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POSSIBLE AETIOLOGICAL SIGNIFICANCE OF THE AGE-PATTERN OF CERTAIN DISEASES

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An interesting feature of disease is its age-distribution. This is commonly described in two ways: (1) age-specific and sex-specific onset (or mortality) rate—which defines the proportion of people, by sex and by age-group, developing for the first time (or dying from) the disease per year; and (2) age-specific and sex-specific prevalence—which describes the proportion of people, by sex and by age-group, actually exhibiting the (morbid) disease at a given instant in time.

Malignant Disease

It has been appreciated for many years that if the logarithm of the age-specific mortality rates for all cancers is plotted against the logarithm of age, a remarkably straight line is obtained for most of adult life. Its slope is about 6. A similar relationship is found for many particular cancers, and notably for those of epithelial tissues; there are, however, some interesting exceptions to this simple 'rule' including acute leukaemias and bone cancers.

Using this kind of graph, a straight line of slope 6 indicates that age-specific mortality rates are proportional to about the sixth power of age. Unfortunately this attractively simple mathematical relationship can be interpreted in various ways. Nevertheless there is one exceedingly important feature that is common to all the interpretations that have been put forward, and, indeed, to all biologically plausible models: the carcinogenic process involves stochastic phenomena. At least two random causal events are needed to explain a sixth power dependence and, on a simple view, the maximum number is seven (Muller, 1951; Fisher and Holloman, 1951; Nordling, 1953; Stocks, 1953; Armitage and Doll, 1954, 1957; Fisher, 1958; Burch, 1962). If the initiation of a cancer depended exclusively on random events, and if the age-specific initiation-rate (in the absence of cohort effects) was found to be proportional to the r^{th} power of age, then $(r + 1)$ random events would be required in the initiation process. However, Platt (1955) pointed out that a 'mutant' cell might well enjoy a proliferative advantage over its non-mutant neighbours without actually being malignant. If, therefore, selective growth of mutant cells occurred between one stage of a multi-stage process and the next, the $(r + 1)$ rule would no longer apply. For example, if, between the second and the third (and final) random event, 'stage-2 cells' increased in number with the cube of time, then we should find that age-specific initiation rates would be proportional to the fifth power of age although only three random causal events are implicated. All post-Platt models of spontaneous human carcinogenesis have, in fact, incorporated this concept of selective proliferation and it has the by no means negligible advantage of describing, in mathematical terms, the histopathological evidence for pre-malignant hyperplasia (Willis, 1960). Any general

genic process involves stochastic phenomena. At least two random causal events are needed to explain a sixth power dependence and, on a simple view, the maximum number is seven (Muller, 1951; Fisher and Holloman, 1951; Nordling, 1953; Stocks, 1953; Armitage and Doll, 1954, 1957; Fisher, 1958; Burch, 1962). If the initiation of a cancer depended exclusively on random events, and if the age-specific initiation-rate (in the absence of cohort effects) was found to be proportional to the r^{th} power of age, then $(r + 1)$ random events would be required in the initiation process. However, Platt (1955) pointed out that a 'mutant' cell might well enjoy a proliferative advantage over its non-mutant neighbours without actually being malignant. If, therefore, selective growth of mutant cells occurred between one stage of a multi-stage process and the next, the $(r + 1)$ rule would no longer apply. For example, if, between the second and the third (and final) random event, 'stage-2 cells' increased in number with the cube of time, then we should find that age-specific initiation rates would be proportional to the fifth power of age although only three random causal events are implicated. All post-Platt models of spontaneous human carcinogenesis have, in fact, incorporated this concept of selective proliferation and it has the by no means negligible advantage of describing, in mathematical terms, the histopathological evidence for pre-malignant hyperplasia (Willis, 1960). Any general

treatment of the problem that ignored this phenomenon would be defective.

There are, however, additional complications. It is widely agreed that carcinogenesis can be broadly divided into at least two distinct phases: initiation and promotion (or development). At Hiroshima the clinical onset of leukæmia in survivors was delayed and it did not reach its maximum rate until six to seven years after the nuclear explosion. There are good reasons for supposing that in many cases irradiation completed the initiation phase of leukæmogenesis but that 'promotion' or, to use a more appropriate term, development, required typically an interval or *latent period* of six to seven years. The distribution of the latent period followed a bell-shaped or approximately Gaussian-type curve, and it was not noticeably age-dependent. Interestingly, the latent period distribution was very similar for both chronic and acute leukæmias, and this suggests that the time of growth from one or a few cells to a clinical leukæmia did not constitute a major part of this time lag. (A detailed discussion of this phase of carcinogenesis has been given elsewhere [Burch, 1963b].) It follows, therefore, that if the intrinsic relation between age-specific initiation rates and age is to be assessed from age-specific mortality rates, the latter must first be corrected for the latent period. If the average latent period is age-independent, age-specific initiation rates will be proportional to a lower power of age than mortality rates. They must also be corrected for cohort effects—that is, secular changes in the age-specific mortality rate.

To try to decide exactly how many random initiating events are associated with the ætiology of a particular malignancy it is necessary to deploy more elaborate mathematical arguments and to appeal to a much wider range of evidence. Although the full details of one such attempt remain to be published, certain of the conclusions have been described (Burch, 1962, 1963a, b, c). Suffice it to say that in the ætiology of a 'typical' cancer in the adult, it is concluded that the first 'mutational stage' is often already present in the zygote (deriving from one of the germ cells) and that three somatic mutations (genic or chromosomal) together with a stage of hyperplasia, are needed to complete the initiation phase.

Non-malignant Disease

At first sight, it is rather astonishing that age-specific mortality statistics for many cardio-vascular diseases display somewhat similar characteristics to those described above (Burch, 1963e). That is to say, age-specific and sex-specific mortality rates are proportional to a constant power of age over much of the life-span. The

steepest curves have a slope slightly greater than 10, while the shallowest (for chronic rheumatic heart disease) has a slope, for both males and females, of about 2.5. Again, there is an implication that these diseases are also caused by a rather small number of random events. Although it is not difficult to imagine how a cancer might develop from one or a few cells, each with a few mutant genes, it is not immediately obvious how a small number of random events could lead, for example, to a condition of arteriosclerosis involving an astronomical number of cells. The same kind of dilemma is presented by auto-immune diseases such as rheumatoid arthritis, chronic discoid and lupus erythematosus, progressive systemic sclerosis, Hashimoto's thyroiditis and many others; age-specific and sex-specific onset rates for these disorders are again consistent with the view that a rather small number of random events is involved in their initiation (Burch, 1963d; Burch and Rowell, 1963).

It is suggested that Burnet's (1959a, b, c) forbidden clone hypothesis may well provide the key to the ætiology of auto-immune diseases of this kind—including various cardiovascular diseases. It has been shown that the minimum number of random events (somatic mutations of some kind) required to initiate a single forbidden clone is one, although it can be two, three and possibly four (Burch, 1963d, 1964; Burch and Rowell, 1963e). Thus one or a small number of events in a stem cell of the lymphoid series can initiate and sustain the growth of a clone containing an enormous number of pathogenic cells. Clonal growth provides the amplification whereby one or a few random events—gene mutations of some kind—can be translated into a widespread systemic disorder.

Other amplification mechanisms can be conceived and somatic mutations could, perhaps, release portions of DNA from the genome which, through self-replication could multiply viral fashion (Burnet, 1963). There is, however, no evidence as yet that such a process occurs in man.

Diseases of the central nervous system of unknown ætiology—such as multiple sclerosis—in which there is gross pathological deterioration, present a special challenge, because the existence of the blood-brain barrier is unfavourable to an auto-immune interpretation involving small lymphocytes. Age- and sex-specific onset rates for multiple sclerosis suggest that there is a subtle difference between the system that is disturbed in this disease, and the system that generates small lymphocytes. In some auto-immune diseases it appears that the latent period is longer in females than in males; in multiple sclerosis it may well be of the

same duration in both sexes although better statistics are required to confirm this impression. The primary disturbance may, therefore, arise in a cell system that generates a clone in which a 'forbidden' humoral factor, capable of diffusing through the blood-brain barrier, is synthesized.

Infectious Diseases

No detailed study has yet been made of the implications of the age-pattern of mortality from infectious diseases. The pattern is sometimes very erratic (e.g. nephritis and nephrosis) and sometimes very regular (e.g. tuberculosis). Cohort changes will influence profoundly any 'intrinsic' pattern and the episodic nature of infections makes it difficult to draw general conclusions. Nevertheless it is distinctly possible that the immediate cause of death from certain infectious diseases may be the emergence of a forbidden clone of lymphoid cells provoked by the infective agent. Such a phenomenon could account—at least in

part—for the association between genetic factors and resistance to infectious agents.

Conclusions

The age-, and sex-specific onset-rates for many diseases are highly distinctive. Where patterns are reproducible from one period to another, and from one country to another, it is clear that there must be an intimate link between the pattern and the underlying aetiology. The regularities associated with malignant disease are striking but those connected with auto-immunity are even more remarkable. Detailed mathematical analysis reveals some very simple and intriguing statistical properties of the cell system at risk with respect to disturbed tolerance auto-immunity (Burch, 1963d; Burch and Rowell, 1963). It is hoped that, as experience in this field of analysis accumulates, it may be possible to apply the technique to diseases of unknown aetiology. At the least it furnishes an additional tool for the unravelling of the causes of disease.

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