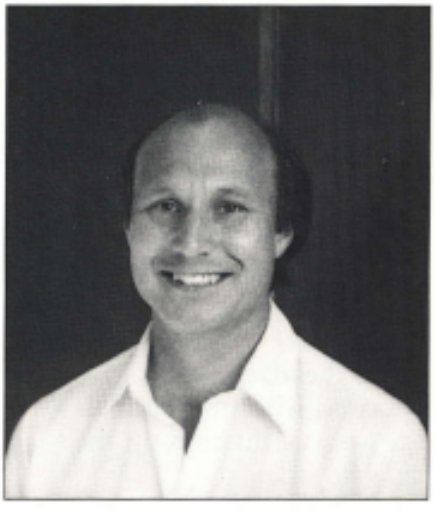
The Mystique of Migraine
Part II: Is it Vascular? — RJ Henbest



RJ Henbest
MD, CCFP, M CI 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 four year old son Benji, this time as associate professor and deputy head of the Department of Family Medicine at Medunsa.

Summary

This paper reviews many research reports concerning the vascular changes which occur during migraine attacks. It looks at the origins of the vascular theory, then describes the foundational research conducted by Wolff and his colleagues, through to recent studies on intracranial and extracranial blood flow. The author discusses and interprets these findings and then identifies the unresolved issues which make him believe that in spite of all the sophisticated research information we should still adhere to the present international classification of headache which calls migraine simply migraine.

S Afr Fam Pract 1992; 13: 265-71

KEYWORDS:
Migraine; Research; Vascular Headache; Blood Flow

Introduction

Sometimes it seems that the more we learn, the more we become aware of how much more there is to know. There seems to be a cycle. We start with a simplistic understanding. Then, as we become aware of the complexities, we become less certain or even confused. Only later do we put the 'many pieces' together to form a coherent picture such that our understanding is once again simple, but no longer simplistic.

With migraine it would seem that we are presently in the 'many pieces' stage. Until recently, we had a pretty straightforward understanding of migraine in terms of the vascular theory. Now we are not so sure.[1] We have more information than ever before, but have not yet managed to put it together. As Edmeads has put it, "The difficulty with even the hardest evidence is that it must be first evaluated and then interpreted, processes that are subjective and fallible."[2] The mystique of migraine remains.

This paper reviews what is known concerning the vascular changes that occur during migraine attacks. It begins with a brief overview of the vascular theory and its origins, followed by a description of the foundational research conducted by Wolff and his colleagues, through to the present day studies of both the intracranial and extracranial blood flow. The paper concludes with a discussion of these findings and the identification of unresolved issues concerning the vascular theory. Subsequent papers will review the evidence for the roles played by neural, haematological, and psychological factors in the pathogenesis of migraine.

The Vascular theory

This theory has been so widely accepted that until very recently, all forms of migraine headache have been classified as "Vascular headaches of the Migraine type".[3,4]

According to the vascular theory, the initial event of the migraine attack is vasoconstriction which leads to cerebral hypoxia. The hypoxia (believed responsible for the aura of classic migraine) results in reactive vasodilation which is considered to be the cause of the pounding headache so characteristic of migraine. The vascular theory also allows for a secondary 'sterile' inflammation as an important contributor to the pain.

... Mystique of Migraine: II

The origins of the vascular theory go way back. Following Harvey's discovery of the circulation in the 17th century, Thomas Willis (1621-1675) articulated a theory that headache was caused by dilation of the blood vessels within the head.[5] Later, Latham (1872) speculated that the visual auras were due to defective blood supply to one side of the brain resulting from contraction of the cerebral arteries.[6]

Wolff and colleagues: laying the foundations

The experimental basis of the vascular theory was laid by Harold Wolff and his colleagues beginning in the 1930s. Their major conclusions and supporting research are described below.[7,8]

Their first conclusion was that the pain of migraine was caused by distension of the extracranial, rather than the intracranial cerebral arteries. In 1938, Graham and Wolff[9] studied the pulsation of the scalp arteries (especially the superficial temporal

Until recently all forms of migraine have been classified as 'vascular headaches of the migraine type'.

artery) during migraine headaches before and after the administration of ergotamine. The intensity of migraine headache paralleled the amplitude of pulsation of the arteries. Ergotamine decreased the intensity of the pain parallel to a decrease in the amplitude of pulsation. In contrast, the intracranial pulsations, measured indirectly by recording the amplitude of cerebral spinal fluid (CSF) pulsations through a lumbar puncture needle, bore no relationship to the headache.

A second conclusion was that the extracranial arteries could produce headache only if they were subjected to an endogenous "pain threshold lowering substance" – distention and increased pulsatility alone were not enough. Migraine sufferers and non-headache subjects were warmed to produce dilation of the scalp arteries. There was no pain. Blister fluid was then injected around the dilated vessels, resulting in the immediate development of headache. Injection of blister fluid around undilated vessels did not cause pain. In 1953, Wolff and Tunis demonstrated that migraine sufferers had decreased pain threshold at the site of the pain during migraine headache as compared to the headache-free interval.[10] In 1960, Chapman and Wolff attributed this decrease in pain threshold to the accumulation of a substance initially referred to as 'headache stuff' and later called 'neurokinin'.[11] They retrieved it from perfusates of the skin, showed its activity was closely related to the intensity of the pain and that its activity decreased sharply with the administration of ergotamine, parallel to a decrease in pain intensity.

Their third conclusion was that visual auras were produced by decreased cerebral blood flow. They had subjects inhale varying amounts of amylnitrate during their auras. A small amount, sufficient to cause vasodilation but not hypotension, cleared the aura. A larger amount, which produced hypotension as well as vasodilation (thereby reducing cerebral blood flow), intensified and prolonged the aura. In 1950, Marcussen and Wolff further tested the hypothesis that the mechanism underlying the aura symptoms was transient constriction of cerebral blood vessels leading to cerebral hypoxia. Patients were asked to inhale carbon dioxide, a cerebral vasodilator, during the development

... thus, headache was associated with intracranial large arterial dilation on the headache side.

of the migraine aura. During inhalation of the gas, the symptoms transiently regressed, but returned to their former intensity once inhalation was stopped.

Subsequent research

The blood flow of the head can be classified in a number of ways including extracranial versus intracranial and cerebral versus noncerebral, but it would seem that the pertinent classification as far as migraine is concerned, is external versus internal carotid blood supply. The internal carotid arteries supply large areas of brain tissue (the cerebrum). The external carotids supply areas that are mainly extracranial, but in addition, have branches such as the middle meningeal artery that are intracranial, but not cerebral.

Internal Carotid/Intracranial/ Cerebral Blood Flow

Cerebral angiography has occasionally been performed during 'fortuitously' occurring migraine

... Mystique of Migraine: II

auras and headaches. The angiograms have been normal.[2] Even when cerebral blood flow has been markedly reduced during auras, vasospasm has not been observed. Likewise, even when the cerebral blood flow has been significantly increased during migraine headaches, angiograms have not shown vasodilation.

Major advances have been made in the understanding of regional cerebral blood flow (rCBF) due to the development of the xenon clearance technique. Methods of measuring rCBF actually measure tissue perfusion. Tissue pefusion is regulated by the arterioles which account for more than 80% of the total cerebrovascular resistance.[13] Two techniques are available: the intra-carotid method and the inhalation technique. With the inhalation technique, Xenon (133Xe) is introduced through the lungs which has the enormous advantage of

Are common and classic migraines distinct entities?

not requiring arterial puncture. Early on, this technique suffered the disadvantage of not clearly distinguishing extracranial from intracranial flow. Now, it is not only feasible to separate intracranial from extracranial flow but also to distinguish carotid from vertebrobasilar circulation.[14]

Using this technique, it has been shown that cerebral blood flow is decreased during the migraine aura and increased during the headache. The decrease during the migraine aura was initially found to be generalized and bilateral despite the focal and lateralized character of the symptoms. Subsequent research by Olesen et al in 1981, showed that the generalized decrease is the final stage in a series of changes.[15,16] The pattern observed was that of a short-lasting increase in cerebral blood flow in the occipital/parietal area followed by a decrease and a gradual spreading of the decrease towards the frontal pole in keeping with the spreading cortical depression of Leao.[17] The decrease was determined to be about 25% and was originally considered insufficient to cause neuronal dysfunction. More recently, Skyhoj-Olesen et al[18] reviewed these findings and suggested that areas of low flow had been missed because of overestimation of flow due to problems of scattered radiation in the xenon technique. Their own studies demonstrated ischemic foci during an attack of migraine with aura. Further evidence for ischemia includes: positron emission tomographic findings of increased cerebral oxygen extraction during auras,[19] focal electroencephalogram (EEG) slowing, the finding of ischemic metabolites in the cerebral spinal fluid (CSF) following an aura,[20] and the detection of areas of edema and infarction on computerized axial tomography (CAT) scans.[21]

Migraine with aura has been shown to be associated with focal posterior blood flow reduction followed by hyperemia in contrast to migraine without aura which has not demonstrated measurable changes in brain tissue perfusion.[22,23,24,25,26] Although aura symptoms last for only 30 to 60 minutes, the focal hypoperfusion can continue for hours and is present during the succeeding headache phase.[18,24,27,28] The small vessels evidently fall prey to the ischemia that they cause, for they may at times exhibit impaired ability to dilate promptly in response to increasing pCo_2.[29] This dysautoregulation may prolong the ischemia and the aura.

Sophisticated pictures have recently been provided by magnetic resonance imaging (MRI) scans. Igarashi and his colleagues found that 29% of migraine patients compared to 11% of age-matched controls less than 40

Migraine may be caused by a reduced number of serotonin receptors – but are they vascular or neural?

years of age, had small foci of high intensity in their white matter. Although one cannot be sure on the basis of this study alone, whether these foci are the cause or effect of migraine, taken together with the other results stated above, they certainly are suggestive of pathologic changes as the result of repeated or severe hypoxia and further suggest that the changes can be irreversible.

Studies of cluster headache have shown that the rCBF increases in both hemispheres during the headache, but is higher in the hemisphere contralateral to the headache. This contralateral preponderance may also be observed to a lesser extent with migraine. Unlike migraine, the increased rCBF of cluster subsides with the resolution of the headache.[14] Additionally, the extracranial blood flow increases to a much greater

... Mystique of Migraine: II

degree in cluster than in migraine (perhaps related to the obervation that the pain of cluster is usually greater), is greater on the side of the headache, and subsides promptly as the headache subsides.[2] Also of note, the increased rCBF does not decrease with the administration of ergotamine, even though the headache does.[31]

External Carotid/Extracranial/Non-cerebral Intracranial Blood Flow

The development of infra-red cutaneous thermography and Doppler ultrasonography have allowed further study of extracranial blood flow, including that of the smaller vessels.

Thermography measures and maps the changes in skin temperature that are caused by changes in cutaneous blood flow. In migraine, a decrease in temperature on the side of the headache has been demonstrated with a return to normal temperature following clearing of the headache by ergotamine.[32]

The Doppler technique involves placing an ultrasonic transceiver over a superficial vessel to measure the direction, velocity and turbulence of blood flow in that vessel. In cluster headache, decreased flow velocity in the ipsilateral supraorbital and frontal arteries between headaches, a further decrease during headache, and an increase following the successful use of ergotamine to terminate the cluster headache have been shown.[33]

Friberg et al,[13] combined rCBF measurements with simultaneous measurements of blood velocity in the middle cerebral arteries (MCA) by means of transcranial doppler ultrasonography. Ten (10) migraine patients with unilateral headache were studied both during an attack and when they had been free of attacks for 5 days. On both occasions they were given intravenous sumatriptan (a designer drug, synthesized to activate a specific subpopulation of serotonin receptors) which relieved the symptoms within thirty minutes without affecting r(CBF). The MCA velocity was normal on both sides on the non-attack day and on the unaffected side during the attack. However, during the attack the MCA

Migraine is part of a widespread disturbance

velocity on the headache side was 26% lower (45 vs 61 cm/second; $p = 0,02$) than that on the nonheadache side where velocity values were normal. This finding was true for patients with and without aura. As the authors concluded, the lower velocity in the MCA can be explained only by dilation of the MCA since rCBF in the MCA supply territory was unaffected. The mean MCA diameter increase was estimated to be 20%. Thus headache was associated with intracranial large arterial dilation on the headache side.

Two other findings of interest are the dense sensory innervation of large vessels in contrast to the small blood vessels of arteriolar size within the brain which are not innervated[34] and the association of migraine with aura with hypertension which implies a tendency towards vascular spasm. Ziegler found a definite history of hypertension in 20% of migraine patients with aura in contrast to 11% of those without aura ($p = 0,02$).[35]

Interpretation and discussion

The evidence supports the following interpretations:

1. The aura of migraine is caused by decreased regional cerebral blood flow (rCBF).

   Migraine in its prodromal stage is associated with cerebral events involving brain cells and cerebral circulation largely supplied by the internal carotid artery. Migraine with aura is initiated by a focal reduction of rCBF which occurs most commonly in the posterior regions of one hemisphere. The neurological symptoms of the aura can be related to the areas of the brain with reduced tissue perfusion. For example, reduced flow in the posterior cerebral artery, resulting in ischemia of the occipital lobes, is associated with the visual phenomena which are the commonest symptoms of the prodromal phase. Dysautoregulation of the vessels may prolong the ischemnia and the aura.

   The decreased rCBF, in the absence of any visible change in the large or medium-sized vessels, suggests that the impediment to flow is in the small cerebral vessels, the arterioles.

2. Ultimately there is an increase in cerebral perfusion, almost certainly mediated by dilation of the small vessels, almost certainly in response to ischemia and almost certainly prolonged by dysautoregulation. The loss of the normal autoregulatory function of

arterioles and their reactivity to arterial carbon dioxide (CO^2) leads to a vicious cycle such that there is a failure to vasoconstrict when the level of CO^2 decreases, which may prolong the increased blood flow.

But, the increased cerebral perfusion probably is not the cause of the headache for a number of reasons: firstly, the hypoperfusion present during the aura can continue for hours and can be present during the succeeding headache phase; secondly, the increase may be generalized even though the headache is localized; thirdly, the headache seems to bear no relationship to the intracranial pulsations; fourthly, the increased perfusion may outlast the headache by hours or days; fifthly, it is not reduced by the administration of ergotamine even though the headache is, and finally, clinical situations in which regional cerebral perfusion is elevated as much as or more than it is in migraine may not be accompanied by headache. Rather, the increased rCBF would seem to be solely a compensatory event for the initial ischemia and not associated with the pain either as cause or effect.

3. Instead, the painful headache phase is, paradoxically, extracerebral. It is not related to cerebral blood flow changes, but to blood flow changes in a different set of blood vessels – namely, excessive dilation and amplitude of pulsation of the branches of the external rather than the internal carotid, one branch of which, the middle meningeal artery, is indeed intracranial. The extracranial blood flow (as inferred from the inhalation technique) behaves differently from the intracerebral blood flow, in that while also elevated during headache, it subsides promptly as the headache subsides.

4. External carotid artery dilation alone is not sufficient to produce pain. A decrease in pain threshold is also required.

   Thus, the original research by Wolff and his colleagues holds remarkably well today. All three of their original conclusions have been borne out by the research to date with one refinement: the aura is due to decreased cerebral blood flow and there is a decreased pain threshold, but the headache, while mainly extracranial, is now known to be more specifically due to dilation of the external carotid system. Four additional comments follow.

Migraine and tension headaches may be part of a continuum – varying quantitatively rather than qualitatively.

Firstly, the study by Skyhoj-Olesen et al,[18] demonstrating ischemic foci during an attack of migraine with aura, together with positron emission tomographic findings of increased cerebral oxygen extraction[19] have reintroduced the theory of a primary vascular cause of the migraine attack, a theory presumed past resuscitation by many.[36] Although reduced regional cerebral blood flow has now been convincingly shown to account for the aura of migraine, what is responsible for the decreased perfusion in the first place? Vasoconstriction is certainly one, but not the only means which could account for the decreased flow. At least two other possibilities would be that of platelet aggregation and mural edema. Further, even if vasoconstriction were the mechanism, it may be secondary to neural or hematological/ hormonal factors rather than being primary.

Secondly there is an apparent paradox posed by both doppler and thermographic studies of a decreased flow through the cutaneous vessels during headaches presumed to be due at least in part to extracranial vasodilation. The paradox is partially resolved in that the vasodilation has been demonstrated in the larger extracranial vessels, while the decreased flow has been found in the smaller vessels. In fact, the distention of the extracranial blood vessels may be secondary to obstruction of the smaller vessels. We also have evidence of vasodilation of intracranial noncerebral large vessels. But, we have no explanation as to why there should be decreased flow through any of the extracranial vessels.

The third comment concerns the debate about whether common and classic migraine are disinct entities or not.[37] The main argument in favour of distinct

entities has been the well substantiated association with changes in cerebral blood flow for classical migraine that has been lacking for common migraine.[38] However, the recent study by Friberg et al[13] found identical and significant blood flow changes in migraine with and without aura and also suggested a common mechanism in that the headaches of both were aborted by a serotonin agonist thought to act predominantly on pathologically distended arteries. These findings suggest that migraine may be caused by a reduced number of serotonin receptors. The question is, are these receptors vascular or neural?

The fourth comment concerns the theory that migraine and tension headaches are part of a continuum – varying quantitatively rather than qualitatively.[39,40,41] This line of thinking goes further than the question of the similarity of common and classical migraine and raises questions about the role of vascular changes in tension headaches.[42]

Unresolved Issues

1. Is the primary event migraine with aura vascular in nature, that is, vasoconstriction of the cerebral arterioles, or is the primary event neural, chemical, mechanical or psychological? Although reduced regional cerebral blood flow has now been convincingly shown to account for the aura of migraine, what is responsible for the decreased perfusion in the first place? Where are the responsible receptors located, on the arterioles, the nerves or platelets?
2. What is the initiating event for migraine without aura?
3. Why is there decreased flow through any of the extracranial vessels?
4. Why do the branches of the external carotid become dilated and pulsate to the point of pain because of a process initiated in the territory of the internal carotid artery?

Conclusion

We now have a fair amount of sophisticated information about the blood flow of the head during migraine attacks. There is substantial evidence that the aura of migraine is due to decreased regional cerebral blood flow and that the headache of migraine is due to dilated vessels of the external carotid system. But, we still do not know whether migraine is a vascular phenomenon, a 'nerve storm' or perhaps even a haematological disorder. In addition, we would do well to remember that migraine is but part of a widespread disturbance and we still know precious little about accompanying changes in the rest of the vascular system, such as renal blood flow. I think it appropriate, at least for the time being, that the present international classification of headache,[4] simply calls migraine, migraine.

... convincingly shown that reduced regional cerebral blood flow accounts for the aura of migraine.

References:

1. Henbest RJ. The mystique of migraine. Part 1: Its nature and diagnosis. S Afr Fam Pract 1991; 12: 512-9.
2. Edmeads J. Vascular headache and the cranial circulation – another look. Headache 1979; 19: 130.
3. Ad Hoc Committee. Classification of Headache. JAMA 1962; 179: 127-8.
4. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. Cephalgia 1988; 7 (suppl 8): 1-96.
5. Willis T. Practice of Physick. London, 1864.
6. Latham P. Clinical lectures on nervous or sick headaches. Br Med J 1872; 1: 305-6; 336-7.
7. Wolff HG. Headache and Other Head Pain. 2nd ed. New York: Oxford University Press, 1963. (1st ed. 1948)
8. Dalessio DJ. editor. Wolff's Headache and Other Head Pain. 4th ed. New York: Oxford University Press, 1980.
9. Graham JR, Wolff HG. Mechanisms of Migraine Headache and Action of Ergotamine Tartrate. Arch Neurol Psychiat 1938; 39: 737-63.
10. Wolff HG, Tunis MM, Goodell H. Studies on headache: evidence of tissue damage and changes in pain sensitivity in subjects with vascular headaches of the migraine type. Arch Int Med 1953; 92: 478-84.
11. Chapman LF, Ramos AO, Goodell H, Silverman G, Wolff HG. A Humoral Agent Implicated in Vascular Headache of the Migraine Type. Arch Neurol 1960; 3: 223-9.
13. Friberg L, Olesen J, Iversen HK, Sperling B. Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet 1991; 338: 13-17.
14. Sakai F, Meyer JS. Regional cerebral hemodynamics during migraine and cluster headaches measured by the

133Xe inhalation method. Headache 1978; 18: 122-32.

15. 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.

16. Lauritzen M, Olsen TS, Lassen Na, Paulson OB. Changes in regional cerebral blood flow during the course of classic migraine attacks. Ann Neurol 1983; 13: 533-41.

17. Leao AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944; 7: 359-90.

18. Skyhoj-Olesen TS, Friberg L, Lassen NA. Ischemia may be the primary cause of the neurologic deficits in classic migraine. Arch Neurol 1987; 44: 156-61.

19. Sigrid H, Gibbs JM, Jones ADP, et al. Oxygen metabolism in migraine. J Cereb Blood Flow Metab 1985; 4: S455-6.

20. Welch KMA, Chabi E, Nell JH, et al. Biochemical comparison of migraine and stroke. Headache 1976; 16: 160-7.

21. Mathew NT, Meyer JS, Welch KMA, et al. Abnormal CT scans in migraine. Headache 1977; 17: 272-9.

22. Olesen J. Causes of Headache. Cephalgia 1989; 9 (supp 10): 168-9.

23. Lauritzen M, Olesen J. Regional cerebral blood flow during migraine attacks by xenon-133 inhalation and emission tomography. Brain 1984; 107: 447-61.

24. Olesen J, Friberg J, Olesen TS, et al. Timing and topography of cerebral blood flow, aura and headache during migraine attacks. Ann Neurol 1990; 28: 791-8.

25. Olesen J, Tfelt-Hansen P, Henriksen L, Larsen B. The common migraine attack may not be initiated by cerebral ischaemia. Lancet 1981; ii: 438-40.

26. Friberg L, Olesen J, Iversen HK. Regional cerebral blood flow during attacks and when free of symptoms in a large group of migraine patents. Cephalgia 1989; 9 (suppl 10): 29-30.

27. Friberg L, Skyhoj-Olesen T, Roland PE, Lassen NA. Focal ischaemia caused by instability of cerebrovascular tone during attacks of hemiplegic migraine: a regional cerebral blood flow study. Brain 1987; 110: 917-34.

28. Anderson AR, Friberg L, Skyhoj-Olesen T, Olesen J. Delayed hyperemia following hypoperfusion in classic migraine: single photon emission computed tomographic demonstration. Arch Neurol 1988; 45: 154-9.

29. Simard D, Paulson OB. Cerebral vasomotor paralysis during migraine attack. Arch Neurol 1973; 29: 207-9.

30. Igarashi H, Sakai F, Kan S, Okada J, Tazaki Y. Magnetic resonance imaging of the brain in patients with migraine. Cephalgia 1991; 11: 69-74.

31. Edmeads J, Hachinski VC, Norris JW. Ergotamine and the cerebral circulation. Hemicrania 1976; 7: 6-10.

32. Lance JW, Anthony M. Thermographic studies in vascular headache. Med J Australia 1971; 1: 240-8.

33. Kudrow L. Thermographic and doppler flow asymmetry in cluster headache. (Abstract). Proceedings of the 2nd International Symposium of the Migraine Trust, 1978: 16.

34. Dahl E. Intracranial arteries: morphological differences in extracerebral and intracerebral vessels. The Bergen Migraine Symposium Suppl 1975; 1: 24.

35. Ziegler DK, Hassanein RS. Specific headache phenomena: their frequency and coincidence. Headache 1990; 30: 152-6.

36. Blau JN. The vascular theory of migraine – resuscitated or more moribund? Headache 1989; 29: 384.

37. Wilkinson M, Blau JN. Are classical and common migraine different entities? Headache 1985; 25: 211-2.

38. McWhinney IR. A Textbook of Family Medicine. Oxford: Oxford University Press, 1989.

39. Featherstone HJ. Migraine and muscle contraction headaches: a continuum. Headache 1985; 25: 194-8.

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

41. Takeshima T, Takahaski K. The relationship between muscle contraction headache and migraine: a multivariate analysis study. Headache 1988; 28: 272-7.

42. Henbest RJ. The nature and meaning of tension headaches. S Afr Fam Pract 1991; 12: 422-33.