This Week's Citation Classic™
CC/NUMBER 20
MAY 14, 1984

Strander H & Cantell K. Production of interferon by human leukocytes *in vitro*. *Ann. Med. Exp. Fenn.* 44:265-73, 1966.
[State Serum Institute, Helsinki, Finland]

Leukocytes isolated from human blood were used for the production of large quantities of human interferon. Cells were incubated with inducing virus and the best inducers of interferon were established. The isolation procedure used for the leukocytes did not diminish their capacity to induce interferon and they could be stored prior to their use for the production of interferon. The procedure described allowed large-scale production of human interferon. [The SCI® indicates that this paper has been cited in over 165 publications, making it the most-cited paper ever published in this journal.]

Hans Strander
Department of Oncology
Karolinska Hospital
S-104 01 Stockholm 60
Sweden

April 4, 1984

"In 1963, I was working part-time at the Institute for Tumor Biology, headed by Georg Klein, at the Karolinska Institute. We were visited by Vainio, who was originally from Helsinki where he was a collaborator of Cantell. There was an interest in Helsinki in doing studies on both the production and action of interferon. Cantell had just arrived from the Henles' laboratory in Philadelphia. I had been following their research so I decided to join the Cantell/Vainio group in Helsinki.

"Interferon production was done in Cantell's laboratory. Cantell had already done a few pilot experiments where it was seen that human leukocytes could produce large amounts of interferon, as had previously been reported by Gresser.[1] I mostly studied the action of the interferon produced. Unfortunately, Vainio then died in a car accident and, after that, I devoted my time fully to the production of interferon in Cantell's laboratory during my remaining five-year stay in Helsinki.

"The work done there on the production of interferon by human leukocytes was also the basis for my thesis, which was later defended at the Karolinska Institute.[2] It was shown in the article discussed here that the large-scale production of human leukocyte interferon could be achieved by using buffy coats isolated from human blood bags. The cell products employed were waste products that did not diminish amounts of blood available for treating patients either with red cell concentrates or fresh plasma. It was also shown in the paper that the human leukocytes could be purified and still were able to produce optimal amounts of interferon. It was shown how the kinetics worked, and what type of viruses should be used as inducers. Also, the multiplicity of the viruses which had to be used was determined. The state of the virus preparations and the number of cells which had to be incubated to give optimal yields were also factors studied.

"It had been established that interferon had an effect on virus diseases and tumor diseases in experimental models.[3,4] Unfortunately, there was no human interferon available for clinical trials. The article in question showed that it is possible to obtain large quantities of human interferon for clinical work.

"The reason this article has been cited so much is probably that it started an era of interferon production in Helsinki, where the laboratory for ten years provided all the human leukocyte interferon which was available for clinical trials and also most of the human alpha interferon available for laboratory work in the world. It was also shown through collaboration between a virus laboratory and a blood center that it was possible to produce interferon on a large-scale basis. In many ways, the article encouraged the future production of large quantities of interferon for work on humans. At the time the article was published, however, the interest was not as strong as it became later, since it was not believed by many people that exogenous interferon therapy in humans would ever be a realistic possibility. Due to the findings in animals, we considered, however, that such work would be important. Also, such studies could provide some clues concerning the human defense mechanisms directed against viruses and tumors.

"For information concerning how far the interferon area has moved using such a product, the reader is referred to a special article."[5]

1. **Gresser I.** Production of interferon by suspensions of human leukocytes. *Proc. Soc. Exp. Biol. Med.* 108:799-803, 1961. (Cited 160 times.)
2. **Strander H.** *Production of interferon by suspended human leukocytes.* Thesis. Stockholm, Sweden: Karolinska Institute, 1971.
3. **Finter N B.** Interferon as an antiviral agent *in vivo*: qualitative and temporal aspects of the protection of mice against Semliki Forest virus. *Brit. J. Exp. Pathol.* 47:361-71, 1966. (Cited 50 times.)
4. **Atanasiu P & Chany C.** Action d'un interferon provenant de cellules malignes sur l'infection expérimentale du Hamster noveaunê par le virus du polyome. *C.R. Acad. Sci.* 251:1687-9, 1960. (Cited 65 times.)
5. **Strander H.** Interferons and disease: a survey. (Burke D C & Morris A, eds.) *Interferons: from molecular biology to clinical application. Thirty-Fifth Symposium of the Society for General Microbiology held at the University of Cambridge, September 1983.* Cambridge, England: Cambridge University Press, 1983. p. 7-33.