Schizophrenia and neurodevelopment

ABSTRACT—Schizophrenia is characterised by the psychotic symptoms of hallucinations and delusions, accompanied by variable degrees of loss of insight. Whilst there is heterogeneity in the clinical profile, and presumably in the pathogenesis of what is currently called 'schizophrenia', it has become absolutely clear over the past decade that schizophrenic symptoms are consequent upon serious brain dysfunction. This new perspective has laid to rest a variety of 'crazy' theories, including the notion that mental illness was a myth, or that schizophrenia could be caused by faulty child rearing.

The use of dopamine-blocking drugs has led to an improvement in symptom control, and diminished the need for prolonged hospital stays. It was hoped that the clear relationship between antipsychotic activity and dopamine blockade would help to elucidate the pathophysiology of schizophrenia, but to date no consistent abnormalities of the dopamine system have been found. Nevertheless, we have learned much about both the aetiology of schizophrenia and the origin of particular symptoms. Much of this has stemmed from increased understanding of the brain abnormalities underlying the disorder.

Structural brain abnormalities

There is now extensive evidence from both neuroimaging and neuropathological studies that structural abnormalities exist in the brains of individuals with schizophrenia. The most consistent findings are summarised in Fig. 1.

Neuroimaging

Ventricular size. It has been known since the 1930s, from pneumo-encephalographic studies, that some individuals with schizophrenia have an increase in cerebral ventricular size. These changes were thought to represent the end stage of a progressive, degenerative process. More recent computerised tomographic (CT) studies have, however, shown that these changes are non-progressive and are present at or before the onset of psychosis [1], raising the possibility that the cerebral abnormalities occurred early in development [2].

Enlarged cerebral ventricles do not occur in all individuals with schizophrenia, and the overall prevalence within the schizophrenic population is not known, but there is a positive correlation with premorbid psychopathology [3] and with cognitive impairment in early onset cases [4].

Temporal lobe abnormalities. Magnetic resonance imaging (MRI) has also been used to investigate cerebral morphology in schizophrenia. The greater resolution of this method has made volumetric measurement of brain structures possible, and several groups have reported reduced volume of temporal lobe structures. In monozygotic twins discordant for schizophrenia, the twin with schizophrenia has a significantly reduced temporal lobe and hippocampal volume when compared with the control twin [5]. Since monozygotic twins have identical genes, this result implicates a non-genetic factor in the causation of the brain changes.

Neuropathology

Gross abnormalities. Many of the neuroimaging findings have been confirmed by examination of post-mortem brains from individuals with schizophrenia. Reduced brain-weight has been a reproducible finding [6], schizophrenic brains being on average 5% lighter than matched normal controls. Brain length is reduced as well as cerebral volume [7]. Many studies have suggested that medial temporal lobe structures are particularly affected, and some have reported abnormalities in sulcal configuration.

Cellular abnormalities. The brain structures which have shown abnormalities on gross examination have been subject to more detailed histopathological study. In particular, Kovelman and Scheibel [8] reported disorganisation of hippocampal pyramidal cells, and suggested that this abnormality represents defective neuronal migration during development. Jakob and Beckmann [9] found apparently misplaced cells in the pre-alpha cell clusters of the entorhinal cortex, and also interpreted this finding as an abnormality of neuronal migration, occurring in fetal development during the period that these cells take up their final position in the developing brain. Several groups have shown that the gliotic changes that would normally be found in association with cellular abnormalities caused

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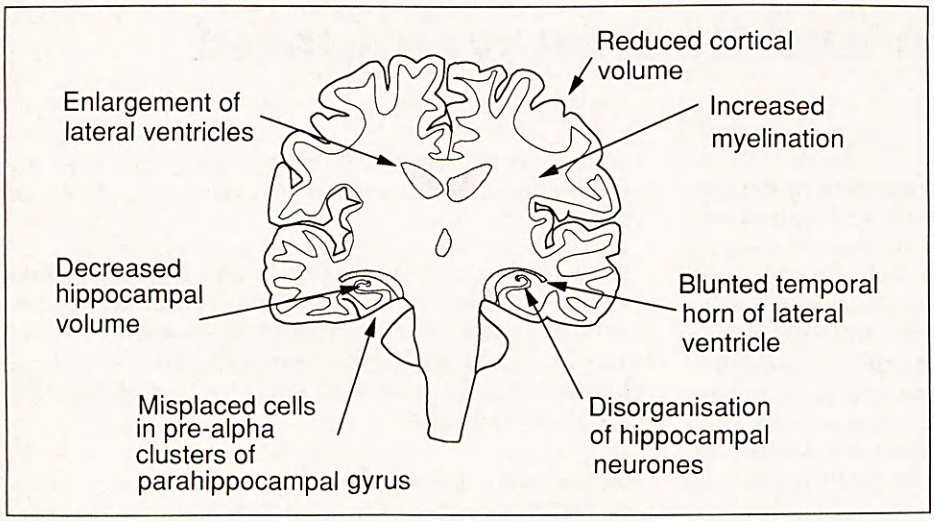

Fig. 1. *Summary of brain abnormalities found in schizophrenia.*

by damage to the central nervous system are absent in schizophrenic brain, adding further support to the idea that these changes occurred in the developing brain, as the adult glial response is absent in early fetal development [10]. The question then arises as to what factors could cause these early brain abnormalities.

Clinical and epidemiological evidence

Obstetric complications and physical abnormalities

Obstetric (ie pregnancy and birth) complications occur more frequently in the history of schizophrenics than in controls [11]. Schizophrenics with a history of obstetric complications are more likely to have enlarged cerebral ventricles [12] and an early onset of illness, but are less likely to have relatives with schizophrenia [13].

Obstetric complications may appear to be the cause of later abnormalities but, of course, they could be secondary to earlier abnormality in the developing fetus. Schizophrenics have an excess of minor physical anomalies, such as curved fingers or low-set ears, which are related to disturbances early in fetal development. These anomalies occur particularly in cases with the 'developmental' profile of early onset and poor premorbid adjustment.

There has been extensive speculation about the time during development when injury to the developing fetus might occur; both neuropathological and epidemiological data suggest that this might be during the second trimester of pregnancy. Recent work examining a somatic marker in schizophrenic monozygotic twins and their normal co-twin showed a difference in fingertip ectodermal ridge count between the twins [14]. These cells migrate during the second trimester, so this evidence supports that from other studies of an insult during this stage of development.

Season of birth and viruses

Schizophrenics are born more often in the winter and early spring than in other seasons [15]. This has led to the idea that a seasonal environmental factor may affect the fetus either antenatally or at birth. The winter excess is not explained by seasonal variation in obstetric complications but there is a suggestion that it may be related to maternal virus infection. Nearly twice as many individuals who later developed schizophrenia were born five months after the peak of the 1957 influenza epidemic, when compared with the average numbers of preschizophrenic births in years when there was no influenza epidemic [16]. It is not known whether the mothers of these individuals actually had influenza at this time (which would have been in the mid-trimester of the pregnancy), although it is known that a large proportion of the population was infected in this pandemic. Very recently, Sham *et al* [17] have shown that the risk–increasing effect of influenza was not confined to the 1957 pandemic. Influenza epidemics in England between 1939 and 1960 had a consistent effect in increasing the number of births of preschizophrenic individuals in the months following the epidemics. A further intriguing finding is that in Britain, schizophrenics of Afro-Caribbean origin seem particularly liable to be born following influenza epidemics. Lack of previous maternal exposure to influenza, and therefore increased susceptibility of mothers during pregnancy, could explain the very high rates of schizophrenia in second generation immigrants (Fahy, personal communication).

Premorbid psychological and social abnormalities

Although the characteristic symptoms of schizophrenia—hallucinations and delusions—rarely occur before adolescence, there is increasing evidence that individuals destined to develop schizophrenia may

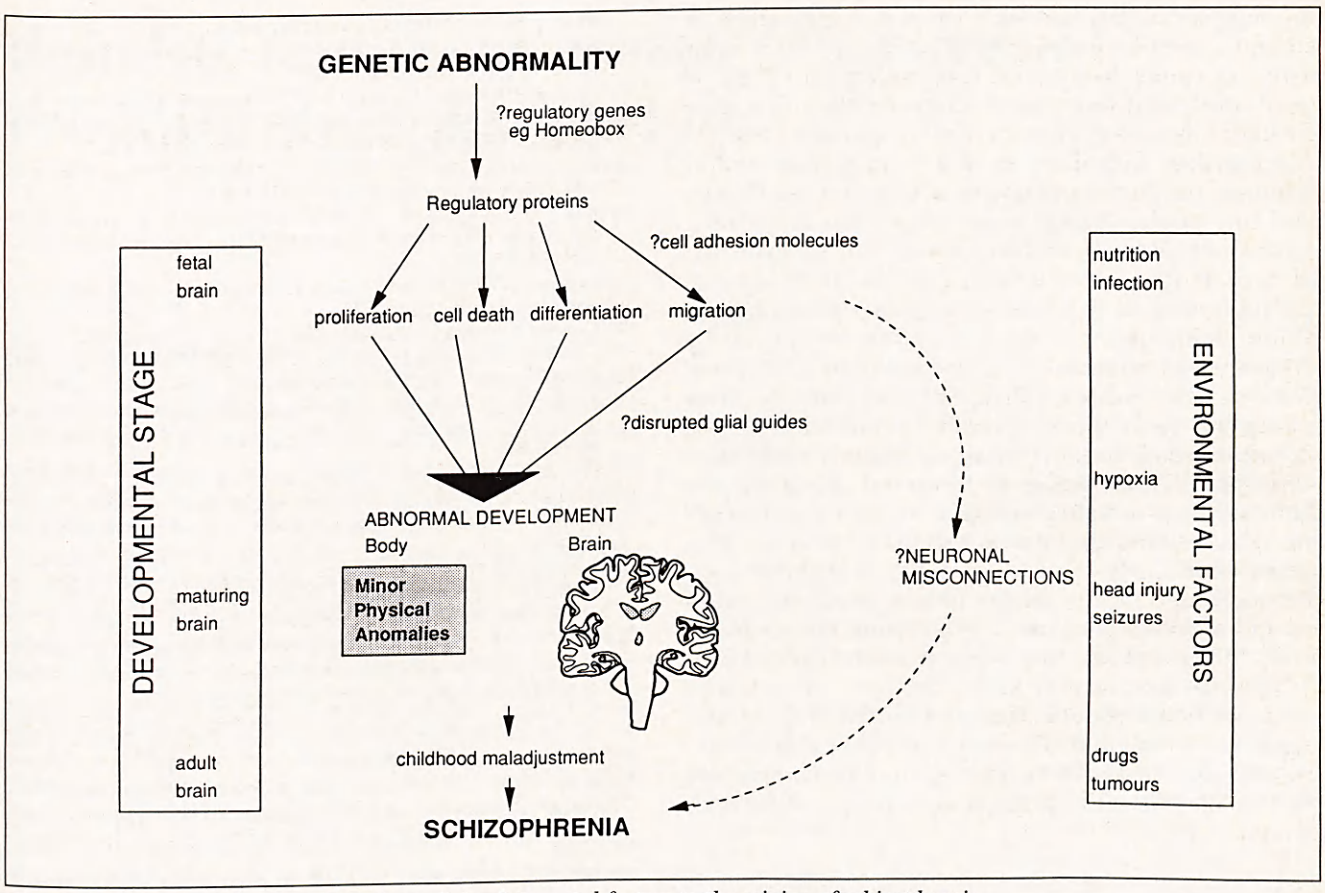

Fig. 2. *Possible contribution of genetic and developmental factors to the origins of schizophrenia.*

have childhood abnormalities of personality or intellectual development. Premorbid IQ scores of schizophrenics are lower than controls [18], and both retrospective and prospective studies have concluded that 25–50% of schizophrenics have behavioural disturbance as children.

A neurodevelopmental theory

When the individual pieces of evidence are put together, a persuasive argument can be constructed that many cases of schizophrenia are neurodevelopmental in origin [19]. This appears to be the case especially for early-onset patients. Early-onset schizophrenia is more likely to occur in males, is frequently preceded by childhood maladjustment, and has a chronic course with more negative symptoms, treatment resistance, and greater cognitive impairment. It is relevant that most developmental disorders, such as autism and dyslexia, are more common in men than women, a finding which may be a result of the increased vulnerability of the male brain to insults during development [20]. There is evidence that the intrauterine environment also influences the development of diseases in middle age, such as hypertension, diabetes and respiratory disorders [21].

Any theory addressing the role of neurodevelopment in schizophrenia must incorporate what is probably the most clear-cut scientific finding in schizophrenia research, namely the strong evidence of a genetic contribution to the disease [22]. It could be that a gene (or genes) coding for aspects of brain development is defective in schizophrenia; therefore an understanding of the genetic control of normal brain development is the first stage in understanding how genes may be involved in the cause of the structural brain abnormalities found in schizophrenia [23]. Figure 2 summarises how genetic and developmental factors might contribute to the origins of schizophrenia.

Are there several types of schizophrenia?

The reader will know that although most cases of schizophrenia present in the second or third decades of life, a substantial minority do not have their onset until middle age or even later. It seems implausible that such cases have a neurodevelopmental origin, particularly since they show other differences; these later-onset cases are more likely to be female, and often have a remitting course with more affective symptoms. These characteristics, together with less evidence of structural brain abnormalities, have led to

the suggestion [24] that such cases may have more in common aetiologically with affective disorders than with neurodevelopmental schizophrenia. Thus, it seems likely that several different conditions may shelter under the umbrella term of schizophrenia.

An analogy with diabetes may be helpful in understanding the heterogeneity of aetiologies which can lead to a similar clinical presentation. Just as few doctors would diagnose diabetes simply on the evidence of a raised blood glucose, few would diagnose schizophrenia on the basis of auditory hallucinations alone. Schizophrenic symptoms can be caused by drugs such as amphetamines, just as the picture of diabetes can be caused by drugs such as steroids. Both conditions can occur secondarily to other diseases: for example, diabetes secondary to pancreatitis, and schizophrenia secondary to temporal lobe epilepsy. Although it is probably mistaken to draw exact parallels, it is striking that early-onset and late-onset diabetes (and early- and late-onset schizophrenia), although superficially similar, have quite distinct clinical and aetiological characteristics. Thus, diseases originally thought of as a single entity may be divided into subgroups as clinical and scientific knowledge advances. Schizophrenia is often thought of as a disintegration of the mind. The very concept of schizophrenia may now be about to 'split up' into its component parts. This latter disintegration is greatly to be welcomed.

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