Eur J Cancer Clin Oncol, Vol. 17, No. 9, pp. 949–967, 1981.
Printed in Great Britain.

0277-5379/81/090949-19$02.00/0

Perspectives in Cancer Research

The Clinical Value of Interferons as Antitumor Agents

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Abstract—*In this article the evidence pertaining to the perspectives for clinical applicability of interferons as antitumor drugs is critically reviewed. The mechanisms by which interferons can influence tumor growth and host defense against tumor proliferation are: a direct inhibitory effect on cell growth, alteration of cellular surfaces and immunomodulatory effects. In a particular situation several of these mechanisms may act syngergistically. In experiments on tumor-bearing animals the effect of interferon therapy consists of inhibition of tumor progression rather than induction of regression. Furthermore, the studies with animal models suggest that doses higher than those given in current clinical trials will be necessary to obtain clearly beneficial effects in man. Clinical trials with leukocyte interferon are well advanced, especially with regard to breast cancer, lymphoma and myeloma. They suggest that fairly small doses can cause tumor regression in some but not all cases. Regressions were also seen in all treated cases of laryngeal papilloma. Leukocyte interferon therapy might be useful to prevent metastasis after surgical removal of the primary tumor in osteosarcoma patients. Clinical trials with fibroblast interferon are less well advanced and the available evidence is rather fragmentary. No clinical trials have so far been done with immune type interferon.*

INTRODUCTION

THE INTERFERON system was discovered more than 20 years ago as a mechanism playing an important role in the natural defence of higher animals against virus infections [1]. From the early beginnings interferons were thought to hold promises for their development into potent and non-toxic antiviral drugs [2]. The idea of their applicability as antitumor drugs [3–7] emerged in the late sixties when the concept of a close relationship between viruses and naturally occurring cancer was very fashionable. Supportive evidence for the antitumor potential of interferon came from the observation that interferons as well as their inducers could inhibit proliferation of experimental tumors in mice, regardless of whether these were induced by infection with oncogenic viruses [8] or by transplantation of tumors which were not apparently related to virus infection [9, 10].

For more than two decades after interferon's discovery, the number of laboratories involved in interferon research steadily increased and considerable advance was made in elucidating the mechanism of interferon production by cells, the mechanism of its action at the cellular level, the molecular characterization of the different types of interferon, and their role in spontaneous cure of natural and experimental infections [11]. Most of this research on interferon would never have been done if, for all these years, the prospect of its widespread clinical use as an antiviral or antitumoral agent would not have been ever present in the minds of interferonologists. However, for a long time no solid evidence was being shown for interferon to be truly useful in the clinic: for want of enough interferon, the implementation of clinical trials had to be postponed from year to year. Only a few laboratories devoted a major part of their efforts to the production of interferon. Since 1966, Kari Cantell at the State Serum Institute in Helsinki perseverantly produced progressively larger amounts of interferon from fresh human leukocytes [12, 13], and at our own Institute a pilot plant was set up in 1973 for the production of interferon from fibroblast cultures [14]. More recently many other teams have ventured into similar enterprises. Interferons from both of these sources have now been given to patients with various diseases, in various doses and for various lengths of time, and the results of

clinical trials are now being published in the scientific journals. While the authors are interpreting their results with caution, some of the current editorial comments as well as press statements are, in our opinion, too jubilant to be honest to clinicians who are not specialized in interferon or related fields and to the public at large. The question of interferon's clinical applicability remains as controversial as it has been in the past. However, the recent achievements in the field of DNA recombinant procedures [15, 16], which seem to have enabled possible future large scale production of interferons, have added new perspective to this old controversy.

In the present paper we want to review and criticize the evidence in favour of interferons as future antitumor substances.

RATIONALES FOR ANTITUMOR POTENTIAL OF INTERFERON

Interferons are primarily known as antiviral agents. The concept of their possible activity against cancer probably has its origin in the very early days of interferon research, when the relation between viruses and cancer was a much debated issue. The first experiments in the direction of an antitumor therapy were, to the best recollection of the author, done on man rather than on animals [17]. Preparations of low potency were given to leukemia patients. Also, some patients were given injections of virus with the purpose of inducing endogenous interferon. Along the same line of thought, the first experiments on laboratory animals made use of virally induced tumors [8, 18], i.e. erythroleukemia induced by murine oncornavirus (Friend leukemia and Rauscher leukemia viruses). Later work made use of experimental tumors that were only indirectly related to virus infection (radiogenic leukemia [19] or mammary tumors [20]) or that had no known relation to virus infection [9, 10, 21–30]. When it became clear that in some of these experimental models certain interferon preparations did indeed inhibit tumor growth, it became necessary to think of mechanisms different from the antiviral effect to explain this action. At present, at least 3 possible mechanisms have been described by which interferon may inhibit tumor proliferation. They will briefly be reviewed here.

(1) *Inhibition of cell growth*

The antiviral effect of interferon is due to a reprogrammation of cellular metabolism. At least two intracellular enzymes with regulatory capacity for protein synthesis are induced by interferon treatment of cells. Both enzymes, an oligonucleotidyl synthetase [31] and a protein kinase [32–34], are synthesized in an apparently inactive form. Activation can be triggered *in vitro* (i.e. in cell extracts) by the addition of double-stranded RNA. It is not known how activation is triggered intracellularly. A current hypothesis [35] is that the enzyme systems remain inactive until a virus starts to replicate in the cell: the nucleic acids that constitute the replicative intermediates would then trigger activation of the regulatory enzymes. Besides the two enzyme systems mentioned, other interferon-inducible regulatory devices may exist within cells. Possibly these may also affect pretranslational (transcriptive) or post-translational events.

While the effect of cellular reprogrammation by interferon is most obviously expressed in the inhibition of virus replication, certain effects may also be induced without viral challenge. The most 'general' effect is inhibition of cell growth. It is sometimes referred to as 'anticellular effect' and was described as early as 1962 by the late Kurt Paucker [36]. In essence he showed that interferon, prepared by infecting mouse L-cells with virus, inhibited cell proliferation in cultures of L-cells. The main difficulty consisted in demonstrating that the effect was due to interferon and not to contaminants, e.g. residual virus. This difficulty of interpretation persisted [37] until, in 1978, preparations of 100% pure mouse interferon were obtained [38, 39]. It then became clear that the growth inhibitory properties of interferon were genuine [21].

All cell strains and lines, normal as well as malignantly transformed, have a certain degree of sensitivity to the growth inhibiting effect of interferon: there is no rule that malignant cells would, in general, be more sensitive than normal cells. Also, there is a wide variability in the sensitivity: some cell lines (such as the human lymphoblastoid cell line, Daudi) are inhibited by as little as 10 units/ml [40, 41] ($= 10^{-8}$ mg/ml; $= 10^{-3.7}$ mmol); some other lines are resistant to a 1000-fold higher concentration [42]. By subjecting a sensitive line to careful selection methods, resistant variants can be obtained [43]. The genotypic and phenotypic differences between such sensitive and resistant lines are a subject of active investigation [44]. The main question, here, is whether the cell growth inhibitory properties are related to the antitumor effect *in vivo*. This is an important question because it may influence the interpretation of experiments in which one tries to predict the antitumor effect in a given model (experimen-

tal on clinical case) from the effect on growth in culture of cells from that particular tumor. For instance, one may try to predict the antitumor effect of two types of interferon (e.g. human leukocyte or fibroblast) from their effect on various cell types (e.g. fibroblasts or lymphoid cells) [45]. Or one may try to predict whether interferon will be active in a clinical case by testing inhibition of the clonogenicity of the tumor in the presence of interferon [46]. The results of such investigations may be overinterpreted, if the inhibition of cell growth is not the foremost important mechanism by which interferon inhibits tumor growth. Along this line it has been shown that tumors induced in nude mice by inoculation of the human lymphoblastoid line, Daudi, are resistant to human interferon [47–49], although *in vitro* this cell line is highly sensitive to the cell growth inhibitory effects of interferon [40, 41]. Also, tumors induced by inoculation of L1210-leukemia cells in mice are inhibited by administration of mouse interferon, irrespective of whether a cell-variant is used that is sensitive (L1210-S) or resistant (L1210-R) to the cell growth inhibitory effect of interferon *in vitro* [50]. However, mice injected with L1210-S cells are protected to a greater extent than those injected with L1210-R cells.

It thus appears that the antitumor effect of interferon as seen in the tumor-bearing animal is not only due to direct inhibition of tumor cell division.

(2) *Alteration in cellular surfaces*

Exposure of cells to interferon results in a variety of morphological and functional alterations of the plasma membrane, as reviewed by Gresser and Tovey [3] and by Friedman [51]. Some of these changes are well characterized, others have only been mentioned in single reports in the literature. Cell surfaces are held to play an important role in the genesis of cancer since they are the carrier substrate of receptor molecules for environmental signals that may limit cell growth, migration and fixation in particular sites in the body. From these considerations arose the concept that alterations in the membrane of cancer cells may be a mechanism by which interferon inhibits tumor development. It is difficult to rationalize any of the observed changes in terms of their possible consequences for tumour development without digressing into vague generalizations. Thus, alterations in transport of nucleosides may be inferred to impair the nucleic acid synthesis in cancer cells. Morphological alterations or altered binding of certain substances to interferon-treated cells may be interpreted to mean that interferon may bring about changes in the number or accessibility of particular membrane receptor molecules. The best documented example of this is enhanced binding of allo-antibody to lymphoid cells after treatment with interferon [52, 53]. One might envision that interferon treatment also results in enhanced expression of tumor-specific transplantation antigens which are held to be a target for the immune attack on tumor cells. However, this concept has not been substantiated experimentally.

(3) *Immunomodulation*

It cannot be questioned that interferons alter the immune system (for review see Epstein [54]). Effects on the afferent arm of the immune response (formation of antibodies and development of cellular immunity) can be either stimulatory or inhibitory, depending on the circumstances under which interferon is brought into the test system. In view of the complexity of the test system it is difficult to propose a unifying concept that may explain this. Perhaps the immunosuppressive effects should be attributed to the inhibitory effect of interferons on cell multiplication which may limit the expansion of lymphocyte clones. Stimulatory effects, on the contrary, may be due to enhanced expression of antibody synthesizing capacity of differentiated B-cells. The effects of interferon on the efferent arm (antibody-dependent or purely cellular effector mechanisms) are often stimulatory. Thus, antibody-dependent cell-mediated cytotoxicity [55, 56], as well as cytotoxicity of specifically sensitized T-cells [57, 58], are enhanced when the effector cells are pretreated with interferon.

Interferon has also been shown to stimulate phagocytosis [59] as well as tumor-cell inhibitory effects of macrophages in culture [60]. Finally, natural cytotoxicity (natural killer, NK) activity of unsensitized peripheral blood mononuclear cells is also enhanced by their preexposure to interferon [61–63]. In the past few years this phenomenon has received a large amount of attention. Two mutually related questions are central to the current debate of this issue. Firstly, what is the role of NK-activity in host defense against naturally occuring malignant tumors? Secondly, can NK-activity be sufficiently increased to cause rejection of tumors that would otherwise be accepted by the host. Only a few clinical entities have been found to be accompanied by decreased NK-activity of pheripheral blood mononuclear cells: severe combined immunodeficiency [64],

Chediak–Higashi disease [65], and an X-linked lymphoproliferative syndrome [66] are so far the only ones mentioned in the literature. Patients with common forms of cancers were not systemically found to have low NK activity. Even on a statistical basis such a difference was only apparent in some but not all studies [67, 68]. Of course, this lack of close correlation cannot be interpreted to mean that the NK-mechanism is irrelevant to the defence against the tumors in these patients. Cancer patients with high levels of NK activity might represent a selected group in which the tumor has in fact developed less easily than if this high activity had not been present. For cancer patients with low NK levels the question may be asked which came first, the tumor or the low NK activity. In patients with localized melanoma, it was found that low NK activity after complete surgical removal was associated with a higher recurrence rate [69]. A second study was carried out in families with a high incidence of melanoma. It was found that the prevalence of low NK-activity levels was higher in patients from such families than in patients with non-familial melanoma. Moreover, the close relatives of these patients also had low NK-activity levels [70]. In experimental systems the situation is somewhat less complicated. From studies in mouse strains with genetically determined, selective impairment of the NK-system (beige mice) it would appear that the capacity of the host to respond with NK-activity is an important determinant of tumor development. Beige mice were found to be relatively less resistant than normal mice to tumor induction by NK-susceptible cell lines, as opposed to normal resistance against cell lines which are susceptible to NK-activity [71].

Enhancement of NK-activity by interferon can easily be measured *in vitro* and is most efficiently expressed as decrease in the number of mononuclear effector cells necessary to lyse one tumor (target) cell. Under the best experimental conditions, interferon can bring about a 4-fold decrease in the effector/target cell ratio necessary for NK-activity [56, 57, 62, 72–75]. It is questionable whether this increase in NK-activity is by itself sufficient to result in a significantly increased resistance of the host to tumor development. It may also be questioned whether the optimal conditions required for this stimulation to occur can be fulfilled *in vivo*.

(4) *Cooperation of different mechanisms*

As outlined in the previous paragraphs, several mechanisms exist by which interferon may counteract the development of tumors. The efficiency and specificity of each of these mechanisms by itself may be insufficient to justify the expection of a strong and selective *in vivo* antitumor effect. However, several of these mechanisms may act synergistically and thus bring about a strong and selective antitumor effect.

So far there are no substantial observations to support this concept. In fact, examples to the contrary do exist. Thus, the enhancement of NK-activity by preexposure of effector lymphocytes to interferon is counteracted by a protective effect of interferon against NK if the target cells are also exposed [61, 73, 76]. It has been argued that tumor cells, as opposed to normal cells, may in general be less prone to be protected by interferon against NK. Thus, the apparently opposed effects of interferon on effector and target cells may constitute a mechanism which imparts selectivity on the NK-system for tumor cells. However, the generality of the phenomenon that tumor cells cannot be protected against NK by interferon is as yet not documented. The concept is somewhat reminiscent of early contentions that interferon was not antivirally active on transformed cells, a finding which was not confirmed later on.

A related question is whether tumor cells *in situ* are as sensitive to NK as cultivated cell lines *in vitro*. The assay systems for NK-activity evidently make use of target cells and *in vitro* conditions selected for high sensitivity. With target cells of low sensitivity to NK, as may be the case with naturally occurring tumors, the enhancing effect of interferon may be either less or more pronounced.

The cell growth inhibitory effect of interferon is not specifically directed against tumor cells. However, small differences in environmental conditions (pH, oxygenation, temperature) may exist between normal and malignant tissue, and this may convey a certain specificity on the inhibitory effect. Examples of this exist in other fields of tumor therapy. Thus, hyperthermia affects cell growth more effectively if pH is low, a condition prevailing in tumor tissue [77]. Also, various forms of tumor therapy, e.g. hyperthermia, chemotherapy and irradiation, given each in sub-effective doses can act synergistically [78].

In conclusion, it is difficult to predict, from *in vitro* studies how strong and how selective the antitumor effect of interferon can be in an *in vivo* situation. For instance, the relative potency of different molecular types of interferon cannot unequivocally be predicted from comparisons using *in vitro* systems such as cell

growth inhibition, NK-stimulation, etc. Preclinical assessment of the antitumor potential of various interferons requires that the *in vitro* parameters be complemented by studies on experimental tumors in animals.

EXPERIMENTS ON TUMOR-BEARING ANIMALS

Most if not all chemotherapeutics which are currently used in cancer patients have a long and rich history of extensive and successful experimentation on tumor-bearing animals. The most successful amongst them have been shown to arrest tumor growth or even to cause tumor regression and a high percentage of definitive cures of experimental tumors. Examples of this are cyclophosphamide [79], melphalan [79] and the vinca alkaloids [80]. Interferon has also been shown to exert an antitumor effect in mice with various virus-induced or transplantable tumors [8–10, 18–28]. However, with a single unconfirmed exception [81], interferon treatment of mice has never been reported to induce tumor regression. The effect of interferon is a delay in tumor progression, which may result in increased survival time of the host.

From studies involving the use of completely pure interferon, there is no doubt left, at this time, that the antitumor effect of impure interferon preparations is accounted for by interferon itself rather than by the impurities [21, 31, 82, 83].

The minimum dose of interferon required for the effect to be measurable in mice (assuming a specific activity for pure interferon of $\sim 10^9$ units/mg protein) is on the order of magnitude of 20 μg/kg/day or 55 μg/m^2/day. The current doses given in experimental trials on man are of the order of magnitude of 0.04 μg/kg/day (500 times less than the effective dose in mice) or 1.7 μg/m^2/day (32 times less than the effective dose in mice). How can one expect a substance to be a highly effective anticancer drug in man if given in a dose 32 to 500-times smaller than that which is only able to delay progression of selected tumors in mice? Although there is at present no coherent answer to this question, clinical trials have been initiated by various investigators and optimism has continued to prevail. Perhaps some investigators are guided by the concept that interferon is different from other anticancer agents by its acting through the host defense mechanisms rather than as an antimitotic. Therefore, its clinical value may not be predictable from studies on tumor models in mice. Perhaps the host defenses that counteract tumor progression in a clinical situation are not faithfully reflected by the murine models. Other explanations for a resilient optimism may be the often encouraging results of the uncontrolled clinical trials conducted so far.

Another argument in favour of interferon as a substance with clinical anticancer potentials may be the fact that there exist multiple molecular species (types and subtypes) of interferon. Each of these may have a different biological function. Perhaps one or several of them will be found to be endowed with an anticancer potential that is several times higher than that of the interferons that are currently available. This may be the case for immune-type interferon, also called type II interferon, or γ-type interferon (IFN-γ). This molecular variant of interferon is in fact a lymphokine produced by lymphocytes after stimulation with specific antigens or mitogens. Experiments in which grossly impure preparations of this interferon were used to treat mice revealed an antitumor effect similar to that seen with classical interferon, i.e. delayed progression. A point which has received considerable emphasis is the fact that the antitumor effect of these γ-type interferon preparations was seen with a dose that was $\sim$100-fold lower than that required in the case of classical interferon [84, 85].

However, these doses were of necessity expressed in biological units. Since the specific activity of pure IFN-γ is not known, it is impossible to relate the dosages to those of classical interferon. If the specific activity of IFN-γ is lower than that of classical interferons, a 10 to 100-fold lower effective dose in terms of biological (antiviral) units may in fact mean the same dose in terms of weight. In conclusion, the case of γ-type interferon is a weak one in that (1) the preparations quoted to be active contained numerous impurities; (2) the antitumor effect of γ-type interferon preparations is not qualitatively different from that of classical interferons in that delayed progression, not regression was seen and (3) the minimum effective dose of γ-type interferon has not unequivocally been shown to be lower than that of classical interferons. In fact, even if IFN-γ were more active, it would still have to be demonstrated that it is not also more toxic than classical interferons.

CLINICAL TRIALS WITH LEUKOCYTE INTERFERON

(1) *Breast cancer*

Gutterman *et al.* [86] reported on an open uncontrolled trial involving 17 patients with recurrence of breast cancer lesions that failed

to respond to radiotherapy, hormone therapy, and, in most instances, chemotherapy. The dosage consisted of 3 or 9 million units (MU) daily by intramuscular injection for 4–12 weeks. Nonresponders were taken off interferon therapy; patients with evidence of regression were placed on a maintenance schedule of 3 MU, 3 times weekly. The responses were rated according to criteria recognized by the UICC. Partial remissions (25 to 50% reduction in the product of 2 largest tumor diameters of at least some tumor localizations and absence of progression in all lesions) were seen in 6 out of the 17 patients. Less than partial remission was seen in 1 patient.

Under the auspices of the American Cancer Society a trial is being conducted, also involving daily intramuscular injections of 3 to 9 MU in patients with recurrence of breast cancer. Although the details of this trial have not yet been disclosed, it has been reported that of the 26 patients who entered the trial at the end of 1980, 6 showed a partial response with post-treatment durations of 14–121 days (87).

(2) *Lymphoma (non-Hodgkin)*

Merigan *et al.* [88] reported on 6 patients with malignant lymphoma, given 5–10 MU daily for 30 days. Three of the patients had a diffuse histiocytic lymphoma resistant to radiotherapy and chemotherapy; no reduction in tumor size was noted in these. Two patients, with nodular lymphocytic, poorly differentiated lymphoma, not previously treated, showed regression of the disease, evident from resolution of enlarged retroperitoneal and peripheral lymph nodes. One patient with a similar histocytologic type of tumor received local radiotherapy followed by interferon; regression was evident from normalization of bone marrow biopsies. These apparent remissions persisted for at least several months.

Hill *et al.* [89] used fractionated intravenous injections of relatively high (0.25 MU/kg daily) to very high (2 MU/kg/day, once weekly) doses in patients with various forms of leukemia. The treatments were given for several weeks. One remission and 4 partial responses were seen in 5 patients with acute lymphocytic leukemia, one partial response in 3 patients with acute granulocytic leukemia and no response in one case of chronic granulocytic leukemia.

Gutterman *et al.* [86] reported on 11 patients with malignant lymphoma. The treatment schedule was the same as that given by the same authors for breast cancer patients (see above). Four of these responded favorably (1 partial and 1 less than partial remission). Six of the 11 treated patients had nodular, poorly differentiated lymphoma. For these patients response criteria were the same as those used for breast cancer trial. One complete and 1 partial response were seen; 3 patients did not respond. The study also included 1 patient with histiocytic lymphoma who showed a less than partial response.

(3) *Myeloma*

Mellstedt *et al.* [90] reported on 4 cases of myelomatosis treated from 3 to 19 months with daily intramuscular injections of 3 MU. Remission was complete in two patients; signs of improvement were evident within one month after initiation of therapy. The two other patients also improved, to the extent that no other therapy was felt necessary. Still remission remained incomplete, despite long-term administration of interferon.

The cooperative trial reported by Gutterman *et al.* [86] also comprised 10 myeloma patients. The treatment schedule was the same as that given to breast cancer and lymphoma patients (3–9 MU daily for 4–12 weeks, followed by maintenance treatment of 3 times 3 MU weekly). Three patients showed an objective response (sustained decrease in abnormal serum Ig by $> 50\%$ or disappearance of Bence–Jones protein). Three patients improved under treatment (at least 25% decrease in serum Ig or at least 50% reduction in Bence–Jones proteinuria). Four patients failed to respond.

Ideström reported on a single case of chemotherapy-resistant myeloma treated for 6 months with daily intramuscular injections of 3 MU [91]. According to the criteria used by Gutterman *et al.* [86] a less than partial response was seen (initially) with subsequent relapse during therapy.

In a study done primarily to test the clinical effectiveness of fibro-blast interferon [92], two myeloma patients who did not respond to this therapy subsequently received leukocyte interferon (3.5 MU 6 times weekly for 5–6 weeks). One of these patients showed a $> 25\%$ reduction in Bence–Jones proteinuria; the second patient failed to respond.

(4) *Juvenile laryngeal papillomatosis*

Juvenile laryngeal papillomatosis is a relatively infrequent tumor probably caused by perinatal infection of the laryngeal mucosa with papillomavirus originating in verereal warts of the mother. The papilloma can persist for several years despite repeated surgical removals and cause progressive destruction of the laryngeal mucosa. In some cases permanent

cannulation of the trachea is necessary. Usually, the tumors spontaneously regress in adolescence.

Haglund *et al.* [93] described 7 cases of juvenile laryngeal papillomatosis treated with 3 weekly injections of 3 MU of leukocyte interferon intramuscularly. All cases showed regression of the lesions, to the extent that cannulation of the trachea became unnecessary. In one case the tumor completely disappeared. It was found that discontinuation of the treatment resulted in recurrence or renewed progression, which again could be arrested by renewed interferon therapy or prevented by maintanance treatment at a lower dosage level.

Confirmation of this beneficial effect of leukocyte interferon therapy on juvenile laryngeal papilloma was obtained by Schouten and Bos [94] and by Göbel *et al.* [95] who compared the effectiveness of leukocyte and fibroblast interferon in such patients (see below).

(5) *Miscellaneous tumors*

One case of Hodgkin's disease treated with interferon has been described in the literature. A temporary decrease in systemic symptoms and in size of lymph nodes and pulmonary infiltrates was seen [96].

Cases of metastatic osteosarcoma treated with leukocyte interferon have been described by Ito *et al.* [97] (3 cases) and by Christophersen *et al.* [98] (1 case). Dosage schedules were of the order of magnitude of 3 MU daily intramuscularly, given for several months. Temporary decreases in the sizes of some metastases with progression of the other localizations were reported in two patients [97].

Partial regressions were noted in 3 patients with bladder papilloma [98].

Sawada *et al.* [99] reported on the treatment of 6 patients with brain tumors (3 glioblastomas, 2 medulloblastomas and 1 astrocytoma). Dosages were in the order of 3 MU intramuscularly and some patients received as much as 270 MU total. No effects were noted. The same authors also treated 2 patients with neuroblastoma, 2 with Wilms' tumor, 1 with yolk sac carcinoma, and 1 with rhabdomyosarcoma. Only in 1 patient (neuroblastoma) was a reduction in tumor size seen.

(6) *Discussion*

As reviewed above, prolonged intramuscular administration of leukocyte interferon preparations seem to bring about partial and sometimes complete remissions in lymphoproliferative disorders such as lymphoma and myeloma, and partial regressions in metastatic tumor nodules in breast cancer patients. There is little room for argument with regression of tumors that are universally reputed as progressively leading to death if left without treatment. The question is not (any more) whether leukocyte interferon preparations can influence cancer. The questions are whether (1) the effect is quantitatively and qualitatively important enough to warrant further investigation and (2) whether it is due to interferon (HuIFN-α) or to some as yet unidentified impurity or mixture of impurities which are comprised in the 99.9% (by weight) of adventitious proteins present in current leukocyte interferon preparations.

As to the first question, it is fairly clear that interferon therapy in its present form does not constitute a major breakthrough in that a high percentage of patients would respond with clear-cut regression. In contrast, it would appear that interferon by itself is at best as good an antitumor drug as some others that are already broadly used, mostly as part of combination regimens. It may thus be possible, by carefully programmed clinical evaluations, to design treatment schedules consisting of other chemotherapeutics in combination with interferon, the benefit of which could be to gain some percentages in remission rate over schedules without interferon. Another aspect of the question is the possibility of increasing the dosage. Currently the size of the daily doses is limited by availability of material and by the toxic side-effects. Although relatively mild when compared to the toxicity of some antimitotics, the side-effects of current interferon therapy are not negligible [100] and may be a limiting factor when one would like to increase doses 10- or 100-fold to reach the level that is effective in experimental animals. It is possible, of course, that the toxic side-effects can be avoided by further purification of the interferon. However, it may also be that such purification will remove substances that are codeterminant or even single determinants of the antitumor effect of current clinical preparations. Thus, one of the more important side-effects is fever. Perhaps the increase in body temperature is one of the codeterminants of the antitumor effect. Reports in the early oncological literature, as well as experimental evidence and recent clinical trials with hyperthermia, support this concept [101]. This then raises a second set of questions relating to the specificity of the antitumor effects as seen in current clinical trials. It was already mentioned that there is a large discrepancy between, on

the one hand, the large daily doses of pure interferon needed to obtain an antitumor effect in mice and, on the other hand, the low doses that seem effective in naturally occurring tumors in man. It may be that, with the advent of clinical preparations, consisting of 100% pure human interferon, one may succeed in increasing daily doses without inordinate side-effects. The question remains as to whether the anti-tumor effect of these high doses of pure interferon will also be more pronounced than those seen with our current interferon treatment schedules.

CLINICAL TRIALS WITH FIBROBLAST INTERFERON

Clinical trials using fibroblast interferon have been lagging behind considerably on those with leukocyte interferon. The main reason for this is that production on a large scale has begun later and is somewhat more complicated than the production of leukocyte interferon. Furthermore, it was not recognized initially that leukocyte and fibroblast interferons consisted of different molecular variants with different biological properties. Therefore the necessity for implementing large-scale production of fibroblast interferon was not felt until relatively late, when production of leukocyte interferon had already been going on for several years.

Whereas clinical information on the effect of leukocyte interferon in malignancy is fragmentary, that about fibroblast interferon is merely anecdotal. Researchers working with fibroblast interferon have a task that is doubly hard. Not only have they to prove that fibroblast interferon is effective; they must also demonstrate that it is superior to leukocyte interferon for the treatment of one or more diseases.

(1) *Breast cancer*

A preliminary trial on 5 patients is being conducted by Prof. Dr. Pouillart at the Institut Curie using fibroblast interferon prepared at our Institute on MG-63 cells (an osteosarcoma cell line that provides higher yields of fibroblast interferon than diploid cells). The treatment schedule (intramuscular injection of 8 MU every 5 days, for 6 weeks) is based on the kinetics of stimulation of NK-activity in patients receiving i.m. injections. After injection of 10 MU the increase was maximal after 48 hr and lasted for about 5 days. Up to this date 3 patients with recurrent metastatic breast cancer, resistant to all other forms of therapy, have received this treatment. One patient showed partial regression of subcutaneous modules, partial regression of small pulmonar nodules (with slight progression of the large pulmonary nodules), and virtual disappearanc of axillary nodules. A second patient ha developed skin necrosis in the irradiation field surrounded by multiple tumor nodules. Durin treatment these subcutaneous nodules regres sed and the necrosis healed. A third patien had multiple metastases in skin and bone. Dur ing treatment a substantial reduction in the size of cutaneous metastases occurred. Yet formation of at least three new nodules was noted and no evidence for reduction in size of bone metastasis could be obtained. These results were judged undecisive but sufficiently encouraging to undertake a confirmatory trial involving treatment of longer duration.

Ogawa and Ezaki [102] treated 2 cases of metastatic breast cancer (3–6 MU/day by intravenous infusion) for 30 days and found progression under therapy.

(2) *Lymphoma*

Two cases of lymphoma treated with intramuscular injections of fibroblast interferon have been mentioned by McPherson and Tan [103]. The doses ranged from 1 to 5 MU/day, given 4 times weekly for about 3 weeks. A clear response was seen in one case (acute myeloblastic leukemia), a partial and only temporary response in the other (chronic myelobastic leukemia). An additional patient with chronic myeloblastic leukemia received 5 i.v. infusions with increasing doses (1.5–7.5 MU) over a short period of time; no response was seen in this patient.

Ogawa and Ezaki [102] treated 4 cases of lymphoma with intravenous infusions of 3–6 MU/day for 8–30 days; no effect on tumor evolution was seen. Furue *et al.* [104] reported on 9 cases of lymphoproliferative disorders treated with intravenous injections (3 MU/day) for various lengths of time (some cases receiving only one injection). Complete remissions were seen in 3 cases (1 case of monocytic leukemia and 2 cases of acute myeloblastic leukemia) given combined treatment with chemotherapy and interferon. At least one of these cases was previously found to be completely resistant to chemotherapy alone. Shimoyana *et al.* [105] treated 4 patients with lymphoma using intravenous injections of 1.5–6 MU given for about 8–30 days. No regression was seen.

Again the total number of treated patients ($\sim$ 16) available as yet is too small to even make recommendations for therapeutic regimens in future trials. Yet a response rate of 4 out of 16

is quite impressive, and a point can perhaps be made for trials with combination therapy.

(3) *Myeloma*

The phase I pharmacotoxicology study of McPherson and Tan [103] comprised 2 patients with myelomatosis. One was given i.m. injections (9 injections of 1–5 MU over a period of ~2 weeks); the other patient received intravenous treatment (4 doses of 1–4 MU). The response was nil in the first and dubious in the second case.

At our Institute 3 patients with myelomatosis (light-chain disease) received intramuscular injections of fibroblast interferon [92]. A dosage of 28 MU per week failed to influence disease progression in a therapy-resistant case. In a second case, that had not previously been treated, a first course of fibroblast interferon (30 MU per week) associated with corticosteroids produced a favourable response, but a second course, without corticosteroids, remained without effect. In this patient subsequent leukocyte interferon treatment was associated with a decrease in urinary light chain excretion and normalization of calcaemia, all other parameters remaining unaltered. A third patient with light chain disease was resistant to chemotherapy *ab origine*. None of the disease parameters responded to either fibroblast or leukocyte interferon therapy (21 MU per week).

Ogawa and Ezaki [102] and Furue *et al.* [104] also failed to see an influence of fibroblast interferon in, respectively, 2 and 1 cases of myeloma, treated for several weeks with doses of ~ MU/day intravenously.

This adds up the number of myeloma cases to ~8, none of which were responsive to fibroblast interferon. This is in rather sharp contrast to the findings of researchers working with leukocyte interferon. The impression that leukocyte interferon does, and fibroblast interferon does not have the ability to influence the course of myeloma is reinforced by our observations in one primary case of myeloma which failed to respond to a 13-week-long treatment course of fibroblast interferon but showed a progressive decline in Bence–Jones proteinuria after subsequent treatment with leukocyte interferon [92].

(4) *Laryngeal papilloma*

Two patients ($3\frac{1}{2}$ and 7 years old) with laryngeal papilloma received subcutaneous injections of fibroblast interferon prepared at our Institute (3–4 MU/day, 3 times weekly, for 3 months). A clear but partial regression of the tumor masses on the vocal cords was observed [94]. After arrest of treatment, the papillomas increased again in size. Göbel *et al.* [95] treated 2 similar cases (children of 4 and 5 years age), giving intravenous infusions of 2–3 MU daily for 6 weeks. No signs of regression were observed. The same children subsequently showed a favorable response to treatment with leukocyte interferon (2 MU daily, subcutaneously, 4 weeks).

The difference in response to fibroblast interferon, as seen by Schouten and Bos [94], and by Göbel *et al.* [95] may be due to the difference in injection route or in duration of therapy.

(5) *Other tumors*

Although melanoma is one of the tumors to be included in the cooperative interferon trials sponsored by various agencies in the United States, very little information is available as yet on the results obtained. One research group, working with fibroblast interferon, has concentrated on this tumor and has reported regression of subcutaneous nodules after intralesional injections. In a preliminary communication the same group of authors reported regression of melanoma lesions in a patient given systemic treatment with fibroblast interferon [49].

Various other types of tumors have been treated with fibroblast interferon. A survey of available information yielded a total of 28 tumors (3 osteosarcomas [103, 106], 2 colon carcinomas [103, 104], 5 renal cancers [103], 4 gastric cancers [102, 104], 1 bronchial carcinoma [104], 1 oesophageal cancer [104], 2 liver cancers [102, 104], 1 ovarian cancer [102], 7 brain tumors [105, 107], 1 rhabdomyosarcoma [105], and 1 neuroblastoma [106]) treated with fibroblast interferon, given intramuscularly or intravenously, for various lengths of time. Only in one of these studies [107] was a favorable response noted. In 2 children with medulloblastoma, intravenous infusions (2–3 times weekly for more than than 2 months, total dosage up to 200 MU) caused regression of the tumor mass left after partial surgical removal. In the same study a partial remission was noted in 2 cases of recurrent glioblastoma, while in 2 other cases no therapeutic effect was seen.

Special mention should be made of a case of metastatic nasopharyngeal carcinoma, successfully treated with intravenous infusions of fibroblast interferon. It should be noted, however, that nasopharyngeal carcinoma, in contrast to most other tumors considered as candidates for interferon therapy, is caused by chronic viral infection (Epstein–Barr virus). Hence, the beneficial effect may have been

generated through inhibition of viral replication [108].

(6) *Discussion*

From the studies cited above it should be clear that, with the possible exception of apparent success in nasopharyngeal carcinoma, fibroblast interferon is as much a miracle drug for cancer as leukocyte interferon. There has been some speculation that it might even be inferior to leukocyte interferon. The sole basis for this contention is that blood titers after i.m. fibroblast interferon injection are inferior to those obtained by i.m. injection of leukocyte interferon. As a result of this finding some workers have resorted to i.v. infusions rather than i.m. injections of fibroblast interferon. From the studies summarized above it should be clear that the clinical effectiveness was not markedly improved by this procedure.

The mechanism of the difference in pharmacokinetic behaviour of the two interferons is still unclear. Trapping or rapid destruction of fibroblast interferon at the injection site has been considered as one possibility; rapid removal from the circulation and uptake into certain organs or cell systems is another possible explanation. Several lines of evidence (for review, see [100]) seem to favour this second possibility. In particular, the enhancement of NK-cell activity was found to be as pronounced in patients receiving i.m. injections of fibroblast interferon as in those receiving leukocyte interferon. This seems to indicate that at least the lymphoid system is reached effectively by i.m. injection of fibroblast interferon.

PROSPECTS FOR THE CLINICAL APPLICATION OF IMMUNE INTERFERON (IFN-γ)

Immune interferon will be the third type, after leukocyte and fibroblast interferons, to be developed into a preparation that can safely be administered to man. While this process is now taking place in several laboratories [109–111], it is being speculated that these preparations will have a more potent antitumor potential than the current preparations of leukocyte (IFN-α) and fibroblast (IFN-β) interferon. The principal basis for these high expectations focused on IFN-γ comes from experiments in mice. Specifically, it was found that the administration of lymphokine preparations rich in IFN-γ could bring about a delay in tumor outgrowth, comparable to that obtained with injections of classical interferon, except that the minimal dose (expressed in units of antiviral activity) required to obtain this effect were about 100-fold smaller [84, 85]. The authors of this study were cautious enough to express the feeling that lymphokines other than IFN-γ present in these preparations may have accounted for part of the antitumor effect.

Another concept underlying the expectations with regard to immune interferon is the synergistic effect between this interferon and leukocyte or fibroblast interferons [112]. It was found that the total antiviral as well as antitumor effects of current preparations of leukocyte or fibroblast interferon might considerably be enhanced by the addition of relatively small amounts of immune interferon [113].

Finally, it has been speculated that IFN-γ might in nature play the role of an immunomodulating lymphokine, and that its interferon-like antiviral activity is but a side-effect. In its capacity as an immunomodulator, IFN-γ may be a lymphokine specifically endowed with anticancer potentials. Some support to this view has come from the observation that preparations of human interferon can stimulate the NK-activity of lymphocytes to a significantly larger extent than preparations of leukocyte or fibroblast interferon [114].

Before preparations of HuIFN-γ can be used in clinical experiments it will be necessary to develop suitable methods for mass production and purification. It has already been found that partially purified preparations are heterogenous in that at least two molecular variants of interferon are present, one of which resembles HuIFN-β [114]. It can be foreseen that clinical trials will not be delayed until this heterogeneity will be resolved or until completely pure HuIFN-γ will be available. Hence, it can also be foreseen that the first clinical trials, whether their results will be positive or negative, will be uninterpretable in terms of which particular molecules have clinical relevance.

THE USE OF INTERFERON IN PROPHYLAXIS OF CANCER RECURRENCE

In many forms of cancer it has become common practice to use chemotherapy as an adjuvant to surgery in order to prevent metastasis. Along this line of thinking one could imagine that prolonged interferon therapy might be useful as an additive to other forms of cancer treatment, e.g to prevent metastasis after surgical removal of a primary tumor or after remission of lymphoproliferative disease induced by chemotherapy or radiation. This field is still largelv unexplored except for one, in fact the most remarkable, study conducted by Strander and his colleagues on osteosarcoma

patients in the Karolinska Hospital in Stockholm [115]. Over a number of years (1972–1979) 44 patients with osteosarcoma were treated with about 10×10^6 units of leukocyte interferon per week in an attempt to prevent metastasis after surgical removal of the primary tumor. The evolution of their disease was compared with that of two control groups: a historical control group consisting of patients treated in the same hospital over a number of years preceding the interferon era and a contemporary control group consisting of patients treated in other Swedish hospitals and not receiving interferon or any other adjuvant therapy. The most significant parameter in such studies is the metastasis-free survival (MFS) rate after a number of years [116–118]. The interferon-treated group had a MFS-rate after 30 months of 54%, compared to 15% for the historical control group and 30% for the concurrent control. Similar results (18% for the historial control and 54% for the treated group) have been reported in a study using adjuvant therapy with cytostatics [116]. Both studies are subject to criticism on the basis of a report that in the last two decades MFS rates in osteosarcoma patients have spontaneously increased with calendar year [118]. This historical change in the natural course of the disease, which would compromise the use of historical controls, has not been confirmed in two other clinical centers [116, 117], including that where the chemotherapy study was conducted [116]. The problem became even more controversial when preliminary results of a placebo-controlled trial were revealed, indicating failure of chemotherapy to affect the course of disease (*loc. cit.* [119]). As a result of this the usefulness of adjuvant chemotherapy in surgically treated osteosarcoma is now heavily contested. In conclusion, the possibility that the improvements in MFS-rates in interferon-treated patients are caused by unidentified confounding variables cannot at present be excluded. Similar variables may also be at play in the comparison between contempory groups treated in different hospitals. Thus the results obtained with interferon therapy in osteosarcoma cry out for corroboration by a double-blind placebo-controlled trial. The practical and ethical problems inherent to the performance of such a trial are enormous, so that the question may stay controversial for years to come. It is true, however, that the side-effects of interferon therapy are much less pronounced than those of chemotherapy and may still diminish when pure interferon will be used. It might then be possible to increase the daily dosage 10- or 100-fold. Perhaps with these doses the effect on MFS-rate will be so pronounced that a placebo-controlled trial will not be necessary to convince the sceptics.

TOPICAL APPLICATION OF INTERFERON AGAINST LOCALIZED TUMORS

Several authors have reported positive results obtained with topical treatment of localized tumors [120, 121]. The rationale is that with intratumoral injection or percutaneous treatment a high local concentration of interferon can be obtained. Thus, the inhibitory effect on cell growth and on the tumor cell killing effect of local lymphocytes may be more pronounced than when the interferon is injected at a distance. In doing these experiments some authors have had the objective to design a practicable therapy for tumors; others have used topical application in an effort to obtain more convincing evidence for the antitumor potentiality of interferon.

In an open, controlled trial Ikic *et al.* [122] have shown that topical treatment of condyloma accuminata—veneral warts associated with papillomavirus infection—can effectively be treated with ointment containing leukocyte interferon. The same authors have also reported regression of facial epithelioma's after peritumoral injection of leukocyte interferon [120, 121]. Similar regression was reported by Horoszewicz *et al.* and Ishihara *et al.* [45, 105] in the treatment of localized nodular melanoma lesions with intra- and peritumoral injections of fibroblast interferon. Of particular interest in these studies was the finding that the injected area became infiltrated with large numbers of mononuclear cells, suggesting mobilization and activation of tumor-cell-killing lymphocytes.

GENERAL CONCLUSION

From the evidence reviewed in the present paper it should be clear that the therapeutic value of interferon in malignant disease remains a controversial issue. There is no doubt that interferons are molecules endowed with extremely high and diversified biological actions and that they play a certain role in the cellular regulation processes which are considered crucial to the malignant behaviour of cancer cells and to the host defense against cancer. Whether these biological activities can be exploited to cure cancer is still very much in doubt. In animal model systems the effect of interferon therapy is poor when compared to the effects of certain drugs that are already broadly used in cancer therapy. The human interferons that have been available for clinical

evaluation until now are certainly not drugs that cure cancer. As to their usefulness in helping to limit the evolution of malignant diseases, statistical studies involving large numbers of patients in collaborative trials will be necessary to allow a conclusion.

There is at present no basis to support the choice of a particular type of cancer as a candidate for successful therapy with interferon. On a theoretical basis interferon is anticipated to be active against any form of malignancy; in much the same way as other immunostimulants (BCG, levamisole) have been proposed as anticancer strategies. This probably explains why the choice of tumors in current trials is rather arbitrary. The fact that certain types of tumor (myeloma, mammary carcinoma, lymphoma, melanoma) have been chosen as a target for large scale collaborative trials should therefore not be interpreted by the public or by the medical profession that oncologists have good indications for those tumors to be particularly responsive to interferon therapy.

The information which will come from the current trials will undoubtedly be very important for the further direction that interferon research will take. An equally or even more important development to be foreseen is the availability, mainly through recombinant DNA technology, of a large number of different interferons in pure form and in quantities allowing clinical evaluation. It is hoped that one of the many interferon types or subtypes will possess extremely high antitumor potentials.

ADDENDUM: SUMMARY OF RESULTS PRESENTED AT THE CONFERENCE ON "THE BIOLOGY OF THE INTERFERON SYSTEM," ROTTERDAM, 21–24 APRIL, 1981

Following submission of this review article, the situation with regard to interferon therapy in cancer was evaluated at an international conference sponsored by the Dutch Toegepast Natuurwetenschappelijk Onderzoek and the Erasmus University of Rotterdam. The laboratory experimental data presented and discussed at this meeting have not profoundly altered the basic concepts underlying the attempts to use interferons as anticancer drugs, as they are summarized and discussed in the present review. However, additional clinical data were presented which may influence the emphasis in future trials. They are briefly summarized here.

Lymphoma

The uncontrolled study conducted by Hill *et al.*[89] on the therapeutic effect of leukocyte interferon in leukemia has been expanded[123]. The study is made exceptional by the high doses given (10 MU/kg/day intravenously, for periods of up to 60 days). All of the 5 patients suffering from acute lymphoblastic leukemia had remissions, as evidenced by complete peripheral blast clearance (5/5 patients) and bone marrow blast clearance (3/5 patients). In acute granulocytic leukemia peripheral blast clearance occurred in 2 out of the 3 patients, and bone marrow clearance occurred in 1 of those.

An uncontrolled study on chronic lymphoblastic leukemia has been initiated in France[124] using relatively long-term treatment with 1.5–6 MU of leukocyte interferon per day for 3–9 months. Favorable responses were noted in some of the 9 patients during therapy: tumor mass reduction in 3 and a drop in peripheral lymphocytosis in 7 patients.

Malignant melanoma

Preliminary results on the American Cancer Society-sponsored trial were reported[125]. Doses of 1, 3 and 9 MU/day were given to 35 patients for 42 days: 7 showed stable disease, 22 showed progression under therapy and 6 patients showed evidence of partial tumor regression, i.e. a temporary response in 1 patient receiving the lowest dosage, minor regression in 2 patients and 3 clear regressions ($\geq 50\%$ reduction in tumor diameter product) of some, but not all, lesions.

In Great Britain an uncontrolled trial is being conducted[126] using 2.5 MU/day of interferon prepared from lymphoblastoid cells (the active component being the same as or very similar to that in leukocyte interferon). Over a 30-day treatment period no regressions were seen in patients receiving only systemic treatment. Shrinking of tumor mass was observed in one patient receiving intralesional injections.

Myeloma

Preliminary results of the American Cancer Society-sponsored trial were reported[127]. Twenty patients received 3–6 MU/day for at least 6 months. Partial regression was noted in 4 patients; in 2 patients the disease stabilized under treatment; and in 14 patients the disease progression remained uninfluenced.

Breast cancer

No further specifications other than those already mentioned[86] were given on the American Cancer Society-sponsored trial, using

leukocyte interferon in breast cancer patients. The use of fibroblast interferon for breast cancer metastasis is now being investigated by several groups in addition to the study of Pouillart *et al.* that was mentioned earlier. In one study (using 3–6 MU/day for 1 month) 3 out of 6 patients were found to respond with major ($\geq 50\%$) and 1 patient with minor ($> 25\%$, $< 50\%$) reductions in tumor size (Quesada, personal communication). Regression of metastases was also seen in a single patient[128] receiving intravenous therapy with fibroblast interferon (3.3 MU, twice weekly for 5 weeks).

Various other tumors

Various reports[123, 128, 129] discussed the results of interferon treatment in single or small groups of patients. Besides the tumor types already discussed, these trials included patients with lung carcinoma, renal cell carcinoma, ovarian carcinoma, bladder carcinoma, hepatoma, testis carcinoma, cervical cancer, hypernephroma and colon carcinoma. Mention should be made of complete regression of a bladder carcinoma in a single patient[123] treated with high doses of leukocyte interferon (≥ 10 MU/kg/day).

Topical treatment

An appealing concept is the treatment of mesothelioma by intrapleural administration of interferon. In one sutdy[130] 2 out of 6 patients were reported to respond favorably to intrapleural administration of 3 MU weekly of leukocyte interferon. A histiocytic reaction developed and tumor cells disappeared from the effusion.

REFERENCES

1. Isaacs A, Lindenmann J. Virus interference: I. The interferon. *Proc R Soc* 1957; **B147**: 258–267.
2. Scientific Committee on Interferon. *Lancet* 1962; **i**: 883.
3. Gresser I, Tovey MG. Antitumor effects of interferon. *Biochim Biophys Acta* 1978; **516**: 231–247.
4. Einhorn S, Strander H. Interferon therapy for neoplastic diseases in man *in vitro* and *in vivo*. *Adv exp Med Biol* 1978; **110**: 159–274.
5. Strander H. Interferons: anti-neoplastic drugs? *Blut* 1977; **35**: 277–288.
6. Krim M. Towards tumor therapy with interferons, Part II. *In vivo* effects. *Blood* 1980; **55**: 875–884.
7. Pollard RB. Usages of interferon and interferon inducers in man. *Focus on Medical Biology* 1980; **58**: 57–62.
8. Gresser I, Coppey Y, Falcoff E, Fontaine D. Interferon and murine leukemia. I. Inhibitory effect of interferon on development of Friend leukemia in mice. *Proc Soc exp Biol Med* 1967; **124**: 84–91.
9. Gresser I, Bourali C, Levy JP. Increased survival in mice inoculated with tumor cells and treated with interferon preparations. *Proc Natl Acad Sci USA* 1969; **63**: 51–56.
10. Gresser I, Bourali-Maury C. Inhibition by interferon preparations of a solid malignant tumour and pulmonary metastases in mice. *Nature New Biol* 1972; **236**: 78–79.
11. Stewart WE, II. The interferon system. Wien, New York; Springer, 1980.
12. Strander H, Cantell K. Production of interferon by human leukocytes *in vitro*. *Ann Med Exp Fenn* 1966; **44**: 265–273.
13. Cantell K, Hirvonen S. Large scale production of human leukocyte interferon containing 10^8 units per ml. *J Gen Virol* 1978; **39**: 541–543.
14. Billiau A, Van Damme J, Van Leuven F *et al.* Human fibroblast interferon for clinical trials: production, partial purification and characterization. *Antimicrob Agents Chemother* 1979; **16**: 49–55.
15. Nagata S, Taira H, Hall A *et al.* Synthesis in *E.coli* of a polypeptide with human leukocyte interferon activity. *Nature* 1980; **284**: 316–320.
16. Derynck R, Remaut E, Saman E *et al.* Expression of human fibroblast interferon gene in Escherichia coli. *Nature* 1980; **287**: 193–197.
17. Falcoff E, Falcoff R, Fournier F, Chany C, Galliot B. Production en masse, purification partielle et caractérisation d'un interféron destiné à des essais thérapeutiques humains. *Ann Inst Pasteur (Paris)* 1966; **111**: 562.
18. Vandeputte M, De Lafonteyne J, Billiau A, De Somer P. Influence and production of interferon in Rauscher virus-infected mice. *Arch Gesamte Virusforsch* 1967; **20**: 235–245.

19. LIEBERMAN M, MERIGAN TC, KAPLAN H. Inhibition of radiogenic lymphoma development in mice by interferon. *Proc Soc Exp Biol Med* 1971; **138**: 575–578.
20. CAME PE, MOORE DH. Inhibition of spontaneous mammary carcinoma of mice by treatment with interferon and poly-I:C. *Proc Soc Exp Biol Med* 1971; **137**: 304–305.
21. RATNER L, NORDLUND JJ, LENGYEL P. Interferon as an inhibitor of cell growth: studies with mouse melanoma cells (40760). *Proc Soc Exp Biol Med* 1980; **163**: 267–272.
22. BALKWILL F, TAYLOR-PAPADIMITRIOU J, FANTES KH, SEBESTENY A. Human lymphoblastoid interferon can inhibit the growth of human breast cancer zenografts in athymic (nude) mice, *Eur J Cancer* 1980; **16**: 569–573.
23. GRESSER I, BOURALI-MAURY C. The antitumor effect of interferon in lymphocyte- and macrophage-depressed mice. *Proc Soc Exp Biol Med* 1973; **144**: 896–900.
24. DE CLERCQ E. Effect of mouse interferon and polyriboinosinic acid polyribocytidylic acid on L-cell tumor growth in nude mice. *Cancer Res* 1977; **37**: 1502–1506.
25. DE CLERCQ E, GEORGIADES J, EDY VG, SOBIS H. Effect of human and mouse interferon and of polyriboinosinic acid.polyribocytidylic acid on the growth of human fibrosarcoma and melanoma tumors in nude mice. *Eur J Cancer* 1978; **14**: 1273–1282.
26. BOURGEADE MF, CERUTTI I, CHANY C. Enhancement of interferon antitumor action by sodium butyrate. *Cancer Res* 1979; **39**: 4720–4730.
27. TAKEYAMA H, KAWASHIMA K, KOBAYASHI M, YAMADA K, ITO Y. Antitumor effect of interferon preparations on murine transplantable tumors. *Gann* 1978; **69**: 641–647.
28. SALERNO RA, WHITMIRE CE, GARCIA I, HUEBNER RJ. Chemical carcinogenesis in mice inhibited by interferon. *Nature New Biol* 1972; **239**: 31–32.
29. GRESSER I, BOURALI C. Antitumor effects of interferon preparations in mice. *J Natl Cancer Inst* 1970; **45**: 365–376.
30. RHIM JS, HUEBNER RJ. Comparison of the antitumor effects of interferon and interferon inducers. *Proc Soc Exp Biol Med* 1970; **136**: 524–529.
31. HOVANESSIAN AG, BROWN RE, KERR IM. Synthesis of low molecular weight inhibitor of protein synthesis with enzyme from interferon-treated cells. *Nature* 1977; **268**: 537–540.
32. ZILBERSTEIN A, FEDERMAN P, SHULMAN L, REVEL M. Specific phosphorylation in vitro of a protein association with ribosomes of interferon-treated mouse L-cells. *FEBS Lett* 1976; **68**: 119–124.
33. ROBERTS WK, HOVANESSIAN AG, BROWN RE, CLEMENS MJ, KERR IM. Interferon-mediated protein kinase and low-molecular-weight inhibitor of protein synthesis. *Nature* 1976; **264**: 477–480.
34. LEBLEU B, SEN GC, SHAILA S, CABRER B, LENGYEL P. Interferon, double-stranded RNA, and protein phosphoryalation. *Proc Natl Acad Sci USA* 1976; **73**: 3107–3111.
35. NILSEN TW, BAGLIONI C. Mechanism for discrimination between viral and host mRNA in interferon-treated cells. *Proc Natl Acad Sci USA* 1979; 2600–2604.
36. PAUCKER K, CANTELL K, HENLE W. Quantitative studies on viral interference in suspended L cells. III. Effect of interfering viruses and interferon on the growth rate of cells. *Virology* 1962; **17**: 324–334.
37. STEWART WE II, GRESSER I, TOVEY MG, BANDU MT, LE GOF S. Identification of the cell multiplication inhibitory factors in interferon preparations as interferons. *Nature* 1976; **262**: 300–302.
38. DE MAEYER-GUIGNARD J, TOVEY MG, GRESSER I, DE MAEYER E. Purification of mouse interferon by sequential affinity chromatography on poly(U)- and antibody-agarose columns. *Nature* 1978; **271**: 622–625.
39. KAWAKITA M, CABRER B, TAIRA H, REBELLO M; SLATTERY E, WEIDELI H, LENGYEL P. Purification of interferon from mouse Ehrlich ascites tumor cells. *J Biol Chem* 1978; **253**: 598–602.
40. HILFENHAUS J, DAMM H, KARGES HE, MANTHEY KF. Growth inhibition of human lymphoblastoid Daudi cells *in vitro* by interferon preparations. *Arch Virol* 1976; **51**: 87–97.
41. ADAMS A, STRANDER H, CANTELL K. Sensitivity of the Epstein–Barr virus transformed human lymphoid cell lines to interferon. *J Gen Virol* 1975; **28**: 207–217.
42. GAFFNEY EV, PICCIANO PT, GRANT CA. Inhibition of growth and transformation of human cells by interferon. *J Natl Cancer Inst* 1973; **50**: 871–887.
43. GRESSER I, BANDU MT, BROUTY-BOYÉ D. Interferon and cell division. IX.

Interferon-resistant L1210-cells: characteristics and origin. *J Natl Cancer Inst* 1974; **52**: 553–559.

44. VANDENBUSSCHE P, CONTENT J. LEBLEU B, WÉRENNE J. Comparison of interferon action in interferon resistant and sensitive L1210 cells. *J Gen Virol.* 1979; **41**: 161–166.
45. EINHORN S, STRANDER M. Is interferon tissue-specific? Effect of human leukocyte and fibroblast interferons on the growth of lymphoblastoid and osteosarcoma cell lines. *J Gen Virol* 1977; **35**: 573–577.
46. EPSTEIN L, SHEN JT, ABELE JS, REESE CC. Further experience in testing the sensitivity of human ovarian carcinoma cells to interferon in an *in vitro* semisolid agar culture system: comparison of solid and ascitic forms of the tumor. In: *Cloning of Human Tumor Stem Cells.* New York: Alan R. Liss, 1980; 277–290.
47. HOROSZEWICZ JS, LEONG SS, ITO M *et al.* Human fibroblast interferon in human neoplasia: clinical and laboratory study. *Cancer Treat Rep* 1978; **62**; 1899–1906.
48. CARTER WA, LEONG SS, HOROSZEWICZ JS. Human fibroblast interferon in the control of neoplasia. In: CHANDRA P, ed. *Antiviral Mechanisms in the Control of Neoplasia.* New York: Plenum Press, 1979; 663–674.
49. HOROSZEWICZ JS, LEONG SS, DOLEN JG *et al.* Purified human fibroblast interferon and neoplasia: pharmacokinetic studies and selective antiproliferative properties *in vivo.* In: KHAN A, HILL NO, DORN GL, eds. *Interferon: Properties and Clinical Uses.* Dallas: Leland Fikes Foundation Press of the Wedley Institutes, 1980; 661–666.
50. GRESSER I, MAURY C, BROUTY-BOYÉ D. Mechanism of the antitumour effect of interferon in mice. *Nature* 1972; **239**: 167–168.
51. FRIEDMAN RM. Interferon action and the cell surface. *Pharmac Ther A* 1978; **2**: 425–438.
52. LINDAHL P, LEARY P, GRESSER I. Enhancement by interferon of the expression of surface antigens on murine leukemia L1210-cells. *Proc Natl Acad Sci USA* 1973; **70**: 2785–2788.
53. LINDAHL P, LEARY P, GRESSER I. Enhancement of the expression of histocompatibility antigens of mouse lymphoid cells by interferon *in vitro. Eur J Immunol* 1974; **4**: 779–784.
54. EPSTEIN LB. The effects of interferons on the immune response *in vitro* and *in vivo.* In: STEWART WE, II, ed. *Interferons and Their Actions.* Cleveland: CRC Press, 1977; 92–132.
55. HERBERMAN RR, ORTALDO JR, BONNARD GD. Augmentation by interferon of human natural and antibody-dependent cell-mediated cytotoxicity. *Nature* 1979; **277**: 221–223.
56. HERON I, HOKLAND M, MØLLER-LARSEN A, BERG K. The effect of interferon on lymphocyte-mediated effector cell functions: selective enhancement of natural killer cells. *Cell Immunol* 1979; **42**: 183–187.
57. ZARLING JM, SOSMAN J, ESKRA L, BORDEN E, HOROSZEWICZ JS, CARTER WA. Enhancement of T cell cytotoxic responses by purified human fibroblast interferon. *J Immunol* 1978; **121**: 2002–2004.
58. LINDAHL P, LEARY P, GRESSER I. Enhancement by interferon of the specific cytotoxicity of sensitized lymphocytes. *Proc Natl Acad Sci USA* 1972; **69**: 721–725.
59. HUANG KY, DONAHOE RM, GORDON F, DRESSLER HR. Enhancement of phagocytosis by interferon-containing preparations. *Infect Immun* 1971; **4**: 581–588.
60. SCHULTZ RM, PAPAMATHEAKIS JD, CHIRIGOS MA. Interferon: an inducer of macrophage activation by polyanions. *Science* 1977; **197**: 674–676.
61. TRINCHIERI G, SANTOLI D. Antiviral activity induced by culturing lymphocytes with tumor-derived or virus-transformed cells. Enhancement of human natural killer cell activity by interferon and antagonistic inhibition of susceptibility of target cells to lysis. *J exp Med* 1978; **147**: 1314–1333.
62. SENIK A, GRESSER I, MAURY C, GIDLUND M, ORN A, WIGZELL H. Enhancement by interferon of natural killer cell activity in mice. *Cell Immunol* 1979; **44**: 186–200.
63. DJEU JY, HEINBAUGH JA, HOLDEN H, HERBERMAN RB. Augmentation of mouse natural killer activity by interferon and interferon inducers. *J Immunol* 1979; **122**: 175–181.
64. LIPINSKI M, VIRELIZIER JL, TURSZ T, GRISCELLI C. Natural killer and killer cell activities in patients with primary immunodeficiencies or defects in immune interferon production. *Eur J Immunol* 1980; **10**: 246–249.
65. RODER J, DUWE A. The beige mutation in the mouse selectively impairs natural killer cell function. *Nature* 1979; **278**: 451–453.

66. SULLIVAN JL, BYRON KS, BREWSTER FE, PURTILO DT. Deficient natural killer cell activity in X-linked lymphoproliferative syndrome. *Science* 1980; **210**: 543–545.
67. LUCERO MA, FRIDMAN WH, PROVOST MA *et al.* Effect of various interferons on the spontaneous cytotoxicity exerted by lymphocytes from normal and tumor-bearing patients. *Cancer Res* 1981; **41**: 294–299.
68. PROSS HF, BAINES MG. Spontaneous human lymphocyte-mediated cytotoxicity against tumor target cells. I. The effect of malignant disease. *Int J Cancer* 1976; **18**: 593–604.
69. HERSEY P, EDWARDS A, MILTON GW, MCCARTHY WH. Relationship of cell-mediated cytotoxicity against melanoma cells to prognosis in melanoma patients. *Br J Cancer* 1978; **37**: 505–514.
70. HERSEY P, EDWARDS A, HONEYMAN M, MCCARTHY WH. Low natural killer cell activity in familial melanoma patients and their relatives. *Br J Cancer* 1979; **40**: 113–122.
71. TALMADGE JE, MEYER KM, PRIEUR DJ, STARKEY JR. Role of NK cells in tumour growth and metatasis in beige mice. *Nature* 1980; **284**: 622–624.
72. SANTOLI D, TRINCHIERI G, KOPROWSKI H. Cell-mediated cytotoxicity against virus-infected target cells in humans. II. Interferon induction and activation of natural killer cells. *J Immunol* 1978; **121**: 532–538.
73. MOORE M, WHITE WJ, POTTER MR. Modulation of target cell susceptibility to human natural killer cells by interferon. *Int J Cancer* 1980; **25**: 565–572.
74. ATALLAH AM, FOLKS T. Interferon-enhanced human natural killer and antibody-dependent cell-mediated cytotoxic activity. *Int Archs Allergy Appl Immun* 1979; **60**: 377–382.
75. EINHORN S, BLOMGREN H, STRANDER H. Interferon and spontaneous cytotoxicity in man. I. Enhancement of the spontaneous cytotoxicity of peripheral lymphocytes by human leukocyte interferon. *Int J Cancer* 1978; **22**: 405–412.
76. BERGERET M, GRÉGOIRE A, CHANY C. Protective effect of interferon on target cells exposed to cellular cytotoxicity. *Immunology* 1980; **40**: 637–743.
77. FIELD SB, BLEEHEN NM. Hyperthermia in the treatment of cancer. *Cancer Treat Rev* 1979; **6**: 63–94.
78. MARMOR J. Interactions of hyperthermia and chemotherapy in animals. *Cancer Res* 1979; **39**: 2269–2276.
79. HIRAMOTO R, GHANTA V, DURANT JR. Evaluation of a cooperative group human myeloma protocol using the MOG 104E myeloma model. *Cancer Res* 1975; **35**: 1309–1313.
80. SWEENEY MJ, BODER GB, CULLINAM GJ *et al.* Antitumor activity of deacetyl vinblastine amide sulfate (vindesine) in rodents and mitotic accumulation studies in culture. *Cancer Res* 1978; **38**: 2886–2891.
81. KASSEL RL, PASCAL RR, VAS A. Interferon-mediated oncolysis in spontaneous murine leukemia. *J Natl Cancer Inst* 1972; **48**: 1155–1159.
82. GRESSER I, DE MAEYER-GUIGNARD J, TOVEY MG, DE MAEYER E. Electrophoretically pure mouse interferon exerts multiple biologic effects. *Proc Natl Acad Sci USA* 1979; **76**: 5308–5312.
83. IWAKURA Y, YONEHARA S, KAWADA Y. Purification of mouse L-cell interferon: essentially pure preparations with associated cell growth inhibitory activity. *J Biol Chem* 1978; **253**: 5074–5079.
84. SALVIN SB, YOUNGNER JS, NISHIO J, NETA R. Tumor supression by a lymphokine released into the circulation of mice with delayed hypersensitivity. *J Natl Cancer Inst* 1975; **55**: 1233–1236.
85. CRANE JL, Jr, GLASGOW LA, KERN ER, YOUNGNER JS. Inhibition of murine osteogenic sarcomas by treatment with type I or type II interferon. *J Natl Cancer Inst* 1978; **61**: 871–874.
86. GUTTERMAN JU, BLUMENSCHEIN GR, ALEXANIAN RA *et al.* Leukocyte-interferon-induced regression in human metastatic breast cancer, multiple myeloma and malignant lymphoma. *Ann Intern Med* 1980; **93**: 399–406.
87. BORDEN EC, HAWKINS MJ, DAO T, HOLLAND J, ZAREMBA K, CANTELL K. Pharmacologic, immunologic and clinical effects of human leukocyte interferon: an interim report. Proc. Conference on Clinical Potentials of Interferons in Virals Diseases and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
88. MERIGAN TC, SIKORA K, BREEDEN JH, LEVY R, ROSENBERG SA. Preliminary

observations on the effect of human leukocyte interferon in non-Hodgkin's-lymphoma. *New Engl J Med* 1978; **299**: 1449–1453.

89. HILL NO, KHAN A, LOEB E *et al.* Clinical trials of high dose human leukocyte interferon. In: KHAN A, HILL NO, DORN GL, eds. *Interferon: Properties and Clinical Uses.* Dallas: Leland Fikes Foundation Press, 1980: 668–680.
90. MELLSTEDT H, BJÖRKHOLM M, JOHANSSON B, AHRE A, HOLM G, STRANDER H. Interferon therapy in myelomatosis. *Lancet* 1979; **i**: 245–247.
91. IDESTROM K, CANTELL D, KILLANDER D, NILSSON K, STRANDER H, WILLEMS J. Interferon therapy in myeloma. *Acta Med Scand* 1979; **205**: 149–154.
92. BILLIAU A, BLOEMMEN J, BOGAERTS M *et al.* Interferon therapy in multiple myeloma: failure of human fibroblast interferon administration to affect the course of light chain disease. *Eur J Cancer* 1981; **17**: 875–882.
93. HAGLUND S, LUNDQUIST PG, CANTELL K, STRANDER H. Interferon therapy in juvenile laryngeal papillomatosis. Personal communication—Interferon Scientific Memoranda, memo No. I-A980, 1980.
94. SCHOUTEN TJ, BOS JH. Interferon, juveniele larynx papillomen en de wenselijkheid van een Nederlandse productive van interferon. *Ned Tijdschr Geneesk* 1980; **124**: 1650–1651.
95. GÖBEL U, ARNOLD W, WAHN V, TREUNER J, CANTELL K. Treatment of laryngeal papillomatosis in children: comparison of human fibroblast and leukocyte interferon. Personal communication—Interferon Scientific Memoranda, memo no I-A986, 1980.
96. BLOMGREN H, CANTELL K, JOHANSSON B, LAGERGREN C, RINGBORG U, STRANDER H. Interferon therapy in Hodgkin's disease, a case report. *Acta Med Scand* 1976; **199**: 527–532.
97. ITO H, MURAKAMI K, YANAGAWA T *et al.* Effect of human leukocyte interferon on the metastatic lung tumor of osteosarcoma. *Cancer* 1980; **46**: 1562–1566.
98. CHRISTOPHERSEN IS, JORDAL R, OSTHER K, LINDENBERG J, PEDERSEN PH, BERG K. Interferon therapy in neoplastic disease. *Acta Med Scand* 1978; **204**: 471–476.
99. SAWADA T, TOZAWA M, KIDOWAKI T *et al.* Clinical use of human leukocyte interferon in neurogenic tumors and some other childhood tumors. Proc. Conference on Clinical Potentials of Interferons in Viral Diseases and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
100. BILLIAU A. Interferon therapy: pharmacokinetic and pharmacological aspects. *Arch Virol* 1981; **67**: 121–133.
101. FIELD SB, BLEECHEN NM. Hyperthermia in the treatment of cancer *Cancer Treatment Rev* 1979; **6**: 63–94.
102. OGAWA M, EZAKI K. A clinical study of fibroblast interferon. Proc. Conference on Clinical Potentials of Interferons in Viral Diseases and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
103. MCPHERSON TA, TAN YH. Phase I. Pharmacotoxicology study of human fibroblast interferon in human cancers. *J Natl Cancer Inst* 1980; **65**: 75–79.
104. FURUE H, KOMITA T, KOBAYASHI H, HAKOZAKI M. Clinical experience with human fibroblast interferon. Proc. Conference on Clinical Potentials of Interferons and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
105. SHIMOYANA M, KITAHARA T, NAKAZAWA M. Clinical experience and antitumor activity of human fibroblast interferon. Proc. Conference on Clinical Potentials of Interferons and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
106. BILLIAU A, DE SOMER P, EDY VG, DE CLERCQ E, DE SOMER P. Human fibroblast interferon for clinical trials: pharmacokinetics and tolerability in experimental animals and humans. *Antimicrob Agents Chemother* 1979; **16**: 56–63.
107. NAGAI M, ARAI T, KOHNO S, KOHASE M. Interferon therapy on malignant brain tumors. Proc. Conference on Clinical Potentials of Interferons and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
108. TREUNER J, NIETHAMMER D, DANNECKER G, HAGMANN R, NEEF V, HOFSCHNEIDER PH. Successful treatment of nasopharyngeal carcinoma with interferon. *Lancet* 1980; **i**: 817–818.
109. DE LEY M, VAN DAMME J, CLAEYS H *et al.* Interferon induced in human

leukocytes by mitogens: production, partial purification and characterization. *Eur J Immunol* 1980; **10**: 877–883.

110. YIP YK, PANG RHL, URBAN C, VILCEK J. Partial purification and characterization of human (gamma) interferon. *Proc Natl Acad Sci USA* 1981; in press.
111. LANGFORD MP, GEORGIADES JA, STANTON GJ, DIANZANI F, JOHNSON HM. Large-scale production and physiocochemical characterization of human immune interferon. *Infect Immun* 1979; **26**: 36–41.
112. FLEISCHMANN WR JR, GEORGIADES JA, OSBORNE LC, JOHNSON HM. Potentiation of interferon activity by mixed preparations of fibroblast and immune interferon. *Infect Immun* 1979; **26**: 248–253.
113. FLEISCHMAN WR JR, KLEYN KM, BARON S. Potentiation of antitumor effect of virus-induced interferon by mouse immune interferon preparations. *J Natl Cancer Inst* 1980; **65**: 963–966.
114. VAN DAMME J, DE LEY M, CLAEYS H, BILLIAU A, VERMYLEN C, DE SOMER P. Interferon induced in human leukocytes by concanavalin A: isolation and characterization of γ- and β-type components. *Brit J Haematol* 1981: in press.
115. BROSTRÖM LÅ. On the natural history of osteosarcoma. Thesis, Karolinska Institute, Stockholm. Acta Orthop Scand 1979; suppl 183.
116. GEHAN EA, SUTOW WW, URIBE-BOTERO G, ROMSOAHL M, SMITH TL. Osteosarcoma: the MD Anderson experience, 1950–1974. In: TERRY WD, WINDHORST D, eds. *Immunotherapy and Cancer: Present Status of Trials in Man.* New York: Raven Press, 1978; 271–282.
117. MIKE V, MARCOVE RC. Osteogenic sarcoma under the age of 21: experience at Memorial Sloan-Ketting Cancer Center. In: TERRY WD, WINDHORST D, eds. *Immunotherapy and Cancer: Present Status of Trials in Man.* New York:Raven Press, 1978; 283–292.
118. TAYLOR WF, IVINS JC, DAHLIN DC, PRITCHARD DJ. Osteogenic sarcoma experience at the Mayo Clinic, 1963–1974. In: TERRY WD, WINDHORST D, eds. *Immunotherapy and Cancer: Present Status of Trials in Man.* New York: Raven Press, 1978; 257–269.
119. KOLATA GB. Delemma in cancer treatment. *Science* 1980; **209**: 792–794.
120. IKIC D, KRUSIC J, CUPAK D *et al.* The use of human leukocytic interferon in patients with cervical cancer and baseocellular cancer of the skin. Proc. Symposium on Clinical Use of Interferon. Yugoslav Acad Sci & Arts, Zagreb, 1975; 239–242.
121. ISHIHARA K, HAYASAKA K. Treatment of malignant lymphoma by intratumoral administration of human fibroblast interferon. Proc. Conference on Clinical Potentials of Interferons and Malignant Tumors (Oiso, Dec. 1980). Japan Medical Research Foundation, ed. In press, 1981.
122. IKIC D, BOSNIC N, SMERDEL S, JUSIC D, SOOS E, DELIMAR N. Double-blind clinical study with human leukocyte interferon in the therapy of condylomata acuminata. Proc. Symposium on Clinical Use of Interferon. Yugoslav Acad Sci & Arts Zagreb, 1975; 229–233.
123. HILL NO, PARDUE A, KAHN K, HILL RW, ALEMAN C, HILL JM, DORN G. Human leukocyte interferon therapy of leukemia and cancer. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.
124. MATHÉ G, GOUTNER A, GASTIABARU J, DE VASSAL F, MISSET JL. Phase II trial of leukocyte interferon in chronic lymphatic leukemia (CLL). In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.
125. KROWN SE, BURK M, KIRKWOOD JM, KERR D, NORDLUND JJ, MORTON DL, OETTGEN HF, The American Cancer Society. Clinical trial of human leukocyte interferon in malignant melanoma preliminary results. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.
126. PRIESTMAN TJ, RETSAS S, NEWTON KA, WESTBURY G. Evaluation of human lymphoblastoid interferon in metastatic malignant melanoma: a phase II study. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.
127. OSSERMAN EF, SHERMAN WH, ALEXANIAN, GUTTERMAN JU, HUMPHREY RL. Human leukocyte interferon in multiple myeloma: the American Cancer Society-sponsored trial. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Pro-

ceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.

128. SERROU B, CUPISSOL D, FAVIER F. Preliminary evaluation of human fibroblastic interferon (HFI) in immunodepressed patients, bearing advanced solid tumors. Correlation between *in vitro* testing and *in vivo* evaluation. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.
129. OSTHER K, CHRISTOPHERSEN IS, MAGNUSSON K. Topical versus systemic interferon treatment. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.
130. WEIMAR W. Interferon therapy for mesothelioma and juvenile laryngeal papillomatosis. In: SCHELLEKENS H, ed. *The Biology of the Interferon System* (Proceedings of Conference held at Rotterdam, 21–24 April 1981). Amsterdam: Elsevier, in press.