THE YALE JOURNAL OF BIOLOGY AND MEDICINE 48, 185-195 (1975)

Control of Adenovirus Acute Respiratory Disease in U.S. Army Trainees

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Received March 3, 1975

Although limited almost exclusively to military trainees, acute respiratory disease (ARD) caused by adenovirus types 4 and 7 had been the leading cause of hospitalization in U. S. Army personnel. This disease which resembles influenza in clinical manifestations led to hospitalization of as many as 50% of military trainees in midwinter and imposed a heavy burden on military hospitals and training programs. In studies undertaken from 1965 to 1970, live adenovirus type 4 and subsequently type 7 vaccines were found to be safe and immunogenic and to confer protection against type specific adenovirus ARD. For the past 5 yr, military trainees have been immunized with both adenovirus vaccines during periods of expected adenovirus disease. Since 1966, use of adenovirus vaccines has been monitored through the adenovirus surveillance program which yields weekly data on incidence and etiology of ARD in basic combat trainees. Since 1973, stable adenovirus vaccines have resulted in excellent control of adenovirus ARD. Potential problems with this immunization program are discussed.

Shortly after adenoviruses were first isolated from explant cultures of human adenoid tissue by Rowe *et al.* (1), Hilleman and Werner of the Walter Reed Army Institute of Research (WRAIR) (2) isolated a new strain of virus, subsequently classified as adenovirus type 4 (Adv-4) from recruits at Ford Leonard Wood, Missouri. It has since been amply confirmed that specific adenovirus serotypes—principally types 4 and 7, and occasionally types 3, 11, 14, and 21—are important causes of acute respiratory disease (ARD) in military trainees (3–6) although these types cause but a small proportion of respiratory tract infections in civilian populations. While many aspects of the epidemiology of adenovirus ARD remain obscure (7), the impact of this disease on military trainees and military training programs is clear and is illustrated by the experience of a platoon of basic combat trainees (BCTs) studied by our laboratory at Fort Dix, New Jersey, during the winter of 1965.

As previously described (8), these 48 men were followed by a WRAIR field team from their arrival at the reception center at Fort Dix and throughout their training were questioned and examined daily to detect symptoms of respiratory tract infection. Daily temperatures were taken, and if over 37.5° C, a more complete examination was made in order to document precisely signs and symptoms of ARD. Twice a week the nasopharynx of each trainee was cultured for bacterial and viral pathogens, while trainees with illness were sampled at onset of illness and when hospitalized. Disease was classified into afebrile, mild febrile, and severe febrile by criteria based upon temperature (8). As shown in Table 1, 92 episodes of respiratory illness were detected in the 8-wk training interval; 51 were afebrile, 17 mild febrile, and 24 severe febrile. The 92 episodes resulted in 24 hospitalizations, of which most, but not all, came from trainees with severe febrile illness. The incidence of disease

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TABLE 1
Incidence and Clinical Severity of ARD in Platoon of Army Recruits by Week of Basic Combat Training (BCT), Jan–Feb, 1965

Illness	No. men/wk BCT									Total
	0	1	2	3	4	5	6	7	8	
Total strength	48	48	48	48	46	41	40	39	39	
Afebrile URI[a]	10	16	13	11	1	0	0	0	0	51
Mild febrile	0	6	3	3	2	1	0	1	1	17
Severe febrile	1	1	7	13	0	2	0	0	0	24
Total	11	23	23	27	3	3	0	1	1	92
Admitted to hospital	0	3	7	11	0	2	0	1	0	24

[a]URI–upper respiratory infection.

rose in the first 2 wk of training (Table 1) to peak in the second and third week of training; this peak reflects that of severe febrile ARD and of hospital admissions.

The etiology of afebrile disease (which did not result in any hospitalizations) was not determined in 36 episodes but was associated with Adv-4 in the remaining 15 episodes. The etiology of febrile ARD, both mild and severe, was more commonly determined. Adenovirus type 4 was associated with 19 of 24 episodes of severe febrile ARD and 7 of 13 episodes of mild febrile ARD. Eighteen of the 24 trainees hospitalized had adenovirus type 4 ARD.

Criteria for hospitalizing BCTs with ARD are, of course, less stringent than for admission to a civilian hospital. Generally, U. S. Army Medical activities hospitalize all febrile trainees with ARD symptoms. This policy was at least in part a response to the necessity for close observation of febrile ARD patients for early signs of meningococcal disease. On the other hand, most trainees hospitalized with adenovirus ARD have fevers over 38.5° C associated with an illness remarkably similar to influenza and are incapable of training. About 7–10% of those hospitalized have radiologic evidence of pneumonitis and rare fatalities from adenoviral pneumonitis in basic combat trainees have been reported (9, 10).

This Fort Dix study illustrates many of the characteristic features of ARD of military trainees during the winter months. The majority of hospitalized or febrile ARD patients have adenovirus infections. During the 8-wk training cycle, nearly 50% of trainees are hospitalized with the majority of hospitalizations in a unit occurring within a 2-wk period. At northern BCT posts this translates to peak rates of 6–8/100 men/wk, or to 600–800 ARD admissions per week. At Fort Dix, four hospital wards in Walson Army Hospital were devoted entirely to acute care of febrile ARD patients. Also three to four wards of the hospital annex were opened and utilized for convalescent care during the ARD season. Further, the loss of 40% of the men of a training company within a 2-wk period necessitated the establishment of an additional training program by the cadre to make up training lost as the result of hospitalization. A significant proportion of trainees (nine in the platoon studied) were "recycled" to other companies in an earlier stage of training, since their illness placed them irretrievably behind their colleagues in the training cycle. Even at 1965 prices, the cost of hospitalization, of extra medical personnel required for ARD wards, and of lost training time, was high.

Initial attempts at control of ARD in recruits utilized inactivated adenovirus vaccines, initially bivalent (types 4 and 7) and later trivalent (with the addition of type 3). Although protection induced by pilot lots of these vaccines was promising

initially, variation in antigenicity of vaccine lots became a significant problem. At best, such vaccines effected a 70% reduction in type specific disease with an overall mean reduction of 40% (8). In 1963 adenovirus seeds for these vaccines were found to be contaminated with the oncogenic virus, SV-40, and the SV-40 genome was found to be incorporated within adenovirus capsids. Consequently, immunization with these vaccines was stopped and their license was rescinded.

Fortunately Couch and Chanock and colleagues at the National Institutes of Allergy and Infectious Diseases were working on development of live adenovirus vaccines. Making use of the observation that adenoviruses infect both the respiratory and gastrointestinal tract, but rarely produce gastrointestinal illness in adults, these investigators tested the hypothesis that adenovirus could be given in enteric-coated capsules to cause an asymptomatic infection of the gastrointestinal tract without respiratory tract infection and that such infection would induce protection against type specific respiratory tract disease. Preliminary experiments showed that volunteers could be infected without illness upon ingestion of type 4 and 7 virus and developed specific antibodies 2–3 wk after infection (11). When adenovirus type 4 vaccine was administered in an enteric-coated capsule to Marine recruit volunteers, it produced a selective intestinal infection which was silent, noncommunicable, and induced serum neutralizing antibodies (12). In 1964, with collaborating Naval medical officers, Chanock demonstrated that the type 4 vaccine, administered to Marine recruits at Parris Island, effectively reduced both hospitalizations for ARD and Adv-4 infections which ordinarily occur in epidemics when recruits are transferred to Camp Lejeune for advanced training (13). Subsequently, in 1965, Buescher and colleagues demonstrated that this vaccine was highly effective in Army trainees at Fort Dix in a situation where trainees are naturally exposed to adenovirus infections within 7–10 days after arrival. In a study involving six companies, the Adv-4 vaccine reduced total ARD hospitalization by 67% and Adv-4 associated hospitalization by 95% (8).

A second trial at Fort Dix in early 1966 uncovered a serious problem with monotypic adenovirus immunization (8). Beginning in February, all trainees in or subsequently entering one of the two training brigades were immunized with live Adv-4 vaccine, while trainees of the other brigade received placebo. Three weeks after immunization, the ARD rates dropped precipitously in the immunized brigade and remained low for 6 wk, when they increased sharply to rates of the unimmunized brigade. This was due to the emergence of adenovirus type 7 in the immunized brigade. While Adv-4 vaccine changed the infecting virus, the overall incidence of ARD was unchanged. It was clear that a monotypic Adv-4 vaccine was not the final answer to control of ARD in military trainees and would be useful only in posts with Adv-4 ARD.

Before adenovirus vaccine could be administered rationally in the nine other BCT posts, a system to monitor the incidence of ARD and the adenovirus serotype etiology of hospitalized ARD was required. The Army Adenovirus Surveillance Program, involving extensive collaboration between the Army area laboratories under supervision of the Fort Baker, California, laboratory, the now Division of Health and Environment, Office of the Surgeon General (OTSG), and the WRAIR, was designed to assess variations in ARD prevalence and to provide contemporary information about disease etiology to facilitate decisions as to when, where, and what type of vaccines were needed to control recruit ARD. The mechanisms and benefits of this surveillance program have recently been reviewed by Dudding *et al.*

(14). Briefly, preventive medicine officers at each BCT post were required to submit weekly reports to the OTSG, specifying (a) the number of trainees from each training company, battalion, and brigade, admitted to the base hospital with an admission diagnosis of ARD (numerator), (b) the number of trainees in each of those units (denominator), and (c) and ARD admission rate per 100 men per week for each unit as well as for the entire BCT population on post, calculated from the above. In addition, preventive medicine officers were required to provide throat swabs and acute and convalescent sera for viral serology from a sample of recruits hospitalized with ARD each week. The purpose was to determine what serotypes of Adv were prevalent on various posts; therefore, specimens were collected specifically from individuals most likely to have adenovirus disease (those with the most severe symptoms and highest fevers who had been hospitalized less than 24 hr previously). One-half the specimens from each post were sent to the Army medical laboratory, Fort Baker, and the other half to the regional Army medical laboratory. These laboratories reported weekly the results of viral isolation and serologic studies. This program proved of great value in providing data necessary for rational use of type 4 and later type 7 vaccine in BCT populations.

During earlier development of adenovirus vaccines, it was discovered that certain human adenoviruses were oncogenic for newborn hamsters and could transform rat cells (15). Among these oncogenic types were types 3, 7, and 21; fortunately, type 4 has not been shown to be oncogenic, so that Adv-4 vaccine could continue to be used in humans. Further studies of Adv-7 vaccines had to await results of studies of the role of adenoviruses in human neoplasia. Certain characteristics of adenovirus induced tumors in hamsters were exploited to determine the role of adenoviruses, if any, in human tumors. First, in adenovirus-induced hamster tumors, the presence of an early, nonstructural T antigen specific for adenovirus groups could be detected by complement fixation or fluorescent antibody techniques. Second, hamsters with tumors developed serum antibodies to this T antigen. Third, messenger RNA specific for adenovirus, could be detected in tumor cells by hybridization techniques with radioactive viral DNA. With the support of Solid Tumor Segment of the National Cancer Institute, National Institutes of Health, Gilden and colleagues examined the sera of 389 advanced solid tumor cases and controls for evidence of antibody to T antigens of adenoviruses (16). No evidence of complement-fixing antibody to T antigen of known oncogenic adenoviruses was found in cancer patients or control sera. By the less specific FA technique, a small and similar prevalence of antibody to T antigens was found in both groups. In a subsequent study, Green *et al.* (17) found no evidence for virus-specific m-RNA in over 200 human cancer specimens examined. These results suggested that adenoviruses are unlikely causes of tumors in man, but if they are, the mechanisms involved are different from adenovirus carcinogenesis in laboratory systems (which were the chief bases for suspecting their oncogenicity in man in the first place). On the basis of these and many other studies, the National Cancer Institute concluded that "adenoviruses . . . were eliminated as causative agents in human cancer" (18).

As a result of these studies, evaluation of live, adenovirus type 7 vaccines were begun with the approval of the Vaccine Development Committee, NIAID, NIH, and the Army Investigational Drug Review Board, Office of the Surgeon General. In preliminary studies undertaken in military volunteers at the U. S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland, and the Army Medical Training Center, Fort Sam Houston, Texas, the safety, infectivity, non-

TABLE 2
Rates of Hospitalization due to Acute Respiratory Disease (ARD) in Study Groups, Fort Dix, 1969

Group	No. of men hospitalized (rate/100 men per 8 wk)			
	ARD due to adenovirus type		ARD not due to adenovirus	Total
	4	7		
Test (231 men)	2(0.9)	1(0.4)[a]	29(12.6)	32(13.9)[b]
Control (920 men)	8(0.9)	123(13.4)	109(11.8)	240(26.1)

Note. The test group received both adenovirus type 4 and adenovirus type 7 vaccines. The control group received adenovirus type 4 vaccine and a placebo.
[a] $\chi^2 = 32.6, P < .0005$.
[b] $\chi^2 = 15.3, P < .0005$.

communicability, and immunogenicity of a live, enteric-coated type 7 vaccine was established (19). It was also shown that the live Adv-7 and Adv-4 vaccines could be given safely with no appreciable loss in infectivity or immunogenicity of either vaccine. In 1969, the protective effect of Adv-7 vaccine was evaluated in six companies of trainees at Fort Dix during an outbreak of type 7 ARD. By random selection, 20% of trainees received both type 7 and type 4 vaccines, while 80% received a placebo and type 4 vaccine (20). As shown in Table 2, the rate of ARD hospitalization was significantly decreased in trainees receiving both vaccines. Adv-7 associated ARD occurred 96% less frequently in the test group receiving the type 7 vaccine. Rates for type 4 disease were low (0.9) and identical for both groups. Rates for ARD not associated with adenoviral infection were similar for both groups, evidence that immunization with type 7 vaccine did not mask detectability of type 7 infection in previously immunized trainees.

A study of the impact of mass immunization with both adenovirus vaccines was instituted at Fort Dix in 1970 (21). All recruits entering the 3rd training brigade received both adenovirus vaccines within 72 hr of arrival on post, while those in the 2nd brigade (as in 1966) received only type 4 vaccine. All trainees reporting to Fort Dix during a single week (one cohort) were formed into six training companies

TABLE 3
Total and Adenovirus-Associated ARD Hospitalization Rates of Study Companies, Fort Dix, 1970

	2nd Brigade (Adv-4)		3rd Brigade (Adv-4, Adv-7)	
	No.	Rate[a]	No.	Rate[a]
Trainees	805		911	
ARD hospitalizations Total	258	32.0[e]	149	16.3
Adv-7 associated	159	19.8[b]	9	1.0
Adv-4 associated	16	2.0[c]	49	5.4
Adv type undetermined	0	0.0	4	0.4
Total Adv associated	175	21.8[d]	62	6.8

Note: Trainees in the 2nd brigade received both adenovirus type 4 and 7 vaccines, while those in the 2nd brigade received only type 4 vaccine.
[a] Rate/100/8 wk.
[b] Chi square = 170.4, $P < .001$.
[c] Chi square = 13.4, $P < .001$.
[d] Chi square = 80.0, $P < .001$.
[e] Chi square = 58.3, $P < .001$.

assigned to one brigade; those reporting during the following week (another cohort) formed six companies in the other brigade. All hospital ARD admissions in one of the six companies constituting each of the ten weekly cohorts was studied for viral etiology. ARD rates from study companies from the two brigades are detailed in Table 3. Total ARD rates were 50% less in the 3rd brigade. This was due to a 95% suppression in type 7 associated ARD in this brigade which received the type 7 vaccine. There was a small but significant increase in the incidence of type 4 associated disease in this brigade. This was evidence of some interference of the type 7 vaccine with protective efficacy of the type 4 vaccine, and may have been due in part to the relatively low potency of the type 4 vaccine used in this study. Despite this, total adenovirus-associated disease was reduced by two-thirds in the brigade receiving the bivalent vaccine. No significant difference in rates of ARD not associated with adenoviruses was seen between the 2nd brigade (10.2/100) and the 3rd brigade (9.5/100). No other respiratory pathogens emerged to replace Adv-4 and 7 as major causes of ARD in this immunized population (22).

At this point it seems desirable to consider how adenovirus vaccines may protect against respiratory tract disease. While serum, as well as local secretory respiratory tract antibodies, are induced by natural adenovirus infection (23), intestinal infection with vaccine virus induces serum and intestinal antibody, but does not induce antibody in the respiratory tract (24, 25). It is remarkable that a vaccine which induces serum neutralizing antibody alone protects against adenovirus respiratory disease. Respiratory tract infection with vaccine virus is readily induced in volunteers immunized with adenovirus vaccines, but uncommonly induced in volunteers with previous evidence of specific adenovirus infection (24). Further, respiratory tract infection with homologous adenovirus is not uncommon in military trainees studied sequentially after adenovirus type 4 immunization, but rarely results in hospitalization (Top, F. H., Jr., unpublished observations). Although studies to quantitate the

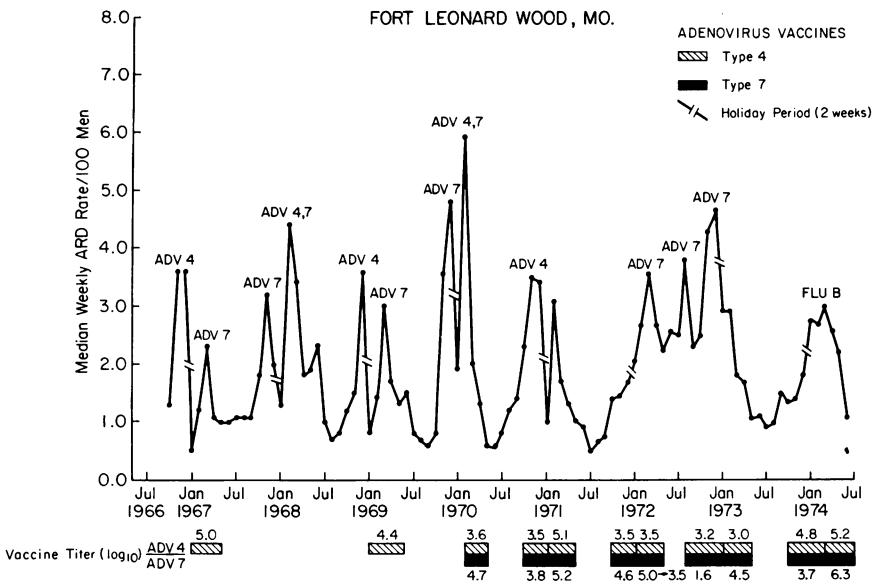

FIG. 1. Acute respiratory disease rates in basic combat trainees at Fort Leonard Wood, Missouri, 1966–1974. The bars at the bottom of the graph indicate vaccination periods with the respective vaccine titers as noted.

effect of adenovirus vaccines on naturally occurring infection in military trainees have not been undertaken, these vaccines do not totally prevent subsequent respiratory tract infection by homologous adenovirus type.

Since 1971, both adenovirus vaccines have been used at U. S. Army BCT posts during periods of anticipated adenovirus ARD. Schedules of immunization have been tailored to individual posts with the objective being control, rather than eradication, of adenovirus ARD. From 1971 to 1973, control was less than optimal, primarily due to virus stability problems with many vaccine lots. The 2–3 log decrease in virus titer within months after manufacture was traced to contamination of the vaccine virus in the core of the tablet by solvent used in the enteric coating process (Bernstein, A., personal communication). Adequate ventilation of solvent during this process through new drying equipment has produced stable vaccines since January 1974. Problems engendered by monovalent immunization alone or by vaccines of low potency are shown in the next three figures. Figure 1 portrays ARD experience at Fort Leonard Wood since 1966 when adenovirus surveillance began. In 1967 and 1969, the use of type 4 vaccine led to the emergence of Adv-7 within 2 mo after beginning immunization. As in Forts Jackson and Dix (Figs. 2 and 3), Adv-7 persisted on post after cessation of type 4 immunization through the subsequent ARD season; only about 2 yr after use of Adv-4 vaccine could Adv-4 vaccine again be used to control ARD at these posts. At Fort Wood both adenovirus vaccines were used beginning in the middle of February 1970, and this resulted in a precipitous decline in ARD rates. A type 4 vaccine of low potency used in the fall of 1971 led to an Adv-4 outbreak, and an unstable type 7 vaccine used from January 1972 through January 1973 resulted in a sustained outbreak of Adv-7 ARD. Since the use of stable type 7 vaccines beginning in January 1973, outbreaks of adenovirus ARD at Fort Wood have not occurred. Increased ARD rates from January through May 1974 were due to influenza B and rubella; less than 5% of ill trainees had adenovirus infections during those months.

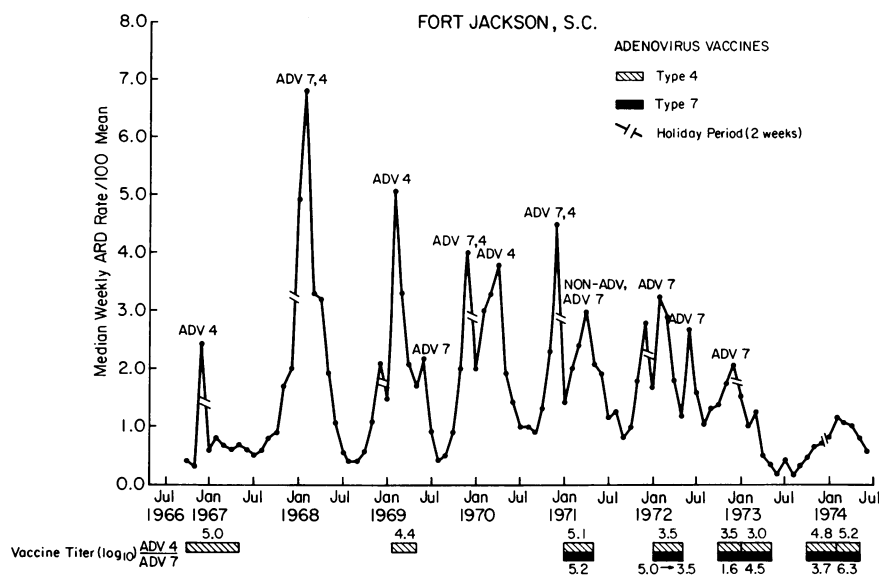

FIG. 2. Acute respiratory disease rates in basic combat trainees at Fort Jackson, South Carolina, 1966–1974. Legend same as for Fig. 1.

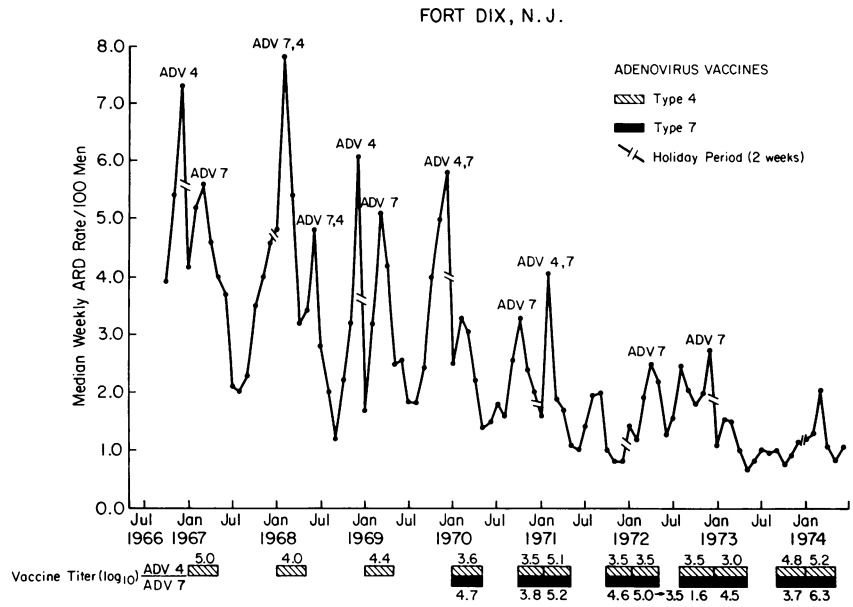

FIG. 3. Acute respiratory disease rates in basic combat trainees at Fort Dix, New Jersey, 1966–1974. Legend same as for Fig. 1.

At Fort Jackson (Fig. 2) the pattern was qualitatively similar but quantitatively less severe than at Fort Wood. Again, unstable type 7 vaccines used in 1972 led to Adv-7 outbreaks (which persisted during the summer months, as at Fort Wood). Since January 1973, ARD rates have rarely exceeded 1.0/100/wk and few adenoviruses have been isolated from trainees with ARD.

ARD patterns are more impressive at Fort Dix (Fig. 3) where, despite similar problems with type 7 vaccines, ARD rates rarely exceeded the 3.0/100/wk expected even during the summer months at Dix prior to 1970. Since January 1973, the rate exceeded 2.0/100/wk in only 1 mo, and adenovirus has been isolated from less than 5% of trainees hospitalized at Walson Army Hospital, a far cry from previous experience there. Vaccines in current use are potent and their use in the six BCT posts during fall 1974 has resulted in blunting of early type 4 epidemics at Forts Knox and Dix. We hope that the last 2 yr experience with potent adenovirus vaccines will prove the rule rather than the exception.

Because of the large number of recruit hospitalizations for ARD, even a modest reduction in disease results in significant savings. Collis *et al.* (26) undertook a cost benefit analysis of the entire adenovirus surveillance program. He estimated that between 1966 and 1971, the total cost of the surveillance program, including vaccine development, vaccine purchases, administration, and laboratory support was $4.83 million. Using his estimate of roughly 27,000 Army ARD hospitalizations prevented during the 2 yr 1970 and 1971 at an average cost of $279 per hospitalization, the dollar estimates of benefits derived from vaccine use was $7.53 million. Thus benefits derived in the 2-yr period of bivalent vaccine use outweighed the total costs of the program over a 5-yr period.

Although rates have been low and training and hospital commanders reasonably happy with ARD control for the past 2 yr, there are potential problems which could affect this program.

Although adenoviruses other than types 4 and 7 have not been encountered in Army trainees since type 21 appeared at Fort Dix in 1967 (27), ARD caused by adenoviruses other than types 4 and 7 remains a frightening possibility. Although their absence may reflect a limited or sporadic possibility of introduction into BCT posts, the critical question of their transmissibility once introduced in the absence of simultaneous transmission of either types 4 or 7 is unanswered. Approximately 85% of Army trainees lack neutralizing antibody to Adv 21 (Top, F. H., Jr., unpublished observation), and this virus has caused significant ARD outbreaks in Dutch (5), Russian (28), Indian (29), and U. S. troops (27). A type 21 vaccine was found similar to types 4 and 7 in regard to safety, infectivity and immunogenicity in military volunteers in studies by our group (30), but the protective efficacy of the vaccine has not been tested.

Primary human embryonic kidney cell (HEK)cultures are far more sensitive and convenient than other cells (31) for adenovirus isolation and have been used in the adenovirus surveillance system since its inception. The effect of proposed legislation dealing with medical experiments involving human fetuses upon the availability of HEK cells (as well as other cell lines such as human diploid fibroblast cells used for vaccine production) is not clear at time of writing.

A third problem is remaining uncertainty as to the role of adenoviruses in human tumors. Previous studies, reviewed above, could not incriminate adenoviruses as a cause of human tumors. Although the techniques used to detect adenovirus specific proteins or m-RNA in these studies were sufficiently sensitive to establish the adenovirus etiology of tumors in hamsters, it is possible that they were not sufficiently sensitive to detect adenovirus fingerprints in human tumors. In view of the latency of certain adenoviruses (especially types 1, 2, 5, and 6) in human tissue (32), it would be surprising if the genome of certain adenovirus types could not be detected in humans. Currently the U. S. Army Medical Research and Development Command, together with the Bureau of Biologics, Food and Drug Administration, and the National Institutes of Allergy and Infectious Diseases, National Institutes of Health, is funding a study to determine the prevalence of adenovirus genome in tissues from patients with and without neoplasia, using a DNA hybridization technique which is 10–100 times more sensitive than the methods used to detect adenovirus m-RNA in previous studies. The results of the study are awaited with considerable interest.

In summary, adenovirus ARD has been the major cause of morbidity in military trainees and the leading cause of military hospitalizations in the United States. Currently this disease is well controlled by immunization with live, oral, enteric-coated adenovirus types 4 and 7 vaccines. It should be evident from this review that the success of this program has resulted from the combined efforts of many interested investigators, both civilian and military. Further experience is required to determine the ultimate impact of adenovirus types 11, 14, and 21 in trainees immunized with types 4 and 7 vaccines, and more sensitive studies of the role of adenoviruses in human neoplasia are required and are in progress.

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