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This Week's Citation Classic

Elkind M M & Sutton H. Radiation response of mammalian cells grown in culture. 1. Repair of X-ray damage in surviving Chinese hamster cells. *Radiat. Res.* **13**:556-93, 1960.

The survival curve of cultured Chinese hamster cells was found to have a threshold. From biophysical principles, it may be inferred that damage must be accumulated to kill a cell and, therefore, a surviving cell is sublethally damaged. Dose fractionation was used to show that sublethal damage is rapidly repaired. [The *SCI*® indicates that this paper has been cited over 420 times since 1961.]

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"Having entered the field of radiobiology in 1953 from a background in physics, I had a natural interest in formal models of dose-effect curves such as those pertaining to cell killing. Because of the discrete and random nature of energy deposition events from ionizing radiation, inactivation models current in the 1950s derived primarily from hit-target theory. These usually presupposed a certain target content per cell and made assumptions connecting the inactivation of one or more targets and cell inactivation.

"In their simplicity, these formal inactivation schemes held for me an element of elegance. Still, they were essentially unsatisfying since no matter how extensive a story one might hope experimentally to develop, the significance of the resulting edifice would depend upon the validity of the particular formalism assumed.

"In 1956, T. T. Puck and P. I. Marcus, using HeLa cells, published the first quantitative X-ray survival curve of mammalian cells in culture.[1] Some of the features contained in their results proved, in the course of time, to be general for mammalian cells whether assayed *in vitro* or *in vivo.* The one that attracted me was the shoulder on the curve. I realized that, independent of any assumptions about target sensitivity or target organization, a survival curve of this shape indicated a requirement for damage accumulation to effect lethality. I also realized that if damage must be accumulated to kill, a cell surviving a moderate killing dose is likely to be sublethally affected. (In contrast, from formal target theory as applied in the 1950s one would conclude that the absence of a threshold on a survival curve means that a single hit suffices to kill and, consequently, that a surviving cell is an undamaged cell.)

"In the context of the foregoing, the question arose. Can surviving cells repair their sublethal damage or is it heritable? By 1958, inspired by the technical advances in mammalian cell cultivation due to Puck and his associates, I had converted my laboratory at the National Cancer Institute from one for yeast to one for mammalian-cell research. Ms. Sutton and I undertook to answer this question by using a dose fractionation technique.

"We reasoned that if cells surviving a dose large enough to surpass the shoulder repaired sublethal damage, this would be evident by a return of a shoulder on the survival curve of the survivors of the second dose. We had essentially no examples to draw upon for the time course of this putative repair since the study of such processes was in its infancy at that time. Hence, we applied the two-dose technique using intervals of minutes to hours. Our results showed not only that repair of sublethal damage was rapid, probably being completed before the first mitosis following an initial exposure, but also that cells were capable of repeated cycles of damage and repair. These results had important implications relative to radiation and public health and to the use of radiation in the treatment of cancer."

Reference

1. Puck T T & Marcus P I. Action of x-rays on mammalian cells. J. *Exp. Med.* **103**:653-66, 1956.