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Regular Review

Interferon: therapeutic fact or fiction for the '80s?

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For many years it had been known that infection with one virus could protect animals against infection with another when, in 1957, Isaacs and Lindenmann[1] discovered that medium from tissue cultures challenged with a killed virus could protect other cells against infection. The substances producing these effects are highly active glycoproteins known as interferons. They are released (in conjunction with many other unidentified molecules) from cells infected with virus or exposed to stimuli which mimic virus infection. Interferons probably act on cell membrane receptor sites causing intracellular production of proteins which mainly inhibit the translation of viral m-RNA.

Interferons are relatively species-specific, having maximal activity in cells from the same or closely related species. Furthermore, there are three major types of human interferon with different molecular structures and different physicochemical and antigenic properties. Preparations are arbitrarily defined by comparison with international standard preparations, and one unit of interferon is roughly the amount which reduces viral replication in tissue culture by half.

Sources of interferon—Most clinical studies have been performed using human leucocyte interferon (HuIFNα). This is made by exposing pooled buffy-coat lymphocytes to a parainfluenza virus which may be inactivated later by acidification. The interferon thus obtained can be purified and concentrated by simple methods to 10^6-10^7 units per ml/mg protein for clinical use.[2] The specific activity of pure human leucocyte interferon is about 10^9 U/mg protein, so clinical material is only about 0·1% pure. Most of the contaminating protein is probably albumin, but other proteins are present which may be biologically active. Interferon preparations have effects other than the inhibition of viral replication; for example, they inhibit cell growth and multiplication,[3] enhance the expression of cell-surface antigens,[4] suppress some functions of T and B lymphocytes,[5] and enhance the activity of natural killer cells.[6 7] Any of these functions may be responsible for the antineoplastic activity[8] of interferons under current scrutiny.

Preliminary clinical studies have also been performed with interferon derived from human fibroblasts induced with a synthetic double-stranded RNA (poly I:C). The yields are enhanced by the judicious use of metabolic inhibitors which suppress synthesis initially of cellular protein and then of RNA.[9] Fibroblast interferon (HuIFNβ) has also been purified to homogeneity ($>10^8$ U/mg protein), but the clinical material has about the same activity as clinical leucocyte interferon. Fibroblast interferon is less stable than human leucocyte interferon, and when injected intramuscularly achieves considerably lower blood concentrations of interferon,[10] probably because it is bound to tissue at the site of injection; whether this affects its therapeutic action is not known.

The antiviral activities of the two interferons have been compared directly against herpes simplex virus in monkeys' eyes,[11] in a clinical trial of herpes keratitis,[12] and against vaccinia in monkey skin.[13] Used topically or intradermally they do not appear to differ appreciably in efficacy. The major advantages of using fibroblasts over buffy-coat leucocytes as a source of interferon are that they may be well characterised and the production of interferon is limited only by resources for bulk cell cultivation. There are, however, technical problems in growing surface-adherent cells on a large enough scale to

make production of interferon worth while, and as yet the manufacture of fibroblast interferon has provided sufficient material for only limited clinical studies.

Another approach[14 15] has been to grow lymphoblastoid cells in suspension cultures; in response to challenge with parainfluenza virus these produce mainly leucocyte and a small amount of fibroblast type interferons.[16] The cell lines which appear to produce interferons most efficiently came originally from patients with Burkitt's lymphoma, and each cell contains the genome for Epstein-Barr virus. All interferons for clinical use and the cells which produce them are extensively tested for safety. Though lymphoblastoid interferon is apparently free of virus and oncogenic activity, its use is being restricted to patients with life-threatening disease or neoplasia.

A third type of human interferon (HuIFNδ) is derived from T lymphocytes by exposure to non-specific immune stimulants or to antigens to which the lymphocytes have been sensitised.[17] This "immune" or "type II" interferon is produced early in acute viral infections and may be important in the initial host response. It is less thermostable and is inactivated at pH 2, distinguishing it from classical viral or type I interferon. Type II interferon has not yet been synthesised and purified in bulk for testing in clinical trials.

Finally, several groups are working on more exotic methods of interferon production: when an interferon protein molecule has been sequenced (and this has been achieved for parts of the molecules of fibroblast and lymphoblast interferons), maybe a small but highly active part of it could be synthesised. Alternatively, the genetic instruction for human interferon protein may be inserted into *Escherichia coli*, which could be grown on an almost unlimited scale; and several groups have now reported success with this technique (see *Nature* 1950;

Details of clinical trials with exogenous interferon in virus diseases

Reference No	Virus	Year	Interferon type	Dose schedule	Result (effect of interferon compared with controls)
				As prophylaxis against virus disease	
18	Vaccinia	1962	Monkey kidney	Intradermal 10^3-10^4 U/0·1 ml, 24 hours before vaccination	Protected skin sites
24	Vaccinia	1978	Human fibroblast	Intradermal 5×10^4 U/0·1 ml, 24 hours before vaccination	Protected skin sites
32	Respiratory virus	1965	Monkey kidney	Intranasal 10^4 U/ml	No protection
36	Influenza	1969	Human leucocyte	Intranasal 10^3-10^4 U/ml during epidemic	Reduced rate of infection
19	Influenza	1973	Human leucocyte	Intranasal 8×10^5 U total on day before virus challenge	Delay in symptoms and virus excretion
19	Rhinovirus	1973	Human leucocyte	Intranasal $1{\cdot}4 \times 10^6$ U total in four days, virus challenge on second day	Significant reduction in cold severity, virus excretion
39	Herpes simplex virus keratitis	1976	Human leucocyte	Eye-drops $6{\cdot}4 \times 10^6$ U/ml twice daily to prevent recurrence	No reduction in rate of recurrence
37	Herpes simplex virus keratitis	1976	Human leucocyte	Eye-drops $11\text{-}31 \times 10^6$ U/ml daily after debridement	Reduced rate of local recurrence of dendritic ulcer
62	Rubella	1975	Human leucocyte	Intramuscular $6{\cdot}5 \times 10^5$ U twice before vaccination	Delay in virus excretion and antibody production
27	Herpes labialis	1979	Human leucocyte	Intramuscular 7×10^4 U/kg/day for five days, trigeminal surgery on second day	Reduced shedding of herpes simplex virus and cold sores
25	Renal transplantation	1975	Human fibroblast	Intramuscular 3×10^6 U twice weekly for three months	No reduction in rate of virus infections
26	Renal transplantation	1979	Human leucocyte	Intramuscular 3×10^6 U/day for six weeks	Delay in cytomegalovirus viraemia. No effect on herpes simplex virus
				In treatment of established acute virus illness	
38	Herpes simplex virus keratitis	1976	Human leucocyte	Eye-drops $6{\cdot}3 \times 10^4$ U/ml three times a day after thermocautery	No effect on rate of healing
20	Herpes simplex virus keratitis	1976	Human leucocyte	Eye-drops 2×10^6 U/ml three times a day after thermocautery	Significantly accelerated healing
12	Herpes simplex virus keratitis	1978	Human fibroblast or leucocyte	Eye-drops 10^6 U/ml once daily	No difference between interferons in efficacy
21	Herpes simplex virus keratitis	1978	Human leucocyte	Eye-drops 10^6 or 30×10^6 U/ml daily with trifluorothymidine	Higher dose accelerated healing
42	Herpes zoster	1975	Human leucocyte	Intramuscular 10^6 U/day for five days (not blind)	Faster lesion crusting and resolution of lesion pain
43	Herpes zoster	1978	Human leucocyte	Intramuscular 8×10^4-5×10^5 U/kg/day	Non-significant reduction in rate of complications
22	Herpes zoster	1978	Human leucocyte	Intramuscular 4×10^4-5×10^5 U/kg/day	Highest dose prevented spread and reduced complications
				In treatment of chronic virus infection	
44	Genital warts	1975	Human leucocyte	Cream 4000 U/g applied five times daily (females)	Resolution of warts in all treated patients by 12 weeks
45	Genital warts	1979	Human fibroblast	Intralesional 300 U/0·1 ml (males)	Minor but significant reduction in wart growth
53	Hepatitis B chronic active hepatitis	1980	Human leucocyte	Intramuscular 12×10^6 U daily for seven days, then reducing	Transient fall in HBV-DNAP (also in one control)
				Uncontrolled observations in treatment of chronic viral disease	
46	Hepatitis B chronic active hepatitis	1976	Human fibroblast	Intramuscular 10^7 U on alternate days, seven doses (one patient)	Reduction in nucleocapsid HBcAg staining on biopsy
47	Hepatitis B chronic active hepatitis	1976	Human leucocyte	Intramuscular $6\text{-}170 \times 10^3$ U/kg/day, variable courses (four patients)	Fall in HBV-DNAP (and in HBsAg later)
48	Hepatitis B chronic active hepatitis	1978	Human leucocyte	Intramuscular 6×10^3 U/kg/day (13 patients)	Permanent fall in HBV-DNAP in three patients (two patients cleared HBsAg)
49	Hepatitis B chronic active hepatitis	1978	Human fibroblast	Intramuscular 10^7 U daily for 14 days (two patients)	Fall in serum HBcAb titre
50	Hepatitis B chronic active hepatitis	1977	Human fibroblast	Intramuscular 3×10^6 U daily for 14 days (two patients)	No effect. HBV-DNAP fell in one untreated control
51	Hepatitis B chronic active hepatitis	1979	Human fibroblast	Intramuscular 10^6 U daily for 82 days (one patient)	Fall in HBsAg, HBcAg, HBV-DNAP
52	Hepatitis B chronic active hepatitis	1979	Human leucocyte	Intramuscular 10^6 U daily (four patients)	Fall in DNAP and eAg, improved liver function tests, and liver biopsy appearances (two patients)
53	Hepatitis B chronic active hepatitis	1979	Human leucocyte	Intramuscular $2\text{-}5 \times 10^4$ U/kg/day for 5 weeks to 5 months (seven patients)	Temporary fall in HBV-DNAP, improved liver biopsy appearances in one patient. eAg cleared in two
54	Cytomegalovirus	1966	Human leucocyte	Intramuscular about 10^3 U/ml (four infants)	No effect
55	Cytomegalovirus	1976	Human leucocyte	Intramuscular $2{\cdot}5 \times 10^5$-10^6 U daily (variable courses)	Viruria cleared in two out of four patients with congenital and one out of five with acquired viruria
56	Cytomegalovirus	1976	Human leucocyte	Intramuscular $1{\cdot}7\text{-}3{\cdot}5 \times 10^5$ U/kg/day for 7-14 days (six patients)	Transient suppression of viruria in one patient
57	Cytomegalovirus	1976	Human leucocyte	Intramuscular 10^6 U daily (three bone-marrow recipients)	Apparent benefit with decreased viraemia in one
58	Chronic rubella	1976	Human leucocyte	Intramuscular 3×10^6 U daily for 14 days (one patient)	Regression of acute vasculitis, resolution of viraemia

HBV-DNAP = Hepatitis-B-virus DNA polymerase. HBcAg = Hepatitis B core antigen. HBsAg = Hepatitis B surface antigen. HBcAb = Hepatitis B core antibody. eAg = e Antigens.

283:323). Interferon protein produced in this way will have to be separated from the products of bacterial fermentation, and if the carbohydrate component of this interferon is necessary for stability or activity, glycosylation of the molecule will need to be performed after fermentation.

Clinical evaluation of interferon and inducers against infections—Clinical studies with interferon have gone through three phases. Apart from a well-controlled study published in 1962,[18] which showed that interferon prepared from monkey kidney cells and given intradermally could protect human skin sites against subsequent vaccination, the early studies (1957-66) using relatively low potency material were either uncontrolled or gave negative results. As difficulties became apparent in manufacturing the large amounts of interferon which appeared to be necessary attention turned to developing and testing a range of interferon inducers. While these were active in studies on animals, they were generally unsuccessful in clinical trials. In the '70s, interest in exogenous interferon was revived by the pioneering effort of Mogensen and Cantell, who used buffy coats from Finnish Red Cross blood units for the mass production of human leucocyte interferon.[2] Research with this material and smaller quantities of fibroblast interferon from several groups has been concentrated on infections with herpes viruses, respiratory viruses, and hepatitis B virus. Production limitations have restricted the numbers of clinical trials of interferon: the important ones are summarised in the table. Several poorly controlled or inconclusive studies are excluded from this list, but uncontrolled observations on the effect of interferon in chronic viral infections are included. When well-conducted studies have failed this has generally been attributed to the use of too little interferon—a view confirmed in some diseases by the success of later studies with higher dose schedules.[19-22] Nevertheless, an important caveat to these studies (and even more so to the trials in cancer) must be that the preparations given were composed almost entirely of material other than interferon and some of the effects may have been due to impurities.

Study of the interferon system in relation to natural or experimental virus infections has indicated the clinical circumstances in which exogenous interferon could be used.[23] Studies on animals have shown that interferon is most active when given before or with the virus challenge.

Interferon in prophylaxis—Studies of the clinical use of interferon in prophylaxis have given conflicting results. Whereas skin sites can be protected against challenge with vaccinia virus by intradermal inoculations of interferon,[18 24] fibroblast interferon given by intramuscular injection three times a week to recipients of renal transplants failed to reduce the frequency of naturally acquired virus infections.[25] A more recent study employing daily human leucocyte interferon delayed the onset of cytomegalovirus viraemia in seropositive transplant recipients.[26] There was no effect on the reactivation of herpes simplex virus infection nor on the eventual outcome of transplantation in these patients. Reactivation of viral illness may also be expected (though there is no immunosuppression) after surgery to the trigeminal ganglia for tic douloureux, and in one study[27] leucocyte interferon given from one day before operation for five days reduced both the frequency and duration of shedding of herpes simplex virus from the oropharynx. Herpes labialis also occurred less often in the patients treated with interferon.

Respiratory diseases—Interferon may be detected in the nasal washings and serum of volunteers infected with influenza.[28 29] Peak concentrations of interferon in nasal washings occur around the time of the fall in virus shedding before antibodies are found, suggesting a cause-and-effect relation. Whether or not interferon has a key role in limiting acute virus infections of man is still not clear. In some diseases, such as respiratory syncytial virus infection in children, interferon is rarely detectable in serum or nasal washings,[30] virus excretion is protracted, and the fall in the virus titre is associated with a rise in concentration of virus-specific IgA antibody,[31] suggesting that resolution of the disease (at least in children in hospital) is not entirely mediated by endogenous interferon.

In another study human leucocyte interferon (14×10^7 U total) given as frequent nasal sprays over four days significantly reduced symptoms and shedding of virus after an experimental challenge with rhinovirus on the second day of treatment with interferon.[19] Material of lower potency has proved ineffective.[19 32] While interferon,[33] like any intranasal liquid,[34] has a short half life in the nasal cavity, it needs to be in contact with nasal epithelial cells for a long period to make them resistant to viral infection.[35] It is therefore difficult to understand how, in Russia, nose drops containing a low titre of human leucocyte interferon could cause the degree of protection indicated by the results of a large clinical study on children during an influenza epidemic.[36] Experiments are needed to find a method of application of interferon that ensures prolonged contact with the mucosa and to find how late in the course of acute respiratory infection exogenous interferon may be given and still have a clinical effect.

Viral diseases of the eye—Eye-drops containing concentrated human leucocyte interferon ($11\text{-}31\times10^6$ U/ml) have been shown to reduce the rate of recurrence of herpetic dendritic ulcers after minimal wiping debridement.[37] Dilute eye-drops ($6{\cdot}25\times10^4$ U/ml) given after thermocautery for herpetic keratitis were no more effective than placebo in accelerating healing or reducing viral shedding.[38] More concentrated interferon (10^6 U/ml), however, was effective in a further similar trial.[20] Without local physical treatment, topical interferon given at low concentrations seems an inefficient treatment of herpetic eye disease, but highly concentrated interferon has not yet been evaluated alone. Nevertheless, the combination of high-dose interferon (30×10^6 U/ml) with trifluorothymidine (an antiherpetic nucleoside analogue, not generally available in Britain), enhanced the rapid healing of herpetic keratitis.[21] In contrast, regular treatment over several months with low-potency ($6{\cdot}4\times10^4$ U/ml) eye-drops did not prevent recurrent herpetic keratitis when compared with placebo[39]; this study is being repeated with more-concentrated material. Both experiments on animals[40] and these clinical studies show that the concentration of interferon eye-drops is crucial and that the efficacy of low-titre material cannot be enhanced by giving it more often. A recent controlled study in Israel[41] of fibroblast interferon against placebo in epidemic adenovirus conjunctivitis has shown promising results.

Herpes zoster—Three controlled trials have been published of the treatment of herpes zoster infection with intramuscular human leucocyte interferon. The first was not double blind and the placebo-treated group was small,[42] but the proportion of patients with persisting pain in the dermatome beyond 15 days was greater in those given placebo than in those treated with interferon, in whom crusting of the lesions also occurred earlier. One group of workers has examined the effect of interferon on herpes zoster infection complicating neoplastic diseases under placebo-controlled double-blind conditions. In children[43] there was a trend towards fewer complications of infection in the interferon-treated group. In the adults[22]

increasing dose schedules were studied and the highest ($5{\cdot}1 \times 10^5$ U/kg/day) inhibited the formation of fresh vesicles in the primary dermatome, prevented dissemination, and reduced complications, including postherpetic neuralgia.

Chronic viral infections—A human leucocyte interferon cream used for several weeks cured vulval warts,[44] while intralesional injections of very small amounts of fibroblast interferon into penile warts had a small but statistically significant inhibitory effect on their growth.[45]

Chronic infections with, for example, rubella, cytomegalovirus, herpes simplex virus, or hepatitis B virus may be influenced by treatment with interferon. Since, however, large numbers of cells may be infected in these conditions, the effect might be expected to wear off when treatment was stopped unless the infected cells had been destroyed. This may explain why, in several uncontrolled studies, high doses of both human leucocyte and fibroblast interferons only temporarily reduced the circulating markers of viral infection in chronic active hepatitis associated with hepatitis B virus.[46–53] Infection may apparently be abolished by treatment in a few of these patients, but in most the fall in viral markers is only temporary. One recently reported placebo-controlled trial showed that leucocyte interferon could consistently lower circulating hepatitis-B-virus-associated DNA polymerase in eight patients but that the effect was only temporary.[54] One patient in the placebo group had spontaneous clearing of detectable DNA polymerase three weeks after completing treatment. Spontaneous cure may occur occasionally in chronic active hepatitis. The beneficial effects seen with interferon in some patients may have been due to an antiviral effect or to an effect on the immune system. Further work is needed to identify the patients who may respond to treatment with interferon and to evaluate the efficacy of higher dose schedules or combination treatment with other promising antiviral agents such as adenine arabinoside.[48]

Chronic infection with cytomegalovirus has also been treated[55–58]; virus was cleared from the urine in a few patients (four out of 25 in published reports), and the virus titre in the urine fell temporarily in some of the remainder. Whether a more favourable result could be obtained with higher doses of interferon is not yet known, but it is not surprising that prophylactic treatment at the doses used did not reverse reactivated infection[58] when higher doses had only a minor delaying effect.[26] In one child with congenitally acquired chronic rubella,[59] infection was no longer detectable after a two-week course of interferon.

Toxicity—Larger doses of interferon have not been used clinically for two reasons: insufficient supplies and dose-related (but reversible) toxicity. The major unwanted effects (with both leucocyte and fibroblast interferons) appear to be bone-marrow suppression, an inhibition of growth in young children,[57] and temporary loss of hair.[60] Mild side effects (fever, headache, myalgia, and malaise) tend to wear off after about a week's continuous treatment and do not occur in patients on corticosteroids.[26]

Interferon and cancer—Mouse interferon has a beneficial effect on some experimental tumours in mice.[61] When human leucocyte interferon was given for 18 months to patients with osteogenic sarcoma who had received standard primary treatment interim analysis showed that they had survived longer without metastases than patients treated concurrently at other centres. Because the design of that trial is open to criticism, control groups should be chosen very carefully in future studies. In uncontrolled studies some remarkable responses have been reported in the size of the tumour in small numbers of patients with juvenile laryngeal papilloma, multiple myeloma, metastasising breast tumours, non-Hodgkin's lymphoma, and some leukaemias.[62] These apparent benefits may have been due, at least in part, to non-specific effects. Placebo-controlled trials are needed to prove without doubt that interferon has activity, with long-term follow-up to evaluate the possible benefit to treated patients.

The temptation to prescribe new agents (particularly new antiviral and antineoplastic drugs) on an uncontrolled basis often seems overwhelming but early favourable results may prevent later, adequate evaluation. So far with interferon a remarkable amount of knowledge has been gained using small amounts of material in well-controlled studies. These have shown that human interferon has activity in some established viral illnesses (notably herpetic eye disease, herpes zoster in malignancy, and genital warts). If hopes for interferon are fulfilled it may become widely available in perhaps 10 years' time. Present supplies should be concentrated in further controlled studies aimed at discovering how best to use it and deciding who most needs it. Many years seem likely to elapse before interferon is used (in the West) to treat common colds.

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