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Cancer and Senescence: Is There a Biological Link?

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Abstract. It is shown that sex- and age-specific death rates from all causes of death other than neoplasms have features that resemble those of corresponding rates for all neoplasms. The same generalization holds in connexion with specific neoplastic and non-neoplastic disorders. In both categories of disease many age-patterns suggest that the rate-governing mechanism for their occurrence is stochastic in character; a rather small number of random events, generally fewer than ten, suffice for their initiation. It is not immediately obvious how a widespread degenerative disorder, sometimes involving an astronomical number of target cells, can be initiated by only a few random events. We infer that all such disorders, together with natural cancers, are *autoaggressive* in nature. They are initiated by random somatic mutations in comparator stem cells of the central system of growth control. Mutant stem cells propagate forbidden clones of cells that attack target cells at one or multiple sites. (In certain disorders, the presence of an extrinsic precipitator in the host in essential to the propagation of forbidden clones). Autoaggressive attacks have consequences that range from the destruction of target cells to their transformation with invasive proliferation. Senescence can be regarded as the cumulative effect of predominantly late-onset autoaggressive disorders. The relevance of studies of twins to this unified theory is discussed.

Key words: Ageing, Autoaggressive disorder, Cancer, Forbidden clone, Somatic mutation, Twins

INTRODUCTION

The idea that carcinogenesis and senescence have similar initiating mechanisms and intimate biological links commands little support. Thus many epidemiologists and experimental oncologists believe that the great majority of cancers are caused by environmental agents. Gerontologists, by contrast, pay rather little attention to environmental factors

although dietary levels are known to influence markedly the lifespan of rodents. Studies of twins reveal a marked genetic influence on the lifespan [14] and ageing is usually regarded as a biological process. Most experimental gerontologists pursue a reductionist philosophy, seeking an explanation for organismal senescence in the ageing of cells in culture.

I have little sympathy with these fashionable views. Preoccupation with environmental carcinogens is in some ways highly commendable but the near exclusion of biological and genetic considerations shows a lack of scientific detachment that must be regretted. Cigarette smoke is alleged to cause 85% of lung cancers and 30% of all cancers in the United States [19], but when due consideration is given to constitutional factors and scientific logic this view is rejected [4,7]. On the other hand, there is little doubt that environmental factors are often important, both in carcinogenesis and senescence. Indeed, we are seldom able to exclude an essential role for what I call *precipitating factors*, of which microorganisms of all kinds, together with allergens, are the best known examples. Death from the number one killer, ischaemic heart disease, seems to entail the action of such an agent [6].

Reductionism has, of course, an indispensable part to play in unravelling the mysteries both of senescence and of carcinogenesis, but we must not lose sight of the whole organism in studying its constituent cells. Holism and reductionism should be regarded as complementary rather than antithetical.

My collaborators and I see natural cancers and senescence as different outcomes from similar pathogenetic mechanisms: both phenomena appear to be initiated by random changes in the central system that, under normal physiological conditions, controls the growth and, in maturity, maintains the size of target tissues throughout the body [2,4,8,9]. In both classes of disorder the kinetics of the pathogenetic processes appear to obey the same general stochastic laws. These include the postulate that any specific initiating event has a constant average rate of occurrence from around birth throughout growth and maturity to death. Given this distinctive and unexpected property it seems unlikely that the two types of disorder arise from fundamentally different biological mechanisms. On the other hand, the effects and consequences of autoaggressive attacks differ enormously, ranging from the destruction of target cells to the promotion of invasive malignant growth.

This unified theory of growth and age-dependent disease has resulted from a fusion, modification and extension of two seminal ideas: Burnet's 'forbidden clone' theory of so-called 'disturbance-tolerance autoimmunity' [11] and Burwell's concept that morphostasis is regulated by the lymphoid system [12]. Both ingredients of our synthesis are essentially biological in character and studies of twins can and have illuminated many of their details. The importance of such studies is discussed below.

THE AGE-DEPENDENCE OF FATAL DISORDERS

Although 'ageing' lacks an agreed definition, the increase with age in the risk of dying is widely regarded as one of its most important manifestations. For my present thesis it is therefore pertinent to consider at the outset the age-dependence of mortality, first from all neoplasms, and second from all other causes (Fig. 1).

The Registrar General's data for sex- and age-specific death rates by 5-year age groups in England and Wales, 1980 [17], are plotted on a logarithmic scale against age, also on a logarithmic scale. A straight line on such a graph of slope b signifies that age-specific death rates increase with the bth power of age. For non-neoplastic diseases in men we see that, from the age of 40 up to 90, death rates increase with a power of age of just over six; over the age range 40 to 70, death rates from all neoplastic deseases have a sixth power dependence on age; at 85 they reach a peak. For women, age-specificity mortality from non-neoplastic disease depends on $(\text{age})^{4.9}$ from 40 to 60 and on $(\text{age})^{8.2}$ from 65 years and above. However, for neoplastic diseases, the age-dependence is less steep than for men, being approximately a fourth power function from 25 up to 85 years of age.

Normally, I deprecate the pooling of heterogeneous data, for many diseases, in this way and I do not propose to draw any detailed quantitative conclusions from Fig. 1.

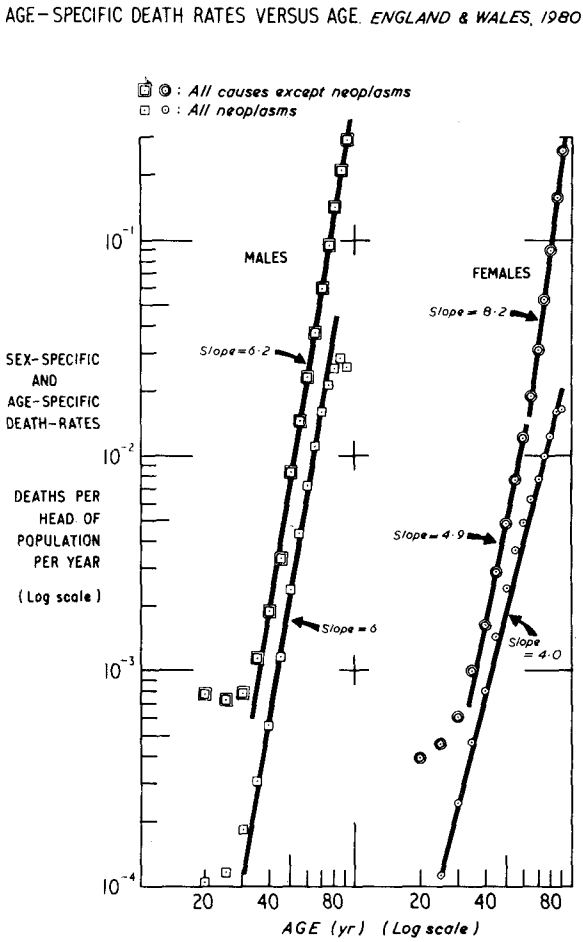

Fig. 1. Sex- and age-specific death rates by 5-year age groups, England and Wales, 1980, versus age [17]. Log-log scales. Symbols ◘ and ◙ relate to mortality from all causes except neoplasms; □ and ○ relate to mortality from all neoplasms. Rates for the age group 20 to 24 years of age are plotted at age 20 years, etc.

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However, I do wish to point to the broad similarity in the forms of the age-dependence, namely, comparable power functions, of these clinically contrasted types of fatal disorder. At the least, we cannot exclude the possibility that similar mechanisms might be involved in the pathogenesis of these varied diseases.

Of course, it is more valuable to examine in detail the various age-patterns of *specific* disorders, within both classes of disease. When we do so, we find that the same general stochastic laws apply throughout; differences between patterns of initiation are governed by the number, types and rates of initiating events [2,4,6,9].

INTERPRETATION OF AGE-DEPENDENCE

This correspondence of the underlying features of the age patterns for both classes of disease is particularly intriguing because, since 1951, much attention has been directed to the interpretation of the age-dependence of malignant diseases and very little to that of non-neoplastic diseases. How has this curious dichotomy developed?

Almost without exception the age-patterns of malignant diseases have been interpreted in stochastic terms [4]. Most attention has been devoted to adult-onset cancers, especially carcinomas, and investigators have postulated that at least two random events, spontaneous or induced, are needed to explain the steeply rising incidence with age. These random events are usually identified with some form of somatic mutation and almost every author (since 1968 I have been an exception) has assumed that these initiating mutations occur in one or a few cells that, at the end of the promotion phase, divide to propagate the tumor.

Undoubtedly, this is a highly plausible and readily grasped concept. From animal experiments we know that a single malignant cell, transplanted into a suitable host, is capable of developing into a malignant growth. On these grounds, we can readily accept that spontaneous or induced somatic mutations in a single cell, say an epithelial cell, will so change its character that a carcinoma will result.

Unfortunately, this same concept cannot readily be extended to most non-neoplastic disorders. (It is not without interest, however, that the Benditts [1] believe that cells in an atherosclerotic plaque are the progeny of a single mutated smooth-muscle cell). Our difficulties become severe when we consider obviously multi-centric or multi-focal disorders of ageing such as osteoporosis, polyarthritis, the loss and greying of hair, bilateral arcus senilis, the loss of 'permanent' teeth, etc. [2,3,9,10]. Neverthless, the age-dependence of all these non-fatal disorders, and fatal ones of a non-neoplastic character, strongly suggests that a few random events (not always in a single cell, but seldom in more than ten cells) suffice to initiate these multi-focal or dispersed degenerative conditions. How does pathogenesis proceed from the few to the many; from, say, one mutant cell to the deterioration of millions?

We cannot easily avoid postulating some form of biological amplification and the diffusion or circulation of a pathogen to multiple sites. Burnet's concept [11] of 'forbidden clones' enables us to bridge the gap between the few to the many. In 1959, Burnet proposed that certain so-called 'autoimmune' diseases develop when somatic mutations in lymphoid cells produce *autoantibodies* that attack target cells bearing complementary antigens. A mutant lymphoid stem cell is said to propagate a clone of lymphocytes and plasma cells and the secreted autoantibodies then attack complementary target cells at one or many anatomical sites. Although Burnet's scheme readily circumvents the diffi-

culty of progressing from the few to the many, we have concluded, for many reasons, that immunoglobulin autoantibodies are *never* the *primary* cause of age-dependent disorders, degenerative or neoplastic [2,4,8]. To begin with, so-called autoimmune diseases occur very commonly both in congenital and acquired hypogammaglobulinaemia.

For more complicated reasons, Burwell and I have inferred that the system from which forbidden clones of pathogenic cells arise is the *central system of growth-control* [8]. Under normal physiological conditions the growth of the body is, we believe, regulated and coordinated by two sections of what, for want of a better term, we loosely call the 'lymphoid system'. A homeostatic mechanism is involved and, normally, it maintains the size of target tissues throughout maturity (Fig. 2). One section, based on T-lymphocytes, governs the growth and size of those target tissues, notably endothelia, to which it has ready access. The other section, involving (perhaps) mast cells as the final executive cells, controls the growth and size of those tissues that lie behind blood-tissue barriers.

In any feedback system of this kind, an outstanding problem is that of specificity. The human organism is immensely complicated and many of its 10^{15} cells are grouped into mosaic elements that, in turn, are assembled into the elaborate architectural structures recognized as individual organs. In spite of this awe inspiring complexity, morphological and functional harmony are normally maintained throughout growth and maturity.

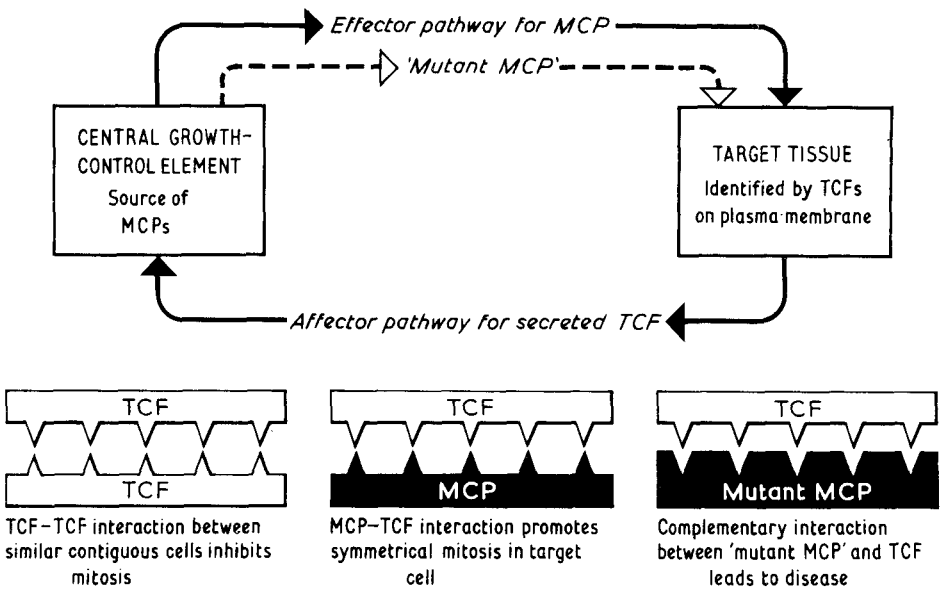

Fig. 2. Outline of unified scheme for the central homeostatic control of growth and the mechanism of autoaggressive disorders [2,4,8]. Each distinctive set of mosaics of a target tissue has its own central controlling element; parhaps three feedback loops are involved. Mitotic control proteins (MCPs), humoral or cell bound, promote symmetrical mitosis in target cells. In autoaggressive disorders the identity relation between cognate MCPs and TCFs is replaced by a complementary and pathogenic relation between the mutant MCP and its target TCF.

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Nevertheless, the growth curve of each major organ differs from that of every other one and hence some measure of independence exists; the specificity of regenerative growth implies a large measure of independence.

We infer that each distinctive mosaic set, of every distinctive tissue, has its own central growth-controlling element. It follows that effectors of growth have to be able to recognize their cognate target mosaic; equally, affectors, secreted from and signalling the size of target mosaics, have to be able to recognize their cognate receptors in the central controlling system (Fig. 2). We call *effectors*, MCPs (mitotic control proteins), and *affectors*, TCFs (tissue coding factors). Both are complicated proteins, the polypeptide components of which are coded by at least eight genes. We conclude that the recognition proteins on the cytoplasmic membrane of a given target cell are identical with those of the affector TCF it secretes [2,4,8]. Recognition – of TCFs on target cells by effector MCPs, and of central control receptors by affector TCFs – is achieved by the most economical and simplest device possible. Two independent arguments lead to the conclusion that the recognition polypeptide components of a specific MCP are identical with those of its cognate TCF; the same coding genes are used for recognition purposes in both central and target cells [2,4,8]. London-van der Waal's self-recognition forces would appear to constitute the basis of mutual recognition at both ends of the feedback loop.

The *comparator* in this homoeostatic system – the device that serves as a constant 'yardstick' for measuring and regulating the growth of target tissues and determining growth potential – is a fixed number of growth-control stem cells [2,4,8]. We infer that these comparator stem cells, having accumulated the appropriate complement of somatic gene mutations, propagate pathogenic forbidden clones (Propagation sometimes requires the presence in the host of a precipitator). The normal MCP is replaced, through somatic mutation, by a mutant MCP with a steric structure that is complementary, rather than identical, to that of its target TCF. This complementarity gives rise to a specific but strong and pathogenic interaction between the mutant MCP and the target TCF. We have proposed that MCP-TCF genes are near-palindromic and that 'somatic mutation' might entail a switch in transcription from the 'normal' strand of DNA over to the anti-parallel, complementary strand [2,4].

In neoplastic disease, the interaction between mutant MCP and target TCF stimulates excessive mitosis of target cells, sometimes hyperplastic but at other times malignant and invasive, either at the outset, or after one or more stages of progression. Progression is caused by an increase in the number of initiated forbidden clones.

We call all those diseases – neoplastic and non-neoplastic – that result from random changes in growth-control stem cells and attacks on target cells: *autoaggressive*. We regard 'ageing' as a conglomeration of those autoaggressive disorders, fatal and non-fatal, that manifest generally late in life.

PHASES OF AUTOAGGRESSIVE DISEASE AND RELEVANCE OF TWINS STUDIES

The following main phases can be delineated.

1. Genetic Predisposition

A specific genetic predisposition is essential to the development of a specific autoaggressive condition. In various classical disorders of ageing, such as greying of hair and the loss

of permanent teeth, 100% of at least some populations are at risk and hence familial and twins studies would fail to reveal a genetic contribution [2,10]. In Huntington's chorea, by contrast, the frequency of the main predisposing allele is under 10^{-6} in Japan, although it approaches 10^{-4} in England and Wales [5]. Genes determine not only predisposition to a disorder as such but also to the particular anatomical site, or sites, that are at risk.

A serious complication arises in connexion with the heterogeneity of disease: what is broadly diagnosed as acute lymphocytic leukaemia – to take an extreme example – probably consists of at least five genetically-distinctive disorders [4]; in studies of concordance for an autoaggressive disorder in twins, meaningful comparisons between MZ and DZ series require homogeneity. Even within a homogeneous disorder – insofar as the initiating process is concerned – the average interval between initiation and death, as with acute myocardial infarction, can differ widely. Death from this common disease appears to depend on an extrinsic precipitator but, in a given environment, the average duration from initiation to death depends on genes [6].

Potentially the most serious complication of all, especially in connexion with twins studies and the concept of *heritance,* concerns the assumption of genetic identity of MZ twin and co-twin. Genuine discordances within such pairs are customarily assigned to environmental factors because the axiom of identity rules out a genetic interpretation. Unfortunately, my theory casts doubt on the general applicability of this axiom to autoaggressive disorders [4] and direct observation of phenotypes [13,15,16,18] certainly rejects it. Predisposition to an autoaggressive disorder is determined by the MCP-TCF genes that are functioning at the completion of cytodifferentiation at, or around, birth. During post-natal life MCP genes, unlike blood group genes, suffer a high rate of spontaneous mutation (DNA strand-switching?) in growth-control stem cells. If, during intra-uterine life, mutation rates are similar, then we may expect that MZ twins will often be rendered discordant for predisposition to autoaggressive disorders. Maternally-induced mutation and gross chromosomal abnormalities and aberrations [15,16,18] will make further contributions to genetic discordance. Mirror imaging is an obvious form of discordance involving, in my theory, 'left-determining' MCP-TCF genes in one twin, say, and 'right-determining' genes in the co-twin. This phenomenon suggests that MZ twins might be unusually vulnerable to 'somatic mutation' at the division of the embryo. If that is the case, then the concordance ratio between MZ and DZ twins will be biassed against MZ twins. Genetic discordances arising from any of these mutational mechanisms might help to explain the failure to observe 100% concordance in MZ twins (correcting for penetrance) for disorders known to have an important genetic component, such as insulin-dependent diabetes mellitus. In interpreting such observations, we need to distinguish between the following: (a) discordance arising from somatic mutation, spontaneous or induced, in one or both twins during intra-uterine life; (b) discordant invasion of MZ twins during post-natal life by an environmental precipitating factor such as a virus; (c) a combination of (a) and (b). To establish (a) it will probably be necessary to identify the polypeptides of the discordant MCP-TCF genes by immunological or biochemical methods.

If these predictions concerning a somatic mutational source of discordance in MZ twins were to be verified, then the concept of heritance would need to be reconsidered. In the theory of autoaggressive disease, a specific genetic predisposition to a 'natural' disorder is essential, but in all infectious and allergic diseases – they are particular forms of autoaggressive disorders – a specific environmental precipitator in also essential [2,4].

2. Initiation Phase

Initiation entails the random occurrence of one or more (r) specific somatic gene mutations in one or more (n) comparator cells of the central system of growth-control [2,4]. The natural process of initiation in growth-control stem cells is virtually unaffected by ordinary environments, although neoplasia may be initiated by one or more mutations induced in peripheral (executive) growth-control cells by carcinogens such as ionizing radiation and chemical initiators. The average rate of occurrence of any natural initiating mutation is effectively constant from around birth to the onset of the disease even when that takes place towards the end of the normal lifespan. In non-neoplastic disorders, such as inflammatory polyarthritis [3] or gingival recession [9] (a classical disorder of ageing known colloquially as 'getting long in the tooth'), clinical severity increases with the number (n) of initiated forbidden clones. In neoplastic disorders progression from, for example, dysplasia, to carcinoma in situ, via microinvasive carcinoma to fully invasive carcinoma, is determined by a stepwise (random) increase in the number of forbidden clones [4].

Large scale studies of the distribution of the interval between onset in concordant MZ twins will shed valuable light on the stochastic properties of the initiation process. In principle, the age-pattern of onset of an autoaggressive disorder in singletons can be used to correct for incomplete penetrance not only in singletons but also in twins.

3. Development Phase. Promotion

Completion of the initiation phase does not necessarily lead to disease. An endogenous defence mechanism, based on immunoglobulin antibodies, is normally directed against mutant growth-control stem cells. In infectious and allergic diseases this defence is completely effective in the absence of the precipitating microorganism or allergen. Similarly, in an effectively immunized host, the concentration of defence antibodies will be sufficient to cope with the invading microorganism and the mutant growth-control stem cell. However, in the absence of an adequate endogenous defence, mutant growth-control stem cells propagate forbidden clones the cells or humoral products of which attack target cells. When the severity of attack exceeds a certain threshold, the symptoms and signs of autoaggressive disease become manifest.

This is the phase of disease that is vulnerable to extrinsic precipitating and exacerbating agents. Given observations about concordance for genetic predisposition and reliable expectations for penetrance, the extent of concordance for onset in MZ twins should provide valuable tests of hypotheses about the role of extrinsic precipitators.

4. Terminal Phase of Fatal Diseases

Death, particularly in many malignant diseases, often follows the occurrence of a single random event, probably within a forbidden clone cell [4]. In certain diseases, notably ischaemic heart disease, the average rate of occurrence of this fatal event in males appears to be double that in similarly predisposed females [6]. Hypotheses about the distribution of intervals between onset and death can be tested with MZ twins data.

CONCLUSIONS

Senescence may be regarded as the collective effect of many predominantly late-onset specific autoaggressive disorders. Natural cancers also belong to the autoaggressive cate-

gory and have the same type of initiating mechanism as non-neoplastic disorders. Studies of twins, particularly MZ pairs, are capable of testing hypotheses of each phase of auto-aggressive disease.

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