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A continuum of psychosis, one human gene, and not much else – the case for homogeneity

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Abstract

The contention of this paper is that psychoses are not a collection of separate and unrelated diseases, but a set of diverse expressions of a single underlying entity. It will be argued that there is a basic homogeneity of pathogenesis, that there are not multiple predisposing genes but a single gene that is associated with significant diversity. Therefore the problem is a unitary one. The challenge is to identify the nature and function of the gene. It will be argued that the gene is that by which homo sapiens has separated from other primate species, and that the diversity arises from selective pressures which continue to act on this specifically human gene.

Keywords: Manic-depressive psychosis; Evolution; Continuum; Sexual selection; Asymmetry; (Schizophrenia)

1. Are there discrete disease entities?

The notion that there are discrete categories of disease is a deeply embedded one. We think in terms of entities, and we are used to the concept of diseases, sometimes with single, e.g. infective, causes. Such habits of thought apply themselves readily to the nosology of psychiatric disease and provide much of the impetus to classifications such as ICD and the successive Diagnostic and Statistical Manuals. It is easy to believe that once there is a word for an entity such as 'schizophrenia' or 'obsessional disorder' that that entity exists in an independent and encapsulated way.

This may be an error. Words can be used as labels for clusters of related characteristics in dimensions of continuous variation. To establish a disease entity as unitary and unrelated to other diseases requires more stringent criteria (Kendell, 1987).

The core of psychiatric nosology – the classification of psychotic illness – is burdened with an unresolved problem of this type. Since Kraepelin (1919) it has been widely held that dementia praecox, or schizophrenia as 'it' later became called, and manic-depressive illness, constitute relatively independent and unrelated diseases. A lot hangs on this assumption. Psychiatric textbooks are organised around separate chapters on schizophrenia and manic-depressive illness. Much of the enthusiasm for systems of operational criteria for diagnosis is generated by the perceived need to distinguish reliably between 'true' schizophrenia and 'true' affective illness. Research programs are designed, refereed and launched on the basis that cases in one category should be included and in the other excluded.

But the assumption of independence may not be justified (Kraepelin, 1920; Crow, 1986; Crow,

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1990). No-one will deny that within the realms of schizophrenic and affective illness there is considerable diversity of presentation and outcome. Variation in symptom pattern (for example in the presence or absence of positive and negative symptoms, thought disorder and affective change) in diseases that are described as schizophrenic is considerable, as also amongst those that are labelled as manic-depressive. Whereas there is little doubt that Kraepelin's prognostic distinction between illnesses that present with a major affective component, that often are associated with a relatively complete recovery between episodes, and those which present with psychotic symptoms that cannot be understood as secondary to mood changes, which have a generally worse outcome, is sound, there are considerable doubts whether the distinction can be regarded as qualitative. The question is whether the variation within each of these realms is qualitatively different from the variation between the realms?

The recent literature suggests that the answer to this question is an unequivocal 'no'. There is no assurance that the variation amongst illnesses described as schizophrenic is qualitatively different and unrelated to the variation amongst illnesses described as affective. For example a formal discriminant function analysis of prototypical schizophrenic and affective symptoms (Kendell and Gourlay, 1970) failed to demonstrate a bimodal separation in consecutive series of admissions with psychosis. On the contrary there is plenty of evidence that there are sources of variation that cross the ill-defined boundary between 'schizophrenic' and 'affective' illnesses. The relevant literature substantially weakens the conclusion that any such boundary can be defined other than arbitrarily. But so deeply embedded in the history of psychiatric nosology is the Kraepelinian binary system (the separation of 'schizophrenia' from 'manic-depressive' illness) that these findings and the ensuing discussion have had negligible impact.

In these discussions 'schizo-affective' illness plays a central role. Introduced by Kasanin (1933) to account for the commonplace observation that many illnesses with 'schizophrenic' symptoms also include significant affective disturbance the concept has survived with uncertain boundaries and equivocal status. For adherents of the Kraepelinian binary system the question of whether schizo-affective disorder really belongs to schizophrenia or is a variant of affective illness is a meaningful one. Such views lead to attempts to demonstrate that some schizo-affective psychoses are really schizophrenic and some are really affective. But the literature to be reviewed below records no success for such endeavours. The contrary view is that the existence and survival of the concept of schizo-affective disorder together with its ill-defined (and perhaps indefinable) boundaries undermine the Kraepelinian binary system; these considerations also challenge the more general view that nosologically distinct psychotic disease entities can be identified. The creation of the concept of schizo-affective disorder (and the subsequent failure to either subdivide or demarcate it from the Kraepelinian prototypes) exemplifies the crisis of the quest for categorical disease entities amongst the psychoses.

2. Recent family and outcome studies

Seven studies have approached the problem from the standpoint that the aetiology is genetic by investigating the relationship between form of illness in proband and first degree relative:

(1) Odegaard (1972) studied a consecutive series of 1378 probands admitted to the Gaustad Hospital in Oslo and classified illness in them and their relatives according to criteria that included reactive, paranoid and other psychoses as well schizophrenia and manic-depression, and also considered the problem of schizo-affective illness. He concluded that 'evidently our conventional diagnoses have a certain genetic background, but the findings are hardly suggestive of any specific or simple form of inheritance....There is (in our material) a gradual transition between this schizo-affective group and the remaining 'nuclear' group.....Actually we seem to deal with a continuum without natural borderlines, but with a gradual series of transitions from the extreme schizophrenic to the affective pole'.

(2) Penrose (1991) reported a survey of 5456 pairs of relatives admitted to the Ontario psychiat-

ric hospitals between 1926 and 1943 and concluded that 'Schizophrenia, affective psychosis, senile psychosis, Huntington's chorea and mental defect are shown to be conditions which remain significantly true to type when mental disease occurs in different members of a family. As a rider to this, however, it is found that schizophrenia and affective psychosis are not very distinct entities and groups of closely related familial cases frequently include both diagnoses'.

(3) Gershon et al. (1982) found schizo-affective forms of illness to represent the most serious liability in a study of affective disorders, and later (Gershon et al., 1988) found illnesses defined by the same criteria to be present in the relatives of patients with DSMIII schizophrenia. They concluded that 'there must at least be gradations of affectivity and schizophrenicity'.

(4) Angst and his colleagues began with a study of schizoaffective disorder (Angst et al., 1983) and progressively have moved to the conclusion (Stassen et al., 1988) that it forms but part of of a spectrum that includes both schizophrenic and affective psychoses -'typical syndrome patterns appear in both populations (probands and relatives). but there is no clear breeding true of either schizophrenia or affective disorder'.

(5) Maier and Lichtermann (1991) and Maier et al. (1993) using RDC criteria and a classification into schizophrenia with and without affective change, schizo-affective disorder, bipolar and unipolar illness concluded that there was substantial overlap in form of illness between adjacent categories. Unipolar schizo-affective and unipolar affective illness were both increased in the relatives of patients with schizophrenic as well as affective psychoses. No non-arbitrary dividing lines could be drawn.

Even those workers who have been amongst the strongest adherents of the Kraepelinian binary system have contributed studies that call the concept in doubt:

(6) For example Cloninger et al. (1985) and Cloninger (1994) have defended the classical Kraepelinian concept arguing that with particular restrictive criteria a bimodal distribution amongst psychotic illnesses can be demonstrated and that there are separate disease spectra of affective and schizophrenic illnesses. But as co-author in a study by Taylor et al. (1993) of 1895 first degree relatives of 166 patients with DSMIII schizophrenia and 71 patients with affective disorders Cloninger found that the risks for schizophrenia and affective disorders (unipolar melancholia and bipolar disorder combined) were significantly higher in the relatives of the schizophrenic probands and of the affective probands than in the relatives of the controls and concluded that 'Despite limitations these... analyses...suggest some familial relationship between schizophrenia and severe forms of affective disorder'.

(7) In the Roscommon family study Kendler et al. (1993) examined the risk of schizophrenia in the relatives of 285 patients with a clinical diagnosis of schizophrenia and 99 patients with a diagnosis of severe affective illness. They concluded that 'schizophrenia shares a familial predisposition with a spectrum of clinical syndromes that includes schizoaffective disorder, other nonaffective psychoses, schizotypal personality disorder, and probably psychotic affective illness, but not nonpsychotic affective illness'. In discussing the 'spectrum concept of schizophrenia' Kendler et al. (1995) conclude that 'schizophrenia and psychotic affective illness could be clearly assigned to the two extremes...' and that within the spectrum 'these five disorders' (i.e. including schizophrenia and psychotic affective illness) 'are manifestations, of varying severity, of the same underlying vulnerability. This vulnerability is strongly transmitted within families'. It seems that few, if any, psychiatric geneticists are now able to defend the position that schizophrenia and psychotic affective disorders represent independent and unrelated disease categories.

The conclusion to be taken from these studies is that no non-arbitrary dividing line can be drawn between schizophrenic and affective psychoses. In terms of phenomenology the point is well made in a study of 46 consecutive admissions with psychosis to the New York State Psychiatric Institute by Endicott et al. (1982) classifying the illnesses by different diagnostic criteria. By the most restrictive (Taylor and Abrams, 1975) criteria 4 patients were diagnosed as suffering from schizophrenia, while by the most liberal criteria (Astrachan et al., 1972)

44 of the patients were given such a diagnosis. The eleven fold difference between the two sets of criteria was accounted for by patients who, by the modal Research Diagnostic Criteria, were suffering from schizoaffective or affective psychoses.

From a longitudinal perspective Marneros and colleagues (1995) have reviewed a substantial body of their own work and conclude that a clear dichotomy into two diseases, or even three diseases, with the entity of 'schizo-affective disease' is highly questionable. Overall the conclusion that there are no disease entities, only continua of variation, is not disproved by the recent literature. But the question must be faced: What is the nature of these dimensions of variation? To what variation in the 'normal' population do they correspond, and what is the nature of the normal function that underlies them?

3. Constancy of incidence over time and place: 'the anthropo-parity principle'

In contrast to the conclusion that no clear boundaries between psychotic states can be drawn are findings concerning homogeneities in incidence. From the WHO Ten Country Study of Incidence Jablensky et al. (1992) drew the conclusion that: 'schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures and have clinical features that are more remarkable by their similarity across cultures than by their difference'.

These authors found that as the criteria for a diagnosis of schizophrenia were more closely drawn (by the presence of first rank symptoms) the differences between centres that were apparent with the use of broader criteria became less, and lost their statistical significance. One possible interpretation is that the differences with the broader definition are a consequence of the very great difficulties (for example as a consequence of differing availabilities of treatment facilities and traditions of seeking care in the different centres) that exist in ensuring that illnesses of comparable severity are included, while the findings with the more restrictive criteria reflect a true underlying uniformity of incidence across cultures. According to this interpretation the value of Schneider's nuclear symptoms is that they define a level of severity (or incomprehensibility) at which it is highly likely that an individual who experiences these symptoms for the first time will seek help.

If one accepts that the WHO studies demonstrate relative homogeneity of incidence across cultures then it is difficult to believe that there have been significant changes over time. If there had been such changes there is no cogent reason why they should have been in the same direction and of the same magnitude in populations (e.g. the Japanese, Indian and European) that have been separated for thousands of years. The obvious interpretation is that rates of onset of psychosis (at least as defined by the presence of nuclear symptoms) are constant with respect to time and space. But if this is true of schizophrenia restrictively defined, and no categorical distinction can be made between this and other psychoses, it seems that the same conclusion must apply to psychotic illness in general. Perhaps psychotic illness (in contrast to common physical ailments) is a characteristic of human populations, i.e. a component of sustained variation, an affliction of humanity.

There are some challenges to the conclusions of the WHO studies. For example there have been claims (Walsh and Walsh, 1970; Kelleher et al., 1974) for high first admission rates in the West of Ireland. The relevant research has been reviewed by Cabot (1990) who criticized the methods of case collection and cross-cultural comparisons, and expressed the hope that 'Ireland will not henceforth be considered a high prevalence area for schizophrenia without more reliable research'. A prevalence study (Ni Nuallain et al., 1990) concluded that 'the continued hospitalization of symptomatically recovered cases has given rise to the mistaken impression that the prevalence of schizophrenia is unduly high in Ireland. The work reported here indicates substantial differences between the results of case ascertainment by hospital admission data compared with those arrived at by standardized interview diagnostic techniques'.

Similarly high rates of schizophrenia have been reported in parts of Croatia (Crocetti et al., 1964; Lemkau et al., 1971). But a recent study (Folnegovic and Folnegovic-Smalc, 1992) aimed at investigating differences in prevalence rates in different parts of Croatia concluded that economic migration and negative selection in the domestic

population were likely to be the most significant factors in differences in prevalence. Reviewing these findings Cooper (1994) concluded that 'nosocomial factors, combined with the effects of selective migration, would seem on present evidence to offer a more likely explanation' of the observed variation.

The claims of Book et al. (1978) for high prevalence rates of schizophrenia in an isolated population in the North of Sweden focus on a single large family constellation. It may be therefore that genetic segregation accounts for this high rate although it is still curious that few families of similarly high density and homogeneity of diagnosis have been reported from elsewhere.

Much has been made of an apparent excess of presentations of schizophrenia amongst Afro-Caribbeans (particularly males) in two urban areas of the United Kingdom (Harrison, 1991; Wessely et al., 1991). However assessments of the numbers of cases to be expected amongst the West Indian subpopulation depend critically upon estimates of its size, and there are serious doubts (Glover, 1993) that this has been accurately estimated in the relevant census data.

4. Are there secular changes in incidence?

There have been claims for a recent decrease in the incidence of the disease (Eagles and Whalley, 1985; Der et al., 1990). A major difficulty in assessing such claims is that diagnostic criteria (unless they are standardised as in the WHO studies) may not remain stable over time. If as seems likely no categorical distinction between schizophrenic and affective diseases can be drawn there is obvious potential for drift, and there is evidence (Kendell et al., 1988; Stoll et al., 1993) that an increase in diagnosis of affective disorders has occurred over the relevant period. Turner (1992) has reviewed evidence for relative constancy of clinical presentation of schizophrenia over time in the historical record.

5. Is there evidence for an environmental factor?

Few hypotheses concerning specific aetiological agents have been proposed. These include perinatal complications (broadly defined) and prenatal exposure to the influenza virus. An investigation of a large number of complications of pregnancy and delivery recorded in the 1958 Perinatal Mortality Survey (Done et al., 1991) suggested that these were unrelated to later risk of schizophrenia. In the same survey (Crow and Done, 1992) 945 mothers who were recorded as affected in the second trimester of pregnancy by the 1957 influenza epidemic gave birth to children who had no excess risk of schizophrenia (three children had developed schizophrenia by the age of 28 years, while according to the original claims concerning the risks associated with influenza there should have been 26.5 cases). A review of the literature on influenza in relation to schizophrenia (Crow, 1994b) concluded that there were substantial discrepancies between studies concerning the size of the putative effect, and contradictions between studies (in one case relating to the same data set) concerning its existence. Those studies (e.g. Crow and Done (1992); Cannon et al. (1994)) that examined rates of schizophrenia in the children of mothers who had actually suffered from influenza in pregnancy reached negative conclusions.

Studies aimed at identifying specific environmental contributions to aetiology have therefore been indecisive. Similar conclusions can be drawn from the most recent studies on discordant monozygotic twins (Torrey et al., 1994).

6. Homogeneity of structural brain changes

Three gross changes in the brain have been reported in morphological studies:

(i) Ventricular size is increased (Johnstone et al., 1976; Weinberger et al., 1979).

(ii) Cortical mass (Zipursky et al., 1992; Ron et al., 1992) or brain size (Brown et al., 1986; Johnstone et al., 1989; Pakkenberg, 1987; Pearlson et al., 1989) is decreased.

(iii) Asymmetry is reduced (Crow et al., 1989b; Bilder et al., 1994)

With respect to the increase in ventricular size an important conclusion is that the variance within the patient group is not increased and there is no evidence of bimodality (Owens et al., 1985; Harvey

et al., 1990; Daniel et al., 1991) Although the findings are less extensive it seems likely that this is true also of the reduction in cortical mass and loss of asymmetry. There is no evidence that these changes are present only in a sub-group of patients. If this is true then one must conclude that a degree of morphological change is characteristic of patients with schizophrenia in general, and that the three changes are related. Perhaps a reduction in asymmetry is associated with a restriction in the last stages of cortical development, and, on the basis that there is a decrease in ventricular size as cortical infolding increases, with a modest increase in ventricular volume.

The conclusion to be drawn is that schizophrenia, and by implication psychosis in general, represents an anomaly of brain size, and more specifically of brain shape. This conclusion, paradoxical if schizophrenia is viewed as a 'functional' psychosis, leads on to the concept that the predisposing genes are associated with rates of brain growth. Specifically it is suggested that the problem relates to individual differences in relative hemispheric brain growth.

7. Arguments for a single gene

A number of arguments can be mounted in favour of the view that a single major gene is involved, and that this gene is the same in most if not all cases :

(i) The facts concerning relative homogeneity of the morphological changes, summarised above, suggest that the genetic influence is relatively uniform between cases, and could be exerted by a single gene.

(ii) The commonplace facts of onset and recovery also argue for a simple mechanism. Individuals who have been well become ill, and some at least are then able to make a recovery between episodes. If onset and recovery are to be explained in terms of activation (or over-activation) and repression of particular genes, then it becomes increasingly difficult to explain such transitions the greater the number of genes that are postulated as involved. One gene would do.

(iii) A somewhat similar argument applies to discordance in twins. If this is not environmental then it must be a reflection of a somatic mutation, an 'epigenetic' difference in gene expression, or perhaps a random difference in development. Whatever the genetic contribution simple discordance (one twin ill and one well) becomes more difficult to explain the more genetic steps that are invoked.

(iv) Karlsson (1974) has argued that the high frequency and relative constancy of incidence across populations in the face of a fecundity disadvantage requires a balancing advantage. The gene must have some associated beneficial effect or it would be rapidly selected out of the population, and the advantage is likely to be expressed in an area related to the dysfunction i.e. in terms of psychology. One can postulate that there is more than one gene and therefore more than one advantage, but the balance of advantage and disadvantage are most unlikely to be the same for each gene. Therefore since both are expressed in the same area there will be competition between the alternative genes such that the one with the best balance of advantage to disadvantage will be selected.

(v) Tooby and Cosmides (1990) argue that where a dimension of variation, e.g. in personality, is maintained in the population by selective forces, e.g. by frequency dependent selection, this will depend upon a single gene or genes that are tightly linked on the same chromosome. This is because if more than one gene is involved the coherence of the genetic influence will be randomly disrupted by each recombination that occurs between the genes. For selection to act the phenotype must be consistently expressed. Therefore if as argued above psychosis represents a component of variation in a continuum that relates to an important psychological function, the relevant variation will be expected to be at a single locus or at a small number of closely linked loci.

8. Loss of cerebral asymmetry

But what might the gene be? The clue comes from the findings concerning asymmetry. If the morphological changes in the brain are asymmetri-

cal (Crow et al., 1989a) this could reflect either (a) an interaction between a bilaterally distributed disease process and the normal asymmetries in the human brain; or (b) an asymmetrical disease process. But the fact that the enlargement of the temporal horn in Alzheimer type dementia is bilateral whereas in schizophrenia it is left-sided (reflecting a loss of the normal asymmetry) suggests that (a) is inadequate as an explanation. Enlargement could have been bilateral and it is not. Therefore it seems there is some association between the disease process and the genetic determinants of symmetry/asymmetry.

The possible role of asymmetry is a clue to a solution to the central paradox of schizophrenia noted above. Why if the disease is primarily genetic and is associated with a fecundity disadvantage do the genes persist? Why are they not rapidly selected out of the population? Where is the advantage?

Anatomical asymmetry is a reflection of the fact that the human brain, to a much greater extent than the brains of precursor primate species, is hemispherically specialised (Corballis, 1991). In the course of human evolution functions have been progressively allocated to one or the other hemisphere, and this change has presumably occurred on the basis of selection for some particularly advantageous function. That function it seems must have been language, the neural basis of which shows a high degree of lateralisation. Such lateralisation must be determined by a gene or genes, and is also associated with significant variation. Whereas for most people language is located mainly in the left hemisphere, for a substantial minority it is localised in the right. An outward manifestation is the tendency for most individuals to develop a preference for and greater skill in the use of their right hands, while a minority have a preference and greater skill with the left.

The genetics of handedness have been studied in particular by Annett (1985) and McManus (1985). They can be accounted for by a single additive gene (that Annett refers to as the 'right shift factor') one dose of which biasses the individual to have language in the left hemispere and to be right-handed. Homozygosity for the right-shift factor has a greater effect than a single dose, whilst in its absence cerebral dominance for language with handedness is randomly determined. According to Annett this gene has been the critical factor in the evolution of language. She believes that a heterozygote advantage (balanced polymorphism) situation exists whereby individuals homozygous for presence or absence of the gene are disadvantaged in terms of cognitive ability relative to those who are heterozygous (i.e. have one copy of the right-shift factor). The evidence for this has been disputed (McManus et al., 1993), but the general thesis that there is a relationship between handskill and cognitive ability is supported by a study of 11 year olds in the National Child Development Study cohort. At the left hand end of the handskill continuum it is those who are closest to the point of equal handskill (the point of 'hemispheric indecision') who are particularly disadvantaged. Those who later developed schizophrenic illnesses were found to be closer to the point of hemispheric indecision than the cohort as a whole (Crow et al., in preparation).

9. An X-Y homologous gene?

The right shift factor is a hypothetical gene. A strong case can be made, on the basis of psychometric studies of X chromosome aneuploidies (Crow, 1993a; Crow, 1994a), that a gene influencing cerebral asymmetry is in the class of X-Y homologous genes -that is genes that have copies located on both X and Y chromosomes. This case is supported in a study of 15,000 sibling pairs by an association, weak in magnitude but consistent with the postulated role of a random factor, between sex and handedness (Corballis et al., 1995).

According to this hypothesis an X-Y homologous gene influencing the relative rate of development of the two hemispheres is associated with significant variation in academic ability and personality structure, and a component of this variation represents the predisposition to psychosis. Because, in the case of X-Y homologous genes (except for those located within the pseudoautosomal region) divergence between sequences on the X and Y can take place, such genes may be associated with the presence of a sexual dimor-

phism (Lambson et al., 1992). Such a dimorphism appears to be present in cerebral asymmetry (Bear et al., 1986). Although there is substantial overlap in the distribution between the sexes the mean for males is greater than for females. This sex difference could be relevant to the mean sex difference in the pattern of intellectual abilities, females as a group having greater verbal fluency and males spatial ability (Halpern, 1992; McGlone, 1980). It could also be relevant to the sex difference in age of onset of psychosis (Crow, 1993a).

10. Sexual selection and human evolution

But one must also ask how does such a sex difference arise? Darwin's theory of sexual selection (1871) attempted to explain differences between the sexes (e.g. deer's antlers, the peacock's tail) that could not be explained on the basis of natural selection alone. He suggested that such features had evolved by the mechanism of male competition and female choice, and believed this mechanism was relevant to the Descent of Man. Could it explain the sex difference in cerebral asymmetry, in the distribution of cognitive abilities and age of onset of psychosis? Some differences between the sexes in mate preference are constant across cultures (Buss et al., 1990): whilst both males and females rate intelligence and kindness and understanding highly in a potential mate, males rate physical attraction higher than females and females rate earning capacity higher than males. These differences presumably reflect the differing interests of the two sexes in procreation – males looking for youth and health as indices of fecundity, and females for good genes and paternal investment. Such preferences in turn are reflected in another cross-culturally stable demographic characteristic – a sex difference in age at marriage, and by implication in age of procreation, males being a mean 1 to 2 years older (Crow, 1993a).

These differences have implications for the possible role of sexual selection in the evolution of language and its structural correlate hemispheric specialisation. If the mean age at procreation in males is 1 to 2 years higher than in females then the variants of the gene present on the Y chromosome will be subjected to later selection than those on the X. This might account for a later peak (perhaps corresponding to greater asymmetry) in, or slower rate of, relative hemispheric development in males than females. One can envisage the point of hemispheric maturation as being subject to a 'debate' between the sexes in which males are exerting an influence toward earlier and females toward later maturity, the mechanism being mate selection and the mediators of these effects being the distribution of alleles in the two homologues of the asymmetry gene on the X and Y chromosomes. One possibility is that the gene is associated with a variable number of tandem repeats and that the number of these repeats on the X and Y is distributed around a different mean as has been described in the case of the locus DXS156 (Chen et al., 1994); such repeats might act as control elements affecting the relative rate of hemispheric development.

The key element in this hypothesis is, as suggested by Annett (Annett, 1985), that significant diversity is associated with the genetic determination of cerebral asymmetry and that a balance of advantage and disadvantage is present. The specific version of the hypothesis proposed (Crow, 1993a; Crow, 1993b; Crow, 1995a) is that cerebral asymmetry is determined by an X-Y homologous gene that is subject to sexual selection, and that the variation is expressed as differing rates or maxima of relative hemispheric development. These rates are associated with different phenotypes in terms of cognitive/personality variation, and a component of this variation represents the genetic predisposition to psychosis.

11. Problems of the theory

The weaknesses of the hypothesis are that no gene has been identified and there is no clear prediction of the relationship between degrees of asymmetry and predisposition to psychopathology. Thus in Annett's theory three genotypes (− −), (+ −), and (+ +) together with a random element account for the distribution of relative hand skill. But apart from the conclusion that predisposition to schizophrenia is associated with a failure of hemispheric specialisation (i.e. equal hand skill or ambiguous handedness) no firm

conjectures concerning the relationship between genotype and pathology are made. Nor does the theory give an account of the genetic transmission of predisposition to psychosis including rates of concordance in twins. Predisposition to psychosis clearly represents no more than a small part of the distribution of relative hand skill. What accounts for this restriction? Nor without some modification of Annett's theory can the hypothesis explain the variation within the psychotic spectrum. Some more complex mechanism is required than two alleles of a single gene. One might speculate either that the handedness genotypes represent major variants upon which further quantitative variations (e.g. in number of repeats) in the same gene are superimposed, or that the handedness gene modulates the effects of one or more other predisposing genes. The latter possibility, being more complex, is less parsimonious as an hypothesis.

12. Conclusions

The conclusions can be stated in terms of three hypothetical postulates (Crow, 1995b), conjectures that if true would be significant but also are susceptible to disproof:

Postulate 1: there are no disease entities, only continua of variation. This conclusion is difficult to challenge on the basis of the recent literature, but its implications are far-reaching. In particular it follows that the genetic contribution to psychosis must be variable, i.e. that either there is a high degree of allelic heterogeneity at the disease locus and/or a random element is involved in determining the phenotype. Kretschmer's conclusion – that there is a relationship between variation within the psychotic spectrum and personality variation in the general population is also difficult to avoid. This diversity is apparently maintained under selective pressure and must therefore be significant.

Postulate 2: there are no aetiologically significant environmental precipitants. Apart from the weak and equivocal nature of the evidence for such specific environmental factors as have been proposed, the most decisive arguments come from the WHO study of incidence. Psychosis it seems is a characteristic of reproducing human populations, not of the circumstances or manner in which these populations live. It is an affliction of humanity, and its origins are closely related to those of the species.

Postulate 3: one human gene, the asymmetry factor, contributes substantially to predisposition to psychosis. According to this postulate the asymmetry gene is the critical factor in the process of increasing hemispheric specialisation and the evolution of language. This hypothetical gene is associated with significant variation (although not, as far as is apparent from studies of hand skill, enough to account for the variation associated with psychosis), and is subject to continued selection. There is a case that the asymmetry gene (or right shift factor) is in the restricted class of genes that are present in homologous form on both X and Y chromosomes.

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