

## Expert opinions

### **Archives of General Psychiatry, June 1991**

We were recently asked by one of the editors of the *Psychiatric Bulletin* to comment on the June 1991 issue of the *Archives of General Psychiatry* because of its exclusive neurobiological approach that month. Having thus been given our brief and now having carefully read the issue, we feel obliged to warmly congratulate the Archives for a superb issue and a superb Journal that has consistently set high standards for the reporting of neurobiological research as applied to psychiatry. The June issue this year was the first to report the use of magnetic resonance spectroscopy (as opposed to imaging) in vivo (more of this later) and had many more excellent contributions on the action of lithium on neurotransmitter and second messenger systems and papers on the role of serotonin and endorphins in a variety of conditions.

Clearly the most exciting article is that of Pettegrew *et al* (p. 563) reporting increased levels of phosphodiesterases and reduced monoesters in the dorsolateral prefrontal cortex of schizophrenics, using nuclear magnetic resonance spectroscopy. This is the first report of the translation of a structural imaging technique, magnetic resonance imaging, back to its original spectroscopic form and utilising it as a high resolution chemical detector allowing non-invasive functional imaging without the use of isotopes (as in PET or SPECT). In their paper, Pettegrew *et al* fit their findings very neatly into a popular *zeitgeist* for schizophrenia, that of a frontotemporal developmental synaptic regression hypothesis. This we believe is merely a reflection of the vagueness of the biochemical processes involved which by inductive reasoning is adaptable to almost anything. The technique nevertheless has immense potential and we are sure it will be a landmark study.

In a commentary in the same issue, Dr Barry Guze (p. 572) discusses the strengths of the technique and states that magnetic resonance imaging provides non-invasive biochemical information to test neurochemical hypotheses and possibly ultimately be of diagnostic usefulness. We would be more conservative. The reported technique measures phosphorus 31 which is implicated in a huge number of biochemical processes both neuronal and non-neuronal and it is difficult to see how very sophisticated theories such as the dopamine theory, for instance can be measured by these very non-specific indices (Proton ( $^1\text{H}$ ) spectroscopy may allow the measure-

ment of even more specific molecules, for instance glutamate, but these types of molecules are still vastly more abundant in general metabolic processes than in specific neurotransmitter pools and measurement of synaptic function will remain difficult).

Two papers in the issue consider the neurochemistry of lithium, both from the same group. They are imperiously titled 'The Mechanism of Action of Lithium I' by Manji *et al* (p. 505) and II (p. 513) by Risby *et al*. The first paper is a neuroendocrine challenge test measuring urinary and plasma metabolites of noradrenaline to a clomipramine challenge. Serotonin function was assessed by prolactin and cortisol responses. The inference of these data was that there was a modest increase in noradrenaline release and a larger serotonin effect as judged by the serotonin dependent prolactin response. The problem here is a conflation of two difficulties; firstly it is always difficult to understand the relevance of neuroendocrine responses to the goings on in relevant areas of the brain. A "window into the brain" is the usual justificatory remark, but the difficulty is compounded with a drug like lithium which has protean effects and it is impossible to know how many trans-synaptic effects are involved in these responses.

The second paper is more mechanistic and may be closer to the primary site of action of lithium. This paper shows that lithium may interfere with nucleotide binding protein (G protein) function, a regulatory subunit for the adenylate cyclase second messenger system. However, they are still forced to conclude that lithium probably has multiple interacting sites of action. We are sure that we already knew that from the vast neurochemical literature. It barely leaves any neurochemical system untouched.

A paper on 5-hydroxytryptamine responsiveness in obsessive compulsive disorder by Lesch *et al* (p. 540) provides a good foil to the lithium paper. This again is a neuroendocrine study this time looking at responses to a 5-HT $1\text{a}$  ligand, ipsapirone. This time no differences between controls and patients. The strength of this study is that OCD is probably a model psychiatric syndrome to apply to a neuroendocrine approach and the negative result, paradoxically, we think validates the approach as there is strong evidence in general for a role for 5-HT in this condition and this study suggests this is probably quite specific. Maybe the fault here was that the

neuroendocrine probe was too specific for tracking down the 5-HT dependent peripheral marker of OCD.

A further contribution on serotonin mechanisms in anorexia nervosa by Kay *et al* (p. 556) finds elevated concentrations of serotonin metabolites in the CSF of patients. These authors say that this work contributes to the understanding of the psychobiology of the illness. Some cynics may say that the illness is all psycho and no biology, but surely with the advent of a wide range of new serotonergic drugs, the possibility of serotonergic substrates for any of these types of conditions at least deserves exploration as the treatment prospects may eventually be dramatic.

Reading through this type of issue of the Archives several emotions spring to mind. Firstly, all the contributions are American except one, and rather than resentment at this we feel jealous. Clearly, the neurobiological approach to psychiatry receives considerable funding, unlike in the UK and Europe. To understand the wisdom and context of this one needs to look wider than the Archives, since they will always be in the position of publishing the highest quality research. To gauge the degree of squandering of resources it might be wiser to consult those lesser Journals who have expanded and formed to accommodate the least publishable units of data. We do not entirely subscribe to the view that the very restrictive peer review of tenders for limited funds, as in the UK, is likely to lead to better focused research and more definite success, particularly in the capricious area of psychiatry. This philosophy suggests a certain arrogant prediction of the natural world that we do not possess and we would wager that important findings will come accidentally from where we least expect them rather than a carefully honed piece of grantsmanship. One of our undergraduate tutors, now one of the world's best known neurochemists, once said in an informal setting that it was more important to do an experiment every day on something or other rather than

spending a lot of valuable hours thinking up the perfect study. But clearly a balance has to be struck and we have to guard against a backlash of cynicism and disappointment which may lead to the return of non-biological approaches in inappropriate circumstances.

Maybe then we could write something about swinging pendulums and changing fashions? So we leafed through the June 1981 issue. The issue was full of contributions about monoamines, serotonin tryptophan and monoamine oxidase enzymes. Going back another ten years to June 1971 the issue is almost entirely devoted to neuropsychology although a glimmer of hope; a paper considering the psychodynamic conflicts in Ernest Hemingway's inner life on the tenth anniversary of his suicide. Ten more years should thus do it so turning to June 1961 we were thwarted again only to find papers on electrophysiology, the biology of vibration perception and works on possible autoimmune abnormalities in schizophrenia. It would seem then that certainly despite the changing winds of fashion in psychiatry (which blow particularly strongly in the States) the Archives has maintained an absolutely true course in its dedication to the presentation of high quality biological research in the field of general psychiatry and fully deserves its number one status as the most popular and widely cited journal in the field. So we congratulate the Archives; it has stuck to its guns through changing fashions and has been and is the foremost journal for biological psychiatry, and in the main avoids controversy because of its position in being able to select only the more significant contributions. There may well be too much of this approach in the States and equally too little in the UK but you will not glean this from the pages of the Archives.

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## Research and development for the National Health Service

(MICHAEL PECKHAM [1991]) *Lancet*, 338, 367–371

Professor Michael Peckham's appointment as Director of Research and Development for the National Health Service in England reflects a new phase in central government's concern to influence

health care research. Responding to the House of Lords' 1988 report *Priorities in Medical Research*, and to continuing doubts about the effectiveness of the Department of Health's own research