DO HYPERPLASTOID CELL LINES "DIFFERENTIATE THEMSELVES TO DEATH"?

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Hayflick and Moorhead (1) clearly differentiated between two classes of mammalian cell lines: 1) Those typified by HeLa are apparently immortal and may serve as models for the study of neoplastic cell proliferation; we refer to them as "neoplastoid." 2) Those typified by WI-38 and by human skin fibroblast cultures eventually cease replicating and may be useful as models for the study of hyperplastic cellular proliferation or wound healing; consequently, we refer to them as "hyperplastoid." Martin and Sprague (2) have recently tabulated some 21 parameters which have been claimed to differentiate between these two classes of cell lines. In mass cultures, the replicative life-span is currently among the most unambiguous differential parameters. Individual clones of either type of culture may cease proliferating, however, and it is this phenomenon which we refer to as "clonal senescence." In the case of human diploid somatic cells, it is probable that some thousands of such clones have been followed in many different laboratories and to the best of our knowledge, all of them eventually stop growing, unless they are induced to undergo malignant transformation. Curiously, much less is known about the replicative life histories of individual clones and sub-clones of neoplastoid cells, even though they are comparatively easy to clone.

There are currently two major theories which have been put forth to explain clonal senescence. In its original form, the Orgel hypothesis (3) ascribed the loss of proliferative potential to an "error catastrophe"—an exponentially increasing cascade of mistakes in protein synthesis. It is reasonable to assume that a few erroneous molecules of a structural protein like collagen, for example, would do a cell lineage no great harm, even if those defective molecules were passed on to the progeny. On the other
hand, if the faulty protein molecules were themselves utilized in the synthesis of other proteins, they would be in a position to greatly amplify errors in protein structure, with the potential involvement of all types of proteins.

An alternative to the Orgel hypothesis (4) is that such cultures undergo a sort of terminal differentiation in vitro, analogous to the kinds of terminal differentiation one observes with many different types of stem cells in vivo, such as hematopoietic cells or myoblasts. Once a cell ceases to replicate, however, abnormal proteins could well accumulate as a secondary degenerative phenomenon and thus the cell could truly undergo senescence. It is conceivable that most or all such abnormal proteins result from post-translational modifications. We therefore propose, in Figure 1, a two stage model of clonal senescence which we believe is consistent with the observations being made in several different laboratories. Stage I, we believe, proceeds via a process of clonal attenuation (to be des-

Fig. 1. A diagramatic representation of a two stage model of clonal senescence. In Stage I a stem cell gradually loses its "stemness" via a process of clonal attenuation (4) (Fig. 4) with the resulting accumulation of terminally differentiated cells which synthesize characteristic sub-sets of normal proteins, possibly including specific "luxury" proteins. In Stage II, secondary degenerative phenomena intervene in post-replicative cells, with the appearance of abnormal proteins; the latter is used in the generic sense and includes abnormal post-translational modifications as well as mistakes in transcription and translation. The diagram is oversimplified, in that it does not show potential cell-cell interactions.