

though in Denmark the Bordet-Gengou bacillus has routinely been isolated from the great majority of cases for eighteen years, skepticism had been voiced as to whether it really caused the disease. This skepticism was based on failure to reproduce the disease in laboratory animals, and on the demonstration by McCordock³ and Rich⁴ of inclusion bodies in the lungs of fatal cases. Inclusion bodies suggested a virus infection. However, attempted transmission experiments with bacteria free filtrates have failed to elicit the disease.^{5, 6} Similar inclusion bodies were later described by McCordock and Smith⁷ in chronic pneumonia not associated with whooping cough. The pulmonary inclusion bodies described cannot, therefore, be considered as evidence of a virus etiology of the disease. Furthermore, Koch's third postulate, that is, reproduction of the disease with a pure culture, was finally fulfilled by Shibley.⁸ He produced typical whooping cough in a chimpanzee, with a strain of Bordet's bacillus which had been subcultured more than sixty times. The incubation period was nine days. During the height of the disease, after the ape had actually whooped, it was killed. Autopsy findings were the characteristic catarrhal tracheitis, bronchitis, peribronchiolitis and acute emphysema. Culture of the bronchi and bronchioles yielded the Bordet-Gengou bacillus. Shortly before this, Macdonald and Macdonald⁶ had completed a daring and quite convincing experiment. They vaccinated two boys, in a family of four brothers, with the Phase I pertussis vaccine of Sauer.⁹ Five months later all four boys were inoculated intranasally with a filtrate of a fresh culture of Bordet's bacillus. They remained free from symptoms for eighteen days, at which time they were reinoculated with a suspension of living organisms. The two unvaccinated boys developed whooping cough seven days later. Hemophilus pertussis was recovered from them by cough plate, and their sera showed specific complement fixing antibodies. The two vaccinated boys had no symptoms.

These experiments of Shibley and the Macdonalds have therefore settled the twenty-seven-year-old argument by convicting the bacillus of Bordet and Gengou as the cause of pertussis.

The organism may be cultivated from a sample of sputum, but the so-called cough plate method used in obtaining the above results is simpler and more reliable in the early stages. This method was suggested by Mauritzen at the Serum Institute in Copenhagen, and was first employed there by Chievitz and Meyer,¹⁰ in 1916. The patient simply coughs on a petri dish of potato-glycerine-blood agar. The dish is held six inches from the patient's mouth and should be coughed on for fifteen seconds. The media is sprayed with droplets. Obviously colonies of bacteria representative of the flora of the patient's respiratory tract will grow out. If the Bordet-Gengou bacillus is present in the droplets sprayed on the media, colonies will appear after forty-eight to seventy-two hours of incubation. Occasionally four days are required. Plates should be incubated as soon as pos-

Incidence of Pertussis Cases found Positive by the Cough Plate Method Classified as to Stages of Disease						
	Madsen 1924	Lawson and Mueller 1927	Debre' Parrie and Prestet 1930	Kristensen 1933	Sauer 1933	Stallings and Nichols 1933
Catarrhal stage	75%	59%	86%	65%	88%	80%
Paroxysmal stage in weeks	1st	57%	53%	58%		84%
	2nd	61%	33%	52%		77%
	3rd	45%	38%	55%	40%	64%
	4th	40%	15%		31%	73%
	5th	9%	6%		7%	66%
Total cases	914	535	66	2144	400	217
Total plates used	?	?	?	2144	?	?

Chart 2.

sible after exposure. Identification of the Bordet-Gengou bacillus is made by its colonial and microscopic appearance, which are peculiarly constant if the media is properly made. Slide agglutination tests are resorted to if doubt exists. For details, reference may be made to the papers noted in Charts 2 and 3 (11 to 20 inclusive). Only minor differences in the media and technic of isolation are recorded. The author of this article used the Standard Danish technic described by Madsen,¹¹ but cannot assert that it is best. A good summary of the morphological characteristics of the Bordet-Gengou bacillus is that of Sauer.¹⁵

DEFECTS IN THE BACTERIOLOGIC TESTS

In considering this laboratory aid, its defects must be mentioned. The first defect is the one common to many bacteriological tests. A single negative test does not mean anything. Isolation of the organism makes the diagnosis. Failure to isolate it leaves one out of patience with the laboratory. The second defect is the time required for growing out and identifying the etiological agent. This can in part be remedied if pertussis is considered as a possibility early in the course of a bronchitis. If one waits a week before taking a cough plate, it is not surprising that the diagnostic paroxysm may appear before the bacteriological report is returned.

DEMONSTRATION OF HEMOPHILUS PERTUSSIS

The frequency with which hemophilus pertussis has been isolated in the catarrhal and paroxysmal stages of the disease is shown in Chart 2. The results reported by Madsen¹¹ embrace the work begun by Chievitz and Meyer at the National Serum Institute in Copenhagen in 1916. The large series of cases reported by Kristensen¹⁴ is a summary of data obtained in the same laboratory for the years 1924 to 1932. The cough plate in Denmark is a routine public health procedure. The plates are exposed by physicians or parents, who then take or mail them to the Institute. The medical and lay public have been educated to the idea that any cough may be pertussis. The high incidence of positive plates reported by Sauer,¹⁵ and by Stallings and Nichols,¹⁶ is probably in a measure due to the fact that the plates were exposed by these workers themselves or by trained assistants.

Incidence of Pertussis Cases found Positive by the Cough Plate Method. Classified as to Week of Disease					
	Gardner and Leslie 1932	Culotta and Harvey 1933	Kline 1933	Kendrick and Eldering 1934	Miller 1934
1 st week	75%	82%	60%	84%	78%
2 nd ..	67%	56%	58%	78%	66%
3 rd ..	75%	19%	30%	83%	43%
4 th ..	25%	2%	7%	31%	50%
5 th ..	—	—	—	11%	25%
Total cases	47	129	15	207	107
Total plates used	107	242	?	257	137

Chart 3.

OTHER METHODS OF CLASSIFICATION

Chart 3 shows the incidence of cases found positive by other workers who classified their results in a different manner—for example, as to the week rather than the stage of the disease. The day of the first cough of any kind was considered the day of onset of the disease. The high percentage of positive plates obtained by Kendrick and Eldering²⁰ of the Michigan State Department of Health at Grand Rapids may be laid in a measure to the fact that the plates were taken by public health nurses, who had been trained in the technic. Pertussis cough plates are a public health procedure there. In fact, they are at times used for release from quarantine.

The salient point of all these data is obvious. The causal organism is readily isolated during the first two weeks of the disease. We have on several occasions obtained positive plates on the very first day of cough. Kline¹⁹ has reported a positive plate in an exposed child two days before the onset of any cough. After the typical paroxysms of whooping begin, the organism is isolated with less and less frequency. Carriage of the Bordet-Gengou bacillus almost always ceases by the end of the fifth week of the disease. Lawson and Mueller¹² isolated the organism from one case in the eighth week of the disease, and Kristensen¹⁴ reported a positive plate in the eleventh week.

These bacteriological data are in accord with the important epidemiological observations of Law-

Epidemiology of Whooping Cough	
(from Lawson, 1933.)	
Mean Duration of Incubation Period—	1,123 cases—13.05 days.
Mean Duration of Catarrhal Stage—	1,561 cases—10.9 days.
Period of Communicability	Studied in families in which multiple cases excluding those from a common source, occurred.
Of 279 Second cases—	
71.3%	infected by person in <u>Catarrhal Stage.</u>
18.2%	" " " " <u>First week Paroxysmal Stage.</u>
7.9%	" " " " <u>Second week Paroxysmal Stage.</u>
2.05%	" " " " <u>Third week Paroxysmal Stage or later.</u>

Chart 4.

son²¹ shown in Chart 4. In a study of over one thousand cases he determined that the mean duration of the incubation period was 13.05 days. Similarly, he found the mean duration of the catarrhal stage was 10.9 days. He then studied the period of communicability in families in which multiple cases, excluding those from a common source, occurred. Knowing the date of onset of 279 second cases, he was able to infer that 71.3 per cent of these were infected by a person in the catarrhal stage, 18.2 per cent were infected by a person in the first week of paroxysmal stage, 7.9 per cent by a person in the second week of the paroxysmal stage, and only 2.05 per cent by a person in the third week of the paroxysmal stage or later.

POTENTIAL VALUE OF THE COUGH PLATE

From a public health point of view, therefore, the potential value of the cough plate is obvious. Its general use permits diagnosis during the period of greatest infectivity, namely, the catarrhal

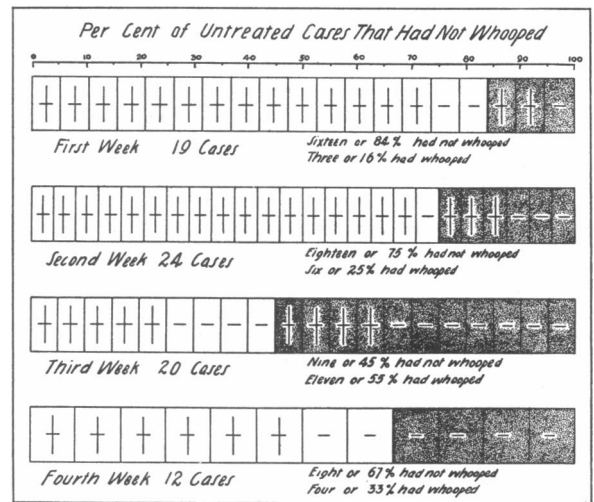


Chart 5.—The positive and negative signs refer to the cough plate. The cases are classified by the day on which the first (and usually only) plate was obtained.

stage. This period can rarely be diagnosed by physical signs or by a blood count. The characteristic hyperlymphocytosis does not appear until the paroxysms, as Thelander and her associates²² have shown. When quarantine has to be delayed until the diagnosis can be made on clinical grounds it is small wonder that it is of little value in curbing the spread of an epidemic.

DATA FROM SERIES OF CASES IN BERKELEY

Chart 5 was compiled from data obtained in Berkeley last year on a limited number of cases which had received no specific prophylactic or therapeutic treatment prior to exposure of the cough plates. It is of interest in that it shows the variability of the duration of catarrhal period.

Of nineteen cases tested during the first week of symptoms, that is of a cough, three had already whooped. Of the sixteen that had not whooped, fourteen had positive plates.

Twenty-four other untreated cases were first seen and tested in the second week of their cough. Of these eighteen, or 75 per cent, had not yet whooped. All but one had a positive plate. Six had begun to whoop. From only three of these did we obtain that causal organism.

Twenty other untreated cases were first seen and tested in their third week of cough. Nine, or 45 per cent, had not yet whooped. Five of them showed positive plates. Of those that had already begun to whoop, only four had positive plates.

Twelve other untreated cases were first seen and tested in their fourth week of cough. Eight of them had not whooped. In six of these eight, the first and only plate was positive. Four untreated children who had already whooped had negative plates.

The diagnosis of the pertussis in patients with negative plates who had not whooped was ultimately made either by a tardy appearance of the whoop or by circumstantial evidence, such as having a brother or sister with either a positive plate or with clinical whooping cough or both. It is obvious that the ratio of eight patients who had not yet whooped to four patients who had already whooped, in the fourth week of the disease, is not a generality. We had few requests for bacteriological tests on whooping children. The diagnosis was obvious. As a matter of fact, these children were tested to see if quarantine was still necessary. Fifteen of the recorded cases tested bacteriologically, and found positive, never developed typical paroxysms. Seven of the fifteen received specific treatment after the cough plate was reported positive. Eight received no specific treatment. Three of the individuals who never whooped were adults.

ADULT PERTUSSIS

Adult pertussis must be commoner than records show. Cases with the typical paroxysms of whooping cough do occur. Hall²³ reported nineteen such cases in adults over fifty-five years of age, and suggests that elderly individuals may be more susceptible than the middle-aged. He mentions that Sir William Jenner almost died of it when over sixty-five. Cases without the typical paroxysms are, however, undoubtedly more common. The importance of these cases from a public health point of view is obvious. For example, in Denmark a school teacher with a chronic bronchitis was proven to be responsible for an epidemic in an isolated community. The writer has been able to culture eight parents of children with pertussis. All had moderate coughs. Hemophilus pertussis was recovered from three of these. Incidentally only one was quarantined.

INTERESTING CHARACTERISTICS OF PERTUSSIS

The data in Chart 5 illustrate three interesting characteristics of pertussis:

1. The marked variation in the duration of the catarrhal period, or the period of what might be called non-specific cough.
2. The greater potential infectivity of individuals in this period.
3. The difficulty of isolating the organism when the patient is having paroxysms. Apparently the

height of the infection precedes the height of the disease. This in turn leads to speculation on the pathologic physiology of paroxysms.

THE BORDET-GENGOU RACILLUS

The secretion or excretion of an exotoxin by the Bordet-Gengou bacillus has not been demonstrated. Postmortem recovery of the organism from any place other than the respiratory tract has not been reported to the writer's knowledge. The bacillus is not invasive. It apparently remains localized in the respiratory tract. In 1909 Bordet and Gengou²⁴ demonstrated the toxicity of split products of their organisms by *in vitro* and *in vivo* tests, utilizing for the latter the peritoneal cavity of guinea pigs. They postulated that this endotoxin was liberated in the bronchial mucosa of man after lysis of the infecting organisms by local ferments. They expressed the opinion that the inflammatory changes and outpouring of tenacious mucus was due to the presence of this endotoxin.

This view is compatible with the bacteriological findings recorded, and would explain the difficulty of isolating the organism after the height of the disease is reached.

Recently, however, cutaneous hypersensitivity to the undenatured protein of the Bordet-Gengou bacillus has been observed by Stallings¹⁶ and others during the disease. Furthermore, subcutaneous and intradermal administration of this protein solution—the H. pertussis undenatured bacterial antigen of Krueger²⁵—has often apparently relieved the paroxysms during their height. (Frawley et al.²⁶.) The rapidity of this effect precludes the possibility of its being active immunization. The effect may be explained as a desensitization phenomenon, which in turn postulates that the paroxysm is a manifestation of hypersensitivity to the bacterial protein rather than a reaction to an inherently toxic split product.

Before closing the discussion of the bacteriological test for pertussis, it is of interest to know that by this means the author was able to prove an instance of two attacks of pertussis in the same individual. The second attack was one year after the first. The child did not whoop during the second attack. Positive plates were obtained both times. In three other instances positive plates were obtained from individuals with chronic atypical cough who, according to their physicians, had histories of typical whooping cough several years previously. Apparently the immunity conferred by one attack is not necessarily lasting.

SUMMARY

1. Pertussis is a widespread disease often attended by crippling or fatal complications. Since the immunization campaigns against diphtheria it has taken a position in the front rank as a cause of death among epidemic diseases.
2. It is a disease of adults as well as of children.
3. Only during the past year has the etiological rôle of the Bordet-Gengou bacillus been established beyond doubt.
4. Both epidemiological and bacteriological observations indicate that the period of greatest in-

fectivity is before the onset of the diagnostic paroxysms.

5. The diagnosis of the catarrhal stage or period of non-specific cough can only be made with certainty by bacteriologic examination. The method of choice is the so-called cough plate.

6. Generalized use of this procedure, with the dependence of quarantine regulations on it, are a logical step in the prevention of the spread of this disease.

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DISCUSSION

A. P. KRUEGER, M. D. (Department of Bacteriology, University of California, Berkeley).—Doctor Miller is to be commended for emphasizing in his paper not only the seriousness of pertussis, but the failure of public health measures, as instituted at present, to reduce its toll. The low immediate mortality connected with the disease has tended to cloak the incidence of serious immediate or remote sequelae. Among these secondary effects should be mentioned the true pneumonic process not infrequently produced by *H. pertussis*.

Doctor Miller's statements regarding the establishment of *H. pertussis* as the etiologic agent in whooping cough deserve particular attention. For many years after Bordet's work, the Bordet-Gengou bacillus was looked upon merely as a possible cause of whooping cough. The recent work of the MacDonaldis and

Shibley have proved beyond any question of a doubt that this organism is the causal agent, and that the disease is not produced by the combined attack of a virus and a bacterium.

From the viewpoint of practical epidemiology the cough plate finds its greatest utility in detecting the early case before establishment of the whoop and in revealing the disease in patients who never develop the characteristic whoop. Doctor Miller's efforts to popularize the use of the cough plate among the medical profession are certainly in the right direction, particularly when one realizes the great importance of patients in the catarrhal stage of the disease in spreading infection. Shedding of organisms in the bronchial secretion is greatest during the catarrhal period, which averages between ten and fourteen days.

It is coming to be more clearly recognized that the immunity following an attack of pertussis is not necessarily a solid one. Second attacks are not rare; and while many of these patients will develop the characteristic clinical picture of pertussis, a fair percentage of them will pass unrecognized as having nonspecific upper respiratory infections. The rôle of these missed second cases in spreading the disease is probably important, and here again free use of the cough plate would constitute a worthwhile public health procedure.

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FRANCIS SCOTT SMYTH, M. D. (University of California Hospital, San Francisco).—Doctor Miller's statistics, from our Public Health records, give us the hard facts regarding the importance of pertussis. Any parent or pediatrician can vouch further as to its distressing significance.

The department of pediatrics in the University of California, having coöperated in a phase of this problem, has had an opportunity to see the application of the cough plate in diagnosis. In some instances this diagnostic aid has been spectacular. I do not believe that we should continue to argue on organisms other than *H. pertussis*, but should make every effort to perfect the cough plate as a means of diagnosis. The next step, of course, is the program of prophylaxis and treatment. While, obviously, it will take considerable fundamental study, I believe such a program must be encouraged. As to the cough plate, while it presents certain difficulties, especially regarding careful preparation of media, we should hasten its adoption in the routines of health departments. This has already been done in Baltimore. I dare say that early in the adoption of the culture study of diphtheria there was necessary a certain amount of adjustment and education. The cough plate is of great value in both diagnosis and quarantine study, and should not remain in academic use only.

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EDWARD B. SHAW, M. D. (384 Post Street, San Francisco).—Quarantine, however well enforced, can never be the final answer to the problem of prevention of whooping cough, or of any of the common contagious diseases (measles, chicken-pox, poliomyelitis) in which the period of most intense communicability precedes the development of clinically recognizable symptoms. There is no doubt that a means of earlier specific diagnosis, such as the cough plate, is of great practical value and renders quarantine more effective through the earlier detection of cases, the recognition of atypical cases, and in providing evidence that our present period of quarantine is sufficiently prolonged.

The cough-plate method is not intricate. It is necessary only that proper media be supplied, that plates be carefully exposed and studied by an adequately trained bacteriologist. Unfortunately, the cough-plate diagnosis is insufficiently accurate to permit one to exclude the disease on the basis of a single negative report. It is to be earnestly hoped that advances in our knowledge of specific prevention and treatment will place an even greater premium on early and precise diagnosis.

It is worth pointing out that control measures are directed particularly to the protection of children of

school age, whereas the most unfortunate sequelae of the disease are seen in still younger children and nurslings. For the protection of this younger group, ordinary quarantine precautions are of little significant value. During early years the only effective precaution is the isolation of the child from everyone who coughs. Only great improvement in treatment, or especially of prophylaxis, will materially reduce the dangers in this critical age group.

Our greatest error in the management of pertussis lies in our failure to regard the disease as really severe, and to regard the patient, with respect to quarantine and treatment, as a significantly ill child.

STRABISMUS—THE PRESENT STATUS OF ITS TREATMENT*

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THIS paper will deal only with the most frequent or concomitant type of strabismus in which all the extra-ocular muscles are capable of contracting; but due to various factors the visual axes are not in a state of parallelism, nor can they be brought to the normal position by the volition of the patient.

UNDERLYING PRINCIPLES

The principles underlying the treatment of this condition are by no means new and really date from the publication of Donders' monumental work on "The Accommodation and Refraction of the Eye," in 1864. It was he who recognized one of the principal factors in the etiology, namely, that in hyperopia (farsightedness) an abnormal effort on the part of the ciliary muscles is necessary in order that clear images may be received on the retinae and that, due to the anatomic and physiologic linkage between the functions of accommodation and of convergence (both are actuated by stimulation of branches of the third nerve), an excess of convergence is an inevitable by-product of the abnormal effort required, which results in the crossing of the visual axes.

It is apparent that this excess of convergence, although equally distributed between the two eyes, cannot be manifest in both eyes at the same time. What happens, therefore, is that the dominant eye fixes the object which has attracted the patient's gaze, and the fellow eye deviates toward the nose to a degree which is roughly proportional, at least in its early stages, to the strength of the nerve impulse which actuates the adductor muscles of the eye. This position, which necessarily becomes habitual, soon results in secondary changes in the muscles themselves. The internal recti tend to become hypertrophied and spastic; the external recti to become stretched and attenuated.

Recent anatomical studies on the osteology of the orbits tend to show that the depth and inclination of the orbital walls may be factors in producing the hyperopia. Certain anomalies of length, strength, and attachment of the extra-ocular muscles do exist and account for a small percentage of ocular deviations of all sorts. Yet

in non-paralytic squint, Donders' principle is always a factor which must be taken into account.

Sherrington's law of reciprocal innervation (the relaxation of the extensors when the flexors are stimulated, and vice versa) was a result, at least in part, of his work on the extra-ocular muscles, and modern students of the problems of strabismus utilize this knowledge, as will be shown presently.

IMPORTANCE OF EARLY CONSIDERATION

Strabismus of the type under consideration naturally manifests itself in childhood, sometimes very early. In the past, all too frequently general practitioners and pediatricians, following the teachings of oculists who were not particularly conversant with, or interested in, the problem, have advised no treatment until about the seventh year of age. This is obviously wrong. There is a rapidly growing recognition of the untoward psychological effects of strabismus, and a greater utilization of the principles of treatment which naturally follow from a study of the etiology is becoming more widely disseminated. It was obvious to Donders and his contemporaries that convex glasses, to minimize the accommodative effort, would have a favorable effect upon the excess convergence, and where strabismus does not develop too early, and too many secondary changes have not occurred before treatment is instituted, excellent results may be secured by the use of glasses. With the development of more accurate methods of refraction which are applicable to young patients, the percentage that can be cured or helped by means of glasses naturally increases. The fact that small uncorrected astigmatic components of the total refractive error exercise a relatively large stimulus to convergence is not sufficiently appreciated by most oculists at the present time. One-half a diopter of uncorrected astigmatism calls for a constant focusing and refocusing of the eyes, and here is one place where Sherrington's law becomes important. This small but constant accommodative effort is necessary even though all the spherical error has been corrected by glasses, and successful relaxation of the internal recti may hardly be expected unless this excessive stimulation is also removed.

SUBNORMAL VISUAL ACUITY OF SQUINTING EYES

It is well known that the visual acuity of squinting eyes is subnormal in about 90 per cent of cases. This is traditionally explained by the fact that when the visual axes are not both directed toward the object viewed, diplopia inevitably results. Diplopia, or double vision, is a very confusing and almost insuperable annoyance, as is clearly shown by the behavior of adults who suddenly acquire diplopia from the paralysis of one or more of the extra-ocular muscles. They instinctively cover one eye to blot out the confusing double images. It has, therefore, been assumed, because no histologic changes in the retina and visual pathways have been discovered to account for the poor vision, that the amblyopia is nature's method of overcoming the confusion which diplopia produces. The physiology and psychology of

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