INFECTION AND IMMUNITY, Mar. 1980, p. 969-978
0019-9567/80/03-0969/10$02.00/0

Vol. 27, No. 3

Fatal Measles Infection in Marmosets Pathogenesis and Prophylaxis

PAUL ALBRECHT,[1]* DOUGLAS LORENZ,[2] MICHAEL J. KLUTCH,[1] JAMES H. VICKERS,[3] AND FRANCIS A. ENNIS[1]

Division of Virology,[1] Division of Blood and Blood Products,[2] and Division of Pathology,[3] Bureau of Biologics, Food and Drug Administration, Department of Health, Education and Welfare, Public Health Service, Bethesda, Maryland 20205

Moustached marmosets (*Saguinus mystax*) were infected intranasally with either of two low-passaged, wildlike strains of measles virus, strain Edmonston or strain JM. The infection resulted in 25 and 100% mortality, respectively, 12 to 14 days after infection. Clinical signs, gross pathological findings, and histology lacked the characteristic features of measles in other primates. A deficient immune response and widespread gastroenterocolitis appeared to be the main causes for the fatal outcome. Fluorescent-antibody staining detected large amounts of measles antigen in lymphatic tissues, the gastrointestinal and respiratory tracts, the salivary glands, pancreas, liver, kidney, and other visceral tissues. Live attenuated or inactivated measles vaccine proved equally effective in preventing fatal measles in marmosets. Challenge with live virus of animals which were primed 1 year previously with inactivated alum-absorbed vaccine resulted in a precipitous response, with a 100- to 1,000-fold increase in antibody titers. This vigorous booster response suggests the existence of a primary deficiency in lymphocyte cooperation in marmosets, which upon adequate priming is followed by extensive clonal expansion and antibody synthesis. Marmosets appear to be the most susceptible primate species to measles infection. They are capable of distinguishing differences in virulence of virus strains with a level of sensitivity not available in other animals.

Measles is a common, frequently serious infection of children or young adults. Death occurs in 1 out of 1,000 individuals who contract the disease (3). Delayed complications of measles which occur years later in the form of a chronic, fatal brain disease known as subacute sclerosing panencephalitis have been recognized (31). A highly successful live virus vaccine was developed and licensed in the United States in 1963.

A considerable drawback felt over the years was the lack of a laboratory animal capable of distinguishing differences in the pathogenic properties of natural and attenuated strains of measles virus. This shortcoming has now been overcome by the observation that marmosets, primates living in parts of Central and South America, contract a fatal disease when infected with natural measles but not when infected with the vaccine virus and that mortality after natural infection depends on the virus strain used, the route of inoculation, and possibly other circumstances.

MATERIALS AND METHODS

Animals. Feral *Saguinus mystax* from Peru were used exclusively. The marmosets were apparently healthy, adolescent to adult animals which had been in captivity for at least 6 months before their use in these experiments. Some had recovered from experimental human hepatitis A virus infection. They had no aberrant clinical signs at the outset of the present experiment.

The animals were housed in cages open on one side and arranged in two tiers. Either a single animal or a compatible male-female pair was housed in each cage. Only one strain of virus was introduced into a room of marmosets for a given infectious experiment. The animals were maintained on dry, commercial monkey diet, fruit, and water.

Viruses. Two natural and one attenuated strain of measles virus were used. The low-passage natural strain Edmonston was recieved from John Enders through Hope Hopps in third passage in human embryonic kidney cell cultures. It received a total of nine additional passages in primary human and monkey kidney cells in our laboratories. Its titer was $10^{3.5}$ plaque-forming units per ml in Vero cell cultures. Strain JM was isolated in this laboratory from a throat swab of a patient with typical measles rash. The virus was isolated in Vero cultures and became cytopathic after seven consecutive cell subcultures. It was identified as measles virus by neutralization with monospecific anti-serum. The titer of the seventh Vero cell passage used in this experiment was 10^5 plaque-forming units/ml.

A commercial vaccine, strain Moraten (Attenuvax, Merck Sharp and Dohme, West Point, Pa.), was used

without further passage as attenuated measles virus. It was derived from the Edmonston strain by 116 passages in human and chicken fibroblast cultures (22). The titer was $10^{3.8}$ plaque-forming units/ml in Vero cell cultures.

Killed measles vaccine was prepared in 1964 by Pfizer as the licensed biologic for human use. Killed measles vaccine has not been used in humans since 1967 due to hypersensitivity, which developed in some children, on reinfection with live virus (18). The virus was grown in primary monkey kidney cells, inactivated by Formalin, and concentrated by adsorption to aluminum hydroxide. It was stored at 2 to 8°C. The vaccine passed the prescribed potency test when evaluated shortly before use in this study.

Cell cultures and media. Vero cells at passage levels 170 through 220 were used for virus titration, virus isolation from marmoset tissues, and antibody determinations. The cells were grown and maintained in Eagle minimum essential medium supplemented with 10% heat-inactivated fetal bovine serum, 0.03% glutamine, 50 μg of gentamicin per ml, and 0.4 μg of Fungizone per ml. Overlay medium consisted of Eagle miminum essential medium containing 5% fetal bovine serum and a final concentration of 0.5% agarose (Seakem agarose, Microbiological Associates, Bethesda, Md.).

Experimental infection and immunization. Undiluted live measles virus was administered intramuscularly in a 0.5-ml volume. For intranasal infection a total volume of 0.5 ml of undiluted virus was sprayed with a nebulizer into both nares and into the pharynx. Killed measles vaccine was administered intramuscularly, 0.5 ml/dose, three times in weekly intervals.

Virus isolation. Peripheral blood mononuclear cells separated on Ficoll-Hypaque or trypsin-dispersed autopsy tissues were mixed with an equal number of Vero cells and seeded in stationary culture vessels. The cultures were observed for 10 days, and if no cytopathic effect developed they were trypsinized and subcultured. At this stage, the monolayers were composed almost exclusively of Vero cells. In several instances second and third subcultures were performed at 3- to 4-day intervals. Isolates were identified in situ by the fluorescent-antibody technique.

Antibody determinations. Early in the study it became apparent that the marmosets' antibody response to measles was poor and that the hemagglutination inhibition test lacked the necessary sensitivity. Therefore, a virus neutralization test was used which yielded titers on the average 50-fold higher than the hemagglutination inhibition test. Vero cell cultures were grown in plastic disposable trays containing 24 wells 16 mm in diameter. The cell suspension was seeded at 250,000, 150,000, or 100,000 cells per well in 1.0 ml of Eagle minimum essential medium and used 1, 2, or 3 days later, respectively.

Heparinized blood was spun at 900 × *g*, and the plasma was collected and inactivated for 30 min at 56°C. Fourfold dilutions of plasma in Eagle minimum essential medium containing 10% fetal bovine serum were mixed with an equal volume of virus diluted to yield 20 to 30 plaque-forming units/well in the control titration. The virus was the Edmonston strain received from John Enders and adapted to Vero cells by six additional passages. The titer of this virus pool was $10^{5.2}$ plaque-forming units/ml. After the plasma-virus mixtures were incubated for 1 h at 37°C, 0.1 ml of the mixture was inoculated into each of two wells and adsorbed for 1 h at 36°C. The inoculum was then replaced with 1.0 ml of agarose overlay, and the cultures were incubated in an inverted position in a 5% CO_2 incubator at 36°C. Four days after infection 0.5 ml of a second agarose overlay containing neutral red (1:10,000) was added. After a total incubation of 6 days the overlays were stripped, and the cell sheets were air dried. The neutralizing antibody titer was expressed as the highest final dilution of plasma reducing the number of virus plaques by 50%. The titer was calculated by the Karber formula (27).

Fluorescent-antibody technique. Cryostat sections were air dried, fixed with acetone, and stained by the indirect technique, using serum from a patient with subacute sclerosing panencephalitis (hemagglutination inhibition titer, 1:4,096) or from a hyperimmunized monkey (hemagglutination inhibition titer, 1:2,048) in the first step and a fluorescein-isothiocyanate-labeled porcine antibody to human gamma globulin (prepared in our laboratory) in the second step. Measles-negative sera from humans or monkeys and tissues from noninfected marmosets served as controls.

Histology. Tissues were fixed in a solution composed of formaldehyde, acetic acid, and saturated solution of picric acid in water in proportions of 25:5:75 (Carnoy solution), embedded in paraffin, sectioned at 7 μm, and stained with hematoxylin and eosin.

RESULTS

Infection with natural measles virus. Infection of marmosets with the Edmonston or JM strain of measles virus resulted in 25 to 100% mortality depending on the route of inoculation and the virus strain used (Table 1). The Edmonston strain was highly pathogenic on intramuscular inoculation but killed only one of four animals inoculated intranasally. The JM strain, in contrast, killed all four animals infected by the intranasal route.

None of the animals dying from acute measles infection showed clinical signs characteristic of the disease in humans or in subhuman primates. Notably absent were rash, coryza, and conjunctivitis. As a rule, the animals became less active, stopped eating, and were moribund the following day. Diarrhea was frequent, but the significance of it was initially overlooked, as diarrhea occurs commonly in marmoset colonies.

Morphology of infection with natural measles virus. Gross findings at autopsy were unrevealing. Occasionally spleen and lymph nodes were enlarged. Careful examination failed to reveal pneumonitis or encephalitis, the most common fatal complications of measles in other primates.

The histological changes were predominantly nonspecific in nature. There was slight to mod-

TABLE 1. *Experimental infection of marmosets (S. mystax) with natural measles virus*

Animal no.	Virus strain	Route of inoculation[a]	Days from inoculation to death	Neutralizing antibody titer		Cause of death
				Preinoculation	Postinoculation (day of bleeding)	
91	Edmonston	i.m.	15	<8	32 (14)	Measles[b]
A34	Edmonston	i.m.	12	<8	8 (12)	Measles
A91	Edmonston	i.m.	12	<8	8 (12)	Measles
M17	Edmonston	i.n.	15	<8	16 (14)	Measles
M9	Edmonston	i.n.	57	<8	215 (35)	Bronchopneumonia[c]
M37	Edmonston	i.n.	32	<8	815 (31)	Septicemia[c]
M50	Edmonston	i.n.	32	<8	2,640 (31)	Chronic nephritis[c]
61-1	JM	i.n.	13	<8	<8 (13)	Measles
57-4	JM	i.n.	13	<8	<8 (13)	Measles
M42	JM	i.n.	14	<8	<8 (14)	Measles
M43	JM	i.n.	14	<8	<8 (14)	Measles

[a] i.m., Intramuscular; i.n., intranasal.
[b] Determined by virus isolation and detection of measles antigen in tissues by fluorescent-antibody staining.
[c] Measles antigen was not detected nor was virus isolated from tissues taken at autopsy.

erate bronchitis (Fig. 1a) and increased cellularity in some areas of the lungs (Fig. 1b). Thymus, spleen, and lymph nodes showed various degrees of lymphocytic depletion. The most prominent changes were seen in the stomach and colon in the form of a focal gastritis and colitis (Fig. 2b through d). The kidneys, liver (Fig. 1c and d), pancreas, and salivary gland contained rare to infrequent foci of parenchymal necrosis.

Histological changes characteristic of measles infection, namely, multinuclear giant cells and viral inclusions, were rare and seen in only a few of the animals. Intranuclear and cytoplasmic inclusions and indistinct giant cells were found focally in epithelial cells of the gastrointestinal tract (Figs. 2b, c, and d), in bronchial epithelium (Fig. 1a), in alveolar cells of the lung (Fig. 1b), in the liver parenchyma (Fig. 1c), and in the pancreatic ducts (Fig. 2a), in that order of frequency. Viral inclusions or giant cells were not seen in the lymphatic tissues.

Fluorescent-antibody staining of measles antigen. The paucity of clinical, gross, and histological findings characteristic of measles in marmosets stood in marked contrast to the large amounts of measles-specific antigen in tissues of moribund marmosets (Table 2). Antigen was regularly found in the bronchial epithelium, in cells lining the alveoli (Fig. 3a), and in the epithelium or the connective tissue, or both, of the stomach, colon (Fig. 3d), and, to a lesser degree, the small bowels. Copious amounts of antigen were present in thymus (Fig. 3b) and lymph nodes. In the spleen, antigen was mostly confined to the lymph follicles (Fig. 3c). Specific fluorescent foci were also found in parenchymal cells of the liver, kidney, pancreas, and the salivary gland. In the respiratory tract, measles antigen was more abundant after intranasal than after intramuscular inoculation (Table 2). On the other hand, subcutaneous inoculation led to more intensive antigen localization in the kidneys and in the connective tissue in visceral organs. None of the animals showed measles antigen in the brain.

Virus isolation. Measles virus was readily isolated from peripheral blood mononuclear cells 4 to 14 days after infection with natural measles virus. No attempt was made to identify the type of cell harboring the virus. Virtually all tissues taken at autopsy yielded measles virus in the first or second coculture with Vero cells.

Terminal bacteremia. Marmosets no. M34, M35, M42, and M43 were bled 14 days after challenge with strain JM, and samples of the blood were cultivated in 100 ml of brain heart infusion broth. Animals M34 and M35, which were previously immunized with measles vaccine, survived the challenge with natural virus (Table 3) and yielded a sterile blood culture on day 14. Animals M42 and M43, which were susceptible to measles infection and were showing first signs of illness 14 days after challenge, yielded *Enterobacteriaceae* (M42) and *Pseudomonas* (M43) in their blood cultures.

Infection with attenuated measles virus. Two marmosets were inoculated with 0.5 ml of measles vaccine and sacrificed 2 weeks later in good health. Measles virus was recovered from all four tissues tested, namely, the lungs, spleen, kidney, and mesenteric lymph node. Virus-specific cytopathic effects became positive in the third Vero coculture, indicating very low amounts of virus in these tissues. Fluorescent-

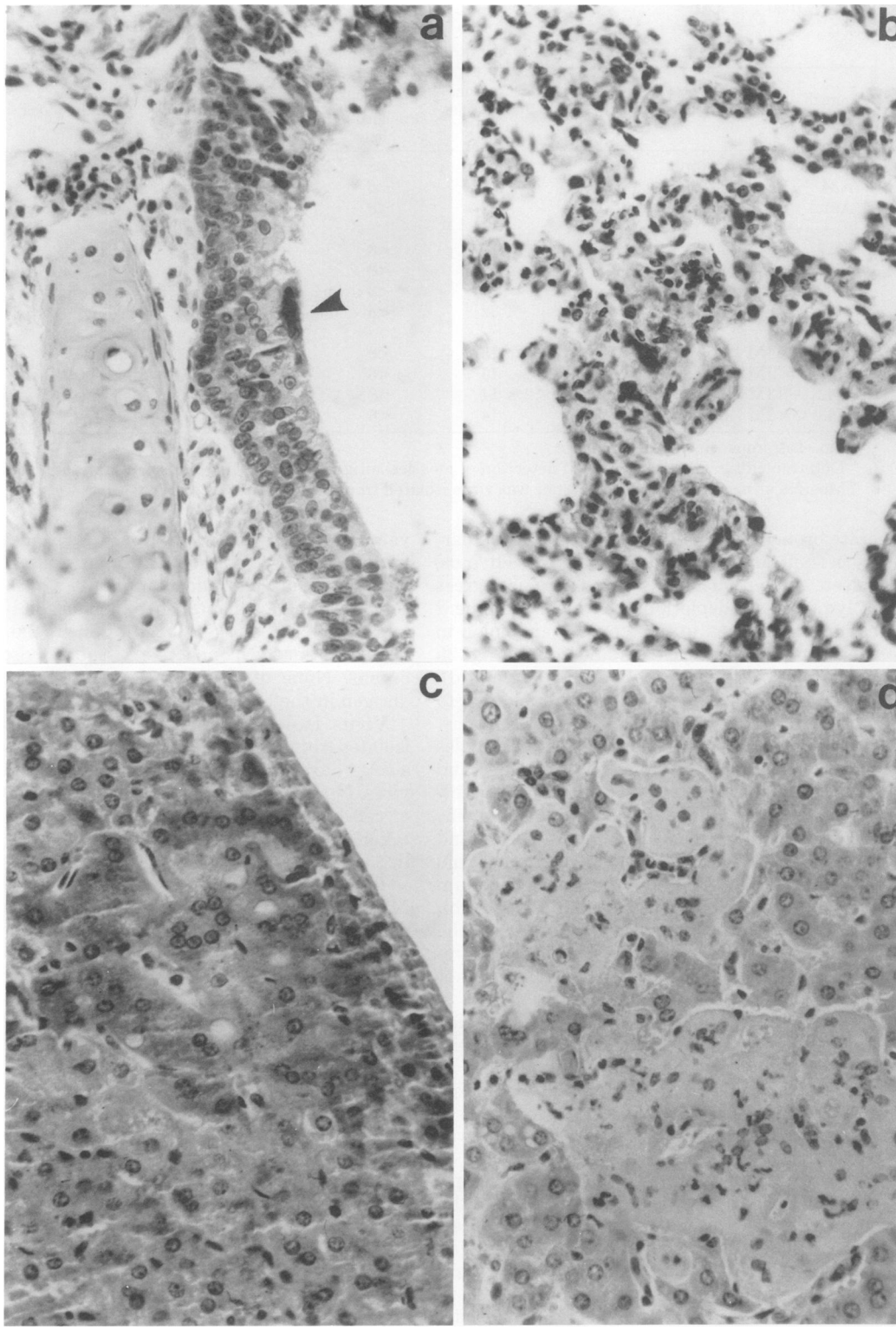

FIG. 1. *Fatal measles infection in marmosets. (a) Intranuclear inclusions and abortive multinuclear giant cell (arrow) in bronchial epithelium. (b) Increased cellularity and indistinct multinuclear giant cells in lung parenchyma. (c) Intranuclear inclusions in fused liver cells. (d) Necrosis of liver cords. Hematoxylin and eosin. ×650.*

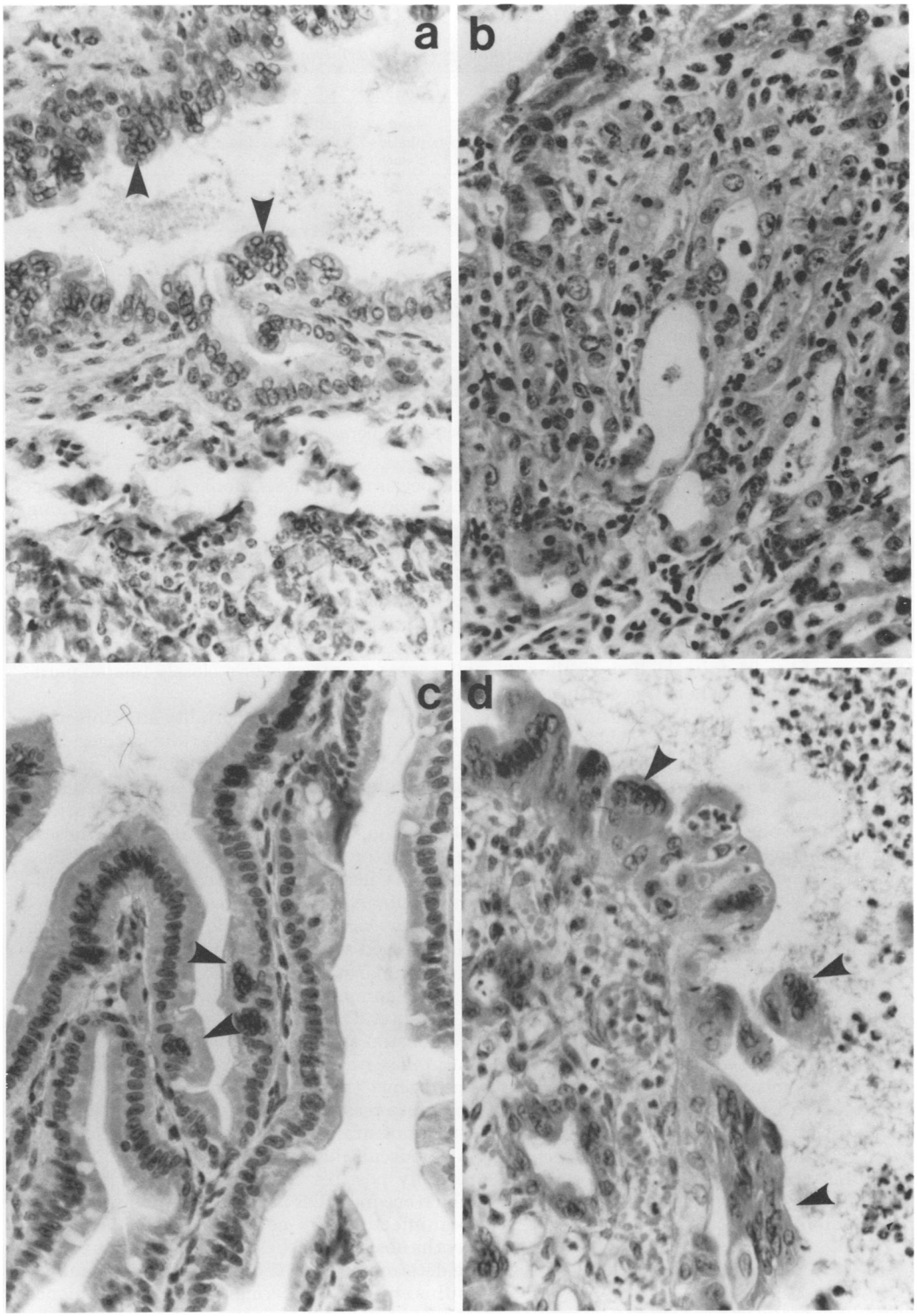

FIG. 2. *Fatal measles infection in marmosets. (a) Multinuclear giant cells in lining epithelium in large ancreatic duct (arrows). (b) Gastritis with extensive destruction of secretory epithelium and inflammatory infiltration of the mucosa. (c) Multinuclear giant cells in the jejunum (arrows). (d) Severe colitis with multinuclear giant cells and inclusions in surface epithelium. Hematoxylin and eosin. ×650.*

TABLE 2. *Antigen distribution in tissues of marmosets (S. mystax) dying of acute measles infection*

Animal no.	Virus strain	Route of inoculation[a]	Days from inoculation to death	Measles antigen in tissues[b]					
				Lower respiratory tract	Lymphatic tissues	Gastrointestinal tract	Liver	Kidney	Connective tissue
91	Edmonston	i.m.	15	1+	2+	ND	0	1+	2+
A34	Edmonston	i.m.	12	2+	3+	ND	±	2+	2+
A91	Edmonston	i.m.	12	1+	3+	ND	±	±	2+
M17	Edmonston	i.n.	15	3+	2+	3+	±	±	±
61-1	JM	i.n.	13	2+	3+	2+	2+	1+	1+
57-4	JM	i.n.	13	3+	3+	ND	1+	±	±
M42	JM	i.n.	14	3+	3+	3+	2+	±	±
M43	JM	i.n.	14	2+	2+	3+	2+	±	±

[a] i.m., Intramuscular; i.n., intranasal; ND, not done.
[b] ± to 3+ = amount of measles antigen in tissues as detected by fluorescent-antibody staining.

antibody staining of tissues showed rare small foci of specific antigen in the thymus, stomach, and colon only.

Immunization with inactivated and live measles vaccine. Five marmosets were immunized with inactivated vaccine, 10 animals were immunized with live attenuated vaccine, and 10 control animals were inoculated with saline (Table 4). Seven of the 25 animals died within a 2-month period. In none of them was death attributable to measles infection. The 28% nonspecific death rate was not too unusual considering the repeated handling of the animals and their known susceptibility to stress and bacterial and parasitic infections in captivity (5, 23).

The animals responded to immunization with moderate antibody titers, which dropped to very low levels 12 months after immunization (Table 5). Reinfection with attenuated or natural measles virus triggered a striking anamnestic response in animals sensitized earlier with inactivated vaccine. Antibody titers increased 100- to 1,000-fold in the acute stage and remained 10-fold higher 18 months after the booster (Table 3).

Three months after immunization with live vaccine two animals were challenged with the highly virulent JM strain. The animal with neutralizing antibody titers of 1:395 was completely protected. The animal with a titer of 1:75 became reinfected but was free of disease. The two susceptible controls died of acute measles 14 days after infection (Table 3).

DISCUSSION

The findings of the present study demonstrate that infection of the moustached marmoset with natural measles virus is associated with high mortality. The same appears to be true of other subspecies of marmoset monkeys. Levy and Mirkovic (28) described a measles epizootic among *Sanguinus oedipus*, *S. fuscicollis*, and *Callithrix jacchus* marmosets that decimated most of their colony over a 6-month period. A recent outbreak of disease characterized by gastritis and colitis occurred at the New England Primate Center and caused 10% mortality. It was probably caused by measles or a closely related paramyxovirus (10).

The different rates of mortality after infection with the Edmonston and JM strains suggest that marmosets may be suitable indicators of measles virus virulence. In a study to be published separately, we found that strain JM, but not strain Edmonston, spread readily among marmosets housed in the same animal room. The possibility has been considered that severe measles epidemics in human populations resulting in high mortality may have been due in part to virus strains of increased virulence. The question remained largely unanswered because of the lack of a suitable animal indicator model.

Parenteral inoculation of marmosets with the Edmonston strain, which in effect bypassed the natural portal of entry, was appreciably more pathogenic than intranasal inoculation. It was therefore reassuring to find that the attenuated variant of strain Edmonston lacked virulence on intramuscular inoculation. Although it is theoretically possible that the immunosuppression which accompanies natural and attenuated measles infection (9) contributed to nonspecific deaths observed in these marmosets, this cannot be determined from the small sample of animals in this study. Considering the extreme virulence of low-passaged measles in marmosets and the likelihood that introduction of the virus into a colony may go unrecognized for a considerable time, it is prudent to use preventive immuniza-

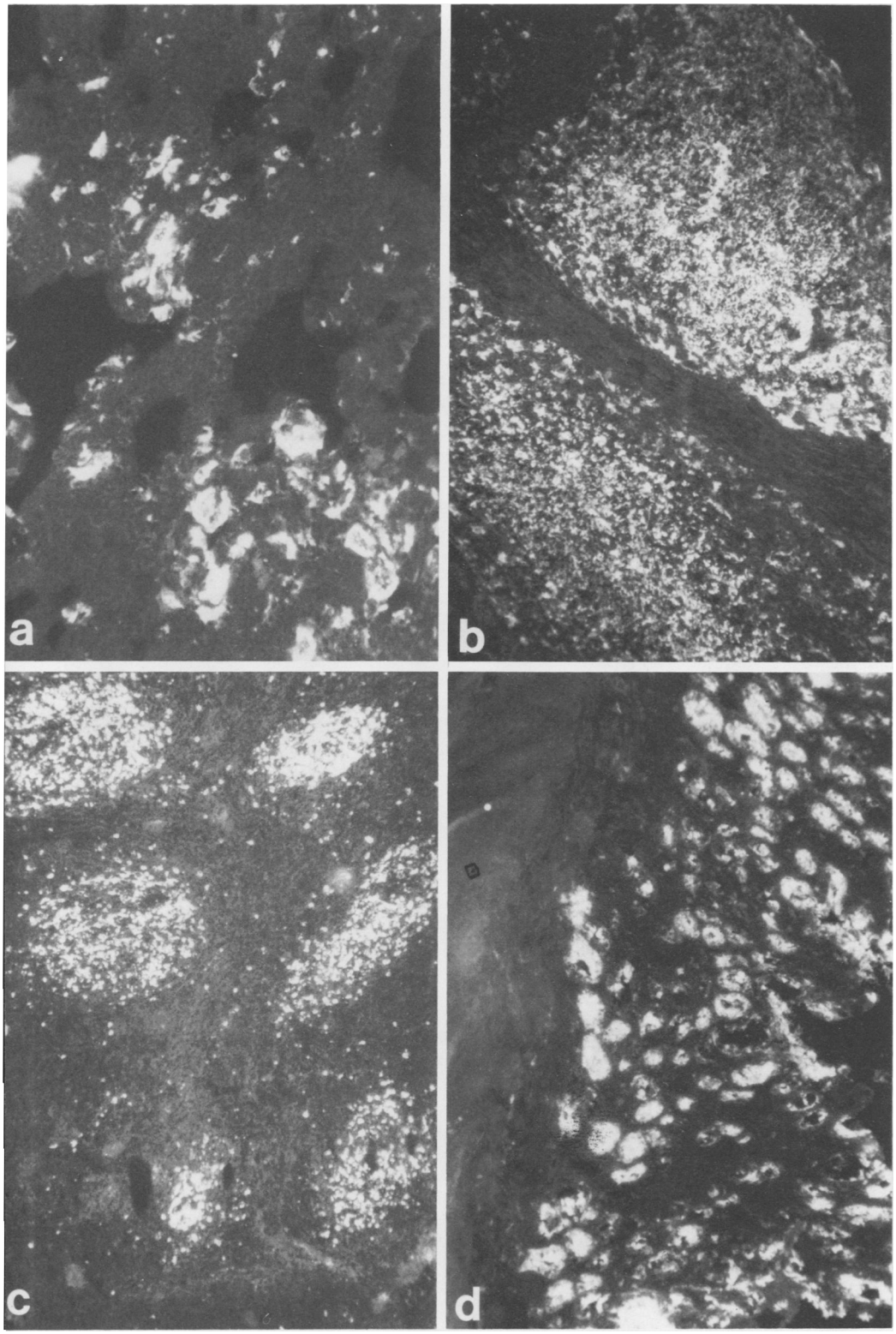

FIG. 3. *Fatal measles infection in marmosets. (a) Measles antigen localized predominantly in giant cells the lung parenchyma. (b) Thymus with extensive measles infection of thymocytes. (c) Measles antigen in mph follicles of the spleen. (d) Diffuse infection of the glandular epithelium in the colon. All micrographs ained by the fluorescent-antibody technique.* ×260.

TABLE 3. *Challenge with natural or attenuated measles virus of marmosets previously immunized with measles vaccine*

Animal no.	Primary vaccine	Time between immunization and challenge (mo)	Challenge virus	Route of inoculation[a]	Postchallenge antibody titer (reciprocal)							
					0	1 wk	2 wk	3 wk	6 wk	3 mo	9 mo	1.5 yr
A21	Inactivated	12	Attenuated	i.m.	20[b]	1,820	15,350	8,790	8,670	710	800	620
A22	Inactivated	12	Attenuated	i.m.	15	4,170	14,930	8,430	4,470	420	140	170
A23	Inactivated	12	Natural (Edmn)	i.n.	195	290	14,070	25,580	14,370	2,060	1,290	2,560
M34	Attenuated	3	Natural (JM)	i.n.	75	30	3,575			790	505	
M35	Attenuated	3	Natural (JM)	i.n.	395	450	515			580	480	
M42	None		Natural (JM)	i.n.	<8		<8[c]					
M43	None		Natural (JM)	i.n.	<8		<8[c]					

[a] i.m., Intramuscular; i.n., intranasal; Edmn, Edmonston.
[b] Fifty percent virus plaque neutralization titer. Ratio neutralization/hemagglutination inhibition antibody titers, approximately 50:1.
[c] Sick on day 14; postmortem finding of widespread measles infection.

TABLE 4. *Immunization of marmosets (S. mystax) with live and killed measles vaccine*

Animal group	Findings in animals dying within a 2-month period after immunization				
	No. died/no. immunized	Day between inoculation and death	Virus isolation	Measles antigen in postmortem tissues	Histology
Live vaccine	4/10	21	Positive[a]	Negative	Bronchopneumonia, enteritis
		31	Negative	Negative	Myocarditis, pericarditis
		34	Negative	Negative	?[b]
		62	Negative	Negative	Bronchopneumonia, pericarditis
Killed vaccine	1/5	45	ND[c]	ND	Bronchopneumonia
Placebo	2/10	17	Negative	Negative	?
		49	Negative	Negative	Pleuropericarditis, peritonitis

[a] Measles virus was isolated from the lung and lymphatic tissues in the third Vero subculture.
[b] Indeterminate.
[c] ND, Not done.

tion with available attenuated vaccines.

None of the three strains of measles virus used in the present study was neuroinvasive as determined by clinical, histological, and immunofluorescent observation. However, neurovirulence after intracerebral inoculation was not tested.

The great susceptibility of marmosets to measles can probably be ascribed to a basically high replicative potential of the virus in marmoset tissues which is aided by a poor, slowly developing immune response. For instance, much lower amounts of measles antigen are found in tissues of rhesus monkeys infected under conditions of infection comparable to those used in this study (41). On the other hand, neutralizing antibodies appear in rhesus monkeys 7 days after infection and reach titers 10-fold higher than in marmosets (20, 21).

Marmosets respond poorly to a number of other antigens (7, 11, 33, 39). Very low antibody titers develop after immunization with influenza A or B antigens (19), *Salmonella typhosa* (19), *Escherichia coli* (12), or sheep erythrocytes (13). The reason for this immune deficiency is not well understood. The total number of lymphocytes and the proportion of T and B cells in the peripheral circulation of marmosets are comparable to those seen in humans (12, 37). Marmosets respond adequately to general lectin mitogens (37). Baer and Lorenz (2) observed that marmosets reacted to tuberculin to a similar degree as guinea pigs and humans. Nevertheless,

TABLE 5. *Immunization of marmosets (S. mystax) with inactivated or live measles vaccine*

Animal no.	Vaccine	Neutralizing antibody titer (reciprocal)						
		0	3 wk	5 wk	7–8 wk	4 mo	8–10 mo	12 mo
A21	Inactivated	<8	95[a]	100	265	185	85	20[b]
A22	Inactivated	<8	205	190	70	65	20	15[b]
A23	Inactivated	<8	835	640	670	290	150	195[b]
B38	Inactivated	<8	31	75	51	29	NA[c]	NA
A3	Live	<8	60	360	400			
A95	Live	<8	210	400	300			
M27	Live	<8			30		20	
M29	Live	<8			725			
M34	Live	<8			75[b]			
M35	Live	<8			395[b]			
M46	Live	<8			365		180	132
M44	Live	<8			100		120	
M45	Live	<8			403		215	

[a] Fifty percent virus plaque neutralization titer. (note: Neutralization titers are approximately 50-fold higher than hemagglutination inhibition titers as performed in this laboratory.)

[b] Animals were challenged with natural or attenuated measles virus (see Table 3).

[c] NA, Not applicable.

some immunological defects are discernible in marmosets. Phytohemagglutinin-induced cytotoxicity of peripheral lymphocytes is markedly reduced (37). The delayed skin response to phytohemagglutinin is absent or weak (19). On in vitro lymphocyte stimulation the animals respond more vigorously to pokeweed mitogen than to phytohemagglutinin (19). Because phytohemagglutinin is known to induce lymphokine production in T cells whereas pokeweed mitogen initiates synthesis of antibody in B lymphocytes (15), it is tempting to speculate that the T-cell component in marmosets is in some way unique.

It is conceivable that the poor antibody response to live and nonreplicating antigens in marmosets may be related to a deficiency of T helper cell function (25). The brisk antibody response in animals challenged with live measles virus 1 year after sensitization with inactivated vaccine may indicate the time or the form of measles antigen (alum adsorbed) necessary for clonal expansion of the immunocytes to provide optimal responses. An equally striking antibody response did not occur in animals boostered 3 months after immunization with live attenuated measles vaccine. Children immunized with inactivated alum-adsorbed measles vaccine also respond to challenge with live measles vaccine with an intensive antibody response, although not of the same magnitude as observed in the present study in marmosets (18, 24).

The unremarkable clinical course of fatal measles infection in marmosets was rather puzzling. Skin rash was not detected in any of our animals, although lesions faintly resembling rash have been noted on occasion in marmosets (28). Since typical measles rash is considered a hypersensitivity reaction to a vigorous immune response (4), the absence of rash may be due to the marmosets' inability to mount this host defense.

Acute episodes of diarrhea in humans have been described as a severe and at times fatal complication of measles in Africa (16, 29). Giant cells are known to occur in the intestinal mucosa in uncomplicated measles in temperate climatic zones (6, 38). Malnutrition and parasitemia are most frequently cited as causes of the severe intestinal form of measles in humans (1, 30). The known extensive parasitemia of marmosets (23) and their demanding nutritional requirements in captivity (5) may be important predisposing factors for the intestinal form of measles in these animals.

A persistent form of intestinal measles infection has been claimed to be the underlying cause of multiple sclerosis in humans (8, 32, 35). The investigation was triggered by the observation that multiple sclerosis patients have nutritional deficiencies thought to be due to intestinal malabsorption and that these deficiencies adversely affect myelin formation in the central nervous system (32). Even though these findings were reported by two groups of investigators (8, 32), they were not confirmed by a third laboratory (40).

Detailed histological studies performed in humans and Old World monkeys suggest that the basic tissue affinities of measles virus in these primates are the same as in marmosets despite the differences observed in the clinical picture (14, 17, 26, 34, 36). In all primates lesions attributable to direct viral replication are found in the respiratory system, the salivary gland, pancreas, liver, kidney, and the lymphatic and gastrointes-

tinal systems (17, 36). It is safe to assume that the fatal course of measles in marmosets results from a combination of immune paralysis and intensive viral damage to selected tissues and organs. The most severe lesions were seen in the gastrointestinal system and probably led to a functional breakdown with protein loss, dehydration, and terminal enteric bacteremia.

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