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Vaccination with live type 4 adenovirus: evaluation of antibody response and protective efficacy

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The importance of adenovirus as a cause of disease in military recruits has stimulated interest in the development of effective adenovirus vaccines. Several studies conducted between 1956 and 1960 demonstrated that inactivated adenovirus vaccines were highly effective in preventing adenovirus disease in military recruits (Davenport, 1962). However, in later studies, variation in antigenic potency of different lots of vaccine and failure to obtain consistently the desired high protection rates were noted (Meiklejohn, 1963). Moreover, it was found that inactivated vaccines may be contaminated with simian viruses. The problem of vaccine safety was further complicated by the discovery of oncogenicity of certain adenoviruses and of the phenomenon of 'hybridization' of adenoviruses with the oncogenic simian virus SV–40 (cf. review by Hilleman, 1966). Recent data provided suggestive evidence that the tumorigenic potential of adenoviruses, SV–40 and adenovirus –SV–40 'hybrids' is inactivated by formaldehyde used for vaccine production (Truffelli *et al.* 1967). Although the latter findings are encouraging, they offer no answer to the problems of potency and contamination with simian viruses.

Because of the inadequacy of inactivated vaccines, other approaches to adenovirus immunization were explored. Investigators at the National Institutes of Health of the United States developed a technique of producing selective intestinal infection by feeding adenovirus in enteric-coated capsules (Couch *et al.* 1963). The virus was shed from the intestine, but could not be recovered from the throat. In two field trials in which, respectively, 134 and 360 recruits were infected by this method, the enteric adenovirus vaccine was found to be safe, non-communicable and highly effective in preventing adenovirus disease (Edmondson *et al.* 1966; Gutekunst *et al.* 1967). Furthermore, tests in newborn hamsters showed no evidence of oncogenic capacity of the vaccine strain (Chanock *et al.* 1966).

In order to explore further the oral-enteric approach to control of adenovirus disease it seemed of interest to study the effect of enteric adenovirus vaccine in a different ecological setting. For this reason, an investigation was carried out at a training centre for military recruits at Ossendrecht, The Netherlands. Surveillance of respiratory infections at the centre over a 9-year period has shown epidemics of adenovirus infection to recur annually in the winter and spring. Since 1964 only adenovirus type 4 was found in these epidemics. The present paper reports

findings from three controlled field trials conducted in 1966 and 1967 in which 2628 men were given type 4 adenovirus contained in enteric-coated tablets. The trials were primarily designed to test the effectiveness of the vaccine in preventing febrile and afebrile adenovirus disease and subclinical adenovirus infection. In addition, serological studies were done to acquire information on other points of interest. These included: (*a*) spread of virus from vaccinated men to contacts; (*b*) magnitude of the antibody response to vaccine and to naturally acquired adenovirus infection; and (*c*) significance of vaccine-induced and naturally acquired antibody as indicator of immunity.

MATERIALS AND METHODS

Vaccine

Live, lyophilized adenovirus type 4 (strain CL 68578) contained in an enteric-coated tablet was prepared by Wyeth Laboratories under contract to the Vaccine Development Branch, National Institute of Allergy and Infectious Diseases, and supplied through the courtesy of Dr D. I. Mullally. A detailed account of the history of the vaccine strain and the preparation of the vaccine was given previously (Chanock *et al.* 1966). The quantity of virus present in a tablet was $10^{4.7}$ to $10^{4.9}$ 50 % infectious doses for human diploid cell cultures. A titre of $10^{5.5}$ was found at the Wyeth Laboratories, using human embryonic kidney tissue (Dr H. Tint, personal communication).

Study population and plan of study

The study was conducted in a military training centre at Ossendrecht, The Netherlands. At intervals of 2 months, groups of about 2400 to 2600 recruits entered the camp to receive an 8-week course of basic training. The vast majority of these men arrived on post on the same day. A small proportion (less than 3 %) of the men entered 1 week later. During the period of basic training, no other recruits were introduced into the camp. The recruits were formed into companies of slightly more than 200 men, all of which followed a similar training schedule. The companies were trained separately and were housed in separate dormitory areas. Recruits from the same company ate together. Opportunities for contact between men from different companies were limited by these circumstances to occasional association at the common mess hall and to attendance at the theatre during off-duty hours.

Three separate trials were undertaken. In each trial, the plan and purpose of the study were explained to the recruits before the beginning of the vaccination programme and the men were asked whether they agreed to take part in the study. All recruits volunteered to participate.

The first trial was performed in August and September 1966. During the second week of training two groups comprising, respectively, 86 and 85 recruits were selected by a random process from one of the 11 companies formed. Recruits of the first group were fed a tablet containing type 4 adenovirus, those of the second group a dummy tablet containing only diluent fluid. Blood specimens were

obtained from 75 men of the vaccine group and from 72 men of the control group before administration of vaccine or dummy and, again, 3 and 6 weeks later. In addition, paired serum samples were taken from a randomly selected 10 % of the recruits of each of the 10 remaining companies on the first or second day after arrival in the camp and, again, during the eighth week of training.

The second trial was conducted from mid-January to mid-March 1967. The recruit population at the time comprised 12 companies. Vaccine tablets were fed to all men of four companies and to a randomly selected 50 % of the men of four other companies; the men of the remaining four companies did not receive vaccine. In all, 1283 men were vaccinated, whereas 1357 men were not vaccinated. The vaccine was given within 2 days of arrival in the camp. No vaccine was administered to the men who entered at the beginning of the second week of the training period. Hence, the size of the vaccinated group was slightly smaller than that of the control group. All unvaccinated recruits were given tablets containing aspirin, phenacetin and caffeine. The appearance of these tablets was similar to that of the vaccine tablets. None of the recruits was informed whether vaccine or a tablet containing no virus was given to him. Similarly, the clinical observers were unaware of the vaccination status of men reporting at sick call. Blood specimens were taken from a randomly selected 20 % of vaccinated and unvaccinated recruits on the day of vaccination and, again, 3 and 8 weeks later.

The third trial was performed from mid-March to mid-May 1967 and was similar to the second trial in all respects. The number of men who received vaccine was 1259, whereas 1281 men were not vaccinated.

Criteria for evaluation of vaccine

The antibody response and protective capacity were used as criteria for evaluation of the vaccine. Assessment of the protective capacity was made by comparing the incidence of febrile and afebrile respiratory illness due to adenovirus in vaccinated recruits with that in unvaccinated recruits. The study of the protective effect was restricted to the two groups of recruits who entered service in the winter (second and third trials). Incidence rates were calculated for a 7-week period including the second to eighth week of training. Illnesses occurring in the first week of training were excluded to allow time for the vaccine to demonstrate an effect. Patients who reported to sick call with respiratory illness were considered febrile if the rectal temperature was 38·0° C. (100·4° F.) or higher. These men were admitted to the sick quarters. Patients reporting with respiratory illness associated with a temperature of lower than 38·0° C. were considered afebrile and treated as outpatients. Specimens for laboratory examination were obtained on patients with febrile respiratory illness from all 12 companies and on patients with afebrile respiratory illness from only six companies (two 100 %-vaccinated companies, two 50 %-vaccinated companies and two non-vaccinated companies).

Laboratory methods

Specimens

Specimens for laboratory examination consisted of a throat swab and a sample of blood on the day of report to sick call, and a second sample of blood about 14 days later. Sera from blood specimens were frozen and stored at −20° C. until tested. Immediately after collection, throat swabs were placed in tubes containing 3 ml. of GLY medium (0·5 % gelatin, 0·5 % lactalbumin hydrolysate, and 0·1 % yeast extract in Hanks's balanced salt solution) and were kept at 2–4° C. until processed. The specimens were inoculated into cell cultures within 16 hr. Before inoculation, swabs were squeezed against the glass; the fluids from the swabs were used without previous centrifugation.

Isolation of virus

For virus isolation attempts, 0·5 ml. of fluid was inoculated into a tube culture of diploid fibroblast cells (N–3) derived from human embryonic lung. The N–3 cell strain was established in our laboratory. The cells were grown in Eagle's minimum essential medium and 10 % calf serum. For maintenance, calf serum was replaced by 2·5 % chicken serum. After inoculation, cultures were incubated at 35° C. on a drum rotating 12 times an hour. If no definite cytopathic effect occurred, the tubes were subjected to three cycles of freezing and thawing. The harvest was inoculated into fresh tube cultures. The total incubation period was 30 days. Adenovirus strains were typed by neutralization tests with rabbit antisera against adenovirus prototype strains.

Serological tests

Neutralization tests were carried out in HeLa cell cultures using fourfold dilutions of unheated serum and test doses of virus calculated to contain 3–10 TCID50 on the fourth day of incubation. HeLa cell cultures were grown in a medium consisting of 20 % horse serum and 0·5 % lactalbumin hydrolysate in Hanks's balanced salt solution. For maintenance, horse serum was replaced by 3 % rabbit serum. The virus used was the prototype strain of adenovirus type 4. Serum dilution and virus were incubated at 37° C. for 60 min. The mixture was then transferred to duplicate tube cultures. The tests were read on the fourth day of incubation. The titres were based on initial serum dilution before addition of other reagents and were expressed as the reciprocal of the highest serum dilution producing complete inhibition of cytopathic effect in both tubes, the fourfold higher dilution showing cytopathic effect in both tubes. If the higher dilution produced complete inhibition in one of the two tubes, the titre was recorded as being intermediate between the two dilutions.

Complement-fixation (CF) tests were done in microtitre plates according to the technique described by Sever (1962). Antigen consisted of a suspension of the prototype strain of type 4. In all serological tests, sera from a single person were always titrated simultaneously.

RESULTS

Antibody response to the vaccine

Frequency

In each of the three trials, sera from randomly selected vaccinated men and controls were tested for neutralizing and CF antibody. The frequency of presence of neutralizing antibody in the two groups of men was comparable at the start of the study. Initial antibody was found in 29 out of 75 (39 %), 61 of 170 (36 %) and 55 of 167 (33 %) of vaccinated men in the first, second and third trials respectively. The corresponding figures for the controls were 78 of 244 (32 %), 64 of 203 (32 %) and 69 of 208 (33 %).

Table 1. *Neutralizing antibody response in initially sero-negative recruits* 3 *and* 8 *weeks after feeding of type* 4 *adenovirus*

Trial	Group	No. of men studied	Percentage sero-positive	
			3 weeks	8 weeks*
1	Vaccine	46	85	85
	Control (50 %-vaccinated company)	49	8	8
	Control (non-vaccinated companies)	117	—†	4
2	Vaccine	109	77	64
	Control (50 %-vaccinated companies)	43	16	19
	Control (non-vaccinated companies)	96	9	14
3	Vaccine	112	87	78
	Control (50 %-vaccinated companies)	45	11	62
	Control (non-vaccinated companies)	94	9	70

* In the first trial sera were collected at 6 weeks after vaccination.
† No sera collected.

Table 1 summarizes the results of neutralization tests in recruits without pre-existing neutralizing antibody. It is seen that 77–87 % of the recruits showed neutralizing antibody at 3 weeks after vaccination. During the following 5 weeks the percentages of sero-positive men declined slightly. The mean antibody titres, not shown in the table, decreased also slightly during this period. The CF test appeared to be much less effective in detecting an antibody response to vaccine than the neutralization test. The percentages of recruits who showed a significant (fourfold or greater) rise in CF antibody at 3 weeks following vaccination were 24 in the first trial, 36 in the second trial and 43 in the third trial.

Eight to 16 % of the controls developed neutralizing antibody during the first 3 weeks of the training period. Development of antibody was detected slightly more frequently in controls of 50 %-vaccinated companies than in those of entirely untreated companies. The differences were not statistically significant ($P > 0{\cdot}25$, χ^2 test).

Data on the antibody response to vaccine in recruits with pre-existing neutralizing antibody are presented in Table 2. The response appeared to be related to the level of pre-existing antibody. An antibody rise was observed most often in recruits with a low initial antibody titre and least often in men with a high titre.

Magnitude

It seemed of interest to compare the magnitude of the antibody response to the vaccine with that to naturally acquired adenovirus infection. Convalescent sera from initially sero-negative recruits with febrile and afebrile respiratory illness from whom adenovirus type 4 was recovered were tested for content of neutralizing antibody. In addition, postinfection sera from controls who showed

Table 2. *Influence of pre-existing neutralizing antibody upon antibody response to feeding of type 4 adenovirus*

Antibody titre before vaccination	No. of recruits studied	Neutralizing antibody rise (fourfold or greater) after vaccination	
		No.	%
4–8	33	26*	79
16–32	61	32	52
64–128	48	11 *	23
⩾256	4	0	0

* $P < 0{\cdot}001$ (χ^2 test).

Table 3. *Magnitude of the neutralizing antibody response in initially sero-negative recruits to feeding of type 4 adenovirus and to naturally acquired adenovirus infection*

Group	No. of men studied	No. of men with indicated antibody titre						Geometric mean antibody titre
		4–8	16–32	64–128	256–512	1024–2048	4096	
Vaccine	221	95	79	36	11	–	–	11
Subclinical adenovirus infection	81	12	23	26	20	–	–	49
Afebrile adenovirus illness	31	1	5	11	8	6	–	137
Febrile adenovirus illness	20	–	1	5	6	6	2	446

serological but no clinical evidence of infection were tested; the sera were collected at the end of the 8-week course of training. To allow comparison of the antibody response to subclinical infection and that to illness, only sera from recruits from one trial, in this case the third trial, were selected. The distribution of antibody titres of these sera and of sera collected from initially sero-negative recruits at 3 weeks after vaccination is shown in Table 3. The postvaccination titres were significantly lower than the titres elicited by naturally acquired subclinical infection ($P < 0{\cdot}001$, two-sided Wilcoxon's two-sample test). Furthermore, it appeared that the magnitude of the antibody response to infection was related to the quality of the clinical response ($P < 0{\cdot}001$, k sample trend test, van Eeden & Rümke, 1961). Antibody titres attained in febrile illness were higher than those

found in afebrile illness. The antibody response to afebrile illness in turn was greater than that to subclinical infection.

Protective effect of the vaccine

Total respiratory illness

Tables 4 and 5 present a summary of the evaluation of the vaccine in the second and third trials conducted in the winter of 1967. Adenovirus was responsible for less than one-fifth of the cases of febrile and afebrile respiratory illness in

Table 4. *Incidence of febrile and afebrile respiratory illness caused by adenovirus in vaccinated and unvaccinated recruits in second trial*

	Vaccination state of companies					
	100%	Nil	50%		Totals	
	Vaccine	Control	Vaccine	Control	Vaccine	Control
	Febrile respiratory illness					
No. in group	878	889	405	468	1283	1357
All illnesses:						
Rate/1000	59	35	22	43	48	38
Adenovirus illness:						
No. tested for virus	40	26	6	17	46	43
No. positive	0	3	0	5	0*	8*
Est. rate/1000†	0	4	0	13	0	7
	Afebrile respiratory illness					
No. in group	455	400	211	226	666	626
All illnesses:						
Rate/1000	336	368	313	460	329	401
Adenovirus illness:						
No. tested for virus	110	76	35	45	145	121
No. positive	2	9	0	6	2‡	15‡
Est. rate/1000	6	44	0	61	5	50

* $P < 0{\cdot}01$ (χ^2 test).

† Estimated rate calculated by applying the percentage of virus positive cases to the rate of all illnesses.

‡ $P = 0{\cdot}01$ (χ^2 test).

controls from the second trial, and for about one-third of the cases of afebrile respiratory illness in controls from the third trial. It is obvious, with the inclusion of many cases of respiratory disease of other etiology, that a comparison of all cases of illness in vaccinated men and controls affords a rather insensitive index of the protective effect of the vaccine. Thus, it was not surprising to find that total afebrile respiratory illness was only slightly reduced in the vaccinated groups.

The incidence of febrile respiratory illness in vaccinated recruits from the second trial appeared to be higher than that in unvaccinated men. This was attributable to a marked difference in incidence between recruits of totally vaccinated and unvaccinated companies. It seems unlikely that vaccination was

responsible for this effect since most patients with febrile respiratory illness in the vaccinated group were admitted during the last 4 weeks of the training period and no adenovirus was recovered from the oropharynx of the patients at the time of illness. Possibly, the outcome was affected by variation in activity of respiratory agents and in reporting to sick call between different companies.

Table 5. *Incidence of febrile and afebrile respiratory illness caused by adenovirus in vaccinated and unvaccinated recruits in third trial*

	Vaccination state of companies					
	100%	Nil	50%		Totals	
	Vaccine	Control	Vaccine	Control	Vaccine	Control
	Febrile respiratory illness					
No. in group	847	820	412	461	1259	1281
All illnesses:						
Rate/1000	33	63	29	33	32	52
Adenovirus illness:						
No. tested for virus	17	41	9	8	26	49
No. positive	0	23	1	7	1*	30*
Est. rate/1000†	0	35	3·2	29	1·2	32
	Afebrile respiratory illness					
No. in group	431	470	210	242	641	712
All illnesses:						
Rate/1000	179	294	248	186	201	257
Adenovirus illness:						
No. tested for virus	48	90	39	32	87	122
No. positive	1	35	3	10	4‡	45‡
Est. rate/1000	3·7	114	19	58	9	95

* $P < 0{\cdot}001$ (χ^2 test).

† Estimated rate calculated by applying the percentage of virus positive cases to the rate of all illnesses.

‡ $P < 0{\cdot}001$ (χ^2 test).

Total febrile respiratory illness was markedly (about 40 %) reduced in vaccinated men from the third trial who underwent training between mid-March and mid-May. During this period about 60 % of febrile respiratory illnesses were due to adenovirus.

Adenovirus illness

The protective effect of the vaccine is clearly shown when the incidence of adenovirus illness in the vaccinated and unvaccinated recruits is compared (Tables 4 and 5). Diagnosis of adenovirus illness was based on recovery of virus from the throat. All adenovirus strains isolated were found to be of type 4. In each of the two trials conducted in the winter of 1967 vaccination effected a significant reduction in the number of patients with febrile and afebrile adenovirus illness.

The incidence of adenovirus illness was estimated by applying the rate of virus-

positive cases to the total illness rate. In the second trial the estimated rates for febrile adenovirus illness were 0 per 1000 in the vaccinated recruits and 7 per 1000 in the unvaccinated; the corresponding rates for afebrile adenovirus illness were 5 and 50 per 1000. This represented a complete reduction in incidence of febrile adenovirus illness and about 90% reduction in incidence of afebrile adenovirus illness. The estimated reductions in incidence of adenovirus illness in the third trial were about 96% for febrile illness and about 91% for afebrile illness.

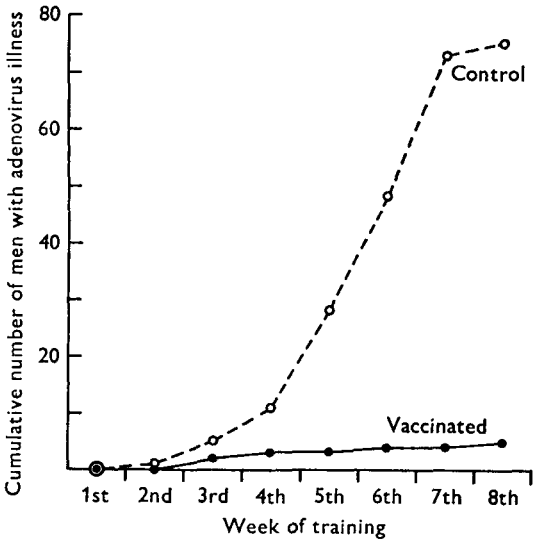

Fig. 1. Cumulative number of recruits with febrile and afebrile adenovirus illness in third trial.

The distribution of adenovirus illness in the vaccinated and unvaccinated groups from the third trial by week of training is shown in Fig. 1. The greatest number of illnesses occurred in the fifth, sixth and seventh weeks of training.

Antibody status and subsequent infection

To obtain information on the relation between antibody status and susceptibility to subsequent adenovirus infection, sera taken from vaccinated and unvaccinated recruits from the third trial at 3 weeks after their entry into the training centre were tested for presence and level of neutralizing antibody. The serological data were then correlated with the infection patterns of the recruits. Clinical as well as subclinical infections were included. Diagnosis of infection was based on significant rises in antibody titre occurring between the third and eighth week of training. The 5-week interval corresponded to the period in which the majority (over 90%) of adenovirus illness occurred.

As seen in Table 6, there was in both groups an inverse relationship between the titre of pre-existing neutralizing antibody and the frequency of serologically detected adenovirus infection ($P = 0{\cdot}01$, k sample trend test; van Eeden & Rümke, 1961). Infection was observed most often in recruits who were devoid of

antibody and least often in individuals with high levels of pre-existing antibody. Antibody stimulated by vaccination appeared to be indicative of a higher degree of protection than that produced by naturally occurring infection. Vaccinated recruits with antibody titres of 4 to 32 were infected significantly less often than were controls with the same antibody titres. A similar difference was found when vaccinated and unvaccinated recruits without pre-existing antibody were compared. The latter finding suggests that enteric infection with adenovirus type 4 is capable of providing protection without concomitant production of detectable antibody titres.

Table 6. *Influence of vaccine-induced and naturally acquired neutralizing antibody upon susceptibility to clinical and subclinical adenovirus infection*

Group	Neutralizing antibody titre at 3 weeks after onset of training	No. of recruits studied	No. showing antibody rise between 3rd and 8th week of training	
			Neutralization	CF
Vaccine*	<4	13	3†	2‡
	4–8	39	6	1
	16–32	34	2 §| 0	
	⩾64	26	0	0
	Totals	112	11	3
Control	<4	129	79†	71‡
	4–8	21	8	4
	16–32	37	10 §| 4	
	⩾64	22	1	1
	Totals	209	98	80

* Sero-negative. † $P = 0{\cdot}02$ (χ^2 test). ‡ $P = 0{\cdot}01$ (χ^2 test).
§ $P = 0{\cdot}01$ (χ^2 test). || $P = 0{\cdot}01$ (χ^2 test).

Subclinical adenovirus infection

From the data obtained in the third trial, it was possible to study the effectiveness of the vaccine in preventing subclinical adenovirus infection. The study was confined to the six companies surveyed for febrile and afebrile adenovirus illness. The purpose of the investigation being to measure the protective effect of the vaccine against subclinical adenovirus infection alone, recruits with febrile and afebrile respiratory illness from whom adenovirus was isolated were set aside. A comparison was made of the frequency of serologically detected adenovirus infections occurring in vaccinated and unvaccinated recruits of the remaining population during the last 5 weeks of training.

The neutralization test showed increases in titre in 8 % of 134 vaccinated recruits and in 40 % of 110 controls. The corresponding percentages for the CF test were 2 and 33. Since the presence of pre-existing antibody might prevent serological detection of subsequent adenovirus infection, the comparison of the frequency of serologically detected infections between vaccinated and unvaccinated recruits was restricted to those without pre-existing neutralizing or CF antibody. Neutralizing antibody rises were then found in 1 of 10 vaccinated men and in 34 of

61 controls. The difference was significant ($P = 0{\cdot}02$, χ^2 test) and represented about 82 % reduction. CF antibody rises were detected in three of 22 vaccinated men and in 26 of 56 controls ($P = 0{\cdot}01$, χ^2 test), giving about 71 % reduction.

DISCUSSION

Outbreaks of adenovirus infection among recruits at Ossendrecht usually develop in the second month of training, whereas in most military training centres in the United States adenovirus infection commonly occurs during the first weeks of training (Hilleman, 1957; Miller *et al.* 1965). It seems likely that the pattern of infection is related to the method of recruitment. Dutch recruits are admitted non-continuously at intervals of 2 months, whereas there is a continuous influx of fresh recruits in training centres in the United States. The late occurrence of adenovirus illness in recruits at Ossendrecht affords a special benefit in vaccination studies in that the protective effect of vaccine may be obtained before the beginning of an outbreak. Enteric type 4 adenovirus vaccine appears to be highly effective in the ecological setting of the present study. The vaccine provided almost *complete protection against febrile adenovirus illness and slightly less protection* against afebrile adenovirus illness. In addition, about 70 % reduction in subclinical adenovirus infection was found as a result of vaccination. No adverse reaction to the vaccine came to our attention. The prophylactic effect of the vaccine on total respiratory illness was less spectacular. This is explained by the fact that a large proportion of respiratory illnesses were not caused by adenovirus.

In contrast to the excellent protective capacity, the ability of the vaccine to produce antibody was poor. The vaccine was capable of providing protection even without concomitant production of detectable antibody. These findings point to the limited significance of the presence of antibody and the height of antibody titres as measures of the existence and degree of immunity. The demonstration that low antibody titres stimulated by vaccination were associated with a higher degree of protection than were the same titres of antibody produced by naturally acquired infection also points that way. Apparently, the antibody-stimulating effect of enteric infection with adenovirus type 4 was only remotely related to the protective capacity of such infection. It seems unlikely that the poor antibody response to vaccination was due to lack of sensitivity of the neutralization test employed. In comparative tests with sera from recruits with naturally acquired adenovirus type 4 infection high antibody titres were found. Similarly, in a previous study of adenovirus immunization in infants we observed high antibody titres after administration of two or three doses of inactivated vaccine, using essentially the same neutralization technique (van der Veen *et al.* 1967).

In previous studies enterically administered type 4 adenovirus did not spread to susceptible contacts (Chanock *et al.* 1966; Edmondson *et al.* 1966; Gutekunst *et al.* 1967). We found that a small proportion of unvaccinated controls without pre-existing neutralizing antibody developed antibody during the first 3 weeks of the training period. Antibody rises were detected slightly more frequently in controls of 50%-vaccinated companies who were in close personal contact with

vaccinated recruits than in men of entirely untreated companies who had less or no contact with vaccinated men. The differences were not statistically significant. Although these findings do not afford unequivocal evidence of lack of communicability of enteric type 4 infection, they nevertheless suggest that, if spread of virus occurs at all, virus is transmitted only with difficulty.

SUMMARY

Live type 4 adenovirus contained in enteric-coated tablets was given to 2628 military recruits. In two trials, the enteric adenovirus vaccine reduced febrile and afebrile adenovirus illness by about 90% or more. Moreover, a decided protective effect against subclinical adenovirus infection as evidenced by seroconversion was found.

The antibody-stimulating effect of enteric adenovirus vaccine was not an adequate measure of its protective capacity. The neutralizing antibody response of recruits given vaccine was poor in comparison with the antibody response to naturally acquired infection with type 4 adenovirus. The latter response was related to the severity of infection.

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