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**There is no such thing as aging**

**Old age is associated with disease, but does not cause it**

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Taking all diseases together (but ignoring deaths from accidents or violence), the total death rate in developed countries such as Britain is 500 times greater at age 80 than at age 20. For vascular disease, chronic respiratory disease, and cancers of the digestive or respiratory tract, this ratio is more than 1000 to 1. Why? What biological mechanisms account for this vast difference in mortality between old and young adults? And, since so many major diseases are much more common in old than in young adults, does this imply that there must be some common biological process called “aging” that causes all of these large differences in mortality? Our answer, particularly for cancer, is that it need not do so.[1](http://www.bmj.com/content/315/7115/1030#ref-1)

What the major diseases of adult life have shared for tens of millions of years is a common set of evolutionary pressures tending to relegate them to old age, but such relegation is likely to involve many different mechanisms. Natural selection acts much more strongly against death in early adult life than against death in old age. Hence, other things being equal, all major adult diseases will tend to be much commoner in old age than in early adult life.

Before asking whether “aging itself” has any direct effects on the development of disease, it may be useful to consider whether there is any fundamental biological process that can usefully be labelled aging. If so, what is it? Is it baldness, greyness, dementia, wisdom, vascular disease, pre-neoplastic changes, immunological deterioration, collagen cross-linking, or genetic changes in particular somatic cells? Many years ago the biologist Alex Comfort commented: “Throughout its history, the scientific study of ageing has been ruinously obscured by theory, and particularly theory of a type that begets no experimental hypotheses.” Perhaps the very existence of aging itself is just such a theory. For example, if we want to understand the mechanisms by which lung cancer arises we should study these and not the mechanisms of some other age-related phenomenon such as the menopause; conversely, if we want to understand the timing of the menopause, of the progressive loss of tissue elasticity due to cross-linking of collagen, or of senile cataracts we should study each of them directly.

When many different age-related phenomena are fully understood, some will probably have part or all of their mechanisms of origin in common, but some may not. For now, unnecessary confusion can be avoided, at least in discussions of the biological mechanisms of particular chronic diseases, by accepting that the underlying mechanisms may be different and by avoiding careless use of such an undefined physical concept as the “aging” of a tissue or an individual.

Consider, for example, the development of carcinomas in organs that are common to both sexes (and hence not strongly influenced by age related changes in levels of sex hormones). Such carcinomas account for about two-thirds of all deaths from cancer in developed countries, and the death rates from them are roughly proportional to the fifth power of age[2](http://www.bmj.com/content/315/7115/1030#ref-2) (which, since the fifth power of 80 is 1024 times the fifth power of 20, yields the 1000-fold difference in mortality already noted between ages 80 and 20). Ever since the 1950s it has been recognised that such a power-law relation could be produced by a “multistage” model in which the process of changing a normal epithelial stem cell into the seed of a growing cancer involves several consecutive changes in the genetic material of that cell, with the rate of progression of a partially altered cell from one stage to another being largely unaffected by age.[3](http://www.bmj.com/content/315/7115/1030#ref-3)

If, for example, there are six stages that are rate limiting (that is, improbable in the time available) then the mortality from cancer would be expected to be approximately proportional to the fifth power of age.[2](http://www.bmj.com/content/315/7115/1030#ref-2) [3](http://www.bmj.com/content/315/7115/1030#ref-3) Roughly the same relation with age would, however, be predicted by many different biological models,[2](http://www.bmj.com/content/315/7115/1030#ref-2) such as those having fewer stages but some selective advantage of partially altered cells over their unaltered neighbours[4](http://www.bmj.com/content/315/7115/1030#ref-4) or more stages but susceptibility to neoplastic change varying substantially between individuals.[1](http://www.bmj.com/content/315/7115/1030#ref-1) Hence, these early multistage models had little predictive power, but they did show that the 1000-fold differences in cancer rates between old and young adults do not necessarily imply any effect of “aging” on the separate cellular processes leading to cancer. This conclusion has been confirmed by animal experiments in which carcinogenic treatments were started at different ages. In some (despite a power-law relation of risk to the duration of treatment) age was of no independent relevance to the production of cancer,[1](http://www.bmj.com/content/315/7115/1030#ref-1) [5](http://www.bmj.com/content/315/7115/1030#ref-5)and in others carcinogenic treatments elicited cancer *less* rapidly in older than in younger animals.[1](http://www.bmj.com/content/315/7115/1030#ref-1) [6](http://www.bmj.com/content/315/7115/1030#ref-6) [7](http://www.bmj.com/content/315/7115/1030#ref-7)

But, although there may be no direct link between any one thing that can usefully be called “aging” and the rates of the separate cellular processes that culminate in cancer, there remains a strong and mechanistically unexplained relation between the life-span and the rates of these processes. Consider, for example, two species such as mice and men that differ 1000-fold in body weight and 30-fold in normal lifespan (2.5 years *vs* 75 years). Suppose that both species have a probability of a few per cent of developing cancer by the end of this life span and that in both the incidence of cancer is roughly proportional to the fifth power of age. It can then be shown that, at age *t* years, the probability per gram of tissue of giving rise to a new cancer tomorrow would be about 10−7 × *t*5 for mice and 10−19 × *t*5 for humans.[1](http://www.bmj.com/content/315/7115/1030#ref-1)These differ by a factor of a trillion. Whether this factor is a billion or a trillion does not matter so much as the fact that it is very large—as it has to be, for if every mouse-sized lump of tissue in the human body had a probability of a few per cent of producing cancer in a mouse-sized life span, humans could not survive.

It is intriguing to consider that just a few tens of millions of years of evolution since mice and men separated have produced this trillion-fold decrease in the constant of proportionality relating cancer rates to the fifth power of age. Presumably human cells have managed to defend themselves against mutation far more effectively than mouse cells, but the details remain obscure, and these vast differences have not yet been accounted for, remaining an important challenge to our understanding. For, if we could produce just a two-fold further decrease in this constant in humans, we could halve the cancer problem.

Similar considerations probably also apply to a wide range of adult diseases: the fact that they tend to arise in the same part of the life-span is not good evidence that they have similar underlying mechanisms, nor is it good evidence that any single, unifying change awaits discovery that could properly be called “aging.” What the many diseases of old age chiefly share is, we suggest, not a common aetiology but a common teleology.

We acknowledge extensive use of previous work by S E Parish and R G Gray.[1](http://www.bmj.com/content/315/7115/1030#ref-1)

**References**

* 1. Likhachev A, Anisimov V, Montesano R, Peto R, Parish SE, Gray RG. There is no such thing as ageing, and cancer is not related to it. In: Likhachev A, Anisimov V and Montesano R (editors). Age-related factors in carcinogenesis. Lyon: IARC, 1986; 43-53. (IARC Scientific Publication 58)
  2. Peto R. Epidemiology, multi-stage models and short-term mutagenicity tests. In: Hiatt HH, Watson JD, Winsten JA (editors). Origins of human cancer. New York: Cold Spring Harbor Laboratory, 1976; 1403-28.
  3. Armitage P, Doll R. The age distribution of cancer and a multi-stage theory of carcinogenesis. Br J Cancer 1954; 8: 1-12.
  4. Armitage P, Doll R. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. Br J Cancer 1957; 11: 161-69.
  5. Peto R, Roe FJC, Lee PN, Levy L, Clack J. Cancer and ageing in mice and men. Br J Cancer 1975; 32: 411-26.
  6. Stenback F, Peto R, Shubik P. Decrease in promotion by TPA with ageing. Br J Cancer 1981; 44: 15-23.
  7. Gray R, Peto R, Brantom P, Grasso P. Chronic nitrosamine ingestion in 1040 rodents: the effect of the age of starting exposure. Cancer Res 1991; 51: 6470-91.