MILESTONE 9

It takes (at least) two to tango

During the first half of the twentieth century, the view that genetic mutations could cause cancer was gaining firm ground (see [Milestone 2](#)). Yet, ideas about viral causes were also widespread, and the genetic model had yet to explain the age distribution of cancer incidence.

A multitude of studies in the 1950s and 1960s applied mathematical models to cancer-mortality rates as a function of age, to explore whether a series of mutations, accumulating over time, could explain the epidemiological data. If cancer was caused by successive mutations (or hits) its incidence should be associated with a certain power of age. This approach led, for instance, Carl Nordling to conclude that, indeed, around seven mutations fitted the age distribution for a range of human cancers. Peter Armitage and Richard Doll reached similar conclusions in a paper from 1954, but, in a further study in 1957, revised their model to conclude that the epidemiological data were consistent with many common forms of cancer developing in two steps, of which one or both could be somatic mutations.

Other work in the 1950s and 1960s, including that of James Neel and Philip Burch, concentrated on childhood cancers whose development in early life reduced some of the complexity of other forms of cancer; this led researchers to deduce that multiple, perhaps as few as two, inherited and/or somatic mutations had a role in [retinoblastoma](#), neurofibromatosis and child-

hood [leukaemias](#) (see also Further Reading).

In a seminal paper in 1971, Alfred Knudson took the idea of multiple hits an important step further. He noted that “what is lacking is direct evidence that cancer can ever arise in as few as two steps and that each step can occur at a rate that is compatible with accepted values for mutation rates”. Knudson analysed 48 cases of retinoblastoma for the occurrence of bilateral or unilateral tumours, and the presence of a family history of the disease. Using Poisson statistics, he showed that the distribution observed was consistent with retinoblastoma being caused by two mutations. In familial cases, one hit was inherited whereas the other one was acquired later; in sporadic tumours, both changes were somatic, with a similar mutation rate for both hits. The Knudson model explained why multiple tumours occurred in both eyes in inherited cases, but only unilaterally in sporadic occurrences.

Knudson and colleagues subsequently extended the two-hit model to secondary tumours in retinoblastoma patients and to other childhood cancers. The now famous two-hit hypothesis was, in later years, to merge with the concept of allelic loss of tumour-suppressor genes when it became clear that the development of retinoblastoma was associated with mutations in both alleles of the retinoblastoma gene *RB* (also known as [RB1](#)), and that one *RB* mutation was inherited in familial cases of the disease (see [Milestone 11](#)).

The current view of cancer has built on these findings: we now know that all human cancers display a multitude of genetic and epigenetic changes, and that a number of such alterations are required for the step-wise progression of tumour development (see [Milestone 14](#)).

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References and links

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URLs

[retinoblastoma](#)

<http://www.cancer.gov/cancertopics/types/retinoblastoma>

[leukaemia](#)

<http://www.cancer.gov/cancertopics/types/leukemia>

[RB1](#)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=592