Hayflick L & Moorhead P S. The serial cultivation of human diploid cell strains. *Exp. Cell Res.* **25**:585-621, 1961.

The authors describe the isolation and characterization of normal human diploid cell strains which have a limited capacity to replicate. The eventual degeneration of these strains leads to the hypothesis that the phenomenon is attributable to senescence at the cellular level. With these characteristics and their extremely broad virus spectrum, the use of diploid human cell strains for human virus vaccine production is suggested. [The *SCI*® indicates that this paper was cited a total of 949 times in the period 1961-1976]

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"The research described in this paper and the circumstances leading to publication produced several amusing incidents and instructive lessons The studies began with the —now naive— intention of isolating cancer-causing viruses from cultured human cancer cells. The strategy was to look for changes in cultured normal human cells inoculated with fluids and extracts from cultured cancer cells. The prerequisite for normal human cells was met by utilizing tissue from aborted human fetuses. The normal cells multiplied vigorously for about ten months, and then, after undergoing about 50 population doublings, they died.

"We worried that the ultimate death of these cells might be caused by some trivial culture condition that we had overlooked. Several critical experiments ultimately convinced us that it was a programmed intracellular event. We also sent cultures to several skeptics who were told in advance when the luxuriating cultures given to them would die. Our predictions were met with disbelief, but when the telephone rang with the good news that the cultures had died when expected, we decided to publish.

"Our original suggestion that the phenomenon might be a manifestation of aging at the cellulaHevel seems even more tenable today. It has given rise to the new field of cytogerontology '

"The cells were found to have other properties of immediate practical importance. We found them to be more sensitive to human viruses than any other cell and suggested that they had many advantages over monkey kidney cells for the production of human virus vaccines. Thousands of cultures were distributed to virologists, but our suggestion that the cells be used for human virus vaccines met with considerable resistance in this country. Ten years later, in 1973, the first poliomyelitis vaccine produced on our normal human cell strain WI-38 was distributed here.

"Efforts to publish the paper itself also met with resistance. The *journal of Experimental Medicine* rejected the paper over the signature of a soon-to-be-named Nobel Laureate, giving as its reason the then prevalent dogma: The largest fact to have come out from tissue culture in the last fifty years is that cells inherently capable of multiplying will do so indefinitely if supplied with the right milieu *in vitro.*

"As to our data on virus sensitivity, the writer said, 'The observations on the effect of viruses on cultures of these (cells) seem extraneous .', and as for our interpretation that the phenomenon represents aging, the letter commented. The inference that death of the cells…is due to "senescence at the cellular level" seems notably rash ' The manuscript was then sent to *Experimental Cell Research* where it was immediately accepted.

"It was also in 1961 that our laboratory first isolated and identified a new mycoplasma species, *Mycoplasma pneumoniae,* the etiological agent of primary atypical pneumonia in man. This paper is also on ISI® 's best-seller list of the 500 most cited papers.

"Both papers resulted from the use of resources 'bootlegged' from grants having entirely different purposes. If our work has had any value, it is a tribute to the then prevailing freedom to pursue interesting leads unfettered by preconceived expectations written into grant proposals. Regrettably, in recent years, such opportunities have become increasingly compromised by myopic administrative demands for strict accountability "