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The Genetics of Schizophrenia is the Genetics of Neurodevelopment

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Why is the genetic research into schizophrenia so brainless?

Genes are now accepted as being important in the aetiology of schizophrenia (Gottesman & Shields, 1982; McGuffin *et al*, 1987), and over the past decade the emphasis in genetic research has shifted away from genetic epidemiology to searching the chromosomal DNA for the genes themselves. Despite this increasing technical sophistication, the application of linkage analysis to families multiply affected by schizophrenia has been accompanied by the familiar controversy over the exact borders of the adult clinical phenotype (Sherrington *et al*, 1988; St Clair *et al*, 1989). Indeed, the preoccupation of researchers with the vagaries of the clinical definition has resulted in repeated attempts to use genetic studies to determine the relative validity of different operational definitions of schizophrenia (McGuffin *et al*, 1984; Farmer *et al*, 1987). To us, such studies beg the question of how precisely genes are involved in the aetiology of schizophrenia; after all, genes code for proteins, not for auditory hallucinations in the third person.

Sadly, much contemporary genetic research into schizophrenia ignores the fact that over the past 15 years there have been remarkable advances in the neuroimaging and neuropathology of the condition. It is now evident that abnormalities exist in the temporal lobes of many schizophrenics, and that these have their origins in the early development of the brain (Murray *et al*, 1985, 1990; Weinberger, 1987). In our view, it is no longer sufficient just to fit genetic models to clinical data. Any adequate model for transmission must be compatible with the literature concerning brain structure in both schizophrenics and normals, and with current knowledge of neurodevelopment.

It seems increasingly likely that unravelling the causes of schizophrenia will depend upon understanding what goes wrong in the genetic and epigenetic specification of brain development. To this end, we briefly review the evidence for structural brain abnormalities in schizophrenia, and their developmental origin. Next, we consider the processes involved in neurodevelopment. Finally, we speculate on what is known of the molecular genetics of neurodevelopment with respect to the production of the aberrant neuronal phenotype which underlies the clinical syndrome of schizophrenia.

Structural brain abnormalities and their developmental origin

Neuroimaging studies

Many schizophrenic patients show enlargement of the cerebral ventricles on computerised tomography (CT), although the exact proportion of cases and the extent of the enlargement is still disputed (Owen *et al*, 1988, 1989). Recently, magnetic resonance imaging (MRI) has been applied to schizophrenic patients, and the finding of increased ventricular size in a proportion of schizophrenics confirmed (DeLisi *et al*, 1990). In addition, MRI studies have shown reduced volume of temporal lobe structures and of the hippocampus in particular (Suddath *et al*, 1989; Bogerts *et al*, 1990*a*). Nasrallah *et al* (1990) reported an inverse relationship between hippocampal size and lateral ventricular volume.

Monozygotic (MZ) twins discordant for schizophrenia have been examined to ascertain the relative importance of genetic and environmental factors in the causation of the structural brain abnormalities. Thus, Reveley *et al* (1982) showed that, on CT, schizophrenic twins have larger ventricles than their non-schizophrenic MZ co-twins. More recently, Suddath *et al* (1990) examined 15 pairs of discordant MZ twins and confirmed with MRI that the illness is associated with enlarged lateral and third ventricles, reduced volume of the left temporal lobe, and smaller hippocampi.

A developmental lesion

Twin studies show that neither schizophrenia nor the associated neuroradiological abnormalities can be explained by genes alone; environmental agents must be involved. Obstetric complications (OCs) are more common in schizophrenics than in other psychiatric patients or normal controls (McNeil & Kaij, 1978; Lewis & Murray, 1987; Eagles *et al*, 1990), and a number of studies suggest that OCs are associated with ventricular enlargement in adult schizophrenics (Cannon *et al*, 1989; Lewis *et al*, 1989). OCs late in pregnancy or at delivery are the most likely to be

detected, but they may merely be markers of some covert event earlier in development (McNeil, 1987). Whatever the exact timing, the comparative rarity of OCs in the histories of schizophrenics with similarly affected relatives compared with non-familial schizophrenics (Lewis & Murray, 1987; O'Callaghan *et al*, 1990) indicates they are unlikely to be a secondary consequence of a purely genetic defect in neuronal development (Owen *et al*, 1988; Goodman, 1988).

Minor physical abnormalities (MPAs) are trivial abnormalities in ectodermal development (e.g. malformed ears or palate). MPAs occur in excess in patients with developmental disorder (Smith, 1976). Schizophrenic patients also show more MPAs than expected (Gualtieri *et al*, 1982; Guy *et al*,1983; Green *et al*, 1987). As the central nervous system (CNS) is itself an ectodermal derivative, MPAs may reflect events which also occur in the CNS. Like OCs, MPAs implicate a pathological process operating very early in life. Unlike OCs, they are found more frequently in familial schizophrenics (Waddington *et al*, 1990), and the possibility that MPAs reflect genetically controlled events is discussed below.

Thus, several lines of evidence suggest that pathogenic processes in schizophrenia are active many years before the onset of the florid psychotic illness, during the vulnerable period when the brain is still developing. Therefore, in order to understand how the abnormalities seen in the brains of some schizophrenics may have arisen, it is necessary to understand the processes which determine brain development.

Brain development and the neuropathology of schizophrenia

The development of the human brain from a group of cells to the adult organ is a staggering undertaking. In the human cerebral cortex alone there are around 10^{10} neurones and perhaps 10 times as many glial cells (Blinkov & Glezer, 1968). The neurones, with over 10 000 connections per cell (Kuffler *et al*, 1984), constitute the computational networks of the brain; glial cells have a variety of supportive functions in the adult CNS and play a primary role in neuro-development (Kuffler *et al*, 1984). Despite its complexity, neurodevelopment can be considered in terms of the basic principles of developmental biology: cells proliferate, migrate, differentiate into mature forms, and, lastly, a proportion die before the adult pattern is established. The process of selective cell death is particularly important, and Kolb (1989) has compared neurodevelopment with the creation of a sculpture, either by chiselling away unwanted parts of a large block, or by starting with granules of sand and glueing them together to form the desired shape. The brain is formed using both strategies: firstly, building up a prototype with excess cells and connections, and then honing it down to the desired construction. In the human embryo, at around 14 days, chemical signals cause ectodermal cells to divide and form a sheet known as the neural plate. This invaginates along the length of the embryo, folding it on itself to form a hollow tube which is the precursor of the entire CNS. Elongation and circumferential growth create the subdivisions of the adult CNS. Proliferation, migration and differentiation occur in the radial plane, the thickness of the tube, and give rise to the laminated cell structures characteristic of the regions known to be abnormal in schizophrenia.

Cell proliferation

Both neurones and glia are generated in proliferative zones which appear adjacent to the inner wall of the neural tube. Mitosis and cell division always occur away from the ventricular surface of this zone, and newborn cells accumulate outside the ventricular zone, in a centrifugal fashion. The basic structure of the spinal cord (Nornes & Das, 1974) and the CA1, CA2 and CA3 regions of the hippocampus (Nowakowski & Rakic, 1981) develop in this manner, with the original young neurones being displaced away from the ventricular surface as more are produced by the ventricular zone.

Thus, neurones and glia are produced as clones from a small number of autonomous progenital cells (Wetts & Herrup, 1982; Temple & Raff, 1986).

We noted earlier that MRI studies have shown decreased volume of the temporal lobes and hippocampi of schizophrenics. Neuropathological studies confirm this (Bogerts *et al*, 1985, 1990*b*; Falkai & Bogerts, 1986; Jeste & Lohr, 1989). The question as to whether the decreased volume is due to developmental or degenerative processes is partly resolved by looking at glial cells. Gliosis is the usual glial-cell reaction to neuronal damage, except in the foetus; its absence in most, but not all, schizophrenics (Falkai & Bogerts, 1986; Bruton *et al*, 1990) raises the possibility of a defect in cell proliferation in the developing brain, particularly affecting the hippocampal formation. This is a phylogenetically ancient structure which develops exclusively from the ventricular zone (Nowakowski & Rakic, 1981). The decreased cell numbers found in the hippocampi of schizophrenics (Falkai & Bogerts, 1986; Jeste & Lohr, 1989) may be a consequence of abnormal control of proliferation in the ventricular zone, either generally or affecting cells destined for a specific site.

Cell migration

Young cortical neurones migrate across an intermediate zone to produce the cortical plate from which the mature cerebral cortex develops. The cells forming the cortical plate are arranged in such a way that the first to be generated remain nearest to the proliferative zone and subsequent generations are to be found progressively further away. This 'inside out' pattern of neurogenesis is characteristic of the development of laminated structures (Hickey & Hitchcock, 1984), and clearly derives from a more complex migratory process than the passive displacement of cells destined for the spinal cord. How is this migration controlled?

Neurones en route to the cortex and cerebellum are intimately associated with elongated glial cells throughout migration (Rakic, 1971). These cells are known as radial glia because of the way in which their processes stretch from the ventricular to the pial surfaces like the spokes of a wheel. Radial glia act as guides for migrating neurones, providing both support and directional information (Eckenhoff & Rakic, 1984). Their interaction with neurones involves several stages. Initially, the young neurone becomes opposed to the glial fibre. Then it migrates along the glial fibre, always away from the proliferative zone, through the intermediate zone to the cortical plate. Finally, contact between the two cells is severed at the correct time and, therefore, position. Once this has occurred, another young neurone from the proliferative zone becomes attached to the fibre and remains so until it has passed the position of its predecessor, thus establishing the columnar architecture of the cortex.

If neuronal migration is disrupted, an abnormality in cell position results. Kovelman & Scheibel (1984) claimed to find such positional disarray of the normally regimented ranks of pyramidal neurones in the CA1/CA2 regions of the hippocampus in schizophrenics. Two subsequent studies failed to find a statistical difference in neuronal disorganisation between schizophrenics and controls, although one of these did report greater disarray among those schizophrenics with a more severe psychosis (Altschuler *et al*, 1987; Christison *et al*, 1989). More definitely, Jakob & Beckman (1986) noted, and Falkai *et al* (1988) confirmed, that pre-alpha neurones normally located in the superficial layers of the entorhinal cortex are displaced deep to their expected position in the brains of some adult schizophrenics. This was particularly true of those cases which present before age 25 years.

A defect in control of embryonic neuronal migration is an appealing explanation, particularly since a variety of rare disorders of cell migration have been associated with schizophrenia (Reveley & Reveley, 1983; Lewis & Mezey, 1985; Lewis, 1987; Blackshaw & Bowen, 1987). Since it is the interaction between neurones and glia that determines migration (Hatten, 1990) it is possible that a defect may lie at their interface. It has been suggested that this cell–cell interaction may be affected in schizophrenia (Conrad & Scheibel, 1987; Nowakowski, 1987) and that the mechanism may involve cell surface glycoproteins called cell adhesion molecules (CAMs); these are discussed later.

Differentiation and connectivity

Differentiation of cells in the nervous system is extraordinarily complex, and includes the generation of many cell types and formation of precise connections. Abnormal cell types have not consistently been described in schizophrenia, but abnormal connections have been considered a possible cause (Randall, 1983; Goodman, 1989). Connections are formed by growing axons which have specialised structures at their tips known as 'growth cones'. These are highly dynamic (Raper *et al*, 1988) and axonal growth is dependent upon the stabilisation of structural microtubules within them, a process itself dependent upon regulatory proteins (Matus, 1988). The factors which guide the growth cone towards the correct target include mechanical constraints, growth over pre-formed glial structures, electromechanical forces, and attraction towards sources of specific chemicals, probably CAMs (Thanos *et al*, 1984; Trisler & Collins, 1987). The growing axons seem to feel or 'sniff' their way to their targets (Raper *et al*, 1988; Stirling & Summerbell, 1988). Once a pioneer reaches its target, changes in CAM expression on its surface attract other axons to follow.

Patterns of connections are further honed after birth by the function of the network itself. For example, in the visual system, the detailed connections of axon terminals in the lateral geniculate nuclei and visual cortex depend upon the quality of visual experience during a critical neonatal period (Hubel & Wiesel, 1970; Greenough *et al*, 1987).

Myelination of axons, a function of mature oligodentroglia, continues well into adolescence (Yakovlev & Lecours, 1967). The ongoing process of myelination provides one way of explaining the late behavioural consequences of an early brain lesion in schizophrenia (Randall, 1983; Weinberger, 1987). For example, Benes (1989) has shown the appearance of strikingly increased myelination of the

subicular and pre-subicular regions during late adolescence. These structures have a strategic location within the corticolimbic circuitry of the brain; the subiculum receives its principal input from the CA1 sector of the hippocampus, a sector which we noted earlier may contain abnormally positioned cells in schizophrenia. Many authorities believe that a dysfunction of the septo-hippocampal system is crucial to the genesis of schizophrenic symptoms. Thus, myelination of parts of this circuitry may in some way permit a pre-existing but latent defect in the hippocampus to become manifest clinically.

Cell death

It was formerly thought that the factors discussed above combined with great economy to produce the desired connections between cells. This no longer appears to be the case. Developing axons form many transient connections during development. These exuberant connections are eliminated by several types of regressive processes and between 30% and 40% of all cells generated in the nervous system die by the time it is mature (Cowan *et al*, 1984). This process is dependent upon trophic factors such as nerve growth factor (NGF) produced by target cells as well as by the formation of functioning connections (Oppenheim, 1981; Henderson *et al*, 1986). Thus, like birds competing for food in the winter, those neurones that lose out in the race to target cells die. Similarly, some axons' collaterals are pruned (O'Leary & Stanfield, 1985) and terminal arborisations of axons or dentritic trees shrink (Wiesel, 1982), with consequent decreases in synaptic densities (Oppenheim, 1981; Rakic *et al*, 1986).

Benes *et al* (1986) found neuronal density to be lower in schizophrenics in layer IV of the pre-frontal cortex, layer V of the cingulate gyrus, and layer III of the motor cortex. They suggest that these abnormalities could have arisen from "an accelerated process of neuronal drop out early in life, perhaps related to a perinatal insult". Benes & Bird (1987) then reported increased numbers of vertical axons in the cingulate cortex of schizophrenics, a finding compatible, as a compensatory phenomenon, with decreased death of primitive neurones. Similarly, Deakin *et al* (1989) attribute the abnormally dense glutamatergic innervation which they postulate in the frontal cortex of schizophrenics to "an arrest or failure of the process by which transient callosal projections normally are eliminated during development". When extra targets for growing axons are provided experimentally, neurones normally destined to die then survive; such a process could provide another explanation of persistence of the heterotopic pre-alpha cells in schizophrenia, discussed above.

Genetic controls in neurodevelopment

At least 30% of human genes are expressed exclusively in the brain (Sutcliffe *et al*, 1984). However, there are far more cells in the CNS than there are genes, and even this massive commitment is not enough for the nervous system to be organised in a point to point fashion under direct genetic control. Instead, brain development involves a cascade of genetic and epigenetic controls, with genes regulating each others' expression, and interacting with local environmental factors to produce an array of regulatory proteins.

We are beginning to learn about the control of the early stages in the process whereby cells of the ectoderm become committed to forming the human CNS. Work on Drosophila has identified several genes whose inactivation leads to a striking hyperplasia of the CNS (Ghysen & Dambly-Chaudiere, 1989).

It appears that 'neurogenic' genes allow a subset of ventral ectodermal cells to become neuroblasts, and then, through lateral inhibition, impose a different fate on the neighbours of the committed cells by preventing them from also becoming neuroblasts. Such genes are highly conserved through phylogeny and it seems quite possible that similar mechanisms of cell specification operate in the human embryo.

'Homebox' (Hox) genes comprise a multigene family whose members play an important role in many animal phyla, specifying patterns in development and particularly the formation of segments. Segmentation acts like a simple ground plan of development; once segments have formed, each one then goes on to develop specific structures, again dependent on gene expression. The original pattern may be obscured as development increases in complexity. Parts of the CNS develop from a simple segmented pattern, so it might be expected that Hox or related genes will modulate particular patterns of gene expression and regional differentiation (Schugart *et al*, 1989). For example, in the mouse, expression of four Hox-2 genes in the developing hind brain shows a segmented pattern, with the limits of expression of these genes being coincident with structural segment boundaries (Wilkinson *et al*, 1989*a*). Thus, these genes appear to be specifying segment phenotype in the hind brain.

Interestingly, the sequence of these Hox-2 genes on the chromosome is the same as their sequence of expression in the tissue. This arrangement, found for

all Hox genes, probably occurs as the genes are activated in temporal sequence during development. Rakic (1988) suggests that in primates at least two sets of such regulatory genes control the formation of the basic cytoarchitectonic structure of the cortex. One set parcels proliferative units within the ventricular zone into a protomap of basic cytoarchitectonic areas in the cortex and controls the number of young neurones generated. A radial glial scaffolding simply translates this map from the ventricular zone to the expanding cortical plate. After the number of proliferative units is established, other homeotic selector genes regulate the individual cellular phenotypes within that unit.

A family of Hox-like genes, the POU-domain genes, has been described (He *et al*, 1989). These exhibit distinct temporal and spatial patterns of expression during brain development in the rat. Certain of these genes (Brn-2 and Tst-1) are widely expressed in the proliferative zone and early cortical plate. Later their expression is restricted to different layers that reflect the mature laminar patterns. Thus, these genes appear to be involved in the generation of neurones in the proliferative zone and in their subsequent migration to the cortex. Both these processes may go awry in schizophrenia (Jeste & Lohr, 1989; Falkai *et al*, 1988) and one can see how a mutation in such a gene could underlie the neuronal phenotype found in the condition.

Other types of genes are implicated in mammalian embryonic development; these include zinc-finger genes and oncogenes. Zinc-finger genes, such as Krox-20 in the mouse, encode a type of protein found in several transcription factors and so it is likely that the protein encoded by Krox-20 regulates the expression of other genes (Chavrier *et al*, 1988). In the mouse hind brain, expression of Krox-20 parallels but precedes the segmented structure seen during development (Wilkinson *et al*, 1989*b*), consistent with the gene having such a regulatory role. Most oncogenes are involved in self-proliferation, some in cell differentiation. Greenberg *et al* (1990) have identified a T-cell oncogene on chromosome 11p which is expressed segmentally in the mouse hind brain early in embryonic development and subsequently in other tissues, including certain cell layers of the hippocampus. Genes such as this that are expressed in the hippocampal formation are particularly interesting in view of the post-mortem studies of schizophrenia mentioned above which implicate a developmental abnormality in this structure (Jakob & Beckman, 1986; Falkai *et al*, 1988).

We have some knowledge of the control of hippocampal and cerebellar development in mice because these structures are predictably affected by well characterised single gene defects causing abnormal cellular migration and heterotopic cells (Caviness & Rakic, 1978; Nowakowski, 1987). In NZB/BINJ mice, young neurones migrate too far, while in the Hld, dreher and reeler mice, the abnormally positioned cells have not migrated far enough. This is reminiscent of the cytoarchitectonic findings in schizophrenia, and several authors (Nowakowski, 1987; Conrad & Scheibel, 1987) have commented on the possibility that these mutations may serve as models for some process which occurs in the disorder.

Cell adhesion molecules

As mentioned previously, migration of young neurones depends upon their interaction with radial glia. This interaction is mediated by CAMs, which are expressed on cell surfaces and which bind to each other, thus linking cells together (Edelman, 1986). CAMs are a large family of glycoproteins whose functions are crucial to the migration of cells; in the adult, CAMs maintain the mature form (Crossin, 1989). The study of CAMs and morphology (Edelman, 1988) is beginning to explain the paradox by which a one-dimensional genome can control the formation of three-dimensional structures. Over 30 different CAMs have been described, comprising these main families. Some have a variety of forms (Murray *et al*, 1986), resulting from changes in messenger RNA originating from a single gene (an epigenetic mechanism), and changes in the amounts of sialic acid associated with the protein core (a post-translational modification).

The role of CAMs in cell migration may be of relevance to schizophrenia. In normal development, cerebellar granule cells assume a complex, regular configuration by translocating along specialised radial glial cells (Rakic, 1971). In the weaver mouse mutant, this process fails to occur and young granule cells do not migrate. At least four separate CAM adhesion/recognition systems are involved in granule cell migration (Lindner *et al*, 1983; Hatten *et al*, 1984, 1986; Hoffman *et al*, 1986; Edmondson & Hatten, 1987) with both these neurones, and the glial cells, expressing adhesion molecules. One of these, termed 'astrotactin', is expressed by granule cells and is necessary for migration (Edmondson *et al*, 1988). Weaver-mice granule cells express less than 5% of the normal granule level of astrotactin and, when examined in microculture systems, weaver granule cells fail to migrate along wide-type astrocytes. However, a combination of weaver glia and wild-type granule cells results in migration as usual. There appears to be a standard mechanism for neuronal migration in different regions of the brain (McConnell, 1988; Hatten, 1990), with the genetic route map

being expressed in the neurones. If this holds true in studies of other mutants where migration is abnormal, then this may have implications for schizophrenia.

Cell adhesion molecules are also important in the establishment of connectivity. Laminin, a CAM associated with the extracellular matrix is expressed along the pathway of the embryonic chick optic nerve while axon outgrowth is occurring (Cohen *et al*, 1987), but the expression ceases once the nerve has developed. Interestingly, in species such as goldfish where nerve regeneration in adults occurs, laminin continues to be expressed throughout life (Liesi, 1985). Development of precise connections may also depend upon the presence of CAMs. By keeping axons tightly bundled while they grow, the task of reaching the correct targets is simplified, just as it is easier to thread a needle with a fresh thread rather than a frayed one. Finally, in the genetic mutant mouse 'staggerer', where cerebellar connectivity is abnormal, Edelman & Chuong (1982) demonstrated a specific abnormality in the major neuronal adhesion molecule, N-CAM. N-CAM is associated with a large amount of polysialic acid in the normal embryo and this proportion decreases markedly as development proceeds, rendering N-CAM in the adult more adhesive. In the homozygote staggerer cerebellum, this embryonal to adult conversion did not occur by 21 days after birth, and as a result the neuronal circuitry was abnormal.

In such processes we now know the gene products involved, CAMs, where and when these products are expressed, the effects of perturbations of that expression and, for N-CAM at least, we know the locus of the gene on human chromosome 11 (McConville *et al*, 1990). It is hardly surprising that researchers have already looked at CAMs in schizophrenia. Lyons *et al* (1988) measured N-CAM in the serum and cerebrospinal fluid (CSF) of patients with schizophrenia and found increases in a serum fragment of N-CAM compared with controls. Adult CSF is, however, a long way from the micro-environment of hippocampal development, and caution must be used in interpreting the significance of such CAM changes.

Cell adhesion molecules may have a more prosaic use to psychiatric geneticists. It is quite possible that some of the minor physical abnormalities (MPAs) common in schizophrenics are due to processes involving abnormal ectodermal expression of CAMs. If this is so, then they may have some genetic aetiology in common with the perturbed neurodevelopmental processes we believe to be fundamental to schizophrenia; that MPAs are more common in familial than non-familial schizophrenia (Waddington *et al*, 1990) lends some support to this notion.

As more genes for CAMs become localised, they join other genes important in neurodevelopment as attractive candidates for linkage analysis and association studies. Kennedy *et al* (personal communication) have already excluded linkage to schizophrenia of the Hox-2 gene cluster on chromosome 17. From the neuropathological findings in schizophrenia we would predict that genes expressed later in development may be more likely candidates. With regard to CAM genes, we have noted that considerable alterations occur in both the messenger RNA and the nascent CAM protein, so the area is complex.

A necessary caveat in explaining the neurobiological findings in schizophrenia only in terms of molecular biology and genetics, is that we know that environmental factors are involved in the disease and in some of the models discussed. Herndon *et al* (1971) and Nowakowski (1987) have shown that identical neuronal phenotypes to those which result in the mutant mice can be produced by environmental hazards such as ionising radiation, excessive alcohol, or maternal viral infection, provided these factors operate at the critical period of brain development. Mednick *et al* (1990) have reported that Helsinki residents who were in their second trimester of foetal development during the 1957 influenza-A epidemic had a significantly increased risk of later schizophrenia. Conrad & Scheibel (1987) suggest that neuraminidase-bearing viruses such as influenza could interfere with the sialation of CAMs in a way analogous to the disrupted embryonal–adult conversion of N-CAM seen in staggerer mice. Finally, hippocampal pyramidal cells are very vulnerable to mild anoxia/ischaemia (Brown & Brierley, 1973; Jorgensen & Diemer, 1982) and such damage could permanently alter hippocampal structure.

Conclusion: putting the brain back into genetic research

It is evident that in seeking to understand the genetics of schizophrenia we should not expect to find a gene that codes directly for first-rank or negative symptoms. Instead we may find a defect in the control of neurodevelopment whose end result is a set of structural changes which predispose to later schizophrenia. The complexity of brain development might permit a variety of genetically determined events to produce a similar morphological and clinical phenotype; environmental interference with the same developmental processes may mimic the pathological and psychopathological picture.

Such a hypothesis implies that schizophrenia is aetiologically heterogeneous (Murray *et al*, 1985); indeed, it is possible that it may occur only when an individual inherits several contributory genes or when an individual with one or more abnormal genotypes also suffers foetal adversity. This view is compatible with recent suggestions that familial data in schizophrenia are best explained by some gene–gene or gene–environment interaction (Risch, 1990).

The practical implication of an aetiological model such as we have outlined is that the clinical syndrome of schizophrenia (or even of the schizophrenia spectrum) may not be the most appropriate phenotype on which to carry out genetic analysis – it may be too remote from gene actions. Certainly, it is now obvious that attempting to use heritability data derived from twin studies to determine the most 'genetically valid' definition of schizophrenia is no more useful than it would be to argue over the nature of the chest pain accompanying myocardial infarction in an attempt to resolve the complex genetics of lipid transport. Furthermore, it may not be sensible to carry out linkage studies which take a behavioural definition such as the DSM–III criteria of schizophrenia (or some wider or narrower equivalent) as the only appropriate phenotype. It makes more sense to incorporate measures of cerebral structure or function into the study, and then also seek linkage with the relevant endophenotype (e.g. abnormal temporal lobe structure).

It remains unclear whether molecular genetic techniques, such as the lod score method in multiply affected families, will ultimately prove as successful in schizophrenia as they have in so many medical disorders. What is no longer in doubt is that psychiatric geneticists need to focus more of their effort on understanding the molecular rules governing neurodevelopment and how these may be transgressed in schizophrenia. The brain needs to be put back into genetic research in schizophrenia!

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