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Efficacy of influenza virus vaccination

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THE EFFICACY OF INFLUENZA VIRUS VACCINATION

by

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THE EFFICACY OF INFLUENZA VIRUS VACCINATION

The problem of vaccination against influenza has had a continuous history of activity since 1933 when the British workers, Smith, Andrewes and Laidlaw (44), first reported the isolation of the virus from persons suffering from influenza. They produced a disease in ferrets, serially transmissable, from intranasal instillations of filtrates of throat washings from influenza patients. Throat washings from healthy patients would not produce the disease and sera from convalescent patients was capable of neutralizing the virus. Formerly the disease had been thought to be bacterial in origin. In 1934 this work was confirmed by Francis (14) in the United States and he worked further to isolate the virus of influenza B in 1940. They found that an epidemic in 1936 and again in 1940 was similar to the disease caused by A in every respect except serological immunity--our first inkling that influenza could not be attributed to one virus. Epidemiologically the two diseases differ in that A usually occurs biannually and B about every five years.

Since it was known the first tissue attacked by the influenza was mucous membrane of the nose and throat, the first method of vaccination attempted was by inhalation. An Australian group (29) showed some immunity could be built up by intranasal vaccination but their results were not

decisive and a United States group (15) later proved the results were inferior to those obtained by subcutaneous vaccination.

Until 1942 no work had been done to definitely prove without doubt that immunization gave protection against influenza. World War II was well under way and there was considerable fear that an epidemic similar to the one following World War I might occur. Two pieces of work laid the foundation for definite clinical studies. Hirst et al (24) used eleven different preparations of influenza virus vaccine on large groups of human beings and measured their antibody responses. They found there was a wide individual variation in antibody response to the same preparation given subcutaneously to different people and that responses were practically the same in those with low prevaccination antibody level and high levels. Within certain limits, the mean antibody response increased as the amount of virus injected and large amounts gave the same level as having the disease. The antibody response showed a marked drop in six to nine weeks after vaccination and even more after five months. Most important, they found when vaccine was prepared from allantoic fluid there was no significant difference in active virus, formalin inactivated virus, heat inactivated virus or virus inactivated by drying. Hence, an easily handled formalin killed virus vaccine could be used as efficiently as the live virus. The second group (22) created

their own epidemic by inhalation of recently isolated active virus. Of the twenty-eight control individuals, ten came down with clinical influenza. Only one case, which had not responded to vaccination, occurred among the forty-four vaccinated persons, twenty-seven of whom had been immunized four months prior to exposure. There was good correlation between the pre-inhalation antibody level and the degree of protection in that most of the clinical cases occurred in the group with the lowest antibody titer. Increase in the antibody titer decreased the morbidity, even in the subclinical cases. This proved protection is given when the proper strains are used in the vaccine.

Because of the fear a severe epidemic might occur during the war, a Commission of Influenza was appointed with Dr. Francis as Chairman. It was a part of the Preventive Medicine Service, Office of the Surgeon General, United States Army, and these people are responsible for most of the work and knowledge we have concerning the efficacy of influenza vaccination today. In 1942, anticipating an epidemic of influenza A on the two year cycle, they vaccinated approximately eight thousand individuals. However, this was the year it skipped so the only information obtained concerned titers, duration, et cetera which will be discussed later. Artificial infection bore out previous studies.

In 1943-44 the most comprehensive study of all was conducted (7)(17) to prove in a controlled clinical trial

the prophylactic efficacy against epidemic influenza of a concentrated inactivated vaccine containing viruses of types A and B. The 1943-44 outbreak was considered the biggest since 1918-19 and Collins (5) further states the incidence in children under ten years and adults over forty years was equal to and greater than, respectively, 1918-19. Six study groups were set up (two in the East, three in the Midwest, and one in Western United States) and they showed clearly for the first time that subcutaneous vaccination of a human population exerts a pronounced effect upon susceptibility to influenza A during an epidemic of high incidence. Their work will be discussed at some length because the standards set were used in most succeeding experiments as well. The virus was obtained from the allantoic fluid of embryonated hens' eggs inoculated forty-eight hours earlier. Formaldehyde 1:5000 was used to destroy the infectious capacity. Virus A was of equal parts of the P. R. 8 and Weis strain. Type B contained only the Lee strain. Control material was made exactly the same as the vaccine with omission of the virus. The following A. S. T. P. Units were used: Cornell, New York Medical Schools, Princeton, Rutgers, City College New York, Michigan, Minnesota, Iowa and California. Approximately 12,500 men were involved. In most instances they were housed in large dormitory units. Vaccine from two firms was mixed together. Each unit was divided in half so alternate men received controls and records were removed after vaccination so examiners had no way of knowing which was which. All

students with typical symptoms of influenza and a sublingual temperature of 100° F. or over were admitted to the hospital. Fresh Typical Colds, Tonsillitis, Infectious Mononucleosis, et cetera were eliminated as much as possible. Influenza A epidemic was first identified in the Midwest in November and it subsequently spread to all units. Data collected, based on clinical evidence alone (serological discussion later), is as follows: incidence in 6,211 men of the control group was 7.11%, while in 6,263 receiving vaccine, 2.22%--a ratio of 3.2 to 1. There were two pronounced deviations (discussed later) and when these are excluded, the ratio is more nearly 6 to 1.

Individually these reports are: Minnesota (36) clinical attack rate 2.7% in vaccinated, 9.06% in control; Iowa (21) 2.17% in vaccinated, 7.01% in control; Michigan (37) 2.27% in vaccinated, 8.58% in control; California (11) 3.92% in vaccinated, 5.97% in control; Princeton (25) 2.8% in vaccinated, 8.5% in control; Rutgers (25) .99% in vaccinated, 6.0% in control; City College New York (25) 1.71% in vaccinated, 8.34% in control; Cornell (28) 1.0% in vaccinated, 2.6% in control. California (11) differed from other groups in several respects and herein probably lies the deviation. A large proportion were civilians and lived in scattered homes, a large number left before the test was completed, many diagnoses were made by questionnaire filled out by the patient without seeing a doctor, antigenic deviation of the

strains of virus as they proceeded from East to West, the vaccine was not mixed and it produced a weak response to one strain. In the above reports, it is interesting to note that in all probability the incidence in controls should be higher but they were somewhat protected by mass immunity of the vaccinated. When complete companies were left out of the program, their incidence ran as high as 20% to 30%. Of further interest is the fact that City College New York and Iowa completed vaccination just at the time the epidemic started and for the first week there was no difference in incidence between the controls and vaccinated; after the first week the curves diverge sharply, indicating the effect of vaccination became evident five to seven days after vaccination.

On the basis of the above findings, the Influenza Commission recommended to the Board that widespread vaccination be carried out in the Army in 1945. Less extensive reports in 1945-46 are available. However, at Yale (26) there was an epidemic of virus B in a group of 550 vaccinated Army students and 1,050 Navy students observed under identical conditions. One hundred thirty-two cases occurred in the unvaccinated group and three in the vaccinated group--a percentage of 12.5 and .5 respectively. At Ann Arbor (18) it was possible to compare the incidence of disease in an Army unit of 600 men vaccinated and 1,100 not vaccinated with an incidence of 1.15% and 9.91% respectively. Strains

encountered differed serologically from the Lee strain of B but did not prevent prophylactic effect of the vaccine.

Prospects that the vaccine would have a "rosy future" were excellent until the epidemic of 1947-48. Heretofore the words antigenic deviation had been mentioned occasionally but this year they were to almost spell doom for the growing popularity for influenzal vaccination. Francis (19) observed 10,328 vaccinated and 7,615 non-vaccinated persons during the epidemic. Although they (the vaccinated) had good A and B titers, the incidence of disease in the two groups was essentially the same, as was their antibody titers against a new A' virus causing the epidemic. Ferrets inoculated with the virus of the prevailing epidemic built up antibodies against it but not to A and B. Sigel and his group (43) found no evidence of protection when 88% of his group were vaccinated. Potency for A and B antibodies was good but this was not the virus of the epidemic. At Kemper Military Academy (47), the attack rate was 20% in vaccinated and 28% in non-vaccinated personnel. The difference was judged to be insufficient to justify the procedure. Salk and his group (41) used both the old and new strains in two separate vaccines and found considerable less attack rate in those getting the new vaccine. Other groups (27) were listed as follows: Bucknell, vaccinated 7.05, unvaccinated 7.3; West Point, vaccinated 20.2, unvaccinated 27.8; University of Chicago, vaccinated 7.00, unvaccinated 7.04.

All groups gave the same answer for failure--antigenic deviation. They concluded that this failure should cast no reflection on previous work done but should be taken as a lesson that a vaccine affording protection one year does not insure protection against subsequent outbreaks.

The foregoing reports on effectiveness of immunization were all taken from the armed forces and schools. In industry there are few accurate reports because of the time, expense and facilities needed for virus studies. A report based on absenteeism (30) from all types of upper respiratory diseases shows the volunteer vaccinated group (1946) lost 1.01 days per employee, while the control group lost .69 days per employee. In spite of this, the vaccinated thought the vaccine was a help. Probably they were people who were extremely susceptible to Upper Respiratory Infections or they would not have volunteered. Also, this is not days lost from Influenza but all types of Upper Respiratory Infections. Contrary to popular belief, even among doctors, all investigators have repeatedly pointed out that the vaccine has no affect on the Common Cold and associated Upper Respiratory Infections (1).

In Nebraska Dr. W. Thompson (45) made a study of 2,625 vaccinated Telephone workers (in a group of 3,473) and concluded the incidence seemed to be about the same in both groups although results were inconclusive because no serological work was done and many diagnoses were made by the

employees themselves. Furthermore, there was no epidemic at this time.

Up to this point, no mention has been made of reactions to the vaccine. Purely voluntary vaccination would never become prevalent if reactions were severe; likewise, severe reactions might be almost as bad as having the mild influenza now epidemic. Reactions are important in a consideration of the efficacy of influenza virus vaccination. There have been two fatal reactions reported (9), both of which were in children with .5 or 1 c.c. doses. Reactions were at first thought to be caused by sensitivity to egg albumin in the vaccine. Using children with definite allergy history such as asthma, eczema, urticaria, et cetera (35), one group showed there was not a single vaccine reactor (.02 c.c. vaccine from egg embryo) who was not positive for egg white. In a few cases a very mild reaction was gotten by using only formaldehyde solution. They concluded use of vaccine was not dangerous in 99.5% of the general population, and not dangerous to the .5% with allergic histories if skin-tested first with .02 c.c. (two or three M. of epinephrine should be used with the vaccine). Only the very rare person with systemic reaction to the skin test dose should not be given vaccine. In 1947 Engelsher (12) stated he believed the reaction to be based on a bacterial allergy rather than egg and this allergy was also frequently associated with sensitivity to aspirin. Salk in 1948 (40)

stated that the reaction is related to the quantity of virus injected but serological data showed that the sensitivity of the human subject is such that the amount of virus injected can be varied within rather broad limits without corresponding variation in antibody response, so the dose of virus can be safely adjusted to sub-reactive levels without sacrificing immunizing affect. In 1949 (33) it was definitely proven concentration of the virus was directly proportional to the amount of reaction; .1 c.c. and 1.0 c.c. shots were given (but with the same concentration of virus) and the reactions were similar. When various concentrations of the virus were used, the worst reactions occurred with the heaviest concentration of virus. This work was done on non-allergic people so we can deduct that reactions are caused both by egg sensitivity in the allergic and virus toxicity in the non-allergic. Reactions are of three types: a typhoid-like reaction of fever, malaise et cetera; an explosive angioneurotic anaphalactic reaction; and a local reaction. In a comparison of reaction from intracutaneous and subcutaneous administration, in 1947 Van Gelder (46) and co-workers obtained the following results:

	No. Examined	Local Reaction				Systemic
		None	Mild	Moderate	Severe	
.1 c.c. Intrader.	- 718	12.6%	63.7%	23.2%	.5%	3.2%
1.0 c.c. Subcut.	- 356	62.7%	7.0%	19.6%	10.7%	9.6%
Control	- 342	93.9%	5.2%	.9%	0%	3.2%

Dingman (10) did not give the serum to anyone with an allergic history and gave smaller doses to the aged and young. His results showed 42 systemic reactions using .1 c.c. intradermal and 529 using 1.0 c.c. subcutaneous in equal populations of people. Other workers (48)(2)(3) substantiated that the incidence of systemic reaction is greatly reduced by using the smaller intracutaneous method. Whether the smaller dose intracutaneously should be given once or repeated, the rapidity of rise in titer, duration of immunity--as compared to subcutaneous dosage--is not so clear cut. Most authorities agree that the rise in antibodies occurs in seven to fourteen days, reaches a peak in two to four weeks and declines. There is still a definite elevation of the titer at the end of a year sufficient to give some protection (25)(37). Weller (48) found the antibody response giving .02 c.c. intradermally very similar to that using 1.0 c.c. subcutaneously. Higgins (23) found the optimal dosage in children from the point of view of tolerance to be .25 to .5 c.c. and believed as much as 1.0 c.c. to be definitely contraindicated. Peterman (32) got an increase of four times over pre-vaccination levels in children by the intracutaneous method and stated it to be greater than by subcutaneous immunization; multiple injections did not raise the titer over the initial reading but did act as booster shots. Bruyn (2) and Van Gelder (41) obtained responses which were similar. Nicholas (31) found

that very young babies who had never been exposed to influenza gave smaller responses and only 25% developed titers high enough to confer immunity. He postulated older children who had been exposed developed higher titers because of the additional amnestic reaction. He also found multiple injections prolonged the high titer but would not raise it. Cohen (4) found no response in children under two years.

Most of the foregoing material deals directly with the statistics accumulated by studying influenzal immunization results. From these results, the prime factor affecting the efficacy of influenza virus vaccination seems to be antigenic deviation. Another factor which may make immunization appear less effective is faulty diagnosis. Unless serological proof is obtained, and it seldom is in practice, the exact protection rendered cannot be ascertained. There is a definite tendency to call any upper respiratory infection accompanied by general malaise influenza. In controlled studies by trained men, the accuracy of diagnosis ran from 90% (37) to 50% (28). At California (11) twenty-nine of thirty cases presenting the typical clinical picture were proven, twenty-one of forty cases proven when only some symptoms were present, and six of twenty-seven cases diagnosed as not influenza had marked rise in titer. At Camp Mackall and Ft. Bragg (6) during an epidemic in which no vaccine was used, clinical diagnosis was 50% to 60% correct. A third factor which

must be considered is the varied susceptibility of humans of different ages and environments. The Commission on Acute Respiratory Diseases (6) found that raw recruits seemed to have the same incidence as healthy, hardened troops, asymptomatic carriers were few, and overcrowding tended to cause explosive outbreaks while non-crowding gave a more protracted epidemic. The serum of the newborn infant has about the same antibody titer as that of the mother but after the first month of life, there is a marked drop which lasts from the twelfth to eighteenth month when it begins to rise, reaching the maximum in twenty to forty year age group. Children under five years of age need the protection which immunization may offer (14).

In summarizing this paper, it seems appropriate to present leading investigators views on the present status of influenza virus vaccination. Antigenic differences between the etiological agent and vaccine used clearly offer the major problem of prophylaxis at present. To combat this (8) the Fourth International Congress for Microbiology presented an international program for collaboration under the direction of Dr. Andrewes in London. All nations will participate in isolating new strains of virus causing influenza and incorporate same into commercial vaccine to be ready for a quick flare up of an epidemic. The Army, Navy and Public Health Departments have appointed laboratories all over the United

States to cooperate in this program. Whether new virus agents can be isolated and vaccine produced in large amounts quickly enough to stop a pandemic is still speculative. If the vaccine can be prepared, it is definitely proven that it will produce immunity and lower the incidence of infection. Salk (39) believes it should be given every year in general immunization to gain the effect of mass immunity, to also protect the non-immunized and stop epidemics before they start. There have been seventeen specific epidemics in the United States since 1918. He thinks a search will reveal viruses with broader specificity. Bad reactions are pretty well eliminated by using .1 c.c. intradermally and good titers are obtained. The Army (42) does not believe large scale vaccination of personnel is warranted under present conditions. Francis (13), the leading investigator in this country, sums up the situation very aptly. "A recommendation for general employment of influenza vaccine by Health Departments is not warranted administratively at the present time. On the other hand, in <u>certain groups</u> the prevention of influenza even in a mild form is to be sought. These comprise the older individuals in whom the case fatality tends to be high, the debilitated, or others to whom infection presents undue risk, industrial groups and essential public service personnel in whom even temporary incapacity constitutes a serious problem, and institutional

groups or university students for whom facilities for care when sick are limited."

In short, at present special groups should be immunized and in event of another pandemic of influenza, a vaccine can be produced which will give definite protection for mass immunization.

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