This rather universal mechanism may gain its specificity in a defined neurotransmitter pathway by the specific receptor population of the questioned neurons. For example, noradrenaline decreases the KCa via the alpha 1 receptor and increases it via the alpha 2 receptor (Aghajanian & Rogawski, 1983); the usually exciting transmitter acetylcholine increases a K conductance via a M2-receptor and produces thereby a special kind of inhibition, which enables phasic instead of regular activity (McCormick & Prince, 1986).

All these changes of the time course result in a different pattern of activity. Because of the relay function of these widely projecting neurons, it appears quite consequent that Dinan connected information-processing and, at the far end, cognition with this membranal function.

However, the mechanism proposed by Dinan involves dopamine as well as neuroleptics: an increase of the CaK due to dopamine (Benardo & Prince, 1986) may be decreased by neuroleptics. Thus, it appears to me that Dinan did not present an alternative to the dopamine hypothesis but supplied the functional part of it. It is to be expected that the introduction of the functional aspect may clarify some open questions regarding this and other neurotransmitter systems.

I am sceptical about the explanatory power of one isolated mechanism – functional pattern as well as receptor-binding – with respect to psychiatric disorders like schizophrenia. I would consider it as an enormous advantage in biologically-orientated psychiatry if one could define a cognitive or behavioural sub-syndrome based on such a functional pattern. After all, there is hope that the appearance of the time dimension in neurobiology will be followed by its consideration in classificatory and diagnostic instruments.

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SIR: Biological psychiatry has developed almost exclusively by focusing on biochemical data, primarily related to monoaminergic functioning. Few theories emerge which take the emphasis from monominergic neurones, which after all represent only a tiny fraction of all brain neurones. Little effort is usually spent in relating receptor binding data to electrophysiological activity in neurones. Dr Aldenhoff's claim that the 'time dimension' is lacking in nearly all biological theories of psychiatric illness is clearly correct. This 'time dimension' can only be incorporated if one uses electrophysiological data. A strictly quantitative analysis of transmitters and their receptors can never provide such a dimension. The tendency to ignore such reality has in my opinion hampered progress in psychiatric research. The dopamine hypothesis of neuroleptic action does not provide a bridge between receptors and cognitive functioning. As a theory it clearly has survival capacity, but in the 25 years since it was originally proposed it has not resulted in the synthesis of a single compound which has improved the treatment of psychotic illness. A glance at prescribing trends in any European country supports such a view. The vast bulk of drugs prescribed for the treatment of schizophrenia were originally discovered prior to 1960.

The calcium-activated potassium conductance theory which I propose (*Journal*, October 1987, **151**, 455–459) is far from flawless. Nonetheless, as Dr Aldenhoff states, it represents a shift of emphasis by introducing electrophysiological data into an area of psychiatric theory which has until now been characterised by tunnel vision for biochemical 'reality'. Whatever the importance (or otherwise) of the theory, the philosophical approach suggested has implications for biological theorising in psychiatry.

Dr Aldenhoff considers that my theory simply provides the functional component to the dopamine hypothesis and not really an alternative. Certainly, Bernardo & Prince (1982) found that dopamine increased calcium-activated potassium conductances, and it is possible that the conductance is maintained by a tonically released dopamine input, the action of which can be blocked by neuroleptics. However, this is unlikely in view of the fact that the conductance was unaltered in the presence of TTX, which would interfere with the release of an inhibitory input (Dinan *et al*, 1987).

The comments of Dr Aldenhoff are of relevance to all involved in research into the biology of psychiatric illness.

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Late Paraphrenia

SIR: We have followed with interest the debate on aspects of late paraphrenia in your correspondence columns since the publication of an article by Holden (*Journal*, May 1987, **150**, 635–639). Some findings of our recent researches in Salford may be of relevance to the issues discussed.

We cannot agree with Grahame (*Journal*, November 1987, **151**, 702) that the differences between 'late paraphrenia' and other 'persecutory states in the elderly' are now resolved. It may be that paraphrenics show many similarities with schizophrenic patients who have an earlier onset of illness, but there are enough differences to warrant further research so that issues may be resolved. Clinically, the acute illness has a more florid course, affect remains intact, the delusions (sometimes fantastic) are very well organised, and the perceptual dysfunction often also occurs in non-auditory modalities. Even more striking is the almost total absence of thought disorder and the relative rarity of first rank symptoms, even though this aspect has been a subject of much debate recently.

There is a high association of symptoms with the presence of peripheral sensory dysfunction, and in a recent paper (Soni, 1988) we have shown that, in some of these patients at least, there is a close temporal relationship between the onset of peripheral sensory disorder and the development of delusions and perceptual dysfunction. When the more acute disturbances of sensation are relieved by appropriate treatments, some of the related mental symptoms improve even before neuroleptics are prescribed.

Perhaps the course and outcome of the illness, so important for the Kraeplinian concept of schizophrenia, needs to be more intensively investigated. In the earlier follow-up studies this appeared to mirror that seen in schizophrenic patients, although being more insidious and the personality disintegration being minimal, even after many years of follow-up. One avenue of research would be to compare, on various parameters, paraphrenic patients with those schizophrenic patients who 'graduate' into this age group and have no clinical evidence of activity of illness ('deficit state'). In a recent study of a 4-year follow-up (Johnstone *et al*, 1986), the negative symptoms of schizophrenia showed relative stability over time, although there were individual variations. In our survey of chronic schizophrenic in-patients in Salford (in preparation) who had been clinically stable for over 5 years, we noticed that many of these 'graduates' (aged 70 years and above) showed a perceptible fall in performance, even though the underlying schizophrenic process had been dormant for many years. If the deficit state symptoms show relative stability in the younger schizophrenic patients, then one conclusion that could be drawn from these observations is that non-illness factors may be important in determining the course and outcome, especially in the elderly.

It is not unreasonable to assume that ageing, and the physical illnesses and insults that accompany it, may be a contributing factor. There is some evidence to suggest that the ageing process can produce decompensation in many illnesses, and the insidious nature of personality deterioration in paraphrenic patients, which is not dissimilar to that seen in 'graduated' schizophrenic patients, may be the effects of decompensation through ageing and the accompanying physical concommitants rather than the disease process itself.

Finally, many paraphrenic patients show associations which cut across the different 'persecutory states in the elderly' even though the clinical presentations are identical. Thus, many have a paranoid, sensitive, and suspicious personality, over half will have some disorder of peripheral sensory function, and around 40% will show some evidence of organicity; this figure may increase with the use of more refined investigatory techniques than are available at present. Such associations are rare in the non-paraphrenic elderly and practically non-existent in other schizophrenic patients, including the 'graduates', and cannot be overlooked. We feel that the final word on the subject has not yet been spoken, and that intensive research may clarify these issues further. As a start, there is a need for refinement of diagnostic and assessment scales for this age group and for using investigatory techniques such as the neuropsychological battery, computerised tomography scan (Naguib & Levy 1987), and nuclear