A Unitary View on the Aetiology of Schizophrenia

SIR: The article by Wexler (*Journal*, April 1986, **148**, 357–362) is interesting and thought provoking. It reminds one of the theory of neural plasticity and shows that brain function is dynamic rather than static. I had earlier formulated a hypothesis on the aetiology of schizophrenia, attempting to explain the conflicting findings in schizophrenic research.

Some individuals are genetically determined to have weak and vulnerable dopaminergic systems. When subjected to stresses, part of the dopaminergic pathway ceases to function. To compensate for the loss, the surviving dopaminergic fibres give off additional nerve terminals and D2 receptors. This overreaction gives rise to a relative increase in dopaminergic activity and manifests as the positive symptoms of schizophrenia. In mild cases, the dysfunction is self limiting and dopaminergic transmission is able to restore to its previous level of functioning, and the process is completed. The psychotic episode is thus named a schizophreniform reaction.

In more severe cases, the dysfunction is more chronic and progressive. It results in actual degeneration of the dopaminergic pathways. These degenerative changes are supported by the CT scan studies, postmortem findings, as well as the regional difference in cerebral blood flow and PET studies. The significant reduction of CCK (hippocampus, amygdala), somatostatin (hippocampus), opiate receptors (caudate nucleus), 5 HT receptors (frontal cortex), angiotensin converting enzymes (globus pallidus and substantia nigra) and GABA (nucleus accumbens) also point to this degenerative shrinkage involving certain parts of the brain. Postmortem findings indicated subependymal gliosis in the diencephalon and hypothalamus in chronic schizophrenia. This is consistent with the CT scan evidence of a moderate enlargement of the third and lateral ventricles reported in approximately half of the chronic patients. Gliosis is usually a response to brain injury. The origin of this gliosis may lie at the midbrain ventral tegmental area where the dopaminergic neurones originate. The A10 group of the ventral tegmental area spreads along the mesolimbic and mesocortical pathways to end at the limbic structures and pre-frontal area. Because the DA content in the pre-frontal cortex is only approximately 1% of the DA concentration in the striatum, pathological evidence of cell loss or gliosis in this area may not be obvious. However, cerebral blood flow and PET studies do reveal the frontal region abnormalities.

Negative symptoms seem to result when the degeneration becomes more extensive and when the mesocortical dopamine system is involved. As the effect of DA antagonist in this system is greatly diminished, the symptoms are irreversible with neuroleptic drugs. It may actually become more prominent when the positive symptoms are under control.

Cerebral lateralisation studies have established the asymmetric distribution of major neurotransmitters in the human brain. Dopaminergic systems are left hemisphere biased. It can be deduced that lesions of the dopaminergic system are reflected as left hemisphere dysfunction and such are found in the CT scan, regional blood flow, PET and EEG studies, as well as a specific increase of dopamine in the left hemisphere.

The reactive compensatory process may not be neurotransmitter specific. Hence an alternation in production of noradrenalin may occur in response to dopamine system degeneration, giving rise to affective symptoms which sometimes occur simultaneously or following schizophrenic systems.

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References

BANNON, M. J. & ROTH, R. H. (1983) Pharmacology of mesocortical dopamine neurones. *Pharmacological Review*, **35**, 53–68.

GLICK, S. D., ROSS, A. R. & HOUGH, L. B. (1982) Lateral asymmetry of neurotransmitters in human brain. *Brain Research*, **234**, 53–63.

HARACZ, J. L. (1985) Neural plasticity in schizophrenia. *Schizophrenia Bulletin*, **11**, 191–229.

STEVENS, J. R. (1982) Neuropathology of schizophrenia. *Archives of General Psychiatry*, **39**, 1131–1139.

Endogenous Subtype of Depression

SIR: I read with interest the Young *et al* article (*Journal*, March 1986, **148**, 257–267).

Their conclusion rests on their use of the SADS. They interpret SADS item 326 as addressing anhedonia. Rather, this item addresses loss of interest or pleasure. Thus, someone who had lost interest in all activities but nonetheless could still enjoy some activities when actively involved in them would be rated 6 on this item. Thus, this is not strictly a loss of pleasure item and neither anhedonia nor DSM-III melancholia can therefore be accurately inferred.

From a theoretical point of view, Klein (1974) has hypothesized that pervasive anhedonia is the underlying hallmark of melancholia, in contradistinction to decreased interest in activities with retained ability to experience pleasure. From a practical standpoint, many patients report significant and often pervasive loss of interest in activities but still retain the ability to enjoy them once involved. SADS does not allow