For much of the later part of the 20th century, a rather straightforward concept dominated thinking about migraine; first proposed in some part by Willis (1664) and best articulated by Wolff (1948), the theory explained the pain of migraine to be due to dilation of cranial vessels. By the latter part of the 19th century, neuronal theories had also been well articulated (Liveing, 1873) and, indeed, Gowers (1888) seemed happy with that concept. It is remarkable that three key approaches revived the vascular theory in the mid-to late-20th century; and the same three key areas—human experimental studies, observations on vascular change and therapeutics—have, some 120 years later, put migraine back into the brain, and thus firmly into the domain of neurology.

This issue of *Brain* describes a study with exactly the type of result that lead Wolff to think of migraine as vascular; yet, taken in context, it provides evidence that leads to precisely the opposite conclusion. Henrik and colleagues (2008) from the Copenhagen group demonstrate in their new study pituitary adenylate cyclase activating peptide (PACAP-38) producing cranial vasodilation and triggering delayed migraine in sufferers but not in controls or migraineurs infused with placebo. Now for the purpose of discussion, I will refer to the delayed attacks as migraine. One might argue that not all attacks fulfil all standard criteria (Headache Classification Committee of The International Headache Society, 2004); however, this argument is optimally debated elsewhere and seems specious at best. The authors sensibly refer to the headache as experimental migraine; a rose by any other name. Why are the new data important? Because the same group using the same methods has shown that vasoactive intestinal polypeptide (VIP), another member (with PACAP) of the secretin/glucagon peptide superfamily, can induce an equal craniovascular vasodilation but does not trigger migraine at all (Rahmann et al., 2007). So it is not the dilation but receptor site activation that is important in migraine. Simply stated, the vasodilation is an epiphenomenon neither necessary nor sufficient for the symptoms.

Another lynchpin of the vascular argument came from the behaviour of cranial vessels in migraine sufferers. It had been shown that ergotamine could produce vasoconstriction in line with its efficacy in migraine (Tunis and Wolff, 1953). When more closely examined, again by the Copenhagen group, it was shown that vascular changes were unrelated to the phase of the attack, indeed blood flow could be reduced or was normal during the pain phase (Olesen et al., 1990). Most recently, using high resolution 3T magnetic resonance angiography, it has been reported in *Brain* that migraine triggered by nitroglycerin occurs without any continuing change in intracranial or extracranial vessels (Schoonman et al., 2008). As the vascular theory has, as it were, constricted in its evidence base with the new data, plausible changes in brain function in the brainstem and sub-cortical structures are now reported (Weiller et al., 1995; Bahra et al., 2001; Denuelle et al., 2004; Afridi et al., 2005a, b) that could readily account for much of the syndrome clinicians have always recognized to be too rich simply to reflect vasodilation.

The most direct, and for our patients, important result of these new data has been a realization that the debate over the vascular versus neuronal action of anti-migraine compounds (Humphrey and Goadsby, 1994) is now full circle in favour of the patients. By this I mean the recognition that a purely neural action is sufficient for anti-migraine efficacy frees patients from any potential vascular complications of anti-migraine therapeutics in the future, as industry pursues non-vasoconstrictor targets for new therapies. Triptans, serotonin 5-HT1B/1D receptor agonists, which are extremely effective treatments (Goadsby et al., 2002) and were developed initially as cranial vasoconstrictors (Humphrey et al., 1990), have been for some time known to have effects on neuronal transmission in the brain (Kaufe et al., 1993). The most recent studies demonstrate that calcitonin gene-related peptide (CGRP) receptor antagonists, developed on the basis of elevated CGRP in acute, severe migraine (Goadsby et al., 1990) and its normalization with treatments (Goadsby et al., 1990), such as olcegepant (BIBN4096BS: Olesen et al., 2004) and telcagepant (MK0974: Ho et al., 2008), are both effective, and without vascular effects (Petersen et al., 2005). These new clinical trial findings bring into focus the translational importance of the data reported in this issue of *Brain* (Henrik et al., 2008). Constriction is not required since dilation is not a key part of the process; thus new therapeutics can have neuronal targets confident in the knowledge that it is both logical and desirable to attenuate the aberrant brain processes that characterize migraine (Goadsby, 2005). Along with a better understanding of migraine as a disorder of the brain,
recent developments are about to provide neurologists with a new class of treatment—CGRP receptor antagonists or, if preferred, gepants. The demise of the vascular theory is ushering a new era for medicine development, understanding of the disorder and, thus, better management of patients with migraine. Research with patients is time consuming, difficult and expensive, but remains the greatest single motivation for translational neuroscience—to improve the lives of those burdened with neurological disorders.

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