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Author(s)	Isomura, Shin; Ichikawa, Takayuki; Miyazu, Mitsunobu et al.
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THE PREVENTIVE EFFECT OF HUMAN INTERFERON-ALPHA ON INFLUENZA INFECTION; MODIFICATION OF CLINICAL MANIFESTATIONS OF INFLUENZA IN CHILDREN IN A CLOSED COMMUNITY

SHIN ISOMURA, TAKAYUKI ICHIKAWA, MITSUNOBU MIYAZU, HIROSHI NARUSE and MOTOHIRO SHIBATA

Department of Pediatrics, Nagoya University, School of Medicine, Nagoya 466, Japan

JIRO IMANISHI, AKIO MATSUO and TSUNATARO KISHIDA

Department of Microbiology, Kyoto Prefectural University of Medicine, Kyoto 602, Japan

TOSHIRO KARAKI

Department of Microbiology, Public Health Research Institute of Kyoto City, Kyoto 604, Japan

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SUMMARY A double-blind, controlled trial to ascertain the preventive effect of human interferon-α (Hu IFN-α) on upper respiratory viral infections was performed on children in a closed community. Drops of Hu IFN-α were instilled into the nasal cavity of 13 healthy children aged one to three years. Fourteen children were given placebos as controls. Administration of the interferon and clinical observations were carried out in the winter of 1980. Serological examination revealed that this was the period of outbreaks of influenza type A epidemics in the community. Clinical manifestations referable to influenza virus infection were milder in the interferon-treated group than in the controls. However, there was no significant difference in the serological responses of the two groups after infection with influenza virus type A.

INTRODUCTION

There have been reports on clinical trials on the effect of interferon (Hu IFN) as a prophylatic agent for common viral infections (Dunnick et al., 1979; Dunnick et al., 1980). Several workers observed possible beneficial effects of topical application of human leukocyte IFN (Hu IFN-α) in prevention of influenza virus infections (Soloviev, 1968; Arnaoudova, 1976; Imanishi et al., 1980). However, the actual value of topical IFN administration especially in childhood, remains to be established. A double-blind, controlled method was employed in this study. The results suggest that nasal administration of Hu IFN-α modified clinical manifestations of serologically confirmed influenza in young institutionalized children.

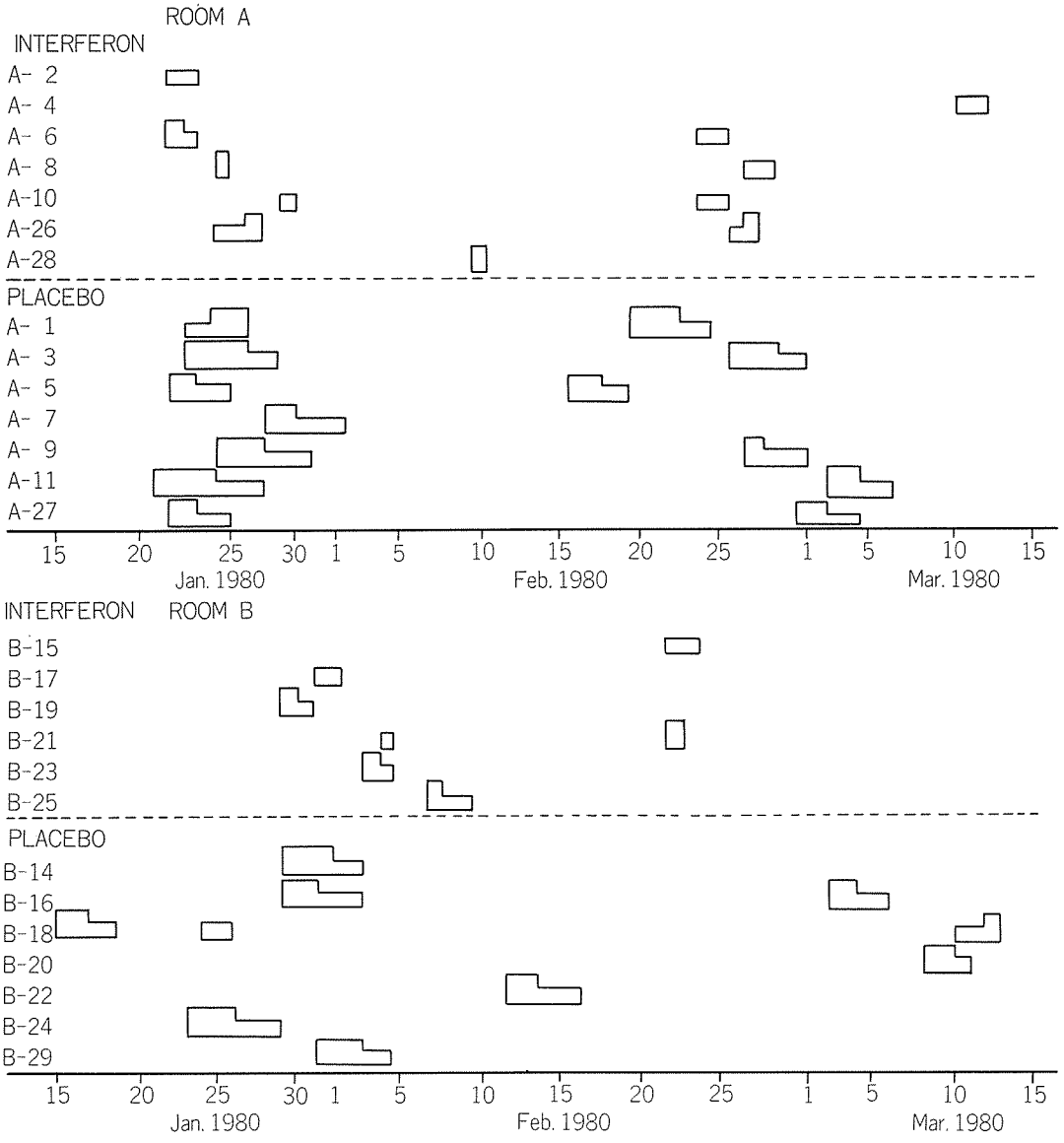
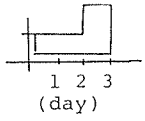


FIGURE 1. Outbreaks of febrile illness during the study period. Symbols indicate period and extents of fever.

For instance 

indicates a body temperature of 37.5 C-38.0 C for 2 days, of above 38.0 C on day 3 and no fever thereafter.

TABLE 1. *Frequency and severity of febrile episodes between Jan. 15 and Mar. 15.*

Case No.	Frequency	Duration of fever (37.5 C) (days)	Maximum body temp. (C)
Room A, IFN			
A-1	once	2	37.8
A-4	once	2	37.8
A-6	twice	2	38.7
		2	37.8
A-7	twice	1	38.9
		2	37.8
A-10	twice	1	37.8
		2	37.8
A-26	twice	3	38.8
		2	38.6
A-28	once	1	38.3
Room A, Placebo			
A-1	twice	4	39.0
		5	38.8
A-3	twice	6	38.3
		5	38.6
A-5	twice	4	38.5
		4	39.0
A-7	once	5	38.3
A-9	twice	6	38.8
		4	38.8
A-11	twice	6	38.4
		4	39.0
A-27	twice	5	38.9
		4	38.9
Room B, IFN			
B-15	once	2	37.8
B-17	once	2	37.9
B-19	once	2	38.3
B-21	twice	1	37.6
		1	38.8
B-23	once	2	39.3
B-25	once	3	39.0
Room B, Placebo			
B-14	once	5	38.8
B-16	twice	5	39.0
		4	38.4
B-18	three times	4	38.7
		2	37.7
		3	38.0
B-20	once	3	38.7
B-22	once	5	38.6
B-25	once	6	39.0
B-29	onec	5	28.9

MATERIALS AND METHODS

1. *Human leukocyte interferon (Hu IFN-α)*

Hu IFN-α was induced by Sendai virus in human peripheral leukocytes. The procedures for its induction and purification were described previously (Imanishi et al., 1980). The preparation was diluted to 5×10^4 international units (IU)/ml with phosphate buffer saline containing 0.2% gelatin. As a placebo, human de-gammaglobulinated plasma was diluted to the same protein concentration as the IFN preparation.

2. *Study designs*

The study group consisted of 27 healthy children (13 boys and 14 girls) of one to three years old, at Suzenkai Orphanage, Nagoya. During the period studied, they were kept in two separate rooms, and Room A was adjacent to Room B. 14 children aged two to three years in Room A and 13 babies aged one to two years in Room B.

They were divided randomly into two groups: 13 (7 in Room A and 6 in Room B) for IFN treatment and 14 (7 in each room) for placebo administration.

Approximately 5,000 IU of the IFN preparation or placebo was applied twice a day to the nostrils from Jan. 15, 1980 to Mar. 15, 1980. Particular members of the nursing staff were chosen to give the nasal drops in order to keep the amount and way of IFN administration constant. A total of about 5×10^5 IU of IFN was administered per child in the period studied.

All the children were examined once a day for signs and symptoms of respiratory tract illness by a physician who did not know the grouping. The body temperature of each child was recorded three times a day by nurses who also did not know the grouping.

The purpose of the study was explained and in-

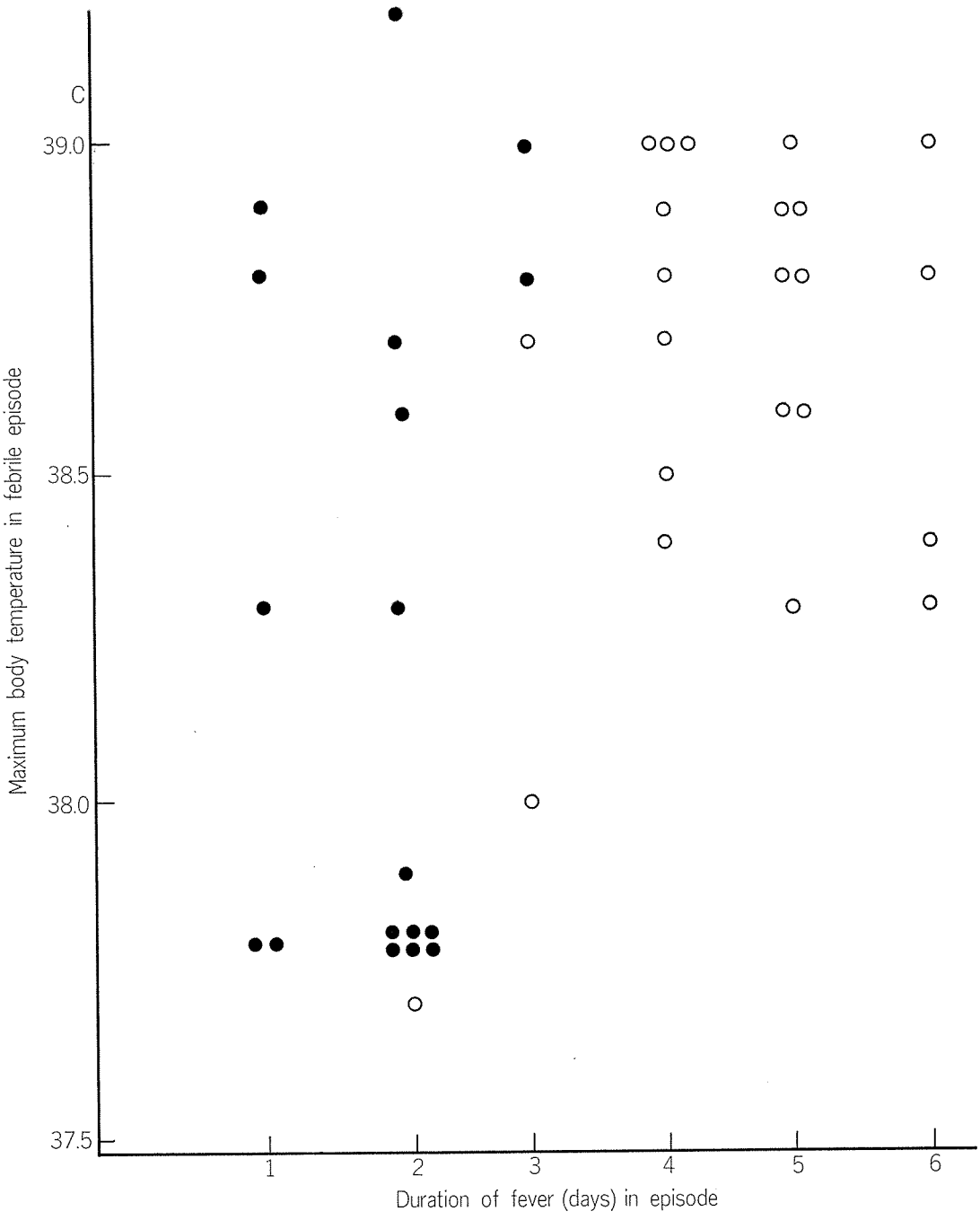


FIGURE 2. Duration of fever and maximum body temperature. ○: interferon, ●: placebo

formed consent was obtained from a parent or the adult legally responsible for each child.

3. *Serological examination*

Serum specimens were collected from the children before and after the experiment. They were stored at −20 C until measurement of hemagglutination inhibition (HI) antibody titers for influenza viruses type A and B, and parainfluenza viruses type I, II and III. The virus antigens and assay systems used for the HI tests were as listed in a previous paper (Imanishi et al., 1980).

RESULTS

1. *Outbreak of febrile illness*

The febrile episodes in each child during the period studied are summarized in Fig. 1. In Room A, outbreaks of febrile illness with signs and symptoms suggesting upper respiratory infections occurred twice, once at the end of January and once in the latter half of February. In Room B, only a single outbreak of similar illness was observed at the beginning of February. These illnesses seemed to be of viral origin, judging from physical findings and results of routine laboratory examinations: normal peripheral blood pictures and negative findings in bacterial throat cultures.

The maximum body temperatures and durations of fever during febrile episodes in IFN-treated children were compared with those in control children (Table 1, Fig. 2). Fever was higher and more prolonged in the control group than in the IFN group.

Other signs and symptoms referable to the respiratory tract infection (e.g., nasal obstruction, nasal discharge, cough) were milder in the IFN group. No adverse effect of IFN administration was recognized.

2. *Serological examinations*

Serological specimens were obtained from some children. In Room A, the antibody titers against influenza virus H1N1 increased in 8 of 9 children tested, and the antibody titers against influenza virus H3N2 increased in 7 of these children. In Room B, the antibody titers against influenza virus H1N1 increased in 8 of 9 children, but none of them showed any increase in antibody titer against influenza virus H3N2 (Table 2). Thus, the HI test revealed that epidemics of the two types of in-

TABLE 2. *HI antibody titers against influenza type A virus before and after the experiment*

Case No.	A/USSR/9277 (H1N1)		A/Kumamoto/ 22/76 (H3N2)	
	pre	post	pre	post
Room A, IFN				
A-2	<16	32	<16	<16
A-4	<16	<16	<16	<16
A-6	<16	128	<16	512
A-8	<16	128	<16	2048
A-10	<16	32	<16	512
A-26	ND[a]	ND	ND	ND
A-28	ND	ND	ND	ND
Room A, Placebo				
A-1	<16	64	<16	512
A-3	<16	64	<16	1024
A-5	ND	ND	ND	ND
A-7	ND	ND	ND	ND
A-9	<16	32	<16	512
A-11	<16	32	<16	1024
A-27	ND	ND	ND	ND
Room B, IFN				
B-15	32	512	256	256
B-17	ND	ND	ND	ND
B-19	<16	64	64	64
B-21	<16	32	<16	<16
B-23	<16	128	<16	<16
B-25	<16	128	<16	<16
Room B, Placebo				
B-14	ND	ND	ND	ND
B-16	<16	64	<16	<16
B-18	<16	128	<16	<16
B-20	64	512	<16	<16
B-22	64	64	128	<16
B-24	ND	ND	ND	ND
B-29	ND	ND	ND	ND

[a] not determined

fluenza A virus (H1N1 and H3N2) took place in Room A during IFN administration, whereas an epidemic of only influenza A virus (H1N1) occurred in Room B. There was no significant difference between the increases of antibody titers in IFN and placebo groups.

None of the children showed increase in antibody against influenza virus type B, or parainfluenza viruses type I, II and III during the experiment.

DISCUSSION

In the pervious paper (Imanishi et al., 1980), it was shown that prophylactic administration of an Hu IFN-α preparation suppressed fever and subjective symptoms due to upper respiratory infections in adult volunteers. The present study showed that continuous intranasal administration of Hu IFN-α to children in a closed community modified the clinical manifestations of viral upper respiratory diseases. The causative agent of illness was not identified because the virus was not isolated, but serological examinations strongly suggested that the epidemics were due to influenza type A viruses (H1N1 and H3N2). There was no significant difference between the increases of HI antibody titers against influenza type A viruses in IFN and placebo groups. These results suggest that administered IFN does not afford protection from infection with influenza virus, but modifies the clinical course of the illness, especially the febrile response.

IFN has been used clinically to prevent influenza virus infections, but results have been equivocal. Soloviev (1968) reported that Hu IFN-α suppressed the rise in the antibody titer against influenza virus A2 Moscow type, and that previous intranasal administration of IFN suppressed the rise in antibody even on inoculation of live influenza vaccine strain. He thus concluded that IFN was effective in the prevention of influenza. Merigan et al. (1973) performed a controlled study by administering Hu IFN-α intranasally before challenge with influenza virus type B. They found that a total of 800,000 IU of IFN did not protect the volunteers from influenza virus infection or alter the frequency or severity of illness. Thus they suggested that much larger quantities are required to prevent influenza virus infection.

The difference between the present findings and these past reports might be due to differences in (a) the infecting virus, e.g. the virulence of the infecting strain; (b) the mode of infection (natural or experimental); (c) the IFN dosage; (d) contaminating protein in the IFN preparation, and (e) the racial, regional and cultural factors.

Influenza virus infections are common and secondarily cause many kinds of diseases. Because of its high morbidity and its high frequency of outbreaks, effective methods for the control influenza have long been sought. The present study gave promising results, and further investigations are now in progress.

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