This Week's Citation Classic®

Isaacs A & Lindenmann J. Virus interference. I. The interferon. *Proc. Roy. Soc. London Ser. B* 147:258-73, 1957.
[National Institute for Medical Research, London, England]

Heat-inactivated influenza virus, added to fragments of chick chorioallantoic membranes, induced the formation of a substance, interferon, which, when added to fresh membranes, inhibited the growth of live influenza virus. [The *SCI*® indicates that this paper has been cited in over 1,040 publications.]

The First Stirrings of Interferon

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I arrived at the National Institute for Medical Research as a postdoc with a Swiss fellowship in July 1956. I wanted to work in virology with Sir Christopher Andrewes. Somebody had claimed that poliovirus (at that time the real star among model viruses) could be cultivated in rabbit kidney cells, and I was assigned the task of confirming this rather important finding. This proved a disappointing experience, because poliovirus just does not grow in rabbit cells.

Probably early in August I was introduced, at teatime, to the worker next door, who seemed to enjoy considerable prestige. "This is Alick Isaacs," I was told. He asked me what I had done before coming to England, and I replied that I had been interested in the phenomenon of viral interference; I had even done some as yet unpublished work on this, showing that inactivated influenza virus was capable of interfering with the growth of live influenza virus even when stuck to the surface of red cells, from where the inactivated virus presumably could not escape.[1] My interlocutor seemed highly interested: How did I know the virus was truly inactivated? How did I know it would not elute from red cells? This, I replied, was all to be read in an obscure paper by some Australians I had come across. This paper, in fact, had been written by Isaacs and Margaret Edney.[2] But when reading it, I had, in my mind, pronounced the name in mid-European fashion as something like "Ee-zak," whereas the man I had been introduced to was called "Eye-sacks." It was only under his intense prodding that it suddenly dawned upon me that I was speaking to the very man whose work I was quoting, and never have I had to congratulate myself more for having read a paper carefully.

We immediately started a collaboration. What a relief from my frustrations with the polio work, which of course went on for several months—disproving something is so much more difficult and brings such trifling rewards compared with showing something new! We repeated the work with red cells[3] but very soon realized that, of the three elements that entered into our experiments (inactivated virus, red cells as carriers of the inactivated virus, and host tissue), the red cells were an unnecessary complication and that it was the interaction of the inactivated virus with the host cells that resulted in the release of a substance, called in laboratory slang "interferon," that inhibited viral growth when applied to fresh tissue. I have attempted to give a more scientific account of these early events elsewhere.[4]

The idea that a substance, independent of the virus used to induce interference, was responsible for inhibition of the challenge virus, met with the usual amount of healthy skepticism, but eventually prevailed, fortunately early enough for Isaacs to reap some recognition (he was elected a Fellow of the Royal Society, an honor that he greatly appreciated, one year before his untimely death in 1967). But even in his moments of elation he cannot have visualized that interferons would be harbingers of the large and still growing family of regulatory peptides, as witnessed by a recent book.[5]

1. **Mooser H & Lindenmann J.** Homologe Interferenz durch hitzeinaktiviertes, an Erythrozyten adsorbiertes Influenza-B-Virus (Homologous interference by heat-inactivated influenza-B virus adsorbed on erythrocytes). *Experientia* 13:147-8, 1957. (Cited 5 times.)
2. **Isaacs A & Edney M.** Interference between inactive and active influenza viruses in the chick embryo. I. Quantitative aspects of interference. *Aust. J. Exp. Biol. Med. Sci.* 28:219-30, 1950. (Cited 40 times.)
3. **Lindenmann J & Isaacs A.** Versuche über Virus-Interferenz (Studies on virus interference). *Schweiz. Z. Allg. Pathol. Bakteriol.* 20:640-6, 1957. (Cited 5 times.)
4. **Lindenmann J.** From interference to interferon: a brief historical introduction. *Phil. Trans. Roy. Soc. London B* 299:3-6, 1982. (Cited 5 times.)
5. **De Maeyer E & De Maeyer-Guignard J.** *Interferons and other regulatory cytokines.* New York: Wiley, 1988. 448 p.

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