A CLINICAL EVALUATION OF VACCINATION AGAINST INFLUENZA

PRELIMINARY REPORT

BY MEMBERS OF THE COMMISSION ON INFLUENZA, BOARD FOR THE INVESTIGATION AND CONTROL OF INFLUENZA AND OTHER EPIDEMIC DISEASES IN THE ARMY, PREVENTIVE MEDICINE SERVICE, OFFICE OF THE SURGEON GENERAL, UNITED STATES ARMY

In the autumn of 1943 members of the Commission on Influenza, and associates, Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army, Preventive Medicine Service, Surgeon General’s Office, United States Army, undertook with Dr. Thomas Francis Jr., as director, to carry out a controlled clinical trial of the prophylactic efficacy against epidemic influenza of a concentrated, inactivated vaccine containing the viruses of influenza types A and B. Preceding studies had shown that a vaccine similarly prepared was capable of furnishing definite protection against experimental infection of influenza A or B. The present account constitutes a preliminary clinical evaluation of the influence of vaccination on the incidence of influenza during the epidemic of influenza A which occurred in November and December 1943.

VACCINE

The vaccine was prepared in the laboratories of biologic firms according to specifications furnished by the commission and purchased at minimal cost with commission funds. Virus was obtained from the allantoic fluid of embryonated hen’s eggs inoculated forty-eight hours earlier. The virus was concentrated approxi-

mately ten times in isotonic solution of sodium chloride following adsorption to, and elution from, the embryonic erythrocytes. The infectious capacity was inactivated by solution of formaldehyde in a concentration of 1:5,000. Phenyl mercuric nitrate 1:100,000, or borate 1:50,000, was then added for bacteriostatic purposes. The material was bottled in 50 cc. amounts in liquid form. The standard requirements for sterility of bulk and bottled biologic products were met.

Each 1.0 cc. of the vaccine was made up of 0.5 cc. representing type A virus recovered from 5.0 cc. of allantoic fluid and 0.5 cc. representing the type B virus recovered from 5.0 cc. of allantoic fluid. The type A component represented equal parts of the PR8 strain and of the Weiss strain, isolated in May 1943. The type B component contained only the Lee strain.

The vaccine was tested by inoculation of mice and eggs to demonstrate that no infectious capacity remained. Its capacities to agglutinate chicken erythrocytes and to induce immunity in mice after intraperitoneal inoculation were also determined as indicative of antigenic activity.

Control material consisting of isotonic solution of sodium chloride to which solution of formaldehyde

was added, was prepared, bottled, and subjected to the same tests for sterility.

THE PLAN OF STUDY

With approval of appropriate authorities, the study was carried out in Army Specialized Training Program units of eight universities in different parts of the United States and in a ninth group comprising the members of Army Specialized Training Program units of five New York medical and dental colleges. Approximately 12,500 men were involved. The populations were highly stable, so that the proportion of men lost from the study was extremely low. In most instances the men were housed as large groups in dormitories.

Vaccine prepared by two different firms was employed in all locations. Except in one unit equal volumes of the two preparations were mixed just before inoculation, so that no selection occurred on this basis. Each

<table>
<thead>
<tr>
<th>Table 1—Results in Group I: Cornell University, Ithaca, N. Y., and New York Medical and Dental Colleges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Norman Plummer, M. C., A. U. S., and Wilson G. Snell, M.D., Cornell University Medical College, New York. Dr. Joseph Woodman participated in the clinical studies at Ithaca.</strong></td>
</tr>
</tbody>
</table>

**Epidemic period:** Cornell, 11/25-12/18; New York Medical Colleges, 11/25-12/18/43.

**Diagnosis:** Patients reporting with temperature of 100 F. or greater. Cases of obviously different origin excluded.

<table>
<thead>
<tr>
<th>Unit</th>
<th>Date Vaccinated</th>
<th>Number in Study</th>
<th>Total Cases</th>
<th>Incidence, per Cent.</th>
<th>Percentage of Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornell University</td>
<td>11/20/43</td>
<td>Vaccinated 93</td>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 454</td>
<td>2</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>547</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>N. Y. Medical and Dental Colls.</td>
<td>11/20-11/3/43</td>
<td>Vaccinated 993</td>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control 977</td>
<td>2</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>1970</td>
<td>0.22</td>
<td>0.22</td>
</tr>
</tbody>
</table>

* The incidence 11/20 to 12/20/43 is based to a large extent on questioning, since unit was on furlough during this period.

These data are considered incomplete. The low incidence is probably related to the difficulty encountered in obtaining proper reporting among the high percentage of men living in private homes.

**Support and assistance in arranging the studies were furnished by Col. Charles M. Walker, Col. Don C. Hildreth, Col. Herbert C. Gibber and Col. Howard C. Moore, respectively, surgeons of the 2d, 6th, 7th and 9th service commands.**

Continued aid and cooperation were furnished by the commanding officers of the different A. S. T. F. units among which the investigations were made, namely Col. Edwin V. Van Deusen, Cornell University; Col. Arthur E. Fox, Princeton University; Col. F. D. Day, Rutgers University; Col. Raymond P. Cod, C. C. N. Y.; Col. Frederick C. Rogers, University of Michigan; Col. Harry King, University of Minnesota; Col. Luke D. Zech, University of Iowa; Col. Francis R. Hunter, Columbia Medical and Dental College; Lieut. Col. Mark R. N. Zwiisman, Columbia Medical and Dental College; Lieut. Col. Francis R. Hunter, Cornell Medical College; Capt. Robert Geiser, Long Island Medical College; Major Albert C. Durat, New York Medical College, and Capt. George F. Dynon, New York University College of Medicine and Dentistry.


1:5,000 and phenyl mercuric nitrate 1:100,000 were added, prepared, bottled, and subjected to the same tests for sterility.


Diagnosis: Epidemic given George the vaccine observer Jonas after, the carried rial Princeton. University made.

Table 2.—Results in Group 2: Princeton University, Princeton, N. J., Rutgers University, New Brunswick, N. J., and College of City of New York

Table 3.—Results in Group 3: University of Michigan, Ann Arbor

Table 4.—Results in Group 4: University of Minnesota, Minneapolis

Cases of influenza were not noted in any dormitory housing inoculated students until at least eleven days after vaccination of the group housed in that dormitory.
An epidemic of influenza A was first identified in the Middle West about the second week in November. The disease was subsequently recognized in other localities within a short time thereafter. The epidemic period in the posts under observation was three to four weeks. The disease was, in general, mild, of three to four days' duration and with a low incidence of complications.

The accompanying data represent tabulations of cases called influenza at the time of illness. The designation cent, while in the 6,263 receiving vaccine there was an incidence of 2.22 per cent, a ratio of 3.2 to 1.

The significance of the results is heightened by the uniformity of trend in practically all instances. The two greatest deviations are noted in the medical school units and in California. In the former the low incidence of the disease is thought to be related to the lack of central reporting. In the latter instance there is no clear difference between control and vaccinated groups; various factors such as furlough, the increased interval since

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### Table 5: Results in Group 5: University of Iowa, Iowa City

<table>
<thead>
<tr>
<th>Unit</th>
<th>Date Vaccinated</th>
<th>Number in Study</th>
<th>Cases by Weeks Ending</th>
<th>Total Cases</th>
<th>Incidence per Cent</th>
<th>Percentage of Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Iowa</td>
<td>12/3-12/4/43</td>
<td></td>
<td>12/11</td>
<td>12/18</td>
<td>12/24</td>
<td>1/1/44</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>590</td>
<td></td>
<td>(9)</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Control</td>
<td>600</td>
<td></td>
<td>(11)</td>
<td>12</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>1,198</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Five cases before vaccination completed. Summarized totals exclude the cases occurring in the first five days following vaccination. Numbers in parentheses indicate those occurring in the first five days. Hémolytique streptococcus pharyngitis occurred concurrently with the outbreak of influenza. Twenty per cent of throat cultures were positive for H. hemolytic streptococcus.

### Table 6: Results in Group 6: University of California, Berkeley

<table>
<thead>
<tr>
<th>Unit</th>
<th>Date Vaccinated</th>
<th>Number in Study</th>
<th>Cases by Weeks Ending</th>
<th>Total Cases</th>
<th>Incidence per Cent</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Iowa</td>
<td>10/10-10/17/43</td>
<td></td>
<td>12/3</td>
<td>10/10</td>
<td>12/17</td>
<td>12/24</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>437</td>
<td></td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Control</td>
<td>435</td>
<td></td>
<td>3</td>
<td>1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>892</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

About 10 cases of streptococcal infection including 2 with scarlet fever occurred during the influenza epidemic. The unit was on furlough 1/1 to 1/13/44. A few were away 1/7 to 1/20/44.

### Table 7: Summary of Clinical Evaluation of Vaccination Against Influenza

The combined totals of all results.

<table>
<thead>
<tr>
<th>Service Group Command</th>
<th>ASTP Unit</th>
<th>Dates of Vaccination</th>
<th>Total Number</th>
<th>Number of Vaccinated</th>
<th>Number of Cases</th>
<th>Incidence, per Cent</th>
<th>Percentage of Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2d Cornell</td>
<td>12/19</td>
<td>1,598</td>
<td></td>
<td>408</td>
<td>978</td>
<td>2.55</td>
<td>8.86</td>
</tr>
<tr>
<td>2 2d N.Y. Med. Schools</td>
<td>10/26-11/4</td>
<td>1,210</td>
<td></td>
<td>600</td>
<td>560</td>
<td>1.16</td>
<td>6.90</td>
</tr>
<tr>
<td>3 2d Princeton</td>
<td>11/2</td>
<td>2,042</td>
<td></td>
<td>700</td>
<td>606</td>
<td>2.88</td>
<td>8.20</td>
</tr>
<tr>
<td>4 2d Rutgers</td>
<td>11/1</td>
<td>1,060</td>
<td></td>
<td>480</td>
<td>977</td>
<td>1.45</td>
<td>3.38</td>
</tr>
<tr>
<td>5 6th Michigan</td>
<td>10/26-11/22</td>
<td>1,776</td>
<td></td>
<td>598</td>
<td>698</td>
<td>2.35</td>
<td>8.35</td>
</tr>
<tr>
<td>6 7th Minnesota</td>
<td>11/5-11/12</td>
<td>1,356</td>
<td></td>
<td>769</td>
<td>697</td>
<td>2.08</td>
<td>8.06</td>
</tr>
<tr>
<td>7 7th Iowa</td>
<td>12/1-12/24</td>
<td>1,188</td>
<td></td>
<td>589</td>
<td>669</td>
<td>1.82</td>
<td>6.67</td>
</tr>
<tr>
<td>8 9th California</td>
<td>10/10-10/17</td>
<td>892</td>
<td></td>
<td>457</td>
<td>435</td>
<td>1.25</td>
<td>7.89</td>
</tr>
<tr>
<td>Total</td>
<td>7,244</td>
<td></td>
<td></td>
<td>6,061</td>
<td>6,511</td>
<td>2.22</td>
<td>7.11</td>
</tr>
</tbody>
</table>

has been made purely on clinical grounds without reference to serologic or other virus studies for identification of individual cases. The division according to vaccinated or control was not done until the epidemic period was thought to have been passed. The results for the respective units were compiled by the investigating teams and, in all but 1 instance, a report was submitted to the Office of the Surgeon General of the Army before the evidence obtained in other locations was known.

It is seen that the incidence of clinical influenza in the 6,211 men receiving control material was 7.11 per vaccination and the protracted incidence of disease may be involved, but no single explanation is offered at present. When these two pronounced deviations are excluded, the ratio of influenza in controls to influenza in vaccinated is 4 to 1. In some of the units, ratios of 5 or 6 to 1 were recorded.

It is of interest to note also that, in general, the difference between vaccinated and control individuals was greatest at the height of the epidemic curve and as the epidemic subsided the differential was less marked.

The results at the College of the City of New York and at Iowa, where vaccination was begun after the
epidemic was in progress, indicate that the effect of vaccine becomes evident in about one week after inoculation. In these instances the attack rates in the vaccinated and controls were not especially different during the first week but then diverged sharply. The duration of the effect is not known.

In this brief report no consideration is given to the results of serologic and virus studies which are under way and which will be incorporated in a subsequent complete report.

**SUMMARY**

The influence of subcutaneous inoculation of a concentrated inactivated vaccine on the incidence of clinical influenza in a series of Army Specialized Training Program units comprising approximately 12,500 men was studied during the recent epidemic of influenza A. Vaccination done shortly before or even after the onset of the epidemic was found to exert a protective effect with a total attack rate of 2.22 per cent among the 6,263 vaccinated and 7.11 per cent among the 6,211 controls, a ratio of 1 to 3.2. The influence of vaccine was most clearly evident at the height of the epidemic prevalence.

The duration of the effect has not been determined.

Office of the Influenza Commission, School of Public Health, University of Michigan, Ann Arbor, Mich.

**Council on Foods and Nutrition**

**ACCEPTED FOODS**

The following additional foods have been accepted as conforming to the rules of the Council on Foods and Nutrition of the American Medical Association for admission to Accepted Foods.

George K. Anderson, M.D., Secretary.

**PREPARATIONS USED IN THE FEEDING OF INFANTS** (See Accepted Foods, 1939, p. 156).

Beech-Nut Packing Company, Inc., Canajoharie, N. Y.

**Beech-Nut Brand Strained Vegetables and Beef, with Rice and Barley.**

**Analysis (submitted by manufacturer).—**

- Total solids 13.95%.
- Protein (as casein) 1.32%.
- Ash 0.15%.
- Calcium 0.48%.
- Iron 0.005%.
- Fat (ether extract) 0.56%.
- Carbohydrates 73.37%.

**Libby, McNiel & Libby, Chicago.**

**Libby's Brand Homogenized Apple Sauce.**

**Analysis (submitted by manufacturer).—**

- Total solids 14.51%.
- Total ash 0.12%.
- Nitrogen 0.03%.
- Carbon dioxide 0.46%.
- Ash (ether extract) 0.03%.
- Salt (as NaCl) 0.18%.
- Total carbohydrates (by difference) 13.95%.
- Calcium 2.18 mg. per hundred grams.
- Iron 0.21 mg. per hundred grams.
- Phosphorus 0.62 mg. per hundred grams.

**Libby, McNiel & Libby, Chicago.**

**Libby's Brand Homogenized Beets.**

**Analysis (submitted by manufacturer).—**

- Total solids 10.25%.
- Total moisture 89.75%.
- Total ash 1.09%.
- Nitrogen 0.163%.
- Protein 3.07%.
- Ash 0.47%.
- Fat 0.047%.
- Carbohydrates (by difference) 7.458%.
- Calcium 17.36 mg. per hundred grams.

**Libby, McNiel & Libby, Chicago.**

**Libby's Brand Homogenized Peaches.**

**Analysis (submitted by manufacturer).—**

- Total solids 13.22%.
- Total ash 0.33%.
- Total moisture 84.78%.
- Nitrogen 0.07%.
- Carbon dioxide 0.44%.
- Ash (ether extract) 0.34%.
- Salt (as NaCl) 0.13%.
- Calcium 5.5 mg. per hundred grams.
- Phosphorus 20.4 mg. per hundred grams.
- Iron 1.01 mg. per hundred grams.

**Council on Pharmacy and Chemistry**

**NEW AND NONOFFICIAL REMEDIES**

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

Austin E. Smith, M.D., Secretary.

**TYROTHRICIN.—** An extract, first isolated by Dubos, obtained from Bacillus brevis, a gram-positive, aerobic, spore-forming soil organism. Tyrothricin possesses antibacterial action against several species of gram-positive organisms.

**Actions and Uses.** Tyrothricin consists of at least two substances, gramicidin and tyrocidin, the former agent being by far the more active component. It seems not unlikely that some of the earlier reports which were claimed to be based on the use of gramicidin were actually concerned with the mixture. Included in the organisms that show some degree of susceptibility are species of pneumococci, streptococci and staphylococci.

Its action on bacteria appears to consist, at least in part, of inhibiting enzymatic action, retarding growth and causing lysis of the bacteria against which it is effective. Its standardization is determined at present by the protection afforded mice infected with pneumococci administered intraperitoneally.

Tyrothricin should be applied locally. It is ineffective when administered orally and is ineffective and dangerous when given intravenously. It has been reported to be of value in the treatment of superficial indolent ulcers, the predominating organism of which is gram positive, mastoiditis, empyema and some other wound infections. Its field of usefulness is limited and it appears to exert no effect unless it can come in direct contact with the organism. Thus it may not exert much effect in the presence of deep-seated infections. Body fluids such as saliva, urine and serum offer a slight inhibiting action, whereas substances from gram-negative organisms are decidedly inhibiting.

It may be used with caution in blood cavities as long as there is no direct connection with the blood stream. But in no instance should proper surgical treatment be ignored when it is indicated. It should be remembered that, although tyrothricin appears to have a field of usefulness in medicine, its use is still in an experimental stage and much work remains to be done before its true status is established and final comparisons can be made with other antibiotics and anti-infective agents in general.

**Dosage.** Tyrothricin must be applied locally, not intravenously or by mouth. It is administered after diluting with sterile distilled water to form an isotonic solution in a concentration which yields 500 micrograms of the drug per cubic centimeter. This concentration is usually effective against the infecting organism, although higher concentrations may be used when indicated. However, higher concentrations may be irritating to the tissues.

**SHARP & DOHME, INC., PHILADELPHIA**

**Tyrothricin Concentrate.** 1 cc. ampul of a solution of tyrothricin, 25 mg. per cubic centimeter, accompanied by a vial containing 49 cc. of sterile distilled water which contains mercuric borate in a concentration of 1:50,000; 20 cc. ampul of a solution of tyrothricin, 25 mg. per cubic centimeter, not accompanied by a diluent.

**ESTROGENIC SUBSTANCES** (See New and Nonofficial Remedies, 1943, p. 401).

The following additional dosage form has been accepted:

**THE SMITH-DORSEY COMPANY, LINCOLN, NEB.**

**Ampul Solution of Estrogenic Substances** (in sesame oil) with Benzy1 Alcohol 3%: 10 cc. Each cubic centimeter contains the equivalent of 20,000 international units of estrone. Three per cent benzyl alcohol added as a preservative.

**THEOPHYLLINE ETHYLENEDIAMINE** (See New and Nonofficial Remedies, 1943, p. 356).

The following dosage form has been accepted:

**CHEPLIN BIOLOGICAL LABORATORIES, INC., SYRACUSE, N. Y.**

**Ampul Solution Aminophylline:** 0.48 Gm. in 2 cc. and 0.24 Gm. in 10 cc.

**VIOFORM** (See New and Nonofficial Remedies, 1943, p. 121).

The following additional dosage form has been accepted:

**CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.**

**Vioform Insufflate:** 8 ounce bottles.