Archives of Disease in Childhood, 1985, **60**, 829–831

Nasal interferon responses in leukaemia

C E TAYLOR, A W CRAFT, J KERNAHAN, M M REID, AND G L TOMS

Departments of Virology, Child Health, and Haematology, Royal Victoria Infirmary and University of Newcastle upon Tyne

SUMMARY Nasal concentrations of leucocyte interferon measured immunoradiometrically were appreciably higher in children infected with influenza viruses than those infected with paramyxoviruses. Regardless of the infecting virus, leukaemic children produced normal amounts of interferon, but this appeared to have little effect on the duration of excretion of virus.

Infections with common respiratory viruses in children receiving chemotherapy for acute lymphoblastic leukaemia may be severe,[1] result in prolonged excretion of virus,[2] and be associated with simultaneous multiple virus isolations.[3] This abnormal handling of viruses may result from impairment of systemic or local, or both defence mechanisms. As part of a study of the defence mechanisms of children with acute lymphoblastic leukaemia we compared the local response of interferon to respiratory virus infections of normal children with those who had leukaemia.

Patients and methods

Patients. Twenty seven children receiving treatment for acute lymphoblastic leukaemia were studied when they developed respiratory tract infection, during which virus was identified by an immunofluorescent technique or isolation of virus. Their ages ranged from 1 to 14 years (mean 6·2 years). Eight of the children required admission to hospital, 19 were managed as outpatients.

Controls. Fifty three normal children were studied during 57 episodes of infection with the same viruses as identified in the leukaemic children or with measles virus. Their ages ranged from 3 months to 7 years (mean 2·4 years). In 47 episodes children were admitted to hospital because of their infection. Nineteen normal children without respiratory tract infections were studied. Their ages ranged from 3 to 12 years (mean 7·6 years).

Assay of interferon in secretions. Nasal and nasopharyngeal secretions were flushed into a standard volume of virus transport medium containing 0·3 μmol/l phenolsulphonphthalein (phenol red) and assayed using an immunoradiometric kit (Sucrosep, Boots-Celltech Diagnostics). Seven aliquots of a pool of nasal secretions were tested, giving a reproducibility of 38% when expressed in $\log_{10}$ units/ml. The volume of secretion collected was calculated from the degree of dilution of the phenolsulphonphthalein in transport medium after the sample had been added. Phenolsulphonphthalein concentrations were determined after addition of 3N sodium hydroxide and centrifugation at 1000 *g* for 10 minutes. The optical density at 560 nm (the optimum wavelength of absorbance for phenolsulphonphthalein in alkali solution) was determined spectrophotometrically and the concentration read from a previously prepared calibration curve. Volumes of secretion greater than 100 μl could be measured by this technique, and a sample of nasopharyngeal secretion assayed on five separate occasions gave a mean (SD) volume of 126 (39·2) μl. Secretions with visible contamination with blood were discarded as unsuitable as haemoglobin absorbed appreciably at 560 nm. Concentrations of interferon were expressed per ml of secretion.

Results

Of the 27 children with acute lymphoblastic leukaemia, nine were infected with respiratory syncytial virus, five with parainfluenza virus type 3, eight with influenza virus type A, and five with influenza virus type B. Of the 53 normal children, 16 were infected with respiratory syncytial virus, seven with parainfluenza virus type 3, eight with measles virus, 14 with influenza virus type A, and 12 with influenza virus type B.

Figure 1 shows the interferon concentrations in the secretions of the infected and non-infected children. No interferon was detected in secretions of

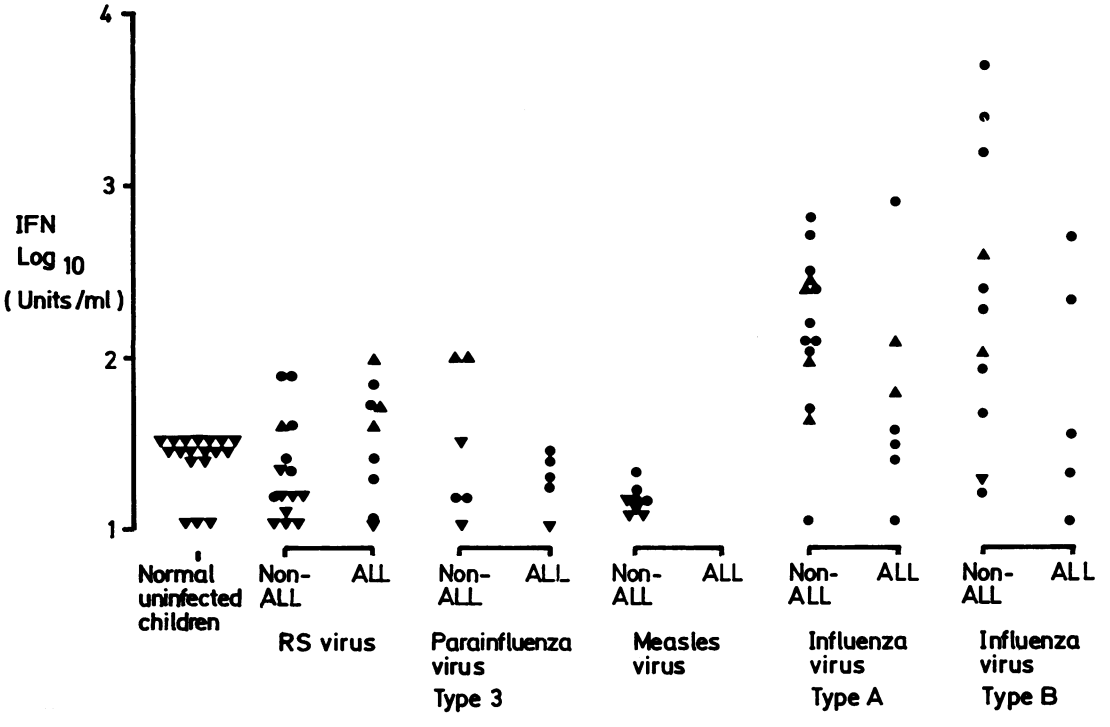

Fig 1. *Alpha interferon IFN concentrations during infection with common respiratory viruses in the nasopharyngeal secretions of normal children and children receiving treatment for leukaemia.*

ALL=Children with acute lymphoblastic leukaemia. RS=Respiratory syncytial virus. ●=Log_{10} units/ml interferon in secretions determined by the immunoradiometric method. ▼=Maximum possible titre of interferon in secretion consistent with a negative result when diluted secretions were titrated by immunoradiometry. ▲=Minimum possible titre of interferon in secretion consistent with titre obtained on titration of diluted secretions by immunoradiometry where the dilution factor was undetermined but greater than 1:10.

the 19 children without respiratory tract infections. Secretion from another child was thick and copious, suggesting a recent respiratory infection, but no virus was isolated. This secretion was positive with 2·0 log_{10} units/ml of interferon. Interferon concentrations associated with the paramyxoviruses, respiratory syncytial virus and parainfluenza virus type 3 were noticeably lower than those with the orthomyxoviruses, influenza virus types A and B. Children with measles also had low concentrations of interferon.

There was no difference between interferon concentrations in the secretions of children with acute lymphoblastic leukaemia and normal children infected with the same virus. No correlation was seen between the age of the children and interferon concentrations, but there was a trend for children admitted to hospital with acute lymphoblastic leukaemia to have higher interferon concentrations than outpatients.

Sequential nasopharyngeal secretions were obtained from eight children with acute lymphoblastic leukaemia and viral infections. Throughout the course of their illness viral antigens could be detected in their secretions by immunofluorescence, and virus was isolated from all specimens from the children infected with respiratory syncytial virus and influenza B virus and from one child infected with influenza virus type A. One child infected with influenza virus type B died. Figure 2 shows the interferon concentrations found in the secretions from these children.

Discussion

The immunoradiometric technique that we used detects specifically alpha 1 interferon, a predominant subtype produced after viral stimulation of peripheral blood leucocytes.[4] Our study showed

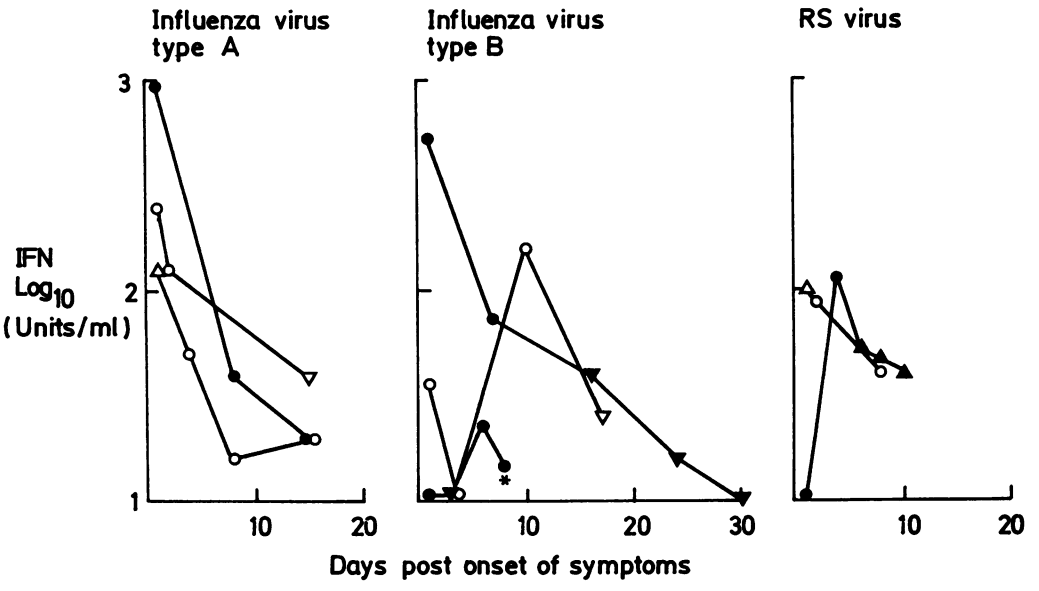

Fig. 2 *Alpha interferon IFN concentrations during infection with respiratory viruses in nasopharyngeal secretions of children receiving treatment for leukaemia.*

RS=Respiratory syncytial virus. ●=Log_{10} units/ml interferon in secretions determined by the immunoradiometric method. ▼=Maximum possible titre of interferon in secretion consistent with a negative result when diluted secretions were titrated by immunoradiometry. ▲=Minimum possible titre of interferon in secretion consistent with titre obtained on titration of diluted secretions by immunoradiometry where the dilution factor was undetermined but greater than 1:10. *=Death.

differences in the secretion of alpha 1 interferon between children with the influenza viruses types A and B and those with the paramyxoviruses, measles virus, parainfluenza virus type 3, and respiratory syncytial virus. This confirms previous reports of higher nasal interferon titres during influenza virus infection than respiratory syncytial virus infection.[5] Respiratory syncytial virus and influenza virus stimulate interferon subtypes with different ranges of activity,[6] however, and similar studies of other interferon subtypes are required.

Regardless of the infecting virus, children with acute lymphoblastic leukaemia produced local interferon at similar concentrations to normal children. Despite the continued presence of local interferon, however, excretion of virus persisted. It is therefore unlikely that a defect in the production of nasal interferon lies behind the abnormal handling of viruses by these children. It may be, however, that the observed persistence of virus results from an inability of the tissues of children with acute lymphoblastic leukaemia to achieve an interferon induced antiviral state.

We thank the Tyneside Leukaemia Research Association who supported this work.

References

1 Craft AW, Reid MM, Bruce E, Kernahan J, Gardner PS. Role of infection in the death of children with acute lymphoblastic leukaemia. *Arch Dis Child* 1977;**52:**752–7.
2 Craft AW, Reid MM, Gardner PS, *et al.* Virus infections in children with acute lymphoblastic leukaemia. *Arch Dis Child* 1979;**54:**755–9.
3 Bruce E, Reid MM, Craft AW, Kernahan J, Gardner PS. Multiple virus isolations in children with acute lymphoblastic leukaemia. *J Infect Dis* 1979;**1:**243–8.
4 Goren T, Kapitovsky A, Kimchi A, Rubinstein M. High and low potency interferon alpha subtypes induce (2′–5′) oligoadenylate synthetase with similar efficacy. *Virology* 1983;**130:** 273–80.
5 Hall CB, Douglas RG, Simons RL, Geiman JM. Interferon production in children with respiratory syncytial, influenza and parainfluenza virus infections. *J Pediatr* 1978;**93:**28–32.
6 Bell DM, Roberts NJ, Hall CB. Different antiviral spectra of human macrophage interferon activities. *Nature* 1983;**305:** 319–21.

Correspondence to Dr G L Toms, Department of Virology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

Received 12 April 1985