EXPERIENCES WITH PROPHYLACTIC TYPHOID VACCINATION

ITS EFFECT ON MENSTRUATION *

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Prophylactic typhoid vaccination has won for itself a well-deserved place among the great preventive measures in medicine. This advance has been accompanied by a considerable literature on the history of the procedure, the various methods employed and the results obtained. It is not the object of this article to review the literature. The facts are easily accessible,[1] and, in general, well known.

During the past two years the vaccine has been used prophylactically at the Presbyterian Hospital, New York, and it is the purpose of the present communication in reporting the results of this experience, to emphasize the facts which have seemed most important and to point out in some detail the especial effect of the vaccine on menstruation.

PREVIOUS CONDITIONS

Stimulated by the excellent results obtained by this procedure in the United States Army and by Richardson and Spooner in the training schools of Massachusetts, the medical board of the Presbyterian Hospital, New York, decided, in the spring of 1911, to offer this opportunity of immunization against typhoid to the nurses and attendants at the hospital. Before starting the inoculations, the hospital records were reviewed in order to ascertain the incidence of the disease among those brought into intimate contact with typhoid patients or the cultures of typhoid bacilli. Beginning with the year 1892, the date of the foundation of the training school for nurses, a period of twenty years was covered, during which

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* From the Pathological Laboratory, Presbyterian Hospital, Columbia University, New York.

1. The following articles give the main facts of interest and contain references to most of the other important papers:

Russell, F. F.: The Military Surgeon, 1909; Boston Med. and Surg. Jour., 1911, clxiv, 1; Jour. Am. Med. Assn., 1912, lviii, 1331; 1912, lix, 1362; 1913, lx, 344; 1913, lxi, 666; Harvey Lecture, New York, 1913.

Spooner, L. H.: Boston Med. and Surg. Jour., 1910, clxii, 37; Jour. Am. Med. Assn., 1912, lix, 1359.

Davis, D. J.: Jour. Am. Med. Assn., 1912, lviii, 537.

Hachtel and Stoner: Jour. Am. Med. Assn., 1912, lix, 1364.

fifty-two cases of typhoid fever in nurses, doctors, orderlies and bacteriologists were treated in the hospital. Only those cases were included which gave a direct history of contact with typhoid patients or cultures. This gave 2.6 as an average yearly percentage of cases in which typhoid was possibly preventable. There were four deaths, a mortality of 7.69 per cent.

The cases were divided as follows: nurses, 39; orderlies, 6; bacteriologists, 4; doctors, 3.

Of the thirty-nine nurses, nineteen, or about one-half, were in training or on duty in the hospital at the time of contracting the disease. The remaining twenty were caring for typhoid patients when taken ill. There were no deaths among the nurses who developed the disease while in the hospital, but of those who contracted the disease outside, two died. Both were graduates of the hospital. All six orderlies were employed at the hospital in wards in which the care of typhoid patients was necessitated, and there were two deaths. The four bacteriologists developed the disease while working with typhoid cultures. Only one was on duty at the hospital at the time of contracting the disease. The others came from other laboratories. There were no deaths. Of the doctors, two were interns at the hospital and one was a substitute. There were no deaths.

The occurrence of the fifty-two cases by years was as follows:

1892	1	1902	1
1893	0	1903	3
1894	0	1904	4
1895	1	1905	5
1896	2	1906	3
1897	0	1907	6
1898*	11	1908	1
1899	1	1909	0
1900	4	1910	3
1901	4	1911	2

* Spanish War.

It will be seen that in four separate years, 1893, 1894, 1897 and 1909, there were no cases, and that for one period of two years there was also a clean record, facts which must be borne in mind in estimating the value of the results obtained through the use of the vaccine over a comparatively short period of time. In 1898, the year of the Spanish War, there were eleven cases. At that time additional wards were opened for the care of typhoid patients and the hospital staff was greatly overworked. Several of the nurses treated at this time came from the army camps.

The conditions described do not differ essentially from those reported by observers in other localities. Thus Spooner,[2] at the Massachusetts General Hospital in Boston, found that there were three or four cases of

2. Spooner: Am. Jour. Pub. Hyg., 1909, xix, 616.

typhoid a year among the nurses and those especially exposed. He found, moreover, that in these patients the disease ran a course of more than usual severity with a greater number of complications and a higher mortality than the average. I did not find this true in our statistics. The mortality was less than that for the hospital in general and the cases were not unusually severe, nor did they show more complications than the average.

Davis[3] gives no definite figures for St. Luke's Hospital, Chicago, but states that "an occasional nurse has had typhoid."

Joslin and Overlander[4] investigated the conditions in six hospitals in Massachusetts for the years 1902 to 1906 and came to the conclusion that one nurse came down with typhoid for each 114 cases treated, and that "the hospital nurse in Massachusetts is about eight times as liable to contract typhoid fever as the ordinary citizen."

Hachtel and Stoner[5] give higher figures for Baltimore. They find that the nurses and attendants are from twelve to twenty times more liable to contract the disease than the ordinary citizen of Baltimore.

One does not need to cite further specific instances. While differing somewhat in the actual figures, all observers are agreed on the main fact, that nurses, doctors and hospital attendants run a considerably greater risk of contracting typhoid than the ordinary citizen, and that in spite of due precautions, a certain number of them contract the disease each year, the source of infection being the typhoid patient or articles which have come in contact with typhoid cases.

VACCINE

The vaccine used is prepared from an old culture of attenuated virulence, isolated about twelve years ago. The organisms are grown on large agar-slants (agar slanted in 250 c.c. Erlenmeyer flasks is very convenient) for twenty-four hours, washed off with sterile salt solution and heated at a temperature of 53 C. (127.4 F.) for one hour. The vaccine is standardized with the ordinary blood-counting apparatus. After sterility is assured, the vaccine is made up to the required dilution with sterile salt solution containing 0.25 per cent. phenol (carbolic acid). It is put up in small ampules, each containing enough for one dose, and in 30 c.c. vaccine bottles for use where larger numbers are to be vaccinated.

The vaccine was carefully compared with that used in the United States Army, a supply of which was very kindly sent to the hospital by Major Russell. In a large number of inoculations no difference could

3. Davis: Jour. Am. Med. Assn., 1912, lviii, 537.
4. Joslin and Overlander: Boston Med. and Sudg. Jour., 1907, clvii, 247.
5. Hachtel and Stoner: Jour. Am. Med. Assn., 1912, lix, 1367.

be detected in the local or general reactions or in the Widal reactions. Therefore, it would appear that the hospital vaccine represents approximately the same potency and lack of toxicity as that used in the army. The vaccine should be fresh and in general should not be used after it is 3 months old, as it has been shown that deterioration begins at about this time.

DOSAGE

The usual dosage recommended is that employed in the United States Army. It consists of three inoculations at ten-day intervals, the first of 500 million, the second and third of one billion each. This method has been well tried and it has been conclusively shown that it confers a sufficient immunity for a period of at least three years. Conditions there, however, differ somewhat from those among nurses and in private practice where a reaction which would not trouble a man in the regular army is considered quite an event. The same dosage as previously noted was given in a considerable number of the cases in this series, and there were enough troublesome reactions to make one consider a variation of the dose. Of course, one's aim in giving the vaccine is to protect the patient against typhoid and not to avoid reactions; but, if one can produce the desired immunity with the smallest amount of discomfort, the cause of typhoid prophylaxis has been aided just so much. The aim, then, should be to inject the maximum number of bacilli with the minimum amount of discomfort and inconvenience to the patient.

One class of nurses received the four doses, recommended by Spooner,[6] of 100 million, 200 million, 400 million and 600 million at five-day intervals. These cases had fewer and less troublesome reactions than the others, but they received only about one-half the total number of bacilli given by the army method. By considering certain general factors to be mentioned presently, one can considerably increase this total without a corresponding increase in the reactions. It is generally quite safe to make the initial dose 200 million and then, being governed by the reactions which occur, one can very often make the second dose 300 to 400 million, the third 500 to 600 million and the fourth 800 million to one billion. In this way one can more nearly approximate the army total dosage without as many disagreeable reactions.

Some people prefer to take their chances on the possibility of having a reaction rather than submit to the inconvenience of a fourth injection, and in vaccinating large numbers, the extra inoculation means considerable added expenditure of time, especially among women in whom the avoidance of the menstrual period causes many delays and much straggling out of the inoculations. Therefore, it has been the more recent routine to use three graduated doses at from seven-day to ten-day

6. Spooner: Jour. Am. Med. Assn., 1912, lix, 1359.

intervals, the first of 300 million, the second of 700 million and the third of one billion. Here, as in the preceding case, one can be governed by the patient's general condition and can often without fear of undue disturbance, make the first dose 350 to 400 million and the second 800 million.

Of course, it is impossible to predict accurately what reaction a person will have, but one can be governed by certain general facts. In the first place, women are more apt to have reactions than men. This fact is brought out in the statistics of Hachtel and Stoner,[7] and was shown in the first twenty-three cases of this series, of whom twelve were doctors and eleven were nurses. The mild and moderate reactions were about twice as frequent among the latter as among the former. Members of families in which there is, apparently, a marked susceptibility to typhoid or in which the disease has run a severe course, are apt to show more marked reactions. In one family which I vaccinated, both of these facts were true, and of the five members, all showed varying degrees of reaction after all of the inoculations except a boy, aged 11. In one there was the most severe local reaction which I have seen, combined with a moderately severe general reaction and in another, the general reaction after the first two doses was sufficient to discourage a third inoculation. Persons who have a low resistance to any form of infection are apt to have troublesome reactions and the same is true of those who are run down or debilitated from any cause. Those suffering from any chronic disease, should, if vaccinated at all, receive the four smaller doses. Naturally, the preceding statements are only general principles of guidance. One will encounter perfectly robust individuals who come in none of the foregoing classes, who, nevertheless, show severe reactions, while, on the other hand, any of the types mentioned may show no reaction whatever. From my experience up to the present time, I believe that it is best to give to the persons of the types mentioned, the four doses at seven-day intervals, beginning with 200 million and increasing each succeeding dose as far as feasible. For all others, I prefer the three graduated doses, using the upper limits for each dose if possible. From a rather limited experience with children I have seen no reason for graduating the dosage according to body weight. As a rule, they stand the inoculations with less inconvenience than adults and I have seen no troublesome reactions following full-sized doses.

With many people, especially business men, a seven-day interval is preferable to one of ten days. The inoculations can thus be given on successive Saturdays, allowing them until Monday to recuperate from any ill effects. It is best where possible to give the injections in the

7. Hachtel and Stoner: Jour. Am. Med. Assn., 1912, lix, 1367.

late afternoon or early evening so that the maximum reaction may take place while the patients are asleep.

PRECAUTIONS

From my experience it has been apparent that whatever the site chosen for inoculation the patient is inclined to wish that the vaccine had been injected elsewhere. It has been found more convenient and perfectly satisfactory to make the inoculation in the left upper arm, just above the insertion of the deltoid, using the right arm in left-handed people. The vaccine is injected into the subcutaneous tissue, care being taken to avoid entering a vein, as in such cases the general reaction is usually more rapid in its appearance and more severe, and the local reaction more troublesome. In cleaning the arm, iodin and alcohol have been found perfectly satisfactory. After withdrawing the needle, the site of inoculation is touched with iodin and no dressing of any kind is applied, as it has been found that collodion, bandages or gauze with adhesive strips simply add to the local annoyance. In exceptional cases, if the local reaction is moderately severe, a dressing of aluminum acetate has been used with good results.

In prophylactic work, one must remember that patients are not inclined to be particularly grateful for any reactions which the vaccine may cause and it is only human nature for them to attribute to the vaccine every ill for months following. As the value of typhoid vaccine is so great and the need for its universal adoption so striking, it is of the utmost importance to observe every precaution to prevent its falling into disrepute in any case. A careful history should be taken in each case and a sufficiently exact examination made to be sure that the patient is in sound health, for it is quite within the range of possibilities that a person might be inoculated in the early stages of some disease, and it would then be difficult to convince the patient or his friends that the disease was not directly caused by the vaccine. In the present work such incidents were encountered. One nurse developed a typical case of scarlet fever two days after the second inoculation, and for the first day or two even the doctor who saw her considered that she was suffering from a rather severe vaccine reaction with an associated rash. From the subsequent course of the case, there was no doubt as to the nature of the disease. In such an instance in private practice, it would be exceedingly difficult to convince the family that there was no association between the vaccine and the scarlet fever. In another case, a man had an attack of bronchopneumonia which began ten days after the third injection. At the onset he believed that his illness was in some way associated with the vaccine, though in this case the disease followed a very definite exposure to cold. Other cases of association of various diseases with the vaccine will be given later.

It is well recognized that the vaccine may cause a temporary change for the worse in an existing chronic condition. For example, Spooner[8] has encountered temporary and not serious exacerbations in chronic arthritis, chronic cholecystitis, subacute urethritis, furunculosis and acne. I have seen similar instances and will mention them later. Other observers have noted the same thing. While the exacerbations are not apt to be serious, their possibility should be recognized and all chronic conditions should be asked for in the history, as in each case one can then decide whether or not it is wise to give the vaccine. I do not believe that it should be given in cases in which there is a history of tuberculosis; but if, in spite of the existence of some chronic condition, it is decided to go ahead with the vaccine, the patient should be fully acquainted with the possibilities and the vaccination procedure should be followed cautiously and the four smaller doses administered.

Another question which arises is that of vaccination where there is a history of a preceding attack of typhoid fever. It has been found that the reactions in such cases are apt to be rather strikingly severe. In the only case of the kind in which I have used vaccination, that of a young man, there was a moderately severe reaction for a day and a half after the first dose, followed immediately by a severe attack of tonsillitis and in ten days by a profuse urticarial rash. As the disease itself confers a life immunity in almost all cases, and as vaccination in such cases is apt to be followed by bad reactions, I have since refused to inoculate patients who give a history of a previous attack of typhoid. At times this preceding history is not definite and in such cases one must exercise one's own judgment. Where there is a reasonable doubt, I believe one should proceed with the vaccination, using the four smaller doses rather cautiously.

In addition to the above precautions, one should explain the effects of the vaccination to patients and tell them just what they may expect in the way of local and general reactions. Patients should be warned to remain quietly at home while the reaction is present. The most severe reaction seen in the present cases seemed to have been increased by the patient's going about as usual on the day following the first inoculation, when the temperature was 101. The next day the temperature rose to 102.6, and in connection there was a splitting headache and slight epistaxis, while on the following day the temperature reached 100, with the accompaniment of nausea and rather severe diarrhea. Patients should also be warned against taking alcohol in any form until all signs of reaction have disappeared, for not infrequently alcohol has apparanetly added considerably to the severity of the reaction. In this connection, a curious fact was noted in three of these cases. Two patients on the

8. Spooner: Jour. Am. Med. Assn., 1912, lix, 1360.

night following inoculation and one on the second night after, when there was no general reaction and their arms had ceased troubling them, took cocktails just before dinner. Almost immediately afterward their arms, at the site of the inoculation, began to pain so severely that they could not remain at the table.

RESULTS

The inoculations were started in May, 1911. The course of procedure was carefully explained and eleven nurses and twelve doctors volunteered for the preliminary vaccinations. In these twenty-three cases, only two inoculations were given, the first of 400 million and the second, after an interval of ten days, of 650 million. In seventeen of these cases, microscopic Widals were done ten days after the first injections, the Widals prior to the vaccination having been negative in all cases at 1:20. In five the Widal was negative in a dilution of 1:20, in twelve it was positive and in two it was positive at 1:100. The results of the Widal test following the second inoculation may be seen in Table 1.

TABLE 1.—RESULTS OF WIDAL TEST IN TWENTY-TWO CASES*

Dilution	Reaction	Number	Percentage
1-20	Negative	3	13.63
1-20	Positive	19	86.36
1-100	Positive	12	54.54
1-200	Positive	6	27.27
1-400	Positive	6	27.27
1-1600	Positive	1	4.54

* Tests made ten to fourteen days after second inoculation.

After these preliminary inoculations, the work was taken up as a routine with each succeeding class in the training-school (Table 2). During the first few months the members of a new class are not on ward duty, and as some leave the school and others enter, the vaccinations are not started until the nurses have been here for several months. Then the class is called together, the vaccination and its importance explained and the vaccine offered to those who desire it. Vaccination is still entirely voluntary in the training-school.

The following table shows the percentage of each class vaccinated:

TABLE 2.—PERCENTAGE OF VACCINATIONS OF NURSES

Class of	In class	Number eligible	Vaccinated	Percentage
1911	29	26	16	61.5
1912	33	31	22	70.9
1913	38	32	27	84.3
1914	13	11	11	100.
1915	30	25	23	92.
Totals	143	125	99	79.2

This table shows that as the work became better known and appreciated, a larger number of the nurses wished the vaccination. Thus in the last two classes, 94.4 per cent. of those eligible for the vaccination have taken it.

Since May, 1911, 143 nurses have been in training. Of these, 99 were vaccinated, 26 refused; in 3 it was considered inadvisable on account of some form of chronic illness, 14 had recovered from typhoid and one had been inoculated with the vaccine before entering the school. Thus, 79.2 per cent. of the eligible nurses were vaccinated and 20.8 per cent. remained unprotected, including the three who wished the vaccine, but whose health did not warrant its use.

In addition, during the same period, May, 1911, to June, 1913, 33 doctors and medical students connected with the hospital, 7 employees in the pathologic department, where the vaccine is compulsory, and 64 outside cases have been vaccinated, making a total of 203 cases; and in this period there have been no cases of typhoid fever either in the training-school or among those vaccinated. There have been no untoward effects from the vaccine and no instances of arm infection.

LOCAL AND GENERAL REACTIONS

Local and General.—The local reactions were similar in all respects to those usually observed.

The general reactions are shown in Table 3. In classifying these reactions, the temperature is taken as the general index as in army cases, but some reactions are put down as mild or moderate where the constitutional disturbances were sufficient to warrant it even though the temperature remained low. It was noted that some of the nurses showed subnormal temperatures following the inoculations, which was often associated with such constitutional disturbances as dizziness, nausea and vomiting.

TABLE 3.—PERCENTAGE OF GENERAL REACTIONS

Reaction	First Dose 203 Cases		Second Dose 200 Cases		Third Dose 169 Cases		Fourth Dose 27 Cases	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
None.....	96	47.6	111	55.5	140	82.8	24	88.8
Mild.....	88	43.3	71	35.5	19	11.2	3	11.1
Moderate..	18	8.9	18	9	11	6.5	0	....
Severe.....	1	0.49	0	....	0	....	0	....

It will be noted that of these cases, 184, or 90.6 per cent., showed either no reaction or a mild one after the first dose; 182, or 91 per cent., after the second; 159, or 94.1 per cent., after the third, and 27, or 100 per cent., after the fourth. The symptoms complained of in the order of frequency were: malaise, headache, general aching, nausea, dizziness, anorexia, vomiting, diarrhea, epistaxis, faintness.

One hundred and ninety reported at the end of six months that they were perfectly well, three had suffered from fatigue for two or three

months, but had recovered, and two thought that their health was still impaired by the vaccine.

WIDAL REACTIONS

The results of the microscopic Widal in fifteen consecutive cases tested ten days after third inoculation, may be seen in Table 4.

TABLE 4.—RESULTS OF WIDAL TEST IN FIFTEEN CASES*

	Positive Reactions	
Dilution	No.	Per cent.
1-20	15	100
1-100	15	100
1-200	11	73.3
1-400	9	60
1-800	5	33.3
1-1600	3	20
1-2000	2	13.3
1-12000	1	6.6

* Test made ten days after third inoculation.

The Widal reaction has been so definitely worked out by so many observers that it is now used here only in exceptional cases and to control new vaccine.

MENSTRUATION

After the first few inoculations the very definite impression was gained that menstruation was apt to be affected by the vaccine. Consequently, careful records of this particular phase of the work were kept in order to determine the amount of the disturbance. A comparison of the army vaccine with that used in the hospital showed no difference in their liability to cause menstrual irregularities. Other workers have briefly noted that these irregularities occur, so that one is justified in concluding that the effects are not due to the peculiarities of any one particular vaccine. A correct judgment of the part played by typhoid vaccine in menstrual disturbances is difficult and any statistics are open to several sources of error.

In the first place, it is well known that nurses are apt to have menstrual irregularities during the first few months of training, which are due to change of environment and method of living. In this work, the vaccinations were not started until the nurses had been in the hospital for from three to six months, and these nurses did not show any more frequent or more marked changes than did the nurses who had been in training for from one to three years. Again, some women are always more or less irregular. Where there was such a history, any disturbances during the course of the inoculations, unless of striking character, were not considered, and the case was put down as unaffected. In some, temporary causes other than the vaccine may have been the causal factors. It is difficult to eliminate such causes and they introduce a certain unavoidable source of error.

In compiling the records of the one hundred cases in which menstruation was studied, only those cases are put down as affected in which the evidence of disturbance by the vaccine seemed to me quite definite, after ruling out all other apparent causes and where the patients themselves felt that the condition was distinctly unusual for them.

Perhaps one can gather the best idea of the nature of the disturbances and their close association with the vaccine by a brief description of some of the more striking cases.

REPORT OF CASES

Case 1.—Vaccination finished early in June. The two following periods were missed. In August appendix was removed and menstruation did not occur again until December. It has been normal since then.

Case 2.—For three periods following the vaccination was about three weeks late each time. Then normal.

Case 3.—Missed period following vaccination and then a condition of scanty flow a week or more late existed for three months.

Case 4.—Menstruated every two to three weeks for three months following the vaccination.

Case 5.—After the third inoculation came on two weeks ahead of time and caused more discomfort than ever before.

Case 6.—Vaccinated the day after menses had ceased. Menses returned again that night.

Case 7.—During the course of vaccination menses came on one week ahead of time, causing patient to go to bed.

Case 8.—Twelve days early. More profuse and of longer duration.

Case 9.—After first inoculation menses ten days early, more painful and scantier.

Case 10.—After third inoculation menses ten days early, more painful and scantier.

Case 11.—Never quite regular. Much worse after vaccination. Skipped two months entirely and later menstruation was more painful.

Case 12.—Five days late after the second inoculation. One week early after the third.

Case 13.—Skipped two periods. Next time in three weeks. Then in less than three weeks.

Case 14.—Skipped three periods.

Thus in fourteen cases there were very distinct changes, due, in all probability, to the effect of the vaccine itself.

A complete tabulation of all the cases shows that a little more than one-half, 53 per cent., showed some type of menstrual disturbance, distinct though at times quite trivial, while 47 per cent. were unaffected. The types of disturbance may be seen in the following table, more than one type occasionally appearing in the same individual:

Menstruation early for one or more periods	25
Menstruation more painful for one or more periods	18
Menstruation late for one or more periods	15
Menstruation more profuse for one or more periods	10
Menstruation skipped for one or more periods	7
Menstruation scantier for one or more periods	6

It should also be noted that where these irregularities occur the patients are more apt to have associated with them a more troublesome general reaction.

The number of cases which show some change is rather striking, even allowing for unavoidable errors. If one merely considers the fourteen very definite instances cited, the percentage is high enough to show that a very striking relationship exists between the vaccine and menstrual disturbances, a fact which is of interest in view of the similar disturbances seen in typhoid fever. All of the cases included above were followed for at least six months. In none was there any disturbance at the end of this time. Therefore, it would appear that the changes are of only temporary significance and that they carry with them no lasting ill effects.

In this connection, one must consider the possible consequences of vaccination during pregnancy. I have a record of only one such case. In this instance, the woman's husband was ill with typhoid and much of his care fell on her. Consequently, in spite of her pregnancy, vaccination was carried out. She did not develop typhoid, nor did she have any ill effects from the vaccine. The menstrual disturbances have impressed me sufficiently, however, to make me conservative about vaccinating pregnant women. At the present time, I would not vaccinate under such circumstances, except under some special indication, such as that shown in the preceding case.

Recognizing that menstrual disturbances do occur, one naturally turns to the question of reducing them to a minimum. I believe that, barring some special indication for haste, the vaccination of women should be so arranged that the first inoculation will come a few days after a period. The second and third injections can then be given at seven-day intervals, leaving about a week's leeway before the succeeding period. If, for any reason, ten-day intervals are necessary, it is best to postpone the third inoculation until a few days after the second period. By giving the vaccine in this way, menstrual difficulties are reduced, though not entirely eliminated.

ASSOCIATION WITH OTHER DISEASES

It has already been mentioned that numerous instances of aggravation of existing chronic conditions are on record. It is, therefore, of interest in a series of cases like the present, where most of the cases can be followed, to note the relation of the vaccine to the development of various diseases.

Diseases of the Respiratory Tract.—Thirteen patients developed symptoms of some such affection during the course of the vaccinations, or so soon afterwards that they attributed them to the vaccine. Five patients developed coryza beginning within one or two days after an

injection, and in one case the cold lasted for six weeks. There were five cases in which tonsillitis began within one or two days after an inoculation. In one case bronchitis developed during the course of the vaccination, and the disease lasted for two months. One patient, already referred to, contracted bronchopneumonia ten days after the third injection. In this case there was definite exposure to cold.

Probably many of these cases were merely coincidences, though one receives the very definite impression that in some cases, at least, the patient's resistance is sufficiently lowered to favor the chances of such infections.

Appendicitis.—This condition was noted in five cases. In only one, however, was the association sufficiently close to justify suspicion of the vaccine as an accessory cause. In this case, there were moderately severe reactions associated with nausea, vomiting and diarrhea, after all three doses. Very soon after the third dose the patient began to have pain in the region of the appendix, which in the course of a short time necessitated an operation.

Tuberculosis.—Three patients in the present series have developed pulmonary tuberculosis since receiving the vaccine. In no case was there any previous history of the disease, and in none was the relation between the vaccine and the disease sufficiently close to be suggestive.

Tachycardia.—In one case there was a history of mild attacks of tachycardia. The patient had two such attacks on the eleventh and twelfth days following the second inoculation, and a third attack within five hours after the third injection. In another case, that of a man who normally had a very slow pulse, the rate doubled within a few hours after receiving the first dose. In a third case with a history of attacks of rapid heart action and arhythmia, there was no effect from the vaccine.

Furuncles.—In one instance a patient began to suffer from furuncles about two weeks after the third injection.

Scarlet Fever.—The development of a case of scarlet fever during the course of the injections has already been mentioned.

Scabies.—One patient was suffering from a rather extensive case of scabies, when he presented himself for the vaccination. He was warned that the vaccine might cause an aggravation of the skin condition, but he desired the vaccine in spite of this possibility. Much to our surprise, without any treatment for the skin affection, it almost completely disappeared during the course of the inoculations, but reappeared a little later.