**This Week's Citation Classic®** CC/NUMBER 4 JANUARY 23, 1989

**Paucker K, Cantell K & Henle W.** Quantitative studies on viral interference in suspended L cells. III. Effect of interfering viruses and interferon on the growth rate of cells. *Virology* 17:324-34, 1962.
[Virus Laboratories, Children's Hospital of Philadelphia and School of Medicine, University of Pennsylvania, PA]

Exposure of L cells to inactivated Newcastle disease virus or to interferon resulted in temporary depression of cellular growth. Its intensity was proportional to the interfering activity of the agents. The growth-inhibitory factor in interferon preparations could not be separated from interferon. [The *SCI*® indicates that this paper has been cited in over 310 publications.]

## Anticellular Effects of Interferon

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September 13, 1988

This paper, published 26 years ago, brings both pleasant and sad memories to my mind. From 1960 to 1962 I had the privilege to work as a young postdoctoral fellow in the laboratories of Werner Henle and Gertrude Henle in Philadelphia. Among other things, these great pioneers of research on viral interference had discovered that a virus can be made fully noninfectious without affecting its interfering capacity.[1] The discovery of interferon[2] was based on this finding.

I was lucky to be placed in the laboratory of Kurt Paucker, a former student and long-time coworker of the Henles. He had decided to analyze interference by inactivated virus in suspended mouse L cells. He had also decided to study interferon, the newly discovered mediator of interference, in this system. In 1962 and 1963 a series of five papers published in *Virology* described the results of these studies.

The advantage of L cells was that they could be maintained indefinitely in the logarithmic-growth phase, and the number of cells could be easily monitored. We counted the cells under the microscope and with a fancy, new electronic device, the Coulter counter. We soon noticed that cell cultures in which interference was induced either by a virus or by interferon consistently exhibited slightly slower growth rates than control cultures. A single exposure to the interfering agents caused a transient depression of the growth. Prolonged contact with the interfering agents had a more dramatic effect, but their removal permitted gradual recovery of the cultures. I believe other workers, before and after us, often failed to see the growth inhibition, because they did not grow cells long enough in the presence of interferon. In a number of control experiments we failed to dissociate the cell growth-inhibitory factor from the interfering activity of the virus or from interferon.

At that time interferon was considered to be a highly specific, nontoxic, broad-spectrum antiviral substance. Our paper was the first report of a non-antiviral, anticellular effect of interferon, and many people working with interferon were reluctant to accept the concept that interferon has "adverse effects" on cells. Our interferon preparations were impure (like all interferons available at that time), and this was diligently pointed out in the early citations to our paper. The final proof of the cytostatic activity of interferons was obtained only 15 to 20 years later, when pure interferons became available.[3,4] The mechanism of the cytostatic activity of interferons is still unclear, but oncogenes, growth factors, and cell-surface changes appear to be involved.[4,5] Today it seems that the anticellular effects of interferons may be more fundamental than their antiviral effects.

The sad part of the story is that, in spite of interferons and other host defenses, both my fine coworkers died of cancer.

1. **Henle W & Henle G.** Interference of inactive virus with the propagation of the virus of influenza. *Science* 98:87-9, 1943. (Cited 65 times since 1945.)
2. **Isaacs A & Lindenmann J.** Virus interference. 1. The interferon. *Proc. Roy. Soc. London Ser. B* 147:258-67, 1957. (Cited 1,040 times.)
3. **Stewart W E.** *The interferon system.* Vienna, Austria: Springer-Verlag, 1979. 421 p. (Cited 1,055 times.)
4. **Streuter M & Taylor-Papadimitriou J.** Regulation of cell growth by interferon. *Cancer Metast. Rev.* 6:199-221, 1987.
5. **DeMaeyer E & DeMaeyer-Guignard J.** *Interferons and other regulatory cytokines.* New York: Wiley, 1988. 448 p.

 

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