Editorial

Immunization against Influenza

Since the initial discovery of human influenza virus in 1933 by Smith, Andrewes and Laidlaw,[1] subsequently designated virus A, and the later discovery of influenza virus B in 1940 by Francis,[2] many fundamental investigations on various aspects of epidemic influenza have served to provide a sound scientific basis for the recent development of means for immunization against the natural disease. Among these investigations may be mentioned the early demonstration that the virus is pathogenic for Swiss mice; the subsequent finding that the virus can readily be cultivated in the allantoic fluid of the chick embryo; and the observation that influenza virus grown in the allantoic fluid of the chick embryo can be adsorbed by the erythrocytes of the embryo and then readily eluted from the red blood cells.[3] Equally important are a series of immunologic studies which have shown that a rise in antibody titer occurs following natural infection; that a similar increase in titer can be induced artificially by subcutaneous injection of active or inactive virus; and that mice can be immunized against an otherwise fatal infection.

Finally the development of methods for laboratory proof of diagnosis, either through recovery and identification of virus or demonstration of rise in antibody titer following recovery from infection, has served a dual purpose in further elucidating the epidemiological and clinical characteristics of influenza. First, by the use of these methods it has been possible to show the cyclic recurrence of epidemics of influenza A every two or three years and of influenza B every four to six years and to establish the fact, long suspected, that localized outbreaks of influenza and even sporadic, isolated cases occur during interepidemic periods. Secondly, it has been possible to confirm the opinion, formerly based on insecure clinical grounds, that there is a wide variation in the severity of epidemic influenza ranging from mild infections, indistinguishable clinically from other mild respiratory diseases, to severe fulminating cases reminiscent of those seen in the pandemic form of the disease. In the final analysis, as pointed out by Salk and Francis,[4] the foregoing contributions and, indeed, many others were essential prerequisites for success in devising a practical method of immunization and in demonstrating its effectiveness.

Based on the investigations briefly summarized above, the Army Epidemiological Board through its Commission on Influenza under the direction of Dr. Thomas Francis, Jr., undertook in 1941 to determine whether in fact a practical method for controlling epidemics of influenza could be developed. In 1942, Francis and Salk[5] devised a simplified method for the preparation of a concentrated and reasonably purified vaccine containing approximately equivalent amounts of influenza virus A and B. This vaccine was then demonstrated to be

[1] Smith, W., Andrewes, C. H. and Laidlaw, P. P. A virus obtained from influenza patients. *Lancet*, 2: 66, 1933.

[2] Francis, T., Jr. A new type of virus from epidemic influenza. *Science*, 92: 405, 1940.

[3] Hirst, G. K. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. *J. Exper. Med.*, 75: 47, 1942.

[4] Salk, J. E. and Francis, T., Jr. Immunization against influenza. *Ann. Int. Med.*, 25: 443, 1946.

[5] Francis, T., Jr. and Salk, J. E. A simplified procedure for the concentration and purification of influenza virus. *Science*, 96: 449, 1942.

capable not only of stimulating the production of antibodies and actively immunizing mice, but also of furnishing definite protection in human beings against experimentally induced influenza A[6] and influenza B.[7]

In the fall of 1943, with the expectation that there might be an epidemic of influenza A, a controlled study in Army Specialized Training Program units was undertaken. As a result it was determined that vaccination with a single subcutaneous injection of 1.0 cc. of a concentrated inactivated influenza vaccine given shortly before an influenza type A epidemic exerted a marked though not complete protective effect, the incidence of influenza being 3.2 times as great in the controls as in the vaccinated. There is evidence to suggest that this difference is not an adequate measure of the effectiveness of vaccination because of an apparent reduction in the attack rate in the unvaccinated controls as compared with the attack rate in groups in which none of the population had been vaccinated.[4]

Results comparable to those described above for influenza A have now been recorded[8] during the epidemic of influenza B in the late fall of 1945 with a ratio of cases in vaccinated versus unvaccinated of 1 to 9.

The fact that human resistance to influenza A and B can be greatly enhanced by vaccination with a single dose of inactivated vaccine would now appear to be well established. How frequently vaccination should be performed for the effective control of epidemics, whether means may be devised for enhancing and prolonging individual protection, and the possible effectiveness of vaccination in the face of severe pandemic influenza are problems still requiring solution.

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[6] FRANCIS, T., JR., SALK, J. E., PEARSON, H. E. and BROWN, P. N. Protective effect of vaccination against induced influenza A. *Proc. Soc. Exper. Biol. & Med.*, 55: 104, 1944.

[7] SALK, J. E., PEARSON, H. E., BROWN, P. N. and FRANCIS, T., JR. Protective effect of vaccination against induced influenza B. *Proc. Soc. Exper. Biol. & Med.*, 55: 106, 1944.

[8] FRANCIS, T., JR., SALK, J. E. and BRACE, W. M. Effect of vaccination against epidemic influenza B. *J. A. M. A.*, 131: 275, 1946.