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The National Institute for Medical Research, Mill Hill
Personal recollections from 1956/57

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Although Switzerland had been spared the destructions of the Second World War, it had suffered from intellectual isolation which led to a kind of mental torpor. In certain areas (Literature, Physics, Chemistry) recuperation occurred rapidly, in others it was more sluggish. For reasons residing mostly in the leading personalities involved, Medical Microbiology was one of the sciences which remained ossified at a pre-war level until the fifties. In order to remedy this state of affairs, the Swiss Academy for Medical Sciences created fellowships for training young investigators abroad. I obtained such a one-year fellowship in 1956. I had been educated as an M.D. and had done postgraduate work in diagnostic bacteriology. My aim was to learn virology at the National Institute for Medical Research in London. The fellowship payed 5 £ a week, which was sufficient for survival.

I started work on July 1st, 1956. The building on the Ridgeway was impressive, and something of its recent military past as H.M.S. *Elizabeth* [1, 18] could still be felt. One wing which housed experimental animals was jokingly referred to as the "battleship". The head of Bacteriology and Virus Research was C. H. (later Sir Christopher) Andrewes (1896–1988) [18, Fig. 2], who was also Deputy Director of the whole Institute. Before going on vacation he thought that I might try my hand at the following problem: The rule that a given virus only grew in tissue cultures derived from animals naturally susceptible to this virus had been found not to be generally valid. With Dona Chaproniere, Andrewes had shown that myxomatosis virus grew in cells from animals not susceptible to the virus. A recent report had claimed that poliovirus could be grown in a permanently established line of rabbit kidney cells. So I was to see whether poliovirus would grow in primary rabbit kidney tissue cultures. I failed miserably, but learned quite a few things. It later transpired that the supposed rabbit kidney cell line was, in fact, one of the numerous "illegitimate" HeLa contaminants that for a while annoyed tissue culturists worldwide.

Andrewes was mainly interested in myxomatosis and in the common cold. A rather unique opportunity for studying the common cold virus when inoculation of volunteers was the only means of assessing its presence was "Harvard Hospital" in Salisbury, a pavilion-type outfit donated entirely, lock, stock and barrel, by the Americans to the British Government at the end of the war and handed over to the MRC. To keep the volunteers, living in strict isolation, happy, excellent cooking was provided. On an occasional trip to Salisbury I must have fallen in an eyebrow-raising way over the victuals, a change from the canteen food for which Britain, at that time, had a deservedly bad reputation.

In 1947 the National Institute for Medical Research had accepted responsibility for running, on behalf of the World Health Organisation, a World Influenza Centre. This was housed in two laboratories adjacent to the one assigned to me, and was led by Alick Isaacs (1921–1967, Fig. 1). When I was introduced to him I did not realize that he was the man whose work on interference between strains of influenza virus, published in Australia, I had thoroughly studied. I have told the story of our first encounter before [2]. His work had shown that influenza virus could be heat-treated so as to abolish its infectivity and its receptor-destroying action (neuraminidase), but without altering its hemagglutinating or its interfering capacity.

At the instigation of my boss in Zürich, Hermann Mooser (1891–1971) I had used this to show that influenza virus, supposedly irreversibly attached to chick red cells, still was capable of inducing interference in embryonated eggs. Mooser, who was a rickettsiologist, had thought, in analogy to interference phenomena among *Rickettsia*, that by this means one could exclude the possibility that interference was caused by the first virus blocking the receptors for entry of the second virus. Neither he nor I were aware that this was flogging a dead horse, because workers in the field had already abandoned the idea of receptor blockade. I told Alick Isaacs about these as yet unpublished [3] experiments, and this sparked his imagination.

Alick's idea went as follows: Interference must be caused either by entry of the whole virus into cells, or by entry of the viral nucleic acid alone. This last possibility was the one he favored, in analogy to what was known of the T bacteriophages. Virus attached to red cells seemed to offer an opportunity to test this hypothesis. The arrangement I had used had to be changed in several respects: Instead of using intact chick red cells, he proposed to use red cell ghosts, allowing the virus to be observed by electron microsopy (intact red cells are opaque to the electron beam). Instead of using embryonated chicken eggs, we were to use fragments of chick chorioallantoic membrane, a recently established technique which allowed ready separation of the susceptible tissue from anything that could be added to it.

If everything went according to plan, this is what he expected to find: Before the start of the experiment, one would check, by electron microscopy, the numbers and the morphol-

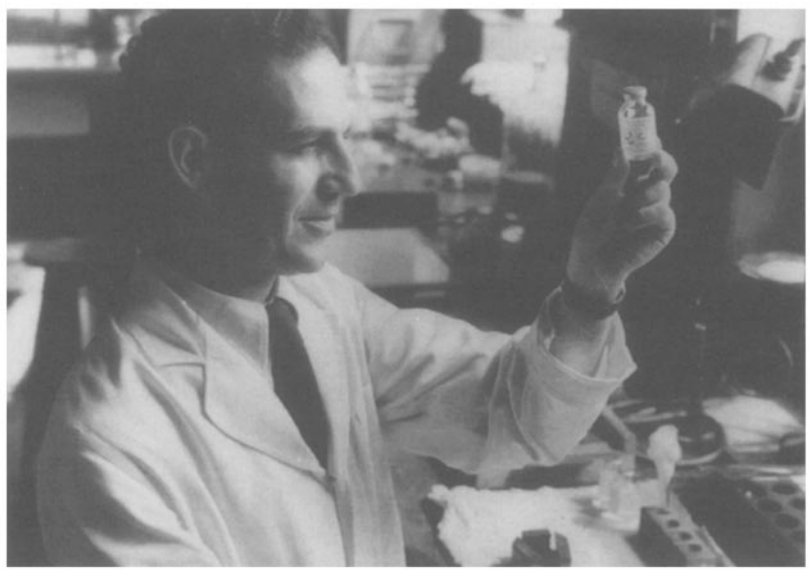

Fig. 1. Alick Isaacs, ca. 1958

ogy of virus corpuscles attached to the red cell ghosts. These would then be used to induce interference in a set of chick chorioallantoic membranes. After this, the red cell ghosts would be recuperated and looked at again in the electron microscope. If only the viral nucleic acid had been injected into the cells lining the membranes, it was conceivable that this might be seen: Empty and collapsed viral shells remaining on the ghosts rather than intact viral particles.

To do this, we of course had to enlist the help of an excellent electron microscopist, Robin Valentine from Biophysics. We did a number of experiments along these lines, but it soon became apparent that the approach via morphology was hopeless. During prolonged contact with the membrane fragments, the ghosts picked up all sorts of debris which made interpretation of the pictures difficult. In addition, we obtained evidence that the virus was not as irreversibly attached to the ghosts as we had supposed. An important control experiment consisted in mixing equal numbers of empty ghosts and virus-loaded ghosts, preparing electron microscopy grids immediately after mixing and again after leaving the mixture in a roller drum for 24 hours at 37 degrees. The first picture showed, as expected, ghosts completely devoid of viral particles side by side with ghosts heavily loaded with virus. In the second picture, however, in addition to this, some ghosts were seen with just a few virus particles stuck to them. Thus, presumably, virus had become detached from the heavily coated ghosts and had become adsorbed on originally empty ghosts.

Another tentative experiment consisted in removing the first set of membranes from contact with the virus-coated ghosts and replacing it with a fresh set of membranes, to see if the interfering potential could eventually be exhausted. Surprisingly, the new set of membranes showed almost as much interference as the first set [4].

Thus we became disenchanted with the use of red cell ghosts, always meant to be simply passive carriers of the virus. New ideas began bubbling to the surface. Perhaps one sentence, which Andrewes had written 14 years earlier in discussing interference in tissue cultures, stirred in our subconscious: "... the virus first upon the scene uses up some essential foodstuff in the cell. An alternative ... hypothesis ... would be, of course, the generation ... of some ... inhibitory substance" [5]. Of course.

We now did new experiments without ghosts. Note that all moves had been exercised or rehearsed in our previous experiments: Use of heat-inactivated influenza virus, preparation of membranes, washing them, transferring them to fresh medium, adding new membranes to previously used fluid, etc. Very rapidly this led to the discovery that, following contact with the interference-inducing virus, the membranes released something into the surrounding fluid which itself was capable of interfering with virus growth in a fresh set of membranes [6]. Before this "something" had assumed more than strictly hypothetical character, I had named it "interferon", and on November 6th, 1956, the entry in Alick Isaacs' lab notebook, now at the National Library of Medicine, NIH, Bethesda [7], reads "In search of an interferon". On November 13th, 1956, he titled his entry "Getting nearer the interferon". When it had become clear that interferon was real, our group was joined by Derek Burke, from Organic Chemistry, who made first attempts at purifying interferon.

Alick Isaacs also showed me influenza virus filaments in the dark ground microscope, a view which impressed me greatly. Because I knew that bacterial flagella, thinner than influenza virus filaments, could be mordanted and stained so as to be visible in the ordinary microscope, I decided to stain influenza virus. I succeeded, but this was a success which came about 20 years too late [8].

Another foreign fellow there was Arild Harboe from Norway. Our stays did not overlap for long enough for me to really understand what he was doing. It is only much later that I came to respect his work as one of those I admire most [9].

I did not attempt to prolong my fellowship beyond one year and left Mill Hill in the summer of 1957. In December I received a letter [10], dated December 3rd, 1957, from the Director of the Institute, Sir Charles Harington (Director from 1942–1962) – saying:

"Since you left the Institute consideration has been given to the possible desirability of patenting "Interferon" (...) The ordinary course that is followed in matters of this kind for discoveries made in the Medical Research Council laboratories, is that the discoverers take out a patent, which is then assigned to the Medical Research Council. The Medical Research Council in turn hands the patent over for development to the National Development Research Corporation (...) Any revenue resulting from the operation of such patents passes to the Corporation. In this instance, the patent would need to be taken out in the names of Isaacs and yourself (...). If, as I hope, you will fall in with this suggestion, you will eventually receive the necessary documents for signature."

I accepted the proposal in a letter [11] dated December 8th, 1957:

"It is a pleasure for me to agree with your proposal relating to "Interferon", the more so since I am convinced that it is the Medical Research Council's policy to make any useful product that might arise as freely available as possible to those needing it. It is also an opportunity for me to show, however modestly, the gratitude I feel towards the National Institute for Medical Research."

The ensuing efforts to prepare enough interferon for clinical trials, in which I had no part, have been studied by Toine Pieters [12]. Traces of my presence in Mill Hill can be found in the annual "Report of the Medical Research Council" for the years 1955–1956 [13] and 1956–1957 [14], in the two-volume book "Half a Century of Medical Research" [15, 16], and in "Historical Perspectives on the Role of the MRC" [17]. What is interesting in these accounts is the almost complete lack of reference to the importance an institution such as the MRC had for scientific research as an international effort and for training foreign postdocs.

Consider the plight of post-war research in, for instance, Eastern Europe. People of my generation or somewhat older had learned some French in school. Soon they had to switch to German, and were later force-fed Russian. But the only useful language for scientific communication turned out to be English. The possibility of learning English, or at least scientific English, was absolutely essential for those who wanted to do science. In addition, the entire atmosphere of a place like Mill Hill, so utterly different from the "Geheimrat"-spirit still prevalent in Europe (and by no means only in Germany), was inspiring and undoubtedly influenced the later developments of European science in a lasting fashion.

Not only did numerous foreigners, like myself, profit immensely from access to the British science establishment which, in the fifties, must have been one of the most efficient, in terms of expenses versus results, in the world. In addition, British science itself may have occasionally profited from the presence of young enthusiasts from all over the world. This is a story which remains to be written.

Note added in proof

An independent and fully documented analysis of the same time period forms chapter 3 of a forthcoming book by Toine Pieters, *Biology Meets Drug Development: The Surprising Record of a 'Miracle Drug', the Interferons.*

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