explanation need not be invoked. The reversion of the incidence function to background rates is a mathematical consequence of multistage carcinogenesis.

The third consequence has to do with the incidence of second malignant tumours among individuals in whom one has already occurred. A computation using the exact solution shows that the age-specific incidence of second malignant tumours is higher than the age-specific incidence of the first malignant tumour (at the same age). While the incidence of second malignant tumours is difficult to study in human populations because of the treatment intervention after the occurrence of the first tumour, animal experiments appear to show that this is indeed true.[13] The explanation has been advanced that physiological and immunological changes after the first malignancy renders the animal susceptible to a second tumour. This may be true but the higher incidence of second tumours is a logical consequence of multistage carcinogenesis.[14]

It is a rare paper that continues to be widely cited 50 years after publication. The paper describing the Armitage-Doll model—often referred to as THE multistage model—is one such rare paper. I congratulate Professors Armitage and Doll on the occasion of the republication of this important and influential paper.

Acknowledgements

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Commentary: The age distribution of cancer and a multistage theory of carcinogenesis

Richard Doll

In 1948, when I began to work with Professor Bradford Hill at the Medical Research Council's Statistical Research Unit, ideas about the causes for cancer were still dominated by those of the great German pathologists of the 19th century. A favourite idea was that cancers arose from embryonic cells that had persisted unchanged in character in adult tissues. The idea that a cancer might arise from a mutation in the hereditary material of a somatic cell had been suggested at least as early as 1930 by McCombs and McCombs[1] and this, I believe, had also been suggested some 15 years before, but I forget by whom. It was not, however, widely believed, which was surprising in view of the fact that Muller's demonstration,[2] as long ago as 1927, that X-rays could produce hereditary mutations in fruit flies was universally applied and its application to humans was not questioned. X-rays, however, were not thought to be able to cause cancer unless they had caused macroscopic damage to tissues.[3] Even as late as 1960 it was possible for Austin Brues, a distinguished American scientist, to write a 'Critique of mutational theories of carcinogenesis'.[4]

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The problem was that the mutational theory, to which Brues referred, postulated a *single* mutation and it was difficult to see how this could be made to account for some of the characteristic features of human cancer such as the rapid increase in incidence with age and the long latent period. It was another idea proposed by Nordling,[5] for which he has received practically no credit, that qualitatively altered the situation and allowed so many of these perplexing characteristics to be explained.

Why then did Armitage and I not refer to mutations, but only to 'changes of state'? This, we said in our article, was partly because of Berenblum and Shubik's[6] evidence for two different types of carcinogenic materials—initiators and promoters—and partly because the nature of the changes was irrelevant to the mathematical analysis. It is difficult after so long a time to know what we had believed at the time, but I am pretty sure that we had mutations in mind. We did not want to describe the changes as such, however, as we did not want to put off the many cancer specialists, who were not happy with the mutational theory, from considering the idea that, whatever they were, the changes in a cell that made it the origin of a cancer clone were not a single event but a series of events, and that the factors that caused the changes to occur might vary in strength throughout an individual's life, irrespective of whether they were external or internal in origin.

What I now find surprising, now that the concept of multiple mutations is so widely accepted, is that so many people fail to see that it accounts for the fact that only a relatively small proportion of people (<20%) are commonly victims of a particular type of cancer even if heavily exposed to known chemical carcinogenic agents. There have been two small groups of men who were very heavily exposed to chemical carcinogens in the course of their work in which all were affected, but they are atypical. The fact that only, say, 20% of heavy cigarette smokers would develop lung cancer by 75 years of age in the absence of other causes of death does not mean that 80% are genetically immune to the disease any more than the fact that usually only one cancer occurs in a given tissue implies that all the stem cells in the tissue that have not given rise to a malignant clone are also genetically immune. What it does mean is that whether an exposed subject does or does not develop a cancer is largely a matter of luck; bad luck if the several necessary changes all occur in the same stem cell when there are several thousand such cells at risk, good luck if they don't. Personally I find that makes good sense, but many people apparently do not.

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