Letter to the Editor

On the monoclonality of tumours

Sir – Alexander (1985) seeks to explain the very large difference between the frequency of in vitro transformation of rodent fibroblast cells and that of in vivo transformation which leads to frank carcinoma in animals and man, by questioning the long held view that cancer develops from a single transformed cell (Alexander, 1985). He proposes that several transformed cells are required to create an environment in which a transformed cell can divide, the key element of this environment being autocrine growth factors. Evidence for this hypothesis derives from the observation that in vitro transformed rodent fibroblasts will not grow from low inocula in plasma but only in serum, which contains growth factors, and from the distribution of secondary cancers in animals injected with malignant cells which indicates that these single foci will only grow to tumours in organs or tissues in which the environment is conducive – i.e. rich in growth factors.

This hypothesis of multi-cellular origin of cancer can be tested by reference to observations on the radiation induction of cancer in man. The causal relationship between cancer and radiation is well established. Radiation (low LET) causes local (on the molecular scale) depositions of energy which are randomly distributed within and between cells. Thus the dependence of cancer on dose will reflect either the number of energy deposition events in each cell required to produce a cancer or the number of cells so affected to produce a cancer.

Human epidemiology is a relatively blunt tool and dose response data are not easily come by. However radiation induced cancer of the breast in young women shows a linear dose response (Tokunaga et al., 1984); a result indirectly confirmed by the lack of a dose rate effect for the disease (Baverstock et al., 1981). Linearity can only be interpreted as implying one event in a single cell as an essential requirement.

Thyroid cancer also exhibits a linear response (Hempelman et al., 1975; Modan et al., 1977). Other neoplasms including leukaemia are often assumed to have a dependence on dose squared and therefore might well involve either two damage sites in one cell or two damaged cells interacting.

In man the frequency of leukaemia induction is \(\sim 10^{-14}\) per cell per Gy assuming that all bone marrow cells are at risk. This is to be compared with rodent fibroblast transformation frequency of \(\sim 10^{-4}\) per cell per Gy. This would suggest (if it is assumed that the initiating events are of similar frequency) that Alexander is invoking foci of \(\sim 10\) transformed cells in vivo in man. For radiation induced leukaemia this would imply a dependence of effect on \(D^{10}\) which would appear to give a very large threshold effect for the induction of cancer by radiation. Clearly no such effect is observed in man. It would be of interest to carry out a similar exercise for breast cancer but estimates of the number of cells at risk are not available.

An additional prediction of the Alexander hypothesis is that the distribution of cancers from whole body irradiation of man should reflect the distribution of organs which provide a suitable environment for development of secondaries since if a tissue has a high natural content of growth factors it should require fewer transformed cells for tumour development. However the tissues of greatest sensitivity to radiation induced tumour induction in man are breast, thyroid, lung, bone marrow and digestive organs. This does not appear to correspond with those most subject to secondary malignancy, viz adrenal, ovary, bone (Murphy et al., 1985).

Carcinogenesis is a progressive process and it may well be that although fully malignant cells require a large supply of growth factors to divide, newly transformed cells in vivo may not necessarily be competent in such circumstances. In fact it may be that they have a selective disadvantage in normal tissue, so giving rise to the low frequency of expression. Alternatively in vitro transformation may involve other processes in addition to those that allow transformed cells to grow in vivo.

If, as may be the case, cancer originates in a stem cell, or the equivalent, the function of which is to divide rarely but to ensure its own integrity by repairing as fully as possible any damage to its genetic complement, then in vitro cell transformation systems, in which the cells are repeatedly stimulated to divide, may not be of much quantitative significance in the study of in vivo carcinogenesis.

Yours etc.

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