SCHIZOPHRENIA
HOPE FROM EMERGING TECHNOLOGIES

Michael Orr

ABSTRACT
The impact of two emerging technologies (brain imaging and molecular genetics) on the understanding of schizophrenia, and the extent to which advances in the understanding of the disorder have been reflected in advances in treatment or an alteration in the prognosis are reviewed.

Treatment of schizophrenia still relies heavily on partly substantiated neurochemical hypotheses about the role of neurotransmitters in the genesis or expression of schizophrenic symptoms. These treatments have had little effect on the prognosis of the more severe types of schizophrenia. Brain imaging techniques and molecular genetics may however offer fresh insights into the nature and transmission of the disorder which could lead to advances in early recognition and prevention, and to radically new ways of classifying psychiatric disorders.

INTRODUCTION
Schizophrenia is the disease entity that offers the greatest challenge to research and to clinical practice in modern psychiatry. It is a common disorder, it affects young people in their prime, and it can have devastating effects on individual potential. At best, an affected individual can expect a single episode which responds to treatment and does not recur; in this instance the issues of continuing concern will be sociocultural and relate to the ongoing stigmatisation of people with a history of mental disorder. At worst, a patient may become virtually completely disabled and require continuing care in hospital. The demands on resources of severely disabled schizophrenics are considerable and recent moves towards a greater emphasis on the treatment of mentally ill people in the community are unlikely to lead to a decrease in the demand for specialist hospital based provision.

Advances in neuropsychiatry and in neuropsychopharmacology have shifted the balance in favour of an improved outcome in those patients whose illness is responsive to treatment. In addition, a clearer understanding of the social factors involved in enhancing the risk of relapse has enabled packages of care to be developed which have decreased the risk of further episodes in individual patients.

Despite this, the fundamental mysteries which have always shrouded this intriguing collection of symptoms and signs remain unresolved. The aetiology is unknown and consensus about diagnosis is a relatively recent achievement which has been more a result of research imperatives than of a fuller understanding of the nature of the clinical phenomena involved. Furthermore, the diagnosis itself is no predictor of severity or risk of long-term morbidity, the heterogeneity of symptoms and types of presentation are testimony to the richness of human brain processes rather than an indictment of investigative science, but they undoubtedly preclude simple enquiry. Any substantive research in schizophrenia will therefore remain painstaking, prolonged, costly and, in all likelihood, incomplete in its conclusions. As with any clinical question in search of an answer, research in schizophrenia has a tradition of seeking to capitalise on emerging technologies. Advances in monoamine research in the sixties and seventies and the identification of a link between the dopamine blocking effects of neuroleptic drugs and their potential to exert an antipsychotic effect have offered an irresistible temptation to postulate a dopamine hypothesis of schizophrenia (Creese et al. 1975), the status of which has fluctuated over the years but which has also shown a remarkable resilience in the light of more recent findings from tomographic imaging techniques.
In a recent review of the current status of the dopamine hypothesis, Reynolds (1989) suggests that, although there is no unequivocal evidence for a dopamine hyperactivity theory as the cause of schizophrenia, increased dopaminergic activity may be a consequence of a neuronal abnormality elsewhere in the brain, e.g. deficits in the fronto-temporal limbic system could disinhibit dopamine neurones in the mesolimbic system. The scope for further enquiry into the role of dopamine systems seemed however to have narrowed considerably.

Two new technologies have stimulated renewed interest in the pathology of schizophrenia. Firstly, the increasing sophistication of brain imaging techniques has permitted a more detailed examination of gross anatomical and functional changes in the brains of patients with schizophrenia, with all the advantages of a non-invasive, in vivo technique. Secondly, the possibilities now being offered by recombinant DNA techniques suggest that molecular genetics may permit a more precise definition and classification of the disorder. The potential impact of these two new areas of work on future research in schizophrenia is discussed in the rest of this paper.

THE IMPACT OF BRAIN IMAGING TECHNIQUES IN SCHIZOPHRENIA

Early studies using imaging techniques showed an increase in cerebral ventricular size in patients suffering from chronic schizophrenia (Johnstone et al., 1974). An increase in ventricular size is however not invariable and is not a feature in younger patients (Farde et al., 1987). Where an increase has been noted, it has been found to correlate with those variants of schizophrenia associated with a poor prognosis (Weinberger et al., 1980) and a history of perinatal morbidity (Reveley and Murray, 1984).

More sophisticated applications of the initial techniques, such as the analysis of regional spin lattice relaxation times (T1), have stimulated investigations into pathological processes in the brains of patients with schizophrenia. For example, Besson et al. (1987) have shown that, schizophrenic patients with a preponderance of negative symptoms (and hence a poor prognosis) have enlarged ventricles and minimal T1 in the left frontal region when compared to patients with low scores on negative symptoms. They also report T1 changes in the left medial temporal area which may however have been due to treatment effects.

There is some evidence that traumatic head injury associated with ventricular enlargement and atrophy can lead to a schizophrenia-like illness (Callaghan et al., 1988). This would suggest that the type of psychosis that arises as a result of neuropathological change relates more to the age at which that change occurs rather than to any specific characteristic of that change.

Other studies using positron emission tomography (PET) and computerised tomography (CT) have shown reductions in glucose utilisation and in cerebral blood flow in the left frontal area of the brain of schizophrenic patients. The accumulating evidence was therefore suggestive of an organic basis to the cognitive and behavioural deficits observed clinically in chronically disabled schizophrenic patients.

PET scanning is also of particular interest in schizophrenia because it permits the imaging of neurotransmitter receptors and could therefore lead to answers about changes in receptor density in certain areas of the brain, and to new ways of testing the dopamine hypothesis.

The question of immediate interest is whether dopamine D1 and D2 receptor density is increased in schizophrenia, irrespective of the effects of treatment with neuroleptics. Prior to the availability of PET scanning techniques, the only source of information was from analysis of brain slices obtained at postmortem. This meant that the patient sample was older and it was difficult to exclude any contaminating effects of treatment over a lifetime of illness. It is therefore not surprising that measurement of dopamine metabolites, of dopamine, or of dopamine receptors did not provide any conclusive evidence of dopamine hyperactivity. PET scanning offers a unique advantage over these earlier methods as it allows useful information on receptor density to be obtained from younger patients, some of whom would be drug free.

Results have however been inconclusive. Wong et al. (1986) showed an increase in D2 receptors in the caudate and putamen of schizophrenic patients but these findings could not be replicated by Farde et al. Crawford et al. (1986) had also reported an increase in D2 receptor density but their patient sample had received treatment with neuroleptics. There is general agreement that PET studies have not answered the question about receptor density and investigators appear to have turned their attention to the use of PET scanning techniques in clarifying the way in which neuroleptic drugs exert their therapeutic effects.

Most of this work has examined the effects of drugs on D2 receptor occupancy in the striatum (Waddington 1989). This may be of limited value in that the dopamine systems believed to be concerned with the expression of schizophrenic symptoms are sited elsewhere in the brain, i.e. the mesolimbic area which is not easily investigated by this technique, and there are virtually no D2 receptors in the frontal or temporal neocortex - areas implicated in other studies.

There has been some interest in the study of D1 receptors and the extent to which a particular neuroleptic drug occupies D1 rather than D2 receptors has been related to its antipsychotic potential and to the likelihood of the emergence of extrapyramidal side-effects.

These studies have nonetheless been able to differentiate between schizophranics and controls, between familial and nonfamilial schizophrenia and even between horizontal and vertical familial transmission (Kaiya et al. 1989). They could also suggest that different patterns...
of cerebral dysfunction may imply different types of pathophysiology. With this in mind, such alternative causative hypotheses such as the retrovirus/transporon hypothesis (Crow 1984) which suggests that a retrovirus (one of a class of agents that are either acquired in utero or incorporated into the genome) could cause schizophrenia, may warrant further scrutiny.

The overall impression from PET and other imaging studies has been that schizophrenic patients show a degree of hypofrontality (as evidenced by decreased blood flow and decreased glucose utilisation) and that hypofrontality correlates with negative symptoms and a poorer prognosis. All studies suggest hemispheric asymmetry in schizophrenia with left sided deficits being prominent. These studies have also strengthened the argument that neuroleptic drugs exert their therapeutic action by virtue of their dopamine blocking effects but have not provided any new evidence to support a dopamine hyperactivity theory of schizophrenia. Another important implication of findings to date is that the detection of significant neuronal deficits in more severely affected patients could suggest that it is no longer correct to view schizophrenia as a 'functional' psychosis (Tyreer & Mackay 1986).

THE CONTRIBUTION OF MOLECULAR GENETICS

Until recently, the only genetic marker studies that had been carried out in schizophrenia were based on the time honoured markers i.e. HLA antigens, blood groups, red cell enzymes and immunoglobulin allotypes. The information derived from these studies was limited.

Advances in molecular biology and DNA technology have allowed the science of genetics to move away from classical markers AND FROM INFERENTIAL PROCESSES on the basis of observable characteristics to the direct examination of the base sequence of chromosomal DNA. It is now possible to link up a particular DNA sequence to any genetically determined disorder without there necessarily being any knowledge of the primary biological/biochemical abnormality.

The techniques involved are derived from recombinant DNA technologies; DNA markers (also called restricted fragment length polymorphisms - RFLP,) are generated by the fragmenting action of certain enzymes (endonucleases) on DNA. This fragmentation by endonucleases is specific to individuals and variations between individuals are inherited in simple Mendelian fashion. The next step in the process is to link a disease to an RFLP, and this would indicate that the susceptibility gene is likely to be sited nearby on the same chromosome. Once the approximate site is known, then the precise site, the sequence and the nature of the protein produced can be identified (Weatherall 1985, 1987). Research into the aetiology of the disorder can then move from questions about 'where' to questions about 'how', i.e. questions about pathogenesis.

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The current state of molecular genetic research in schizophrenia would suggest the following:

i. a genetic contribution to schizophrenia is beyond dispute.

ii. schizophrenia is only one of a spectrum of disorders that can arise as a result of a mutant gene on chromosome five. This would suggest that what is inherited is a predisposition to psychiatric disorder, the qualitative expression of which may depend on other factors which would include acquired brain damage and social factors.

iii. traditional ways of approaching a classification of schizophrenia, and probably of psychoses in general, which have hitherto been based on phenomenology and on clinical course, will be more heavily influenced by an enhanced knowledge of the genetic component of the disorder, given that several genotypes may have the same phenotype and that one genotype may predispose to several phenotypes.

iv. unitary theories of psychosis are likely to be mistaken because the evidence suggests that schizophrenia and manic-depressive disorder do not share a common genetic defect. Defects at a single major locus predispose to only one type of psychosis and, although family members may suffer from other kind of psychiatric disorder from that exhibited by a proband, the type of disorder to which family members are at risk is within the 'spectrum'
of the core diagnosis. Genetics may well end up defining disease entities in psychiatry.

v. there may well be an increase in the potential for genetic counselling of families of patients with schizophrenia.

CONCLUSIONS

The contribution of brain imaging techniques and of molecular genetics to research in schizophrenia has been enhanced by the timelines of their availability. The research stimulated by the dopamine hypothesis had concentrated activity to a narrow area of enquiry which was starting to run out of new avenues to explore. Most investigators had recognised the limits of the dopamine hypotheses, the current status of which has already been discussed, but there was no clear way forward beyond the hypothesis and research activity was in danger of slowing down.

Brain imaging opened the way to new vistas of the gross anatomical features of the brain and to new and exciting ways of exploring neurotransmitter activity. It has provided evidence of neuronal deficits in schizophrenia which challenge its traditional definition as a functional illness and implies that rehabilitation medicine could have as relevant a role as social care based rehabilitation programmes in the continuing care of those patients who need it. This is particularly topical in view of the Government's White Paper on Community Care which lays a heavy emphasis on the differentiation between the health care and the social care components of community care.

Molecular genetics have introduced a new framework for conceptualising psychiatric disorders and, as techniques are refined even further, may lead to a way of classifying psychiatric illness which will represent a radical departure from the traditional methods based on phenomenology and on clinical course. There may also be opportunities for a more precise definition of the molecular basis of the disorder, and that in turn could lead to more effective treatments, especially in those more severely affected patients who show little or no response to neuroleptic drugs.

If both these technologies fulfil their early promise, schizophrenia in the twenty first century may well be very different disease to that described by Kraepelin and Bleuler in the early part of this century.

REFERENCES


