potentiated. The importance of solving this problem may call for an unprecedented European-scale collaboration.

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Pathology, Phenomenology, and the Dopamine Hypothesis of Schizophrenia

SIR: The recent review by McKenna (*Journal*, September 1987, **151**, 288–301) is one more of a growing spate of hypothetical papers attempting to reconcile various pathological, clinical, and neurochemical findings into a unitary hypothesis for schizophrenia (Weinberger, 1987; Smajuk, 1987). Since there is no pretext for assuming that schizophrenia is a unitary and homogenous disease process, such exercises seem dangerous in that they limit rather than expand the avenues for research into the biology of schizophrenia. In addition, the three reviews cited make a case for differing unitary hypotheses; they beg the validity of each others claim's, and taken together argue for aetiological heterogeneity.

Notwithstanding this, there are also some specific points in Dr McKenna's argument requiring clarification. The hypothesis relies heavily on the assumption that the dopamine hypothesis in schizophrenia is unchallenged, ignoring the serious drawbacks to the dopamine theory (Hornykiewicz, 1982). In addition, the hope by Dr McKenna that the D_2 receptor binding seen in earlier single dose PET studies would be confirmed have not been realised. Using a more selective ligand (11C raclopide) and a more accurate semi-quantitative method, Farde *et al* (1987) were unable to show increased D_2 receptor numbers *in vitro* in drug-free schizophrenic patients. Finally, the heavy reliance of Dr McKenna's synthesis on prefrontal cortical dopamine and hippocampal dopamine systems extrapolated from animal studies is spurious, since in human tissue the levels of dopamine in these regions is negligible (Adolfsson *et al*, 1979) and D_2 receptor binding sites are not detectable *in vitro* or *in vivo* (DeKeyser *et al*, 1985, 1987), and, indeed, current attempts to identify a mesocortical dopamine system in man remains fruitless.

While Dr McKenna's article is an elegant review of the current status of the biology of schizophrenia, since the neurochemical substrates incorporated in his theory have not been demonstrated in man, care should be taken in its interpretation.

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SIR: Dr Kerwin raises points concerning the existence of human limbic and cortical dopamine projections, the validity of the dopamine hypothesis, and the unitary nature of schizophrenia itself.

The existence of dopamine projections to the septo-hippocampal system and prefrontal cortex is generally accepted in primates, based on biochemical (e.g. Bjorklund *et al*, 1978) and histological (Porrino & Goldman-Rakic, 1982) findings. In man, the relevant evidence has been summarised by Camus *et al* (1986): both regions contain appreciable amounts of dopamine and its metabolites, which are significantly reduced in Parkinson's disease. Substantial numbers of D_2 receptors have been found in the human hippocampus. In the human prefrontal cortex, dopaminergic nerve terminals have been