The Mystique of Migraine – Part III: Is it Neurogenic? Is the Brain Responsible?

– Prof RJ Henbest

Prof RJ Henbest

MD, CCFP, M Cl Sc (Fam Med)
The Dept of Family Medicine: Medunsa
PO Box 222, Medunsa 0204

Curriculum vitae

Ronald J Henbest was born in Edmonton, Alberta (Canada) where he qualified in 1974 with a BSc in Maths and Psychology and in 1978 with an MD from the University of Alberta. He then completed two years postgraduate study (residency) in Family Medicine with the Department of Family Medicine at the University of Western Ontario (Canada) and obtained his CCFP from the College of Family Physicians of Canada. Ron joined the Department of Family Medicine at Medunsa in 1980. He has a particular interest in the doctor-patient interaction and its importance for healing. He returned to the University of Western Ontario in 1984 to take their Master of Clinical Science Degree in Family Medicine (MClSc), which emphasizes patient care, teaching and learning, and research. His thesis on Patient-Centred Care involved the development of a method for measuring patient-centredness and testing it against patient outcomes. In 1989, Ron returned to his home city, Edmonton, for a period of 21 months where he was engaged as an associate professor in the Department of Family medicine at the University of Alberta. During this time, he also completed further training in systemic family therapy. In October 1990, Ron returned, with his wife Judy and son Benji, this time as associate professor and deputy head of the Department of Family Medicine at Medunsa.

Summary

This third paper on the mystique of migraine deals with the question whether the brain itself is responsible and, by referring to various studies, reviews the evidence for the roles played by neural factors. This evidence is evaluated in terms of (1) a phenomenon, (2) structures, systems and substances and (3) an unstable process (the autonomic nervous system). Other related observations from studies of EEGs, VEPs, magnesium and trauma-triggered migraines, are also addressed.

S Afr Fam Pract 1993; 14: 107-15

KEYWORDS:
Migraine; Brain; Autonomic Nervous System; Research; Review.

Introduction

Even as the early foundations of the vascular theory were being laid,[1,2] a rival theory was emerging. Edward Liveing (1873), perhaps as a result of an increasing interest in epilepsy, proposed that the phenomena of migraine were due to "nerve storms".[3]

Towards the end of the nineteenth century, varying attempts were made to reconcile the two theories in terms of the sympathetic nervous system controlling the cranial vasculature. In 1898, Moebius made one of the most succinct and perhaps telling statements ever made about migraine: "Parenchyma is the master, circulation the servant."[3]

By the twentieth century, vigorous controversy existed between the vascular and neurogenic schools of thought. Then in 1938,[4] Graham and Wolff's demonstration that migraine headache was accompanied by increased pulsatility of the superficial temporal arteries and resolved by ergotamine-induced reduction of this pulsatility virtually brought the controversy to a close. A few years later, Schumacher and Wolff[5] showed that the visal aura of migraine could be abolished by inhalation of amyl nitrite, a cerebral vasodilator. The vascular theory, seemingly having been established beyond doubt, became enshrined in the international classification of headache[6] that was to last until 1988.[7] Subsequent attention was directed primarily to the various mechanisms that might trigger the vascular changes underlying migraine.

Of note however, Wolff himself, thought that the change in mood and/or appetite that frequently preceeds the prodrome suggested a change in hypothalamic activity[8] and by the late 1970s there was increasing dissatisfaction with the vascular theory. Friedman[9] spoke of a primary neural change and accumulation of substances sensitizing the dilated arteries to pain. Graham[10] saw the prodrome as the basic disorder and the headache as an abnormal compensatory event. He thought the basic disturbance was located in the brain centres governing the response of the neurovascular systems. Diamond and Dalessio[11] suggested neurogenic vasoconstriction of the great arteries of the internal carotid leading to decreased flow and proposed a "unified theory" in which stress leads to neurogenic vasospasm.

. . . Migraine: III

Lance described migraine as, "A heightened neurovascular reaction to any rapid change in the internal or external environment,[12] and hypothesized that migraine was a disturbed protective response to real or imagined threats to the integrity of the brain. Somewhat ironically, it was a study of the cerebral blood flow, itself, in migraine, by Olesen et al,[13,14] in 1981, that has raised the most significant doubts about the vascular theory as described later.

No satisfactory understanding yet of the pathogenesis of migraine which integrates the vascular and neurogenic theories.

This paper addresses the question, "Is the brain, itself, responsible for migraine?" and reviews the evidence for the roles played by neural factors in terms of: 1) a phenomenon, 2) structures, systems, and substances, and 3) an unstable process (the autonomic nervous system). Related observations from studies of electroencephalograms (EEGs), visual evoked potentials (VEPs), magnesium, and trauma-triggered migraines are also presented.

A Phenomenon: The Spreading Depression of Leao

This phenomenon was first described in rats by Leao, a Brazilian neurophysiologist, in 1944.[15] Spreading depression is a wave of inhibition of the spontaneous cortical neuronal activity that travels over the cerebral cortex at a rate of 2 to 5 millimetres per minute. It is preceded by a short-lasting phase of neuronal excitation. The waves of abnormal and depressed cortical electrical discharges spread like ripples across a smooth surface of water and do not respect vascular territories. The cerebral blood flow changes accompanying this inhibition starts with a short-lasting increase in blood flow in an area about 2 or 3 millimetres wide attributed to dilatation of pial vessels. This transient increase disappears after a minute or two and is followed by a decrease in flow of about 20 to 30%, lasting about an hour. Spreading depression can be elicited in animals by a variety of stimuli including trauma, electrical, and chemical influences. It can occur after hypoxia and during recovery from hypercapnia.[16] As early as 1958, Milner postulated that the aura symptoms were caused by this neurophysiological phenomenon rather than hypoxia.[17]

Studies of the cerebral blood flow in migraine by Olesen et al in 1981,[13,14] demonstrated a spreading wave of oligaemia. By measuring regional blood flow simultaneously in many areas of the cerebral hemisphere they found that, during attacks of migraine, diminished cerebral blood flow (a wave of oligaemia) began in the occipital lobe and spread forward across the hemisphere at a rate of 2 to 3 millimetres per minute. The oligaemia preceded the symptoms of the aura and persisted well after the headache had resolved. The oligaemia transgressed the vascular boundaries of the major cerebral arteries, making it unlikely that vasospasm was its cause.

The finding of spreading depression in animals and its possible existence in the human brain is an important part of the neural hypothesis of the causation of migraine. The cerebral blood flow changes observed in migraine are similar to those observed in spreading depression. In both, there is a spreading wave of oligaemia, beginning in the occipital lobes and spreading forward, that does not spread according to vascular territory. The rate of spread of visual field defects associated with migrainous attacks occurs at about the same speed as the rate of spread of oligaemia. Because of the similarity, experimental spreading depression in animals and the aura of migraine have been postulated as having identical mechanisms.[18] Of interest, the spreading depression in animals is not limited to the cortex but may also occur in brainstem or hypothalamic structures.[19] In addition, the time course of the spread of oligaemia seen in migraine does not occur in ischemic cerebrovascular disease, adding support to the hypothesis that the primary event is neurogenic rather than vascular.

Present evidence suggests that the underlying mechanism of migraine is neurogenic, with vascular biochemical and inflammatory changes occurring secondarily.

However, the relationship of the spreading depression to oligaemia is not completely understood. The long held view that migraine auras are due to vasoconstriction of major vessels no longer holds. We now know that neuronal events can modify intraneuronal metabolism and initiate

. . . Migraine: III

appropriate changes in the microcirculation. Therefore, in patients suffering from migraine with aura, it would seem that the initiating event is neural followed by secondary vascular changes. This idea is supported by the clinical findings of multifocal and varied transient neurologic events during the aura. Important to point out though, is that a direct measurement of spreading depression in humans has not yet been possible. In animals, many stimuli applied to the cortex have induced the phenomenon of spreading depression, but so far, stimuli applied to the human cortex have failed to do so. Thus, comparisons between changes in cerebral blood flow accompanying the spreading depression in animals and changes in blood flow in humans during migraine remain inferential.

Structures, Systems and Substances

A number of neural structures, systems, and substances have been proposed for the primary neural event in migraine. These include or involve a number of nuclei, opposing noradrenergic and serotoninergic systems, the trigeminal nerve, various monoamines and the endogenous opioids.

Brainstem monoaminergic neurons and pathways: Noradrenergic and Serotoninergic Systems

Lance has suggested that a pair of antagonistic systems, the noradrenergic and serotoninergic sytems, operating in the brainstem is central to the migraine attack.[20] The noradrenergic system originates in the locus ceruleus of the brain stem; the serotoninergic system originates in the raphe nuclei; both project to the cerebral cortex. Stimulation of the locus ceruleus activates the noradrenergic perivascular fibres causing vasoconstriction which reduces blood flow; whereas, stimulation of the dorsal raphe nucleus increases blood flow in the ipsilateral cortex. The locus ceruleus supplies noradrenergic fibres to the intracranial blood vessels and varied rates of discharge from the locus ceruleus can induce changes in blood flow similar to those seen in migraine.[21] Experimental evidence in monkeys supports the presence of this antagonistic system.[22,23] Both systems

---

Migraine has its effects in multiple organ systems including the nervous, circulatory, gastrointestinal and haematological.

---

increase extracranial scalp blood flow by activation of reflexes that pass through the greater superficial petrosal branch of the facial nerve. These reflexes, part of the parasympathetic outflow that passes to the sphenopalatine ganglia and the scalp and facial structures, cause vasodilatation. These primary neuronal events and their secondary vascular phenomena are thought to activate pain perception via an endogenous "opiate system."

In this view, an episodic and excessive discharge of brainstem monoaminergic neurons and pathways is thought to be at the root of the pain of migraine. However, it would seem unlikely that migraine can be accounted for on the basis of an antagonistic system solely involving a monoaminergic vasoconstrictor system and a parasympathetic vasodilator system. Rather, it is much more likely that a multitude of transmitters is involved.

Neurotransmitter defect and impaired central inhibition

In 1975, Appenzeller hypothesized that the migrainous diathesis is a result of uninhibited increases of firing rates (perhaps genetically determined) of raphe neurons.[24] This was thought to result in periodic excessive discharges complicated by altered levels of vasoactive substances in the brain. Linked to this hypothesis was the proposal that the activity of serotonin neurons (the raphe system neurons are composed of the largest number of neurons in the central nervous system that contain serotonin) is self-regulating via a negative feedback system. These initially neurogenic events were thought to result in secondary vasomotor changes affecting both intra- and extra-cranial blood vessels and the well-known manifestations of migraine attacks with or without aura. This hypothesis also offers an explanation for the hyperalgesia found in migrainous subjects. Depletion of serotonin from the brain, either by experimental lesions in the midbrain raphe or by P-chlorophenylalanine has been shown to markedly increase the brain's responsiveness to noxious stimuli. Drugs that reduce brain serotonin increase raphe firing rates. Thus, drugs which increase brain serotonin should decrease raphe unit firing, but this has not been confirmed by experimental study.

. . . Migraine: III

The Trigeminovascular System

One of the neural structures that has received notable recent attention is the trigeminal ganglion.[25, 26, 27, 28]

The pain of headache is thought to be due to depolarization of perivascular sensory axons, with those surrounding the large vessels being of greatest importance. The network of relevant sensory fibres is thought to originate in large part from neurons within the trigeminal ganglia. The trigeminal nerve not only innervates

---

A return to the hypothesis that migraine is due to "nerve storms".

---

the meninges but also the larger cerebral arteries and the superior saggital sinus.[25] This dense sensory innervation correlates with the fact that these vessels, unlike most areas of the brain, are pain sensitive. The nervous connections between the trigeminal ganglia and cerebral blood vessels have been termed the trigeminovascular system.[24]

Anatomic tracing and immunohistochemistry studies in laboratory animals have provided new and important information about the sensory innervation of cephalic blood vessels.[26] Neuropeptides are synthesized by messenger RNA and ribosomal mechanisms within trigeminal ganglia cells. The trigeminal nerve has been shown to release a number of neuropeptides, including substance P, neurokinin A (NKA), calcitonin gene-related peptide (CGRP) and galanin which have all been identified within sensory axons surounding the vessels of the circle of Willis.[28] No doubt more neuropeptides as well as other chemical neurotransmitters will be discovered.

At least one of the peptidergic mechanisms of pain transmission, substance P, operates not only in the 'vessel to neuron' direction, but also in the reverse 'neuron to vessel' direction.[23] The theoretical implications of this are profound. Not only may the vessel send pain signals to sensory neurons and, thus, the brain, but the brain may, via sensory neurons, send messages to the vessels which may control their motility, their calibre, their pain sensitivity and, perhaps, the activity of other peptide or non-peptide substances in the vessel wall and even its lumen. Thus the trigeminal nerve may be involved not only in the transmission of painful sensory stimuli, but also in the initiation of a sterile neurogenic inflammatory response.[24]

The anti-migraine actions of the ergot alkaloids and sumatriptan likely relate to neuronal blockade of neuroeffector functions of trigeminovascular fibres, perhaps blockade of neurotransmitter release from primary afferent fibres innervating cephalic vessels.[26]

The relevance of the close proximity of certain peripheral neural structures to the middle meningeal arteries has also recently been emphasized.[29] The auriculotemporal nerve, a projection of the trigeminovascular system, loops around to embrace the middle meningeal artery just prior to its entry into the cranium, which would put it in an opportune place to help monitor an auto-regulatory system.

The painful aspects of the migraine attack may originate in and/or be perpetuated by reverberations up and down this trigeminovascular system. The trigeminal innervation of intracranial blood vessels provides, among other things, a reasonable anatomical basis not only for the vascular dilatation phase and for the pain in migraine, but also for its unilateral distribution. Not only does the trigeminal vascular system functionally unify the previously disparate neural and vascular substrates, but it may be the common final stage mechanism which is activated by other influences to generate the pain of migraine.

Endogenous Pain Control/Opiate System

Abnormalities of the endogenous pain control mechanisms that operate in the central nervous system to modulate the transmission of pain signals and ultimately the perception of pain have been found in migraine.[30] The endogenous pain

---

Could migraine be a disorder of generalized vasomotor dysfunction?

---

control system is sometimes referred to as the "opiate" system as it involves the opiate neuropeptides: endorphins, enkephalins, and dymorphins.

Cerebrospinal fluid levels of enkephalin have been found to be decreased during migraine headaches in comparison to headache free intervals.[31] Enkephalin is the

. . . Migraine: III

neurotransmitter for the interneurons located in the central nervous system, especially those located in the gelatinous substance of the spinal cord and its rostral extension in the brainstem, the nucleus of the trigeminal tract. There, these interneurons inhibit the transmission of pain signals from the primary sensory neurons to the spino- and trigeminothalamic tracts.

An Unstable Autonomic Nervous System

A long-held and widely accepted belief is that migraine patients have an unstable autonomic nervous system.[32] Both intracranial and extracranial arterial tone is regulated by the sympathetic division of the autonomic nervous system as well as by a variety of circulatory humoral agents.[33]

The foundational studies on the reactivity of the cranial arteries in patients with migraine headaches were done by Tunis and Wolff in 1953.[34] They demonstrated that: 1) the caliber of the temporal artery was significantly larger in migraine patients (when headache free) than in nonheadache controls, 2) the caliber during headache attacks was even larger than that during headache-free periods, 3) migraine patients exhibited greater variability of the contractile state of the observed vascular bed than controls, and 4) the variability of the temporal-artery pulse-wave contours became more striking about 72 hours prior to the onset of headache and was maximal at the height of the headache. They concluded that the pulse wave changes associated with the headache attack were but an accentuated part of a continuous physiological process present in those prone to migraine headaches.

Migraineurs showed sympathetic hyperfunction during attacks.

Based on these findings, others hypothesized that migraine was a disorder of generalized vasomotor dysfunction.[35] Subsequently, a number of studies were published that reported conflicting results. Several investigators found evidence for overactive central and peripheral vasoconstrictor mechanisms in that heat stimulus applied to the body trunk produced a significantly smaller increase in hand blood flow in classical migraine patients than in controls.[36, 37, 38] Others found no such differences in hand blood flow[39, 40] and others concluded that the studies thus far had major methodological problems and that there was no conclusive evidence that migraine subjects have generalized vasomotor dysfunction.[41]

Later, Cohen, Rickles and McArthur[42] found that migraine subjects had a more stereotyped, rigid response pattern across stimulus situations than non-migrainous subjects. They tested head and hand temperature, frontalis electromyography, heart rate, galvanic skin response and finger pulse volume. Subjects participated in rest, orienting, reaction time, time estimation and mental arithmetic tasks.

Two studies provide evidence that stimuli which elicit temporal artery dilation in control subjects elicit vasoconstriction in migraine subjects. In the one study, subjects had to learn to control pulse waves of the digits with biofeedback, receive false feedback, listen to a relaxation tape or hear a tape on how to grow an avocado. Equal numbers of migraine and control subjects were subject to each condition. While the digital pulse waves did not differentiate the controls and headache subjects, the temporal artery pulse waves did. All tasks taken together, the non-headache subjects essentially showed a continual vasodilation over time while the migraine subjects exhibited sustained vasoconstriction.[43] Similar results were found by Bakal and Kaganov with the presentation of 80 dB white noise.[44]

Cerebrospinal fluid levels of enkephalin decreased during headaches.

There is also evidence that migraineurs show sympathetic hyperfunction during headache attacks[45, 46] and sympathetic hypofunction between attacks.[47, 48] Three studies have reported cardiovascular sympathetic hypofunction as evidenced by remarkable BP reduction after tilting, and lower noradrenaline levels in migraine patients during headache free intervals.[49, 50, 51] A recent study by Mikamo[52] included patients suffering from muscle contraction headaches as well as those suffering from migraines. Migraine patients showed greater cardiovascular sympathetic hypofunction as demonstrated by

. . . Migraine: III

significantly greater orthostatic hypotension (systolic BP immediately after standing: controls -6.1, MCH -12.4, Migraine -19.3). There was no clear evidence of parasympathetic hypofunction or hyperfunction in either headache group and noradrenaline levels showed little difference. Thus, there is a difference in blood vessel reactivity in spite of similar noradrenergic function.

If Sokolov's theory of orienting and defensive behaviour, that predicts that a person will have cephalic (temporal artery) vasodilation to orienting stimuli and vasoconstriction to noxious defensive stimuli,[53] is accepted, then these studies provide evidence that migraine headache patients are hypersensitive to a variety of stimuli and interpret innocuous stimuli as potentially dangerous.

EEGs, VEPs, MG, and Trauma

An increased incidence (approximately twice) of both focal and nonfocal abnormalities have been observed on the EEGs of patients with migraine.[8] Recent studies of the EEGs of patients with migraine are compatible with a fluctuating asymptomatic neural disorder. For example patients who experience migraine with aura have been found to have increased frequency dispersion and asymmetry of alpha rhythm (increased slow wave activity).[54] The records were mostly normal when separated from attacks by ten asymptomatic days. Abnormalities increased significantly before the onset of the prodromal symptoms and clearly outlasted the headache.

Alterations in visual evoked potentials (VEPs) recorded close to an attack have been observed[55] and a method for the electrodiagnosis of migraine (using flash and pattern amplitudes and frequencies) has been proposed.[56]

Brain magnesium (Mg) has been found to be low during migraine attacks without changes in pH.[57] Mg is known to influence vascular tone.[58] Experimentally Mg defiency has also been found to be associated with spreading cortical depression,[59] central neurotransmitter release[60] and platelet hyperaggregation.[61] Mg is an important element in those physiological systems that become transiently aberant in migraine sufferers and thus could provide the link between the physiological threshold for a migraine attack and the mechanisms of the attack itself.

> Are these patients hypersensitive to a variety of stimuli, and do they interpret inoccuous stimuli as potentially dangerous?

Yet another interesting association is that between migraine attacks (including those associated with complex neurological phenomena) and even mild blows to the head.[62] Occurring mostly in children, adolescents, and young adults, they generally develop after latent periods. Their various expressions are identical to those of classical or complicated migraine.

Discussion

So what have we got and how does it work? Can the varying pieces of evidence for a neural theory be put together? Can a neural theory account for the evidence used to support the vascular theory? Can the neurogenic and vascular theories be integrated?

So far we have a phenomenon that is not only a neural event, but a central neural event, in fact, a cortical event, referred to as the spreading depression of Leao. We also have a number of neural structures and systems including nuclei in the midbrain (the locus ceruleus and the raphe nuclei) in which neural disturbances might arise. We also have the trigemino-vascular system to carry it all out. In addition, we have what apears to be increased sensitivity of the autonomic nervous system and altered endogenous pain control mechanisms.

It is difficult to integrate Wolff's vascular theory with the spreading depression of Leao. Firstly, there is no evidence that spreading depression can be precipitated by cerebral hypoxia. Secondly, there is no evidence that spreading depression can lead to cerebral vasodilation. Wolff interpreted the effect of inhalation of carbon dioxide on the migraine aura as indicating the involvement of vasoconstriction induced cerebral hypoxia in the pathogenesis of the aura symptoms. However, a recent study of rats inhaling carbon dioxide found it also to affect the propagation of spreading depression, which offers an alternative explanation for Wolff's observations.[63]

One way around this is offered by Spierlings[64] who suggests the uncoupling of the aura from the headache and connecting both to a factor X. Thus factor X (the "migraine process") leads to two things: spreading depression which is

. . . Migraine: III

responsible for the aura symptoms, and vasodilation and decreased pain threshold which are responsible for the headache which in turn leads to increased activity of the sympathetic nervous system and autonomic symptoms. Migraine with aura then is due to both processes being present, migraine without aura when only the latter is present. This would explain the simultaneous occurrence of aura and migraine and the occurrence of headache without aura and aura without headache.

Spreading depression may well cause focal neurological events (the aura) associated with migraine, but these deficits can also stem from the locus

---

An interesting association between migraine attacks and mild blows to the head.

---

ceruleus and its secondary effects on blood flow to the cortex. The pain, however, is mediated through an interaction between the endogenous system of pain control that influences monoaminergic neuronal regulation of cerebral blood flow and its relation to trigeminal nerve discharge, which if excessive, causes headache.

Neurogenic vasospasm at the base of the brain and the pial arteries produces a reduction in local cerebral blood flow with subsequent alteration in cerebral metabolism, including local tissue acidosis. These local changes then cause vasodilatation of the intracranial vessels. To increase the blood flow, the extracranial blood vessels dilate, which liberates the various vasoactive substances that have been mentioned.

To date, an understanding of the pathogenesis of migraine that integrates the vascular and neurogenic theories, not to mention all of the available clinical and experimental data, remains lacking.

Conclusion

Present evidence suggests that the underlying mechanism of migraine is likely neurogenic (with the brain being the primary and initiating organ) with vascular, biochemical, and inflammatory changes occuring secondarily. Further, it appears that the stimulus for headache must ultimately activate the trigeminovascular system and serotonin is clearly one of the factors that may do so.

However, in view of the rapid and continuing increase in our knowledge and understanding of the complexity and interconnectedness of how the human body works, it would seem that a broad concept of migraine, not related primarily to either the vascular of neurological (brain) systems, would allow the most scope for further advancement. Migraine may be considered a constitutional disorder of neurotransmission, activated paroxysmally by multiple and often unknown factors, with effects in multiple organ systems including at least the nervous, circulatory, gastrointestinal, and haematological systems.

Subsequent papers in this series on the mystique of migraine will review the role of haematological factors, psychological aspects and discuss the meaning of migraine.

References

1. Henbest RJ. The mystique of migraine. Part 1: Its nature and diagnosis. S Afr Fam Pract 1991; 12: 512-19.
2. Henbest RJ. The mystique of migraine. Part II: Is it vascular? S Afr Fam Pract 1992; 13: 165-71.
3. Edmeads J. What is migraine? Controversy and stalemate in migraine pathophysiology. J Neurol 1991; 238: S2-5.
4. Graham JR, Wolff HG. Mechanisms of migraine headache and action of ergotamine tartrate. Arch Neurol Psychiat 1938; 39: 737-63.
5. Schumacher JA, Wolff HG. Experimental studies on headache. Arch Neurol Psychiat 1941; 45: 199-214.
6. Ad Hoc Committee. Classification of Headache. JAMA 1962; 179: 127-8.
7. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. Cephalgia; 7 (suppl 8): 1-96.
8. Wolff HG. Headache and Other Head Pain. 2nd ed. New York: Oxford University Press, 1963.
9. Friedman AP. Migraine. Med Clin North Amer 1978; 62: 481-93.
10. Graham JR. Migraine headache: Diagnosis and management. Headache 1979; 19: 133-41.
11. Diamond S, Dalessio DJ. The Practising Physician's Approach to Headache. 2nd ed. Baltimore: Williams and Wilkins, 1979.
12. Lance JW. Migraine: Current approach to prevention and treatment. Drugs 1980; 19: 307.
13. Olesen J, Tfeldt-Hansen P, Henriksen L, Larsen B. The common migraine attack may not be initiated by cerebral ischaemia. Lancet 1981; ii: 438-40.
14. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981; 9: 344-52.
15. Leao AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944; 7: 359-90.

. . . Migraine: III

16. Leao AAP. Further observations on the spreading depression of activity in the cerebral cortex. J Neurophysiol 1947; 10: 409-19.
17. Milner PM. Note on a possible correspondence between the scotomas of migraine and spreading depression of Leao. EEG Clin Neurophysiol 1958; 10: 705.
18. Appenzeller O. Pathogenesis of migraine. Med Clin North Amer 1991; 75: 763-89.
19. Pearce JMS. Neural aspects of migraine. In: Blau JN. ed. Migraine. London: Chapman and Hall, 1987: 247-63.
20. Lance JW. The Pathophysiology of migraine: A role for the monoamines. In: Saper JRW, editor. Prostaglandins in migraine and other headaches: A Symposium. Greenwich: CT, 1989; 26-31.
21. Tegeler CH, Bell RD. Vascular headache. Otolaryngologic Clin North Amer 1987; 20: 65-82.
22. Goadsby PJ, Piper RD, Lambert GA, et al. Effect of stimulation of nucleus raphe dorsalis on carotid blood flow in the monkey. Am J Physiol 1985; 248: 257-62.
23. Goadsby PJ, Lambert GA, Lance GW. Differential effects on the internal and external carotid circulation of the monkey evoked by locus coerulus stimulation. Brain Res 1982; 249: 247-54.
24. Appenzeller O. Pathogenesis of vascular headache of the migraine type: The role of impaired central inhibition. Headache 1975; 15: 177-9.
25. Moskowitz MA, Reinhard JF, Romero J, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine? Lancet 1979; 11: 883-5.
26. Moskowitz MA. The neurobiology of vascular head pain. Ann Neurol 1984; 16: 157-68.
27. Moskowitz MA. Sensory connection to cephalic blood vessels and their possible importance to vascular headaches. In: Rose FC (ed) Advances in headache research. John Libbey. London 1987: 81-6.
28. Moskowitz MA. Basic mechanisms in vascular headache. Neuro Clin 1990; 8: 801-15.
29. Suess LE, Cuetter AC. Hypothesis: a

. . . Migraine: III

rationale for migraine. Headache 1988; 28: 347-9.

30. Mosnaim AD, Diamond S, Wolff ME, Puente J, Freitag FG. Endogenous opiad-like peptides in headache. An Overview. Headache 1989; 29; 368-72.

31. Anselmi B, Baldi E, Cassacci F, Salmon S. Endogenous opioids in cerebrospinal fluid and blood in idiopathic headache sufferers. Headache 1980; 20: 294-9.

32. Cohen MJ. Psychophysiological studies of headache; is there similarity between migraine and muscle contraction headaches? Headache 1978; 18: 189-96.

33. Caviness VS, O'Brien P. Headache. N Engl J Med 1980; 302: 446-9.

34. Tunis MM, Wolf HG. Studies on headache: Long-term observations of the reactivity of the cranial arteries in subjects with vascular headache of the migraine type. Arch Neurol Psychiat 1953; 70: 551-7.

35. Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. J Neural Neurosurg Psychiatry 1960; 23: 23-32.

36. Appenzeller O. Vasomotor function in migraine. Headache 1969; 9: 147-56.

37. Downey JA, Frewin DB. Vascular responses in the hands of patients suffering from migraine. J Neurol Neurosurg Psychiat 1972; 35: 258-63.

38. Elliot K, Frewin DB, Downey JA. Reflex vasomotor responses in hands of patients suffering from migraine. Headache 1973; 13: 188-96.

39. French EB, Lassers BW, Desai MG. Vasomotor responses in the hands of migrainous subjects. J Neurol Neurosurg Psychiat 1967; 30: 276-8.

40. Hockaday JM, Macmillan AL, Whitty CWM. Vasomotor reflex responses in idiopathic and hormone dependent migraine. Lancet 1967; 1: 1023-6.

41. Morley S. Migraine: A generalized vasomotor dysfunction? A critical review of the evidence. Headache 1977; 17: 71-4.

42. Cohen MJ, Rickles WH, McArthur DL. Evidence for physiological response stereotype in migraine headache. Psychosom Med 1978; 40: 344-54.

43. Price KP, Tursky B. Vascular reactivity of migraineurs and non-migraineurs. A comparison of responses to self-control procedures. Headache 1976; 16: 210-17.

44. Bakal DA, Kaganov JA. Muscle contraction and migraine headache: Psychophysiologic comparison. Headache 1977; 17: 208-15.

45. Hsu LKG, Crisp AH, Kalucy RS, Koval J. Early morning migraine: nocturnal plasma levels of catecholamines, tryptophan, glucose, and free fatty acids and sleep encephalographs. Lancet 1977; 2: 447-51.

46. Anthony M. Biochemical indices of sympathetic activity in migraine. Cephalalgia 1981; 1: 83-9.

47. Herman P. The pupil and headaches. Headache 1983; 23: 102-5.

48. Gotoh F, Komatsumoto S, Araki N, Gomi S. Noradrenic nervous activity in migraine. Arch Neurol 1984; 41: 951-5.

49. Cortelli P, de Caroli P, Sturani A, et al. Cardiovascular and biochemical assessment in migraine patients submitted to tilt test. Funct Neuro 1986; 1: 285-90.

50. Havanka-Kannianinen H, Tolonen U, Myllyla VV. Autonomic dysfunction in adult migraineurs. Headache 1986; 26: 425-30.

51. Havanka-Kanniainen H, Juujarvi K, Tolonen U, Myllya VV. Cardiovascular reflexes and plasma noradrenaline levels in migraine patients before and during nimodipine medication. Headache 1987; 27: 39-44.

52. Mikamo K, Takeshima T, Takahashi K. Cardiovascular sympathetic hypofunction in muscle contraction headache and migraine. Headache 1989; 29: 86-9.

53. Sokolov EN. Perception and the conditioned reflex. New York: Permagon Press, 1963.

54. Nyrke T, Kangasniemi P, Lang H. Alpha rhythm in classical migraine (migraine with aura): abnormalities in the headache-free interval. Cephalgia 1990; 10: 177-81.

55. Raudino F. Visual evoked potentials in patients with migraine. Headache 1988; 28: 231-3.

56. Marsters JB, Good PA, Mortimer MJ. A diagnostic test for migraine using the visual evoked potential. Headache 1988; 28: 526-30.

57. Ramadan NM, Halvorson H, Vande-Linde A, Levine SR, Helpern JA, Welch KMA. Low Brain Magnesium in migraine. Headache 1989; 29: 416-9.

58. Altura BM, Altura BT. Magnesium and vascular tone and reactivity. Blood Vessels 1978; 15: 5-16.

59. Mody I, Lambert JDC, Heinemann V. Low extracellular magnesium induces epileptiform activity and spreading depression in rat hippocampal slices. J Neurophysiol 1987; 57: 869-88.

60. Coan EJ, Collingridge GL. Magnesium ions block an N-methly D-asparate receptor-mediated component of synaptic transmission in rat hippocampus. Neurosci [Letters] 1985; 53: 21-26.

61. Baudouin-Legros M, Dard B, Guichency P. Hyperreactivity of platelets from spontaneously hypertensive rats. Role of external magnesium. Hypertension 1986; 8: 694-9.

62. Haas DC, Lourie Id. Trauma-triggered migraine: an explanation for common neurological attacks after mild head injury. J Neurosurg 1988; 68: 181-8.

63. Gardner-Medwin AR. The effect of carbon dioxide and oxygen on Leao's spreading depression: evidence supporting a relationship to migraine. J Physiol 1981; 316: 23P-24P.

64. Spierings ELH. Recent advances in the understanding of migraine. Headache 1988; 28: 655-8.