The capacity of normal tissues and organs to repair radiation-induced damage depends on the proliferative status of their renewing target-cell populations. The rapidly responding tissues, whose renewing populations cycle quickly, have less repair capacity than the slowly responding tissues. [The *SCI®* indicates that this paper has been cited in over 120 publications.]

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My interest in mathematical modeling problems in radiotherapy and radiobiology was stimulated by an association that began in the late 1970s with H. Rodney Withers, then head of the Section of Experimental Radiotherapy at the M.D. Anderson Hospital and Tumor Institute in Houston, Texas. Withers had long been interested in ways to improve the results of radiotherapy by altering the pattern of *dose fractionation.* (Radiotherapy for human cancer is usually given in multiple small doses, or fractions, a practice derived empirically.)

The key to an alteration that might be therapeutically advantageous derived from evidence that large-dose fractions were injurious to slowly responding normal tissues, those tissues and organs that manifest delayed radiation injury and that are presently the limiting factor in the aggressiveness of treatment. In particular, there was scattered clinical evidence that when a change to larger doses per fraction was accomplished with equivalent acute reactions (those of the mucosa and skin, which occur early during treatment and allow the therapist to adjust doses accordingly), late reactions were unexpectedly more severe with the larger-dose fractions. Perhaps the first modern evidence of this kind came from a study of the effect of dose fractionation in the treatment of breast cancer by E.D. Montague,[1] a member of the staff of G.H. Fletcher, then head of radiotherapy at M.D. Anderson Hospital. His successor, L.J. Peters, published a similar finding in 1975.[2]

My contribution (derived on New Year's Eve in 1979) was to note that these results could be interpreted in terms of a difference in the cell-survival curves of the target cells whose depletion resulted in detectable injury, namely, that late-effects target cells were characterized by survival curves with relatively greater curvature. This was confirmed by reanalysis of published studies of the responses of early and late responding normal tissues in experimental animals.

A further consequence was that the repair capacity of normal tissues could be quantitated by the $\alpha/\beta$ ratio of target-cell survival parameters. This difference could in turn be interpreted in terms of the time available for repair of radiation injury prior to progression of target cells in the division cycle,[3] during which injury is fixed and no longer repairable.

The frequent citation of this paper has probably resulted from the simple procedure it provided to quantitate tissue repair capacity—many studies have illustrated the dissociation between acute and late radiation effects in regard to changes in dose fractionation. These have suggested that an improvement in radiotherapy might result from a change to much smaller-dose fractions, a strategy called hyperfractionation. These topics are the main concerns of my recently published book[4] co-authored with J.H. Hendry.

1. Montague E D. Experience with altered fractionation in radiation therapy of breast cancer. *Radiology* 90:962-6, 1968.
2. Bates T D & Peters L J. Danger in the clinical use of the NSD formula for small fraction numbers. *Brit. J. Radiol.* 48:773, 1975.
3. Thames H D. An "incomplete-repair" model for survival after fractionated and continuous irradiations. *Int. J. Radiat. Biol.* 47:319-39, 1985.
4. Thames H D & Hendry J H. *Fractionation in radiotherapy.* London: Taylor & Francis, 1987. 200 p.