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Citation	Biken journal : journal of Research Institute for Microbial Diseases. 1982, 25(1), p. 29-42
Version Type	VoR
URL	https://doi.org/10.18910/82492
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APPLICATION OF A LIVE VARICELLA VACCINE TO HOSPITALIZED CHILDREN AND ITS FOLLOW-UP STUDY

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(Received December 14, 1981)

SUMMARY One hundred and 50 patients, including 35 immunocompromised patients were given a live varicella vaccine. The occasions for vaccinations were 11 times for protection of successive nosocomial infection on occurrence of cases of varicella in a pediatric ward (97 subjects), once for the same purpose in a nursery (13 subjects) and non-urgent vaccination for 7 immunocompromised patients, 32 healthy susceptible children and 1 nurse. Viral doses used were 250 to 5,000 PFU. Without exception successive outbreaks of varicella in the ward and nursery were prevented when the vaccine was used 1 to 5 days after the onset of varicella. Humoral and/or cellular immunity was acquired in 97.1% of the high risk group and 91.9% of the non-high risk group. As for the clinical reactions, rashes and fever were seen in 47.1% and 17.6%, respectively, of the high risk group and 8.0% and 0.9% of the non-high risk group. The symptoms were generally mild.

A follow-up study on the vaccinated subjects from 6 months to 3 years and 10 months after vaccination showed that in the high risk group 23 of 25 cases had sustained antibody determined by immunoadherence hemagglutination (IAHA) or fluorescent antibody to membrane antigen (FAMA) test and 23 of 25 cases gave a positive skin reaction, and 24 of 24 cases had sustained antibody and 20 of 21 cases gave a positive skin reaction in the non-high risk group. Of 32 patients in the high risk group, 2 showed herpes zoster and 4 developed clinical varicella after 13 occasions of contact with varicella patients. Both varicella and zoster symptoms in the vaccinees were mild except in 1 case with leukemia in relapse, who showed moderate symptoms.

In a retrospective study, 11 of 31 unvaccinated high risk patients in our hospital caught natural varicella during treatment or remission and in 6 of them the disease was moderate or severe. Herpes zoster occurred in 3 of 31 cases and was severe in 2. Thus the benefit of varicella vaccination is unquestionable; it prevented suc-

cessive outbreaks in the ward and protected high risk patients from severe or fatal varicella. However, revaccination is advisable if immunity against varicella declines to an undetectable level in high risk children who are receiving immunosuppressive therapy.

INTRODUCTION

Once varicella occurs in a hospital, it is inevitable that subsequent nosocomial infections occur, since varicella is a highly contagious disease with a long incubation period and is communicable even before onset of eruptions. But no effective prophylactic or therapeutic measures are yet available. Varicella infection often becomes severe and can be fatal in patients receiving steroids or other immunosuppressive agents, particularly those with leukemia (Pinkel, 1961; Finkel, 1961; Rifkind, 1966; Scheinman and Stamler, 1969; Gershon et al., 1972; Schrimpf et al., 1972).

Application of live varicella vaccine (Takahashi et al., 1974; 1975) has prevented nosocomial secondary varicella infections and protected immunocompromised patients (high-risk group) from fatal varicella in our hospital since 1976. This report presents the results of vaccination and of subsequent follow-up studies on persistence of immunity against varicella for a maximum of 3 years and 10 months after vaccination, with a discussion of the characteristics and use of the vaccine.

MATERIALS AND METHODS

1. Vaccine

Attenuated live varicella vaccine (Oka strain) (Takahashi 1974, 1975) was used. The virus dose employed ranged from 250 to 5,000 PFU (plaque forming units) per person.

2. Subjects for vaccination

Between August 1976 and December 1980, varicella occurred eleven times in the pediatric ward and once in the nursery of Yamagata City Hospital Saiseikan. At each time, hospitalized children and their siblings with access to the hospital and children in the nursery without history of varicella received

varicella vaccine with the consent of their parents. Details of the vaccinated subjects are given in Table 1.

3. Clinical and immunological examinations after vaccination

Vaccinated subjects were carefully observed for development of a rash and fever and the clinical course of underlying diseases for at least 4 weeks, or even longer in occasional cases, following vaccination. The children with underlying diseases received serum immunoglobulin assay, hematological examinations and liver function tests after vaccination.

Paired sera obtained before and 4 to 6 weeks after vaccination were tested for antibody against varicella-zoster virus by the neutralization (NT) test (Asano and Takahashi, 1978) and later by tests for the immunoadherence hemagglutination (IAHA)

TABLE 1. *Details of vaccinated subjects*

Urgently vaccinated	
110 (high risk children, 28)	
Non-urgently vaccinated	
40 (high risk children, 7)	
High risk children	
Nephrotic syndrome	15
Acute lymphatic leukemia (ALL)	6
Malignant lymphoma	1
Neuroblastoma	2
Hepatoblastoma	1
Anaphylactoid purpura	3
Congenital pure red cell anemia	2
Idiopathic thrombocytopenic purpura	1
Urticaria	1
MCLS (Kawasaki disease, Kawasaki et al., 1974)	1
Infantile spasm	1
Allergic gastroenteropathy	1

and fluorescent antibody to membrane antigen (FAMA) (Yamada et al., 1979). Vaccinated individuals who did not show an antibody response were subjected to the skin test using varicella skin antigen (Kamiya et al., 1977; Asano et al., 1981) and the reaction was evaluated according to the criteria of Kamiya et al. (1977).

4. *Follow-up studies on vaccinated subjects*

With the exception of those who died or moved to distant places, 104 subjects (including 25 high risk children) vaccinated between 6 months and 3 years and 10 months before June 1980, were followed up by inquiries with respect of subsequent exposure to natural varicella and development of symptoms of varicella or herpes zoster. Serum antibody titers were usually determined by the IAHA test, but occasionally by the FAMA test, and skin tests were performed using varicella skin antigen in all the vaccinated high-risk patients and some of the non high-risk patients.

RESULTS

1. *Prevention of spread of varicella in the pediatric ward and nursery by urgent vaccination*

As described in the Materials and Methods, varicella occurred 12 times in the pediatric ward and nursery, and immediate vaccinations were carried out on children without a history of varicella in the ward. As a result, there

were no subsequent cases of varicella in the pediatric ward and nursery on any of the twelve occasions. With regard to the interval between the occurrence of varicella and vaccination, 59 children received vaccination on the day of onset of the disease and 17 patients on day 2, 19 on day 3 and 15 on day 5 after the onset.

2. *Clinical reactions and immunological responses after vaccination*

Clinical reactions after vaccination are shown in Table 2. Of the 34 high-risk patients, 16 (47.1%) developed a rash and 6 (17.6%) exhibited fever. The incidences of a rash and fever in the non-high risk group were lower i.e., 9/113 (8.0%) and 1/113 (0.9%), respectively. Fever usually lasted 1 to 1 to 2 days, and in all cases was associated with a skin rash. The rash usually appeared 14 days after vaccination in the non-high risk group and 16 to 35 days after vaccination in the high risk group. These symptoms were generally mild, except in 2 cases in the high risk group, a child with infantile spasms receiving ACTH and another child with malignant lymphoma under treatment with corticosteroid and cyclophosphamide. These children were vaccinated without suspension of chemotherapy and ex-

TABLE 2. *Clinical and immune response after vaccination*

	No. of subjects vaccinated	Incidence of eruptions	Incidence of fever (≥37.5 C)	No. of subjects showing rise in antibody titer	No. of subjects with positive skin reaction	No. of subjects acquiring immunity
High-risk group	34+1 ^a	16/34 ^b 47.1%	6/34 ^c 17.6%	29/34 85.3%	4/4 100%	33/34 97.1%
Non high-risk group	113+2 ^a	9/113 ^d 8.0%	1/113 ^e 0.9%	83/99 83.8%	8/8 100%	91/99 91.9%
Total	147+3 ^a	25	7	112/133	11/12	124/133

^a Cases of varicella immediately after vaccination.
^b Number of eruptions: 1 or a few, 4 cases. 10-40, 10 cases. numerous, 2 cases.
^c Temperature: 37.5 C, 1 case. 38 C, 3 cases. 39 C, 1 case.
^d Number of eruptions: 1 or a few, 8 cases. about 20, 1 case.
^e Temperature: 37.9 C.

hibited numerous vesicles with a temperature of 38 to 39 C lasting for 2 (infantile spasms) and 10 (malignant lymphoma) days. There was no clinical evidence of aggravation of underlying diseases after vaccination in any of the cases studied.

Immune responses in the vaccinated subjects are also shown in Table 2. Twenty-nine of 34 high risk patients exhibited an NT antibody response and 4 of the others developed a positive skin reaction: thus a total of 33 of the 34 patients (97.1%) acquired immunity to varicella. In the non-high risk group, an antibody response was observed in 83 of 99 cases and all 8 cases with a negative antibody response gave a positive skin reaction; so the vaccination conferred immunity to at least 91 (91.9%) of the 99 subjects.

3. Follow-up studies on vaccinees

i) Immune status of vaccinees

A follow-up study of the vaccinated subjects

Correlation between varicella skin test reaction and serum antibody titer (high risk group)

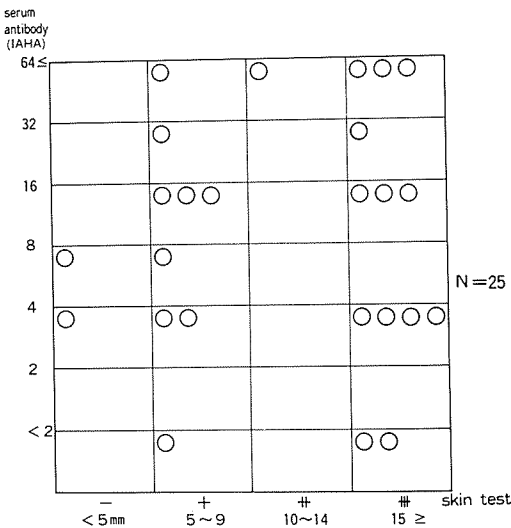


FIGURE 1. Vaccinated children of high-risk group were follow-up for serum antibody and cellular immunity by the varicella skin test 6 months to 3 years and 10 months after vaccination. Each circle represents one person.

at 6 months to 3 years and 10 months after vaccination showed that 23 of 25 subjects had positive serum antibody titers by the IAHA or FAMA test. The 2 subjects that did not have positive serum antibody titers gave a positive reaction in the varicella skin test, and one of them did not develop any sign of infection despite contact with varicella. The varicella skin test was positive in 23 of 25 cases and negative in 2 who gave a positive reaction for serum antibody. One of the 2 subjects also came in contact with varicella but did not develop any signs of infection (Fig. 1).

Twenty-four subjects from the non-high risk group were examined by the IAHA test, and all showed a positive antibody titer. The varicella skin test was performed on 21 of these individuals, of whom 20 gave a positive reaction. The subject giving a negative reaction was seropositive and did not develop symptoms after exposure to varicella (Fig. 2).
ii) Clinical varicella infection and occurrence of herpes zoster

As shown in Table 3, of 32 subjects from the high-risk group, 13 came in contact with

Correlation between varicella skin test reaction and serum antibody titer (non high risk group)

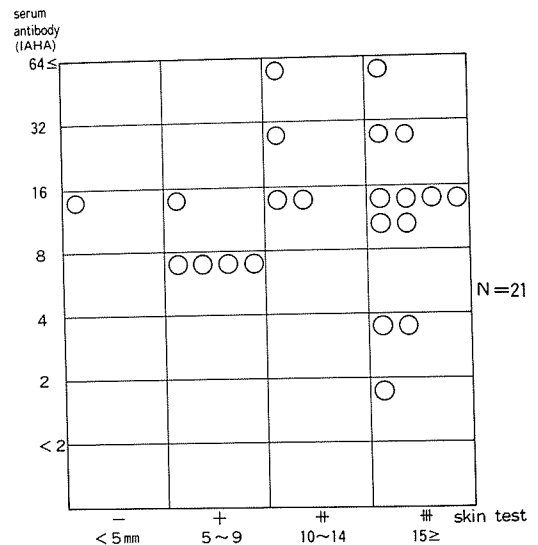


FIGURE 2. See the legend in Fig. 1.

TABLE 3. *Incidence of herpes zoster and natural varicella infection after vaccination against varicella (Follow-up period: 6 months to 3 years and 10 months)*

	High risk group	Non-high risk group
No. of subjects studied	32	79
Herpes zoster	2 ^a	0
Natural varicella infection	4 ^b	2 ^c
Occasions of contact with varicella patient	13	33

^a All mild (1 case of nephrotic syndrome 11 months after vaccination, 1 case of ALL, 7 months after vaccination).

^b Three cases (ALL, MCLS, neuroblastoma) were mild with less than 20 eruptions and no fever. On case (ALL) in relapse was moderately severe with generalized eruptions and temperature of 38 C for 3 days.

^c All were extremely mild with few eruptions and no fever.

varicella. Four of them developed symptoms of varicella but the other 9 were protected. In 3 cases, the infection was remarkably mild with less than 20 eruptions and no fever. The other case was of relapsed ALL, varicella was moderately severe with generalized rash and a temperature of 38 C for 3 days. Two subjects, one with nephrotic syndrome and the other with ALL developed mild herpes zoster 7 and 16 months respectively after vaccination. Rash without fever appeared in the loin in one and on the face in the other, and disappeared in 10 to 14 days and neither case had residual neuralgia.

Of the 79 subjects in the non high-risk group who could be followed, 33 came in contact with varicella infection and only 2 developed varicella which was extremely mild. None developed herpes zoster.

Data on the serum antibody titers, varicella skin test reactions and immunosuppressive therapy of individual patients in the high-risk group at the time of vaccination and in the

follow-up study are summarized in Table 4.

4. *Clinical severity of natural varicella in non-vaccinated high risk patients*

To delineate the clinical course of natural infection with varicella in high-risk children, we examined 31 immunocompromised children who had experienced natural varicella at this hospital retrospectively with respect to the degree of severity of varicella. Of the 31 patients, 23 had nephrotic syndrome, 3 had malignancies (1 ALL, 1 neuroblastoma and 1 rhabdomyosarcoma), 2 had rheumatic fever, 2 had systemic lupus erythematoses, and 1 had rheumatoid arthritis. In 20 cases with infection occurring before the onset of the underlying diseases, the varicella was of low grade. Eleven patients were infected during treatment for the underlying disease or in remission, and in 6 of them the infection was moderately severe or severe. Herpes zoster occurred in 3 patients, of whom 2 developed a severe form, which in 1 was associated with corneal ulceration.

DISCUSSION

Since the report of clinical trials of a live attenuated varicella vaccine (Takahashi et al., 1974), appraisal of the effectiveness of the vaccine and problems concerning its practical application have been widely discussed (Brunell, 1977 a; b; Sabin, 1977; Plotkin, 1977; Kempe and Gershon, 1977; Gershon, 1978; 1980; Dudgeon, 1980). With regard to the question of whether varicella, a common infectious disease usually with a favorable prognosis, should be controlled by vaccination, we have the following opinions.:

1. Varicella, when naturally infected, can be severe or even fatal in patients receiving immunosuppressive therapy, especially in those with leukemia or other malignant neoplastic diseases.
2. An outbreak of varicella in a hospital can not be prevented even with the greatest possible care. Once it occurs, subsequent

TABLE 4. *Results of vaccination and follow-up in individual high risk children*

Case No.	Age y.m.	Diagnosis	Period after vaccination y.m.	Viral dose (PFU)	On vaccination		
					Antibody response	Varicella skin test	Clinical reaction
1.	7	NS	3-10	1,000	—	‡	—
2.	3	ALL	3-10	1,000	+	ND	—
3.	3	NS	3-10	1,000	+	ND	—
4.	0-8	Pure red cell anemia	3-10	1,000	+	ND	—
5.	4	AP	3-10	1,000	—	ND	E (+)
6.	5	Pure red cell anemia	3-10	1,000	+	ND	—
7.	0-9	ITP	3-6	1,000	+	ND	—
8.	4	ALL	3-4	1,000	+	ND	E (+) F (+)
9.	6	NS	3-3	1,000	+	ND	—
10.	3	NS	3-0	1,000	+	ND	—
11.	5	NS	2-11	3,000	+	ND	E (+)
12.	13	NS	1-9	500	+	ND	E (+)
13.	11	NS	1-5	500	+	ND	E (+)
14.	4	NS	1-5	500	—	‡	E (+)
15.	4	NS	1-5	500	+	ND	E (+)
16.	4	NS	1-5	500	—	+	E (+) F (+)
17.	2	NS	1-5	500	+	ND	E (+) F (+)
18.	2	ALL	1-2	500	+	ND	E (+) Herpes zoster
19.	1	AP	1-1	500	+	ND	—
20.	5	NS	1-1	500	+	ND	E (+) F (+)
21.	4	Urticaria	1-1	500	+	ND	—

At the follow-up			Immunosuppressants			
Antibody titer (IAHA)	Varicella skin test	Immuno-suppressive therapy	Drugs and total dose (mg) used before vaccination		Drugs and total dose (mg) used from vaccination till follow-up	
4	≡	Y	P 9060	Cph1330	P 12270	Cph10850
16	++	N	P 3030 6MP13550 AraC100	MTX80 VCR135	MTX60 VCR6	P 770
4	≡	N	P 5035			P 805
16	++	Y	P 2175			P 6045
128	≡	N	P 1163			P 542
8	—	Y	unknown			P 8867
128	≡	N	P 1000			
32	≡	Y	P 1285 6MP2000	MTX40 VCR12	P 2310 6MP41650 rad2000	MTX180 VCR18
128	≡	N	P 7813			P 875
<2 (FAMA) 4	≡	N	P 120			P 4843
<2 (FAMA) <2	≡	Y	P 320		P 20100	Cph9100
4	—	Y	P 6200			P 7590
128	++	Y	P 14190	Cph15880	P 7740	Cph16800
16	≡	Y	P 3225			P 5405
4	≡	Y	P 7035		P 5895	Cph4105
4	+	Y	P 17725	Cph8750	P 5704	Cph7100
8	++	Y	P 160			P 5523
<2 (FAMA) <2	+	Y	P 1380 MTX22.5	VCR4.5	P 1605 6MP8975 DM232 MTX35	AraC1375 Asp12000 rad2000
128	+	N	P 500			P 675
16	≡	N	P 350			P 1140
4	≡	N	P 658			P 45

Continued . . .

TABLE 4. *Continued.*

Case No.	Age y.m.	Diagnosis	Period after vaccination y.m.	Viral dose (PFU)	On vaccination		
					Antibody response	Varicella skin test	Clinical reaction
22.	0-11	Neuroblastoma	0-6	350	+	ND	E (+)
23.	3	NS	0-6	350	+	ND	(-)
24.	3	NS	0-6	350	+	ND	(-) Herpes zoster
25.	1	Allergic GEpathy	1-5	350	-	+	(-)
26.	0-5	MCLS	Till varicella infection 0-6	1,000	+	ND later varicella	-
27.	2	ALL	Till varicella infection 3-6	1,000	+	ND	E (+) later varicella
28.	2	Neuroblastoma	Till varicella infection 2-0	3,000	+	ND	E (+) F (+) later varicella
29.	0-4	Infantile spasms		3,000	+	ND	E (++) F (##) Moved
30.	0-9	Hepatoblastoma		1,000	+	ND	- Died
31.	2	ALL	Till varicella infection 0-11	500	+	ND	- later varicella Died
32.	2	ALL		500	+	ND	-
33.	9	NS		5,000	+	ND	-
34.	9	Malignant lymphoma		750	+	ND	E (##) F (++)

Abbreviations

NS: Nephrotic syndrome.
 ALL: Acute lymphoblastic leukemia.
 ITP: Idiopathic thrombocytopenic purpura.
 AP: Anaphylactoid purpura.
 E: Eruption.
 F: Fever.

P: Prednisolone.
 6MP: 6-mercaptopurine.
 Cph: Cyclophosphamide.
 MTX: Methotrexate.
 Y: yes.
 N: no.

At the follow-up			Immunosuppressants			
Antibody titer (IAHA)	Varicella skin test	Immuno-suppressive therapy	Drugs and total dose (mg) used before vaccination		Drugs and total dose (mg) used from vaccination till follow-up	
16	++	N	P 610	Cph9650	P 850	Cph2300
16	++	N	P 40		P 1640	
32	+	Y	P 2115		P 7685	Cph4220
4	+	Y	P 4325			
		N	P 250		P 50	
		Y	P 1515 6MP3600	MTX20 rad2950	P 1680 MTX192	VCR20
		N	VCR11.9 rad2950	Cph4560	Cph4200	VCR21
ACTH5						
			5FU375	MMC3.75		
		Y	P 705 6MP3420	VCR6	P 1225 6MP10800	VCR4.8 MTX134
			P 1585 L-Asp70,000 MTX12	VCR3.75 6MP2500 rad2,000 r		
			P 1585 L-Asp70,000 MTX12	VCR3.75 6MP2500 rad2,000 r		
			P 1445 6MP5850 rad2,400 r	VCR75 Cph2,200		

AraC: Cytosine arabinoside.
VCR: Vincristine.
MMC: Mitomycin C.
5FU: 5-Fluorouracil.
DM: Daunomycine
NT: Neutralization Test.

IAHA: Immune Adherence Hemagglutination Test.
Asp: L-Asparaginase.
rad: radiation.
ND: Not done.

nosocomial infections arise because of (a) the long incubation period during which the infection is undetectable, (b) communicability of the disease even before onset of symptoms, (c) the high contagiousness of the disease, (d) the absence of effective prophylactic or therapeutic measures, and (e) the fact that zoster immune globulin (ZIG) or plasma (ZIP) is not usually available in emergency.

3. High-risk, or immunocompromised children always have the chance of varicella infection during visits to the outpatient clinic, at school, kindergarten or nursery, or from siblings at home, as they often gain remission and prolonged survival due to recent progress in treatment.

For the above-mentioned reasons, we are faced with the danger of nosocomial varicella outbreaks in the pediatric ward with 38 beds in our hospital. Isolation of cases failed to prevent subsequent infections within the ward. Intravenous administration of cytosine arabinoside to patients seems to make the course milder, but cannot stop subsequent infections (Katsushima et al., 1976). Since the introduction of live vaccine in August 1976, however, there have been no successive cases of varicella infection after nosocomial outbreaks, and the vaccine has been found to be safe for protection of high-risk children from varicella.

In view of the dramatic protective effect and innocuousness of the vaccine observed in our series on the first two occasions of urgent vaccination, we have set the following criteria for varicella vaccination and have followed them since 1977 with satisfactory results.:

1. High-risk children should be vaccinated when in remission.
2. If a high-risk patient comes in contact with varicella, he (or she) should promptly receive vaccination.
3. Vaccination should be undertaken promptly when a varicella outbreak seems imminent, i.e. when a case of varicella occurs in a sibling of a hospitalized patient.
4. Once there is a case of varicella among

hospitalized children, all patients should be checked for susceptibility to infection and vaccinated, except those who are to be discharged shortly.

5. Susceptible siblings of hospitalized patients who visit the ward should be vaccinated.
6. Physicians, nurses and others with susceptibility to varicella who are engaged in medical care of children should also be vaccinated.

In addition, healthy children in the day nursery for children of hospital staff and other healthy children whose guardians wish them to be vaccinated, have been vaccinated after receiving informed consent from parents or guardians.

Asano et al. (1977a, b) reported that 18 children including high-risk patients were effectively protected from varicella infection by immediate vaccination on the occasion of outbreaks of varicella in hospital. They reported also a protective effect against development of the disease in household contacts by vaccination within 3 days after exposure, and a satisfactory antibody response with negligible adverse reactions even in high risk patients.

In two institutional outbreaks of varicella, Baba et al. (1978) conducted controlled trials on the vaccine, observing protection of vaccinated subjects and reporting the potential usefulness of the varicella skin reaction as a rapid diagnostic test for detection of susceptible individuals.

Izawa et al. (1977) observed reasonable effectiveness and safety of varicella vaccine in all 11 children with acute leukemia and 6 children with malignant solid tumors studied. Clinical trials by Nakagawa and Katsushima (1978) also demonstrated the efficacy of the vaccine in a series of 8 cases of acute leukemia. Ha et al. (1980) reported that the incidence of a clinical reaction was about 70% in children with acute leukemic who had received vaccination without suspension of chemotherapy.

Since the report of Asano et al. (1977a),

many studies in Japan, including our previous studies have shown the protective effect of emergency vaccination in the ward (Katsushima et al., 1977; Mizuno et al. 1977; Takeuchi et al. 1977; Goto et al. 1978; Ueda et al. 1978; Watanabe et al. 1980). All these studies confirmed the protective effect of vaccination. In the series reported here, vaccinations within 5 days after the onset of varicella in the hospital, were satisfactory in preventing subsequent infection. There have been no problems about side effects of the vaccine.

In the present study both eruptions and fever (≥ 37.5 C) were significantly less frequent in the non-high risk group (8.0 and 0.9%, respectively) than in the high risk group (47.1 and 17.6%). Rashes tended to develop later (16–35 days after vaccination) in the high risk group. The reason why clinical reactions occurred more frequently in our study than in those of others remains uncertain. Possibly natural infections were modified by vaccination, because in our study mainly cases were vaccinated in emergency. It also seems likely that mild forms of eruption escaped notice in previous studies. The mildest cases had only one vesiculoid lesion or several erythematous papules.

There are few reports of follow-up studies on the protective effect of vaccination against varicella infection. Asano and Takahashi (1977) reported that the serum antibody titer elicited by vaccination is lower (approximately 1/4 to 1/8) than that brought about by natural varicella infection, and that continuation of immunity evoked by vaccination is an important problem since high-risk patients continue to receive immunosuppressive therapy after vaccination. Kamiya et al. (1977) and Baba et al. (1978) reported that a positive reaction was obtained in the varicella skin test after vaccination as in natural infection, indicating acquisition of cell-mediated immunity by vaccination. Asano and Takahashi (1978) found that 98% of 181 individuals vaccinated were seropositive for neutralizing antibody two years later, and that of these, 80 subjects

came in contact with varicella or herpes zoster patients during the two-year period but only one of them developed varicella and showed only a mild course. This incidence indicates a significant preventive efficacy of the vaccine. They also obtained evidence of re-elevation of the serum antibody titer as a booster effect consequent on contact with varicella. A follow-up study by Takeuchi and Kawakami (1979) revealed mild varicella infection in 13 (7.3%) of a total of 179 healthy children in the period from 3 to 5 years after vaccination. They found that 3 of 34 subjects examined for serum antibody by the IAHA test 4.5 to 5 years after vaccination had become negative. Seven subjects tested in their series gave a positive varicella skin reaction including one who was seronegative. In follow-up observations on 34 vaccinated children with acute lymphatic leukemia, Kamiya (1979) observed no case of occurrence of apparent varicella infection during 21 occasions for infection. Herpes zoster occurred in 3 of 26 cases studied, as compared with 4 of 35 cases of leukemia with natural varicella infection (Takahashi et al., 1981).

In our investigation, the children were followed by estimation of their serum antibody titer and by a concomitant varicella skin test 6 months to 3 years and 10 months after vaccination. Of 25 high-risk patients who could be followed up, dissociation of humoral immunity and cellular immunity was noted in 4 patients, though neither immunity became negative in any of them. Two of them escaped infection in spite of contact with varicella. One other patient, who was seropositive and gave a negative skin test developed herpes zoster. Dissociation was seen in only 1 of 24 non-high risk subjects studied, who gave positive reaction for serum antibody and a negative skin test reaction. Thus a higher percentage of these subjects showed sustained immunity. Moreover the exceptional subject was protected from infection in spite of contact with varicella. The varicella skin test is of value not only in ascertaining susceptibility to in-

fection in emergency vaccination, as described by Baba et al. (1978), but also in detecting sustained immunity in follow-up surveys.

In our study, 13 of 32 high risk patients came in contact with varicella, and 4 of them eventually developed symptoms of infection. Symptoms were mild in 3 cases and moderate in 1 case. Of 79 non-high risk subjects, 33 came in contact with varicella and 2 developed very mild varicella. It would be reasonable to infer from these findings that, in mild cases, basal immunity against varicella was well retained preventing severe infection. The case of moderate infection was a patient with relapse of ALL with meningeal and testicular infiltration receiving high doses of immunosuppressants and radiation therapy. Herpes zoster was encountered in 2 cases, but was mild in both. It is certain that the vaccine was "taken" in these cases, because they exhibited a significant rise in serum antibody titer after the vaccination, occasionally with development of a rash. Therefore, the occurrence of clinical infection after vaccination suggest subsequent decrease in immunity to varicella. Thus in high risk children, it seems advisable to make checkups on its immune status periodically and to give a booster injection whenever it seems necessary since these children often need continued immunosuppressive therapy even after vaccination. Patients requiring vaccination can easily be detected by the varicella skin test, as cell-mediated immunity appears to play an important role in protection against varicella (Gershon, 1980).

According to Kamiya (1976) mortality from varicella is 30.2% in children with leukemia

and 5.7% in children in remission of leukemia in Japan. In the United States, 30% of infected children with malignancies including leukemia develop severe varicella with fatality in 7% (Feldman et al. 1975). There have been reports emphasizing the danger of severe varicella infection not only in children with malignant tumors but also in those on corticosteroids or immunosuppressive drugs (Pinkel, 1961; Finkel, 1961; Rifkind, 1966; Scheinman and Stamler, 1969; Gershon et al., 1972; Schrimpf et al., 1972). In this paper, 31 children receiving immunosuppressive therapy at our hospital experienced natural varicella infection. The infection was mild in 20 of these children who were infected before onset of underlying diseases, but was moderate or severe in 6 of 11 children who were infected after the development of underlying diseases. Three children had herpes zoster, which was severe in 2, resulting in prolonged residual corneal ulceration in one. These observations reconfirm that in about half the high-risk children in which natural infection with varicella occurs, the course is moderate or severe irrespective of whether the children are under treatment or in remission.

As indicated by results of immunization with the live attenuated varicella vaccine and follow-up studies, the clinical benefit of vaccination is unquestionable, especially in high risk children. The complete prevention of nosocomial successive infections by emergency vaccination has relieved patients, medical doctors and nursing staff from all the hazards and troubles inherent in varicella infections in the pediatric ward.

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