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EDITORIAL

Synapses, sea slugs, and psychiatry

This year's Nobel Prize in physiology or medicine, announced on 9 October 2000, has gone to Arvid Carlsson, Paul Greengard, and Eric Kandel. The citation states that the prize is shared for pioneering discoveries in slow synaptic transmission, which are "crucial for an understanding of how the normal functioning of the brain and how disturbances in this signal can give rise to neurological and psychiatric diseases" (www.nobel.se/announcement/2000/medicine.html). Carlsson proved the importance of dopamine as a neurotransmitter and subsequently its role in Parkinson's disease and schizophrenia. The strongest pillar of the dopamine theory of schizophrenia is the linear relation between potency of antipsychotic drugs and their dopamine antagonist potential. The theory has taken some knocks recently. A minority of patients remain symptomatic despite the demonstration in vivo using positron and single photon emission tomography of effective dopamine receptor blockade; the efficacy of atypical antipsychotic drugs with low affinity for dopamine receptors; the growing acceptance of a premorbid fall off in the anticipated trajectories in behaviour and intellect which seems to point the finger at brain and social development rather than neurotransmitters. Nevertheless, the theory survives.[1]

Greengard wrote recently that the relevance of Carlsson's work for schizophrenia was one of his inspirations for pursuing dopamine transmission.[2] His contribution was to show how transmitters such as dopamine exert their effects by inducing in the cell a series of biochemical events involving phosphorylation and dephosphorylation, which amount to signal transduction.

Kandel's work has also focused on neuronal signalling, but in particular, the mechanisms by which learning and memory are effected at the level of the single cell. His partner for much of this work has been *Aplysia californica*, the humble sea slug, whose simple nervous system and set of reflexes designed to protect its gills has been the perfect "preparation" for studying conditioning (it is fitting that the conditioned reflex earned Pavlov the same honour in 1904). Kandel, an émigré from prewar Vienna, studied psychiatry and psychoanalysis in Boston in the early 1960s. He does not mind being referred to as a psychiatrist, although would certainly not claim to be one currently competent to practice (ER Kandel, personal communication, 13 October 2000). He has published some memorable articles on the relation between his work and that of modern neuroscience in general, to psychiatric disorders, and to Freudian theory, including the brilliantly titled *Psychotherapy and the single synapse*,[3] updated recently.[4]

Freud was not awarded a Nobel Prize—modern critics may question whether he was more eligible for the one in literature than medicine. However, his Austrian contemporary, Wagner von Jauregg, became the first psychiatrist laureate in 1927 for his observations on the beneficial effects of induced fever (for example, malaria) on the symptoms of neurosyphillis—not, it has to be said, a treatment that has stood the test of time. But European psychiatry at the fin de siecle was resolutely biological. Egaz Moniz, the Portuguese neurosurgeon who developed psychosurgery, shared the prize in 1949, although the invention of arterial angiography was perhaps a more enduring legacy. Neuroscientists have been so rewarded on many occasions—but as in this year, the contributions tended to be at the "basic" level[5]—for example, Golgi and Cajal (1903), Sherrington and Adrian (1932), Eccles, Hodgkin, and Huxley (1963), and Gadjusek (1976).

Exceptions are Konrad Lorenz and Niko Tinbergen for their popular work on animal ethology, awarded in 1973. Similarly, American scientist Roger Sperry, who shared the prize in 1981, is best known for his work with "split brain" patients, in whom the distinct and at times independent abilities of the right and left cerebral hemispheres were unveiled. We should also mention Cormack and Hounsfield, who were honoured for developing computed axial *x* ray tomography in 1979; and the inventors of magnetic resonance imaging in medicine have been tipped for a similar fate. For once it is no exaggeration to say that these technological developments have revolutionised the way we see the brain. Finally, Nobel laureates in other fields—notably Francis Crick and Gerald Edelman—have turned their attention to the neurosciences and have had a significant impact.

The importance of all this is that it shows the protracted maturation and continuing uncertain status of psychiatry as a scientific discipline. It is anticipated that the work of the winners of this year's prize and its consequences will lead to ever more effective treatments for major mental illness and degenerative disorders of the nervous system.[6] However, equally inspiring is work in the cognitive and social sciences. Such work does not seem to be accorded the same status as that in biology. Only when cognitive, social, and biological sciences are integrated, or when their separate spheres of influence on mental life and behaviour are demarcated, will we have a truly scientific, and hopefully clinically relevant, cognitive neuropsychiatry.[7 8]

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EDITORIAL COMMENTARIES

Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study: the Rotterdam Scan Study

In the paper from the Rotterdam Scan Study (this issue pp 9-14),[1] de Leeuw *et al* take another step towards understanding the conundrum of white matter disease (leukoarosis) and its associations with aging and gender. This will hopefully lead towards better understanding of cognitive decline with age, Alzheimer's disease, and vascular dementia.

The assessment of the role of white matter disease in these processes poses several problems. White matter disease is difficult to quantify. The existence of upwards of some 12 different scales for assessing white matter lesion load, few of which have been validated for interobserver or intraobserver variability, or tested in populations other than the one in which they were generated, testifies to the difficulty of trying to make some sense out of different degrees of "spotty brains".[2] This difficulty in quantification combined with small sample sizes in some previous studies, may have confounded the difficulty of trying to tease out any association between vascular risk factors (hypertension, diabetes, carotid atheroma), so called vascular dementia, Alzheimer's disease, and "normal" age related cognitive decline. Further difficulty is the clinical distinction of Alzheimer's from vascular dementia. Increasing recognition of the overlap in risk factors between Alzheimer's disease and vascular dementia,[3 4] suggests that in fact attempts to make too rigid a distinction between the two may have been counterproductive rather than helpful in studies of possible disease mechanisms.

de Leeuw *et al* studied a large well characterised population of normal people aged between 60 and 90 years with MR scanning. They carefully measured and rated the white matter lesions in the periventricular and subcortical regions in different brain regions. A strength of the study is the use of two independent raters who were able to achieve excellent interrater agreement for white matter lesion load. Periventricular and subcortical white matter lesion load increased with age in men and women and in all regions of the brain. However, women at all ages tended to have a greater lesion load than men, particularly in the frontal lobes where this difference reached statistical significance for frontal capping. As the distribution of possible confounding variables such as hypertension, diabetes, and carotid atheroma was equal between the sexes, it is unlikely that this finding is the result of some other association.

The major problem in this study was the declining response rate with age, from 73% of all those invited to come for a scan in the 60–70 year age group to only 48% in the 80–90 year age group. Therefore, as the authors rightly point out, their study may have underestimated the true prevalence of white matter disease in the general population. The authors report elsewhere on the association with diabetes,[5] carotid atheroma,[6] atrial fibrillation,[7] and cognitive ability.[8]

The authors speculate on two points in need of future study. Firstly, that the increased white matter lesions in women may be the cause of the observed increase in dementia in women compared with men of the same age. Secondly, they suggest that this might be due to loss of a protective effect of oestrogen in postmenopausal women. However, they did not collect data in the present study to test this hypothesis, rather it was a suggestion based on work elsewhere.[9] Possible protective mechanisms for oestrogen suggested by the authors (reduced susceptibility to ischaemia, increased cerebral blood flow, protection against oxidative stress, enhanced synaptogenesis, and prevention of neuronal atrophy) simply serve to highlight the fact that although we are better informed about associations of white matter disease, cognitive decline, aging, vascular risk factors, and actual dementia, we still know relatively little about which is cause, which is effect, and the primary underlying mechanism of these processes. However, the demographic time bomb presented by increased survival into old age certainly justifies greater imaginative effort on the part of epidemiologists, imagers, neuroscientists, and geneticists to sort out the primary cause.

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Vascular depression: new light on an established idea?

The paper by Thomas *et al*[1] (this issue, pp 83–87) furthers the concept of "vascular depression". The concept is a venerable one, dating back at least to the scholarly work of Felix Post.[2] It found new vigour in the work of Robinson and others,[3] whose investigations provided important empirical support for older clinical findings. New in Robinson's studies was their demonstration of regional specificity, with the greatest burden of depression in patients whose cortical infarcts were small and/or located in the left frontal region (thus refuting "meaningful" explanations of depression in reaction to the extent of functional incapacitation). More recent work has shown associations between depression and cardiovascular risk factors or neuroimaging evidence suggestive of microvascular pathology (reviewed by Thomas *et al*[1]) These later studies have tended to emphasise the importance of subcortical lesions, and have led to widespread speculation that microvascular change can provoke demyelination and other lesions that in turn disrupt long association fibres and, possibly, the circuitry that regulates mood and various drives.[3]

Thomas *et al* have tested and extended these notions by showing a relatively specific association between late life clinical depressions and atherosclerotic cerebrovascular disease confirmed at postmortem. Surprisingly, their investigations did not show an association of depression with cerebrovascular risk factors, nor with direct pathological evidence of microvascular pathology. We do not know whether these patients had MRI evidence of such pathology, as has been shown often before. Thus, we do not know whether some unusual attribute of the present sample explains its absence of microvascular disease, or whether there is instead a disjunction in this regard between suggestive MRI evidence and direct pathological examination. We need also to note that this was a small study in terms of statistical inference, and that its negative findings especially must therefore be regarded as tentative. Surely more work of this sort, preferably including MRI correlation, would be of enormous interest.

Whatever its underlying cause or mechanism, the emerging entity of "vascular depression" should serve as a reminder that most important psychiatric diagnoses are syndromes that can have multiple aetiologies and pathogenetic pathways. This principle helps us to understand why "major depression" in late life (for which cerebrovascular disease is probably a prominent provoking element) may differ importantly from early life depressive disorders that have similar defining criteria. Contrasting aetiologies and mechanisms may explain, for example, why the later life disorders may have a different clinical appearance and may tend toward chronicity and refractoriness to treatments that commonly succeed with younger patients,[4] including in particular the selective serotonin reuptake inhibitors.

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A S DAVID

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Notes