Significance of Bacteriological Methods in the Diagnosis and Control of Whooping Cough*

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A YEAR ago at the meeting of this society we[1] reported our first year's experience with routine cough plate examinations for *B. pertussis*. We presented particularly the methods employed, a summary of the year's findings, and a discussion of the practicability of the procedure under the conditions in our community. In the present report we wish to add the data of the second year and point out the ways in which our laboratory findings are being applied in the local health department in a program of whooping cough control, and finally, to outline the criteria employed in our choice of cultures and technic for the preparation of specific vaccines used in our whooping cough prevention study.

A few comments on the *etiology of pertussis* are pertinent. Some workers have been deterred from attacking the pertussis problem because of the doubt raised by some, notably pathologists, as to the etiologic significance of *B. pertussis* and the emphasis they place on the possible rôle of an elusive filtrable virus in the disease. Intranuclear inclusions and interstitial bronchopneumonia have been noted in a certain per cent of pertussis autopsies. McCordock and Muckenfuss[2] regard this particular type of pneumonia as a type reaction to the presence of a virus and a bacterium. McCordock and Smith[3] have analyzed the various possible interpretations of their findings of inclusion bodies and interstitial bronchopneumonia in whooping cough. By analogy with swine influenza they suggest that since similar inclusions are sometimes found in children with no history of whooping cough, pertussis may be a mild virus disease which is of little consequence without a simultaneous or secondary bacterial infection complicating the condition. In other words, the Bordet-Gengou bacillus represents the bacterial component in a hypothetical virus-bacteria complex necessary for the production of the whole picture of whooping cough. Even were this proved, the diagnosis of the disease and probably specific methods for prevention would depend upon the bacterial component. The fact remains, however, that such a virus has not been demonstrated while the association of *B. pertussis* with the disease is unquestionable.

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The finding of this organism in cases of whooping cough—from the mildest to the most severe infections—approaches 100 per cent as the technic approaches perfection, and the organism is not found in the absence of this disease. Further, pertussis has been produced by the culture in laboratory animals as evidenced by more recent reports such as those of Sauer and Hambrecht,[4] Rich, Long, Brown, Bliss and Holt,[5] and Shibley,[6] who used special technic to assure the freedom of the culture from a filtrable virus; and experimental pertussis in children has been reported by MacDonald and MacDonald.[7] Added to this are the encouraging reports of some, notably Madsen and coworkers [8] and Sauer [9] on the results of specific vaccines prepared from recently isolated cultures. A summary of various data in favor of the etiologic rôle of *B. pertussis* by Miller [10] gives considerable material relevant to this subject.

On the basis of the accumulated evidence we believe there is no excuse for us to cease our efforts toward whooping cough prevention. Rather, there is good reason for proceeding on the assumption that *B. pertussis* is the cause of whooping cough; and accepting this, the study naturally centers around the organism *B. pertussis.*

THE BACTERIOLOGICAL DIAGNOSIS OF WHOOPING COUGH

Methods—The technic employed in cough plate diagnostic procedure has been outlined in previous communications.[1, 11] The exposure of cough plates has been done almost entirely during the past year by 25 nurses in the Bureau of Public Health Nursing.* This is part of a coöperative plan instituted about a year ago between the Health Department of Grand Rapids and the physicians of the city. Upon the request of a physician the nurse in the particular district secures a diagnostic cough plate, and the laboratory findings are reported to both physician and City Health Department. If the first plate is negative or unsatisfactory and the diagnosis of whooping cough has not been ruled out in the meantime, a second plate is obtained. If either plate is positive or if both are negative and the patient has definite clinical signs of whooping cough, isolation is established and release plates are taken as explained later under the section on release measures.

Between November 1, 1932, when diagnostic cough plate service was instituted on a routine basis and August 1, 1934, 984 plates were examined, not including 40 which have been reported as unsatisfactory for some reason such as insufficient inoculation or overgrowth with contaminants. The results are summarized in Table I.

TABLE I

SUMMARY OF COUGH PLATE EXAMINATIONS

Clinical Diagnosis	Number of Cough Plates		
	Positive	Negative	Total
Whooping cough through 4 weeks	254	160	414
Post-whooping cough 5 wks. to 6 mos. after onset	13	242	255
Other than whooping cough	0	218	218
Clinical data not available	0	97	97
Totals	267	717	984
Unsatisfactory			40

In clinical whooping cough, the correlation of the stage of disease with positive cough plate findings is always of interest and significance. Particularly, such findings give us an indica-

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tion of the probable period of infectivity and therefore of a reasonable isolation period. In Table II are the results of plates from 332 cases of whooping cough.

TABLE II

WHOOPING COUGH CASES: SUMMARY OF PLATES CORRELATED WITH STAGE OF DISEASE

WEEK OF DISEASE	Positive	Negative	Total	% Positive
1	91	25	116	78
2	80	45	125	64
3	58	36	94	62
4	25	54	79	32
5	10	56	66	15
6	1	30	31	3
Totals	265	246	511	

By comparison with our report of a year ago,[1] it will be seen that with the addition of more material, the percentages of positive plates during different weeks of disease have been changed somewhat but the essential picture is the same. The data suggest that a relatively high per cent of patients are infective throughout the first 3 weeks of disease, a progressively smaller per cent continue so through the 4th and 5th weeks, while only an occasional individual remains so after the 5th week.

Comment—The increasing number of physicians taking advantage of the cough plate diagnostic service is an indicator of the assistance bacteriological findings give them. While 22 used the cough plate service during the first year, 70 have received laboratory reports during the second. Many instances attest to the aid these reports have given in establishing the diagnosis of the atypical, light, or second attack of whooping cough, and in obtaining an early diagnosis before the characteristic cough has developed. The experience of these 2 years leaves little room for doubt as to the practicability and value of the bacteriological diagnosis of whooping cough.

BACTERIOLOGICAL FINDINGS AS A BASIS FOR ISOLATION AND RELEASE PROCEDURES

The data on the presence of *B. pertussis* at various stages of the disease (see Table II) suggest that if an arbitrary isolation period were to be chosen at the termination of which over 90 per cent of the patients would be noninfective, it would be 5 weeks. A week earlier than this, an appreciable number would still be infective.

The feasibility of using release cultures in whooping cough has been recognized by certain authors, for example Lawson and Mueller,[12] but we have seen no report of their actual application. For the past year we have been attempting such a test. The relatively low incidence of whooping cough in the city during this time has made possible the extra labor involved in the various divisions of health department and laboratory, though it has limited the quantity of our data. As an indication that the regulations as tested are not considered impossible from the standpoint of administration, they were recently incorporated in the local communicable disease regulations, as follows:

1. Cases and suspected cases shall be reported.
2. Patients shall be isolated on the basis of either clinical or bacteriological diagnosis.
3. A warning placard shall be placed on the home.
4. Patients shall be released 35 days after onset of disease (first symptoms), if the cough plate is not employed.
5. A patient may be released on the 28th day after onset of disease if there have been two consecutive negative cough plates taken at least 24 hours apart, the first one taken not earlier than the 21st day after onset.

If one of the first two release plates is positive, the third plate should not be taken before the 28th day.

6. Every effort shall be made to encourage voluntary isolation of a patient while the first cough plates are being examined or until the clinical diagnosis has been made.

Results of the application of bacteriological release—The findings of actual release plates agree very closely with what might be expected from the accumulated data on the per cent of positives during the various stages of the disease. The results to date are summarized in Table III.

TABLE III
RELEASE COUGH PLATE FINDINGS

Release cough plates		Patients for release		
Week obtained	Number of plates	Total patients	Released	%Released
4th	86	58	33	57
4th and 5th	125	69	63	91
4th, 5th & 6th	155	83	82	99

In starting our study of release procedures, we were not always able to obtain a complete series of plates from each patient, so the 3 periods analyzed —the 4th week; 4th and 5th; and 4th, 5th, and 6th weeks; respectively—are considered as separate units. For instance, if a patient had 1 or more positive plates during the 4th week and hence was not ready for release, but for some reason further plates were not secured, data pertaining to him were included only in the first period.

Our findings show that 33 of 58 patients or nearly 60 per cent were released on the basis of negative cultures taken during the 4th week. Further plates, all negative, were submitted by some of the 33 patients after the 4th week, thus strengthening the basis for their early release. Of the second group—those included during the 4th and 5th weeks—only 6 of 69 individuals, or less than 10 per cent, remained positive at the end of the period. In the cumulative data of the 4th, 5th, and 6th week interval, only 1 of 83 cases had not been released at the end of the 6th week. In general, the application of the cough plate method shortens the isolation period for the majority of cases and lengthens it for a relatively small group.

It is of interest to follow the findings of a series of plates from a few individual cases for release. In Table IV are shown 5 such series. George and Jerry, who are typical of over half the cases, had 2 consecutive negative plates during the 4th week. Allowing 4 days for incubation of the plates before the laboratory report is made, such patients would be released about 28 days after onset. Donald's and Richard's first release plates were positive and it was the end of the 5th week before they could be released. Marvin's case proves the desirability of more than 1 release plate, since his first was negative followed by 2 positives. A requirement of more than 2 negative plates would no doubt add an occasional positive finding

TABLE IV
A FEW TYPICAL FINDINGS IN CASES FOR RELEASE

Patient	Cough plates: results and day of disease		Day of release by laboratory report
	Diagnostic	Release	
George	+ 4	−23−24	28
Jerry	+ 9	−25−26	30
Donald	+ 7	+24−29−30	34
Richard	+ 9	+23+24−30−31	35
Marvin	+14	−27+29+34−35−40	44

but we believe the additional burden not warranted. Further, continued isolation through the 4 day interval between receipt of the plate at the laboratory and the negative report adds a margin of safety.

With the regulations as tested, our findings suggest that in whooping cough, bacteriological release can be made as efficient as in certain other diseases where it is accepted without question. Whether the procedure can or should be applied generally is a question for study under the conditions of different communities.

B. PERTUSSIS VACCINE PREPARATION

If *B. pertussis* is the etiologic agent in pertussis, there is a sound basis for expecting some protection against whooping cough from a suitably prepared, properly administered vaccine. In general, the literature since 1906, when trials of vaccine were begun, does not give convincing support for such protection. An analysis of the different reports, however, shows little basis for comparability of results. Some workers have used vaccine after the onset of disease, some after exposure but before symptoms, a few at a considerable time before exposure, and some at undefined times. The age groups, geography and epidemiology have all supplied variable factors; the dosage has not been sufficiently considered; and adequate controls frequently have been lacking. In the light of more recent knowledge of the antigenicity of cultures and with the encouragement of the more recent results of Madsen and coworkers [8] and of Sauer,[9] there is good reason for a reinvestigation of the value of *B. pertussis* vaccine. The problem is one for a carefully controlled, longtime study, and conclusive evidence must await an analysis of the results obtained by different investigators.

In the meantime, much is to be gained in a definition of conditions under which different investigators are working. It encourages open discussion of the different factors involved which may lead to some general agreement on the essential requirements for technical procedures. It is in this spirit that we briefly outline the methods employed in the preparation of *B. pertussis* vaccine as used in our study—not as the perfect solution of the complex problem. The methods represent to us a starting point for future studies—a line of procedure to be adhered to in its essentials for a sufficient time to give our results meaning and to furnish a sound basis of judgment.

Selection of suitable cultures—The first point is the suitability of the cultures to be used. Lack of conformity among different workers on this point could provide ample explanation for widely divergent results.

If certain profusely growing old laboratory strains of *B. pertussis* were satisfactory, vaccine preparation would be relatively simple. We have reason to question their suitability since we know that they may be serologically quite distinct from cultures just isolated from patients with whooping cough—cultures which, in general, form a homogeneous serological group, "Phase I" of Leslie and Gardner. Madsen [8] and Sauer [9] have recognized this in their specification of "recently isolated" cultures. The date of isolation has been a helpful temporary criterion but it is an inexact and superficial one. Just where shall we draw the line between a "recently isolated" and an "old" culture? Can we be sure in substituting a week-old culture for one 6 months old that we have improved the antigenicity of our vaccine? We agree with Hawley and Simmons [15] in connection with typhoid vaccine, that their practical problem may be more concerned with determining and maintaining the desirable state of their culture than with the search for one recently isolated.

In *B. pertussis* vaccines the essential problem is to determine the antigenically effective state and the means of sustaining it. Above all, we need *adequate criteria* for judging the state of the culture. While the final test is whether the vaccine protects against whooping cough, we must have practical laboratory indicators for accepting or refusing any particular culture for a lot of vaccine. Accepting the thesis that the culture just isolated from a patient with whooping cough is the most likely to be antigenically active in a vaccine, we have studied numbers of such cultures in an effort to arrive at the significant characteristics by which to judge them. In these studies,[16] we have made use particularly of serological relationships, pathogenicity for mice and guinea pigs and the intradermal test in the rabbit. We believe they have demonstrated that certain characteristics are of such uniformity and significance as to furnish reliable guidance in judging the antigenicity of cultures. In the present state of our knowledge we accept the following *criteria for selecting cultures* for a vaccine:

1. *Typical morphology and growth characteristics* including hemolysis on Bordet-Gengou medium. These are described by various authors, including ourselves.[1]

2. *Agglutination to high titer* by smooth strain anti-serum (Phase I, Leslie and Gardner). For agglutination tests we use the rapid method previously described.[11]

3. *Phase I agglutinin production* in the rabbit. The rabbit is injected intravenously at 3 day intervals with 0.2, 0.4 and 0.8 c.c. per kg. weight, successively, of a 10 billion per c.c. saline suspension of organisms killed with a preservative such as merthiolate 1:10,000, or phenol 0.5 per cent. A bleeding on the 6th or 7th day after the 3rd dose is usually from 1:2,000 to 1:5,000 final titer, rapid test (1:10,000 to 1:25,000, equivalent titer) with any Phase I culture.

4. Typical *rabbit skin reaction* of hemorrhagic necrosis. A dose of 0.1 c.c. of a 1 billion per c.c. living, saline suspension of a Phase I culture gives a characteristic reaction. Typically, within a few hours there is an ischemic, indurated area at the site of inoculation. By 24 hours there is a purplish hemorrhagic center which progresses to necrosis, scab formation and final scarring. This reaction has been recognized by several workers and recently described by Gundel and Schlüter.[20] Its value in studying *B. pertussis* cultures was discussed in a previous paper.[16]

While developing these criteria, we have also given attention to the date of isolation. In general, we have used 6 cultures for each lot—all isolated within 3 months and 3 of them within 1 month. We believe this age factor is unimportant, provided the cultures have the characteristics described. Further, we are not convinced that several cultures are superior to one, properly chosen, but we continue to employ several while this point is under study.

Choice of technical methods—Having decided upon the cultures, we are confronted with the necessity of choosing technical procedures. Our objective should be to grow the cultures in such a way as to maintain their *antigenicity;* to determine the conditions of *maximum growth* consistent with maintenance of the antigenic state; to kill and preserve them *without denaturing* the active antigens; and, finally to provide a *safe* product. In choosing particular technic, we have been guided by practicability in so far as it did not conflict with these essential requirements.

We have found that cultures maintain their Phase I characteristics on the Bordet-Gengou medium used for cough plate,[1] so have used this medium in growing cultures for vaccines. We are trying out a similar medium with added veal infusion and peptone, in line with that used in Copenhagen and described by Miller.[14] This supports a heavier growth, and our adoption of it awaits only further tests of the antigenicity of the cultures.

The *kind of blood* to use in the medium has been emphasized by Sauer [17] in his insistence upon human blood. As to the maintenance of Phase I antigenic properties, we have found

no difference between human and sheep's blood. As to the safety factor, there are no convincing theoretical grounds, and in our experience with the inoculation of several hundred children, there is no experimental basis for any fear in this regard. Since we have found human and sheep's blood equally satisfactory, we use sheep's blood as it provides a far more uniform, constant, and less limited supply than is available from human sources. In the meantime, this point is under continued study.

We need to know the *optimum state* with respect to antigenicity in which to administer the vaccine. Most vaccines have been suspensions of whole organisms. Kreuger, Nichols and Frawley [18] recently described a water-clear pertussis antigen prepared by grinding washed cultures in a ball mill for 12 hours and subsequent filtration through a collodion membrane. We shall watch the use of this with great interest. As for our own studies, our first aim is to satisfy ourselves in a carefully controlled series of injections, as to the results of the *whole culture vaccine*. If definite protective value can be established for such vaccines by different investigators, and the conditions of their success defined, there will be a sound basis for the judgment of modified and improved antigens.

The question of *washing the suspension* arises. We have to choose between an unwashed product which carries with it agar, blood and other medium derivatives and a washed vaccine relatively free from them. A washed product surely is preferable if significant antigenic properties are not lost. Since we have found the washed live culture capable of giving a typical skin reaction and a vaccine, even after 3 washings, capable of stimulating Phase I agglutinins rapidly and in high titers, we decided on a *washed product*. The growth is washed off the medium into physiological salt solution, its turbidity adjusted roughly to approximately 10 billion organisms per c.c. by comparison with known suspensions, and the organisms washed once by centrifugation and the supernatant fluid discarded. The sediment is resuspended in saline and filtered through cotton.[11]

As to the killing and preserving of the vaccine in such a manner as to leave the active antigens unimpaired, there is need for further study—in this as in other vaccines. We have avoided the use of heat and have killed the cultures by chemicals. We have used merthiolate 1:10,000 and in some lots phenol 0.5 per cent. In either case we obtain a vaccine which is effective in stimulating Phase I agglutinin production in the rabbit.

The method of *standardization of the density of suspension* is another point for consideration. Our first counts by Wright's method showed a great variation. We made an extended series of counts by this method and in different types of chambers in comparison with the determination of per cent of suspension by the Hopkins tube, and concluded that the Hopkins method gives far more uniform results and that it is an immeasurably more simple method of standardization. Our comparative tests indicate that a 0.3 per cent suspension by this method represents approximately 10 billion organisms per c.c. The suspension to be tested is adjusted roughly by turbidity to slightly heavier than that required, a volume of 5 c.c. is centrifugated at 2,500 r.p.m. in a Hopkins tube for 30 minutes, estimations made from the measured sediment and the suspension adjusted to 0.3 per cent.

In brief, our vaccine is a once-washed, 0.3 per cent suspension of Phase I *B. pertussis* grown on Bordet-Gengou medium enriched with 15–20 per cent sheep's blood. The organisms are killed

with a preservative such as merthiolate 1:10,000 or phenol 0.5 per cent allowed to act at cold room temperature for a week or more. The product is tested for purity and sterility by the usual procedures of staining, aerobic and anaerobic broth cultures and Bordet-Gengou medium cultures; for safety by guinea pig tests; and for antigenicity as indicated by agglutinability with Phase I serum and by ability to produce Phase I agglutinins in the rabbit rapidly and in high titer.

COMMENT

As public health workers, we need to realize the seriousness of whooping cough as a communicable disease of childhood. The important place it holds as to cause of mortality, morbidity and pathological sequelae is emphasized in a recent report of the League of Nations Health Committee.[21] It is pointed out in this report that the death rates from whooping cough and measles have declined more slowly during the past 30 years than have those from diphtheria and scarlet fever, and consequently their relative importance as a cause of death has increased. During 1926–1930, in 6 countries including the United States, whooping cough was responsible for about one-third of the total deaths from diphtheria, scarlet fever, whooping cough, and measles. In the period 1927–1929, the same proportion held true in the United States for the total deaths, while in the age group 0–4 years, whooping cough was responsible for 43.5 per cent of all deaths from these 4 diseases; diphtheria, 30.6 per cent; measles, 19.1 per cent; and scarlet fever, 6.6 per cent.

The need for a study of whooping cough control measures is obvious. While the problem is a complex one, we should not avoid it as being impossible of solution. A note of hope is struck in an editorial of the *British Medical Journal*[19]:

> A survey of all this recent work leaves us with hope that this plague of the nursery and school, which in 1932 caused 300,000 infections in the United States and upwards of 6,000 deaths, will in time be as controllable as diphtheria now is to those who choose to benefit by methods at our command.

We believe that bacteriological methods as discussed in this paper offer reasonable promise of aid and deserve a thorough trial under conditions as favorable to their success as we can make them. The more widespread their use, the more centers there will be for studying various phases of the whole problem—for it is only in such centers that there is the necessary background for a comprehensive study of the subject.

SUMMARY

We have summarized the results of nearly 2 years' routine laboratory examinations for *B. pertussis* and have pointed out their application to the diagnosis of early, light and atypical whooping cough; to isolation and release procedures; and to the study of specific methods for whooping cough prevention.

Whooping cough isolation and release procedures which have crystallized out of our bacteriological study are now under test as a part of Grand Rapids Health Department communicable disease regulations.

Criteria for the selection of cultures and for the choice of technic employed in preparing vaccines for whooping cough prevention studies have been discussed.

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Weight of Children

1. Averages of weight of children in 1934 show no consistent or striking differences from averages of weight for the period 1921 through 1927.

2. The variability of body weight (measured by the standard deviation) is not, for boys, consistently different in 1933 and 1934 from that observed in the 1921–1927 period. For girls, weight is more variable in both 1933 and 1934 than in the earlier period.

3. The proportion of boys 12 per cent or more below average weight has not increased in 1933 or 1934, while the proportion of girls so designated is slightly greater, both in 1933 and in 1934, than that observed for the years 1921–1927.

4. Average annual gains in weight are lower for the year 1933–1934 than those calculated for the 1921–1927 period. The average for the several age-sex groups, of the ratio

$$\frac{\text{Average annual gains in weight, 1933–1934}}{\text{Average annual gains in weight, 1921–1927}}$$

equals 91.5 per cent. Comparing this ratio with similar average ratios for the separate years 1921–1927 shows, however, that the relative gain for 1933–1934 is not significantly lower than that recorded in 1924–1925, a year in which general economic conditions were presumably much better than in 1933–1934. This finding, together with the fact that the actual weight of children has not decreased in the past decade, is taken as evidence that the recent economic depression has not materially affected the growth in weight of a representative sample of school children.

5. A supplementary study of the weights and weight increments of children from families in different levels of economic status in 1933 and 1934 shows that approximately the same differences are to be found as have been observed in times previous to the depression. From this it is concluded that there has been no obliteration or widening of class differences during the depression.—

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