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## COMPLICATIONS OF SMALLPOX VACCINATION, 1968\*

### National Surveillance in the United States

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**Abstract.** In 1968, 572 persons in the United States had confirmed vaccination complications. Of these, 82.5 per cent had received Vaccinia Immune Globulin. Sixty-eight per cent of the patients were primary vaccinees, 7 per cent were revaccinees, 20 per cent acquired vaccinia not by vaccination but by contact, and 5 per cent had unknown histories of vaccination. There were nine deaths: four caused by postvaccinial encephalitis, four associated with vaccinia necrosum, and one caused by eczema vaccinatum. There were 74 complications and one

death per 1,000,000 primary vaccinations. Morbidity and mortality rates were highest for infants, with 112 complications and five deaths per 1,000,000 primary vaccinations. Eczema vaccinatum was more severe for contacts than for vaccinees. Although the risk with revaccination is less than a tenth that with primary vaccination, vaccinia necrosum develops in patients with immunologic disorders whether or not they have been previously vaccinated. These estimates, based on surveillance, must be considered minimal.

**I**N 1967 Neff and others presented results of the first studies on the incidence of complications of smallpox vaccination in the United States since Vaccinia Immune Globulin and thiosemicarbazones came into general use.<sup>1,2</sup> They found that complications occurred most frequently in children under one year of age. The United States Public Health Service and other groups subsequently recommended that primary vaccination in the United States be deferred to the second year of life. These studies were retrospective; cases that occurred in 1963 were studied in 1964 and 1965. Clinical and epidemiologic details of some cases had been lost.

This study and its companion study<sup>3</sup> were designed to gather more complete information on the risks of smallpox vaccination, with the use of multiple sources of reports of complications. Patients with suspected complications of smallpox vaccination in 1968 were identified through several sources in addition to the American Red Cross, which furnished 99 per cent of the reports of 1963 complications. An estimate of the number of persons vaccinated during 1968 was obtained from the National Immunization Survey.

#### MATERIALS AND METHODS

##### Detection of Suspected Complications

Patients with suspected complications of smallpox

vaccination were detected through seven sources. The first was the American Red Cross Vaccinia Immune Globulin distribution system, which supplied the names of physicians or patients given Vaccinia Immune Globulin (VIG). The physicians were asked for clinical and epidemiologic information on their patients shortly after receiving VIG. Secondly, the several consultants to the Red Cross VIG program supplied the names of patients suspected of having complications of vaccination who came to their attention but did not receive VIG. Thirdly, state and territorial epidemiologists supplied the names of several patients with complications although these conditions are not all officially reportable. Fourthly, the Burroughs-Wellcome Company supplied information on patients receiving thiosemicarbazone (Marborant). Fifthly, companies producing smallpox vaccine made available files on complications allegedly attributable to their products. Sixthly, the Encephalitis Surveillance Unit of the National Communicable Disease Center made available the reports of postvaccinial encephalitis which they received from state health departments. Seventhly, the Viral Exanthems Unit of the National Communicable Disease Center reported specimens submitted to its diagnostic laboratory for confirmation of vaccinia.

\*From the Domestic Branch of the Smallpox Eradication Program, National Communicable Disease Center.

†Inclusion of trade names is for identification only and does not imply endorsement by the Public Health Service of the U. S. Department of Health, Education, and Welfare.

Patients receiving VIG from the American Red Cross during 1968 represented 82.5 per cent of the cases in this study. The Red Cross VIG distribution system and its list of consultants have been in existence for eight years and are published in many standard therapeutic guides.<sup>4,5</sup> For the last four years, approximately 8500 to 9500 ml of VIG have been distributed each year. In 1968, 9385 ml of VIG were distributed to 563 patients. There were 119 patients reported who did not receive VIG: 69 were reported by the Red Cross VIG consultants who learned of the patients but did not release VIG for them, and the other 50 were reported by drug companies, the Encephalitis Surveillance Unit of the National Communicable Disease Center and miscellaneous sources.

Each patient's clinical record was obtained and analyzed by us, and in several the diagnosis was changed. The cases were classified according to the definitions used by Neff et al.<sup>1</sup> Pertinent clinical and epidemiologic information on each patient was summarized on a standard form. Complete information was obtained on all but 11 of the 682 patients. Of the 671 patients for whom clinical data were available, 572 were treated for a bona fide complication of smallpox vaccination. Of the others, 22 with eczema, 18 with other skin conditions, 18 with varicella and six with various conditions causing decreased resistance to infections were given VIG

prophylactically and had no vaccinal complications. Thirty-five cases were found to be unrelated to vaccinia; most of these were caused by herpes, varicella or drug reactions.

#### Population Vaccinated during 1968.

In 1968 the National Bureau of the Census, in cooperation with the National Communicable Disease Center, conducted a survey designed to evaluate the immunization status of the United States population.<sup>6</sup> This survey was based on a sample of 35,000 households comprising approximately 100,000 persons in 50 states and the District of Columbia. The standard error of estimate for numbers of smallpox vaccinations was less than 1 per cent for each age group.

An estimated 5,594,000 primary vaccinations and 8,574,000 revaccinations were done in 1968 (Table 1). Over half the primary vaccinations were in children under the age of five years; most revaccinations were in persons over the age of 10 years. The estimated total number of vaccinations in the United States during this 12-month period was 14,168,000. There was no major shift in the number or distribution of smallpox vaccination between 1963 and 1968.

#### RESULTS

The vaccination status of the 572 patients with

TABLE 1. Complications of Vaccination by Diagnosis and Vaccination Status.

AGE (YR)	NO. OF VACCINATIONS	NO. OF CASES						
		POSTVACCINAL ENCEPHALITIS	VACCINIA NECROSUM	ECZEMA VACCINATUM	GENERALIZED VACCINIA	ACCIDENTAL INFECTION	OTHER	TOTALS
<b>Primary vaccinations*:</b>								
<1	614,000	4 (3)†	0	5	43	7	10	69
1-4	2,733,000	6	1	31	47	91	40	216
5-9	1,553,000	5 (1)†	1 (1)†	11	20	32	8	77
10-14	295,000	0	0	1	2	1	1	5
15-19	111,000	0	1 (1)†	2	3	2	0	8
20+	288,000	1	2	7	13	4	5	32
Unknown	0	0	0	1	3	5	2	11
Totals	5,594,000	16 (4)†	5 (2)†	58	131	142	66	418*
<b>Revaccinations:</b>								
<1	0	0	0	0	0	0	0	0
1-4	478,000	0	0	1	0	1	1	3
5-9	1,643,000	0	1 (1)†	4	1	3	2	11
10-14	1,440,000	0	0	1	0	0	0	1
15-19	1,217,000	0	1	2	0	0	0	3
20+	3,796,000	0	4 (1)†	0	9	3	6	22
Totals	8,574,000	0	6 (2)†	8	10	7	9	40
<b>Contacts:</b>								
<1	0	0	0	4	0	9	1	14
1-4	0	0	0	38 (1)†	1	16	6	61
5-9	0	0	0	8	0	7	0	15
10-14	0	0	0	0	0	2	0	2
15-19	0	0	0	1	0	1	0	2
20+	0	0	0	9	1	9	0	19
Unknown	0	0	0	0	0	0	1	1
Totals	0	0	0	60 (1)†	2	44	8	114
Grand totals	14,168,000	16 (4)†	11 (4)†	126 (1)†	143	193	83	572

\*Includes 31 patients with unknown vaccination status.

†Deaths attributable to vaccinia shown in parentheses.

vaccine-associated illnesses is shown in Table 1. Of these, 387 (68 per cent) were known to have received primary vaccinations, and 40 (7 per cent) revaccinations. Of the 36 given revaccinations whose previous vaccination dates were known, 20 (56 per cent) had been vaccinated more than 10 years previously. One hundred and fourteen (20 per cent) were not vaccinated at all, but acquired vaccinia from a recently vaccinated playmate or sibling. The vaccination status of 31 patients was unknown. Because of the preponderance of primary vaccinations over revaccinations among patients whose vaccination histories were known (10:1), these 31 patients are arbitrarily grouped with those receiving primary vaccinations throughout this report, bringing the total to 418.

#### Postvaccinial Central-Nervous-System Disease

"Postvaccinial central-nervous-system disease" includes a variety of disorders manifesting signs and symptoms of classic encephalitis, encephalopathy, demyelination or neuropathy. These entities are attributed to vaccinia because of their temporal relation to smallpox vaccination and because of the absence of any other etiology. The pathology of these diseases is similar to that seen with other viral central-nervous-system disorders.

Table 2 is a line listing of the 16 patients with postvaccinial central-nervous-system disease. Nearly every patient had fever at the onset, and in a large proportion of them, convulsions developed. Nearly half the patients became comatose during their illness. Laboratory tests were of little value except to exclude other causes. All but two patients had lumbar punctures done no later than three days after the onset of the illness. Over half showed no cerebrospinal-fluid abnormality, and the others showed only a modest increase in cells (10 to 520

cells per cubic millimeter) and protein (50 to 140 mg per 100 ml).

None of the 16 patients had underlying illness known before vaccination or found during or after hospitalization. Four survivors had residua. One was blind for two months after onset and now is considered to be a hyperirritable, brain-damaged child. Another is thought to have psychiatric difficulties. A third may have a seizure disorder. The patient with postvaccinial myelitis is quadriplegic and requires continued institutional care.

Despite supportive therapy, each of the four patients who died had a fulminant course lasting for one to six days. Post-mortem examination revealed only severe cerebral swelling in two patients and diffuse petechial hemorrhage over the entire cortex in another. The fourth showed diffuse cerebral edema, focal areas of demyelination and marked lymphocytic perivascular cuffing with glial proliferation. Post-mortem examination ruled out other pathologic changes such as bacterial meningitis, tumor or tuberculosis. Clinically and pathologically these cases fit the established criteria for postvaccinial central-nervous-system disease.<sup>7-9</sup>

#### Vaccinia Necrosum (Progressive Vaccinia)

Table 3 lists the patients with vaccinia necrosum detected in 1968. Three patients had diseases or conditions not commonly associated with immunologic deficiency or vaccinia necrosum: a child with microcephaly and cerebral palsy; a man with a depressed immunoglobulin M while he was receiving anticoagulants; and a woman receiving antimetabolite therapy for psoriasis.

The 11 patients all demonstrated progression of their vaccination sites and systemic symptoms such as fever. Seven patients had metastatic lesions on varying parts of the body. The disease was diag-

TABLE 2. Postvaccinial Central-Nervous-System Disease.

AGE	DIAGNOSIS	VACCINATION STATUS	VACCINATION TO ONSET (DAYS)	PRESENTING SIGNS & SYMPTOMS	OUTCOME
6 mo	PVE*	Primary	14	Fever, somnolence	Death
7 mo	PVE	Primary	9	Vomiting, stiff neck, convulsions	Death
9 mo	PVE	Primary	17	Apnea, Jacksonian seizure, coma	Death
9 mo	PVE	Primary	13	Vomiting, irritability, coma	Hyperirritability
14 mo	PVE	Primary	10	Fever, opisthotonos, coma	Recovery
16 mo	Guillain-Barré syndrome	Primary	10	Fever, 6th-nerve paralysis	Recovery
17 mo	PVE	Primary	6	Fever, convulsions	Recovery
18 mo	PVE	Primary	9	Fever, hyperactivity, convulsions	Recovery
2 yr	PVE	Primary	9	Focal motor seizure	Possible seizure disorder
2 yr	PVE	Primary	12	Personality change, fever, confusion	Possible psychiatric disturbance
5 yr	Postvaccinial myelitis	Primary	10	Fever, headache, paraparesis	Quadriplegia
5 yr	PVE	Primary	7	Fever, convulsion	Recovery
5 yr	PVE	Primary	14	Headache, stupor, coma	Death
6 yr	PVE	Primary	15	Fever, lethargy, stiff neck	Recovery
6 yr	PVE	Primary	19	Fever, headache, convulsions	Recovery
42 yr	PVE	Unknown	13	Fever, malaise, coma	Recovery

\*Postvaccinial encephalitis or encephalopathy.

TABLE 3. *Vaccinia Necrosum*.

AGE	SEX	VACCINATION STATUS	UNDERLYING DISEASE	VIG	THIOSEMICARBAZONE	OUTCOME
22 mo	M	Primary	Bruton's hypogammaglobulinemia	+	+	Recovery
7 yr	M	Primary	Microcephaly with cerebral palsy	+	0	Death
16 yr	F	Primary	Aplastic anemia	+	+	Death
58 yr	F	Primary	Psoriasis on antimetabolite	+	0	Recovery
45 yr	F	Unknown	Hodgkin's disease	+	0	Recovery
6 yr	M	Revaccination	Acute myelogenous leukemia	+	+	Death
19 yr	F	Revaccination	Hodgkin's disease	0	+	Recovery
26 yr	F	Revaccination	Hodgkin's disease	+	0	Recovery
59 yr	M	Revaccination	Ischemic heart disease on anticoagulants	+	0	Recovery
62 yr	F	Revaccination	Chronic lymphocytic leukemia	+	0	Death
64 yr	M	Revaccination	Lymphoma	+	0	Recovery

nosed as early as seven days and as late as 49 days after vaccination.

Four patients died. One was a 62-year-old woman with chronic lymphatic leukemia, vaccinated for severe recurrent herpes simplex, who was hospitalized over 60 days before dying of overwhelming infection and debilitation. A six-year-old boy with acute myelogenous leukemia in remission had an exacerbation of his leukemia while he was responding to vaccinia necrosum therapy and died. The child with microcephaly died after a fulminant course of under one month. The remaining death occurred in a 16-year-old girl with previously undetected aplastic anemia who died less than a month after vaccination despite therapy with VIG, thiosemicarbazone and idoxuridine.

#### Eczema Vaccinatum

There were 126 cases of eczema vaccinatum (Table 1). Eczema vaccinatum developed in 14 patients whose eczema was in complete remission at the time of vaccination. Four patients' eczema had been inapparent in the areas of skin that became involved by vaccinia.

Eczema vaccinatum in contacts was usually more severe than in patients who were vaccinated themselves. Among the vaccinated patients, 59 per cent were hospitalized, with a mean hospital stay of seven and six-tenths days. Among those who acquired vac-

cinia via contact, 80 per cent were hospitalized, with a mean hospital stay of 12.9 days (Table 4).

The contact that resulted in transmission of vaccinia was usually of an intimate nature. Children acquired vaccinia from siblings, and parents from their children. The interval from vaccination of the contact to onset of eczema vaccinatum was determined in 40 (67 per cent) of the 60 cases (Table 5). In 63 per cent of the contacts, the interval was over 10 days, suggesting that in most cases the fully developed vaccination lesion was the source of vaccinia.

Seven of the patients with eczema vaccinatum received thiosemicarbazone as well as VIG. Six were contact cases of eczema vaccinatum. These patients were all hospitalized and all severely ill. A 22-year-old woman, five months pregnant at the time, acquired vaccinia from her child. Severe eczema vaccinatum developed, and she was treated with thiosemicarbazone and VIG. She had a spontaneous abortion eight days after the onset of her illness and three days after the start of thiosemicarbazone therapy. There was only one death that was attributable to eczema vaccinatum. This patient had contact-acquired vaccinia and did not receive thiosemicarbazone.

#### Generalized Vaccinia

There were 143 cases of generalized vaccinia

TABLE 4. *Days of Hospitalization Attributable to Vaccination Complications, According to Diagnosis.*

DIAGNOSIS	NO. OF CASES	HOSPITALIZED CASES			
		NUMBER	RANGE (DAYS)	MEAN (DAYS)	TOTAL DAYS IN HOSPITAL
Postvaccinal encephalitis	16	16*	1-60	11.3	180
Vaccinia necrosum	11	8	6-84	37.5	300
Eczema vaccinatum (contact)	60	48	2-41	12.9	621
Eczema vaccinatum (vaccinated)	66	39	2-18	7.6	297
Generalized vaccinia	143	42	2-23	5.8	245
Accidental infection	193	56	2-16	5.4	305
Other	83	29	1-21	6.8	197
Totals	572	238	1-84	9.0	2145

\*1 child permanently hospitalized has arbitrarily been assigned 60 days' hospitalization time for purposes of these calculations.

TABLE 5. Complications of Vaccinations, According to Interval between Vaccination and Onset.

DIAGNOSIS	NO. OF CASES ACCORDING TO INTERVAL									TOTALS
	1-2 DAYS	3-4 DAYS	5-6 DAYS	7-8 DAYS	9-10 DAYS	11-12 DAYS	13-14 DAYS	15+ DAYS	UNKNOWN	
Postvaccinial encephalitis	0	0	1	1	6	1	4	3	0	16
Vaccinia necrosum	0	0	0	3	0	2	0	6	0	11
Eczema vaccinatum (contact)	0	1	3	5	6	4	5	16	20	60
Eczema vaccinatum (vaccinated)	1	9	4	17	17	3	3	4	8	66
Generalized vaccinia	4	8	14	33	33	15	7	14	15	143
Accidental infection	2	15	20	51	38	13	11	10	33	193
Other	1	6	8	17	21	9	5	5	11	83
Totals	8	39	50	127	121	47	35	58	87	572

(Table 1). Most patients had mild illnesses, and only 29 per cent were hospitalized (Table 4).

The clinical spectrum of generalized vaccinia was broad. Eleven of the patients had an underlying condition, including two with dysgammaglobulinemia, four with allergies, one with steroid therapy and four with miscellaneous skin diseases. In most cases the clinical descriptions obtained were insufficient to distinguish patients with vesicular or pustular rashes from those with maculopapular or erythema-multiforme-like rashes. There were no deaths, and no patients suffered serious sequelae.

#### Accidental Infection

There were 193 cases of accidental infection (Table 1). The most common form of autoinoculation was accidental infection of the eye, which occurred in 143 of the 193 cases. In most patients, the lesions occurred in the eyelids or conjunctiva and were noted five to 12 days after vaccination (Table 5). The cornea was involved in seven patients. Sixteen of the 143 patients with ocular vaccinia received idoxuridine with or without VIG.

Other accidental implantations occurred at various sites around the body. Although they often caused discomfort, they did not leave serious residua.

#### Other Complications

There were 83 cases with other types of vaccination complications (Table 1). Erythema multiforme accounted for 48 of these cases, including nine patients with the Stevens-Johnson type of bullous erythema multiforme. Unusually large and painful primary takes, with or without bacterial superinfection, accounted for 13 cases. Superinfection of miscellaneous skin rashes and burns occurred in 18 patients.

Five patients had particularly unusual complications. A child with dormant idiopathic thrombocytopenic purpura had a recrudescence three days after primary vaccination. In another child toxic epidermal necrolysis developed three days after primary vaccination. A woman receiving steroid therapy because

of low blood sugar had secondary implants of vaccinia on her face. In a 47-year-old man with no previous vaccination "take" generalized vaccinia and substernal pain developed 10 days after primary vaccination; serial electrocardiograms give evidence of a transient pericarditis. Finally, a two-year-old child received hot-water burns on 25 per cent of his body two days after primary vaccination. Two weeks after he was hospitalized, satellite lesions developed around the burn sites, which were healing satisfactorily. One day later he died of cardiac and respiratory arrest. Post-mortem examination revealed severe bacterial pneumonia, and the role of vaccinia in his death is not clear.

#### Hospitalization Duration Attributable to Vaccinia

The relative severity of vaccination complications is reflected in the number of hospital days attributable to them. These are shown in Table 4. Of the 572 patients, 238 (including the nine who died) were hospitalized for 2145 days. The patients with vaccinia necrosum were hospitalized for a total of 300 days. The days needed to treat the underlying diseases of the patients with vaccinia necrosum are difficult to separate from the days needed to treat the vaccinia; only the days during which the lesions of vaccinia necrosum were present are counted here.

#### Complication Rates

The incidence rates for each complication per 1,000,000 vaccinated persons are presented according to age group and vaccination status in Table 6. The data from which the rates are calculated are shown in Table 1. The rates underestimate the morbidity caused by smallpox vaccination by neglecting 114 cases that occurred in contacts and could not be assigned to either the primary or the revaccination category.

Vaccination complications were far more common among persons receiving primary vaccination than among those revaccinated. There were 74.7 complications per 1,000,000 primary vaccinations and 4.7

TABLE 6. Complications Associated with Smallpox Vaccination—Cases per 1,000,000 Vaccinations.\*

AGE (YR)	POSTVACCINAL ENCEPHALITIS	VACCINIA NECROSUM	ECZEMA VACCINATUM	GENERALIZED VACCINIA	ACCIDENTAL INFECTION	OTHER	TOTAL
Primary vaccination:							
<1	6.5	—	8.1	70.0	11.4	16.3	112.4
1-4	2.2	0.4†	11.3	17.2	33.3	14.6	79.0
5-9	3.2	0.6†	7.1	12.9	20.6	5.2	49.6
10-19	—	2.5†	7.4	12.3	7.4	2.5†	32.0
20+	3.5†	6.9†	24.3	45.1	13.9	17.4	111.1
Totals	2.9	0.9	10.4	23.4	25.4	11.8	74.7
Revaccination:							
<1	—	—	—	—	—	—	—
1-4	—	—	2.1†	—	—	2.1†	4.2†
5-9	—	0.6†	2.4	0.6†	1.8†	1.2†	6.7
10-19	—	0.4†	1.1	—	—	—	1.5
20+	—	1.1	—	2.4	0.8†	1.6	5.8
Totals	—	0.7	0.9	1.2	0.8	1.0	4.7

\*Omits 114 patients with contact-acquired vaccinia.

†Rate computed on basis of 3 cases or less.

complications per 1,000,000 revaccinations. The persons at highest risk were infants under one year of age, who experienced 112.4 complications per 1,000,000 primary vaccinations. The milder complications, principally generalized vaccinia and "other" complications, accounted for most of this increase in infants under one year of age. The rates for the life-threatening illnesses of post-vaccinial encephalitis and vaccinia necrosom were 2.9 and 0.9 respectively per 1,000,000 primary vaccinations. There were three deaths in the 614,000 infants under one year of age given primary vaccination. No deaths resulted from primary vaccination of children between one and five. The overall death rate was one per 1,000,000 primary vaccinations and one per 4,000,000 revaccinations, and one death occurred in a previously unvaccinated contact of a person given primary vaccination.

#### DISCUSSION

This study has several differences from and many similarities to the study of vaccination complications occurring in 1963. The current study uncovered many more cases, principally by using additional sources of reports. The overall rates are therefore higher than those reported for 1963. Patients were evaluated shortly after the occurrence of their illnesses, and only a small percentage had major unknown items in their clinical or epidemiologic history. The proportion of all complications labeled "generalized vaccinia" was greater in the 1963 report. We believe that more complete clinical descriptions would have enabled us to diagnose more of the 1963 complications as erythema multiforme.

The statistics presented here for the frequency of smallpox-vaccination complications should be considered minimal estimates of the risks of vaccination. Although several case-detection methods were employed, a few severe and many minor complications may not have been detected. Studies of 1963 vaccination complications in four states demonstrated

that direct survey techniques uncover at least 10 times as many cases of generalized vaccinia, accidental infections and mild eczema vaccinatum as the VIG distribution system detects.<sup>2</sup>

The surveys for 1968 vaccination complications conducted in 10 states confirm that finding and clarify the reliability of the national surveillance data.<sup>3</sup> Incidence rates for clinically less severe complications (accidental infection, generalized vaccinia and erythema multiforme), calculated from data gathered by systematic surveys, are 10 or more times higher than the rates presented in this paper. Most of the life-threatening complications (vaccinia necrosom, encephalitis and severe eczema vaccinatum) occurring in the 10 states, on the other hand, were detected by the national surveillance program. A small number of unusual complications, including a case of fetal infection with vaccinia, were not detected by the national surveillance techniques.

The incidence rates calculated for "generalized vaccinia" are difficult to interpret. Many of the patients given this diagnostic label had rashes that were not clinically well defined. Some simply had maculopapular rashes. Other patients were not closely followed, so that the evolution and nature of their rashes are not clear. A variety of classifications of rashes occurring after vaccination have been proposed.<sup>10-11</sup> We have preferred to call all such rashes except erythema multiforme "generalized vaccinia." It should be understood that "generalized vaccinia" is a heterogeneous group.

Smallpox vaccination causes production of both specific antibodies and cellular or delayed-hypersensitivity phenomena. Vaccinia necrosom results when the immunologic mechanisms fail, generally because some underlying disease or condition impairs the production or function of immunologically competent lymphocytes.<sup>12,13</sup> The presence of these underlying abnormalities outweighs the immunity that may persist from previous vaccinations. In this respect vaccinia necrosom differs from other vaccination complications in its potential for developing

in those given revaccination as well as those receiving primary vaccination. Immunologic disorders, reticuloendothelial neoplasms and so forth are contraindications to vaccination regardless of the patient's vaccination history.

This study was not a controlled trial, and only guarded conclusions should be drawn about the efficacy of the various treatments of vaccination complications. Vaccinia necrosum was universally fatal before the introduction of VIC and thiosemicarbazone treatment.<sup>14</sup> These agents must be considered of real therapeutic benefit for that entity. The case fatality ratio for untreated eczema vaccinatum has been reported as 6 to 80 per cent.<sup>14-16</sup> Fifteen of the 114 patients with eczema vaccinatum in this series were severely ill, requiring weeks of hospitalization, careful fluid and electrolyte management and occasionally even skin grafts. VIC and thiosemicarbazone must have real benefit for eczema vaccinatum since only one patient died, and she did not receive thiosemicarbazone.

Many of the patients with accidental implantations on the eye were treated with idoxuridine as well as VIC. Idoxuridine inactivates vaccinia virus *in vitro*.<sup>17</sup> Studies of the effectiveness of idoxuridine in vaccinia ulcers of rabbit corneas are inconclusive, although in rabbits treated solely with immune globulin more corneal scarring may develop than in those given idoxuridine.<sup>17</sup> Although no conclusions can be made about the efficacy of idoxuridine in vaccinia conjunctivitis in this series, many physicians are presently using it.

Eczema vaccinatum in this series as well as in others<sup>1-15</sup> appears to be more severe when it occurs in contacts than in persons who are vaccinated. Patients with severe eczema are usually not vaccinated and therefore acquire vaccinia only through contact. Contact may result in simultaneous multiple inoculations at several sites, causing more severe illness than vaccination. The presence of eczema in household contacts is an established contraindication to vaccination, but some health workers apparently do not take sufficiently careful family histories to reduce the incidence of contact eczema vaccinatum. The occurrence of several well documented cases of eczema vaccinatum in patients with eczema in remission at the time of vaccination suggests that a history of eczema should be a contraindication to smallpox vaccination.

Rigid observation of the accepted contraindications to vaccination might have prevented some of these complications. Theoretically, all cases of eczema vaccinatum are preventable. Some proportion of complications occurring in children vaccinated before the first birthday might be avoided if vaccination were deferred until the second year of life. Vaccinia necrosum can be avoided if the underlying disease is detected before vaccination. When all cases of eczema vaccinatum, all complications occurring in infants and the preventable cases of vaccinia necro-

sum are excluded, 377 cases and four deaths remain of the total of 572 cases and nine deaths. Further reduction in morbidity and mortality could presumably only be accomplished by reduction in the number of infant and childhood vaccinations performed.

This study reaffirms the fact that the morbidity and mortality associated with smallpox vaccination in the United States are considerable. The last cases of documented smallpox in the United States occurred in the importation epidemics in Seattle (1946), New York (1947) and Texas (1949). There have been 723 cases with 111 deaths in Europe since 1950, resulting from outbreaks that followed importations.<sup>18</sup> The United States may have had more than 111 deaths attributable to vaccination during this period. The vaccination policies in the United States should be re-evaluated, considering the risks of the present policy, the risks of importation and spread of smallpox and the risks of alternative vaccination policies.

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## PLATELET TRANSFUSION THERAPY\*

### The Selection of Compatible Platelet Donors for Refractory Patients by Lymphocyte HL-A Typing

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**Abstract** Five patients with bone-marrow aplasia had become refractory to platelet transfusions from random donors. The response to platelets from available family members of each of the patients was then studied. Three patients had excellent responses to platelets from a single sibling, and two each responded to platelets from two siblings. The lymphocytes of the donors and recipients were typed for HL-A antigens by the lymphocyte cytotoxicity test. Genotypic analysis of the phenotypes revealed that the excellent responses occurred with

platelets from HL-A identical siblings.

The patient's serums exhibited no lymphocyte cytotoxicity against the respective seven HL-A identical siblings whereas cytotoxicity was demonstrated to nine of 11 HL-A nonidentical family members. Three patients have received 8 units of platelets per week for 11, 15, and 24 months from HL-A identical siblings without the development of cytotoxic antibodies.

HL-A lymphocyte typing of family members can be used to predict platelet compatibility.

PLATELET transfusions have significantly reduced the risk of thrombocytopenic hemorrhage in patients with leukemia and aplastic anemia.<sup>1-6</sup> Prolonged transfusion support, however, frequently results in the development of resistance to infused platelets. This is manifested clinically by transfusion reactions, shortened platelet survivals and failure to maintain hemostasis effectively.<sup>7</sup> Alloantibodies directed against specific platelet antigens have been demonstrated by complement-fixation and other techniques.<sup>8</sup> Although platelet typing has been used on occasion to select compatible platelet donors for infants with isoimmune neonatal purpura, these techniques have not been satisfactory in the selection of donors for patients who have become refractory to platelets after multiple platelet or whole-blood transfusions.<sup>9,10</sup>

In recent years the lymphocyte has become a primary target cell for characterizing the major antigenic system, designated HL-A, involved in tissue histocompatibility.<sup>11-14</sup> Several of the recognized HL-A antigens, as well as other antigens found on lymphocytes, are also known to be present on platelets.<sup>14,15</sup> While evaluating one of our patients who was refractory to platelets from unrelated (random) donors, we noted that platelets from her two brothers gave an exceptional response. Lymphocyte typing was performed on each member of this family with antisera detecting HL-A antigens. The HL-A genotypes of the patient and her two brothers were found to be identical. Subsequent study of four other families disclosed a similar correlation between response to

platelets and HL-A genotype of donor and recipient lymphocytes.

The purpose of this paper is to demonstrate the usefulness of HL-A lymphocyte typing as a practical method for selecting compatible platelet donors for patients who are refractory to platelets.

#### PATIENT SELECTION

Five patients with bone-marrow aplasia were studied. In all of these the diagnosis had been established for at least four months, and all had received multiple blood transfusions. Signs of thrombocytopenic hemorrhage were present on admission, and all patients were demonstrated to be refractory to infused platelets obtained from random donors.<sup>16</sup>

#### DONOR SELECTION AND PLATELET PREPARATION

Platelet concentrates from random donors and family members were prepared by the acidification technic of Chappell.<sup>17</sup> Random donor platelets were obtained from individual 500-ml blood donations.† Family-member platelets were obtained by plateletpheresis‡; each unit (U) consisted of platelets separated from 500 ml of whole blood. All plasma and red cells were returned to the donor before consecutive units were withdrawn. Each transfusion consisted of the combined concentrates from 4 U of either random-donor or family-member platelets suspended in a total volume of approximately 100 to 200 ml of donor plasma.

Platelets from random donors were given to recipients of the same ABO red-cell group. Platelets

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