

EDITORIAL

## Mutation and psychosis: a suggested explanation of seasonality of birth<sup>1</sup>

The salient problem in the aetiology of the recurrent psychoses is the relationship between genetic and non-genetic factors. The genetic contribution to both schizophrenic and affective illness is well documented by family, twin and adoption studies, but the extent of discordance in monozygotic twins suggests there are also significant non-genetic factors. What these may be remains obscure. Moreover, age of onset probably is not related to a contribution from the environment (Crow & Done, 1986) and some analyses (Rao *et al.* 1981; McGue *et al.* 1986) suggest the non-genetic component is smaller than one might suppose from a naïve interpretation of the findings in monozygotic twins.

The greater the burden of explanation placed on genes, the more difficult it is to understand how these conditions persist at relatively high prevalence in spite of their deleterious effects on fertility. The difficulty is greatest in the case of schizophrenia, where the influence on fertility is profound (MacSorley, 1964; Stevens, 1969; Haverkamp *et al.* 1982), but it is present also in the affective disorders (Vogel, 1979; Baron *et al.* 1982). The paradox has stimulated attempts to identify possible advantages associated with the gene, and thus to explain schizophrenia as a 'genetic morphism' (Huxley *et al.* 1964). According to this view, carriers of the gene, not necessarily themselves affected, possess a physiological or procreative advantage which ensures its survival. However, such an advantage is not easy to identify.

An alternative, perhaps not mutually exclusive, explanation is that the psychoses are maintained by a high rate of mutation. This was suggested for schizophrenia by Böök (1953) and by Lewis (1958). It has been dismissed by Huxley *et al.* (1964) and Penrose (1968) on the grounds that the mutation rate required is too high to be plausible. Penrose estimates a rate of between 1 in 200 and 1 in 2000 per gamete per generation to be necessary to maintain the frequency of the disease, and compares this with an estimated rate of 1 in 100000 for other human genes.

### SEASONALITY OF BIRTH

An influence of the prenatal environment is difficult to exclude. The arguments (Crow & Done, 1986) which suggest that age of onset is independent of discrete environmental events do not rule out that an agent acting *in utero* initiates disease after a delay of many years. Such a possibility is suggested by the apparent effect of season of birth – the small but seemingly consistent increase in risk of psychotic illness among those born in the winter months (i.e. January to March in the Northern hemisphere). The effect was first reported by Tramer (1929); in a recent review Bradbury & Miller (1985) included 42 subsequent studies. On a conservative estimate they considered that 13 of these studies had avoided major shortcomings and ten reported a seasonality effect. Nine of these effects occurred predominantly or exclusively in the winter months, and none in the summer. Bradbury & Miller consider the finding as firmly established.

A number of explanations have been considered. Lewis & Griffin (1981) suggested that seasonality of birth is an artefact of the way that data in such studies are collected and recorded that it is a result of the 'age-incidence' and 'age-prevalence' effects. This possibility has been considered by a number of workers (e.g. Templer, 1982; Watson *et al.* 1984; Pulver *et al.* 1983; Shur & Hare, 1983) and discounted, since the effect is present when these artefacts have been excluded.

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Another explanation is that the seasonal bias arises from the procreational habits of the parents. According to this explanation, parents who transmit a gene predisposing to psychosis are more likely to have children in the winter months. Buck & Simpson (1978) identified 1039 siblings of schizophrenic probands but found no evidence that the former differed from the general population with respect to their birth dates. A more complex possibility is that the effect relates to parental age. There is evidence (Goodman, 1957; Dalen, 1977) that the ages at parturition of mothers of schizophrenics are increased with respect to the general population. This may be relevant to schizophrenia, since month of birth in the general population is related to the age of the mother (Dalen, personal communication), but has yet to be systematically assessed.

If artefacts of ascertainment and deviations in parental procreative patterns can be excluded it has to be considered that some environmental influence, present at or before birth, increases subsequent risk of psychosis. The possibilities which have been mooted (Bradbury & Miller, 1985; Torrey, 1987) include obstetric complications, vitamin deficiencies, intra-uterine infection and environmental temperature. Each of the first three seems likely to show greater variations with time and place than is suggested by the literature on seasonality of birth. Moreover, the relative constancy of prevalence of schizophrenia (Jablensky, 1987) in a number of countries indicates that these factors do not contribute substantially to the incidence of the disease. For these reasons environmental temperature deserves to be considered, although at first sight it is difficult to see when and how it might have an effect.

Month of birth and environmental temperature have been investigated by several workers. McNeil *et al.* (1975) pursued the hypothesis that high temperature might adversely affect maternal nutrition and found no systematic relation of schizophrenia to mean temperature at the time of conception and early gestation. Hare & Moran (1981) found significant negative relationships between birth rates of patients with schizophrenia in the second quarter and environmental temperature in the first quarter, or first half of the year. Such findings suggest an influence relatively late in pregnancy or early in postnatal life. However, in an investigation of birth seasonality in relation to the incidence of infectious disease and temperature Watson *et al.* (1984) found no particular relation to temperature in the year of birth, but schizophrenic births were increased in the years following those with high levels of infectious disease. This suggests an effect prior to conception (Levick, 1985). There has been no systematic investigation of the relationship between schizophrenic births and environmental temperature in the months preceding conception.

## INSERTIONAL MUTAGENESIS AND BIRTH SEASONALITY

An attempt to relate seasonality of birth to the persistence of psychosis is presented in the hypothesis that the effect reflects a high rate of mutation in the psychosis gene, and that these mutations occur at a particular stage in reproduction (Crow, 1984, 1986*a,b*). This hypothesis predicts that the seasonality of birth will be seen particularly in those patients who lack a family history of psychosis. Such evidence as there is supports this contention (Kinney & Jacobsen, 1978; Shur, 1982; Pulver *et al.* 1983; McNeil, 1987). However, the questions remain of how temperature (or any other season-dependent variable) could have an effect on the genetic material of a homeothermic organism, and at what stage such an effect could occur.

The solution proposed is that the changes occur at meiosis and in the male gonads. The extra-abdominal location of the mammalian testis in the scrotum exposes it to temperature changes not encountered by the female gonads. The conventional explanation of this anatomical arrangement is that spermatogenesis proceeds at a lower temperature than oogenesis. No such temperature restrictions can apply to spermatogenesis in non-mammals, and there appears to be no empirical support for this hypothesis. An alternative explanation is that exposure to increased temperature variation increases the rate of mutation (perhaps at restricted sites) in the haploid genome, and that this increase is of adaptive advantage. According to this view, the extra-abdominal location of the testis is a mammalian evolutionary development which increases the rate of mutation.

It is now clear (Shapiro, 1983) that a major contribution to genomic change is made by mobile

genetic elements or transposons. A number of classes of such elements, including the endogenous retroviruses (Varmus, 1982), have been identified; some are present in the human genome (Mager & Henthorn, 1984; Paulson *et al.* 1985; Musich & Dykes, 1986). Such an element might play a part in the aetiology of psychosis (Crow, 1984, 1986*a*). Of particular interest is evidence that in some situations at least, transposition of these elements is stimulated by relatively small changes in temperature. This is true for example of the Tn3 element in bacterial plasmids (Kretschmer & Cohen, 1979), hybrid dysgenesis determinants in *Drosophila* (Bregliano & Kidwell, 1983) and the Ty element in yeast (Paquin & Williamson, 1984). It is also clear that transposition in some mammalian species can occur at relatively high rates. For example, hybrids of certain mouse strains which carry integrated leukaemia viruses acquire new germ-line copies of the viral sequence in 18.6% of individuals (Jenkins & Copeland, 1985).

## PATERNAL AGE

If psychosis is in part the result of new mutations occurring at a critical stage in the course of reproduction this should be reflected in the epidemiology of the disease. Moran (1965) explored the possibility that the increase in maternal age in schizophrenia is due to mutation in the mother's germ cells during her lifetime, somewhat as is observed in some cases of Down's syndrome. He found that the relative excess of births to older mothers was too great to be explained on the basis of a constant rate of new mutations over the mother's lifetime, and appears to have abandoned this theory.

Hare & Moran (1979) returned to the problem in 1979. In two series of patients attending the Bethlem and Maudsley Hospitals they found that maternal age was very significantly above expectation for the general population. In the second series they assessed paternal age also, and found this was raised more than that of the mother, the fathers age being higher for schizophrenia than for other diagnostic groups. Raised maternal age could be accounted for by regression on the father's age. Therefore, raised paternal rather than maternal age requires explanation. Partly because they observed a similar, although less marked elevation of paternal age in other diagnostic groups (affective psychosis, neurosis and personality disorder), Hare & Moran concluded that the most likely explanation was that a constitutional characteristic of the fathers of individuals who develop psychiatric disease predisposes to late parenthood.

However, the argument is not overwhelming. The increase in paternal age observed by Hare & Moran was greater for schizophrenia (2.48 years) than for other diagnoses (0.86–1.65 years). Particularly when the uncertainties concerning the boundaries between schizophrenia and other conditions are taken into account it seems worth considering that the age of the father is more directly involved in the aetiology of schizophrenia (and perhaps other psychiatric conditions). Penrose (1955) discussed situations in which germ-line mutation in the father played a role, of which he considered achondroplasia was an example. Recently an association of paternal age with atrial and ventricular septal defects and situs inversus has been recorded (Lian *et al.* 1986).

## THE CONTINUUM OF PSYCHOSIS

A quite separate argument, that the gene which predisposes to psychosis is associated with an unusual degree of variation, relates to the delimitation of schizophrenia from other conditions. The classical Kraepelinian view (the binary concept) is that schizophrenia and manic-depressive illness are independent disease entities. However, Kraepelin himself recognized that states intermediate between the two prototypical psychoses (later designated 'schizoaffective' by Kasanin, 1933) were an embarrassment to this view (Kraepelin, 1920). An alternative formulation is that the psychoses are related to each other along a continuum. This concept preserves the Kraepelinian insight into the relationship between mood disturbance, periodicity and outcome but allows for the existence of intermediate states. According to this view, the continuum extends from unipolar through bipolar affective illness and schizoaffective psychosis to schizophrenia, with increasing degrees of defect. Along this continuum, disease in a particular proband is associated with approximately similar

diseases in the relatives. However, no clear demarcation can be made on a genetic basis between one point on the continuum and the next (see, for example, Angst *et al.* 1983, and Angst & Scharfetter, 1987).

It is suggested (Crow, 1986*b*, 1987) that this continuum rests on a genetic foundation and that variations in the form of psychosis are directly related to variations in the structure of the gene. Therefore the location and basic structure of the gene are constant, but variations in the fine structure account for different forms of psychotic illness. Particular interest relates to the possibility that changes in genetic structure occur on a short time scale. Thus there is evidence (for example as summarized by Rosenthal, 1970, pp 166–167, 215–216, and as seen in the studies of Penrose, 1968, and Powell *et al.* 1973) that affective illness in a parent increases the risk of schizophrenia in a child. In a continuum context this may be but an extreme instance of a more general phenomenon – the tendency of disease at one point on the continuum to predispose to diseases of greater severity (which are generally associated with earlier age of onset) in the next generation.

For example, in the affective disorders it is generally accepted that bipolar illness is a more severe form of illness than unipolar. In family studies an excess of unipolar and bipolar illness is usually found among the relatives of bipolar probands, whereas for unipolar probands the excess is predominantly of unipolar illness; in the summary of Smeraldi *et al.* (1977) the ratio of unipolar to bipolar first-degree relatives is 17.8 for unipolar probands and 1.63 for bipolar; Gershon *et al.* (1982) give comparable figures of 10.8 and 1.3 for previous studies and 5.7 and 1.9 for their own. This difference could represent a liability for unipolar illness to become bipolar between generations. In samples of first degree relatives, children are less numerous in most studies than other relatives, both with respect to absolute numbers and lifetime at risk. Therefore, if there is a generational trend this could account for the apparent asymmetry in the relationship between unipolar and bipolar disorder. When a unipolar proband is examined, the bipolar illness which may be present in his children is small relative to the unipolar illness present in siblings and perhaps parents. In the case of a bipolar proband the relative risk of bipolar illness in siblings, and perhaps parents, will be increased. In the data of Smeraldi *et al.* the relative risk of bipolar to unipolar illness is 0, 0.17, and 0.49 in parents, siblings and children of a unipolar proband; and 0.49, 1.33 and 1.0 in parents, siblings and children respectively of a bipolar proband. These findings appear consistent with an increase in the risk of conversion, from unipolar to bipolar illness, between generations. Consistent with this, in their adoption study of bipolar probands Mendlewicz & Rainer (1977) found an increase in unipolar but not bipolar illness amongst the parents.

A comparable inter-generational trend can be seen in the relationship between affective disorder and schizoaffective psychosis. Thus Gershon *et al.* (1982) observed a small increase in the risk of schizoaffective disorder in children of their affective probands relative to siblings and parents, and in the relatives of schizoaffective probands. Angst *et al.* (1979) found a ratio of affective: schizoaffective: schizophrenic illness of 23:7:11 in the parental generation, and 11:5:13 in the siblings. It would be of interest to examine possible intergenerational trends at other points on the continuum, for example, between non-psychotic and psychotic affective disorder, between schizoaffective disorder and schizophrenia, and between schizophrenia without, and with, degrees of defect. The interpretation of such a trend, if it exists, is that an increase in the severity of psychosis not infrequently accompanies its transmission between generations and that this increase represents a change in the structure of the gene (Crow, 1986*c*). According to the present viewpoint, such changes occur when transmission is through the male line. A prediction is that the form of psychosis will be better preserved between generations in mother-child than in father-child pairs.

## THE NATURE OF THE ELEMENT

The theory requires a genetic element which retains certain characteristics, e.g. the capacity to cause disease, but which is also variable in that in some forms it causes disease which is more severe and persistent, and perhaps of earlier onset. One possibility is that the element has the form of an

integrated pathogen which includes a variable component, and that this component regulates the way in which the pathogen is expressed. A recent paradigm is the the LINE L1Md element in the mouse. This has the structure of a mobile genetic element and includes a protein coding sequence and variable 5' tandem repeat; it is suggested (Loeb *et al.* 1986) that the length of the tandem repeat regulates transcription of the protein. The suggestion that a component of the element is variable between generations implies that the 'virogene' is located at a 'hot-spot' in the genome, i.e. a point of rapid change.

The 'virogene' concept has certain advantages over more conventional theories. For example, it provides an explanation for the occurrence of the illness in episodes and also for the fact that onset occurs at a relatively late age. It provides a potential explanation of seasonality, and of the capacity of the gene to cause disruption of function and possibly of structure within the brain. In each of these instances a genetic element with the capacity to function independently of the host genome could account for aspects of the phenomena of psychosis. Heuristically, the concept specifies certain types of genetic structure which can be considered as candidates for the psychosis gene.

The hypothesis has implications for epidemiology. Whereas horizontal transmission of illness between individuals in postnatal life, such as would be expected on the theory that the disease is caused by an exogenous infective agent, appears to be excluded (Crow & Done, 1986) more recondite influences on rates of illness may be present. As Hickey (1982) pointed out, an element which is mobile within the genome may also be replicated from one haploid genome to the other. In this way in a sexually reproducing population it could spread, even though it had deleterious effects on the host. Another possibility relates to mutations (transpositions or unequal crossing-over) occurring in the course of male gametogenesis. If the probability of such a mutation occurring is a function of the age of the father at the time of the child's conception, population rates of illness will vary with mean parental age i.e. with the generational interval. Such effects may be relevant to secular changes in the incidence of disease, such for example as have been suggested for schizophrenia in the nineteenth century (Hare, 1983), and for affective illness in the present century (Klerman *et al.* 1985; Price *et al.* 1985).

## LOCATION OF THE VIROGENE

The location of the element within the genome may also be relevant to its persistence. Some mobile elements interact with other components of the genome, such as growth factors or proto-oncogenes. This is known to be the case for retroviruses (Varmus, 1982), and it seems to be true for other types of mobile element, e.g. Rechavi *et al.* (1982) and Katzir *et al.* (1985). The interaction between the element and contiguous genetic structures could be the reason for its survival, i.e. it could be a symbiotic relationship. Such symbiosis might depend upon a direct interaction, the virogene could simply potentiate the effects of the growth factor. If this were the only explanation there appears to be no reason why the association should not become a stable one, in which forms of the virogene element which were constant and dependable promoters of the growth factor would be selected. An alternative possibility is that the virogene element remains unstable because it confers flexibility, and perhaps the potential for further development, on this part of the genome. One can envisage a ratchet-type mechanism whereby a stepwise increase in a particular cerebral development is associated with increased survival and retention of a degree of instability retains the potential for further advance. In this way one can see a reason why a 'hot-spot' of change might be preserved at a site in the genome committed to an aspect of cerebral growth.

A strong candidate for this site is the locus concerned with cerebral lateralization. Morphological asymmetries of the hemispheres in man are well established, for example, by the work of Geschwind & Levitsky (1968) and Galaburda *et al.* (1978). Such asymmetries are a late evolutionary development. For example, asymmetries in the Sylvian fissure related to those described by Geschwind and colleagues are absent in the rhesus monkey and present to a lesser degree in the chimpanzee than in man (Yeni-Komshian & Benson, 1976). Somewhat analogous skull asymmetries are described in some, but not other subspecies of gorilla (Groves & Humphrey, 1973). It is

conceivable that the mechanism of the asymmetry lies at the basis of the disproportionate brain growth seen in man (Jerison, 1973; Pilbeam & Gould, 1974). Clearly, overdevelopment of the left planum temporale accounts for relatively little of the excess brain weight. However, it might represent the continued activity of a mechanism whose incremental effects on either side of the brain have built up its overall capacity in the course of human evolution.

The concept of psychosis as a disorder of specifically human cerebral functions and of the left hemisphere has quite a long history. Thus Crichton-Browne wrote in 1879 that 'the cortical centres which are last organized, which are the most highly evolved and voluntary, and which are supposed to be located on the left side of the brain, might suffer first in insanity', and in 1915 Southard summarized his own studies of the neuropathology of schizophrenia as showing that 'the atrophies and aplasias when focal show a tendency to occur in the left cerebral hemisphere'. He added: 'Aside from the left sidedness of the lesions very striking is the preference of these changes to occupy the association centers of Flechsig' and 'for this there is probably good *a priori* reason in the structure, late evolutionary development, and consequent relatively high lability of these regions'. Similarly, Parfitt (1956) refers to Miskolczy's concept of schizophrenia as a disorder of those brain areas which are particularly human and suggests describing the disease as a 'genetic encephalopathy'.

The case for selectivity for the left hemisphere has been strengthened by recent brain studies (Crow, 1986*a*). For example, thinning of the parahippocampal gyrus relatively greater on the left side of the brain is described (Brown *et al.* 1986), and an increase in dopamine content of the amygdala on the left but not on the right side is reported (Reynolds, 1983). Several authors (e.g. Golden *et al.* 1981; Largen *et al.* 1983; Reveley *et al.* 1987) have reported a relative decrease in CT scan density on the left side, a finding which may reflect an increase in cerebrospinal-fluid spaces. Colter *et al.* (in preparation) found reduced width of the left side of the brain in the occipital region in early onset cases, and Zipursky *et al.* (1987) describe a relative reduction of tissue mass in the left hemisphere. Each of these findings is compatible with the hypothesis that the defect is one which directly affects the development of morphological asymmetries in the brain.

## SUMMARY

The persistence of psychosis at a high and relatively constant prevalence in the various populations of the world is rendered difficult to explain by the absence of identified environmental precipitants and by reduced fertility of affected individuals. The problem is not confined to schizophrenia but applies also to affective disorder. The 'virogene' concept attempts to explain this paradox as follows.

- (1) Psychosis in general is, as suggested by Böök (1953) and Lewis (1958) for schizophrenia, associated with a high rate of mutation.
- (2) The new mutations occur at a specific site (a 'hot-spot') in the genome and consist of rearrangements (e.g. transpositions or new insertions occurring as a result of unequal recombination) in a sequence which has a degree of potential autonomy, i.e. an integrated pathogen or 'virogene'.
- (3) The mutations occur specifically in the courses of gametogenesis in the male. By its location in the scrotal sac and its extended time course, gametogenesis in the male is susceptible to insertional mutagenesis as a function of variations in environmental temperature. Such temperature-dependent mutations are reflected in the seasonality of birth seen in both schizophrenic and affective illnesses. The increased likelihood of such mutations occurring with time is held to account for the association of psychosis with increased paternal age.
- (4) Such new events are held responsible not only for 'sporadic' cases in individuals without a family history of psychosis, but also for increases in severity of illness between generations. Psychosis is viewed as a continuum extending from unipolar through bipolar affective disorder and schizoaffective illness to schizophrenia with increasing degrees of defect. Jumps in severity of illness account for transitions within families between unipolar and bipolar, between bipolar and schizoaffective illness, and between schizoaffective illness and typical schizophrenia. Such shifts are generally in the direction of increased severity and occur in transmission through the male line.

(5) The virogene has the structure of a mobile genetic element, e.g. a retroviral sequence or LINE element. It includes a variable component (e.g. a tandem repeat) which regulates its expression.

(6) The virogene is associated with the cerebral mechanisms of laterality in a symbiotic relationship, such that the element either facilitates the action of a growth factor responsible for asymmetrical brain growth or confers upon it a degree of genetic flexibility which has survival value. This mechanism is responsible for the increase in brain weight which has allowed *Homo sapiens* to evolve social structures and means of communication which distinguish this species from other primates.

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