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Hayflick L. The limited *in vitro* lifetime of human diploid cell strains. *Exp. Cell Res.* 37:614-36, 1965.
[Wistar Institute of Anatomy and Biology, Philadelphia, PA]

Contrary to a 50-year-old dogma, cultured normal human and animal cells are not immortal but have a finite capacity to replicate and function. This was interpreted to be a manifestation of aging at the cell level. [The *SCI*® indicates that this paper has been cited in over 1,515 publications.]

WI-38—From Purloined Cells to National Policy

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This is the only *Citation Classic* ever written that describes events that led to a major university and the NIH seeking to have the author prosecuted.

A paper authored by us four years earlier was also a *Citation Classic*.[1] We reported then that cultured normal human diploid cells have a finite capacity for division and interpreted that finding to be aging at the cell level. It launched the field of cytogerontology.

Prior to our work, the dogma insisted that, once cells divide in culture, they will do so forever if properly maintained. To gerontologists, this meant that normal cells, potentially immortal when released from *in vivo* constraints, cannot be the source of age changes. Our observations disproved this dogma and focused attention on the cell as the site of fundamental events causing aging. We showed that the only immortal cultured cells are those that are abnormal and frequently have properties of cancer cells.[2]

All of the cell strains described in our first paper were lost when an electrical freezer failed two months before publication.

In the present paper, I described the properties of the normal human diploid cell strain, WI-38, whose popularity produced the great number of citations to this paper. I reported that (a) the limited division capacity of cultured normal cells was not an artifact and (b) normal adult cells divide less frequently than those derived from fetuses. A striking inverse correlation with donor age now has been demonstrated for several different cultured normal human cell types.[2]

A fetal strain has the capacity for about 50 population doublings, and cells can be frozen at all doubling levels. After reconstitution, the number of remaining doublings is equal to 50, minus the number of doublings that occurred prior to preservation. WI-38 has been frozen for 27 years, and its extraordinary memory is as accurate today as it was in 1962. This is the longest time that living normal human cells have ever been frozen.

WI-38 also has great practical value. It was capable of growing virtually all the then-known human viruses and some previously unknown. Virus diagnostic and research laboratories throughout the world clamored for starter cultures.

We suggested that WI-38 was safer than primary cells used for the production of most human virus vaccines because it did not contain dangerous viruses that frequently contaminated the primary cultures then in use.[1-3] For the first 10 years, we distributed WI-38 starter cultures, including original ampules at the earliest doubling levels, gratis, to cell-culture manufacturers and vaccine producers throughout the world including the USSR.[2,3]

It took 10 years to prove to the Division of Biologics Standards (now incorporated within the FDA) that WI-38 was superior to primary monkey kidney cells for the production of human virus vaccines. Although our view originally met enormous resistance, eventually our success was so great that, in 1975, public servants from this division and from the NIH entered my laboratory uninvited, confiscated WI-38, and claimed them for themselves. Stanford University, convinced by the NIH that I had stolen government property, called the campus police and asked them to contact the district attorney. They soon dropped the case, but only after my expenditure of $10,000, borrowed to pay attorney's fees.

I brought suit against the NIH for return of the stolen ampules, and after six years of litigation, they requested an out-of-court settlement.[2-4] They agreed to return to me most of the WI-38 ampules and all disputed funds plus interest. They also changed their collective minds, agreed that I had not engaged in wrongdoing, and admitted that the issue was in reasonable dispute.[2-4] The NIH had maintained that it was perfectly fair for commercial organizations, the Russians, and themselves to sell WI-38 (tens of millions of dollars were realized), but they viewed as theft the inventor or his institution profiting. Eighty-five scientists condemned the NIH for its action.[4]

Now, attitudes of scientists, the public, and the NIH toward ownership of self-reproducing systems like cell populations have been reversed completely.[2-5] D. Nelkin writes, "Today Hayflick's actions would not be controversial. It is now accepted practice for scientists and institutions to profit directly from the results of academic research through various types of commercial ventures."[5]

O Tempora! O Mores!

1. **Hayflick L & Moorhead P.** The serial cultivation of human diploid cell strains. *Exp. Cell Res.* 25:585-621, 1961. (Cited 1,910 times.) [See also: **Hayflick L.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*. Philadelphia: ISI Press, 1986. p. 144.]
2. **Hayflick L.** The coming of age of WI-38. (Maramorosch K, ed.) *Advances in cell culture*. New York: Academic Press, 1984. Vol. 3. p. 303-16.
3. ———. History of cell substrates used for human biologicals. (Hayflick L & Hennessen W, eds.) *Continuous cell lines as substrates for biologicals. Developments in biological standardization*. Basel, Switzerland: Karger, 1989. Vol. 70. p. 11-26.
4. **Strehler B L et al.** Hayflick-NIH settlement. *Science* 215:240-2, 1982.
5. **Nelkin D.** *Science as intellectual property: who controls scientific research?* New York: Macmillan, 1984. p. 20.

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