Scientifically Speaking

War on cancer—interferon

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Washington, DC—In the seemingly endless search for weapons in the war on cancer, enthusiasm about new potential anticancer agents is kindled over and over again. Today, optimism centres on interferon, a natural, presumably non-toxic, antiviral protein that appears to have antitumour properties as well. The American Cancer Society (ACS) is backing interferon to the tune of at least \$2m (maybe more), which is the largest sum it has ever put in a single basket. As a result, oncologists at 10 US institutions (listed at the end of this article) have geared up for a limited, though highly publicised, clinical trial. (For the present, the Government's National Cancer Institute, which for many years has provided modest support for interferon studies, has taken a wait-and-see attitude about upping the ante by adding federal funds to the trial.)

Limited stocks

Some cancer specialists have expressed concern that the ACS is making a mistake by initiating an interferon trial right now, when data are preliminary and interferon is in painfully short supply. Nevertheless, the society (which has entered the interferon sweepstakes with some misgivings) is going ahead, mindful of the fact that false hopes are easily raised. In an effort to put things in perspective, Frank J Rauscher, jun, senior vice-president for research at ACS and former director of the National Cancer Institute, cautions, "Interferon is just one of thousands of substances being tested for antitumor activity. Speculation which raises high hopes because of the society's unusually large financial commitment is premature. Interferon needs to be checked out because its value has not yet been proved. We can only find out by trying whether or not it is really any good. The only way we can do this is to buy the material and get started."

It is the limited supply and, therefore, high cost of interferon that explains why the clinical trials, already under way in some places, will include no more than 150 patients with advanced cancer of one of four types: melanoma, multiple myeloma, non-Hodgkin's lymphomas, and cancer of the breast. In clinical studies, each has shown some response to interferon. Original plans to include patients with advanced squamous cell cancer of the lung and cancer of the bladder have been set aside until more interferon is available. As it is, the ACS will spend its entire \$2m to buy 40 000 million units of interferon from the Central

Public Health Laboratories in Helsinki, Finland, where Kari Cantell developed a method of extracting it from the buffy coat of white blood cells left over from the Finnish Red Cross's blood donor programme. At the moment, Finland is the world's major supplier of interferon, although it is likely to be available from other sources within the next couple of years. The ACS order is for almost one-third of the Finnish group's yearly yield.

Interferon was discovered in 1957 by a British research scientist, Alick Isaacs, and Jean Lindenmann of Switzerland, who showed that it is produced naturally in response to viral infection and that it "interferes with" viral replication. Since then, people have looked to interferon as the answer to virus infections ranging from herpes zoster to the common cold. Early studies on animals supported the idea that interferon, which seems to be species-specific, also inhibits tumour growth by affecting mitosis. Preliminary data from experiments in which human interferon was given to cancer patients lend additional credence to the idea that it is both antiviral and antitumour, though probably by different mechanisms.

There are at least three types of human interferon. Leucocyte interferon, such as that produced in Cantell's laboratory, has probably been used clinically more than others so far. But investigators are also interested in fibroblast interferon, which is induced from cultured fibroblasts of infant foreskins, and in immune interferon, produced by cells in the immune system. To date, immune interferon has not been tested in man. Evidence suggests that the three interferons work in different ways.

Worldwide trials

In addition to the ACS trial in the United States, clinical trials of interferon are either going on or are being planned in Britain, France, Germany, Austria, and Japan. But the largest trial has been taking place in Sweden, where Hans Strander, of the Karolinska Hospital in Stockholm, is treating victims of osteogenic sarcoma with interferon. He began using interferon in 1971, and now has data on 34 patients. Osteogenic sarcoma generally yields dismal data: within a year of surgical removal of the primary tumour, 80% of patients show up with metastases in the lung. In Strander's interferon series, two and a half years after surgery 64% of his patients were free of metastases, as compared with 30% of patients in a control group at other Swedish hospitals. In overall survival, 73% of Strander's patients were alive two and a half years later, compared with 35% of the controls. Strander's protocol calls for three million units of intramuscular interferon a day for a month after surgery, and then intravenous injections three times a week for the next year and a half.

Although most of Strander's work has been with osteogenic sarcoma, he also has had some positive results of interferon therapy in a few patients with advanced Hodgkin's, juvenile laryngeal papilloma, and multiple myeloma. An added attraction of interferon in cancer patients, reported by Strander and several

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others, is that it tends to eliminate or at least minimise the viral infections that plague cancer victims.

If Strander's evidence led ACS people to think favourably about an interferon trial, it was a request by Jordan U Gutterman, of the University of Texas MD Anderson Hospital and Tumor Institute in Houston, that pushed them to their final decision. Thanks in large measure to New York philanthropist Mary Lasker, of the Albert and Mary Lasker Foundation—who gave him money to buy interferon—Gutterman has been conducting experiments on patients with a variety of cancers with, he says, some success. (Gutterman, who hopes to publish his data in the *New England Journal of Medicine* once he has a paper written, is reluctant to say anything specific about his work for fear the *NEJM* will turn him down.) So far, about 70 patients have been given interferon at MD Anderson. In the spring of 1978, with Lasker's blessing, he decided to "go big" and asked the ACS to give him \$1.7m to buy interferon—half the cost of studies they hope to do on 50 patients with a variety of cancers and 50 others with metastatic breast cancer.

Gutterman got part of what he wanted. The cancer society's advisory panel roundly voted against the idea of concentrating that much effort on research at a single institution. Instead, the panel decided to pick up the whole tab for the interferon purchase and give it to investigators at five institutions (the first five listed at the end of this paper). Later, they decided to make it 10.

Purity and patience

While oncologists tackle the problems of clinical trials, basic researchers are trying to purify interferon (the stuff that is being given to patients now is a highly impure soup), and to produce it in large quantities. Among those who are approaching the problem by way of purification and chemical synthesis is Sidney Pestka, of the Roche Institute of Molecular Biology in Nutley, New Jersey. In December, Pestka reported success in

purifying human leucocyte interferon in quantities "sufficient for physical and chemical characterisation." At the Massachusetts Institute of Technology in Cambridge, David V Levine has managed to boost interferon production from foreskin fibroblasts by culturing them on microscopic dextran beads rather than in roller bottles. He recently produced 10 878 units of interferon by that procedure from a volume of starter material that would have yielded only 963 units in roller bottle culture. Wellcome Research Laboratories in Great Britain recently reported large-scale production of immune interferon. And, as would readily be predicted, efforts are under way in several laboratories to manufacture interferon by means of recombinant DNA techniques. Optimism about interferon production in really large quantities, however, is tempered by a record of repeated failures, extending now for more than a decade, of attempts to characterise the protein so as to enable its synthesis by the vatful.

Production difficulties aside, even if interferon were plentiful there are reasons not to be overenthusiastic about its promise of worth in clinical trials against cancer. Data such as Strander's are encouraging, but they come from very few patients observed over a very short time, as these things go. And some other clinical trials of interferon have not given as heartening results as are coming from Sweden. The National Cancer Institute may merely be sagely husbanding its dwindling resources in not plunging into the interferon swim.

US institutions concerned with clinical trial are: University of Texas MD Anderson Hospital and Tumor Institute, Houston; Sloan-Kettering Institute for Cancer Research, New York City; Roswell Park Memorial Institute, Buffalo, New York; Columbia University College of Physicians and Surgeons, New York City; Stanford University Medical Center, Palo Alto, California; Yale University School of Medicine, New Haven, Connecticut; University of Wisconsin Center for Health Sciences, Madison; Mount Sinai School of Medicine, New York City; Johns Hopkins University Oncology Center, Baltimore, Maryland; University of California at Los Angeles Center for Health Sciences.

No reprints will be available from the authors.

STRANGE ENCOUNTERS

References—content of the referee's letter

Much care, or little, or none, may go into the preparation of a referee's letter about a candidate for a job. Too many referees do little more than present a synopsis of the candidate's career—information that is contained in more detail, and more accurately, in the account that the candidate himself has given in his application. Sometimes a referee writes as if the candidate is destined to rank with the immortals of science, although, in fact, it is evident that he is an average fellow.

Another referee, supporting a candidate's application, may write as though it was his own department, even his personal achievement, that he is recommending rather than the candidate. It has been known for a referee to state in his letter about a candidate that he would himself be willing to consider an invitation to accept the appointment (he enclosed an 18-page summary of his curriculum vitae).

Occasionally, a referee has to assess two candidates for the same job. When their seniority, qualifications, and experience are so on a par that neither has an obvious advantage over the other, the referee has a special obligation to indicate other qualities of each of them and eventually to give guidance that might help the appointments committee to select the more suitable one. Instead, too many referees faced with this problem opt for the neutrality of writing exactly the same letter about each. Sometimes it is an embarrassing position, but the referee who accepts the responsibility of giving an opinion on more than one candidate for a single job should complete his task responsibly.

It is the omissions from referees' assessments that may cause most trouble to all concerned in making an appointment. Few who have served over some years on appointments committees can be without experience of unsuccessful and even disastrous appoint-

ments that have been made because some referee—even a group of referees acting together—failed to give information relating to shortcomings that, had they been known, would properly have excluded the candidate from further consideration.

Difficult moral and ethical problems may need to be faced by referees, and solved by them. And a referee must never use his position to foist a tiresome colleague at his own hospital on to his unwitting colleagues in another institution: it has been done, it will be done again, and we should be ashamed.

A chairman, once, disappointed by his committee's majority choice of candidate for a consultancy, told the runner-up, whom he had hoped to see selected, that he should revise his list of referees. The young man went back to the department in which he worked and rummaged through his chief's confidential files until he found the carbon copy of the letter about himself. He photographed it, and repeated the exercise in the offices of his other two referees.

One of the three letters contained nothing that he thought unacceptable; the others mentioned aspects of his work and of his personality that he thought would not have been mentioned by anybody genuinely trying to get him the job. He took the photographs to a lawyer and tried, unsuccessfully, to start proceedings against the two referees on the grounds that what they had written was defamatory and likely to have influenced the appointments committee against his candidature.

The lawyer was probably wise. The chairman was foolish, if not worse. The referees were not blameless, for they might have saved a lot of anxiety if, instead of agreeing to act as referees, they had told the candidate that they could not support his application. But how, then, would the appointments committee have known that the candidate was unsuitable for the job, which he was?—WILL MACREDIE.