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Around the world, twenty million people are afflicted with schizophrenia. The first part of our special feature discusses the biochemical changes that occur in this disease.
mirror. These so-called prodromal symptoms gradually give way to more intense symptoms which still may be insufficiently strong to fulfill the classic diagnosis of schizophrenia. When the whispering of trees in the wind becomes voices deliberately insulting the sufferer, schizophrenia is becoming established.

Hallucination may be auditory, visual or tactile, and may be best understood as over-amplification and distortion of sensory input, perhaps linked with dopamine upregulation as discussed below. The sufferer explains these abnormal sensory inputs as persecution. They are described as delusional symptoms. Furthermore, very unpleasant and terrifying symptoms of so-called “thought broadcasting” may develop, in which the individual may believe the world can read his thoughts. Insight is lost and the illness is established.

### Genetics

The development of new techniques for genetics has greatly outstripped the problem of defining schizophrenia. Schizophrenia affects 20 million people worldwide, out of which 10 million are in the developed world, and treatment costs are the highest for any single disease. Yet there are no objective diagnostic tests for it. Despite huge amounts of money spent on lifetime care and development of new drugs, the diagnosis of schizophrenia is still made by reference to standard criteria often open to variable interpretation by clinicians. Later in this article, new diagnostic tests being developed for schizophrenia are described.

The absence of accurate objective diagnostic tests for schizophrenia has been a major problem in defining populations for genetic studies. Although putative gene sites have been found, there has often been poor statistical reliability, and replication studies have failed to confirm the presence of the gene association in wider populations. An additional difficulty in interpretation is that many of the gene locations for schizophrenia, there is clearly a genetic-environmental interaction. This is most obviously apparent in identical twins. It has been shown that where one twin has schizophrenia, there is only a 50 per cent chance of the other also developing the disease. Where is the site of this gene/environment interaction? How important is psychic stress? Are there physical insults such as viruses involved? How do social deprivation factors such as poor nutrition affect vulnerability to schizophrenia? These fundamentally important questions are beyond the scope of this review, although the impact of dietary stresses on important biochemical pathways are now better understood.

### Pathophysiology

The serendipitous discovery of the first tranquiliser in the 1950s opened the way for drug companies to develop new ranges of receptor antagonists for the newly discovered neurotransmitters. But problems soon emerged. For example, only some of the symptoms were treated by these new tranquiliser, that is, the negative symptoms were largely unaffected. Also, the neurodevelopmental features of the illness were not explained by the simple hypothesis of an upregulated dopamine receptor.

The problem of negative symptoms was at first explained by depletion of dopamine in chronic illness (“burned out schizophrenia”), but the presence of positive and negative symptoms occurring at the same time in patients — a not infrequent finding — is difficult to explain and further supports the conclusion, that some explanation other than the simple neurotransmitter hypothesis is required.

### Receptor Occupancy

A major problem in the psychopharmacology of schizophrenia has been in understanding why it takes so long (of the order of seven to 10 days or more) to respond to treatment. This does not correspond to the time taken to occupy the receptor — hours rather than days. The simple receptor-blocking model needs modification.

There had always been some misgivings about the early post-mortem findings of increased numbers of dopamine receptors in the schizophrenic brain, because these studies were inevitably carried out in patients who had died after prolonged treatment with neuroleptics. The response to prolonged treatment with neuroleptics was known from animal studies to be an increase in the number of dopamine receptors. The development of positron emission tomography enabled studies to be made of the number of dopamine receptors in the living brain of untreated schizophrenic patients. The majority of these studies showed no evidence of increased dopamine receptor numbers. In 1995, an editorial in the British Journal of Psychiatry stated categorically that there was “no evidence of a primary abnormality in the dopamine receptor”. In the absence of evidence of a primary abnormality in receptor ligand binding, there are two other ways to explain a functional increase in dopaminergic activity:

1. abnormalities in dopamine neurotransmitter suppressor systems, e.g. gamma amino butyric acid (GABA) or 5-hydroxytryptamine (5HT) underactivity
2. post-synaptic (second messenger) modification of neurotransmitter function

These two possibilities are currently being extensively investigated and may operate simultaneously. While the first possibility (abnormality in long tract neurotransmitter suppressor systems) has been under investigation for some time, post-synaptic modification of the transmitter signal has only recently been investigated in schizophrenia. The evidence for the different possibilities is discussed below.

Dopaminergic overactivity Although there is no evidence of an abnormality in dopamine receptor binding in schizophrenia, there is good evidence that psychotic symptoms can be induced by a functional increase in dopaminergic activity using dopamine agonists such as amphetamine, phencyclidine, cocaine and levodopa. Dopaminergic overactivity in the visual system is associated with an increase in visual acuity and this may explain the over-amplification and distortion of vision in schizophrenia. Over-amplification of other sensory systems in schizophrenia may explain hallucinatory phenomena.

Suppressor system underactivity 5-HT agonist activity is thought to explain, in part, the effectiveness of clozapine. On the other hand, excess agonist activity, for example, with hyseric acid diethylamide (LSD) induces psychotic symptoms. The loss of GABAergic neurons in the hippocampi of brains of schizophrenic patients examined at postmortem, supports the possibility of underactivity in the suppressor system.

Post-synaptic modification A disorder of cell signalling might explain not only upregulation...
ulation of the dopamine system in schizophrenia but could also underlie the neurodevelopmental features of the illness. These cell signalling systems have been described independently in numerous scientific publications over the past 20 years. The logic of the interconnections of the signalling systems has recently been described by Downward. When the ligand (for example, dopamine) binds to the receptor, enzyme activity associated with the intracellular part of the receptor is altered. This in turn acts on intracellular mediators which alter the activity of the effector enzymes. These effector enzymes may generate further mediators (second messengers), which may increase or decrease the ongoing signal. Some effector enzymes may alter gene expression.

Although the existence of phospholipid-derived cell signalers acting postsynaptically as second messenger mediators had been known in neurophysiology and biochemistry for many years, it has only recently begun to influence research in psychiatry.

EMERGING THEORIES

Attention is now being paid to modification of the dopamine receptor response by phospholipid-derived cell signalers. There have also been studies of phospholipid metabolism in schizophrenia as precursors of the lipid cell signalling system.

Phospholipid-derived cell signalers
Arachidonic acid is well understood as the precursor of the prostaglandin signalling system. The phospholipid molecule consists of a glycerol backbone with three attached head groups, designated Sn1, Sn2 and Sn3. The Sn1 and Sn2 head groups are commonly fatty acids. It has been known for many years that the enzyme phospholipase A2 selectively releases arachidonic acid from the Sn2 position of phospholipids in cell membranes, and that arachidonic acid then enters the cyclo-oxygenase pathway as the precursor for the prostaglandin cell signalers. But in the 1980s and 1990s, Piomelli and colleagues described another role for arachidonic acid as a cell signaler. They showed that cytosolic phospholipase A2 was activated by the dopamine D2 receptor and that the resulting release of arachidonic acid modified the post-synaptic dopamine signal. Since then, these results have been widely replicated in neurophysiology.

Figure 1 shows how the arachidonic acid cell signal is terminated by a series of uptake enzymes which incorporate the released arachidonic acid into the phospholipids in the cell membrane. At the same time that this basic neurophysiology was being developed, independent studies were being pursued in clinical psychiatry of abnormalities in phospholipids, in particular arachidonic acid. By 1972, lithium had been clearly established as having a stabilising effect on cell membranes in manic depressive illness. It was recognised that the simple amine hypothesis (excessive release of dopamine giving rise to states of excitement, for example, in mania and schizophrenia, and reduced release of dopamine producing depression) was not tenable. A modified amine hypothesis was suggested whereby the receptor effects were modified by membrane events. Horrobin in 1977 suggested a role for prostaglandins in schizophrenia based on a number of observations, including substantial descriptions of relief of schizophrenic symptoms during fevers and reduced rates of autoimmune disease such as rheumatoid arthritis.

Investigators working on membrane abnormalities in manic depressive illness then began to look for abnormalities in membrane phospholipids. These studies have been reviewed. Abnormalities of fat metabolism had been reported in the 1930s in schizophrenia but little notice was taken of them. It was not until the 1950s that advances in technology allowed the accurate measurement of fatty acids. Even then, little notice was taken of polyunsaturated fatty acids.
acids in human disorders. Sinclair\textsuperscript{21} pointed out that Eskimos had a very low incidence of heart disease despite their largely fatty diet. He showed that the diet was high in polyunsaturated fatty acids and opened the way to the understanding of the importance of these essential fatty acids in human metabolism.

Studies of phospholipid metabolism
Phospholipid metabolism studies have been reviewed in the US\textsuperscript{22} in an important paper in which recommendations for financial support were made for this field of research. Following early findings,\textsuperscript{23} many studies of red cell membrane phospholipids have now shown deficiencies in arachidonic acid in the phospholipids of the membrane in schizophrenia. The cause of the reduction in arachidonic acid might be a deficiency of synthesis, increased breakdown or some other, as yet unknown, related signalling deficit. Gattaz\textsuperscript{24} had previously found increased activity of phospholipase A\textsubscript{2} in plasma. At that time this was an isolated finding, but in the light of the emerging understanding of the importance of arachidonic acid as a cell signaller, others replicated the findings of increased activity of phospholipase A\textsubscript{2} in schizophrenia by MacDonell \textit{et al.}\textsuperscript{25} There had been previous reports of increased lipid peroxidation in schizophrenia\textsuperscript{26} and the possibility arose that this finding was associated with the increased activity of phospholipase A\textsubscript{2} and the deficit of arachidonic acid. At the same time, studies of phospholipid metabolism in the brain, of both treated and untreated schizophrenic patients, using nuclear magnetic resonance spectroscopy, showed increased evidence of membrane breakdown.\textsuperscript{27} Current studies of phospholipid metabolism in the brain, using nuclear magnetic resonance spectroscopy are unable to measure levels of arachidonic acid directly. The US Government at the National Institutes of Health in Washington is now funding new studies of arachidonic acid in the human brain.

These studies of the arachidonic acid cell signaller in schizophrenia have been aided by the development in Scotland of a simple skin patch test using methyl nicotinate to stimulate the production of prostaglandin D\textsubscript{2} in the skin by the activation and release of arachidonic acid. Horrobin\textsuperscript{28} had previously described impaired skin flushing in schizophrenia using oral nicotinic acid. Skin capillary vasodilation induced by prostaglandin D\textsubscript{2} causes redness in the

\begin{figure}
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\caption{The reduced topical methyl nicotinate response in schizophrenia}
\end{figure}
patch which can be rated or measured objectively.\textsuperscript{29} This has now been widely replicated. About 80 per cent of schizophrenic patients fail to flush or flush poorly. The photographs in Figures 2 and 3 (p190) show the responses of a healthy subject and a schizophrenic patient to methyl-nicotinate. Figure 4 (p190) shows the dose response curve for methyl-nicotinate in controls and schizophrenic subjects.

Another non-invasive measure being developed by the group at the Highland Psychiatric Research Foundation uses expired breath to measure lipid peroxidation as hydrocarbons.\textsuperscript{30}

An understanding of dopamine signal transduction seems likely to be enhanced by these new approaches, which incorporates the current understanding of the cell signalling system.

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