day old cultures of mouse muscle, the differences in speed and extent of growth of virus were greatest in the younger tissues. If degree of viral multiplication were dependent only on the number of muscle cells available for invasion, the female to male ratio of virus should have been highest in the 12-day old cultures because they contained a greater number of cells than the 5-day old ones at time of infection.

It is striking that differences in degree of growth of EMC virus in cultures of muscle from male and female mice could be demonstrated only with inocula of certain size. With small dose of virus, the difference between the 2 sexes was maximal; as quantity of infecting agent was increased, it became less marked until it was no longer noted when 200 to 300 LD_{50} were used. The reason for this phenomenon is not apparent.

Summary. When EMC virus was grown in cultures of mouse muscle, it multiplied more rapidly and to a greater degree in the tissue obtained from female animals. The quantity of virus used to produce infection was an important determinant in demonstration of this phenomenon. The sex differences did not appear to be related to the number of cells present in the muscle culture at time of viral inoculation.

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Hemagglutination-Inhibition Antibody Responses in Human Adenovirus Infections. (26970)

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Although neutralizing antibody responses in persons infected with adenoviruses tend to be type-specific, heterotypic responses occur frequently(1). Furthermore, because of certain unusual aspects of adenovirus neutralization tests it is difficult to equate the findings from different laboratories or even those obtained in the same laboratory at different times(1). Complement-fixing (CF) antibody responses generally show no type-specificity in human adenovirus infections(1).

Preliminary data indicating that adenovirus hemagglutination-inhibition (HI) antibody responses in man might be type-specific have been presented(2). This report is concerned with additional data subsequently obtained from a study of paired sera from 36 children naturally infected with adenovirus types 1, 2, 3, or 5 and from 27 adults naturally infected with adenovirus types 4 or 7.

Materials and methods. The children with adenovirus type 1, 2, 3, or 5 infections were residents of an institution (Junior Village) and were part of a population whose microbial experiences were the subject of intensive study(3). Paired sera were selected so that they spanned the first known isolate of a given adenovirus serotype in a child, yet did not include adenoviruses of other serotypes. The first serum of each pair antedated the adenovirus isolate and second was collected at varying times thereafter as indicated in the tables.

The adults with adenovirus type 4 or 7 infections were naval recruits from whom these particular serotypes were isolated during a study of respiratory illness. The first serum from these individuals was obtained at onset

of illness; the second was collected approximately 21 days later.

HI tests were carried out exactly as has been described previously(4) using prototype strains of the various serotypes. In brief, rhesus erythrocytes were used for adenovirus types 3 and 7 and rat erythrocytes for types 1, 2, 4, and 5. All sera were treated with kaolin and adsorbed with rhesus and rat erythrocytes. Erythrocytes were al-

TABLE I. Hemagglutination-inhibition and Complement-fixing Antibody Responses of 8 Children Infected with Adenovirus Type 1

Age of child in mo. at time of virus isolation	Days after virus isolation 2nd serum collected	HI titer with indicated antigen T1	T2	T3	T4	T5	T7	CF titer
9	27	<10*	<10	<10	<10	<10	<10	<8
		40	<10	<10	<10	<10	<10	32
12	36	<10	<10	40	<10	<10	<10	16
		10	<10	20	<10	<10	<10	64
12	36	80	<10	<10	<10	20	<10	8
		80	<10	<10	<10	<10	<10	64
12	78	<10	<10	80	<10	<10	<10	32
		80	<10	160	<10	<10	<10	64
22	44	10	80	20	<10	10	<10	64
		40	80	20	<10	10	<10	128
23	51	<10	<10	<10	<10	20	<10	8
		80	<10	10	<10	80	<10	64
33	35	<10	<10	<10	<10	<10	<10	16
		80	<10	<10	<10	<10	<10	32
37	30	<10	40	<10	<10	<10	<10	32
		20	40	<10	<10	<10	<10	128

* In this and subsequent tables the first row of data pertains to first serum specimen, the second row to second serum specimen from a given individual.

TABLE II. Hemagglutination-inhibition and Complement-fixing Antibody Responses of 9 Children Infected with Adenovirus Type 2

Age of child in mo. at time of virus isolation	Days after virus isolation 2nd serum collected	HI titer with indicated antigen T1	T2	T3	T4	T5	T7	CF titer
8	36	<10	10	<10	<10	<10	<10	<8
		<10	20	<10	<10	<10	<10	<16
11	83	10	<10	20	<10	<10	<10	32
		10	80	<10	<10	<10	<10	64
12	30	80	10	<10	<10	≥320	<10	<8
		80	≥320	<10	<10	≥320	<10	16
16	117	20	160	10	<10	40	<10	16
		80	≥320	<10	<10	20	<10	16
18	43	20	160	20	<10	<10	20	32
		20	160	<10	<10	<10	10	32
22	57	40	<10	20	<10	<10	<10	16
		40	20	10	<10	<10	<10	32
27	44	<10	≥320	<10	<10	<10	<10	<8
		<10	160	<10	<10	<10	<10	<16
28	76	<10	80	40	<10	40	<10	NT*
		40	≥320	<10	<10	80	<10	NT
38	62	160	<10	<10	<10	80	<10	16
		160	80	<10	<10	80	<10	32

* In this and subsequent tables NT indicates that sera were not tested for CF antibodies because one or both specimens were anticomplementary.

TABLE III. Hemagglutination-inhibition and Complement-fixing Antibody Responses of 9 Children Infected with Adenovirus Type 3

Age of child in mo. at time of virus isolation	Days after virus isolation 2nd serum collected	HI titer with indicated antigen						
		T1	T2	T3	T4	T5	T7	CF titer
8	43	20	<10	<10	<10	<10	<10	NT
		40	<10	20	<10	<10	<10	NT
10	22	<10	<10	<10	<10	<10	<10	<8
		<10	<10	10	<10	<10	<10	32
11	48	40	<10	<10	<10	<10	<10	16
		20	20	20	<10	<10	<10	32
15	28	≧320	<10	<10	<10	<10	<10	64
		≧320	<10	20	<10	<10	<10	64
18	26	<10	80	<10	<10	<10	<10	16
		<10	80	20	<10	<10	<10	64
18	29	<10	<10	<10	<10	<10	<10	<8
		<10	<10	40	<10	<10	<10	<16
18	29	160	<10	<10	<10	160	<10	32
		≧320	<10	20	<10	≧320	<10	128
31	43	<10	<10	<10	<10	160	<10	8
		<10	<10	10	<10	80	<10	16
39	27	<10	<10	<10	<10	160	<10	<8
		<10	<10	<10	<10	160	<10	16

lowed to sediment at 37°C. A 1:100 dilution of adenovirus type 6 rabbit serum was used as the diluent in tests involving adenovirus types 1, 2, and 5. Both sera of a pair were always tested at the same time.

Complement-fixation tests were performed as described previously(5) using an antigen prepared from adenovirus type 2 unless otherwise noted.

Results. Each of the pairs of sera was tested for HI antibody against 6 adenovirus serotypes (viz. types 1, 2, 3, 4, 5, and 7) and also for adenovirus CF antibody. The results are shown in Tables 1-6.

Considering first the responses of the children (Tables 1, 2, 3, and 5), a significant (4-fold or greater) homotypic HI antibody rise was found in 24 of the 36 (67%) children studied. If rises from a titer of <10 to 10 are included, 30 of the 36 (83%) children could have been considered to have shown an HI antibody rise to the homotypic virus. Only one child had no homotypic HI antibody in either serum specimen. A relatively low frequency of heterotypic HI rises was noted. Of 168 instances where such an event could have been detected (*i.e.* an HI titer in the first serum of 80 or less) 11 fourfold rises (7%) occurred. Six of these heterotypic reactions were type 1 responses in persons infected with type 5 virus.

Only 11 of 30 children (37%) showed a significant (4-fold or greater) CF antibody response and this low frequency prevailed even among those children with type 2 infections.

The data obtained from adults infected with adenovirus types 4 or 7 (Tables 4 and 6) show that 24 of 27 individuals (89%) showed a significant homotypic HI antibody response and that all could have been considered as showing a homotypic response if rises from <10 to 10 are included. Of the 106 instances where heterotypic HI responses could have been detected 21 rises (20%) actually were observed. Adenovirus types 4 and 7 were the only serotypes isolated from this particular population in the time period studied.

In contrast to the findings among children, 24 of 27 adults (89%) showed a significant CF antibody response. When the 3 individuals who failed to show a significant CF response were tested with CF antigens prepared from the homotypic type of virus, one (GL 500) showed a significant rise and the other 2 did not.

Discussion. These data indicate that the

TABLE IV. Hemagglutination-inhbition and Complement-fixing Antibody Responses of 17 Adults Infected with Adenovirus Type 4

	HI titer with indicated antigen						
Patient	T1	T2	T3	T4	T5	T7	CF titer
GL 222	160	20	160	<10	160	<10	<8
	≧320	≧320	160	≧320	≧320	<10	≧64
224	<10	40	≧320	<10	20	160	64
	160	80	≧320	80	20	80	256
234	10	20	20	<10	10	<10	<8
	40	20	40	80	10	<10	64
241	<10	<10	80	<10	<10	<10	<8
	<10	<10	160	160	<10	<10	≧64
257	80	<10	20	<10	40	<10	<8
	≧320	40	40	80	80	<10	64
489	20	20	160	<10	80	<10	32
	≧320	≧320	160	40	≧320	<10	≧128
497	≧320	160	40	<10	40	10	16
	≧320	≧320	40	80	80	10	64
500	<10	20	10	<10	<10	<10	<8
	40	≧320	20	80	<10	<10	<8
512	≧320	<10	<10	<10	<10	40	16
	≧320	20	<10	40	<10	40	≧128
516	<10	160	<10	<10	80	<10	<8
	10	≧320	<10	10	≧320	<10	128
529	80	≧320	<10	<10	40	<10	<8
	160	≧320	<10	10	40	<10	64
530	10	10	≧320	<10	160	<10	<8
	10	<10	160	40	160	<10	32
573	160	<10	20	<10	80	20	8
	160	<10	20	40	80	20	≧128
574	40	≧320	80	<10	≧320	<10	16
	20	≧320	80	80	160	<10	≧128
585	≧320	<10	40	<10	<10	<10	<8
	≧320	<10	20	40	<10	<10	64
588	≧320	≧320	40	<10	20	40	<8
	≧320	≧320	80	10	20	80	128
597	≧320	20	<10	<10	≧320	<10	<8
	≧320	160	<10	40	≧320	<10	32

HI antibody response to adenovirus infections in man is probably about as specific as that of neutralizing antibody. Thus, in a study(6) of heterotypic neutralizing antibody responses in naval recruits infected with adenovirus types 4 or 7, it was found that significant rises occurred in 60 out of the 240 instances (25%) in which sera were tested against the serotypes used in the present investigation. It is unlikely that the heterotypic responses to types 1, 2, and 5 in either study were due to actual concurrent infection with these viruses since these serotypes are only rarely encountered in adults and were not isolated from any of the subjects studied.

Conversely, types 1, 2, 3, and 5 were quite common at all times in the population from which the children in the present study were drawn(3). Since serum pairs from children often spanned a considerable period of time, it is probable that at least some of the apparent heterotypic responses were actually instances of multiple infection. No heterotypic responses were noted in children to types 4 and 7, which did not occur in the nursery population. Although weekly throat specimens from each child had been tested for adenoviruses, the most sensitive laboratory methods were not always employed and anal specimens were not routinely examined

for these viruses. Thus, it was quite possible to have missed the occurrence of a heterotypic infection or to have missed the earliest week of homotypic virus excretion. The latter event is the most likely explanation of those instances in which children were found to have pre-existing homotypic antibody.

While the difference in specificity of HI

TABLE V. Hemagglutination-inhibition and Complement-fixing Antibody Responses of 10 Children Infected with Adenovirus Type 5

Age of child in mo. at time of virus isolation	Days after virus isolation 2nd serum collected	HI titer with indicated antigen						
		T1	T2	T3	T4	T5	T7	CF titer
10	19	<10	<10	<10	<10	<10	<10	≥64
		80	<10	<10	<10	40	<10	128
24	27	80	<10	20	<10	<10	<10	NT
		≥320	<10	<10	<10	80	<10	NT
25	44	<10	160	80	<10	<10	<10	NT
		20	≥320	20	<10	10	<10	NT
26	69	≥320	160	20	<10	<10	<10	NT
		≥320	160	20	<10	40	<10	NT
28	58	40	40	10	<10	<10	<10	NT
		160	80	10	<10	20	<10	NT
29	27	10	80	20	<10	<10	<10	64
		<10	80	20	<10	10	<10	64
29	31	10	80	160	<10	<10	<10	64
		160	≥320	80	<10	20	<10	128
32	43	40	40	80	<10	<10	<10	8
		≥320	40	40	<10	10	<10	32
33	85	40	80	<10	<10	<10	<10	16
		40	80	<10	<10	20	<10	16
37	82	≥320	<10	<10	<10	20	<10	32
		≥320	<10	<10	<10	80	<10	32

TABLE VI. Hemagglutination-inhibition and Complement-fixing Antibody Responses of 10 Adults Infected with Adenovirus Type 7

Patient	HI titer with indicated antigen						
	T1	T2	T3	T4	T5	T7	CF titer
GL 214	≥320	80	<10	≥320	80	<10	256
	≥320	160	<10	80	80	20	256
282	40	80	<10	<10	40	<10	<8
	40	160	<10	40	40	80	<8
291	<10	<10	<10	<10	<10	<10	<8
	10	10	<10	<10	20	80	≥64
350	160	<10	<10	<10	10	<10	<8
	80	<10	<10	<10	10	80	≥64
353	≥320	160	<10	<10	<10	<10	16
	160	160	<10	<10	<10	40	64
490	10	80	10	20	80	<10	8
	10	40	≥320	20	80	≥320	≥128
507	≥320	80	<10	<10	<10	<10	16
	160	80	<10	<10	40	40	128
513	≥320	<10	10	<10	10	<10	16
	≥320	40	≥320	40	10	80	≥128
536	<10	10	<10	<10	<10	<10	<8
	<10	10	<10	<10	<10	20	16
575	160	<10	20	<10	20	<10	8
	160	<10	≥320	<10	20	40	32

antibody responses in children and adults might have been a function of the particular serotypes involved rather than of the age of the subjects, such an explanation is unlikely in view of what is known about serologic responses of children and adults in general. Further study of adenovirus type 3 infections, which occur commonly in both children and adults, should resolve this question.

The CF antibody response appeared to be a quite useful indication of adenovirus infection in adults but was of much less value among children. The latter were more apt to have pre-existing CF antibody, but this factor alone was not responsible for the relatively low rate of significant responses. Thus, of 9 adults with pre-existing CF titers of 8 or 16 all showed significant rises. Of 12 children with the same pre-existing CF titers only 5 (42%) showed significant responses.

Although much remains to be learned about adenovirus HI antibodies such as the time of their first appearance, duration of their persistence, and relationship of heterotypic responses to prior adenovirus infections, the data presently available indicate that they should prove to be useful tools in clinical and epidemiologic studies of adenovirus infections in man.

Summary. Paired sera from 36 children naturally infected with adenovirus types 1, 2, 3, or 5 and from 27 adults naturally infected with adenovirus types 4 or 7 were studied for homotypic and heterotypic hemagglutination-inhibition (HI) antibodies and for complement-fixing (CF) antibody. Homotypic HI responses were observed in most instances. Heterotypic HI responses were relatively uncommon among the children but occurred in adults with about the same frequency as has been reported for heterotypic neutralizing antibody responses in the same type of population. Significant CF antibody responses were detected in most of the adults but in less than one-half of the children.

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Effect of Immune Serum on Hemorrhagic Shock and on Metabolism of Endotoxemia by the R.E. System.* (26971)

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The irreversible phase of traumatic shock has been attributed to a loss of the R.E. system's capacity to take up and destroy endotoxin, which is being continuously absorbed into the circulation from the intestine(1). If this is a correct hypothesis, serum containing antibodies to endotoxin might be useful to prevent development of the irreversible phase, because such serum antibodies facilitate uptake of endotoxin by R.E. cells(2).† In a normal R.E. cell uptake of enodtoxin is

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