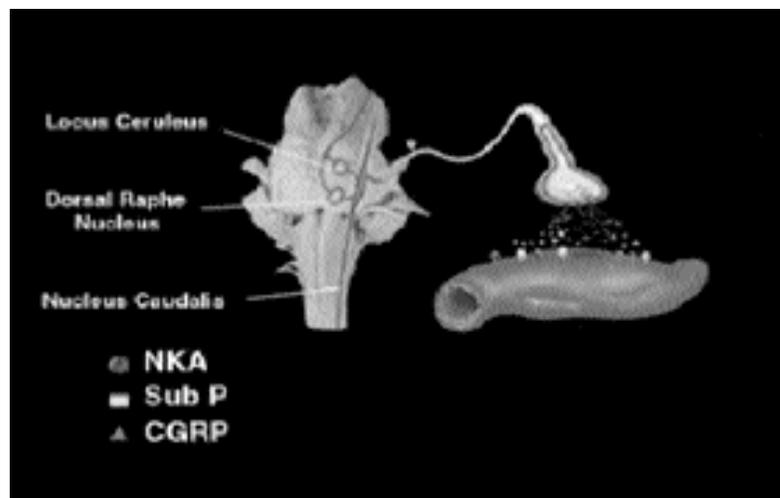
### NATURE/NURTURE



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FIGURE 4

## TRIGEMINOVASCULAR MODEL



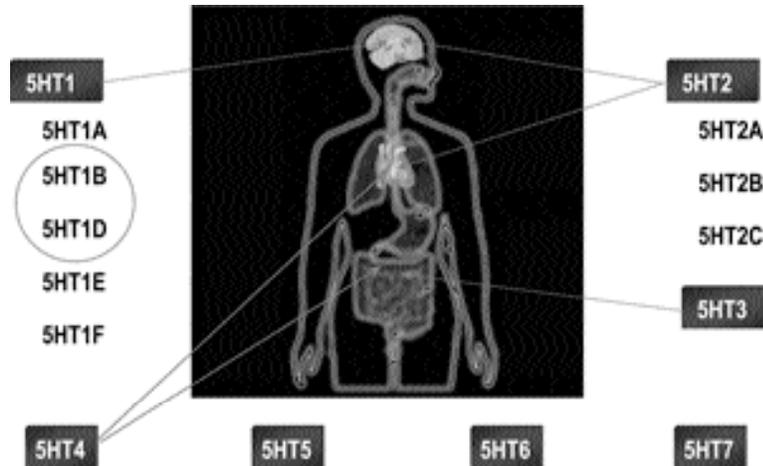
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development of the triptan class of drugs. Thanks to the work of Patrick Humphrey and others, the first true antidote for migraine and its associate sequelae arrived in the early 1990s. Historically, medical professionals had recognized that serotonin levels fell during the pain phase of migraine. Infusions of serotonin relieved migraine pain but often with disastrous results (figure 5). Serotonin proved to be extremely “dirty” in a pharmacologic sense. As a result, the triptan drugs were developed as serotonin analogs with limited activity at one or two sites.<sup>3</sup> With a rapid onset of action and precise receptor specificity, these agents offered hope that the migraine process, whether triggered by emotional stress or cheap red wine, could be arrested before the pain became entrenched. To a large extent, this hope has been fulfilled. In fact, there are currently millions of migraine sufferers who have benefited from these wonderful pharmacologic “smart bombs.” However, the burden of chronic headaches continues. These drugs, which proved to be so useful in the treatment of the episodic phase of the disorder, are of little value and may worsen the disorder in its chronic phase. Therefore, a distinction must be made between episodic, phasic, paroxysmal migraines and its chronic counterpart. It is also interesting to note that several years ago the Danish government found that over one-third of sumatriptan users were actually taking the drug inappropriately, largely by overusing the medication.

FIGURE 5

## RECEPTOR SITES FOR SEROTONIN (5-HYDROXYTRIAMINE, OR 5-HT)



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Chronic headache does not conform to the traditional biomedical rules. The acute disorder becomes parasitized by emotional issues, drug rebound, sleep disorder, co-dependency issues, etc. The elegant trigemino-vascular model no longer applies and our designer drugs become relatively useless. Patients and physicians alike become increasingly frustrated. It is no wonder Oliver Wendell Holmes stated, "If you want to show somebody the difficulties of a medical practice, give them a headache patient." Unfortunately, with all of our technology and knowledge, this is no less true today.

In response, the headache scientists have pushed the limits of the medical model to near breaking point. Some have speculated that repeated acute attacks, left untreated or partially treated, might actually lead to "disease progression". They further extend that migraine may very well be like multiple sclerosis, in that recurrent attacks will increase the burden of disease. The evidence of this, of course, is scant and consists of two disparate observations: 1) the deposition of iron in the periaqueductal gray matter of chronic headache sufferers; and 2) the presence of unidentified bright objects in the brain of migraine sufferers.<sup>6</sup> These are interesting observations, but their significance is still unclear. Moreover, I can truly assert from intimate personal and clinical knowledge that migraine is not an irreversible disease. In fact, I firmly believe the term disease should be abandoned when it comes to migraine. I realize this will not sit well with neuroscientists who have

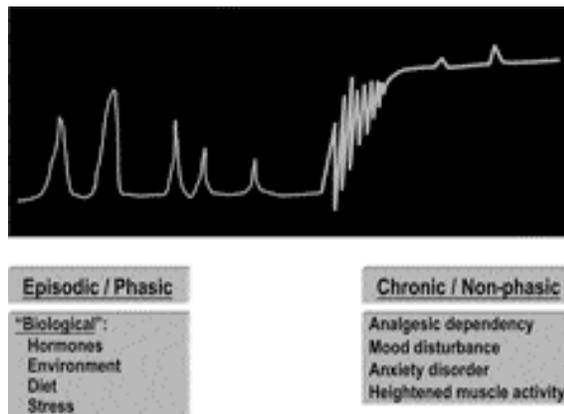
dedicated their lives to unraveling the neurobiology of migraine and to elevating migraine to the status of a real illness. Let me assert that migraine is real. It is as real as a kidney stone. It just refuses to conform to the 19th century concept of disease. This is because one cannot force migraine into this narrow biomedical paradigm without losing the dynamic and changeable quality of the disorder. This unique quality is what makes migraine so challenging. There is no disorder as frustrating or rewarding to treat. Where in medicine can we find examples of overnight cures, dramatic fixes and miraculous conversions? We physicians must remain humble in the face of this enigmatic disorder. Frequently, I will see a patient who has quite honestly tormented me for months or years. I will have prescribed every drug in the pharmacopoeia, only to be met by the same “nothing is working” on visit after visit. Then, one day the patient arrives looking happy, and I indulge in a private moment of triumph and self-congratulation. This can be short-lived as the patient explains that he/she has been off all drugs for several months, and the reason for the improvement is the sudden shift in life fortune, be it divorce, a new job, etc.

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Many chronic headache patients give a long history of intermittent and episodic headache (figure 6). This is a trial to be sure, but not a constant misery. Then, they seem to be “transformed” by a major life event. This event may also precipitate symptom transformation in migraine. This is where the disease model often breaks down. Therefore, we need a new paradigm which incorporates the elementary insights that life

FIGURE 6

EVOLUTION OF “TRANSFORMED MIGRAINE”



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influences symptoms and experiences modify brain function. We actually already have the model in operation, we just need to develop it further, fine tune it, and “close the circle.”

### THE SENSITIZATION MODEL

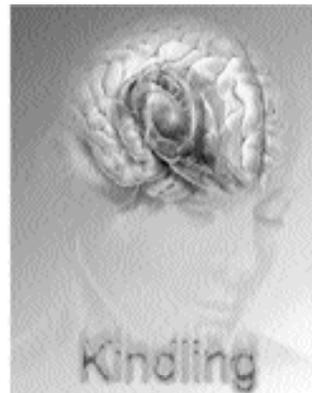
Every migraine sufferer knows that there is a window of opportunity within any one attack. It strikes quickly, and the chances are you will abort the headache rapidly. The basis for this phenomenon has been expounded by Burstein.<sup>1</sup> Pain scientists have long understood sensitization, but his contributions have shown that pain is pain, and that migraine obeys the same fundamental principles. Like most pivotal insights, in retrospect, this seems ludicrously simple! Through elegant clinical experimentation, Burstein has further demonstrated that intense pain leads to changes at both peripheral and central sites. In other words, the longer and more intense a nociceptive stimulus, the more likely the body will respond with a variety of adaptive maneuvers which sensitize the nervous system (figure 7).

The viable value of these ancient sensitization mechanisms is crucial: it forces the organism to lie low, protect and immobilize the damaged, painful area. During the course of a migraine, the same mechanisms occur, and the processes superimpose themselves on the migraine biology. Pain is amplified and becomes less responsive to the triptan family of drugs. It would now be a perfectly logical extension to ask oneself, “Is sensitization occurring at other levels in the nervous system (especially in the limbic system)?”

FIGURE 7

#### LIMBICALLY AUGMENTED PAIN SYNDROME *THE VULNERABLE LIMBIC SYSTEM*

- Corticolimbic Sensitization induced by kindling**
- Chronic, resistant to usual treatments**
- Assoc. with mood disturbance, anxiety**
- Alterations in sleep, energy, libido, memory/conc.**
- Behavioral disturbance and stress intolerance**



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**LIMBICALLY AUGMENTED PAIN SYNDROMES (LAPS)**

In another pivotal study, Rome and Rome<sup>4</sup> pointed out that a sensitized limbic system augments and amplifies pain perception. This occurs not only during an acute attack, but continually over a lifetime. Every nociceptive stimulus has a sensory-discriminative aspect and an affective-emotional dimension. Importantly, the latter is mediated by the limbic circuitry.

In another insight, the Romes pointed out that a vulnerable limbic system (in other words, a vulnerable person), might be sensitized after years of emotional trauma, loss or abuse. This sensitized limbic system will then augment or amplify pain, leading to the rather pithy title of “limbically augmented pain syndromes” (LAPS). Furthermore, the same molecular and cellular events probably underlie sensitization at all levels. The only difference is that in the limbic system, there is a higher level of complexity. Rather than single neurons or groups of neurons, we witness change at a neural network level.

This insight feels intuitively right. When I see a difficult and intractable headache patient, I do not worry about iron deposition in the periaqueductal gray matter or unidentified bright objects. Rather, I ask, “What is wrong with this person’s life?” Even though we now lack an appropriate experimental model, I know through experience that altering the lifestyle will yield results. In other words, the removal of harmful drugs and the management of depression, anxiety, sadness, and catastrophizing, etc., will lead to dramatic change.

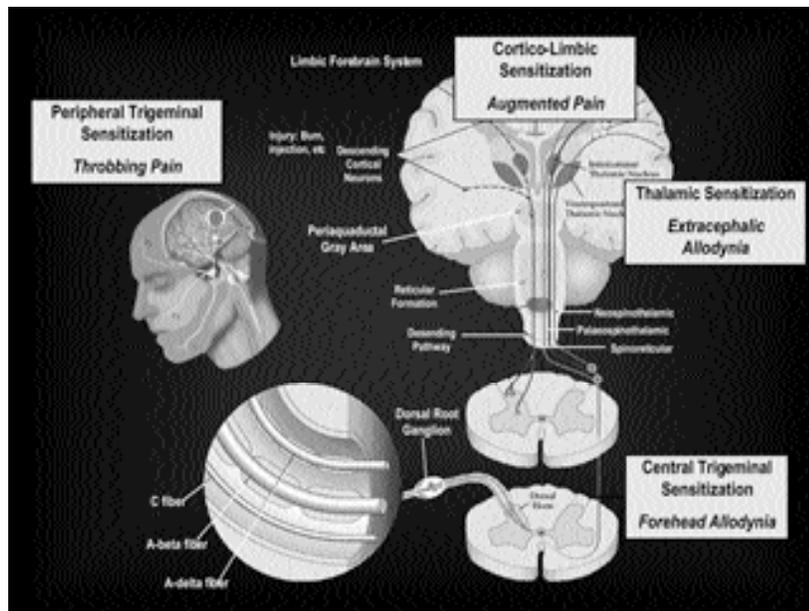
These changes occur in the brain, but at a level of complexity with which we are not traditionally familiar or comfortable. Doug Bremner and others<sup>7</sup> at Yale University have pointed out the obvious: experience modifies brain in structure and in function. In addition, the limbic sensitization model of Rome and Rome dovetails nicely with the Bremner model. Together you have a brain capable of amplifying, augmenting, distorting, and transforming incoming nociceptive traffic. The world of emotion and perception can and do become entangled in an emotional/perceptual complex (and oftentimes cannot be easily disentangled).

For the clinician, the issue now is care and not cure. We must understand healing as a process occurring over time, and not an acute event. Where does all this lead? Quite simply, it leads to a new model. This new model does not discard the work of basic neuroscientists, but instead embraces and places it in the complex puzzle of human experience along with cultural, social and behavioral factors. This proves to be an integrative model that embraces the totality of the person (the cylinder, and not just the square or the circle). The practical ramifications are several:

- We need to change our educational approach to students and resident physicians. We must stop pretending that the world and the patient constitute some neat puzzle to be solved by our scientific ingenuity. Let us begin to educate them to look for signs of dysfunction within the limbic system. If you do now know what to look for, how can you ever recognize it? We are still producing physicians who are deaf to the complex symphony of human misery.
- The therapeutic approach to the chronic patient must be different than the approach to the episodic patient. For the latter, triptans, narcotics and other pharmaceuticals might be all that is necessary. For the chronic headache patient, however, a multi-disciplinary team approach is mandatory. This cannot always mean that this approach will be curative, but at least the physician has a better chance of survival! The emphasis here is care, not cure. Management is often typically long in duration and in results. It has no well-defined CPT code and does not generate huge sums of money. It is usually rejected by insurance companies who are as locked into the conventional model of thinking as the most basic scientist. How often I have been impressed over the course of my career with the fact that an insurance

FIGURE 8

## THE SENSITIZATION MODEL



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company would gladly give up \$25,000 for a procedure which is doomed to failure while avoiding any suggestion of a “psychological” approach.

Despite the fact that it might be protracted and unspectacular, the multi-disciplinary team approach is the most successful way to manage chronic headache. When and if somebody develops a way to cure life and all of its ailments, then I will embrace it avidly and abandon the interdisciplinary approach.

- Physicians need to test for LAPS. In the last century, Lord Kelvin stated:

*When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.*

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A brief computerized questionnaire which would highlight the main features of LAPS would go a long way towards demythologizing this disorder. What we are looking for is nothing short of a “CAT scan of the mind.”

### CONCLUSION

I believe it is high time we abandon this dualistic and dichotomous model. There is only one brain, but multiple manifestations. Let us move away from the stagnant concept of disease. Let us understand that migraine is a fluid, dynamic and changeable disturbance. It is not only rooted in genetics and neurobiology, but also profoundly impacted by the matrix in which every human finds him/herself entangled. We doctors must begin to treat the whole person, definitively, finally, and not just in word alone. There is no brain versus mind dichotomy, there is only the nervous system in all its complexity. Dr. Harold Wolff in his address to the American Neurological Association in Atlantic City in 1961 stated:

It is unprofitable to establish a separate category of illness to be defined as psychosomatic. Rather, man's nervous system is implicated in all categories of disease. This formulation brings to human pathology a unifying concept. It could freshen the eye to see the major problems of medicine and to challenge the best minds to new feats of exploration. It emphasizes that in pathologic reactions

in man, his goals, purposes and aspirations are of the utmost importance.

### DISCLOSURE

Dr. O'Carroll is on the speaker's bureau for Merck, GlaxoSmithKline, Forest Laboratories, and Cephalon. ♣

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