background Na^+ conductance in pacemaking activity is unproven, only the hasty would suggest that it is unlikely. Arrested pacemaker cells have membrane potentials of −35 mV: some outward current must flow in these preparations, presumably during diastole. Whatever the current is, it does not appear to be generated by I_f or by Ca^{2+} channels[7] and it might well be a background Na^+ conductance.

Contrary to the statements of DiFrancesco *et al.* the responses to vagal stimulation are not mimicked by inhibiting I_f or by resetting the activation potential of I_f to more negative values. The inhibition of I_f by Cs^+ does not hyperpolarize the membranes of arrested pacemaker cells whereas vagal stimulation does[7]. In beating hearts vagal stimulation completely stops the generation of pacemaker action potentials, and the membrane potential settles positive of the peak diastolic potential: inhibition of I_f merely slows the generation of pacemaker action potentials with no evidence that the potential will settle positive of the peak diastolic potential. Vagal stimulation continues to slow the heart after I_f has been blocked by Cs^+ (Ref. 5). If I_f was the target for vagally released ACh it would be expected that vagal stimulation would become ineffective once this current was inhibited.

The membranes of arrested preparations hyperpolarize under the influence of vagal stimulation. These responses are associated with a substantial decrease in membrane conductance. The simplest explanation, which we agree is unproven, is that an inward current is decreased by vagal stimulation. Since these responses persist after I_f has been blocked by Cs^+, I_f is not the current being inhibited.

We agree with DiFrancesco *et al.* that our hypothesis would be much more attractive if it had been shown that a background Na^+ current could be modified by transmitters. However, this would require recordings to be made from preparations in which the consequences of activating extrajunctional receptors had been blocked, while internal messenger systems were kept intact and the transmitters were applied rapidly to avoid desensitization. Alternatively, the responses of innervated myocytes to nerve stimulation should be analysed. To our knowledge neither of these types of experiment have been attempted.

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Pain and somatosensory activation

In a recent article in *TINS*[1] on the cortical representation of pain, Per Roland states that previous animal research of nociception is inconclusive and, together with clinical observations of human lesions, does not provide coherent evidence that a particular brain region is important in pain perception; in fact, he states that 'the role (if any) of the cortex in pain perception is still dubious'. He then describes two positron emission tomography (PET) studies of cerebral activations made during experimentally induced pain, and concludes that some cortical areas may be involved in certain aspects of pain but that these regions may not be essential to pain reception. By contrast, we suggest that animal experiments and clinical studies of human lesions indicate that the cerebral hemispheres, particularly the somatosensory areas, are important for pain perception and chronic pain states, and that the latest imaging studies in humans support this view.

There are detailed wartime reports of pain perception deficits due to parietal cortical injuries[2,3], which are corroborated by patient studies[4,5], using computed tomography (CT), magnetic resonance imaging (MRI) and postmortem necropsy studies[6,7]. These studies describe cortical lesions in and around somatosensory areas as well as pain and temperature abnormalities. Additionally, many of these patients had symptoms consistent with a thalamic syndrome (but without an observable thalamic lesion), emphasizing the importance of the somatosensory cortex in persistent pain. Recently, a patient with a tumor compressing the second somatosensory area (which had been localized using MRI) underwent detailed psychophysical sensory testing, which revealed contralateral mechanical and thermal pain deficits. These deficits were normalized again after surgical resection of the tumor[8].

There is also a wealth of data in non-human primates and other vertebrates that indicate the anatomic substrate (i.e. the spinothalamocortical connectivity) for the role of the somatosensory cortex in discriminative nociception[9–13]. Although not as extensively studied, nociceptive responses have been identified in the somatosensory cortex of the rat, cat and monkey[14–16]. Furthermore, Kenshalo has correlated cortical nociceptive responses in the first somatosensory area (SI) of the macaque to behavioral indices of pain perception[17]. While the animal evidence suggests that many other cortical areas, including the anterior cingulate gyrus, receive projections from thalamic nociceptive areas in the medial thalamus, the receptive field characteristics are not conducive to the sensory discrimination aspect of nociception but to attention, learning and affect[18].

Given the evidence for a predominant role of the somatosensory cortex in the pain system it

may, at first, seem surprising that the only common area to be activated in the two PET studies was the anterior cingulate gyrus. However, this result should not be overemphasized. Dr Roland suggests, as does Jones' group in London, that there is clinical evidence for the role of the anterior cingulate in pain[19,20]. This evidence is presumably the large number of patients who have received relief from intractable pain after ablations of this area[21]. Yet, it is puzzling (as others have already pointed out[19]) that this consistent activation results from an aspect of pain that has been minimized in the experimental as compared to the clinical situation. The Montréal group does, in fact, attribute the activation of the cingulate to discriminative aspects of pain, for which they cite preliminary experimental evidence[19]. However, the bulk of animal and clinical evidence suggests a role for this area in the affective rather than the discriminative components of pain processing[18]. Moreover, if the anterior cingulate is important for discriminative pain in humans ablations of this area should raise the pain threshold. This does not typically occur after prefrontal leucotomy, which includes area 24 (Refs 22, 23). It seems likely that activation of the anterior cingulate gyrus results from a residual affect related to experimental pain or that, during the painful but not the warm (control) state, it represents cognitive processing unrelated to pain. As Dr Roland points out, this is a very heterogenous cytoarchitectonic area in terms of function – motor, attention, learning and memory. In contrast to that of the anterior cingulate, the response of the somatosensory area in pain, first reported in the study by the Montréal group, had been predicted by the clinical and experimental literature concerning pain (intensity) perception and by chronic pain syndromes[4–7,9–17]. This was not discussed and deserves emphasis.

Several years ago, we began to develop a single photon emission computer tomography (SPECT) blood flow technique to study cortical responses associated with pain perception in awake humans. Using hexamethyl propyleneamine oxime (HMPAO) as a regional blood flow tracer and MRI superimposition for precise localization, we have now found substantial and reproducible decreases in blood flow in the vicinity of SI in response to a tonic painful thermal stimulus[24]. This was the only consistent change in the cortical signal to pain (innocuous stimulation gave increases in cerebral blood flow in SI). The apparent inhibition of neural activity with this tonic stimulus is in contrast to the activation of multiple areas observed in the two PET studies, which used a transient, repeated stimulus. However, this difference in results may reflect differential processing of tonic and transient noxious stimuli by subtypes of peripheral nociceptors[25]. This differential processing might be maintained throughout the CNS[26]. In this light, the result obtained by the Montréal group of a significant activation in SI may be complementary to the SPECT result in SI. Recent electroencephalographic evidence suggests that initial somatosensory activation in response to pain (decreased α power) progresses to somatosensory inhibition (α augmentation) after the first minute of painful stimulation[27]. Earlier imaging studies with techniques using ^{133}Xe also suggest parietal blood flow increases as well as decreases during experimental pain[28,29].

Altogether, the various lines of evidence point to an important role of the cerebral cortex, notably the somatosensory cortex as well as other areas, in pain perception in health and disease. The role of the cortex is, perhaps, not so much 'dubious' as it is complex and challenging: multiple representations of pain in the cortex as well as multiple somatosensory renditions of pain (activation or inhibition). Ultimately, in view of recent animal and lesion studies, the interpretation of functional imaging studies is a most compelling challenge because of the immense clinical problem of pain.

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