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This Week's Citation Classic®

Cantell K & Hirvonen S. Large-scale production of human leukocyte interferon containing 10^8 units per ml. *J. Gen. Virol.* 39:541-3, 1978.
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A procedure was described by which human leukocyte interferon could be concentrated 5,000-fold and purified over 100-fold on a large scale with over 50 percent recovery. [The *SCI*® indicates that this paper has been cited in over 210 publications.]

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In an earlier *Citation Classic*[1] my friend and coworker Hans Strander described the first phases of the production of human leukocyte interferon in my laboratory. The work was started in 1963, and four years later we began to foresee the system's potential for the production of sufficient amounts of interferon for small-scale clinical trials.[2] At that time the purification process looked like a formidable problem, and I did not think that we would be able to accomplish the work in my laboratory. We received advice from many sources, however, and progress was made little by little.

Meanwhile, Strander returned to Stockholm and became an oncologist. In 1969 he injected tumor patients with our crude, concentrated interferon and encountered a number of side effects.[3] His studies provided a strong impetus for obtaining more refined preparations. The leukocyte interferon turned out to be amazingly stable. It tolerated treatment with acid ethanol, and this finding opened the way to its purification. The scheme of the purification procedure took shape in 1973.[4]

One of my first interferon papers dealt with the effect of topical interferon on experimental virus infections in rabbits' eyes.[5] It took 15 years to obtain suitable interferon preparations for similar studies in humans, and it took another 10 years to learn how to use interferon for the therapy of herpetic eye infections. Most of the eye studies using our interferon were carried out by Rainer Sundmacher in Freiburg, Federal Republic of Germany. The main point was to use highly potent interferon in combination with surgery or synthetic antivirals.[6] It was sufficient to administer just two interferon drops daily, but the concentration was critical. The healing times of the corneal ulcers were reduced by increasing the interferon concentration. We set ourselves the goal of preparing "super-interferon" containing 100 million units per ml. In two-and-a-half pages this *Citation Classic* described how such "super-interferon" was obtained by slight modifications of the purification procedure. My highly competent, long-time coworker, Sinikka Hirvonen, played an important role in working out the modifications.

This paper has evidently been used as a general reference for the preparation of human leukocyte interferon, although there would have been more suitable papers for this purpose. Later studies have shown that natural leukocyte interferon is a mixture of at least 10 different alpha interferons.[6] In the 1980s large quantities of lymphoblastoid and recombinant interferons have become available. Comparative clinical trials will determine whether natural leukocyte interferon is still needed.[7]

In 1981 I received the Scandinavian Fernstrom prize for my work on leukocyte interferon.

1. **Strander H.** Citation Classic. Commentary on *Ann. Med. Exp. Fenn.* 44:265-73, 1966. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press, 1986. p. 84.
2. **Cantell K, Strander H, Hadhazy G & Nevanlinna H R.** How much interferon can be prepared in human leukocyte suspensions. (Rita G, ed.) *The interferons.* London: Academic Press, 1968. p. 223-32.
3. **Strander H, Cantell K, Carlström G & Jakobsson P Å.** Systemic administration of potent interferon to man. *J. Nat. Cancer Inst.* 51:733-42, 1973. (Cited 190 times.)
4. **Cantell K, Hirvonen S, Mogensen K E & Pyhälä L.** Human leukocyte interferon: production, purification, stability, and animal experiments. (Waymouth C, ed.) *The production and use of interferon for the treatment and prevention of human virus infections.* Rockville, MD: Tissue Culture Association, 1974. p. 35-8. (Cited 490 times.)
5. **Cantell K & Tommila V.** Effect of interferon on experimental vaccinia and herpes-simplex virus infections in rabbits' eyes. *Lancet* 2:682-4, 1960. (Cited 80 times.)
6. **Sundmacher R, Cantell K & Neumann-Haefelin D.** Combination therapy of dendritic keratitis with trifluorothymidine and interferon. *Lancet* 2:687, 1978.
7. **Cantell K.** Clinical performance of natural human leukocyte interferon. *Immunobiology* 172:231-42, 1986.

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