# The Enigma of Pertussis

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Marc Daniels died at the age of 46, in 1953. Most of his working life was spent in the study of tuberculosis. After the Second World War he worked in many European countries in which tuberculosis was rife and then, in 1946, joined the Medical Research Council. The work in which he was so deeply involved, on the emerging forms of chemotherapy and on BCG vaccination, set a gold standard for the conduct of clinical trials, which still operates. These early MRC studies were the first properly controlled trials in tuberculosis but had an impact far beyond this particular disease. They showed the importance of such trials, the need for their careful planning, the solution of the many statistical and ethical problems and the organisation required. It is hard now to remember how relatively recent these ideas are; one reason why the work of innovators is easily forgotten is that it becomes so firmly embedded in the ideology of science that later generations assume that the ideas have existed for ever. Another lesson is that trials need to be done quickly and early: the first MRC report on isoniazid was published a mere six months from its start.

We are still sadly short of much important information about pertussis, some of it susceptible to the kind of study of which Marc Daniels was such an effective protagonist. By the mid-1970s it was possible for the author of an extensive review of pertussis to say that the disease had become something of a medical curiosity. Even at that time this was certainly not true in the developing countries. In several of the wealthier countries, notably Britain, the situation was just about to change in a very dramatic way, which brought pertussis back into prominence as a subject of great public health importance and led to a resurgence of studies on many basic aspects of the disease.

### The Recent History of Pertussis

At the beginning of this century pertussis was a major cause of childhood mortality, causing more deaths than any of the infective diseases of children except measles. In infants, it was a more frequent cause of death than measles. Then, throughout the century there followed a major decline in case fatality, long before immunisation was introduced and continuing after its general introduction in the post-war decades. Notifications, however, fell sharply only after the mid-1950s and other countries, for example the USA, experienced similar changes, one of the many controversies being whether this decline could be related in any way to vaccination programmes, or whether it represented a continuation of previous trends unrelated to immunisation[1].

In 1974 the question of possible brain damage following pertussis-containing vaccine was brought into sharp public focus as a result of a television programme and many articles in newspapers, leading to a loss of confidence in the vaccine among parents and Health Service staff, and a steep fall in vaccination rates. So, in 1975-76, pertussis posed several very important practical questions. The first one, was the vaccine having any effect, was answered by two large epidemics of pertussis, the largest since a general programme of immunisation against the disease was introduced in 1957. The sequence of events does not, of course, itself prove that a previous vaccine had an effect, but there is much detailed epidemiological evidence which makes this conclusion inescapable. The question of whether the vaccine carried a risk of neurological damage was answered about as fully as it was possible to do by the National Childhood Encephalopathy Survey carried out by Miller *et al.*[2]. The unanswered questions were: What impact does pertussis have on the current generation of patients who develop the disease? What sort of an illness is it, how serious is it, what complications may ensue? Does it cause long-term pulmonary damage? The reasons why these questions could not be answered were twofold. First, the steep fall in mortality and more anecdotal evidence about decline in severity made it clear that the disease had changed in recent decades so that older studies could not be validly used in any cost-benefit equation. The same argument applied to the problem of long-term damage, but here a second difficulty also emerged; the older studies addressing this question were few in number and, by modern standards, lacking in control data which would ensure their epidemiological validity.

### The Illness and its Complications

The main features of pertussis are well known, the paroxysmal bouts of coughing and choking often culminating in vomiting and cyanosis, which may occur as many as 50 times in 24 hours. The apnoeic attacks, especially common in infancy and at that age often

occurring without a preceding coughing bout, and the generally long duration of the illness make an intensely unpleasant experience.

There is much misunderstanding between affected families and doctors because the patients generally look well and have few or no abnormal signs on examination between the attacks, and the attacks are seen by mothers at home and by nurses in hospital but less often by doctors in either case. There is a great list of complications, and clinical or radiographic evidence of lung involvement is quite common. In the series collected at St George's Hospital, 24 per cent had abnormal chest radiographs and similar findings have been reported from many other countries. Fits are not uncommon and encephalopathy still occasionally occurs.

However, although chest complications especially are potentially important, we believe that attempts to measure the impact and severity of pertussis merely by enumerating complications are misleading. Some so-called complications are of little or no importance, the definition of a complication being to some extent arbitrary and, most importantly, the use of complications as an index of severity diverts attention from the central features of the disease which give it its chief impact.

### Impact on the Patient and Family

Another aspect of severity to which little attention has usually been paid is the extent to which the illness affects the life of the patient and his family. There have been many studies of this kind in relation to chronic illness, but few have focussed on acute illnesses and none on whooping cough. As part of a group of studies carried out recently at St George's Hospital, we decided to examine this aspect of the disease[3]. Dr I. D. A. Johnston and Miss M. Hill, an MSc student in clinical psychology, interviewed the parents of 21 children admitted to hospital with pertussis. They did this on two occasions, the first shortly after admission and the second during convalescence at the patients' homes. The questions were of a structured but relatively open-ended kind, useful in providing a systematic approach without unduly limiting the scope of the answers, and were aimed at providing information about the illness and the problems it posed for patient and family, at determining the effect of the illness on the behaviour of patient and family and at identifying the parents' attitudes and fears. They included behaviour checklists for the patient and the family which could be roughly quantified. One incidental finding, which the late convalescent interview made possible, was confirmation of the prolonged nature of the illness, with a mean duration of 11.7 weeks but lasting over 16 weeks in more than a quarter of the children. The behaviour of the children was severely affected during the illness and had still not returned to normal at the second interview about two months later; the effect of admission to hospital, which has been extensively studied in other contexts, may have contributed at this later stage. Families, too, were greatly affected in their behaviour patterns, although these had generally returned to normal by the time of the second interview.

There is no doubt that pertussis was an intensely distressing experience for the parents as well as for the patient. Not surprisingly, the apnoeic or choking attack was most distressing and many parents commented on their feeling of helplessness at these times. During the acute stage most parents were concerned that their child might die; later their main worry was of permanent chest damage. The possibility of brain damage was also of concern in the acute stage. There was much physical stress, too, particularly the extensive disruption of sleep and consequent fatigue of the parents. Most parents were being woken at least five times every night, for a mean of 24 nights (range 7–60) before the patient's admission. Some were awakened 10–15 times each night or sat up with their child all night. It is not surprising that in these circumstances strains on the marriage often emerged especially as some husbands, like some doctors, doubted the severity of the illness, as they were often away when the child had its worst episodes.

### Pertussis in Adults

These patients were all children, but pertussis is not uncommon in adults. In Dr W. O. Williams' study in South Wales 10 per cent of the cases were adults [4] and even the crude notification figures showed adults as 3.3 per cent of cases in the 1977-79 epidemic. Pertussis is often said to present atypical features in adult life and some of the few studies of adults indicate that whooping is uncommon. Others, however, show a picture very similar to that found in children and it seems that the disease often goes undiagnosed because it is unexpected in adults. Certainly it can be severe at any age. In the recent epidemics a general practitioner in his thirties developed cough syncope following the paroxysms; Williams saw grandparents aged 77 both with the disease and I have seen a woman of 65 with its typical features.

Nevertheless, the disease in adults may be atypical or mild and this is of epidemiological importance, since Nelson in the USA has provided evidence that, in his community, adults may be the main source of infection for susceptible children[5]. One reason why adult pertussis may have become more common is the decline in immunity in the population generally. At the turn of the century the median age for pertussis was $<4$ years and 85 per cent of the population had had the disease by the age of seven years, so that few adults were susceptible. The spread of pertussis from and to adults in hospitals has been observed on several occasions.

### Pertussis in the Third World

A final clinical point is the contrast between pertussis in wealthy and poor countries. Some years ago Morley[6] showed that whooping cough in Nigeria was very severe and that, as for measles, the mortality rate approximated to that found in fever hospitals in London in the first decades of this century; the actual figures were 15.5 per cent of 479 admissions in Nigeria from 1957 to 1981, and 11.9 per cent deaths of 17,003 admissions to the London Fever Hospital between 1911 and 1929. Certainly this fits

in with the records of the Grove Fever Hospital, now the site of St George's Hospital and Medical School. The postmortem books show many records of children who died there of pertussis well into the 1940s. Recent data on pertussis in the Third World is, however, much more scanty and much less information is available than in the case of measles. A study in Kenya[7] in the mid-1970s estimated the infant fatality rate at 3.2 per cent and WHO figures of the late 1970s estimated that pertussis accounted for the deaths of 250,000–450,000 child deaths p.a., making it about as important as tuberculosis as a cause of death in childhood [8]. Accurate recent records about Third World pertussis are very definitely needed, but the data we have suggest that, as in other infections, the impact of the disease is greater than it is in wealthier countries.

## Treatment

Can pertussis be treated? A multitude of treatments has been employed at various times and it is sad to note, many decades after clinical trial methods were firmly established, that the evidence for many of the more modern remedies is little greater than for the traditional ones. One reason for this was the decline of interest in the disease before its recent resurgence, another is the great difficulty in assessment of severity, making pertussis a peculiarly difficult disease to measure.

As regards antibiotics, MRC trials in the 1950s[9] established that the number of coughing spasms was lessened by the use of chloramphenicol or chlortetracycline both given in high doses. The effect was, however, a small one and could be detected only in the patients treated early in the disease. The disease has changed since these trials were done, and in any case these two agents, for well-known reasons, are not now considered suitable for childhood infections. There is now some evidence that erythromycin mitigates the severity of the disease but no adequate trials of substantial size have been carried out and any effect is likely to be small[10]. Some antimicrobial drugs, including erythromycin, have been proposed as chemoprophylaxis for family or institutional contacts as an alternative to control by immunisation. This could be especially useful in young infants who are both susceptible to the disease yet too young to have been fully immunised against it. Scattered reports have appeared suggesting that erythromycin could be used in this way but two recent placebo controlled trials showed no benefit from this method. The treated contacts showed no advantage over their controls and the method was in fact difficult to apply in field conditions[11, 12]. Indeed, one reason for failure may have been the problem of timing since in the larger study an average of two weeks elapsed between the first sympton in the index case and the administration of drug, or placebo, to the contact.

Whether or not antibiotic treatment has any effect on established disease or in preventing it in contacts, some, especially erythromycin, do reduce naso-pharyngeal carriage of the organism, so that one justification for their use is that the risk to contacts may be diminished. This may be so, but many failures to prevent infection in this way have also been described, perhaps because the effect of erythromycin in reducing naso-pharyngeal carriage is not as rapid or as complete as is sometimes supposed. More studies of these relationships are needed, especially in closed communities in which a point source of infection is sometimes identifiable.

## Does Pertussis damage the Lungs?

The paucity of previous controlled observations and the changes in the disease in recent decades have deprived us of valid information on possible long-term lung damage caused by pertussis. This problem has now been studied by I. D. A. Johnston working jointly in the Department of Communicable Diseases and the Department of Social Medicine and Clinical Epidemiology at St George's Hospital Medical School. The study involved the identification, from both hospital and from community sources, of children who had had whooping cough in 1971–79, and the use of controls, two for each index case, randomly selected from the same class as the index case. Groups of cases and controls were studied at their schools, at the same session, the observer being 'blind' to their identity as cases or controls. This school-based study had the great advantage of eliminating many potentially confounding variables such as local exposure to respiratory infection, air pollution and, to some extent, socio-economic variables. Respiratory questionnaires were used, employing well-validated questions from the large body of previous work on childhood respiratory disease, together with other relevant questions, giving information on such matters as breast feeding, previous hospital admission, vaccination, family size, parental smoking, social class and aspects of family history. The questionnaire was blandly entitled to avoid any particular attention to whooping cough. At the school visits the groups of children were measured to obtain weight, height, skinfold thickness at four sites and arm circumference, and the chest was inspected and auscultated, including assessment of the 'loose cough' sign. Spirometry was performed using an 'S' model spirometer, measuring the $FEV_{0.75}$, $FEV_1$ and FVC and deriving the FEV/FCV%, the FEF25–75; the mean transit time was read on a printout from the microprocessor.

The opportunity was taken to apply the respiratory questionnaire to all children in the classes containing an index case plus control group, so that, on completion of the study, we had 360 cases and 711 controls but, in addition, about 4,000 additional questionnaires which acted as another set of control data underpinning this aspect of the survey.

The results have been published elsewhere[13], but, in brief, questionnaire data revealed a significant excess, in children who had whooping cough, of previous chest illnesses, hay fever and eczema, especially marked in the group who had been in hospital for whooping cough, who showed a two- to three-fold excess of past respiratory illness (Table 1). The same trends were observed in the tendency to current symptoms, that is, within the preceding year (Table 2).

In the lung function tests, however, although there

**Table 1.** Reported chest symptoms at any age (%).

| | Cases n = 360 | Controls n = 711 | |
|---|---|---|---|
| Croup | 18 | 9 | * |
| Pneumonia | 8 | 3 | *** |
| Bronchitis | 16 | 8 | *** |
| Wheezy bronchitis | 15 | 8 | *** |
| Wheeze | 17 | 9 | *** |
| Asthma | 7 | 4 | |
| Hay fever | 12 | 7 | * |
| Eczema | 19 | 12 | ** |

* $P<0.05$ ** $P<0.01$ *** $P<0.001$

**Table 2.** Reported chest symptoms in last year (%).

| | Cases n = 360 | Controls n = 711 | |
|---|---|---|---|
| Morning cough | 13 | 7 | *** |
| Day/night cough | 23 | 13 | *** |
| Morning phlegm | 6 | 3 | * |
| Day/night phlegm | 8 | 4 | * |
| Wheeze | 25 | 12 | *** |
| Breathlessness | 16 | 7 | *** |
| Cough/cold lasting 2 weeks | 38 | 33 | |

* $P<0.05$ *** $P<0.001$

were small differences in some of the sub-groups, none was significant and, overall, the mean measurements were the same in test and control groups, with the observations sharing narrow confidence limits (Tables 3 and 4).

**Table 3.** Lung function tests.

| Test | Adjusted Lung Function* Cases | Controls | Difference between cases and controls | 95% confidence limits for difference |
|---|---|---|---|---|
| $FEV_{0.75}$ | 1.571 | 1.564 | + 0.007 | − 0.017 to 0.030 |
| $FEV_1$ | 1.689 | 1.686 | + 0.003 | − 0.022 to 0.028 |
| FVC | 1.904 | 1.896 | + 0.008 | − 0.021 to 0.036 |
| FEF 1/s | 2.119 | 2.127 | − 0.008 | − 0.058 to 0.073 |

* Lung function adjusted to height = 128 cm

**Table 4.** Lung function tests. Forced expiratory ratio and mean transit time (MTT).

| | Cases | Controls |
|---|---|---|
| $FEV_1$/FVC % | n = 333 | n = 670 |
| | 89.2 | 89.1 |
| MTT (sec) | n = 211 | n = 458 |
| | 0.47 | 0.47 |

It appears, therefore, that children who have had pertussis have had and do now suffer an excess of respiratory illnesses compared with their controls. Is this excess caused by whooping cough or does it precede it, indicating a susceptibility to respiratory infection which might include an increased likelihood of developing pertussis, or pertussis of increased severity? Or, of course, both these factors might be operating. We cannot answer this question with complete confidence but an analysis of the ages at which the cases had whooping cough suggests that the undue susceptibility to chest illness shown by these children preceded their attack of whooping cough and then continued after it.

The lung function tests do exclude any possibility that, in the present generation of British children, whooping cough has any substantial effect on ventilatory function. Two caveats are necessary. First, the size of the study would not suffice to detect reliably rare pulmonary complications: for example, if, as was long ago supposed, whooping cough was followed by bronchiectasis in one in 200–300 children, such an effect could only have been detected in a much larger study. Second, in view of the abnormal experience of respiratory infections of these children and the controversy about methods of testing for small airways disease, could important findings be missed by our measurements? This seems unlikely but, in collaboration with Dr J. Warner, we have carried out another study, now being analysed, in which a number of children who had pertussis in infancy, together with suitable controls, have been tested at Brompton Hospital for bronchial sensitivity to histamine, together with skin tests and detailed lung function studies including flow-volume curves and nitrogen washout tests.

## Advances in Pathogenesis

Bordetella pertussis shows an astonishing variety of biological effects in experimental animals (Table 5), some of

**Table 5.** Biological activities of Bordetella pertussis.

| | |
|---|---|
| Pertussigen | Lymphocytosis-promoting factor<br>histamine sensitisation<br>islet activation |
| Filamentous haemagglutinin | |
| Agglutinogens | |
| Endotoxin (lipopolysaccharide) | |
| Dermonecrotic toxin | |
| Adjuvant effects | |
| Extracytoplasmic adenylate cyclase | |

the most striking being the induction of lymphocytosis, a high degree of sensitivity to the lethal effects of histamine, and resistance to the hyperglycaemic action of adrenaline, and there has been much effort to characterise these effects more fully, both chemically and by analysis of their precise physiological mechanisms[14]. In addition to the well-established actions, a recent addition is the finding of an extracytoplasmic adenylate cyclase which is ingested by leucocytes and diminishes their phagocytic capacity[15]. At one level these actions may seem obscure experimental findings of no practical importance but they do point to actions which might have some significance in accounting for the strange pathogenesis of pertussis and

perhaps too for the unwanted effects of vaccine. It is still, however, not possible to make a clear line of explanation between the experimental findings and the human disease, although it is hard to escape the conclusion that the lymphocytosis is likely to have the same origin in man as in the experimental animal. A major advance has been the isolation in crystalline form of a material which carries three of the best recognised actions of the organism. This has been named pertussigen or pertussis toxin. Its subunit structure is beginning to be analysed. There is certainly enough evidence to include pertussis as a 'toxin' disease analogous to cholera or tetanus. There are profound general and systemic effects, yet only local activity of the organism on the respiratory mucosa, with no evidence of systemic invasion. So obvious targets to be borne in mind in improved vaccines are the main pertussis toxin, and other toxins shown to be relevant in experimental systems.

Another focus of interest is the earliest stage of infection, when the organism attaches to human ciliated respiratory epithelium to which it shows a specific attachment. This has been known from morphological data for a very long time but the mechanisms and antigens involved are now being elucidated in much greater detail. Workers at the Centre for Applied Microbiology and Research are studying a number of pertussis components as candidates for a subcellular vaccine. In Japan two infants died after pertussis vaccination in 1974 and 1975, so vaccination was discontinued and then reintroduced for older children only. As in the UK a large epidemic followed, with a peak of 41 deaths from the disease in 1979. Japanese workers have now developed a component vaccine containing two main protective antigens; the filamentous haemagglutinin, thought to be concerned with attachment to cilia, and the leucocytosis promoting factor haemagglutinin, thought to represent the main toxin[16]. This has now been given to four million Japanese children and, with help from WHO, is being tested in several other countries. There are problems in assessing the results, as few infants have been included in the series so far, and other questions of the appropriateness of different laboratory models for the newer vaccines are still to be defined. There are hopes, too, for vaccines from recombinant DNA techniques, since *E. coli* plasmids have been inserted into *B. pertussis* and transformation of plasmid-derived DNA has been demonstrated.

## Conclusion

In summary, over the last decade we have found that pertussis is still an important disease in many countries and that current vaccines, although imperfect, are strongly protective. Our study has shown that children who have had pertussis have an abnormally high morbidity from respiratory disease. This may well precede or in part precede, the attack of pertussis, but whatever the mixture of pre-existing susceptibility and effects of the disease itself, we see a group of children who warrant special attention in preventive programmes.

Progress on analysis of the active components of *B. pertussis* has been rapid. One component vaccine has been extensively tested and others are on the way. The ethical and administrative problems involved in efficacy and safety testing of these vaccines are great.

There are still great gaps in our understanding of how the pertussis toxins relate to the human disease. In particular the pathophysiology of the choking bouts and the apnoeic attacks which give the disease its particular character is still mysterious, and our capacity for making useful interventions in the progress of this distressing disease is still sadly limited. The epidemiological data make it clear that, until extremely effective vaccines can be universally and continuously used, pertussis will remain with us and continue to deserve study both for its public health importance and for its fundamental interest as a model of a particular kind of host-parasite relationship, the pathogenesis of which is at last becoming susceptible to detailed analysis in biochemical and immunological language.

At present, parents of children with whooping cough are as distressed as Mary Barker, who wrote to her husband Abel on 26th May 1661, to say, 'I am in a sad condition for my pore children who are all so trobled with the chincough that I am afraid it will kill them. I am fane to have a candell stand by me to go into them when the fitt comes', and a few days later, '. . . all sadly troubled by the chincough. Moll is much the worst. They have such fitts that it stopes theare wind, and puts me in such frits and feares that I am not myselfe'.

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