Cell population kinetics of irradiated experimental tumours

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Undisturbed growth of experimental tumours is, in general, characterized by a continuous decrease in growth rate with time. According to the basic theory of growing cell populations developed by Steel (1), growth fraction, cell cycle time and cell loss factor are the main parameters that determine growth of tumours. There is a variety of experimental methods available to quantify these parameters, but serious problems exist to determine variations with time, especially when they occur relatively fast. Therefore, a theory of non-exponential growth of cell populations is difficult to approach. Another important but not yet solved problem is to relate cell proliferation to the histological structure of tumours (2).

Even more complicated is the situation in tumours after treatment with radiation or cytotoxic drugs. Following subcurative radiation doses, solid tumours usually continue to increase in size for a few days. Since at the same time, the fraction of clonogenic tumour cells is reduced by one to three orders of magnitude, there exists a large discrepancy between volume response and surviving tumour cells. Later on, the tumours begin to shrink as the tumour cells that have been sterilized as a result of treatment lyse and are resorbed. Concurrent with these events, surviving tumour cells begin to proliferate and repopulate the tumour, resulting in volume regrowth.

These competing processes of resorption and repopulation, that are the major factors determining the volume response curve of a tumour, have been studied for the solid transplantable rhabdomyosarcoma R1H of the rat following local irradiation with a single X-ray dose of 15 Gy (3). Several parameters were sequentially measured over a time interval of 25 days after irradiation: The ratio of tumour to host cells was determined by flow cytometry; the numerical density of tumour cells was obtained by stereological analysis of histological slides; the clonogenic fraction of tumour cells was assayed by plating an appropriate number of tumour cells and scoring the colonies; tumour volume was assessed by measuring two tumour diameters at right angles to each other. All parameters investigated except tumour volume undergo drastic changes during the first 2 weeks after irradiation.

From the directly measured parameters the following values and their variation with time could be derived: The number of tumour cells decreased by a factor of 5 within the first 10 days after irradiation, whereas the total number of cells per tumour increased by a factor of 4. This comes from the fact that the number of host cells increased drastically after irradiation as is shown in Fig. 1. Immediately after irradiation, 45 % of the cells present are of host origin, 2.5 % are clonogenic tumour cells and 52.5 % are non-clonoge-

nic tumour cells. The number of host cells increases by a factor of 10 within 10 days (probably due to infiltration by blood-borne cells), decreases during the following 10 days and increases again due to tumour growth. The doubling time of clonogenic tumour cells was calculated by regression to amount to 4.4±0.3 days whereas the number of non-clonogenic tumour cells decreases with a halving time of 3.5±0.7 days. After Day 15, the number of non-clonogenic tumour cells seems to increase at a rate comparable to that of the clonogenic cells. This corresponds to a constant fraction of 20-25 % of non-clonogenic tumour cells being present in repopulating tumours.

A mathematical model (4) was developed that describes the experimental data by considering cell proliferation, immigration and emigration of phagocytes, desintegration of non-clonogenic cells, and necrosis. This model reproduces the time-course of the experimental data of irradiated tumours as well as that of undisturbed growth of the controls.

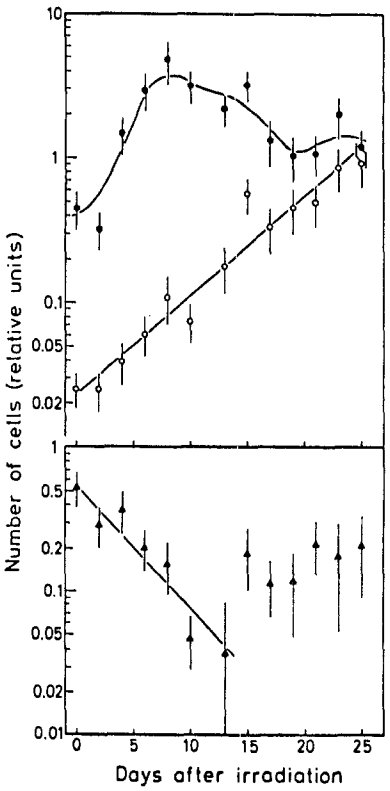

Fig. 1. Number of host cells (●), of clonogenic tumour cells (○), and of non-clonogenic tumour cells (▲) in the R1H rhabdomyosarcoma of the rat after X-irradiation with 15 Gy.

1) Steel, G.G., (1977), Growth Kinetics of Tumours, Clarendon Press, Oxford.

2) Brammer, I., Zywietz, F. and Jung, H., (1979), Europ. J. Cancer 15, 1329.

3) Jung, H., Beck, H.-P., Brammer, I. and Zywietz, F., (1981), Europ. J. Cancer 17, 375.

4) Beck, H.-P., (1981), this issue.