

SYSTEMATICS OF THE AGE-DEPENDENCE OF SOME NEUROLOGICAL DISORDERS

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The age-dependence of malignant diseases has received various interpretations, whereas that of nonmalignant diseases has been relatively neglected. Nevertheless, the age-distributions of diseases in both categories conform to the same stochastic laws.

Many, and perhaps all, natural disorders with a reproducible age-pattern can be described in terms of a simple model: The disease process is initiated in a genetically-predisposed person through the random occurrence of a small number (r) of somatic gene mutations in each of a small number (n) of growth-control stem cells. Each specifically-mutant stem cell propagates a "forbidden clone" of descendant cells. These cells, or their humoral products, attack those target cells that carry complementary recognition macromolecules. The resulting disturbance to target cells leads to the symptoms and signs of autoaggressive disease. In the classical infectious diseases, an extrinsic factor — the invading microorganism — is essential to the release of forbidden clones from restraints imposed by the host's endogenous defence mechanism.

This general thesis is illustrated with reference to the age-distributions of: Wilson's disease; idiopathic facial (Bell's) palsy, recovery and denervation groups; poliomyelitis; Parkinson's disease; schizophrenia; and multiple sclerosis. Clinically-distinctive forms of a given disease, such as Huntington's chorea or Bell's palsy, often have a distinctive age-pattern.

In addition to differences in n and/or r , it can be inferred that each such clinically-distinctive form of a disease is characterized by a distinctive predisposing genotype. The age-dependence of each stage of a progressive disease has a special interest.

Thus, the onset of "definite and probable" cases of Parkinson's disease (Mayo Clinic data) requires two forbidden clones, each of which is initiated in a predisposed person by five specific somatic mutations. Late deaths from Parkinson's disease (as recorded by the Registrar General of England and Wales) require a third such forbidden clone.

Progression in this neurological disorder, as in certain malignant diseases, corresponds to an increase in the number of pathogenic forbidden clones. The internal mathematical and biological consistency of this type of quantitative evidence powerfully corroborates the forbidden clone theory of age-dependent autoaggressive disease.

INTRODUCTION

Until recently, the age-dependence of nonmalignant diseases has failed to attract the interest of theoreticians. However, the title and contents of this Session, and especially the pioneering studies of our Chairman, Professor Gedda, reveal a new awareness of the importance of the time dimension, not only for the genetics and onset of disease, but for biology at large (Gedda and Brenci 1969, 1970).

By contrast, the age-dependence of malignant diseases has, since the 1950s, inspired many

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theories and interpretations. These have been reviewed elsewhere (Burch 1965). The reason for this contrast in attitudes is not too difficult to seek. At a commonsense level, the various interpretations that have been offered of the age-dependence of malignant diseases would appear to be entirely inapplicable to most of the nonmalignant degenerative diseases. One important feature is shared by the several theories of malignancy: the disease process is held to be initiated by a small number of random events. These events have generally been identified with some form of somatic gene, or chromosomal, mutation and estimates of the number required to initiate late-onset cancers have generally ranged from two to around six. Excepting a recent theory (Burch 1968*a*, 1970), these somatic mutations have been located in one or more cells of the tissue that becomes neoplastic. We can readily accept that a small number of mutations occurring, say, in an epithelial cell, could give rise to a unifocal carcinoma. (It is, however, very difficult to account in these terms for the multifocal origin of so many malignancies — see Smithers 1962, Willis 1967, Burch 1968*a* and 1970.)

These arguments regarding the pathogenesis of neoplasia were based upon the mathematical relation between sex-specific and age-specific death-rates, and age. When such data are plotted on log-log scales a curve that is linear over the greater part of the lifespan is often obtained. This is found both for cross-sectional (vertical) and cohort (horizontal) analysis. An uncomplicated example, showing death-rates from cancer of the pancreas, is illustrated in Fig. 1 (England and Wales, 1960-63), Fig. 2 (Japan, 1960-63) and Fig. 3 (U.S. Whites, 1960-1963). When an average interval, or latent period, of 2.5 yr is allowed between the completion of initiation and death, a curve of initial slope, six, is obtained from the statistics for all three populations. However, a decreased slope is observed at high ages in the statistics for England and Wales (Fig. 1) and U.S. Whites (Fig. 3): in the statistics for Japan (Fig. 2), a well defined mode is observed. The detailed form of the curves in Fig. 2 (and in Figs. 1 and 3, so far as they go) is consistent with the model that seven independent somatic gene mutations, occurring randomly in a single cell of a genetically-predisposed person, initiate cancer of the pancreas (Burch 1966, 1968*a*). The mode arises when, at high ages, most of the people predisposed to the disease have already contracted it.

Although many authors have readily accepted this type of explanation in the context of malignant disease, a serious challenge presents itself when we study the age-dependence of nonmalignant diseases. In many instances, their age-patterns display mathematical features that closely resemble those of the malignant diseases (Burch 1968*a*). Again, it becomes very difficult to resist the implications that many nonmalignant diseases are also initiated by a rather small number of random events.

Examples of the age-patterns for fatal cerebrovascular diseases are illustrated in Fig. 4. Age-specific death-rates for cerebral haemorrhage (left panel), when corrected for latent period (2.5 yr males, 5 yr females), are closely proportional to the sixth power of age over most of the lifespan: the corresponding rates for cerebral thrombosis (right panel) remain proportional to the tenth power of age up to the highest age-group. It is difficult to believe that 7, or 11, somatic mutations in, say, cells of blood vessels in the central nervous system could give rise to a fatal pathology. This paradox was recognized by Armitage and Doll (1954), but they were unable to resolve it.

Burnet's (1959) "forbidden clone" theory of disturbed-tolerance "autoimmunity" offered an escape from this dilemma (Burch 1963). Burnet postulated that initiating somatic mutations occur in mesenchymal (e.g., lymphoid) stem cells. Mutant stem cells that escape the vigilance of a defence system propagate a "forbidden clone" of descendant cells, each of which

CANCER OF PANCREAS: JAPAN 1960-1963

CANCER OF PANCREAS: ENGLAND AND WALES 1960-1963

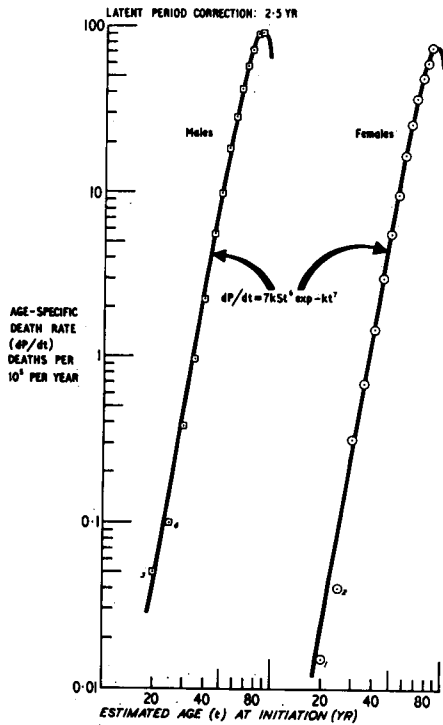


Fig. 1. Sex-specific and age-specific death-rates (dP/dt) from malignant neoplasms of the pancreas, England and Wales, 1960-63, versus estimated age, t , at initiation. [Data taken from *Segi and Kurihara 1966*]. Numbers alongside points represent numbers of deaths. For clarity, data are plotted not as histograms, but as points at the centre of quinquennial age-groups. An average interval, or latent period, of 2.5 yr is allowed between the end of initiation and death from cancer of the pancreas. Values of parameters in eqn. [2] are: $n = 1$, $r = 7$, $k_M \approx 3 \times 10^{-14} \text{ yr}^{-7}$, $k_F \approx 2 \times 10^{-14} \text{ yr}^{-7}$, $S_M = 3.1 \times 10^{-2}$, $S_F = 2.6 \times 10^{-2}$.

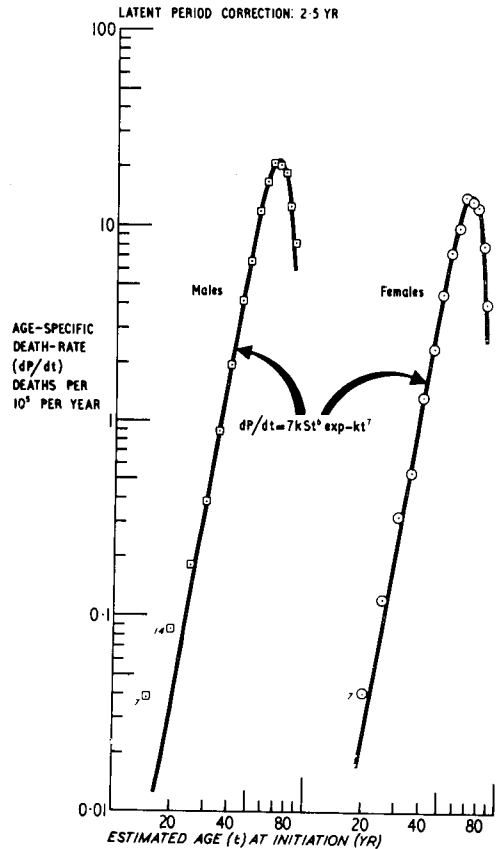


Fig. 2. As for Fig. 1. Data for Japan, 1960-63.

A clear-cut mode is seen in these statistics, in contrast to those for England and Wales (Fig. 1) and U.S. Whites (Fig. 3). Nevertheless, the same basic stochastic function, $dP/dt = 7kSt^6 \exp(-kt^7)$, fits all the data. In Japan, the value of the kinetic constant k is higher, and that of S , the proportion of the population predisposed, is lower than in the Western countries. For the Japanese statistics: $n = 1$, $r = 7$, $k_M = k_F \approx 1 \times 10^{-13} \text{ yr}^{-7}$, $S_M = 6.0 \times 10^{-3}$, $S_F = 3.9 \times 10^{-3}$.

carries the genetic errors of its progenitor. These mutant descendant cells, or their humoral products, attack complementary target cells which might be astronomical in number and located at one, two or multiple anatomical sites. Because of the "amplification" provided by the growth of the forbidden clone, we can readily conceive how a small number of random somatic gene mutations — or only one — might give rise to extensive and/or multiple lesions

CANCER OF PANCREAS. U.S.A. WHITE 1960-1963

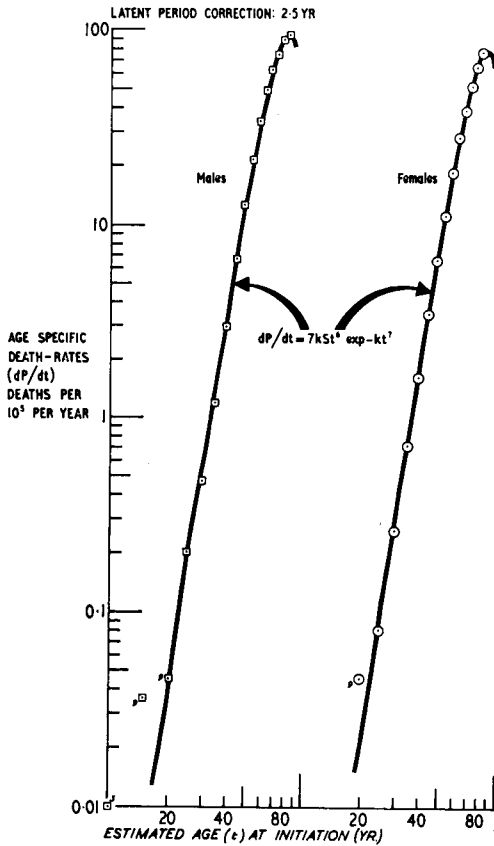


Fig. 3. As for Fig. 1. Data for the U.S. White population, 1960-63.

Values of parameters in eqn. [2] are: $n = 1$, $r = 7$, $k_M \approx 3 \times 10^{-14} \text{ yr}^{-7}$, $k_F \approx 2 \times 10^{-14} \text{ yr}^{-7}$, $S_M = 3.1 \times 10^{-2}$, $S_F = 2.7 \times 10^{-2}$.

SEX-SPECIFIC AND AGE-SPECIFIC DEATH RATES ENGLAND AND WALES, 1970 (REGISTRAR GENERAL 1972)

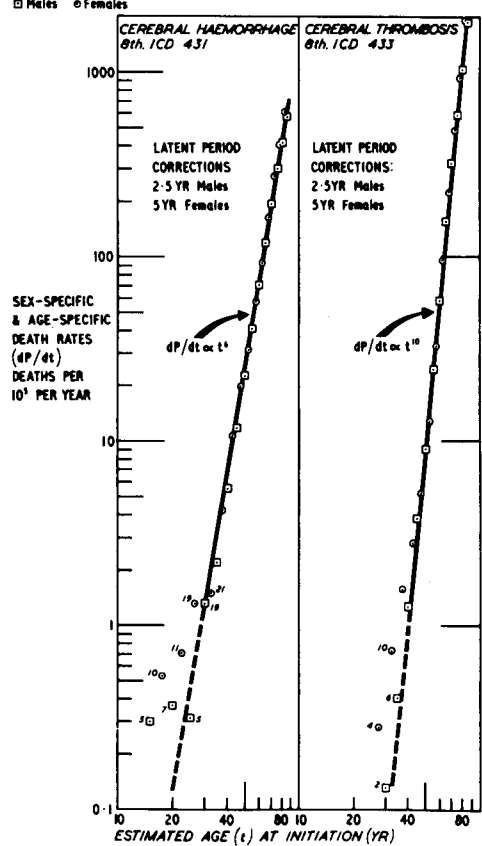


Fig. 4. Sex-specific and age-specific death-rates from cerebral hemorrhage (left panel) and cerebral thrombosis (right panel), England and Wales, 1970 [Registrar General 1972].

For both diseases, latent period corrections are 2.5 yr for males and 5.0 yr for females. This ratio of 2 to 1 (F/M) is found when the target tissue of the autoaggressive attack lies on the blood side of blood-tissue barriers and when the primary pathogenic agents are forbidden clones of T-lymphocytes [Burch 1968a].

in a given target tissue, such as the endothelial lining of blood vessels in the central nervous system. Burnet (1959) holds that the normal function of the cells that, on somatic mutation, initiate "autoimmune" disease, is that of classical immunity of either the cellular or humoral kinds. However, this interpretation fails to give a convincing explanation of certain quantitative details of the evidence (Burch 1968a).

Burwell (1963) argued from his transplantation studies — and wider biological considerations — that the primary and intrinsic function of the lymphoid system is that of the central

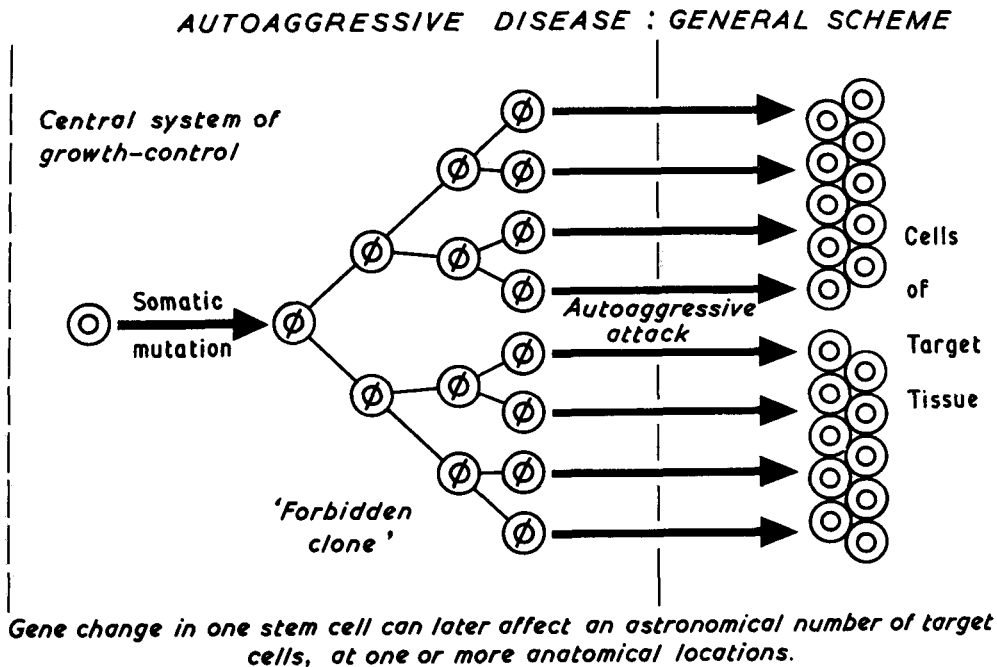


Fig. 5. Outline of scheme for autoaggressive disease. Forbidden clones of cells, resulting from somatic gene mutations in growth-control stem cells, attack the cells of target tissue located at one or more anatomical sites.

regulation and coordination of growth. We now believe that at least two histologically-distinctive systems are devoted to this fundamental rôle (Burch and Burwell 1965). The control of the growth of tissues on the blood side of blood-tissue barriers (mainly endothelia) is, we believe, exercised by thymus-dependent, or T-lymphocytes. But many tissues, such as neurons, are located behind blood-tissue barriers where even small lymphocytes cannot penetrate. In such locations, the effectors of symmetrical mitosis are necessarily humoral. They appear generally to migrate with the α_2 -globulin serum protein fraction and, in some instances at least, to be α_2 -macroglobulins (Burch 1968*a*). Circumstantial evidence suggests that basophilic granulocytes and mast cells might be connected with their synthesis (Burch 1968*a*). According to our deductions, immunoglobulin autoantibodies are never the primary pathogenic agents in natural "autoimmune", or, to adopt the more general term, "autoaggressive" disease.

In summary, we conclude that a complex system of central growth-control regulates the growth of target tissues throughout the body, utilizing negative feedback loops. Evidence concerning the age-dependence of disease, and the anatomical distribution of lesions, implies that each distinctive tissue has its own central control element. The human body might comprise as many as 10^{10} "distinctive tissues": most classical "tissues", as characterized by ordinary histological criteria, consist of vastly complicated assemblies of mosaic elements (Burch 1968*a*). Normal growth is timed and regulated through a genetically-programmed,

deterministic sequence. Autoaggressive disease arises from a breakdown in the central system of growth-control. A specific disease arises in a genetically-predisposed person through the occurrence of a particular set of random somatic gene mutations. Initiation of the timing of disease processes is essentially stochastic, rather than deterministic, in character. This scheme is illustrated in Fig. 5.

AGE-DEPENDENCE OF NATURAL DISEASE: GENERAL

For those numerous diseases — neurological and nonneurological, malignant and non-malignant, infectious and noninfectious — that exhibit reproducible age-patterns, in different environments, we have drawn the following generalizations:

1. A specific disorder of this kind is confined to a genetically-specific subpopulation that constitutes a fraction, S , of the general population.
2. The disease process is initiated by the random occurrence of r specific gene mutations, in each of n specific and independent growth-control stem cells.
3. The average rate, m_i , of each specific somatic mutation is effectively constant in ordinary environments from around birth to the end of the lifespan. If L is the number of growth-control stem cells at somatic mutational risk, in each of the n independent sets at risk, we define a kinetic constant, k equal to Lm^r , where m is an average value for the r somatic mutations. (We require $mt \ll 1$ for all t — that is, initiation age — of interest.) Values of m , and hence of k , sometimes differ from one genetically-distinctive population to another. The commonest observed difference is between men and women: in a number of instances, $k_F = 2k_M$.
4. An interval (latent period) elapses between the last random initiating event and the first onset of disease. The duration of this interval can be shortened by various environmental factors and severe mental stress. In the classical infectious diseases such as measles, mumps, poliomyelitis, etc., the latent period is short and of the order of the incubation period. We deduce that antigens on infecting microorganisms, or allergic agents, compete for defence antibodies whose physiological function is the suppression of the growth of forbidden clones.

AGE-DEPENDENCE OF NATURAL DISEASE: MATHEMATICAL RELATIONS

The above generalizations have simple mathematical consequences. Provided S is constant with time, and the disease is nonfatal and not associated with fatal diseases, its sex-specific and age-specific prevalence, P_t , is given by (Burch 1966, 1968a):

$$P_t = S \{1 - \exp(-kr^t)\}^n \quad [1]$$

The sex-specific and age-specific initiation-rate at age t is obtained by differentiation:

$$dP/dt = \{nrkSt^{r-1} \exp(-kt^r)\} \{1 - \exp(-kt^r)\}^{n-1} \quad [2]$$

For a fatal disease that is not associated with other fatal diseases, and for which the interval between initiation and death is short, the right-hand-side of eqn. [2] needs to be divided by the factor $(1 - P_t)$. When S is small, this factor approximates to unity at all t .

OBSERVED AGE-DEPENDENCE OF SOME NEUROLOGICAL DISORDERS

The age-dependence of Huntington's chorea, by clinical type, has been analysed in detail elsewhere (Burch 1968*b*, 1973). Distinctive clinical types have characteristic age-patterns. Age-specific onset rates for the relatively early onset, rigid-akinetic form of the disease, are described by that version of equation [2] in which $n = 1$, $r = 2$ and $k \simeq 1.4_8 \times 10^{-3} \text{yr}^{-2}$. The age-pattern of the classical choreic form of the disease, accompanied by emotional impairment, is described by the equation in which $n = 1$, $r = 4$ and $k = 5 \times 10^{-7} \text{yr}^{-4}$: the rather small proportion of classical cases without emotional impairment has a somewhat later onset, described by $n = 1$, $r = 5$ and $k = 4 \times 10^{-9} \text{yr}^{-5}$. More complicated interpretations based on other diagnostic criteria cannot be ruled out, but the age-distributions of large unselected series can be described satisfactorily by combinations of these three mathematical functions (Burch 1968*b*, 1973).

This example shows that what may be loosely regarded as a single nosological entity — Huntington's chorea — is, in fact, a heterogeneous mixture of clinically- and chronogenetically-distinctive disorders.

Wilson's Disease

To judge from the age-distribution of cases from the world literature reviewed by Cumings (1959), the kinetics of the fatal process do not appear to be heterogeneous despite the clinical heterogeneity of the disease. It would, however, be interesting to analyse the age at onset and death for a large series with reference to the main presenting signs (see O'Reilly 1967). Patients showing a variety of neurologic disorders should be compared with those presenting with an unexplained cirrhosis. In a combined series of British and Chinese patients, cases with hepatic symptoms tended to have an early age of onset, but numbers are too small for a definitive comparison (Strickland et al., 1973).

It should be noted that the sex ratio, S_M/S_F , for the reviewed cases in Fig. 6 is about 1.4. This high value cannot easily be reconciled with the commonly accepted simple autosomal recessive scheme of inheritance. If the excess of males is not due to bias of reporting, then either some form of sex-limitation and/or recessive X-linked inheritance, in addition to autosomal factors, would appear to be implicated.

One study of pedigrees supports the simple autosomal recessive scheme (Cox et al. 1972), but another shows various inconsistencies (Strickland et al. 1973). These latter authors found, among other anomalies, that affected cases in a family tended to be of one sex and unaffected siblings of the opposite sex. Strickland et al. (1973) were unable to propose any alternative to the autosomal recessive scheme: novel hypotheses and further studies of pedigrees are needed to resolve these anomalies.

Idiopathic Facial (Bell's) Palsy

In a series of untreated patients, two clinically-distinctive groups can be delineated: a recovery group in which no permanent denervation can be detected, and a denervation group in which neurological impairment is permanent (Taverner 1969).

The age-distribution of patients in the first group, from an untreated series of my colleague Dr. D. Taverner, is shown in Fig. 7. A markedly different, bimodal distribution, is obtained

WILSON'S DISEASE

LATENT PERIOD CORRECTION=4 YEARS (both sexes)

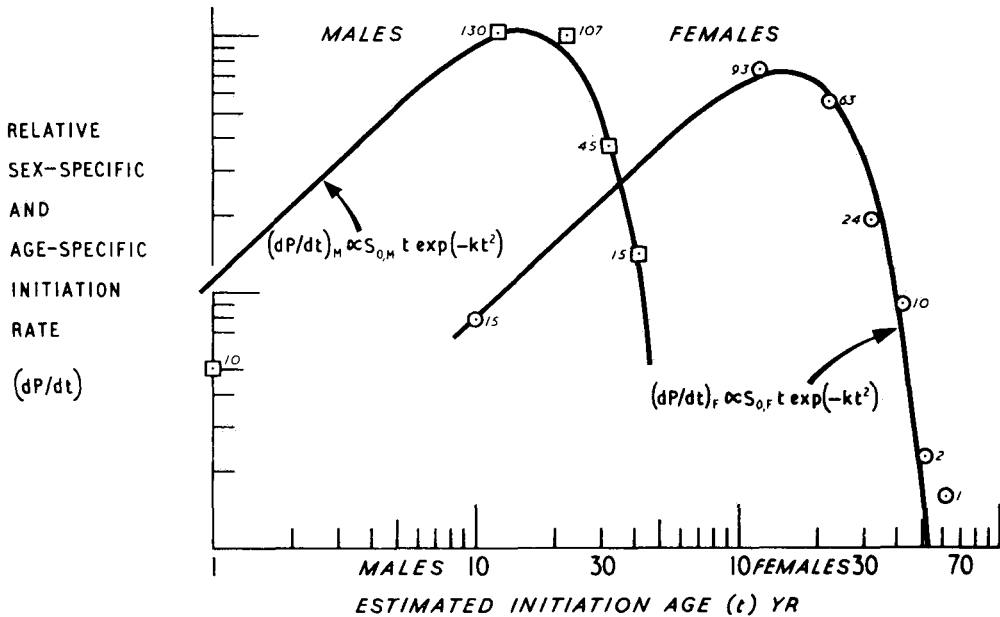


Fig. 6. Age-distribution of cases of Wilson's disease (mainly age at death), reviewed and abstracted from the world literature by Cumings (1959). The age scale for females is displaced from that for males by one decade. The theoretical curves, with $n = 1$, $r = 2$ in eqn [2], estimate the kinetics of the initiating events that cause death. The value of k is approximately $2.2 \times 10^{-3} \text{ yr}^{-2}$ and $S_M/S_F \approx 1.4$.

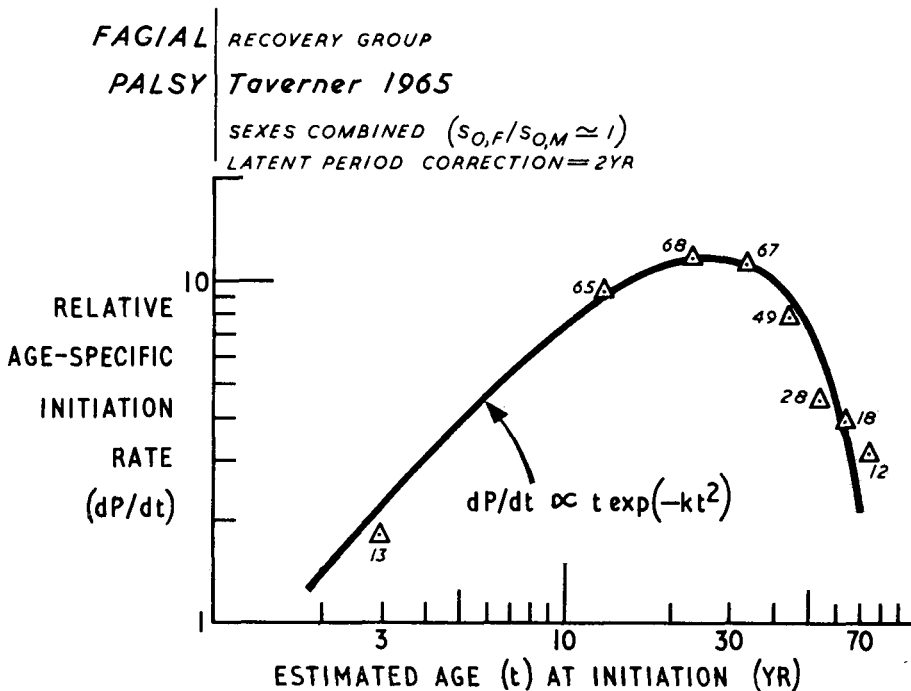


Fig. 7. Age-distribution of onset of idiopathic facial (Bell's) palsy in the recovery group [Taverner 1965]. In eqn. [2] we have $n = 1$, $r = 2$, $k \approx 6.6 \times 10^{-4} \text{ yr}^{-2}$.

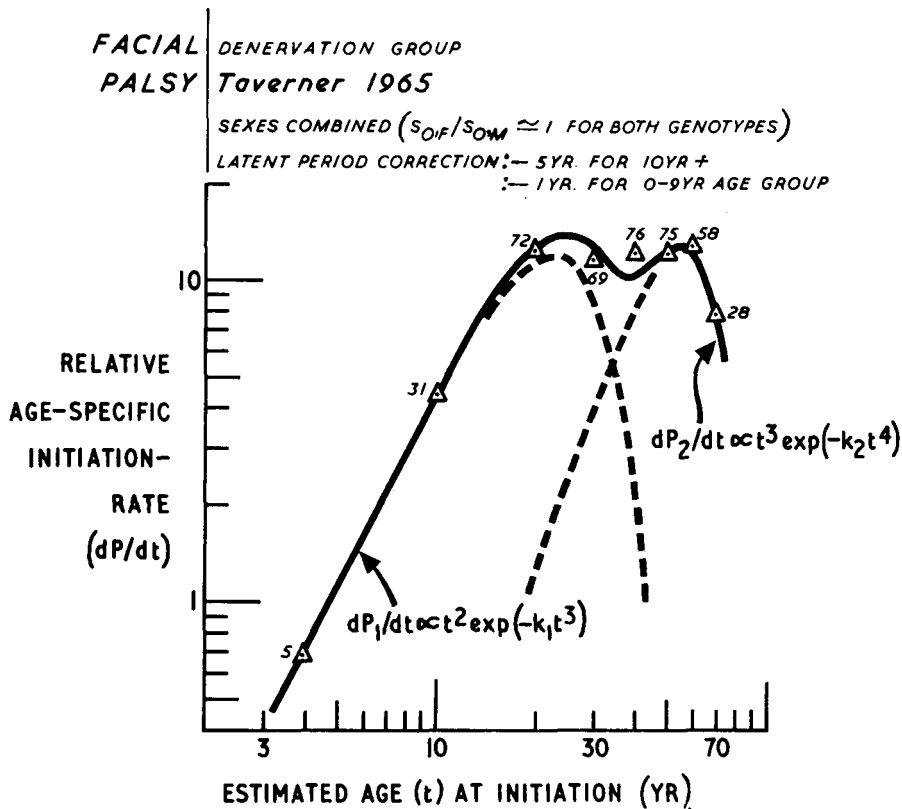


Fig. 8. Age-distribution of onset of idiopathic facial (Bell's) palsy in the denervation group [Taverner 1965]. Two stochastic functions are required to describe this distribution: (a) $n = 1$, $r = 3$ and $k \approx 5.5 \times 10^{-8} \text{ yr}^{-3}$; (b) $n = 1$, $r = 4$ and $k \approx 8 \times 10^{-8} \text{ yr}^{-4}$. No appreciable sex differences are seen in this series or in the series illustrated in Fig. 7.

for the series of untreated patients with denervation (Fig. 8). Probably, this group is genetically heterogeneous consisting of two (at least) subgroups with age-patterns characterized by $n = 1$, $r = 3$, and $n = 1$, $r = 4$, respectively, in contrast to $n = 1$, $r = 2$, which describes the recovery group. The outcome in Bell's palsy depends on the nature of the damage to the nerve fibres and this in turn depends on the site of the lesion (Taverner 1969). Many investigators believe that the incidence of Bell's palsy varies with season and Leibowitz (1969) has demonstrated a temporal clustering of cases. This finding supports the hypothesis that at least some cases of Bell's palsy have a viral-infectious etiology (Leibowitz 1969). The age distribution of diseases known to be of viral origin is therefore of interest.

Poliomyelitis

In 1949, New York City experienced its third largest epidemic of poliomyelitis with 2496 cases; in 1950, some 1064 were reported (Abramson and Greenberg 1965). The age-distribution of all these cases is illustrated in Fig. 9. Apart from the point at under 1 yr,

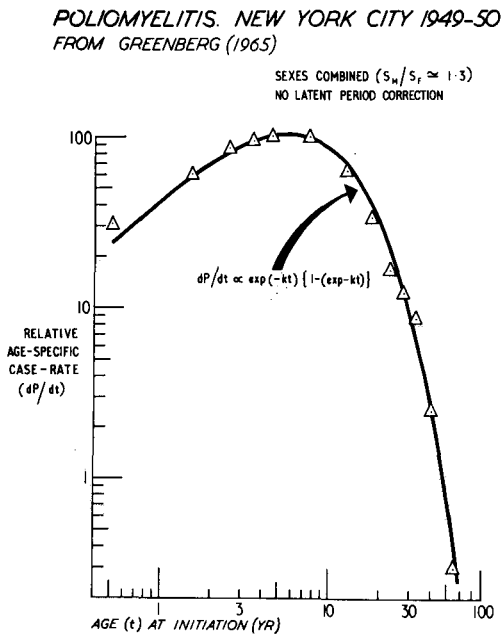


Fig. 9. Age-distribution of cases of poliomyelitis, all forms, New York City, 1949-50 [Abramson and Greenberg 1965].

The theoretical curve is based on $n = 2$, $r = 1$, $k \approx 0.13 \text{ yr}^{-1}$. The correction for latent period is zero.

and the age-groups 15 to 34 yr, a good fit is given to the equation in which $n = 2$, $r = 1$. Nevertheless, this might be in part deceptive. When cases are considered by type: nonparalytic, spinal, or bulbar, the proportions do not stay constant with age: neither does the sex-ratio (all cases combined) remain independent of age (Abramson and Greenberg 1965). Furthermore, the proportion of fatal cases changes markedly with age. Ideally, data are needed by age, sex, clinical type, and fatal/nonfatal. This detail was not given in the original paper and the analysis shown in Fig. 9 must be regarded as tentative: it may well conceal genetic heterogeneity. Alternatively, the analysis of kinetics might be substantially correct, with the clinical outcome depending on nongenetic factors.

In general, the age-dependence of the onset of many other infectious diseases (Burch 1968*a* and unpublished) is consistent with "autoaggressive statistics". Such findings suggest that an infectious disease is a special form of autoaggressive disease in which an infective microorganism, is essential to the expression of one or more pathogenic forbidden clones. I have argued that antigens on the microorganism compete for specific immunoglobulin antibodies that otherwise would ensure the suppression of the forbidden clones (Burch 1968*a*). This theory has the great advantage of explaining the "carrier state" in which a person carries the infective agent without manifesting the usual symptoms and signs of the associated disease. Such persons, who often constitute the bulk of the population in severe epidemics, have not developed pathogenic forbidden clones.

The conformity of the age at onset of infectious diseases to autoaggressive statistics means that age-patterns alone cannot discriminate between infectious and noninfectious disease, although the latent period for classical infectious diseases of childhood is very short. Conspicuous space-time clustering provides the best epidemiological evidence for the horizontal transmission of an infective microorganism.

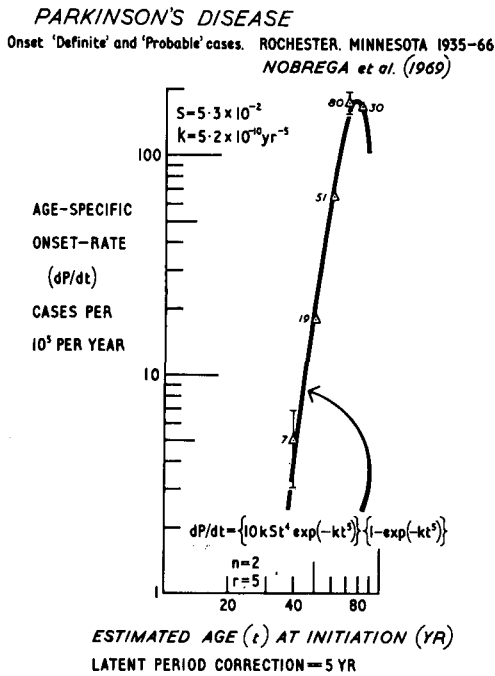


Fig. 10. Age-distribution of onset of "definite" and "probable" cases of Parkinson's disease, Rochester, Minnesota, 1935-66. [Nobrega et al. 1969]. In eqn. [2]: $n = 2$, $r = 5$, $k \approx 5.2 \times 10^{-10} \text{ yr}^{-5}$, $S \approx 5.3 \times 10^{-2}$. Secular increases in the recorded incidence of the disease suggest that S , which is an average for the whole period 1935-66, might be underestimated.

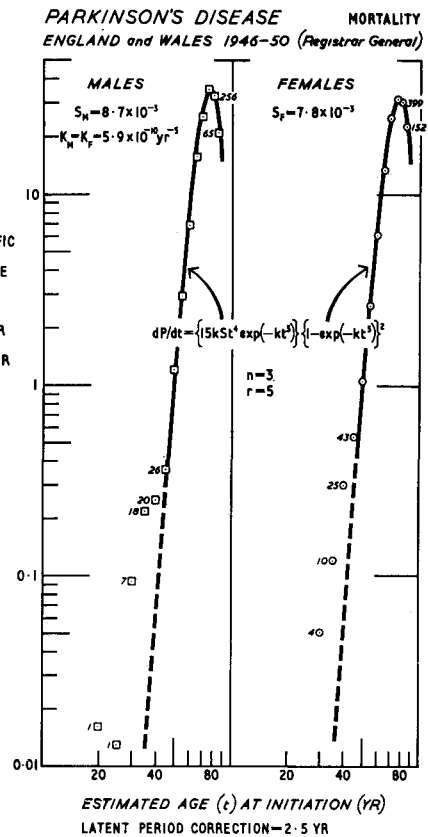


Fig. 11. Sex-specific and age-specific death-rates attributed to Parkinson's disease in England and Wales, 1946-50. In eqn. [2]: $n = 3$, $r = 5$, $k \approx 5.9 \times 10^{-10} \text{ yr}^{-5}$, $S_M = 8.7 \times 10^{-3}$, $S_F = 7.8 \times 10^{-3}$.

Parkinson's Disease

This is an example of degenerative disease of insidious onset that sometimes progresses to a fatal outcome. The age-distribution of the diagnosis of combined "definite" and "probable" cases of Parkinsonism in Rochester, Minnesota, 1935-1966, is shown in Fig. 10 (Nobrega et al. 1969). These data indicate that "definite" and "probable" Parkinsonism results from two forbidden clones ($n = 2$), each of which is initiated by five somatic mutations ($r = 5$) in a single stem cell.

An interesting relationship is seen between the distribution of the age of diagnosis (Fig. 10), and the distribution of the age at death from Parkinson's disease in England and Wales, 1946-1950 (Fig. 11). Death above the age of about 40 yr follows, it appears, from the presence of three forbidden clones ($n = 3$), each of which is initiated by five somatic mutations ($r = 5$) in a single stem cell. The onset of "definite" and "probable" cases requires only two such forbidden clones. The kinetic constant k for the initiation of each clone in the Minnesota popu-

lation, about $5.2 \times 10^{-10} \text{ yr}^{-5}$, is very similar to that (about $5.9 \times 10^{-10} \text{ yr}^{-5}$) for the England and Wales population.

As in certain forms of malignancy (Burch et al. 1973), progression of the disease process evidently corresponds to an increase in the number, n , of pathogenic forbidden clones. This relationship between the age-dependence of successive stages of a progressive disease provides powerful quantitative support for our theory. It would not be surprising if the earliest stages of Parkinsonism are initiated in genetically predisposed persons by a single forbidden clone ($n = 1, r = 5$).

Schizophrenia

In 1964, I published an analysis of the age-distribution of admissions to hospitals in New York State (Malzberg 1955), with the diagnosis of schizophrenia (Burch 1964). Despite difficulties of diagnosis, which were reflected in secular changes in the statistics spreading over the period 1919 to 1951, it was possible to conclude that the disease process is started by a single forbidden clone, initiated by two somatic gene mutations ($n = 1, r = 2, k \simeq 1.25 \times 10^{-3} \text{ yr}^{-2}$). The average latent period (λ) between the end of initiation and admission to hospital was twice as long for women as for men ($\lambda_F = 9 \text{ yr}; \lambda_M = 4.5 \text{ yr}$). According to our general theory, this implies that the primary pathogenic agents are mutant small lymphocytes (mutant T-lymphocytes) and that the target tissue is located on the blood side of a blood-tissue barrier (Burch 1964, 1968a). The endothelial lining of certain blood vessels in the brain would appear to be the most likely target tissue, a proposal that is supported by the careful necropsy studies carried out by Johnson and Richardson (1968).

Occasionally, schizophrenia is diagnosed as the primary cause of death. I therefore used the statistics of the Registrar General, England and Wales, 1950-56, to explore the relation between age-specific death-rates from schizophrenia and age. The results are shown in Fig. 12.

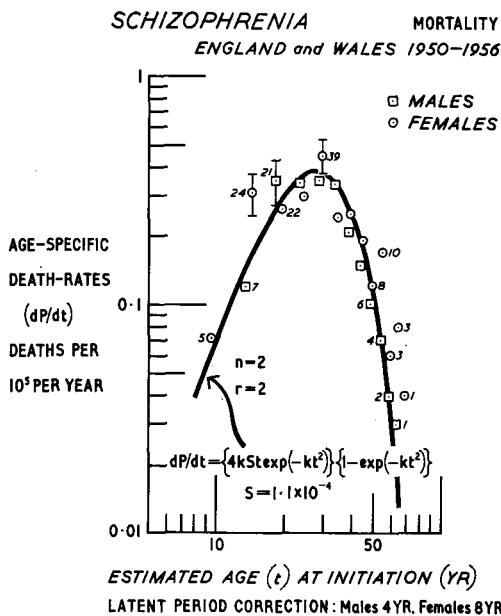


Fig. 12. Sex-specific and age-specific death-rates for schizophrenia, England and Wales, 1950-56. In eqn. [2]: $n = 2, r = 2, k \simeq 1.37 \times 10^{-3} \text{ yr}^{-2}$ and $S = 1.1 \times 10^{-4}$.

Although numbers are small and diagnosis presents the customary difficulties, the mortality data give a surprisingly good fit to the equation in which $n = 2, r = 2, k \approx 1.37 \times 10^{-3} \text{ yr}^{-2}, \lambda_F = 8 \text{ yr},$ and $\lambda_M = 4 \text{ yr}.$ This relationship between onset and mortality — analogous to that for Parkinsonism — suggests, therefore, that a small fraction ($\sim 1\%$) of the subpopulation of schizophrenics is at risk with respect to a fatal attack brought on by a second forbidden clone, with kinetics similar to those of the first.

Multiple Sclerosis

Because of the difficulty in estimating the precise age of onset of this insidious and heterogeneous disease, most large surveys give age-specific prevalence rather than onset-rates. In view of the fatality associated with multiple sclerosis, prevalence data are of little value in assessing the kinetics of the initiation process. Death provides an unambiguous end point and, although multiple sclerosis presents diagnostic difficulties, age-specific mortality data yield important evidence for analysis. Sex-specific and age-specific death-rates from multiple sclerosis in England and Wales, 1946-1950, are shown in Fig. 13. Except for an occasional wild point, the data give a good fit to the stochastic equation in which $n = 3, r = 2.$ In other words, death from multiple sclerosis in England and Wales, 1946-1950, followed the formation of a third forbidden clone. This suggests the hypothesis that the first onset of the disease requires the initiation of a single forbidden clone and that progression towards a fatal outcome involves the initiation of a second forbidden clone.

MULTIPLE SCLEROSIS MORTALITY
ENGLAND AND WALES 1946-1950 (Registrar General)

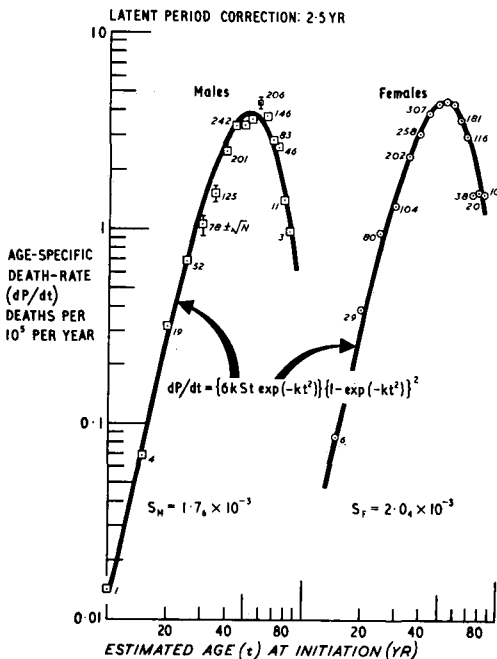


Fig. 13. Sex-specific and age-specific death-rates multiple sclerosis, England and Wales, 1946-50. In eqn. [2]: $n = 3, r = 2, k \approx 4.9 \times 10^{-4} \text{ yr}^{-2}, S_M = 1.76 \times 10^{-3}$ and $S_F = 2.04 \times 10^{-3}.$

These mortality data do not, of course, resolve the issue as to whether an infective agent is necessary to the growth of forbidden clones. However, they do imply that a specific genetic predisposition is essential. The sex ratio, S_F/S_M , of 1.16, is consistent with the hypothesis that a dominant effect X-linked gene, of frequency in England and Wales of about 0.84, contributes to the predisposing genotype. The frequency of autosomal factors predisposing to the fatal form of the disease would then need to be $(1.76 \times 10^{-3})/0.84$, or approximately 2.1×10^{-3} . A wide range of familial evidence reviewed by Berry (1969) is consistent with a genetical interpretation, although the possible importance of local environmental, especially viral, factors complicates analysis. However, reports of associations between HL-A antigens and multiple sclerosis, summarized by Jersild et al. (1972), confirm that genetic factors predispose to the disease.

CONCLUSIONS

The age-patterns of numerous well-defined diseases are reproducibly similar in different environments and at different periods of time. It follows that the timing of the onset of such diseases is likely to depend, in the main, on endogenous factors. Investigation of such factors is therefore essential to the understanding of the pathogenesis of age-dependent diseases.

I have found that a simple theory accounts for the age-dependence of many, and possibly all, well-defined diseases, both neurological and nonneurological. The timing of the onset of a specific disease is contingent upon the occurrence of a specific set of random events in a genetically-predisposed person. Analysis of the properties of these random initiating events leaves little doubt that they are a special form of somatic gene mutation. Thus, their average rate is unaffected by ordinary environments and it remains effectively constant from around birth to the end of the lifespan. In certain diseases, rates correlate with the complement of chromosomes (for example, X and 21 in man); and logical analysis of the main features of the empirical evidence implies that the random events alter the stereochemical relations between central and target recognition macromolecules (Burch 1968*a*). A slight modification of Burnet's (1959, 1972) forbidden clone theory of "autoimmune" disease accounts for these various findings and deductions. In general, r specific somatic gene mutations, in each of n independent growth-control stem cells of a predisposed person, initiate the growth of n forbidden clones of mutant pathogenic cells. These cells, or their humoral products, attack target cells bearing complementary recognition macromolecules.

We can conclude that the timing of disease largely depends: (a) on genetic constitution, and (b) on the spontaneous occurrence of a specific number and type of somatic gene mutations. In the case of the classical infectious and allergic diseases, onset requires the simultaneous presence of a precipitating factor (microorganism, allergen) that allows the growth of forbidden clones that would otherwise be suppressed by the host's defence mechanism. Infective and allergic agents can also modulate the onset and course of noninfectious diseases.

Special interest attaches to the clinical progression of certain diseases, both malignant (Burch et al. 1973), and nonmalignant, including Parkinsonism, schizophrenia and multiple sclerosis. The quantitative details of the age-distribution of distinctive phases of certain diseases show that progression from one phase to the next is determined by the formation of a new forbidden clone. Thus, in Parkinson's disease, "probable" and "definite" cases above the age of 40 yr require the presence of two forbidden clones, each of which is initiated by five somatic mutations in a single stem cell (Fig. 10): death from the disease above the age of 40 yr

requires the formation of a third forbidden clone by five mutations, the kinetics of which are similar to those that initiate the first two forbidden clones (Fig. 11). This type of quantitative relationship between phases can scarcely be an accident and it lends strong support to the forbidden clone concept and the autoaggressive theory of age-dependent disease.

I conclude that the timing of the onset of an organic disorder is one of its most important features, not only from the viewpoint of the sufferer, but also for the understanding of the mechanisms of disease.

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