6 The tissue kinetics of cell loss

N. A. WRIGHT

6.1 Introduction

The preceding chapters in this book have largely been concerned with the morphological description of the death of cells, with its mechanisms, and the role of cell death in maintaining tissue homeostasis; in this chapter, however, we approach the phenomenon as a problem in cell population kinetics. Cell-renewal systems, such as the intestine and bone marrow, maintain a constant population size; hence cell loss must equal cell production. In malignant disease, cells are constantly being lost from the population by necrosis, migration to form metastases, exfoliation from surfaces and also by tumour differentiation. These phenomena immediately place us in the sphere of quantification; the aim of tissue kinetics is to define each cell population in terms of its size, its flux and its time, and in the present context, we need to express cell loss in terms of the number of cells involved, the rate at which they are being lost (flux) and the time they take to be lost to the population. Studies on the mechanism of cell loss, though naturally important, do not come within the scope of the present treatment, although we shall be concerned with the various proliferative states from which cells can be lost.

This chapter then is about the measurement of cell loss, about its importance as a kinetic parameter and its effects upon other kinetic parameters, notably those of proliferation. This, however, is a difficult task; cell kineticists have been largely concerned with the measurement of cell production and the factors controlling it, rather than cell loss. Although cell death is a well-recognized phenomenon in foetal tissues in organogenesis (see Glücksmann, 1951), it is only comparatively recently that cell deletion has been considered as a kinetic event in cell-renewal systems or expanding cell populations (Wyllie, Kerr and Currie, 1973a), and few authors have attempted to measure rates of cell loss in normal tissues. This lack is probably a reflection of the comparatively recent observation that cell death, almost exclusively by apoptosis, does occur within the proliferative compartments of a renewal system such as the small intestine (Murray and Rumsey, 1976).

On the other hand, the presence of large areas of frank necrosis in both human (Refsum and Berdal, 1967) and experimental tumours (Steel, 1967, 1968) rapidly led investigators to an early analysis of the role of cell loss, determining not only the pattern of tumour growth in the unperturbed state (Steel, 1968, 1977), but
also the response of the tumour to irradiation (Denekamp, 1972) and cytotoxi
chemotherapy (Bagshawe, 1968), and our knowledge of cell loss in tumours i
 correspondingly greater.

These comments apply to the actual removal of a cell, but there is a body o
opinion which regards the loss of reproductive capacity, rather than physic
space, as the only important parameter of cell loss (Bagshawe, 1968), and in som
situations this argument is reasonable. The ability of a tumour to regenerate afte
irradiation, or of a tumour to regrow after chemotherapy, depends upon th
survival of cells with reproductive capacity, now usually called 'clonogenic cells
Thus when we are considering cell loss as a factor affecting the ability of a tissu
to mount a regenerative response, there is little point in measuring the overall ce
loss; it becomes important to concentrate solely upon these clonogenic cells, an
assess their survival characteristics in isolation. We have now begun to discuss th
kinetic organization of tissues in relationship to cell loss phenomena, and, befor
proceeding to a more formal statement of definitions, to a survey of technique
and to some illustrative examples, it would be well to look briefly at the kinet
structure of the populations we shall be considering and the important events i
the life cycle of proliferating cells.

6.2 The cell cycle

Many dynamic phenomena which occur in cell populations are age-dependent:
that is to say, a migration or death process only occurs in cells after the effluxio
of a certain amount of time, and here time is measured since the occurrence of
particular event; for example, cells which are born in the zona glomerulosa of th
mammalian adrenal cortex are thought to migrate inwards to die in the zon
reticularis (Wyllie et al., 1973a; Wright and Voncina, 1977), and consequently th
deletion of an adrenal cortical cell is dependent upon its age. Many other lo
processes are age-dependent in that they occur at a specific point in the cell cycl
in which case age is measured from cell birth at the previous mitosis. The concep
t of the cell cycle is central to our discussion, and a useful diagrammatic represe
nation is shown in Fig. 6.1. Cycling cells pass through a defined series of event:
the period of DNA synthesis usually occurs towards the end of the cell cycle, an
is termed the S phase. The $G_1$ phase occurs before S, and $G_2$ after S and befor
mitosis. In these phases the cells prepare for DNA synthesis and mitosis respectivel
and the time taken for cells to complete this cycle is called, not unreasonably, th
cell cycle time. In most cell populations in vivo, cells are continually leaving th
cycle to perform other life-cycle events, and these avenues are also depicted i
Fig. 6.1; cells leave the cycle to lose reproductive capacity and differentiate, and i
renewal systems such as the epidermis or bone marrow to die in the normal proces
of keratinization and exfoliation, or sequestration in the spleen respectively. Thu
the normal process of cell death is age-dependent. Cells can also leave the cycle t
enter a putative resting state, sometimes called $G_0$, from which they can re-ente
the proliferative cycle if conditions are appropriate. By no means all workers ar