# Section of Epidemiology and State Medicine

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[*April* 24, 1936]

## Prophylaxis, Treatment and Bacteriology of Pertussis

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THERE can be few of us here who have not had whooping-cough. Many of us have seen our own children splutter and vomit their way through this unattractive illness, and many have keenly felt their impotence while watching wretched, underfed babies cough out their lives in the bronchopneumonia that so often terminates the disease.

My own interest in the matter dates from a visit to Denmark a good many years ago, when I saw the bacteriological-diagnostic service in full operation, and from a subsequent epidemic in my own family, when I found that neither my excellent doctor nor myself could tell which of the children had been attacked and which had not. I also recall the farcical inferno of the whooping-cough out-patient department at my old hospital, which I had myself run in complete ignorance of the disease I was supposed to be tackling.

We all, of course, desire to prevent and alleviate the ravages of whooping-cough, which vies with measles for the first place amongst the baby-killing acute infections; yet we have not been very prompt in taking up the new weapons that bacteriology has forged for us. This can hardly be because we are proud of our handling of the disease, for hitherto the medical practitioner has been able neither to diagnose nor to treat it, much less to prevent it. His impotence in clinical diagnosis is due to the late and very inconstant appearance of the sole characteristic symptom, the whoop.

Certain American writers have very sensibly suggested the abandonment of the name whooping-cough and the substitution of the old term pertussis, with the idea of weaning the medical profession and public from its age-long diagnostic reliance on the very unreliable whoop. My agreement with this view is indicated in the title of this paper. It has recently been confirmed by experience of a school epidemic in which only one-fifth of the cases whooped at all (Smith, R. E., 1936), and few even had recognizably spasmodic coughs.

The recognition that bacteriological research has made great and practical advances in the handling of this disease is only now beginning to filter into general practice, and the need for continued propaganda on the subject is my main excuse for occupying your time.

Bacteriological progress has been based on the acceptance of Bordet's discovery of a small hæmophilic bacillus, now generally termed *Hæmophilus pertussis*, as the cause of the disease. This is still questioned by a few writers, who, somewhat obstinately, as it seems to me, pin their faith on the ill-grounded hypothesis of a virus. Let us very shortly review the evidence for and against the bacillus as sole ætiological agent:—

(1) The bacillus is constantly present in the acute stages of the illness, and is absent in other illnesses and in health.

These absolute statements need so little qualification that we may leave them unqualified [Kline, 1933; Willcox, 1935; Kristensen B., 1932].

(2) The period of expectoration of the bacillus coincides with the period of infectivity.

(3) Specific antibodies are constantly demonstrable as the disease advances.

(4) With pure cultures of *H. pertussis* injected intratracheally into apes, an illness of entirely the same type as human pertussis has been produced by a number of independent workers (Sauer and Hambrecht, 1929; Rich, Long *et al.*, 1932; Inaba and Inamori, 1934; Shibley, 1934).

(5) A crucial experiment by the Macdonalds (1933) on their own children showed that true whooping-cough follows the intranasal instillation of pure cultures of *H. pertussis*. In both ape and human experiments the organism is recoverable in pure culture from the lesions. I feel that it would need considerable hardihood to maintain that Koch's postulates are not reasonably satisfied by this array of evidence.

Now let us see what there is to be said for a virus. A number of clinicians and certain pathologists (Rich, 1932; McCordock, 1931-2; Nicolau and Matiesco, 1933), express the view that the extreme infectiousness of whooping-cough, the solid immunity it confers, the interstitial type of pneumonia complicating it, and the infiltrative, degenerative lesions of nerve ganglia to which it not infrequently gives rise, are all indications of a virus infection. On this view the bacillus is a secondary invader, comparable to *H. influenzæ* and the pyogenic cocci in influenza. In support of this McCordock and Mackenfuss (1932) bring evidence of inclusion bodies seen in the pneumonic lesions of about a third of the cases of fatal whooping-cough examined. Further support is drawn from criticism of the animal experiments in which whooping-cough has been alleged to be transmitted with pure cultures of *H. pertussis*, for, it is urged, similar spasmodic coughs can be experimentally caused by *H. influenzæ*, *B. bronchisepticus*, and other bacteria.

Now none of these points has any direct evidential value. Extreme infectiousness is probably the result of unusually profuse droplet-expulsion. The immunity is not so solid as is often supposed; second attacks are fairly common. Thus Miller (1935) observed and proved by the cough-plate method four recurrences among a very moderate number of cases.

Again, the interstitial character of the pneumonia complicating the disease is certainly no proof of the presence of a virus. Lesions of this type can be produced in animals by intratracheal injections of *H. pertussis*, and also with several other microbes (Sprunt, *et al.*, 1935). The nervous lesions can be satisfactorily explained by the action of the powerful endotoxin absorbed from the respiratory tract.

As to the notion that the bacillus is a secondary invader, we may well ask, "Why then is it most profuse at the onset of the illness, and generally absent in the late stages?"

The inclusion bodies, which are demonstrable only in a minority of such cases as come to the post-mortem room, if they prove a virus infection at all, prove only a secondary or terminal infection.

In reply to the argument that the experimental transmission of the disease to apes is illusory, as it is impossible to prove that they really have whooping-cough, it may be answered that a spasmodic cough with positive cough-plate tests, being the basis for the diagnosis in man, must also be accepted in apes, whether or no any whooping is to be heard.

Nor is the position weakened by the fact that a spasmodic cough may be produced in apes by other microbes. So it can in man. Influenza epidemics often produce a cough so spasmodic that the physician is left for a long time guessing at the diagnosis; and according to Brown (1926) occasional infections with *B. bronchisepticus* can give rise to typical whooping-cough symptoms. Of course, in both cases, cough-plates are entirely negative for *H. pertussis*.

Finally a number of direct experimental attempts have been made to demonstrate a virus in whooping-cough sputum and in fresh cultures of *H. pertussis*, but they have been entirely unsuccessful (Culotta, Harvey and Gordon, 1935; Shibley, 1934; Macdonald and Macdonald, 1933). By producing pertussis in apes with the 60th

subculture of a freshly isolated strain of the bacillus, Shibley proved that either no virus participated, or at least that any virus present must be living symbiotically with the bacillus—a highly unlikely combination which would require a deal of proving.

To sum up: There is a convincing body of evidence that *H. pertussis* is the infecting agent of whooping-cough, and the view that a virus plays a part is without substantial foundation. Our definition of the disease pertussis ought in future to be based primarily on the causative organism, and might run thus: "An infection of the respiratory tract with *H. pertussis*, generally giving rise to a spasmodic cough."

## DIAGNOSIS

The evidence on which a diagnosis may be based can be divided into clinical, hæmatological, and bacteriological.

*Clinical diagnosis* is, as we have said, impossible in the early stages, when infection is at its worst, and both isolation and treatment can do most good. In perhaps half of all cases it either remains uncertain to the end, or is made on merely circumstantial evidence.

*Hæmatological evidence* consists of the lymphocyte count and the complement-fixation test. Both of these are good tests, but neither gives the early diagnosis that we so much need. A lymphocytosis of considerable degree is fairly constant from the third week of the disease until convalescence sets in. During the vital catarrhal stage and again in convalescence a leucopenia is the rule. It is important to estimate the absolute number of lymphocytes, since their ratio to polymorpho-nuclears may be reduced by a secondary infection.

Specific complement-fixing antibodies appear in measurable amount about the same period and with considerable regularity. Like all specific antibodies, however, their presence only proves that the subject has recently been under the stimulus of the specific antigen, not that he is suffering from present infection. Thus it has recently been shown that adults in contact with whooping-cough acquire a positive complement-fixation reaction (Bennholdt-Thomsen, 1934), without showing any clinical symptoms. This, incidentally, brings one more support to the modern view of epidemics as community infections in which the clinically recognizable case is merely an extreme instance.

TABLE I.—ACQUISITION BY HEALTHY PERSONS OF A STRONGLY POSITIVE COMPLEMENT-FIXATION REACTION DURING CONTACT WITH WHOOPING-COUGH.

(After Bennholdt-Thomsen, 1934)

| Persons | 1st complement-fixation test | Period of attendance on wh.-c. patients Days | 2nd complement-fixation test |
|---|---|---|---|
| Nurse | 0 | 42 | +++ |
| Nurse | (+) | 52 | +++ |
| Nurse | 0 | 77 | +++ |
| Nurse | + | 14 | ++++ |
| Nurse | 0 | 25 | ++++ |
| Doctor | 0 | 53 | ++++ |
| Mother | 0 | 30 | ++++ |
| Grandmother | 0 | 74 | ++++ |

The third method of diagnosis is the *bacteriological*, which is now sufficiently well known to need no detailed description. Nothing has yet been discovered better than the cough-plate method, using Bordet's fresh blood-medium. If one could find a substitute for fresh blood the whole process would be greatly simplified and popularized.

All the recent figures support the view that at least three-quarters of cases can be diagnosed from the very earliest onset, though the diagnostic process takes at least three days, owing to the slow growth of the specific organism.

TABLE II.—SUCCESSFUL ISOLATIONS OF *H. pertussis* IN CASES PROVING CLINICALLY OR BACTERIOLOGICALLY TO BE WHOOPING-COUGH. (Reproduced from the *Lancet*, 1932 (i), 11.)

| Stage of illness | A. D. G. and P. H. L. (47 cases) | Danish (Madsen, 1924) (914 cases) | American (Sauer and Hambrecht, 1930) (200 cases) |
|---|---|---|---|
| | Per cent. | | |
| First week (catarrhal phase) | 75 | 75 | 98 (catarrhal phase) |
| Second week (spasmodic phase) | 67 | 57 | — |
| Third week | 75 | 61 | 65 (spasmodic phase) |
| Fourth week | 25 | 45 | — |
| Fifth week | 0 | 40 | 0 (phase of decline) |
| Sixth and later | | 9 | — |

Progress has been due mainly to Danish and American workers. So far as I am aware, only two bacteriological contributions have been published here, that of Sugare and McLeod in 1929 and that of Leslie and myself in 1931 and 32. In Denmark, as we all know, the method has been in regular use for many years, and in various parts of the U.S.A. it has become an established routine.

Whereas the value of the cough-plate method in diagnosis is no longer open to question, its use in determining the isolation period of infected persons is still in the experimental stage. American workers differ considerably on this question. Kline, for example, writing in 1933, thinks the method too unreliable for practical use. On the contrary, Kendrick and Elderling (1935) feel that they can safely release patients on the twenty-eighth day after onset if two plate-tests on consecutive days during the fourth week have proved negative. Well over half their patients were released at the end of the fourth week, that is, a week earlier than the clinical standard for untested patients. I think I am right in saying that six weeks is a more general period, but in any case the number of man-hours saved from the sick-room is economically well worth the work done.

TABLE III.—RELEASE COUGH-PLATE FINDINGS

(Kendrick and Elderling, 1935.)

| Release cough-plates | | Patients for release | | |
|---|---|---|---|---|
| Week obtained | No. of plates | Total patients | Released | Percentage released |
| Fourth | 86 | 58 | 33 | 57 |
| Fourth and fifth | 125 | 69 | 63 | 91 |
| Fourth, fifth, and sixth | 155 | 83 | 82 | 99 |

There is as yet little direct proof that children released after negative tests are incapable of transmitting infection, but in the light of the old clinical observation that a patient is almost harmless once the whoop has set in, the *a priori* probability is very high. We shall return to this point in a moment.

There is no doubt that some individuals continue to cough up the bacillus in the fifth and sixth weeks and exceptionally even till the eighth or eleventh. Clearly the testing-procedure is more likely to lead to a rational handling of such cases than the application of any rule of thumb.

It is suggested by R. E. Smith (1936) that environment and season affect the duration of the infection both in its community and its individual aspect. Last year I assisted Dr. Smith to test this idea in a small outbreak at a Public School, which occurred and ran its course in the exceptionally fine warm weather of late spring and early summer. There were only 26 cases in this outbreak, although 130 of the 600 boys were unprotected by a previous attack. Diagnostic cough-plate tests, carried out by Miss Straker, of the London School of Hygiene, in 25 cases, were positive in 20, or well over three-quarters of the cases. In one of these the first test was negative, and was repeated, with a positive result. Of the five boys who yielded no bacilli only one is stated to have had a spasmodic cough, and none whooped. Can we be sure of the diagnosis in such circumstances?

At Dr. Smith's suggestion I carried out a series of release-tests, starting in the third week of the disease, the results of which are shown in Table IV. A series of three double plate-tests was made in every case.

TABLE IV.—PERTUSSIS RELEASE COUGH-TESTS.

(R. E. Smith's warm-weather school-epidemic, June-July 1935.)

| Case No. | Day of bacteriological Diagnosis | Negative release tests Days | Day of discharge | Contact with susceptibles after release | Resulting infections |
|---|---|---|---|---|---|
| 1 | −4, −9 | 22, 23, 24 | 28 | ++ | 0 |
| 2 | +5 | 29, 30, 31 | 30 | ++ | 0 |
| 3 | −12, −15 | 21, 29, 30, 31 | 34 | (+) | 0 |
| 4 | +6 | 22, 23, 24 | 27 | ++ | 0 |
| 5 | +16 | 21, 23, 30 | 35 | + | 0 |
| 6 | −3 | 22, 23, 24 | 28 | + | 0 |
| 7 | −5 | 16, 17, 18 | 22 | + | 0 |
| 8 | +5 | 24, 25, 26 | 30 | + | 0 |
| 9 | +7 | 22, 23, 24 | 30 | (+) | 0 |
| 10 | +3 | 27, 28, 29* | 32 | + | 0 |
| 11 | +3 | 18, 19, 20 | 25 | + | 0 |
| 12 | +4 | 21, 22, 23 | 23 | − | − |
| 13 | +12 | 30, 31, 32 | 38 | (+) | 0 |
| 14 | +7 | 22, 23, 24 | 35 | (+) | 0 |
| 16 | +4 | 29, 30, 31 | 34 | (+) | 0 |
| 20 | +5 | 24, 25, 26 | 27 | − | − |
| 21 | −3, +7, +10 | 17, 18, 19 | 20 | − | − |
| 25 | +5 | 14, 15, 16 | 23 | + | 0 |

18 cases. Average day of discharge, 29. Resulting cases, 0.

* Case 10; weakly positive plates on 21, 22, and 23.

If we take the six-weeks' standard sponsored by the Ministry of Health and the Board of Education, the number of days saved per head by the release-tests was 13, which represented about £13 worth of schooling per head. In certain cases it meant also the ability to take important examinations, such as the school certificate, which would otherwise have been missed. If a bacteriological service had been available, the cost of the testing would probably have run to about 30s. per head, so that a net saving of over £10 per head would be effected, apart from the imponderable value of the freedom.

The absence of any return cases supports the view that the test, as performed, is a safe indication of non-infectivity.

Before leaving the subject of bacteriological tests we may consider the question whether the somewhat elaborate and expensive procedure is really worth while. Only well-equipped and well-staffed laboratories can tackle it successfully, and the method is by no means 100% successful, except under ideal conditions. These facts make many physicians and public health officers very sceptical about their possibilities (e.g. Greer, 1935). I think the answer is that even at the present time, with our ill-organized, and in many ways inadequate, pathological service, the method could easily be worked in the larger centres and for certain classes of outbreaks. Well-to-do folk will be found ready to pay adequate fees both for diagnostic and release-tests, and private schools will be extremely glad of a means of establishing with certainty the nature of a catarrhal outbreak at the earliest possible moment. Finally the Public Health Authorities would become interested as soon as a more widespread enlightenment gave rise to a definite demand.

*Skin test.*—I have, so far, said nothing about the intradermal test, which has been tried by a number of workers either for diagnosis or for the determination of susceptibility. It does not yet seem possible to judge what the value, if any, of such a test will prove to be. Krarup (1933) in a summary of the literature and a description of his own experiments concludes that the test is worthless. Probably, however, insufficient attention had been paid to the antigenic variation of the bacillus. Siebler and Okrent, however, in 1934, think that Sauer's vaccine affords a good intradermal test of immunity and susceptibility. 186 subjects were classified into susceptibles and immunes, according to their previous history. The test gave 80%

of positive results in those unprotected by previous whooping-cough, and 76% of negative results in the protected class. Immunization of children changed the reaction from positive to negative in practically 100% of cases. The test, which is clearly not applicable to diagnosis, is thus an immunity test like the Schick-reaction for diphtheria. In a recent article Paterson, Bailey, and Waller (1935) describe a skin-test with Sauer's vaccine, the results of which are interpreted in exactly the opposite sense to those of Siebler and Okrent. Previous whooping-cough was found to give rise to a positive reaction, as also did an immunizing course of vaccine. The great majority of subjects unprotected either by an attack or immunization gave negative reactions. The test would thus appear to be an allergy-test, comparable to the tuberculin-reaction. Thus there is, at present, nothing but confusion in this field, and much further work will be needed before any clear judgment can be made.

*The use of vaccines in whooping-cough.*—This appeals to me far more in its prophylactic than in its therapeutic aspect. Prophylaxis is capable of scientific proof whereas it is only exceptionally possible to form a scientific judgment on the results of treatment.

Up to 1931 whooping-cough vaccination was under an ever-deepening cloud. General opinion condemned it as worthless and the American Pharmacological Council had removed the vaccines from its list of useful remedies.

A test made in London about that time with a vaccine produced by Bordet himself appeared to be unsuccessful. Soon afterwards Leslie and I found that the vaccine was made with bacilli in the rough phase and was therefore probably useless as an antigen. Even last year a paper by P. Bordet (1935) shows no recognition of recent advances in the principles of vaccine preparation.

The work of Leslie and myself revived and amplified Jules Bordet's early observation that fresh *H. pertussis* is antigenically different from *H. pertussis* adapted to the laboratory life, and we produced prima facie evidence that only the fresh phase could be expected to produce useful antibodies. The serological distinction between the various phases is shown in the accompanying chart.

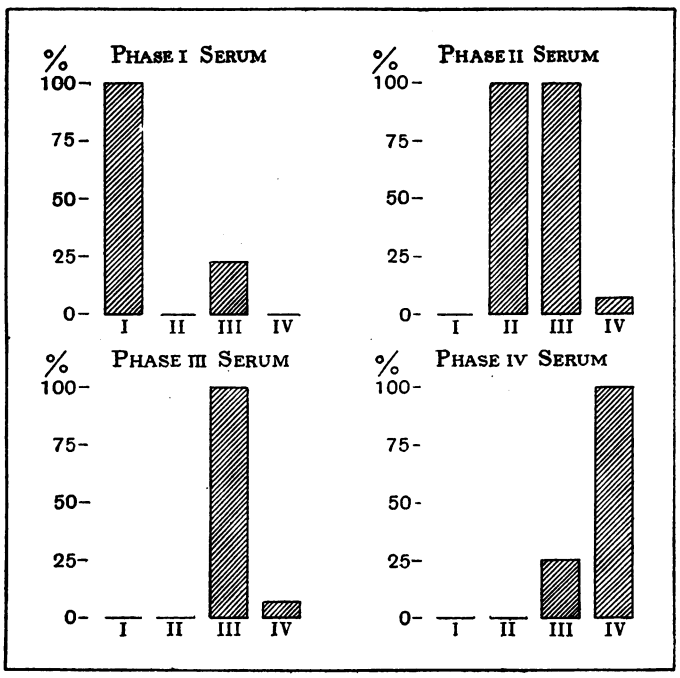


Chart showing cross-agglutination tests with phase serums. Minor agglutinins expressed as percentages of the titre to the homologous serum-strain. (Reproduced from the *Journal of Hygiene*, 1931, p. 432.)

Table V shows our most successful immunizing experiment, in which all the guinea-pigs immunized with Phase I bacilli (smooth) survived, whereas those immunized with Phase III (rough) vaccine succumbed to the test doses of virulent or toxic Phase I bacilli. Other similar experiments, though less clear cut, pointed in the same direction.

TABLE V.—IMMUNITY EXPERIMENT No. 1.

| | Phase I vaccine: | | | | | Phase III vaccine (living): | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nature | Two doses of mgm. | Guinea-pig weight | Test dose | Result | Loss in weight per cent. | Two doses of mgm. | Guinea-pig weight | Test dose | Death in days | Loss in weight per cent. |
| Heated 55° C. | 2·0 | 320 | 63 | Lived | 31 | 1·0 | 292 | 67 | 4 | — |
| ,, | 1·0 | 359 | 58 | ,, | 33 | 2·0 | 311 | 64 | 2 | — |
| ,, | 4·0 | 369 | 57 | ,, | 29 | 4·0 | 354 | 59 | 5 | — |
| 0·4 % formalin | 4·0 | 366 | 57 | ,, | 38 | | | | | |
| ,, | 1·0 | 377 | 56 | ,, | 19 | | | | | |
| ,, | 2·0 | 397 | 54 | ,, | 26 | | | | | |
| ,, | 4·0 | 309 | 32 | ,, | 8 | 4·0 | 304 | 33 | 14 | 32 |
| ,, | 1·0 | 328 | 31 | ,, | 22 | 2·0 | 352 | 29 | 14 | 34* |
| ,, | 2·0 | 362 | 29 | ,, | 17 | 1·0 | 385 | 28 | 46 | 31 |
| Heated 55° C. | 4·0 | 357 | 29 | ,, | 13 | | | | | |
| ,, | 1·0 | 378 | 28 | ,, | 11 | | | | | |
| ,, | 2·0 | 403 | 27 | ,, | 0 | | | | | |

All the guinea-pigs were females.

Dose $= \frac{\text{mgm} \times 1{,}000}{\text{Wt. (grm.)}^{0\cdot72}}$ expressed as nearest whole number.

* Killed in a moribund condition.

This work seemed to revive hope in various quarters, and several American workers took the matter up. The Danes also, who had previously used cultures not recently isolated, though always maintained on fresh blood-medium, proceeded to make their vaccines with perfectly fresh strains.

The results have, in my opinion, been distinctly promising, indeed they verge on a real proof of the efficacy of the method.

In addition to the recognition of the necessity for smooth, Phase I, cultures, Sauer (1934) has shown that large doses are probably more effective than small. Reactions are no more serious than in other familiar forms of inoculation. The growth of knowledge on this subject is summarized in Tables II, III, and IV.

TABLE VI.—WHOOPING-COUGH IMMUNIZATION IN FAROE ISLANDS
(Madsen)

I. Epidemic of 1923-4. Exposed population vaccinated with moderate doses of vaccine from *stock* cultures on blood-medium. (Total, 22,000 million bacilli.)

| | 2,094 vaccinated | 627 unvaccinated |
|---|---|---|
| Escaped infection ... ... ... | Practically none | Practically none |
| Mild cases ... ... ... ... | Almost all | Fair number |
| Severe cases ... ... ... ... | Hardly any | Many |
| Fatal ... ... ... ... ... | 5 (0·2%) | 18 (3%) |

II. Epidemic of 1929. Exposed population vaccinated with moderate doses of vaccine from *freshly isolated* cultures on blood-medium. (Total, 22,000 million bacilli.)

| | 1,832 vaccinated | 446 unvaccinated |
|---|---|---|
| Escaped infection ... ... ... | 458 (25%) | 8 (1·8%) |
| Mild cases ... ... ... ... | 1336 | 225 |
| Moderate ... ... ... ... | 29 | 170 |
| Severe ... ... ... ... | 8 | 35 |
| Fatal ... ... ... ... ... | 1 (C.M.=0·0%) | 8 (C.M.=1·8%) |

*Type of vaccine* = carbolized suspension of bacilli from Bordet-Gengou medium; 10,000 mill. per c.c. Three doses of 0·5, 0·7, and 1 c.c. at weekly intervals. C.M. = Case-mortality.

Table VI shows Madsen's account of prophylaxis in two Faroe Island epidemics (Madsen, 1925, 1933).

In the first, where stock cultures were used for the vaccine, no protection from attack was afforded, but attenuation of the disease and a reduction of mortality were claimed.

In the later epidemic of 1929, when the vaccine was made with freshly isolated cultures, a certain amount of protection seems to have resulted, as well as a pronounced attenuation of symptoms. The death-rate appeared to have been reduced rather more than in the first epidemic.

TABLE VII.—WHOOPING-COUGH IMMUNIZATION OF SCHOOL CHILDREN
(Frawley)

I. Four *small doses*, 0·1, 0·5, 1·0, and 1·0 at weekly intervals. No protection evident; but illness milder.

| Type of attack | Vaccinated | Unvaccinated |
|---|---|---|
| Mild ... ... ... ... ... | 26 | 7 |
| Moderate ... ... ... ... | 10 | 26 |
| Severe ... ... ... ... ... | 6 | 27 |

II. Four *large doses* of 2 c.c. at weekly intervals. 505 vaccinated; 80 of these intimately exposed to infection; 49 *of them escaped*; 31 contracted wh.-c.

| Duration of paroxysmal stage | Vaccinated | Unvaccinated |
|---|---|---|
| Less than 1 week ... ... ... | 25 | 9 |
| 1 to 2 weeks ... ... ... ... | 5 | 49 |
| 2 weeks or more ... ... ... | 1 | 116 |

Type of vaccine = "undenatured antigen" of freshly isolated strains.

Table VII shows the results obtained by Frawley (1934) in America with a so-called undenatured antigen, made by mechanical disruption and subsequent filtration through collodion of freshly isolated cultures. Using small doses he, like the Danes, achieved no absolute protection, but was able to convince himself of a strongly attenuating effect.

A further trial, however, with larger doses gave evidence of very considerable protection—about 60% protected, and a great reduction of severity in the symptoms of those attacked.

Finally, we have Sauer's results (Table VIII). He lays stress not only on fresh cultures, but also on the growth of the vaccine on human blood and on maximal dosage.

TABLE VIII.—WHOOPING-COUGH. IMMUNIZATION OF CHILDREN.
(Sauer)

*Large doses* of vaccine from *freshly isolated* cultures grown on *human blood*.
*Total*: 8,000 million in 4 weekly doses.

300 selected private cases immunized each having one or more susceptible brothers or sisters as controls.

28 families became infected, 4 months to 6 years after immunization; containing 39 vaccinated and (?) 45 unvaccinated children.

Attacks among the 39 vaccinated = 0.
,, ,, (?) 45 unvaccinated = 45.

Additional casual exposures of vaccinated children outside family.
Number exposed = 145.
Number attacked = 0.

The results may be summarized as follows: Of a considerable number of immunized children in families in which unimmunized brothers and sisters could act as controls, 39 immunized and 45 controls were thoroughly exposed to infection. None of the immunized children contracted the disease, whereas apparently all the controls did. I say "apparently" because the account does not make it quite clear whether it was all or only a large proportion of the controls who contracted whooping-cough.

In any case, if we can trust the evidence, the case for prophylactic vaccination seems well on the way to proof.

Supposing that Sauer's remarkable success was of the nature of a fluke, we could still maintain that attenuation with great diminution of serious complications is a realizable aim; indeed it is possible that this is a more practical aim than a complete immunity, which is likely to be much less lasting than that conferred by an attenuated attack.

We have already mentioned the rather dramatic experiment of two American pathologists, Dr. and Mrs. Macdonald (1933) on their four children, to prove the prophylactic efficacy of fresh pertussis vaccine.

Two of the children were immunized and two kept as controls then, after a considerable period of isolation, all four were treated with fresh living cultures of *H. pertussis*, instilled into the nose and throat. Very small doses were used, about 100-150 bacterial cells per patient. The two uninoculated children developed typical whooping-cough; the two inoculated ones remained perfectly healthy.

This experiment, though very striking, is not absolutely conclusive, since it is not known with what certainty this means of artificial infection operates. It may have been the law of chance and not the vaccine that protected the two vaccinated subjects.

In addition to these selected pieces of evidence there are numerous accounts of epidemics apparently brought to a successful end by inoculation of susceptibles. Thus, in an Oxford school, the nature of a catarrhal outbreak was ascertained by blood-counts at the end of the second week, and all exposed susceptibles were inoculated with Parke-Davis' pure pertussis vaccine. Of 16 boys only one developed the disease. This, however, has little or no evidential value, as is illustrated by a rather similar account by Grüneberg in Germany. Here, under similar circumstances there were 25 susceptible contacts, and 10 of them were inoculated. None of the 10 developed whooping-cough; but then neither did any of the uninoculated 15.

I think we may say that the effects of inoculation can never be assessed when it is carried out during small scale outbreaks. Some significant indirect support for the prophylactic value of vaccines may be drawn from the knowledge that immunization, like the disease itself, produces complement-fixing antibodies with great regularity, and modern immunology leads us to associate actual immunity closely with this type of antibody.

It is perhaps unfortunate that, as several authors have stated, the antibody response of small infants is distinctly feeble, since they are the persons one most wants to protect. But we cannot draw the conclusion that the inoculation has no effect in such cases.

To sum up: I feel that the position of prophylactic vaccination is substantially better than it was four or five years ago. The evidence that has accumulated justifies the provisional belief that it is effective both in reducing the chances of attack and in attenuating the disease in those attacked. It is, of course, desirable that further statistics of really evidential value should be obtained.

*Serum-prophylaxis.*—It seems probable that the serum or blood of convalescents or immune adults has a certain prophylactic effect, though the data presented in the literature fall short of a real proof. The latest contribution to the subject in our country is that of Paterson, Bailey, and Waller (1935), who, in a well-devised experiment, gave convalescent serum to a group of pertussis-contacts. A similar control-group, which received no serum, showed a much greater incidence of pertussis than the injected group (42% as against 11% in the controls). Further, the illness, when it occurred in the immunized subjects, was, on an average, milder. It is a pity that the statistical significance of the figures is not discussed. So far as it goes, however, this work supports the favourable view already expressed.

*Treatment.*—I do not propose to discuss in any detail the difficult subject of specific therapy. It is very seldom that the results of treatment of any disease can be subjected to a sound statistical analysis. We no longer pretend to "cure" infectious illnesses, which generally cure themselves if we leave them judiciously alone; and our claims to ameliorate symptoms, however true, are very hard to prove. Our best hope is to anticipate or accelerate by suitable injections the immunity otherwise only acquired in the attack.

The voluminous literature of vaccine therapy in pertussis leaves me with the feeling that it offers no real hope. Occasional apparent successes, if not merely accidental, may be attributed to non-specific factors. A recent trial by Begg and Coveney (1936) of the best modern type of vaccine proved no more satisfactory than the Ministry of Health's 1931 tests or Bordet's rough vaccine.

Serum therapy is thoroughly discussed by R. E. Smith in his article now in the Press. He comes to the conclusion that convalescent human serum or blood is of value in the early catarrhal stage, though not later; but he does not claim that the data are such as can be statistically assessed. Paterson, Bailey, and Waller, while finding serum good as a prophylactic, could see no value in it for treatment. All we can say at the present is that its possibilities should be further explored; but that unless the exploration can be done systematically and on a large scale, we shall probably never reach a final judgment. The few attempts so far made to employ the serum of immunized animals—such as calves or cocks—have not produced any important results.

In conclusion, we may say that pertussis has been the Cinderella of infectious diseases and that, in consequence, its incidence and mortality have declined in recent years at a much slower rate than those of diphtheria and scarlet fever. With the new powers of control afforded by the bacteriological discoveries of the last ten years, we may hope to see a substantial improvement as soon as the country as a whole becomes, in transatlantic phraseology, sufficiently "whooping-cough conscious."

[My thanks are due to Dr. R. E. Smith and the Editor of the *Quarterly Journal of Medicine* for permission to quote from Dr. Smith's unpublished paper.]

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