Brit. J. Psychiat. (1971), 118, 451–2 *ABSTRACT*

Schizophrenia: Initiation and Development

By P. R. J. BURCH

According to a recent theory, schizophrenia is confined to people with a particular genetic predisposition and the disorder arises from a specific breakdown in the central part of the system that controls growth (Burch 1964, 1968). We call diseases of this general class *autoaggressive*. Their pathogenesis has two distinctive phases: *initiation* and *development*. Initiation, which is a purely random process, entails a form of spontaneous somatic gene mutation in growth-control stem cells. The initiation of schizophrenia is described by the Weibull equation:

$$dP/dt = 2k\,S\,t\exp(-kt^2). \quad (1)$$

Where dP/dt is the age-specific initiation rate at age t, k is a kinetic constant ($\simeq 1{\cdot}25 \times 10^{-3}y^{-2}$) and S is that fraction of the population genetically-predisposed to schizophrenia. This assumes that initiation requires the spontaneous mutation of two specific genes, in any one cell, of a set of similar growth-control stem cells. The mutant stem cell divides to initiate the growth of a 'forbidden clone' of small lymphocytes. These cells are of the type involved in allograft rejection and delayed hypersensitivity reactions: they are thymus-dependent and do *not* synthesize immunoglobulins (Burch 1968). During *development*, lymphocytes proliferate and attack target cells (perhaps endothelial cells of small blood vessels) that carry recognition molecules complementary to those borne by the mutant lymphocytes. When the severity of attack exceeds a certain threshold, symptoms and signs of disease emerge. The average interval or *latent period*, between the completion of initiation and the first onset of schizophrenia is about 4·5 years for men and 9 years for women (Burch 1964). However, extrinsic factors (notably micro-organisms) and severe mental stress can precipitate onset once the forbidden clone is initiated (Burch 1968). Studies of the intervals between the onset of disease in the two members of monozygotic (MZ) twin pairs can test some key features of this theory (Burch, 1968).

Abe (1969) has carried out such an investigation (i) for pairs of MZ twins living together; and (ii) for pairs living apart at the time of onset in the 'first' twin. He found that the rate of onset in the 'second' twin during the first two years after onset in the 'first' was much higher in the 'together' than in the 'apart' group. This suggests that the stress of living with a schizophrenic co-twin can precipitate the onset of disease if a forbidden clone is present, or if it is initiated within about two years after onset in the 'first'. The interval over which initiation could occur in the 'second' twin so as to allow stress interaction with the 'first', approximates to the mean latent period (7 to 8 years for the 'together' group) plus the interaction interval of some two years, that is, about 10 years altogether. We can integrate equation (1) to calculate the probability, $P_{t_1}^{t_2}$, that a forbidden clone will be initiated over any age interval, t_1 to t_2. Assuming the MZ co-twin to be genetically-predisposed and, therefore, S = 1:

$$P_{t_1}^{t_2} = 1-\exp\{-k(t_2^2 - t_1^2)\},$$

$$\text{and } (1 - P)_{t_1}^{t_2} = \exp\{-k(t_2^2 - t_1^2)\} \quad (2)$$

The most probable age for the *initiation* of schizophrenia is 20 years (Burch, 1964). We can estimate the interaction effect if we assume that a forbidden clone initiated in the 'second' twin at any time during the 10-year interval between 15 and 25 years of age leads to the onset of schizophrenia during the two-year interaction period. From equation (2) we obtain $(1 - P)_{15}^{25} = 0{\cdot}6$, which represents the proportion of co-twins still well at the end of the two-year interaction period. This is equivalent to 15/25, as compared with the 12 well patients out of a total of 25 observed by Abe (1969) for the 'together' group. If no interaction or common exogenous factors operate, then the probability, $(1 - P)_{t_1}^{t_2}$, that initiation does not occur in the 'second' twin over the two-year interval $t_1 = 19$ to $t_2 = 21$ years, is 0·9. Thus, for no interaction, we expect 24·3/27 co-twins to be well two years after onset in the 'first', which may be compared with 22/27 observed by Abe (1969), for the 'apart' group. I conclude that when MZ twins are living together and the 'first' becomes schizophrenic, this event can act as a severe precipitating factor for the co-twin, and/or that a common extrinsic factor precipitates the onset of

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disease in both twins. Abe (1969) deduces that the second explanation cannot be valid in all instances of near-simultaneous onset. His findings therefore strongly support the proposal (Burch, 1968) that severe mental stress can precipitate the onset of schizophrenia once the pathogenic forbidden clone has been initiated by spontaneous somatic gene mutation.

At intervals well beyond the interaction period, the observed proportion of co-twins not schizophrenic should approach the value $(1 - P)_{t_1}^{t_2}$ given by equation (2). Because this depends on t_1, I have assumed two groups, one in which initiation occurs in 'first' twins at $t_1 = 10$ years and another, with $t_1 = 30$ years. (These bracket the most probable t_1 of 20 years.) Weighted values of $(1 - P)_{t_1}^{t_2}$ calculated in this way are 0·55 at $(t_2 - t_1) = 10$ years, compared with 0·46 observed by Abe (1969), for his whole series; 0·25 at $(t_2 - t_1) = 20$ years, compared with 0·30 observed; and 0·21 at $(t_2 - t_1) = 22$ years, the longest follow-up period, compared with 0·22 observed. In view of the small numbers observed, the close agreement is partly fortuitous. Nevertheless, Abe's (1969) overall data support the theory (Burch 1964, 1968) that the pathogenesis of schizophrenia involves first, a random *initiation* phase described by equation (1), followed by a *development* phase which can be accelerated by extrinsic factors, and especially by severe mental stress.

Abe's (1969) findings also confirm the assumption that if one twin of a MZ pair develops schizophrenia, then the co-twin is always, or nearly always, genetically predisposed. Discordance between MZ pairs is due simply to the failure of initiation and development processes to go to completion. My own polygenic theory (Burch, 1964), which postulates the inheritance of specific alleles in homozygous form at two autosomal loci, was derived from the following considerations: an analysis of the population frequency of predisposed persons; the homogeneity of age-distributions as given by diagnostic criteria in New York State (1949-51); the consistent twins studies of several investigators; and, especially, the twins and familial observations of Kallmann. With the vindication of Kallmann's findings for twins by Shields, Gottesman and Slater (1967), my basic genetic hypothesis requires no revision, but an addition is needed to account for the different clinical types of schizophrenia.

I propose that the clinical type depends on the exact anatomical location and extent of the 'target tissue' attacked by the lymphocytes in the forbidden clone. The pattern of attack will depend on genetic factors additional to those which determine general predisposition (Burch, 1968). In our theory, a 'target tissue' represents a much finer sub-division than the 'tissue' defined by ordinary histological criteria: taking fine distinctions into account, the total number of distinctive 'tissues' in man could well be as high as 10^{10} (Burch, 1968). The average latent period between the end of initiation and the onset of schizophrenia is twice as long in women as in men (Burch, 1964). This ratio characterizes autoaggressive diseases in which the target tissue lies on the blood side of blood-tissue barriers (Burch, 1968; Burch and Rowell, 1970). Hence, I suggest that the target tissue in schizophrenia might be the endothelial lining of certain blood vessels in the brain: their exact location and extent determine the type and severity of the disease. Some observations agree with this proposal (Johnson and Richardson, 1968).

Elsewhere, I have considered in detail the kind of additional evidence that is needed to test rigorously the autoaggressive theory of age-dependent disease (Burch, 1968).

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