

# VACCINATION AGAINST INFLUENZA \*

THOMAS FRANCIS, jr., M.D.

*Henry Sewall Professor of Epidemiology,  
Chairman of the Department of Epidemiology and Virus Laboratory,  
University of Michigan School of Public Health, Ann Arbor, Mich., USA*

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## *Active virus*

The initial studies on vaccination of human subjects with influenza virus were undertaken to determine whether the administration to man of active virus by the subcutaneous or intracutaneous routes would incite infection, and in order to gain evidence of the degree of antibody response which could be elicited. Utilizing the PR8 strain of type A virus it was found that virus propagated in chick embryo—Tyrode's culture, given by either route, did result in the production of neutralizing antibodies to titres comparable with those observed in convalescent patients (Francis & Magill<sup>10, 11</sup>). The peak was reached in the second week and a relatively high level persisted during the observation period of six months. There was little evidence that additional doses after the peak was reached had any significant influence in adults. Even at that time the suggestion was made that those with the higher titres initially did not exhibit as great increments as those with lower titres.

Stokes, Chenoweth, Waltz, Gladen & Shaw<sup>57</sup> prepared Berkefeld filtrates of swine virus and of human virus A from 10% mouse-lung suspensions, and then inoculated members of a children's institution with three doses intramuscularly, while retaining as controls an uninoculated group approximately twice as large. During an outbreak of respiratory disease in February 1936, they recorded an incidence of 12.5% and 12.4% of febrile illness in the controls and in the groups vaccinated with swine virus, respectively, but only 2.7% in those receiving the PR8 vaccine, although only 31% of this latter group showed an increase of antibodies after vaccination. The nature of the disease was not clearly established, but

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it did occur in a season in which influenza B was subsequently shown to have been very prevalent. Nevertheless, certain serological tests suggested that some cases of influenza A were occurring. The incidence of afebrile disease was uninfluenced.

The following year (see Stokes, McGuinness, Langner & Shaw<sup>58</sup>) an expanded study in similar institutions was carried out with culture virus of the PR8 strain. In this instance some strains of influenza virus A were recovered from patients with influenza and a reduction in febrile illness indicated that vaccination with active virus had been influential in reducing the incidence of influenza in children, and it was suggested that some of the differences in effect observed in the various institutions might be related to the length of interval between inoculation and appearance of disease.

### *Inactivated virus*

In the same winter Smith, Andrewes & Stuart-Harris<sup>56</sup> attempted a controlled prophylactic study, among military forces in England, of subcutaneous vaccination with filtrates of a 10% suspension of the WS strain from mouse lung, inactivated by 1 : 2,000 formalin. The disease occurred before vaccination was fully carried out, and the incidence was low. No effect of the vaccination was noted. A polyvalent vaccine similarly prepared was employed in 1938-9, but no evidence of protection was observed in the group under study (Stuart-Harris and co-workers<sup>59, 60</sup>). Taylor & Dreguss<sup>61</sup> observed no significant effect in their study of vaccinated and unvaccinated individuals, and attention was drawn to the fact that the epidemic strain differed from the WS strain of the vaccine.

The next extensive studies were those of Horsfall, Lennette, Rickard & Hirst<sup>30</sup> with material prepared from chick-embryo tissue previously inoculated with PR8 strain of A virus and a strain of canine distemper virus. The minced embryo suspension was inactivated with 1 : 4,400 formaldehyde, and 1.0-ml doses were given subcutaneously to individuals in a number of institutions. From 30% to 60% of the populations, totalling some 16,000, were vaccinated; the others served as controls. Although a difference in total incidence between vaccinated and controls was observed during an epidemic period, there was a significant reduction in only two of ten vaccinated groups; in two other groups the incidence was higher among the vaccinated than among the controls. The ineffectiveness was attributed, in part, to the lack of potency of one large batch of the vaccine. Brown et al.,<sup>1</sup> using a similar preparation, reported an inconstant but final reduction in incidence from 25% in the controls to 13% in the vaccinated groups. Dalldorf, Whitney & Ruskin,<sup>2</sup> in a limited study of the same material, noted no difference. Siegel et al.<sup>52</sup> employed different vaccine preparations through three successive outbreaks of influenza A in 1937, 1939, and 1941, but observed no difference between vaccinated and unvaccinated groups.

### *Conclusions*

At this stage, then, there was little consistent evidence from field trials that subcutaneous vaccination afforded effective protection against influenza in times of epidemic, even though studies had adequately shown that vaccination with various materials could induce an increase in antibody titre comparable to that observed after infection. The persistence of satisfactory levels of antibody for a period of several months was the rule, and continued emphasis was placed upon an apparent correlation between the height of the level of antibodies and resistance to the disease. The only conclusions which could be drawn, therefore, were that if influenza was not prevented in the vaccinated individuals it was because (a) the vaccine was not of sufficient potency to excite antibody levels to uniformly adequate heights; (b) the strains in the vaccine were not sufficiently similar to those causing the epidemic; or (c) the level of antibodies in the blood, resulting from vaccination, was not sufficiently high to control influenza.

There were obvious reasons for suggesting that the materials employed in the vaccination studies were not particularly potent in virus content. Eaton & Martin<sup>4</sup> noted that the titres obtained with the complex influenza-distemper vaccine were not as high as those in convalescent patients.

Quantitative determinations of antibody levels, in an attempt to appraise the nature of clinical illness occurring in the study groups, had not been followed extensively until the investigations of Rickard, Horsfall, Hirst & Lennette.<sup>40</sup> These were difficult to interpret because a large number of individuals with high titres who showed no increase in convalescence were classified as having a different disease, influenza Y. This conclusion was dependent to some extent upon Horsfall & Rickard's<sup>31</sup> conclusion that the serological response of the patient convalescent from influenza A was uniform against all strains of type A. Hence, if no increase was observed the causative agent must be of another type.

### *Effect of concentration on response to active virus*

It had been demonstrated in mice vaccinated intraperitoneally with active virus that there was a progressive increase in the active immunity obtained as the amount of virus in the inoculum increased up to the point where maximal infective doses were resisted (Francis<sup>7</sup>). Subsequent to these vaccination studies in man, Hirst, Rickard, Whitman & Horsfall<sup>28</sup> carried out a study comparing the effects of different amounts of active and inactive virus obtained from infected chick embryo and from allantoic fluid. The two most concentrated vaccines were prepared by high-speed centrifugation. Using adequate numbers of human subjects, and measuring their antibody levels by the Hirst antihæmagglutination technique, they found with active influenza virus that the antibody titres

attained increased as the amount of virus in the inoculum increased. As shown in the following tabulation, however, the increase was not in direct proportion.

Vaccine 56 contained the equivalent of	0.05 ml of PR8 allantoic fluid
Vaccine 55 contained the equivalent of	0.5 ml of PR8 allantoic fluid
Vaccine 57 contained the equivalent of	5.0 ml of PR8 allantoic fluid
Vaccine 64 contained the equivalent of	24.0 ml of PR8 allantoic fluid
	+ 10.0 ml of WS allantoic fluid

An increase of ten times the dose as between vaccines 56 and 55 gave no more than a 20% increase in titre, and to obtain levels in the same range as those observed in patients convalescent from influenza A—i.e., twice as high as those reached with unconcentrated fluid—ten times as much virus (vaccine 57) was required as was present in unconcentrated allantoic fluid (vaccine 55). A sixfold increase in the amount of virus administered beyond that quantity resulted in no significant enhancement of the titre. These results clearly indicated that unconcentrated, infected allantoic fluid definitely stimulated antibody production, but that there was a sharp increase in the effectiveness as a concentration approximately ten times greater was approached, beyond which there was little additional gain. In the case of B virus, a concentration only four times greater than that of unconcentrated allantoic fluid was required. One other feature of interest was that the titres fell rapidly during the six weeks after vaccination—a finding at variance with other studies. One can ask whether the process of concentration itself influenced the antigenic potency by removal of stabilizing substances. Addition of the distemper virus had no influence on the increase in titre.

#### *Effect of inactivation*

When unconcentrated allantoic fluid was inactivated, the antigenicity in terms of antihaemagglutination was not influenced.

In contrast, a series of preparations of formalinized allantoic fluid tested in 1941 showed sharp deterioration of immunizing potency for mice, even though antibody was still elicited in man.<sup>12</sup> Inactivation of mouse-lung virus has usually resulted in a definite decline of immunizing potency to about one-tenth the original, even with mild agents such as ultra-violet light or soaps. Smith, Andrewes & Laidlaw<sup>55</sup> had stated that certain formalinized preparations appeared to be as effective as active ones, but they were not thoroughly titrated.

In 1942, Hirst, Rickard & Whitman<sup>27</sup> and Hare, McClelland & Morgan<sup>21</sup> demonstrated that virus could be concentrated from allantoic fluid by freezing and then thawing at a low temperature. In the latter state, virus precipitated and separated from other constituents of the fluid. Both groups of investigators (Hirst et al.,<sup>27</sup> Hare, Morgan, Jackson &

Stamatis<sup>22</sup>) demonstrated that after inactivation a concentrated vaccine induced better antibody responses than had been obtained with unconcentrated vaccine and as good, at least, as those obtained with active centrifuged material.

### 1942-5: Concentrated and Inactivated A and B Vaccines

The Commission on Influenza of the US Armed Forces Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army proceeded at this stage to undertake studies, in 1942-3, of the effect of concentrated vaccine containing influenza viruses of types A and B, inactivated with formalin. The studies were devised so that alternate persons would receive vaccine of a control inoculation. The records of vaccination were kept separate, so as to avoid reference to them until the study was completed. Determinations of the antibody levels induced by the vaccine were made, and close, continued clinical observation was kept of the illnesses in the experimental groups. In addition, material for virus study and for serological determinations was obtained from cases of respiratory disease.

For the study at Cornell University Medical College, N.Y., allantoic vaccine concentrated by freezing was employed. (Difficulties in the preparation were presented by the problem of rendering and maintaining large amounts bacteriologically sterile.)

For the study in Michigan a process was employed which takes advantage of the adsorption of influenza virus onto the erythrocytes of the chick. McClelland & Hare<sup>33</sup> in their original paper suggested this as a method of concentration, since the virus could be detected as adsorbed onto the red blood cells. By this means, the major portion of the virus can be removed by the erythrocytes from the allantoic fluid while most of the normal protein remains in the fluid. Hirst<sup>25</sup> had shown that the virus readily eluted from the erythrocytes at or above room temperature. The agglutination is carried out in the cold and the supernatant fluid is removed; to the mass of agglutinated red cells is added one-tenth of the original volume of physiological saline and the material is then kept at 23°-37°C for from one to two hours, during which time virus elutes from the red cells (Francis & Salk<sup>13</sup>). The vaccine is then constituted so that 1.0 ml contains the PR8, type A, strain and the Lee, type B, strain, each obtained from 5.0 ml of the allantoic fluid. Virus is inactivated by formalin 1:2,000, and a mild bacteriostatic is added.

Because of the preceding two-year cycle of influenza A observed in the USA, the winter of 1942 was expected to bring an outbreak of that disease. It did not occur. Late in the season—in March 1943—a mild, unsuspected prevalence of influenza B was detected, largely by serological tests. No influenza A appeared in the group of approximately 8,000 persons studied.

It had been possible, however, to demonstrate that excellent antibody responses to both types of virus had occurred, and that in four months a decline of about one-third from the peak titre had taken place (Salk, Pearson, Brown, Smyth & Francis <sup>49</sup>).

Since it had been found, however, that infection could be induced experimentally without serious risk, it seemed desirable to test the efficacy of vaccination in this way. Henle, Henle & Stokes <sup>23</sup> had reported that a mixture of allantoic fluids containing PR8, WS, and Mel strains of type A virus inactivated by formalin, given four months earlier, or inactivated allantoic fluid containing PR8 alone given two-and-a-half weeks earlier, protected all but one of 44 children against inhalation of a recently isolated strain cultivated in eggs (F-99). Ten out of 28 controls became ill.

On the other hand, our studies of resistance to B influenza virus had shown that four months after being sprayed with this virus in allantoic fluid a majority of the people thus infected had symptoms when sprayed again with the same virus, and one-third had just as severe illness the second time, even though their antibody levels were markedly higher than the original titres. On the other hand, a group of 66 vaccinated subjects was selected and sprayed with a strain of type A virus relatively closely related antigenically, but not identical with that used in the vaccine. Of 36 unvaccinated controls, half developed fever of 100°F (37.8°C) or more and symptoms of influenza; of 28 vaccinated four-and-a-half months before, 32% had similar experience; among the 38 vaccinated two weeks before testing, 6, or 16%, had fevers of 100°F—but none higher—in sharp contrast to the other groups (Francis, Salk, Pearson & Brown <sup>15, 16</sup>).

In a group of 96 tested by inhalation of test B virus (Salk, Pearson, Brown & Francis <sup>47, 48</sup>) 11, or 41%, of 27 unvaccinated individuals became ill; of the 79 vaccinated either four-and-a-half months or four weeks—or at both times—before testing, only 8, or 10%, had fevers of 100°F (37.8°C) and none reached 101°F (38.3°C). These results indicated a stronger effect of subcutaneous vaccination than was observed against influenza A, although the B test may have been somewhat less severe. In comparison with the resistance exhibited four months after actual intranasal infection, the effect of subcutaneous vaccination was much more impressive.

In 1943 a more extensive investigation was made by the Commission on Influenza in a series of army units in colleges throughout the USA, with vaccine prepared by adsorption and elution but incorporating equal parts of PR8 and Weiss strains as the A component and Lee strain as B component. The study comprised six different groups of investigators working in nine different universities, and an effort was made to maintain comparable conditions throughout. In all but one area, alternate men of each unit served as vaccinated and controls, the latter being inoculated with physiological salt solution to which formalin (1 : 2,000) and phenylmercuric nitrate (1 : 100,000) had been added ; the same lots of vaccine were employed

throughout; the same basic plan of clinical observation and handling, and of etiological studies, was maintained.<sup>5, 8, 20, 26, 34, 41, 46, 62</sup> There were 6,263 vaccinated individuals and 6,211 inoculated controls. Most of the vaccination was done in late October and early November, and was soon put to the test by an epidemic of A influenza. In the total group an incidence of 2.2% of hospitalized cases was observed among the vaccinated persons and 7.1% in the control group, with a consistent and significant reduction in all but the one study in California, where a number of deviations in the pattern of the study occurred, and where Eaton & Meiklejohn<sup>5</sup> attributed the lack of effect to the occurrence of an antigenically divergent strain of virus. In five of the nine units the incidence in the controls was between three-and-a-half and six times as great as in the vaccinated—an effect which may be considered minimal since the frequency of illness among those who had been neither vaccinated nor inoculated was greater than that among controls of the vaccinated groups, thus suggesting a reduction in risk among the controls through the reduction of susceptibility in the group as a whole, owing to the presence of vaccinated individuals.

The results clearly demonstrated that a consistent and pronounced lowering in the incidence of clinical influenza A was attained by subcutaneous vaccination with inactive influenza virus.

Since in two locations (Hale & McKee;<sup>20</sup> Hirst, Plummer & Friedewald<sup>26</sup>) the epidemic began at about the time of vaccination, the curves of incidence of disease in vaccinated persons and controls could be followed. In the first week no differences were observed, but after six or seven days the curves diverged sharply as the incidence in the vaccinated group decreased; this indicated that the prophylactic effect of vaccine began at a time when circulating antibodies are ordinarily beginning to rise.

In 1945, by virtue of the uniform vaccination of the entire personnel of the US army, and the occurrence of an epidemic of influenza B, it was possible through the Commission on Influenza to gain information about the effect of the same type of vaccine against that disease. At the University of Michigan there were 1,100 men in the unvaccinated naval unit, and 600 in the army unit, all of whom were vaccinated. The units lived under similar conditions and were under the medical supervision of the same personnel. During the ensuing epidemic of influenza B, 109 cases, an incidence of 9.9%, occurred in the unvaccinated group and only seven cases, or 1.2%, in the vaccinated (Francis, Salk & Brace<sup>14</sup>) (see table I). At Yale University, with similar circumstances and numbers, there were three cases, or 0.5%, among 550 vaccinated army personnel, and 132, or 12.5%, among 1,050 unvaccinated naval students (Hirst, Vilches, Rogers & Robbins<sup>29</sup>).

Although these investigations did not employ alternate controls within the same units, the groups were so similar in all other respects as to make them readily comparable. The difference in incidence in the two groups certainly appears to be the effect of vaccination. Further support for this

**TABLE I. RESULTS OF VACCINATION AGAINST INFLUENZA IN SIX COMMUNITIES**

Location	Vaccinated			Unvaccinated		
	number	cases found	incidence (%)	number	cases found	incidence (%)
Michigan, Mich. . .	600	7	1.2	1,100	109	9.
Yale, Conn. . . . .	550	3	0.5	1,050	132	12.5
Alabama, Ala. . . .	30	2	6.7	95	18	18.9
Washington, D.C. .	360	7	1.9	4,280	352	8.2
Glasgow, Scotland	115	2	1.7	105	9	8.6
Woolwich, England	609	31	5.1	622	68	10.9

conclusion is found in the fact that the vaccinated army units in the same geographical areas had a sharply lower incidence of influenza during the epidemic period than did naval personnel. The fact that a stronger effect was observed against influenza B than in the earlier studies against influenza A is in keeping with the results noted with experimental infection after vaccination, and also with the readier immunizing effect of B virus in mice. In addition, the fact that all members of the one group of units were vaccinated and all those in the control units were unvaccinated may have helped to enhance differences in the mass resistance of the two groups. This influence was exhibited despite the fact that distinct differences could be demonstrated in the serological character of the epidemic strains from that of the Lee strain in the vaccine.

A small group at the University of Alabama also showed a reduced incidence in the vaccinated individuals (Friedman<sup>19</sup>). Norwood & Sachs<sup>38</sup> observed a sharp reduction in an industrial plant in Washington. Two groups were studied by Dudgeon, Stuart-Harris, Andrewes, Glover & Bradley<sup>3</sup> with vaccine of the same character as that used in the USA. The incidence of influenza B was low, and the inoculations were not undertaken until the outbreak was under way. Nevertheless, the results at both Glasgow and Woolwich tended to be in favour of the vaccine.

### 1946-53

#### *Problem of strain characteristics*

After a lapse of three years from the influenza A epidemic of 1943, an outbreak of the disease was anticipated in the winter of 1946-7. At the end of October 1946, a vaccination study was again instituted at the University of Michigan, where 10,328 persons received eluate vaccine containing the same strains as in previous years; 7,615 were unvaccinated.

When influenza occurred during March 1947, no evidence of protective effect was demonstrated. The incidence in vaccinated subjects was 7.19% and in controls 8.09% (Francis, Salk & Quilligan<sup>17</sup>). Although the outbreak did not begin until four months after vaccination, the evidence was clear that the antibody titres of the vaccinated individuals, when measured against the vaccine strains, remained at about the same level as those observed two weeks after vaccination. On the other hand, the titres of the vaccinated persons were no higher than those of the controls when tested against epidemic strains.

Further evidence of the inefficacy of the vaccine was the high frequency of the disease observed in vaccinated groups, even though comparable numbers of controls were not available (Sigel et al.<sup>53</sup>). Data from the US army as a whole yielded no evidence of efficacy.<sup>51</sup> In a controlled study, Fowle & Weightman<sup>6</sup> noted incidences of 7.05% in 1,250 vaccinated individuals, and 7.3% in 794 unvaccinated persons. Loosli, Schoenberger & Barnett<sup>32</sup> observed the same incidence, 9.5%, in 790 vaccinated and 1,230 unvaccinated individuals, in a test of three different preparations of vaccine. Van Ravenswaay<sup>63</sup> observed 20.2% incidence in 237 vaccinated and 27.8% in 284 unvaccinated persons.

The British studies<sup>37</sup> involved a variety of institutional and military groups totalling 20,000 persons. The vaccine was prepared by red blood-cell adsorption and elution with either the Mel or the PR8 strain of A virus. The incidence of influenza was low; infection was absent in many of the units, and the actual identification of influenza was lacking in others. In two schools a mild reduction of incidence was noted: in one, from 22% among controls to 11% in vaccinated individuals, and in the other from 17.3% to 11%. Otherwise, no differences were observed.

The absence of prophylactic effect was so clear-cut as to differ sharply from, and enhance the significance of, the results of 1943 and 1945. Studies from numerous laboratories clearly showed the serological difference of the epidemic strains from the PR8 and Weiss type A strains incorporated in the vaccine.<sup>17, 32, 39, 53, 54</sup> Antibodies to the epidemic strains were not generally induced by vaccination, or occurred only to low levels, although excellent responses to the vaccine strains were demonstrable. There was no significant difference in mean titres to the 1947 strains among vaccinated and unvaccinated persons in the acute stage of the disease, and the antibody increase observed in convalescence was essentially the same in the two groups (Francis, Salk & Quilligan<sup>17</sup>). Furthermore, many sera from the 1943 epidemic, which showed a marked rise to the PR8 strain, failed to show an antibody increase to the 1947 strains. That the strains were of type A was shown by the fact that the majority of convalescent patients exhibited an antibody rise to PR8 or to other A strains; this was demonstrable by neutralization, haemagglutination-inhibition, or complement-fixation tests. That vaccinated individuals

showed less rise to the PR8 than to 1947 strains after infection is to be expected because of their high post-vaccination titres to that strain.

The experience of 1947 clearly established an affirmative answer to one question which had been constantly present. Can strain differences demonstrable serologically be of significance in immunization? In order to meet the antigenic variant, the Commission on Influenza recommended that a representative of the 1947 strains, which were designated A-prime, be incorporated in the subsequent vaccines.

Since that time the studies of the Commission have continued in US military installations, with various preparations of vaccine designed to give further information. The major studies are those conducted each year at Fort Dix, New Jersey, and at Fort Ord, California, both in recruit populations.

In the winter of 1947-8, the first of these studies, by Salk & Suriano<sup>50</sup> at Fort Dix, was concerned with comparing the effect of an "old-formula" vaccine containing PR8, Weiss, and Lee strains, prepared by adsorption and elution, with a vaccine containing PR8, FM1 (1947), and Lee, prepared by Sharples centrifugation. The second vaccine induced much better antibody titres to the A-prime strain while the first, although a year old at the time of use, induced somewhat better responses to the PR8 and Lee strains. There was a slight prevalence of A-prime influenza during the period of observation, and while the bulk of respiratory disease in the population was non-influenzal, a significant reduction in the number of cases was demonstrable in the group receiving vaccine containing the FM1 strain.

In 1948-9 the incidence of influenza was so small as to furnish little information about the effect of vaccination upon the disease. However, serological results obtained with monovalent vaccines in that and in the succeeding year have been reported.<sup>36</sup> It was readily demonstrated by these means that in man the FM1 vaccine stimulated antibody rises to the PR8 strain of nearly the same magnitude as to itself, although the reciprocal with PR8 vaccine was lacking, as shown in 1947. These data provided a beginning for further interpretation and understanding of strain differences.

The following year, 1949-50, influenza caused by A-prime virus was more prevalent. The studies at Fort Ord again tested monovalent vaccines, PR8 (A), FM1 (A-prime), and Lee (B), together with control saline inoculations.<sup>35</sup> Equal numbers of each unit received one of the four preparations.

The incidence in the four training groups is shown in the following tabulation:

<i>Vaccine</i>	<i>Number vaccinated</i>	<i>Number of cases</i>	<i>Incidence (%)</i>
FM1 strain	528	5	0.9
PR8 strain	553	21	3.8
Lee strain	536	23	4.3
Control	534	25	4.7

The identification of cases was based upon complement-fixation and haemagglutination-inhibition tests. No difference in the incidence of non-influenzal respiratory disease was noted between the groups. Thus, despite the low incidence, careful examination revealed that FM1 vaccine had been effective against the current A-prime strain which exhibited a measurable serological difference from that of the vaccine.

In 1950-1, in the same installations, two vaccines and saline control were tested. The A vaccine contained equal parts of the PR8, FM1 (1947 A-prime), and Cuppett (1950 A-prime) strains at a level of 500 chick-cell agglutinating (CCA) units, 200 higher than in the previous three years. The Lee strain represented the B vaccine at 500 CCA units. Results of this year have not been published but, at Fort Dix, Dr. J. E. Salk and Dr. E. Lennette (personal communication) observed a 4:1 difference in favour of the vaccinated individuals, and at Fort Ord similar results were noted.

Information from the present year (1953) with still more potent vaccine containing only A-prime strains is incomplete, but preliminary data again indicate a great advantage for the specifically vaccinated group, although the epidemic strain differs serologically from those in the vaccine.

The accumulated evidence with epidemics caused by A-prime strains, then, has been uniform in establishing the fact that influenza vaccine containing strains of that group continues to be effective. It also demonstrates that protection can be obtained by the use of vaccine strains which are not identical with those prevalent. This is important with regard to both cross immunity and antigenic composition.

In 1951-2, influenza B was prevalent. Once more, the data are incomplete, but, where the incidence was sufficient to permit measurement, the influence of vaccine was apparent. For example, at a children's institution equal numbers within each cottage received polyvalent A vaccine, B vaccine (Lee, 700 CCA units), or saline.<sup>24</sup> Although serological differences between the epidemic strain and that in the vaccine were clearly demonstrable, the incidence in the B-vaccinated group, as shown in the following tabulation, was about one-third that in the other two.

<i>Treatment</i>	<i>Number treated</i>	<i>Cases</i>	<i>Incidence (%)</i>
B vaccine	207	15	7.2
A vaccine	218	39	17.9
Saline	212	44	20.8

The outbreak was essentially pure influenza B. It is of interest that the children in the B vaccinated group who developed the disease were the youngest children, and their antibody titres had shown a sharp decline from the immediate post-vaccination titres. This rapid decline in antibody level in three months has not been commonly observed in other studies; it appears to be a factor of age.

*Use of adjuvants*

In addition to the problem of strain characteristics, the concentration of virus antigen in vaccine is an important factor. In order to obtain high antibody levels, the amount of virus must be maintained well above the minimal level. In the earlier materials prepared by adsorption and elution the amount was essentially that derived from 10 ml of allantoic fluid. Later, an arbitrary level of 300 CCA units per ml was set, and the antibody responses were less marked. Subsequently, the concentrations have been increased to levels of 700-750 CCA units per ml and good titres have resulted. There is, however, the fact that some strains, especially the A-prime group, are less effective even in these amounts, owing to either an inherent antigenic defect or a lesser stability of the inactivated material.

A number of earlier studies had suggested the possibility of using lipids to enhance the effect but, because of serious accompanying reactions, the materials were not acceptable for human use. Recently, Salk and his associates have conducted extensive investigations of the use of virus first emulsified in Arlacel A (mannide mono-oleate)<sup>a</sup> and then suspended in a light mineral oil, a combination found by Freund and his associates<sup>18</sup> to eliminate the unfavourable local abscess production or extensive encephalomyelitic disturbances encountered with certain other preparations.

The studies have developed in a progressive manner, from observations of the responses in experimental animals receiving various combinations of virus and adjuvant to the testing in man of the efficiency and practicability of selected preparations. It was shown first in mice and monkeys that extremely high titres, in the thousands, of haemagglutination inhibitor or neutralizing antibody (in ovo) could be obtained with mixtures of adjuvant and quantities of virus which, in aqueous form, resulted in titres of approximately 128. In monkeys the titres continued to rise progressively from levels of 256 in one week to a peak of 16,000 or more in eight weeks. After four months some decline in titre was commonly observed, but when moderate amounts of virus are considered the levels remain in the thousands at the end of a year. Moreover, an amount of virus which in the usual vaccine had little antigenic effect could, in conjunction with adjuvant, still elicit high titres (Salk, Laurent & Bailey;<sup>45</sup> Salk & Laurent<sup>44</sup>).

The extended studies in man have been presented in two publications (Salk, Bailey & Laurent;<sup>43</sup> Salk<sup>42</sup>). Basically, they demonstrate effects in man paralleling those observed in monkeys. The titres obtained with adjuvant vaccines greatly exceed those obtained with similar amounts of virus in aqueous vaccine. Antibody response to a polyvalent adjuvant vaccine containing 100 CCA units of each of three virus strains reached peak titres of approximately 2,000 in four months, declined in one year to levels of 512-1,024, and remained at around these levels during an additional

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<sup>a</sup> Obtained from the Atlas Powder Co., Wilmington, Del., USA

year of observation. In comparison, persons receiving a preparation of aqueous vaccine containing 133 units of each strain had levels of approximately 256, which, with a slight decline, persisted thereafter at half the six-week level. In general, the maximum response to aqueous preparations is reached in two weeks in adults, and at this time usually significantly exceeds the mean titres obtained with adjuvant material. It has been clearly shown, however, that, in the presence of adjuvant, amounts of virus in the range of 10 CCA units can result in levels of antibody well above those following aqueous vaccine containing ten times as much virus. This readily offers opportunity for incorporating a number of strains differing antigenically, whereas the quantities required make this more difficult in polyvalent aqueous preparations. In this connexion, the data indicate that, with the abundant responses obtained, there is a greater capacity to overcome differences in antigenic structure of various strains. It may be pointed out, too, that the contingency of incorporating a new strain immediately into vaccine may well be met by the relatively little attention which need be given to high titres required for production of aqueous material.

The only untoward reactions observed to date occurred in a group of persons given vaccine prepared with a certain lot of Arlacel A. These reactions took the form of cyst-like accumulations which developed at the site of inoculation, in about 1% of the subjects, two to four months later. Although many possibilities were considered, it eventually appeared that the cause was impurities or unnecessary substances in that particular lot of emulsifier. These have been removed without altering the efficiency of the material, and later preparations have not exhibited this reactivity. In the meantime, tests have been devised for determining the presence of such harmful materials in experimental animals.

The possibility of carcinogenic effect has also been explored, and the resultant data indicate that the materials employed do not possess the characteristics associated with the carcinogenic action of oils. Similarly, the risk of sensitization appears to be minimal.

The efficacy of adjuvant vaccine in protecting man against influenza has not yet been established, but if antibody levels are the deciding factor the evidence weighs heavily in its favour. The cost of its production is also considerably less than of aqueous vaccine. As with other prophylactic materials, additional data are needed as to the best and most stable strains for use in stimulating antibodies, and for giving wide coverage; accurate knowledge of ideal proportions, and exploration of other materials which may be of still further advantage as adjuvants would also be of great value.

Vaccination against influenza has been shown to be uniformly effective under a variety of conditions, when vaccines of proper constitution and potency are employed. Although the writer has consistently held that the epidemiological and serological data have indicated the probability that strain differences are important in the recurrences of influenza, he

has also emphasized that the degree of variation so far observed is a limited one, representing more a rearrangement of viral components than complete loss or gain of basic constituents.<sup>9</sup> This is in disagreement with the thesis that the old antigens progressively disappear and are replaced by new, unrelated ones. Current analyses in our laboratory strongly support the concept that the antigenic constitution of influenza virus of a particular type can be mapped. It is the expectation, then, that vaccine can be so composed as to contain the different antigenic components required and will induce, as desired, the broad resistance which otherwise is acquired only by repeated exposures to the disease. There remains the problem of virulence, but most of the data indicate that even highly virulent strains can be counteracted by adequate vaccination, or by infection with mild strains. For example, mice infected with unadapted egg-passage lines become resistant to the highly virulent mouse line of the strain concerned. Moreover, relatively new antigenic strains are not necessarily highly virulent, as evidenced by the mild character of A-prime strains in 1946-7 and later. It is believed that the severity of influenza in the autumn of 1918 was the result of enhanced virulence through adaptation of a strain which had been in circulation and, certainly, was related antigenically to known strains of influenza virus. The fatality with which it was associated clearly seems to be related to physiological factors in the human host, as well as to the immunological factors which determined incidence. The latter can now be controlled.

In conclusion, the outlook for increasingly broad and effective prophylactic immunization against the range of influenza viruses is extremely promising. The studies from which present knowledge has developed represent a continued investigation of a complex field, moving with the accumulating evidence towards better understanding and practical prevention of the disease.

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# INFLUENZAL PNEUMONIA : CAUSATION AND TREATMENT \*

J. MULDER, M.D.

*Professor of Internal Medicine, University of Leiden, Netherlands*

C. H. STUART-HARRIS, M.D., F.R.C.P.

*Professor of Medicine, University of Sheffield, England*

Influenza is still a disease with an impact upon the community which can be measured in terms of mortality; yet, compared with the historic outbreaks of 1889-90 and 1918, recent epidemics have been mild. However, even recent epidemics severe enough to affect 5%-10% or more of the population have been accompanied by an appreciable rise in the death-rate, particularly in the elderly and in spite of the general use of chemotherapeutic agents. Thus the influenza A epidemic in Holland in 1948-9 caused about 2,200 deaths during an eight-week period; moreover, an occasional outbreak with an alarming mortality has been experienced, such as that in 1951 in the town of Liverpool, which suffered an even greater mortality than in 1918. In these exceptionally virulent recent epidemics, however, almost all the deaths have occurred among those aged 55 or over, whereas as many as 50% of the deaths in 1918 occurred in the age-group 20-40. A steady fall in the death-rate in the younger members of the community affected by influenza has been experienced since 1938, which suggests that chemotherapy may be capable of influencing the course of the complications in these cases.

The authors' experience of recent epidemics of influenza has convinced them of the need for awareness of the therapeutic problem which may be posed, and which contrasts with the relative ease of therapy of ordinary primary bacterial pneumonia and bronchopneumonia. Also, it is important that the general practitioner should be aware of the danger signals of severe or fulminating influenzal pneumonia, particularly because so much depends upon the speed with which therapy is begun. The relative infrequency of the fulminant case is often a source of additional difficulty when, as during an epidemic, so many patients may demand attention that daily visits become impracticable. The purpose of this article is to summarize the facts known about the pulmonary complications of influenza, and to suggest therapeutic regimes which should be pursued.

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### Clinical Varieties of Bronchial and Pneumonic Complications of Influenza

There are two main varieties of complication of the lower respiratory tract which require recognition and differential diagnosis : (a) influenzal bronchitis and bronchiolitis; (b) influenzal pneumonia.

#### *Influenzal bronchitis and bronchiolitis*

Influenzal bronchitis or broncho-bronchiolitis is seen at all ages and is a serious condition only in the elderly or in those already afflicted by some chronic disease of the respiratory tract or of the heart. Mucopurulent bronchitis is thus suspected when the initial dry cough of influenza becomes productive and is accompanied by signs in the chest, such as generalized rhonchi or wheezing, and perhaps by a mild degree of dyspnoea. It varies greatly in severity but usually clears up promptly in patients with previously healthy lungs once the temperature is normal.

Bronchiolitis is suspected if the temperature remains elevated on the third or subsequent days of an attack of influenza, if the patient coughs frequently and has a mucopurulent sputum, and if examination of the chest reveals patches of fine râles at one or both lung bases. Such patients become dyspnoeic, but not excessively so; they do not complain of pleural pain, and x-ray of the chest may either reveal no abnormality or else show increased bronchial markings. Recovery even without antibiotics is usual, although several days may pass before the abnormal signs disappear from the chest. If, however, the patient has pre-existing disease such as bronchiectasis or severe emphysema, or cardiac disease such as hypertensive or valvular heart disease, bronchiolitis may cause death. Certain, also, of the deaths from acute influenza which occur in elderly people are probably due to bronchiolitis rather than to an actual pneumonic process.

Influenzal bronchitis and bronchiolitis, although certainly related to influenza virus infection, are probably also accompanied by invasion by pathogenic nasopharyngeal bacteria. Throat washings or sputum taken from patients during the early days of illness constantly reveal influenza virus. On the other hand, cultivation of the sputum for bacteria usually reveals one or more common pathogens of the respiratory tract. A preponderance of *Haemophilus influenzae* is found in the most seriously affected patients and the pathogenic role of non-encapsulated *H. influenzae* in broncho-bronchiolitis seems to have been established. The fibrinous necrotizing variety of tracheo-broncho-bronchiolitis caused by pyogenic cocci (most often *Staphylococcus aureus*) is always associated with broncho-pneumonia and is described below.

#### *Influenzal pneumonia*

Consolidation of the lungs either may develop during the course of the febrile phase of influenza virus infection, or may follow after an interval of

time which may be brief or may last for several days, and during which the patient may have made an apparent recovery from the primary attack of influenza. There is no one constant and invariable clinical picture to which the term "influenzal pneumonia" can be applied; nor can the majority of cases of influenza with consolidation be certainly distinguished from severe cases of pneumonia occurring at times when influenza virus infection is not prevalent. Nevertheless, the fulminant cases present a characteristic picture and, if for no other reason than to draw attention to these patients, the term "influenzal pneumonia" deserves to be retained.

A pneumonic process is suspected when the patient convalescing or convalescent from influenza again becomes febrile, complains of cough, dyspnoea, and pain of pleural type. Sputum, which may be mucopurulent, purulent, or frankly bloodstained, is usually evident at this stage. A leukocytosis is also frequent. Physical signs in the chest are those of frank consolidation, with dullness often suggesting a small effusion, bronchial breathing, and abundant râles. Râles may also be evident in other areas where dullness cannot be elicited, and x-ray of the chest usually shows scattered areas of relatively dense opacity resembling a bronchopneumonic process. Occasionally, and particularly in cases of pneumonia following several days after the original attack, the consolidation may be lobar in type and may affect one or several lobes.

The supervention of consolidation of the lungs in a patient during the acute stage of influenza is more difficult to recognize. In the most fulminant of all cases, dyspnoea, bloody sputum, cyanosis, and a collapsed state of the circulation may be the main findings. Death in such cases may supervene within 24-48 hours. It is a striking fact that pleural pain may not be in evidence and that the physical signs of consolidation are frequently obscured. If pain is present, it may be retrosternal in location and experienced chiefly during coughing. Râles, which are scattered diffusely over the chest but are particularly numerous towards one or other lung base, weak breath sounds or patchy bronchial breathing, and relatively slight impairment of percussion are the only findings at first. X-rays, however, show patches of mottled opacity suggesting a bronchopneumonia. The leukocyte count may show a leukocytosis but sometimes there is a leukopenia. Later, if the patient survives, the classical signs of consolidation may appear, and râles may lessen, except in the areas chiefly affected. However, other complications such as pleural effusion, lung abscesses, or pneumothorax may develop and cause an alteration in the signs. In any event, influenza which leads without pause into pneumonia is frequently a severe disease with a slower response to therapy than the variety of pneumonia which occurs some days after recovery from the influenza. It is important to recognize that the clinical picture and the response to treatment depend upon the bacterial species concerned in the lung invasion.

### Bacteriology of Influenzal Pneumonia

Bacteria believed to be concerned in the pneumonic process are found in the sputum in cases of influenzal pneumonia, and all fatal cases of influenza, except possibly some of those in the aged or enfeebled, are attributable to bacterial action. Pneumococci predominate in the sputa of patients who develop pneumonia some days after the onset of influenza. Staphylococci of the ordinary pyogenic variety occur in a lesser percentage of cases, but particularly in cases of pneumonia concurrent in time with the influenza virus infection. In view of the normal relative infrequency of staphylococcal pneumonia, and the fact that pneumococcal infection is the predominant cause of ordinary non-influenzal pneumonia, attention deserves to be drawn to the increase in staphylococcal infection which occurs during an epidemic of influenza. Thus 104 (80%) of 130 cases of pneumonia in Sheffield in non-influenzal periods between 1947 and 1951 yielded pneumococci in the sputum. During these periods *Staph. pyogenes* was found in the sputum in only seven instances. During two periods of prevalence of influenza virus A-prime infection—January to March 1949, and January to March 1951—166 cases of pneumonia yielded 114 instances (68%) of pneumococcal infection. Also, during these influenzal periods 33 patients yielded staphylococci either alone or with pneumococci.

During the 1949 influenza A epidemic in Rotterdam, Bruins Slot<sup>1</sup> observed 37 cases of pneumonia, 17 of which were caused by *Staph. aureus*. Fifteen instances of serologically confirmed influenza virus A-prime infection were found among the latter cases. Similarly, one of us (J.M.) has personally observed 25 cases of staphylococcal pneumonia unassociated with primary septicaemia, 18 of which were superimposed on influenza virus A or B infection. It is the authors' opinion, therefore, that the occurrence of severe staphylococcal pneumonia, characterized pathologically by a fibrinous necrotizing inflammation of the tracheal and bronchial epithelium and purulent bronchopneumonia, is a sign of the existence of influenza virus A or B infection.

Unlike experience in 1918, pneumonia caused by the haemolytic streptococcus is relatively rare at present, and organisms such as *Klebsiella pneumoniae* have not been more prominent at times of influenza epidemics than during normal periods.

The exact role of the influenza virus infection in relation to influenzal pneumonia is difficult to discern. There is no doubt of its occurrence but no one can be sure whether the virus infection is limited to the pharynx or whether, as the authors believe, epithelial lesions occurring in the trachea and bronchi are due to virus rather than bacterial action. It is unlikely, except in cases of severe and fulminant pneumonia, that the influenza

<sup>1</sup> Bruins Slot, W. J. (1950) *Ned. Tijdschr. Geneesk.* 94, 3438

virus plays a role in continuing pulmonary infection, and thus treatment directed towards the bacterial component is usually adequate. It is by no means certain, however, that this conclusion is valid for particularly virulent epidemics such as that of 1918. The potentially pneumotropic property of influenza virus cannot be ignored, and some strains of influenza virus may multiply more readily in the human lung than others. Since the first isolation of the influenza viruses in 1933, however, few variations in pulmonary complications in different epidemics which could be attributed to the virus have been encountered. The complications of influenza B appear to be the same as those of influenza A.

### Diagnosis

Clinical methods alone may fail to differentiate many cases of influenzal pneumonia because the picture often resembles that of ordinary bacterial pneumonia. However, as these patients are also those who respond most readily to therapy with, for example, penicillin or the sulfonamide drugs, no harm results from incomplete diagnosis. The same cannot be said for the cases of influenzal staphylococcal pneumonia, or, indeed, for severe instances of any variety of influenzal infection. The problem of recognition of the latter cases is, however, a considerable one, first, because such patients should be treated at as early a stage of the disease as possible, and second, because bacteriological assistance and facilities for radiological examination may not be available in the home. The clinical features which should suggest the possibility of pneumonia in patients with either the symptoms of influenza (headache, shivering, myalgia) or a history of recent recovery from influenza are as follows :

(1) *Age*. The probability of complications increases at ages over 50, and patients of 60 and over require to be watched and repeatedly examined. Nevertheless, some cases of the most fulminant form of staphylococcal pneumonia occur in young and middle-aged adults, so that no age-group can be considered as exempt from this complication.

(2) *Previous history of a staphylococcal infection*, such as a furuncle or skin infection in the patient or other members of the family.

(3) *Previously existing chronic disease*, such as diabetes, bronchiectasis, chronic bronchitis, emphysema, and all forms of heart disease.

(4) *Persistent high fever* on the third or fourth day of the disease.

(5) *Occurrence of dyspnoea, cyanosis, chest pain, and a productive cough*. Any or all of these point to the probability of a chest lesion, but the degree of subjective dyspnoea may be slight compared to the rise in respiration-rate, and chest pain may be central in situation rather than in the usual lateral location of a pleural pain. Sputum may not be raised

at all in the most gravely ill patients, but a purulent, blood-streaked, or frankly bloody sputum are usual in any of the varieties of influenzal pneumonia, so that the patient should always be asked to cough in the presence of the doctor in order to permit inspection of any material which may be expectorated.

(6) *Frank signs of consolidation* may exist, but cases of influenzal pneumonia may exhibit extensive radiological changes although the clinical signs are equivocal or even suggestive only of a diffuse bronchitis. Patches of weak breath-sounds and abundant râles may therefore be of greater significance than the absence of bronchial breathing or of dullness.

(7) *Existence of a leukocytosis in excess of 14,000 total leukocytes per mm<sup>3</sup>* is in favour of a bacterial complication. A leukopenia may, however, be found in severe bacterial influenzal pneumonia, so that, as with so many of the other signs, a negative finding does not rule out the possible existence of a pneumonic process.

(8) *Occurrence of a feeble rapid pulse, low blood pressure, cold extremities, and sweating* may indicate peripheral circulatory failure which occurs in the severest clinical grades of pneumonia. Thus, the patient with influenzal-staphylococcal pneumonia may resemble superficially a case of myocardial infarction with resultant pulmonary oedema and shock-like state.

In addition to the observation of purely clinical findings, the most helpful step is to examine the sputum bacteriologically. A simple film of sputum stained by Gram's stain will often reveal the existence of staphylococcal pneumonia, for in this condition vast quantities of staphylococci are nearly always present. Cultivation of the sputum is, however, essential if the predominant organism is to be identified, and particularly if the sensitivity of the bacterial species to antibiotics is to be ascertained. Fortunately, the majority of cases of staphylococcal pneumonia are still initially caused by penicillin-sensitive organisms, although resistant strains may appear after therapy with penicillin. Film and cultivation will also reveal pneumococci, or haemolytic streptococci, or *H. influenzae*. The use of special selective media for the latter, or of mouse-inoculation for the detection of pneumococci, is not likely to be of assistance from the standpoint of therapy although it is necessary for exact bacteriological diagnosis.

Radiological examination is a further essential step in the differential diagnosis of influenzal pneumonia and will, of course, be carried out as a matter of routine in hospital practice. For the benefit of practitioners who are unable to obtain facilities for radiological examination, or who are treating the patient at home, it may help to point out the existence of relatively severe cases of influenzal bronchiolitis which may closely resemble pneumonic cases for a brief period. The essential difference is that the bronchiolitic cases (who show no gross radiological abnormality)

may undergo rapid remission of symptoms and signs. Such patients should probably be regarded as pneumonic cases, if a radiological examination is unobtainable, and should be treated accordingly.

Finally, the sequelae of influenzal pneumonia which include lung abscess, pleural effusion or empyema, various degrees of atelectasis, and even rarely pneumothorax, require careful attention in spite of previous chemotherapy. Every effort should be made to obtain the admission to hospital of patients whose conditions fail to resolve within a reasonable period of time (5-10 days), as the differential diagnosis from chest disease such as pulmonary tuberculosis or bronchial carcinoma requires radiological, and possibly bronchoscopic, investigation.

### Treatment

The essential difficulty in the treatment of influenzal pneumonia is the need to begin therapy as early as possible, which in practice means that it will often have to be started before a bacteriological diagnosis concerning the causative bacterial species is available. Unfortunately, the standard dosage and method of treatment for bacterial (pneumococcal) pneumonia—which, in most countries, is based upon penicillin with or without the addition of sulfonamides—has proved regularly effective only in the pneumococcal types of influenzal pneumonia. The staphylococcal cases require much more energetic and early treatment with penicillin and, in the authors' experience, may even then prove resistant to therapy. Experience with the various antibiotics derived from the *Streptomyces*—chloramphenicol, aureomycin, and oxytetracycline<sup>2</sup>—is still inadequate for a firm statement to be made concerning their merits in comparison with penicillin. In infections with *H. influenzae*, however, these drugs are effective, and they should also be used in cases infected with penicillin-resistant strains of *Staph. pyogenes*. In any event, it is necessary to stress the fact that the sulfonamide compounds such as sulfadiazine and sulfadimidine, if used alone, are effective in a much lower proportion of cases of influenzal pneumonia than with ordinary bacterial pneumonia. Their routine use will therefore cause delay in the institution of therapy in precisely those patients whose need for effective antibiotic treatment has existed from the onset of the pulmonary complication. For this reason, their routine use is deprecated. It is doubtful whether much is gained by combining sulfonamide therapy with other agents such as penicillin. On the other hand, combined antibiotic therapy with penicillin and streptomycin may perhaps avoid the emergence of penicillin-resistant staphylococci, although experience with such therapy is still inadequate. Combined

<sup>2</sup> Oxytetracycline is the non-proprietary name for Terramycin.

therapy with other antibiotics is as yet experimental in nature, and recommendations cannot be made at present. There is no particular advantage to be gained by administering antibiotics by inhalation.

The following regime is suggested for patients in whom a definite clinical diagnosis or a presumptive diagnosis of influenzal pneumonia has been made. After the initial clinical examination, aided when possible by radiological examination, the following steps should be taken :

(1) Obtain specimen of sputum, stain by Gram's method a sample thoroughly washed in physiological saline, and set up cultures on blood-agar. Rapid antibiotic-sensitivity tests on the predominant species in the sputum can be carried out by cultivating the sputum on plates with discs containing different antibiotics. If no sputum is available but the patient presents the aspect of a mild or moderately ill case of pneumonia, treat as for pneumococcal infection. If the patient is severely ill, treat as for staphylococcal infection.

(2) If pneumococci predominate in the sputum, treat with penicillin by intramuscular injection of 50,000-100,000 units of ordinary aqueous penicillin every four hours (daily dosage 300,000-600,000 units). If preferred—but only in mild or moderately ill cases—procaine penicillin may be given as 300,000 units intramuscularly twice daily (600,000 units per day), either alone or with 100,000 units of ordinary sodium penicillin. Treatment should be continued for at least 14 days.

(3) If staphylococci predominate in the sputum and the patient is severely ill, penicillin may be given by intramuscular injection at the rate of 1,000,000 units initially, followed by 500,000 units every four hours. If the patient is desperately ill, 1,000,000 units every two hours may be given for the first 12 hours, followed by a lower rate of dosage. This regime may be modified in staphylococcal infections with a lesser degree of clinical severity, but the daily dosage should still be of the order of 1,000,000-2,000,000 units.

(4) If no bacteriological facilities are available, the clinician should be guided by the response to treatment with penicillin at the standard dosage of 50,000-100,000 units intramuscularly every four hours, but should use the higher scale of dosage for all fulminant cases.

(5) If penicillin-resistant staphylococci are reported in the sputum, or the patient fails to respond within 72 hours of initiation of therapy, then a change should be made to a different regime. Oxytetracycline or aureomycin is preferred by the authors because oral therapy (which may be impracticable in severely ill patients who have difficulty in swallowing) can be supplemented by intravenous therapy with the same agent. The requisite daily dosage is still under study, but 4 g daily by mouth should be given for at least 10 days, with lesser daily dosage if intravenous injections are substituted. Treatment may have to be given for at least three

weeks or more. It seems unlikely that any advantage will be obtained by combining either of these antibiotics with penicillin or streptomycin.

(6) *H. influenzae* infections should be treated with penicillin in high dosage (4,000,000 units daily in adults) or preferably with chloramphenicol, aureomycin, or oxytetracycline at the rate of 0.5 g every six hours.

(7) Infections with *K. pneumoniae* should be treated with streptomycin, either alone or with the addition of sulfadiazine or sulfadimidine. If no response is obtained, chloramphenicol, aureomycin, or oxytetracycline may be tried, but the response cannot be predicted.

(8) *Streptococcus haemolyticus* infections may be severe. Optimal treatment has not been studied, but the authors suggest the same dosage of penicillin as in staphylococcus infections.

Ancillary treatment in addition to antibacterial therapy is obvious. Oxygen is of chief value in patients with abundant bronchial secretion and deep cyanosis. It is unnecessary as a routine measure. Peripheral vascular failure may be helped by the use of cortisone and later of adrenocorticotrophic hormone but antibacterial treatment should also be given, and experience is so far totally inadequate for firm recommendation. The use of drugs such as digitalis is not, in the authors' view, of critical importance unless auricular fibrillation or congestive heart failure co-exist. In the latter instance, and also in patients with abundant bronchial secretion, diuretics of the mersalyl (mercury salicyl-allylamide-o-acetate of sodium) variety may assist.

### Prophylaxis

Mass prophylaxis of bacterial complications in influenza is impracticable and probably undesirable, because of the possible encouragement of resistant bacterial species or of superinfections with organisms such as fungi, especially *Candida albicans*. Prophylaxis is more reasonable, however, in patients with influenza who are known carriers (nasal or skin) of staphylococci, or who have had a recent infection with staphylococci, in diabetics, and in patients with chronic respiratory-tract or cardiovascular disease. Thus, patients with chronic bronchitis, bronchiectasis, or possibly chronic nasal sinusitis or otitis media, are candidates for the development of a superimposed bacterial infection of the bronchioli and the lung. It is difficult, at present, to lay down rules for the guidance of those who desire to attempt prophylaxis. Sulfonamide compounds are probably prophylactic against pneumococcal or haemolytic streptococcal infections. It is not these organisms, however, but staphylococci and *H. influenzae* which are most dangerous to the subjects already suggested above. Penicillin might be effective prophylactically against staphylococci but there is always the risk of causing the emergence of penicillin-resistant strains. Peni-

cillin in normal dosage is prophylactically ineffective against *H. influenzae* infections. Less risk appears to exist in the case of chloramphenicol, aureomycin, and oxytetracycline at a level of 2 g orally a day, and these agents are capable of exerting an action against all the bacteria concerned. If used, however, these agents should be given for a period not in excess of a week, and careful watch should be kept for possibly harmful effects, especially with chloramphenicol in regard to the development of inhibition of the bone-marrow.

### **Mobilization after Uncomplicated Influenza**

The elderly patient convalescing from influenza is in a debilitated and weakened condition. The respiratory-tract epithelium has probably not returned to a completely normal state until three to four weeks after the acute illness. It is therefore desirable to urge caution before return to normal occupation, and avoidance of exposure to inclement weather or overcrowded public places.

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# THE INFLUENZA PROGRAMME OF WHO \*

A. M.-M. PAYNE, M.D., M.R.C.P.

*Division of Communicable Disease Services, World Health Organization*

Influenza recognizes no man-made boundaries; indeed, many of the achievements of man increase the speed and extent of its spread. The appearance of epidemic influenza is viewed with concern in the country initially involved, among neighbouring nations, and indeed in all continents. It was natural, therefore, that the nations of the world should call on their own intergovernmental Health Organization to play a co-ordinating role in the struggle against the disease.

It may be useful first to examine briefly the reasons for concern at the appearance of epidemic influenza, since it will help to define the objectives of a worldwide plan.

The first reason is the memory of the 1918-19 pandemic. Many readers will recall the appalling suddenness with which it killed healthy young people, the speed with which it spread, and the futility of all efforts to control it. It paralysed whole cities, even whole countries; food distribution broke down, and the economic loss was enormous. It killed more than 15 million people. No one knows whether this disaster will ever occur again, for no one knows the combination of circumstances which brought it about. However, assuming that it was caused by a variant of the influenza virus, there is a real basis for anxiety because, within certain limits, the virus shows no stability in nature and, as far as is known, a variation that has occurred once may occur again.

The second cause of concern is the highly infectious nature of the disease and the fact that it appears to produce no permanent immunity. When influenza is epidemic one tends to think—not, whether one will get it, but when will one get it? Allied to this is its short incubation period and the speed with which it spreads. If smallpox broke out 500 miles away, for example, one would not feel anxious, but with influenza one would quite rightly fear that it might arrive within a short period.

The third reason is the effect of influenza on the economics of a country. This is naturally very difficult to measure; however, we have only to look at records such as national insurance claims or records of absenteeism in factories to realize that it may be considerable.

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\* To be published in Spanish in the *Boletín de la Oficina Sanitaria Panamericana*

Finally, but not least, influenza or its main complication, pneumonia, does kill. In Liverpool, for example, in 1951 the weekly death-rate exceeded the highest figures of the 1918 pandemic, although this time it was mainly the old who died; in the Netherlands in 1949, 2,200 people died within a short period.

This, then, is the objective of the WHO influenza programme : first, to plan against the possible recurrence of a pandemic; second, to devise control methods to limit the spread and severity of the disease; and lastly, to limit the economic effects of an epidemic. Which of the three is regarded as the most important depends on the point of view. However, in the light of present knowledge they can all only be approached in one way.

Before showing how this is being attempted, it is necessary to touch briefly on some technical questions which are really the roots of the whole problem. These are considered in much more detail by Dr. C. H. Andrewes and Dr. T. Francis, jr.<sup>a</sup> Nevertheless, a summary here will help to explain the way in which the WHO programme was developed.

Three main types of the virus of influenza have so far been discovered; the two most important of them—A and B—comprise several subgroups. In the case of virus A these may differ so much as to afford little or no protection, after infection or vaccination, from subsequent infection by a virus of a different subgroup.

This was demonstrated in 1947 (Francis et al.<sup>4</sup>) when a vaccine made from a strain of virus A (PR8) which had given good results in the 1943-4 outbreak,<sup>7</sup> failed to give any protection at all. It turned out that the virus causing the 1947 epidemic was of another subgroup (FM1) now often referred to as A-prime (Salk & Suriano<sup>6</sup>) which differs considerably from PR8. This subgroup of virus A was first detected in Australia in 1946 (Cam). In retrospect that was a most important observation, because if we had known then what we know now there would have been time to prepare a vaccine before the 1947 outbreak. Nevertheless, the danger of the sudden appearance of a new strain of virus remains one of the most serious problems.

Apart from the antigenic variation just described, strains of virus may differ considerably in their ability to spread and to kill. For example, in 1951 the so-called "Liverpool" strain of A-prime virus caused a lethal outbreak in that town, whereas the so-called "Scandinavian" strain spread widely but caused only mild influenza (Isaacs et al.<sup>5</sup>). Yet these strains were so similar antigenically that they were only distinguished by the use of ferret antisera. The strains differed also in their power to stimulate antibody production. The latter quality is obviously highly important in selecting strains for incorporation in vaccines.

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<sup>a</sup> See pages 9 and 125.

The third technical point is that during an epidemic the virus breeds true, within certain limits; that is to say, an outbreak caused by one strain of virus A is not related to one caused by a different strain, even if it occurs nearby and at about the same time. For example, in this year's (1953) epidemic the virus responsible for influenza in southern England was sufficiently different from that found in northern France to make it clear that there was no relation between the two outbreaks, even though the Channel is a trivial obstacle to the influenza virus. On the other hand the virus responsible for the epidemic in the United States of America was similar to the British virus. However, this does not justify the conclusion that the outbreaks were related, because a closely related strain had previously been detected in both countries in 1951 and may have remained there ever since. How the virus maintains itself in the intervals between epidemics is not yet known.

The consequences of these facts are :

(1) that successful vaccination against influenza depends on knowledge of the virus causing the epidemic;

(2) that continuous vigilance is necessary to detect new and potentially dangerous strains of virus at the earliest possible moment; and

(3) that epidemiological reports can be correctly interpreted only in terms of laboratory studies of the viruses responsible.

These are the technical conclusions which must be considered in planning to attain the objectives already set out. It will be seen that the essential knowledge required is early information regarding the nature of the virus causing an outbreak, and a careful analysis of its characters, especially its antigenic structure; and that this information must be gathered from as wide a geographical area as possible. This was appreciated as long ago as 1941, when the US Armed Forces Commission on Influenza, under the chairmanship of Dr. T. Francis, jr., set up a network of laboratories for the isolation of influenza virus, with a central reference laboratory known as the Strain Study Center under Dr. T. P. Magill; its function, as the name implies, was to study and compare strains of virus isolated in different places. Valuable though the work done by this organization was, its usefulness was inevitably restricted by national boundaries.

On 3 April 1947 at its third session the attention of the Interim Commission of the World Health Organization was drawn to the problems and dangers of epidemic influenza by a proposal of the Representative from the Netherlands that a small committee should be appointed to consider the problems.<sup>8</sup> After discussion, the Commission instructed the Executive Secretary to send an observer to the Fourth International Congress on Microbiology, to be held in Copenhagen in July of that year, to obtain from the experts gathered there as complete information as possible on the subject. At Copenhagen an informal meeting of 45 interested people was

held at the Rigsdag on 25 July, and after discussion a small committee of nine members from nine countries was chosen to consider how the views expressed could best be put into practice. At the committee's request Dr. C. H. Andrewes (United Kingdom) prepared a memorandum embodying the suggestions made, which was placed before the Interim Commission at its fourth session in September 1947.<sup>9</sup>

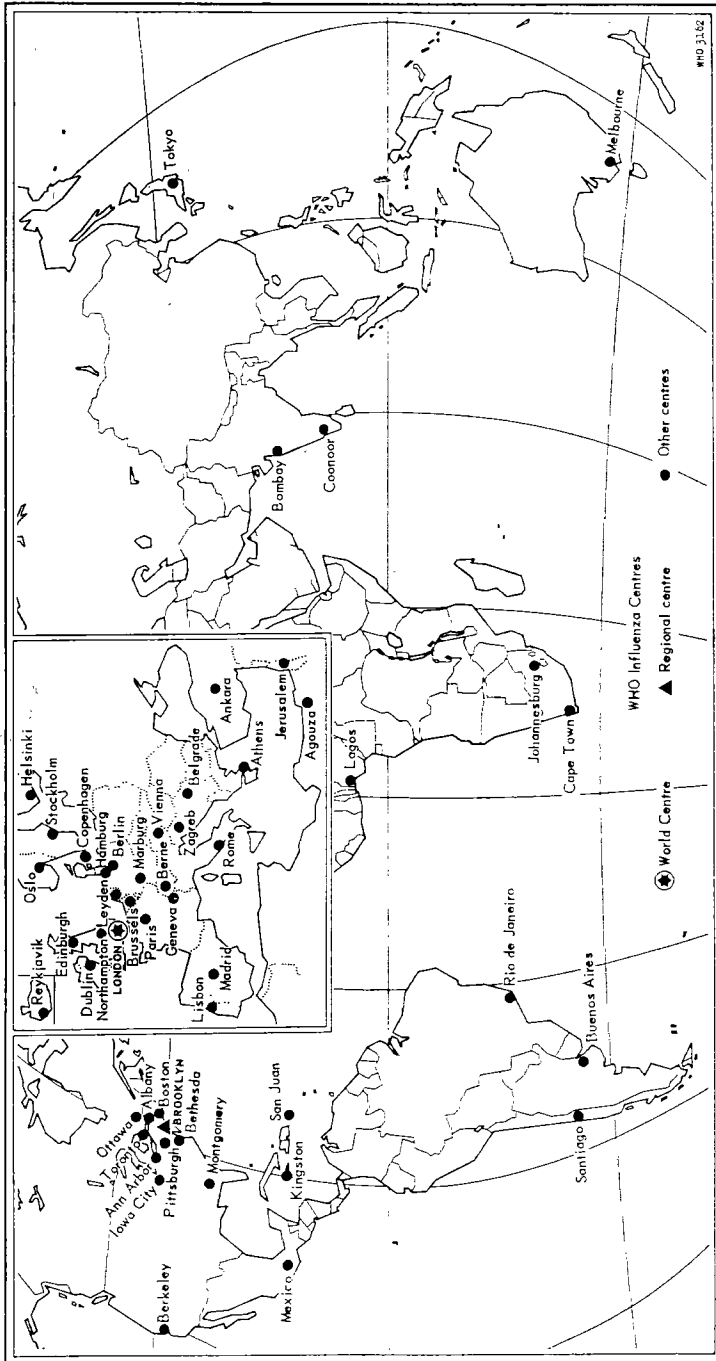
The proposals were that a World Influenza Centre (WIC) should be set up with responsibility for collecting and distributing information, carrying out and co-ordinating laboratory work on influenza, and training laboratory workers. It would work in close co-operation with a number of regional laboratories. The Interim Commission<sup>9</sup> accepted the proposals and decided to establish and finance an international influenza centre in England, and to ask Dr. Andrewes to begin the work as recommended in his memorandum. The Medical Research Council of Great Britain agreed to the establishment of the WIC at the National Institute for Medical Research in London, and the WHO influenza programme had begun.

Work commenced at once, but the organization of a worldwide network of laboratories takes time, and indeed is not completed yet, since in a number of countries there are no virus laboratories and no trained virologists. During the winter of 1947-8 the USA was invited and agreed to participate in the co-operative programme (Culbertson;<sup>2</sup> see also Davis<sup>3</sup>). The Strain Study Center under Dr. Magill, already mentioned, was designated the National Strain Study Center for the United States of America, and the programme was largely built around it, utilizing the existing facilities for investigating influenza, especially those under the Armed Forces Commission on Influenza. An Influenza Information Center was established at the National Institutes of Health, Bethesda, Md., to administer the programme under a committee designated by the Surgeons-General of the Army, Navy, Public-Health Service, and Air Force, and to act as the liaison office between the WIC in London and the co-operating laboratories in the USA.

As the network developed it became clear that there would be great advantages both in speed and in convenience if a single reference laboratory served the whole of the American region. Accordingly the US Strain Study Center accepted designation as the Strain Study Center for the Americas, and now acts for the whole continent exactly as the Centre in London acts for the rest of the world. The two reference laboratories co-operate closely so that the overall world picture can be seen.

There is now a total of 54 WHO-designated influenza centres in 42 countries, but of these 27 are in Europe and 11 in North America. In Central and South America there are 6, in the Eastern Mediterranean Region there are 2, in the African Region 3, in South-East Asia 2, and in the Western Pacific 3. A complete list of centres will be found in Annex 1 (page 161) (see also fig. 1).

FIG. 1. WHO INFLUENZA CENTRES



There are other laboratories co-operating informally in various regions, especially in the USA, but it is clear that the network is not yet worldwide. Efforts are being made to extend the coverage with the help of the WHO regional offices (see Annex 3, page 168). As a temporary solution a number of Influenza Observers (see Annex 2, page 167) have been designated. They are unable to undertake laboratory studies but they furnish epidemiological reports.

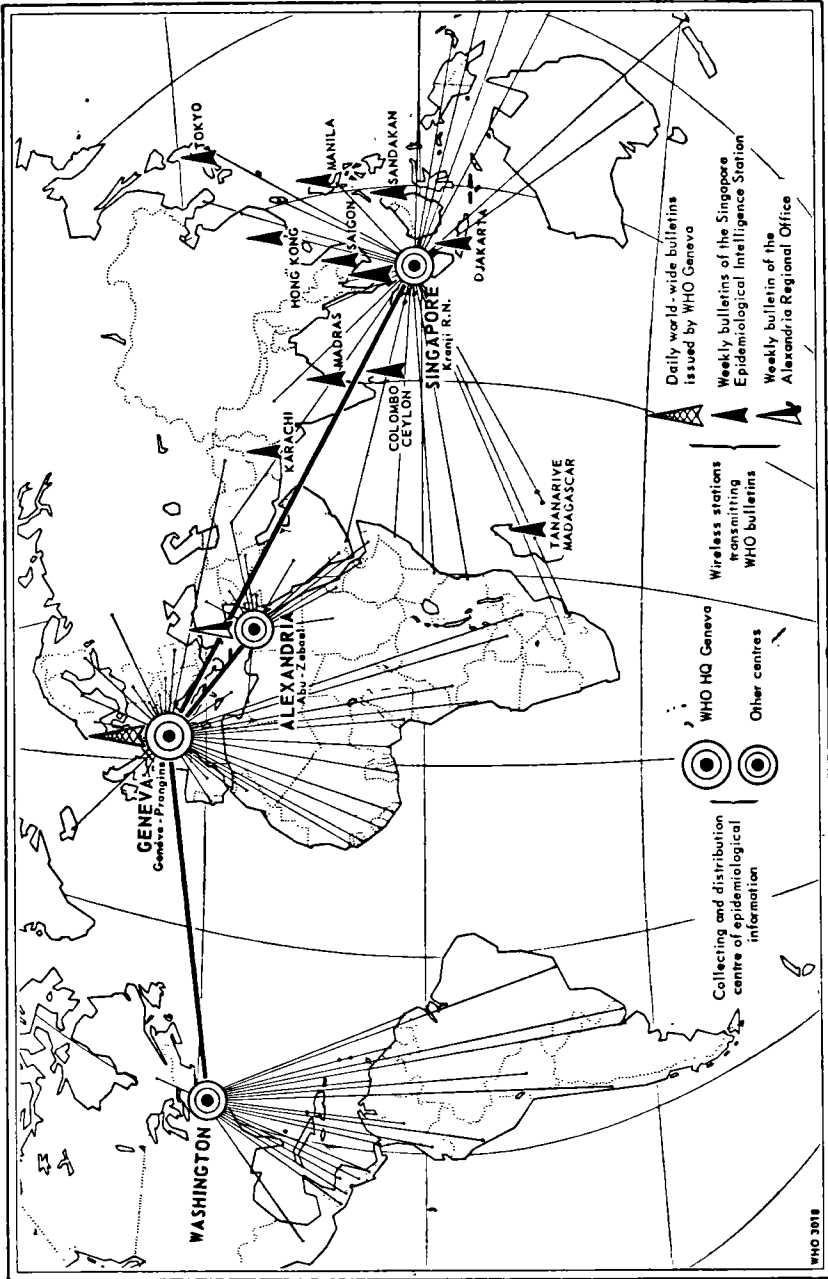
The functions of an Influenza Centre are twofold :

First, to report with all speed the occurrence of influenza within a country, with an estimate of its extent and severity. This information is sent in parallel to the Epidemiological Information and Morbidity Statistics Section at WHO Headquarters in Geneva, to the appropriate regional office, and to the appropriate reference laboratory in London or New York. In the American Region the arrangement is slightly different. The reports from the USA and Canada are first collected by the national Influenza Information Centers which then transmit the information in the same way.

The collection of epidemiological information regarding influenza presents many difficulties. It is well known that notifications are relatively meaningless, because the clinical diagnosis of influenza has no scientific accuracy, and also, during an epidemic the more overworked a practitioner is the less time he has for notifying his cases. In addition, the speed with which influenza spreads makes a delay of only a few days in collecting and distributing the information highly important. What is needed is not a record of actual numbers of cases but some kind of index of the presence of influenza-like disease, based for example on absenteeism among public-transport workers, in factories, or in schools. If such information were collected regularly in selected towns, "normal" figures could soon be established, the simplicity of the information would greatly accelerate the speed of collection, and it might prove possible to follow the trend of an epidemic without the present time-lag. In time of epidemics information regarding the incidence of influenza is collected telegraphically from national health administrations. Frequently, however, the first news of an outbreak reaches the WHO Epidemiological Services from an Influenza Centre and is followed by reports of laboratory results. The information is distributed in the several epidemiological weeklies issued and airmailed from Geneva, Alexandria, Singapore, and Washington, and—if sufficiently important—by cable and in the daily epidemiological radio bulletins (see fig. 2). In addition, summaries are sent by airmail to all Influenza Centres at regular intervals so that the information regarding the prevalent virus which is needed for the proper use of vaccines is available as soon as possible. Of course, if the pandemic recurred much greater use would be made of radio and cabled information.

The second function of an Influenza Centre is to identify the type of influenza by serological tests and preferably by virus isolation. The results

FIG. 2. NETWORK OF EPIDEMIOLOGICAL RADIO-TELEGRAPHIC COMMUNICATIONS



are reported in the same way, and the viruses isolated are dried, frozen, and dispatched by air to the appropriate reference laboratory as soon as possible for further study and comparison with strains isolated elsewhere.

The latter function raises difficulties other than the mere mechanical ones of transport. When an unusual strain is isolated, it is natural to wish to characterize it fully before passing it on to others. This takes time and it is just these unusual strains which are potentially so important. They may be needed at once for the manufacture of vaccine because they may have unusual virulence and ability to spread. It is essential for the WHO programme that these strains should be made freely available the moment any unusual characters are recognized. The sense of international responsibility shown by the workers co-operating in this programme has been truly remarkable.

Strains showing obviously unusual characteristics, collected by the two reference laboratories, are exchanged without further delay, so that they are available for vaccine production in both hemispheres if necessary; they are also sent to other Influenza Centres on request. Most strains, however, do not show such unusual features and they are subjected to careful antigenic analysis and characterization by the reference laboratories to clarify their relationship with other strains. In order to avoid changes in the virus which may occur as the result of passage in the laboratory, early egg-passage material should be sent to the reference centres. As the epidemic proceeds, the epidemiological and virological evidence accumulates and when it is complete the epidemiological data are interpreted in terms of the laboratory results.

It has already been mentioned that it is not known how the influenza virus maintains itself between epidemics, nor is it fully understood how epidemics are generated. Sometimes good evidence of geographical spread of the virus is found, sometimes the disease suddenly appears simultaneously all over a large area as if a preliminary seeding of the virus had taken place throughout the population. The relative importance of the two methods seems to vary in different areas but it is easy to see the practical significance: if the spread is predominantly geographical (as appears to have been the case in the 1948-9 A outbreak in Europe, which began in Sardinia and spread through Sicily, Italy, and thence through western Europe) (Chu et al.<sup>1</sup>) there may be time to vaccinate key-persons before the epidemic wave arrives. If, on the other hand, the virus seeds itself almost invisibly and then the epidemic breaks out everywhere at once, it is really too late to do anything which will have much effect. It is therefore highly important to understand more about the genesis of epidemics, since the future application of control measures will to a large extent depend on it. This investigation is one of the main functions of the two reference laboratories and obviously the study can only be made with international co-operation.

Actually a good deal of progress is being made and this is reviewed in the contribution on the epidemiology of influenza by Dr. C. H. Andrewes.<sup>b</sup>

In co-ordinating the work of a large number of laboratories in many different countries, it is found that technical procedures vary in different places and sometimes the results obtained are not comparable. The experience of workers varies too, and many virologists ask for advice and guidance on new techniques. It is also important that new knowledge should be disseminated as widely and as quickly as possible, so that its practical application is not delayed. Sometimes special problems arise which need co-ordinated research for their solution. Sometimes several workers, unknown to each other, work for long periods on the same approach to the same problem, causing unnecessary duplication and waste of effort.

To overcome these difficulties WHO has evolved a system of Expert Advisory Panels and Expert Committees. Leading workers in a great variety of fields are invited to serve on these Panels, and undertake to advise on technical matters concerned with their own speciality and to keep WHO informed of important advances. From time to time, as determined by the World Health Assembly, Expert Committees, consisting generally of from six to ten members, are convened to report and advise on specific problems. The reports of the committees, after approval by the Executive Board of WHO, are usually published in the *Technical Report Series*.

An Expert Advisory Panel on Virus Diseases has been established to advise on influenza and other virus diseases, and an Expert Committee on Influenza<sup>c</sup> was convened in 1952. The committee reviewed the work of the WHO programme and made suggestions for more effective international collaboration. It studied certain technical questions, including the methods of comparing and typing strains, and diagnostic procedures, and gave precise details of recommended methods for performing diagnostic complement-fixation and haemagglutination-inhibition tests. It also described the preparation of antisera for the comparison and typing of strains of influenza virus, and the preparation and use of crude cholera filtrate for the destruction of inhibitors. Other subjects briefly reviewed included influenza virus vaccines, the collection and distribution of epidemiological information, control measures, and the therapy of influenzal pneumonia.

The recommendations of the Expert Committee should go a long way towards ensuring comparable results in different laboratories, and this will be aided by the proposed provision by WHO of standard diagnostic reagents to laboratories in the WHO network. A freer exchange of new knowledge

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<sup>b</sup> See page 9.

<sup>c</sup> The report of this committee has been published as *World Health Org. techn. Rep. Ser.* 1953, 64.

can also be hoped for, as well as improved facilities for training workers in the techniques of virology.

It should, perhaps, be emphasized that although the WHO influenza network of laboratories was primarily organized for the study of influenza, very many, if not all, of the laboratories undertake a great deal of work on other virus diseases. The network is therefore potentially able to embark on a co-operative international study of other virus diseases, should such a need arise, and, with that in mind, it is regarded as important that training should cover virology in general and not be confined solely to the techniques used in the study of influenza.

Finally, what has the WHO influenza programme achieved so far, and what of the future? Space does not permit a full account. Indications as to some of the results have already been given; others are reviewed by Dr. Andrewes, and details can be found in various publications, notably the *Bulletin of the World Health Organization*, to which references will be found in his paper.<sup>d</sup>

Possibly the most important achievement is that workers in 42 different countries are working in harmony towards a single end, with no financial reward and sometimes with a partial sacrifice of individual credit for the work. As a result, our knowledge of influenza virus variation and the epidemiology of influenza has increased enormously. The type of virus responsible for an outbreak is now usually known early enough for the information to be of practical value to countries not yet affected. For example, this year it was possible to inform the governments of certain countries which vaccine was the correct one to use before any influenza had broken out there. The choice of strains of virus for inclusion in vaccines clearly requires international consultation. This year, too, when telegraphic news was received of the Japanese epidemic, an unusual virus isolated in Japan in 1951 was at once dispatched by airmail to both Australia and the USA, in case it was responsible, and in time for a limited production of vaccine, had it been necessary. The virus was not responsible, but the mechanism is there and is working satisfactorily.

There are still many unsolved problems in influenza which are thoroughly reviewed by other contributors to this monograph and which need not be repeated here. There is hope that some of them will be solved in the near future, as a result of the extensive research now in progress in many parts of the world.

The WHO influenza programme is now a going concern and will continue to grow and improve in efficiency. It is there to apply on an international scale the new knowledge gained by national research, and to supplement that knowledge by international collaboration. Whether influenza will ever be controlled no one can tell, but the time when it

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<sup>d</sup> See page 9.

will be possible to limit the effects of epidemic influenza to a significant degree appears to be within sight, and the WHO programme is helping to bring that day nearer.

## Annex 1

### WHO INFLUENZA CENTRES

#### International

##### *World Influenza Centre*

Dr. C. H. Andrewes  
National Institute for Medical Research  
The Ridgeway, Mill Hill  
London, N.W.7

##### *Strain Study Center for the Americas*

Dr. T. P. Magill  
State University Medical Center  
New York College of Medicine  
335 Henry Street  
Brooklyn 2, N.Y.

#### African Region

##### NIGERIA

Virus Research Institute  
Yaba  
Lagos

##### UNION OF SOUTH AFRICA

Dr. J. H. S. Gear  
The South African Institute for Medical Research  
Johannesburg  
in collaboration with  
Professor M. van den Ende  
Department of Pathology  
University of Cape Town  
Cape Town

#### American Region

##### ARGENTINA

Dr. A. S. Parodi  
Section of Virus Epidemiology and Immunity  
Instituto Bacteriologico Carlos G. Malbran  
Avenida Velez Sarsfield 563  
Buenos Aires

##### BRAZIL

Dr. J. G. Lacorte  
Chefe de Seccao de Virus  
Instituto Oswaldo Cruz  
Caixa postal 926  
Rio de Janeiro

**American Region (continued)****CANADA**

Dr. F. P. Nagler  
Canadian Influenza Information Centre  
Laboratory of Hygiene  
Department of National Health and Welfare  
45, Spencer Street  
Ottawa

Dr. C. E. van Rooyen  
The Connaught Medical Research Laboratories  
University of Toronto  
Toronto

**CHILE**

Dr. Raul Palacios  
Virus Section  
Instituto Bacteriológico de Chile  
Santiago

**JAMAICA**

Dr. L. Grant  
Department of Pathology  
University College of the West Indies  
Mona, St. Andrew

**MEXICO**

Dr. Gerardo Varela  
Instituto de Salubridad y Enfermedades Tropicales  
Esq. Carpio y Plan de San Luis  
Mexico City 17

**PUERTO RICO**

Dr. J. E. Pérez  
School of Tropical Medicine  
University of Puerto Rico School of Medicine  
San Juan 22

**UNITED STATES OF AMERICA**

Dr. Dorland J. Davis  
Influenza Information Center  
National Institutes of Health  
Federal Security Agency  
Bethesda 14, Md.

Dr. M. F. Schaeffer  
Communicable Disease Center  
US Public Health Service  
Montgomery, Ala.

Dr. E. H. Lennette  
Division of Laboratories  
California State Department of Public Health  
1392 University Avenue  
Berkeley, Calif.

**American Region** (*continued*)UNITED STATES OF AMERICA (*continued*)

Dr. A. P. McKee  
State University of Iowa  
Iowa City, Ia.

Dr. M. Finland  
Boston City Hospital  
Thorndike Memorial Laboratory  
Boston, Mass.

Dr. T. Francis, jr.  
Department of Epidemiology  
University of Michigan School of Hygiene and Public Health  
Ann Arbor, Mich.

Dr. I. J. Gordon  
Division of Laboratories and Research  
New York State Department of Health  
Albany, N.Y.

Dr. J. E. Salk  
University of Pittsburgh School of Medicine  
Pittsburgh, Pa.

**Eastern Mediterranean Region**

## EGYPT

Dr. Mohamed Aly & Dr. I. M. Hassan  
Serum and Vaccine Laboratory  
Agouza (Guizeh)

## ISRAEL

Dr. H. Bernkopf  
Hadassah Medical School  
The Hebrew University  
Jerusalem

**European Region**

## AUSTRIA

Dr. E. Petrowsky  
Bundesstaatliche bakteriologisch-serologische Untersuchungsanstalt  
Währingerstr. 25a  
Vienna 9

## BELGIUM

Dr. P. Nélis  
Laboratoire Central d'Hygiène  
2 Parc du Cinquantaire  
Brussels

## DENMARK

Dr. J. Ørskov & Dr. P. von Magnus  
Statens Seruminstitut  
80 Amager Boulevard  
Copenhagen

**European Region** (*continued*)**FINLAND**

Dr. Kari J. Penttinen  
Valtion Serumlaitos  
Fabianinkatu 24  
Helsinki

**FRANCE**

Professeur R. Dujarric de la Rivière, Professeur Pierre Lépine, &  
Mlle G. Cateigne  
Institut Pasteur  
28, rue du Docteur Roux  
Paris 15<sup>e</sup>

**GERMANY (WEST)**

Professor K. Herzberg  
Hygienisches Institut der Universität Marburg  
Marburg an der Lahn  
Professor E. G. Nauck  
Bernhard-Nocht-Institut für Schiffs- und Tropenkrankheiten  
Bernhard-Nocht-Strasse 74  
Hamburg 4

**(BERLIN—WEST)**

Professor D. Henneberg  
Robert Koch Institut für Hygiene und Infektionskrankheiten  
Föhlerstrasse 2  
Berlin N 65

**GREECE**

Dr. S. G. Pavlidis  
Ministry of Hygiene  
Central Public Health Laboratory  
37, 28th October Street  
Athens

**ICELAND**

Dr. B. Sigurdsson  
University of Iceland Institute for Experimental Pathology  
Keldur  
Reykjavik

**IRELAND**

Dr. P. N. Meenan  
St. Vincent's Hospital  
St. Stephen's Green  
Dublin C.2

**ITALY**

Professor I. Archetti  
Istituto Superiore di Sanità  
Viale Regina Margherita 299  
Rome

**European Region** (*continued*)

## NETHERLANDS

Professor J. D. Verlinde  
Instituut voor Praeventieve Geneeskunde  
Wassenaarscheweg 56  
Leyden  
  
in collaboration with  
Professor J. Mulder  
Interne Universiteitskliniek  
Leyden

## NORWAY

Professor Th. Thjøtta  
K. W. Wilhelmsen og frues Bakteriologiske institutt  
Rikshospitalet  
Oslo

## PORTUGAL

Dr. A. A. C. Sampaio  
Dr. Ricardo Jorge Laboratório de Bacteriologia Sanitaria do Instituto  
Superior de Higiene  
Campo dos Mártires de Pátria, 91  
Lisbon

## SPAIN

Dr. F. Pérez Gallardo  
Escuela Nacional de Sanidad  
Facultad de Medicina  
Pabellon No. 1  
Ciudad Universitaria  
Madrid

## SWEDEN

Dr. A. Svedmyr  
Statens bakteriologiska laboratorium  
Box 764  
Stockholm 1

## SWITZERLAND

Professor E. Grasset  
Institut d'Hygiène  
Université de Genève  
Geneva  
  
Professor C. Hallauer  
Institut für Hygiene und Bakteriologie  
Berne

## TURKEY

Dr. Niyazi Erzin  
Refik Saydam Central Institute of Hygiene  
Ankara

**European Region** (*continued*)**UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND**

Dr. L. Hoyle  
Public Health Laboratory  
General Hospital  
Northampton

Dr. R. H. A. Swain  
Bacteriology Department  
University New Buildings  
Teviot Place  
Edinburgh 1

Dr. F. O. MacCallum  
Central Public Health Laboratory  
Colindale Avenue  
London, N.W.9

**YUGOSLAVIA**

Dr. A. Terzin  
Bakteriološko Odelenje  
Savezni Epidemiološki Institut  
Bulevar Jugoslovenske Armije 16  
Belgrade

in collaboration with

Dr. Jelka Vesenjok  
Institute of Microbiology  
University of Zagreb  
Zagreb

**South-East Asia Region****INDIA**

Dr. I. G. K. Menon  
Pasteur Institute of Southern India  
Coonoor

Dr. D. W. Soman  
Haffkine Institute  
Parel  
Bombay 12

**Western Pacific Region****AUSTRALIA**

Dr. W. J. O'Connor  
The Commonwealth Serum Laboratories  
Department of Health  
Parkville, Victoria  
in collaboration with  
Sir Macfarlane Burnet  
Walter and Eliza Hall Institute for Medical Research  
Melbourne

**JAPAN**

Dr. Saburô Kojima  
National Institute of Health of Japan  
Tokyo

**Annex 2****WHO INFLUENZA OBSERVERS****American Region****BOLIVIA**

Instituto Nacional de Epidemiologia  
La Paz

**DOMINICAN REPUBLIC**

Dr. J. J. Ravelo  
Laboratorio de Salud Publica  
Secretaria de Estado de Sanidad y Asistencia Publica  
Ciudad Trujillo

**ECUADOR**

Instituto Nacional de Higiene  
Guayaquil

**Eastern Mediterranean Region****PAKISTAN**

Dr. M. M. Siddiq Husain  
Bureau of Laboratories  
Military Hospital  
Karachi

**South-East Asia Region****CEYLON**

Dr. K. G. B. Stork  
Medical Research Institute  
Colombo 9

**Western Pacific Region****FEDERATION OF MALAYA**

Dr. S. R. Savor  
Institute for Medical Research  
Kuala Lumpur

**NEW ZEALAND**

Dr. F. S. MacLean  
Division of Public Hygiene  
Department of Health  
Wellington  
Sir Charles Hercus, D.S.O., O.B.E.  
University of Otago Medical School  
King Street  
Dunedin, C.1  
Dr. Selwyn Hills  
Auckland Hospital  
Auckland

**PHILIPPINES**

Division of Laboratories  
Department of Health  
Manila

## Annex 3

## WHO REGIONAL OFFICES

Address	Telegraphic address
World Health Organization Palais des Nations Geneva Switzerland	UNISANTE, GENÈVE
Regional Office of the World Health Organization for the Americas 1501, New Hampshire Avenue, N.W. Washington 6, D.C. USA	OFSANPAN, WASHINGTON
Regional Office of the World Health Organization for Eastern Mediterranean P.O. Box 1517 Alexandria Egypt	UNISANTE, ALEXANDRIA
Regional Office of the World Health Organization for South-East Asia Patiala House Hardinge Avenue New Delhi India	WORLDHELTH, NEW DELHI
Regional Office of the World Health Organization for the Western Pacific P.O. Box 2932 Manila Philippines	UNISANTE, MANILA
Regional Office of the World Health Organization for Africa P.O. Box 6 Brazzaville French Equatorial Africa	UNISANTE, BRAZZAVILLE
Regional Office of the World Health Organization for Europe Palais des Nations Geneva Switzerland	UNISANTE, GENÈVE

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