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## Purified interferon as protection against rhinovirus infection

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### Abstract

**In a double-blind placebo-controlled study a preparation of human leucocyte interferon purified by affinity chromatography using a monoclonal antibody and applied by repeated nasal sprays reduced the incidence and severity of colds in volunteers challenged with human rhinovirus 9. Although interferon itself caused some symptoms, these were minor compared with the clinical colds. Interferon activity was still detectable in nasal washings as long as 26 hours after the last dose in about half the volunteers on active treatment.**

### Introduction

In 1973 Merigan *et al*<sup>1</sup> showed that  $14 \times 10^6$  units (about 50  $\mu\text{g}$ ) of partially purified human leucocyte interferon could protect volunteers against infection with rhinovirus 4. Since then better methods of application have been looked for, so that a lower dose can be used.<sup>2-5</sup> The lack of interferon available for clinical trials over the last decade has been eased recently by the cloning of human interferon genes in bacteria.<sup>6</sup> As the first in a series of experiments to examine the effects of new interferon preparations on respiratory infections, the previous study<sup>1</sup> has been repeated using highly purified human leucocyte interferon.

### Subjects and methods

*Interferon*—This was induced in pooled buffy-coat leucocytes stimulated with Sendai virus and partially purified by selective

precipitation.<sup>7</sup> It was purified by immunoadsorption chromatography on monoclonal antibody NK2 bound to Sepharose 4B ( $4 \times 4$  cm).<sup>8</sup> The preparation, purification, and checks of sterility of interferon and placebo (phosphate-buffered saline with human serum albumin 2 mg/ml) have been described.<sup>9</sup> The yield of interferon was 53% by immunoradiometric assay and the specific activity of the purified interferon (NK2) was  $1.6 \times 10^8$   $\mu\text{g}/\text{mg}$  protein. The antiviral activity was  $10^7$  U/ml by plaque reduction of vesicular stomatitis virus in monkey kidney (V3) cells, by inhibition of Semliki Forest virus RNA synthesis in embryonic bovine tracheal cells, and by immunoradiometric assay.<sup>10</sup> Both interferon and placebo preparations contained less than 2.5  $\mu\text{g}/\text{l}$  endotoxin by limulus lysate assay. Interferon and placebo solutions were indistinguishable and coded in four batches (two from each treatment group).

*Virus*—Rhinovirus 9, obtained from a filtered nasal washing pool held at the Medical Research Council Cold Unit, had been passaged in volunteers but not in tissue culture. Approximately 25 tissue-culture infective doses (TCID<sub>50</sub>) were administered as nasal drops. Back titrations performed after administration showed that one group of volunteers had received 21 TCID<sub>50</sub> and the other 10 TCID<sub>50</sub>.

*Volunteers*—The studies were approved by the ethical committee at Northwick Park Hospital.<sup>11</sup> Volunteers at the hospital and at the Common Cold Unit were selected and screened as described.<sup>9,12</sup> Volunteers at the Common Cold Unit were screened for haematological and plasma biochemical abnormalities both before the trial and six days after virus inoculation—that is, three days after completing interferon treatment. They were isolated in groups of two or three. Clinical symptoms and signs of colds were assessed independently by JW according to the routine at the Common Cold Unit,<sup>12</sup> and daily nasal secretion weights were measured as additional independent evidence of colds.

### STUDIES

*Kinetics of intranasal interferon*—Five healthy volunteers at Northwick Park Hospital were each given seven separate doses of interferon ( $4 \times 10^6$  U/ml), using the Risdon spray gun<sup>1</sup> calibrated to deliver 0.25 ml through a spray nozzle. One dose consisted of one spray per nostril (total dose  $2 \times 10^6$  U) given to the volunteer sitting with the neck extended. Nasal washings were collected at intervals from five to 60 minutes after dosing and the interval between doses was four to 16 hours. Antiviral activity in the nasal washings was assayed by determining the inhibition of cytopathic effect of Semliki Forest virus in embryonic bovine tracheal cells. Antigenic activity was determined by an immunoradiometric assay. The lower limits for detection of interferon were 10 U/ml by bioassay and 32 U/ml by immunoradiometric assay compared with the international standard preparation MRC 69/19B. Nasal washings from 22 volunteers who took part in the rhinovirus challenge study were also analysed.

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**Tolerance of repeated intranasal sprays**—Ten volunteers at the Common Cold Unit were randomly selected to receive interferon ( $5 \times 10^6$  U/ml) or placebo in repeated doses without virus challenge. Three doses were evenly spaced over one hour and repeated three times a day (starting at 0800, 1400, 1900) for four days. The total dose given was approximately  $9 \times 10^7$  units. Six additional volunteers in subsequent rhinovirus challenge studies who had high rhinovirus 9 antibody titres before the trial were given saline instead of virus and provided additional information on the tolerance of this schedule of interferon.

**Rhinovirus challenge study**—On admission to the Common Cold Unit all volunteers were checked for the presence of neutralising antibody to rhinovirus 9 using a rapid microtest technique. Volunteers with high antibody titres were excluded from virus challenge and the rest (23 patients) were randomised in pairs matched approximately for ages and antibody titres to receive different treatments (either interferon or placebo) according to the schedule above: three doses in one hour repeated three times a day for four days. Virus inoculation was given 26 hours after starting treatment—that is, two hours after completing the fourth set of interferon or placebo nasal sprays. Daily nasal washings were taken for rhinovirus isolations in HeLa cells and for interferon titrations on days 2 to 5 after virus inoculation. Pretrial and convalescent sera were compared in parallel for rising antibody titres.

## Results

### INTERFERON KINETICS

Nasal washings were assayed for interferon activity both by bioassay and immunoradiometric assay. Although the results of both correlated well (fig 1), immunoradiometric assay tended to give titres  $0.5$ – $1.0$   $\log_{10}$  U/ml higher. When the samples where interferon was detectable by only one assay were excluded, the mean discrepancy between single tests on 58 samples was  $0.48$  (SD  $0.3$ )  $\log_{10}$  U/ml. The decay with time of recoverable interferon activity is shown in fig 2. After inoculation of  $2 \times 10^6$  units of interferon,  $2.5 \times 10^5$  units by immunoradiometric assay were recovered in the nasal washings at five minutes, and the half life of recoverable activity was 20 minutes in the first hour.

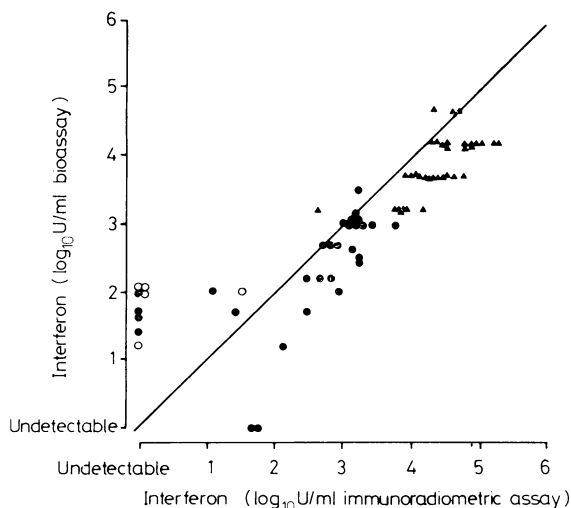


FIG 1—Comparison of results of interferon assays of nasal washes from volunteers given intranasal sprays of  $2 \times 10^6$  U interferon alone (▲) or  $7.5 \times 10^6$  U over one hour and rhinovirus 9 (●) or rhinovirus 9 with placebo (○).

In the rhinovirus challenge studies interferon was detected in nasal washings taken about two hours after a set of interferon nasal sprays had been completed (geometric mean titres 500 U/ml by bioassay and 1000 U/ml by immunoradiometric assay). Furthermore, five out of 11 nasal washings taken about 26 hours after the last dose of interferon contained detectable antiviral activity (mean titre 40, range 15–100 U/ml) and in four out of 11 activity was detected by immunoradiometric assay (mean titre 50, range 35–125 U/ml). Of 55 nasal washings taken from 11 volunteers given rhinovirus and placebo, only five from different volunteers were positive by bioassay (titres 25–100 U/ml) and only one by immunoradiometric assay.

### INTERFERON TOLERANCE

None of the five volunteers given seven single doses of interferon at intervals over one week had any symptoms, although one developed a transient urticarial rash two days after the last dose. Of 16 volunteers given repeated sprays of interferon or placebo but not challenged with virus, eight received interferon: five had mild symptoms with total clinical scores of 1.5–2.5. These volunteers complained of nasal stuffiness (three), sore throat (one), mild epistaxis (two), or used more handkerchiefs than usual (one). The symptoms occurred after treatment had finished in three volunteers. The two volunteers given placebo had total scores of 1; one had sneezing and the other nasal stuffiness with sore throat. None of the eight volunteers given interferon reported any symptoms characteristic of intramuscular administration of interferon<sup>9</sup> or had a clinically appreciable rise in six-hourly pulse rate or oral temperature, but 4 volunteers given placebo and rhinovirus 9 who had colds had temperatures of  $37.8^\circ\text{C}$  or above. None of the volunteers in any group had clinically important changes in biochemical values, haemoglobin, or total and differential white cell counts between pre- and post-trial values.

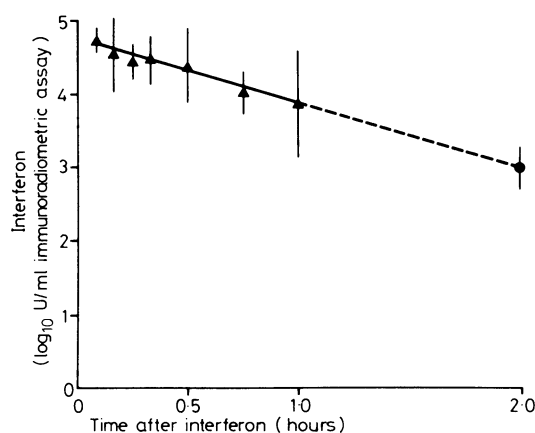


FIG 2—Interferon titres in nasal washings after nasal spray in five volunteers (▲) after single doses of  $2 \times 10^6$  U and (●) in 11 volunteers challenged with rhinovirus 9 two hours after treatment with interferon  $7.5 \times 10^6$  U in three doses during one hour.

### RHINOVIRUS CHALLENGE

There were no differences in the frequency or severity of colds after 21 TCID<sub>50</sub> or 10 TCID<sub>50</sub> of rhinovirus 9 so the results of the two trial groups (of 9 and 14 volunteers) have been combined. Of the 23 volunteers who entered the virus challenge study, one in the placebo group developed an intercurrent illness unrelated to a cold and treatment was stopped. A wild virus was grown from the pretrial nasal washing of one volunteer in the interferon group. (Her flatmate was also in the interferon group and had a doubtful cold but excreted rhinovirus 9 and had a rise in rhinovirus 9 antibody titres from  $<2$  to 96, so she was included in the analysis). Two others in the interferon group had higher pretrial neutralising antibody titres (24 and 64) than expected by repeat assays of paired specimens. None of these three volunteers given interferon had clinical colds or excreted rhinovirus 9, and they were excluded from analysis.

Of the two groups remaining, one consisted of eight volunteers given interferon with pretrial antibody titres of less than 2 (seven) or 12 (one) and one of 11 volunteers given placebo with titres of less than 2 (seven), 8 (two), or 16 (two). The clinical colds experienced by these groups are listed in table I. One of the 11 volunteers receiving placebo and five of eight receiving interferon had no cold ( $p=0.48$ , Fisher's exact test). On the other hand, seven volunteers receiving placebo and none receiving interferon had moderate colds ( $p=0.013$ ). Moreover, of the three colds in the volunteers given interferon, two were graded as very mild (total clinical scores 9.5 and 17.5) and one as doubtful (score 5). Mean daily scores and nasal secretion weights were shown for both groups in fig 3 and illustrate further the protective effect of this schedule of interferon.

**Virus isolation**—Viruses were isolated by inoculating nasal washings into confluent tube cultures of sensitive 0-HeLa cells. The frequency of positive isolations on each day is shown in table II. Nasal washings

from a healthy subject to which varying concentrations of rhinovirus 9 and NK2 interferon were added were also tested and showed that interferon could delay the appearance of rhinovirus cytopathic effect in HeLa cells (which are regarded as relatively insensitive to human leucocyte interferon). Nevertheless, 0.5 and 1 TCID<sub>50</sub>/ml rhinovirus 9 were completely inhibited by 100 or 1000 U/ml NK2 interferon respectively. Therefore, all nasal washings negative for rhinovirus were

TABLE I—Clinical grades of colds, rhinovirus 9 shedding on any day, and seroconversion (rise in serum neutralising antibody of over fourfold) in volunteers treated with interferon or placebo and challenged with rhinovirus 9

Grade of cold	No of volunteers receiving:					
	Interferon			Placebo		
	Total	Virus secretion	Seroconversion	Total	Virus secretion	Seroconversion
Nil	5	3	2	1	1	0
Doubtful or very mild	3	2	1	2	1	1
Definite colds:						
Mild	0	0	0	1	1	1
Moderate	0	0	0	7	7	4
Total	8	5	3	11	10	6

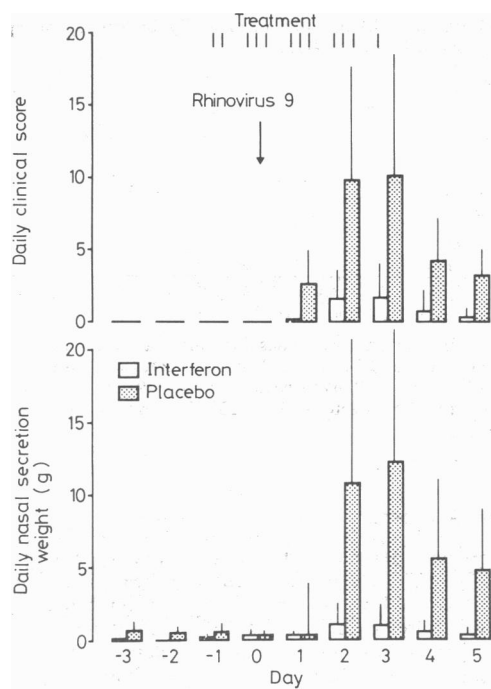


FIG 3—Clinical scores and nasal secretion weights (mean and 1 SD) in groups of volunteers given interferon (eight subjects) or placebo (11 subjects) and challenged with rhinovirus 9. Each treatment consisted of  $7.5 \times 10^6$  U given in three doses over one hour.

TABLE II—Virus recovered in nasal washings of volunteers treated with interferon or placebo and challenged with rhinovirus 9, tested alone and in the presence of calf anti-lymphoblastoid interferon. (Differences between total No positive on each day were tested by Fisher's exact test)

Day after virus inoculation	Positive isolations from nasal washings in subjects receiving:				Significance of difference
	Interferon (n = 8)		Placebo (n = 11)		
	No*	%	No*	%	
2	1 + 2	38	9 + 1	92	P = 0.047
3	1 + 3	50	10 + 0	91	NS
4	3 + 2	63	9 + 1	91	NS
5	3 + 1	50	6 + 4	91	NS
6	5 + 0	63	5 + 4	82	NS
Total	13 + 8	53	39 + 10	89	

\*The second figure in this column is the number of nasal washings positive for virus in the presence of calf anti-lymphoblastoid interferon.

incubated at one hour at room temperature with  $1.2 \times 10^4$  neutralising units of calf antihuman lymphoblastoid interferon. They were then negative for interferon activity by bioassay, but eight samples in the interferon and 10 in the placebo groups became positive for rhinovirus.

Three out of eight volunteers on interferon and six of the 11 on placebo had a fourfold or greater rise in neutralising antibody titre to rhinovirus 9. Only three volunteers in the interferon group had no evidence of infection by symptoms, nasal rhinovirus 9 excretion, or increase in antibody, whereas all the placebo recipients showed some evidence of infection ( $p = 0.12$ ).

All but two volunteers given interferon reported upper respiratory symptoms after leaving the Common Cold Unit. The volunteer excluded because of a wild virus isolated in quarantine nasal wash developed symptoms on the eighth day after rhinovirus 9 inoculation. (She did not develop an increase in antibody to rhinovirus 9). One volunteer excluded because of a high antibody titre developed symptoms 15 days after virus inoculation. When all the colds of doubtful aetiology were included, symptoms started on average 5.2 days after virus and lasted 4.5 days in the interferon group whereas symptoms started 2.4 days after virus and lasted 9.2 days in the placebo group. It was not possible to gauge accurately the severity of symptoms in volunteers after they had left the Common Cold Unit, but they seemed to have been mild. The volunteers were still "blind" at this stage so as not to influence their reporting.

## Discussion

In planning this experiment we took account of previous difficulties in showing protection against rhinovirus using a lower dose schedule of fibroblast interferon<sup>13</sup> and that prolonged contact of interferon with nasal mucosal explants was necessary to induce an antiviral state.<sup>2</sup> We therefore decided to follow the previous protocol<sup>1</sup> with minor modifications. Firstly, the concentration of interferon given was some tenfold greater and was highly purified. Secondly, although the frequency and method of application were the same, the treatment was discontinued 12 hours earlier (two treatment sets) than previously. Thirdly, rhinovirus 9 was used instead of rhinovirus 4. Before the clinical experiment both rhinoviruses were shown to be equally sensitive to the inhibitory effect of NK2 interferon in fetal tonsil cells. We chose a strain of rhinovirus that appeared more virulent than rhinovirus 4, which produced only five colds in 16 seronegative volunteers.<sup>1</sup> In the present study, therefore, fewer volunteers were needed to show significant protection.

The results of the interferon nasal clearance study support the observations of Aoki and Crawley,<sup>14</sup> who showed the half life of intranasally applied solutions to be about 15 minutes. Residual interferon may have been present from the previous dose, but the amount was unlikely to have been appreciable. Surprisingly, interferon activity was present 26 hours after treatment despite an intervening nasal wash. This was probably NK2 interferon and not naturally produced leucocyte interferon. Interferon activity was detected by both immunoradiometric assay and bioassay two days after the last dose of interferon in one volunteer who was not susceptible to rhinovirus 9 infection; a similar observation had been made in the previous trial.<sup>1</sup> The titres of interferon in these washes were low (10–100 U/ml) compared with the dose inoculated but the results suggest that interferon may persist in the nose, possibly by binding to nasal epithelial cells. The mean titre of interferon in nasal washes two hours after three doses of interferon was that expected after a single dose, assuming a half life of 20 minutes. Repeat sprays were, however, more likely to ensure that all surfaces in the nose were thoroughly exposed to the interferon preparation. Two alternative methods for giving intranasal interferon, by nebuliser and by cottonwool pledget, have been tested recently.<sup>5</sup> Although protection was achieved using less interferon by these methods, repeated sprays are theoretically a more acceptable and useful means of application.

In this study, we have deliberately used an excess of highly purified interferon against a virulent virus challenge in circumstances when it would be expected to work best—that is, in the prevention of infection. How interferon modified colds is not

clear; although symptoms were dramatically reduced, virus infection and seroconversion were not completely prevented. Possibly interferon only delayed the onset of the inevitable cold, but the limited evidence suggests that late colds were extremely mild. Although volunteers may have been susceptible to and caught their flatmates' colds when they finished treatment, virus isolation studies seem to show that virus persisted in the nose during treatment. Theoretically, with continued interferon treatment, virus replication would be reduced. It would then be necessary to continue treatment only until antibodies were formed to prevent clinical colds completely. An antiviral agent used widely in the prophylaxis of minor upper respiratory disease would clearly have an advantage if it allowed subclinical infection and an immune response. Furthermore, if interferon reduced absolute virus shedding and nasal secretions, transmission of colds could also be reduced.

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# After-exercise thermography and prediction of deep vein thrombosis

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## Abstract

**A total of 112 patients participated in a prospective study of after-exercise thermography as a screening method for predicting risk of postoperative deep venous thrombosis. The fibrinogen-uptake test was used to detect thrombosis after elective surgery. The incidence of the complication showed no significant difference between patients who had had positive and those who had had negative thermograms.**

**Thermography does not seem to be useful for predicting risk of postoperative thrombosis.**

## Introduction

After-exercise thermography shows a highly distinctive pattern in some patients. This pattern has been claimed to indicate deep venous insufficiency.<sup>1</sup> In a prospective study of 109 patients<sup>2</sup> the pattern was associated with high risk of postoperative

thrombosis as detected by the fibrinogen-uptake test. As post-operative thrombosis is a multifactorial condition, devising a simple test to predict this risk presents great problems. We therefore conducted a prospective study to see whether after-exercise thermography in our hands could detect high-risk patients.

## Patients and methods

We studied 112 patients (63 men, 49 women) aged 51-86 years (mean age 67.6 years). All were participating in a study of prophylaxis against postoperative thromboembolism. Dextran 70 was given to 53 patients and a combination of dextran 70 and dihydroergotamine to 59 patients. Elective hip replacement was performed in 65 cases and abdominal surgery in 47.

After-exercise thermography was performed preoperatively with the AGA 680 Medical System. A resting thermogram was recorded with the patient's legs 15-20° above heart level after the unclothed legs had been exposed to room temperature for 10-15 minutes. The patient was then instructed to walk around the room or do knee-bends for two minutes. As soon as possible after the exercise a second thermogram was recorded with the patient positioned as before. A network of linear hot spots crossing the anterior tibia, not present on the initial thermogram, was regarded as positive.<sup>3</sup>

The <sup>125</sup>I-fibrinogen-uptake test was used to detect postoperative thrombosis. The test was performed as described by Kakkar *et al*,<sup>3</sup> but with slight modifications.<sup>4</sup> Measured activity was correlated with the precordial activity. An increase in uptake of 20% or more as compared with adjacent points on two consecutive measurements was accepted as the criterion for deep venous thrombosis. The thermo-

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