NEUROLOGICAL COMPLICATIONS OF PERTUSSIS IMMUNIZATION

BY

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Since Madsen (1933) first drew attention to the possibility of serious consequences following active immunization against whooping-cough, reports of neurological sequelae of such immunization have come from various parts of the world. These sequelae (post-inoculation poliomyelitis is not being considered here) have ranged from transient convulsions with complete recovery to gross crippling, mental retardation, and death.

A survey of the literature, greatly facilitated by Köng's (1953) review of cases reported up to 1951, revealed records of 107 cases. A further case is now reported (the seventh from Great Britain), together with a review of the literature.

Case Report

A male child was born at full term on September 28, 1954, weighing 5 lb. 13 oz. (2.635 kg.) following an uneventful pregnancy (apart from an attack of acute salpingitis at 11 weeks, associated with a negative Wassermann reaction and gonococcal complement-fixation test, which responded rapidly to chloramphenicol) and an uncomplicated labour. His parents and two elder brothers were normal, physically and mentally, and there was no family history of allergy, mental disorder, convulsions, or other neurological ailments.

No abnormalities were found in the neonatal period, apart from a minor degree of hypospadias not considered worth treating, and the child thrived from the outset.

Until May 25, 1955 (aged 8 months), progress was normal and he had had no illnesses. The mother, an intelligent woman, considered him more advanced than his normal brothers had been at the same stage, and the milestones of development were well in keeping with the criteria of normality enumerated by Illingworth (1953).

On May 25 he was given a first inoculation of 1 ml. of combined diphtheria–pertussis vaccine (containing a plain suspension of 20,000 million *Haemophilus pertussis* and 25 Lf of fluid diphtheria formol toxoid). That night he was whimpering and unsettled, an unusual feature for him. Early next morning he was drowsy, hypotonic, and pyrexial, and the following morning—that is, within 48 hours of the injection—convulsive episodes began, described by a doctor then attending him as "involving a preliminary cry which is not his usual sound, clutching at the chest, queer breathing, and spasms of all four limbs." Rolling of the eyes was also noted. The pyrexia settled that day, but the fits persisted (one to four daily) despite bromides. That day, too, the child was no longer sitting up, could not support his head, and was indifferent to his environment.

Because the fits and associated features persisted, he was admitted to hospital three weeks after the inoculation. Observation revealed a child without interest in anything, who, if placed in a sitting position, could remain thus unsupported for only a few seconds, and who was having bouts of fits, each lasting a few seconds and each bout a few minutes. Apart from these findings, physical examination revealed no abnormalities, and the blood count, cerebrospinal fluid, and urine examinations were normal. The Wassermann reaction and Mantoux (1/100) were negative. Several weeks later skull *x*-ray films and lumbar encephalography showed no abnormality apart from the left lateral ventricle appearing slightly larger than the right.

At 11 months of age the child was severely retarded mentally, and phenobarbitone, ¼ gr. (16 mg.) twice daily, was needed to control his fits.

At 15 months grand-mal episodes became associated with the original convulsive pattern, and it was found necessary to increase the dose of phenobarbitone to 1 gr. (65 mg.) daily, and introduce phenytoin sodium, ¾ gr. (50 mg.) thrice daily.

Electroencephalography on May 16, 1956 (aged 19½ months), was considered diagnostic of epilepsy with the epileptic activity generalized and no focus. The main activity was in the delta range and of high frequency.

At 2 years of age no significant progress had been made mentally; fits were controlled with phenobarbitone, 1 gr. (65 mg.) twice daily, and primidone, 250 mg. twice daily; and there were no focal neurological signs.

At 3 years the child remained grossly retarded mentally, with no speech or understanding of speech, inability to do anything for himself, and an I.Q. of 23 on the Griffiths mental development scale. Fits were less severe and were controlled with primidone, 250 mg. twice daily, alone. Localizing neurological signs were absent, as were signs of disease elsewhere.

In the accompanying review of the literature, the 107 case reports from 25 sources mentioned in Table I were examined.

TABLE I

Authors	No. of Cases	Source
Anderson and Morris (1950)	1	Britain
British Medical Journal (1949)	1	,,
Brody (1947)	2	U.S.A.
Byers and Moll (1948)	15	,,
Cohen *et al.* (1955)	2	,,
Doull *et al.* (1936)	3	,,
Escardo and Vazquez (1950)	1	Argentina
Globus and Kohn (1949)	2	U.S.A.
Grace (1950)	2	Canada
Halpern and Halpern (1955)	15	U.S.A.
Kendrick and Eldering (1939)	1	,,
Köng (1953)	2	Switzerland
Laplane (1950)	1	France
Livingston (1954)	7	U.S.A.
Low (1955)	1	,,
Madsen (1933)	2	Denmark
Miller and Stanton (1954)	2	Britain
Rambar *et al.* (1941)	1	U.S.A.
Sako *et al.* (1945)	2	,,
Sutherland (1953)	1	Britain
Taylor (1938)	1	U.S.A.
Toomey (1949)	38	,,
Tudor (1951)	1	,,
Vahrman (1950)	1	Britain
Werne and Garrow (1946)	2	U.S.A.

General Data

Sex of Affected Children.—Byers and Moll (1948) thought that the difference in sex incidence in their cases was similar to that encountered in relation to other substances causing gross injury to the developing nervous system. In the 22 other instances where the sex of affected children is stated a similar, though less striking, difference is present (Table II).

TABLE II

	Males	Females	Total
Byers and Moll	12	3	15
Others	14	8	22

Age When Inoculated.—This varied from 4 days to 3 years, most inoculations being done between 6 and 15 months. These figures simply reflect the ages when immunization is usually carried out, and the only conclusion to be drawn from them is that neurological sequelae may occur at any age in which immunizations are done.

Vaccines Used.—The vaccine used is recorded in 68 instances: in 28 a pertussis vaccine was used alone; in 12 a combined diphtheria–pertussis vaccine; and in 28 a combined diphtheria–tetanus–pertussis vaccine. The vaccines were prepared in a variety of ways by different manufacturers, and included fluid, alum-precipitated, aluminium hydroxide adsorbed, and detoxified formalized preparations. In Byers and Moll's (1948) study of 15 cases alone, the products of eight different manufacturers were identified, and in

Toomey's (1949) series of 38 cases at least six different pharmaceutical laboratories were concerned.

No significance can be attached to the number of times when pertussis vaccines alone or combined vaccines were used. These merely reflect the trends in immunization practice and the nature of the material under review. Thus, in the 10 cases reported up to 1945, pertussis vaccine was used alone in all, and thereafter combined vaccines became implicated too because of their increasing use. Further, in the report of Halpern and Halpern (1955), for instance, a triple vaccine was implicated in all 15 cases simply because their questionary was concerned only with triple vaccine immunization.

It is generally agreed that the pertussis antigen in all these vaccines is responsible for the reported neurological sequelae. There are good grounds for this view. Thus, the clinical manifestations of neurological complications following injections of pertussis antigen alone and of combined antigens containing pertussis are so strikingly similar that a common factor in all these vaccines is very probable. That this factor is pertussis antigen is suggested by the observations of Miller and Stanton (1954) that neurological complications of pertussis vaccination "are different from those encountered in other prophylactic inoculations in that the illness is always cerebral" and that "the neurological sequelae of a particular prophylactic inoculation appear to be similar in distribution to the neurological complications of the infective disease concerned." Complications of whooping-cough include convulsions and upper-motor-neurone type paralyses (Banks, 1949), and Cockburn (1951) points out that the convulsions may be the precursors of mental deficiency in a small number of cases. This is precisely the sort of pattern observed in the cases under review, irrespective of whether pertussis antigen alone or combined vaccines containing pertussis antigen were used.

Dose of H. Pertussis in Vaccines Used.—In 28 instances the number of *H. pertussis* organisms in the injection followed by neurological complications is recorded. This ranged from 1.5 to 45 thousand millions with no particular tendency for reactions to be associated with larger doses (Table III).

TABLE III

Dose (in 1,000 millions of organisms) ..	1–15	16–30	31–45
No. of cases	8	12	8

Injection Associated with Reaction.—In 61 instances where the injection order is given, neurological sequelae occurred for the first time, as shown in Table IV. These figures indicate that a reaction may occur with any injection, and, possibly, a decreasing likelihood for subsequent injections to provoke reactions the more previous ones there have been that have not done so. In seven cases neurological sequelae followed more than one of the injections (the first

TABLE IV

Injection order	1st	2nd	3rd	4th
No. of cases with neurological sequelae ..	26	20	12	3

of these injections producing sequelae is recorded in Table IV). It is notable that only one of these seven children recovered rapidly and completely (a case of Grace's, 1950). Of the remaining six children, two died 24 hours (Low, 1955) and 7 weeks (Brody, 1947) respectively after the last inoculation, and four were left with sequelae ranging from recurrent convulsions to gross physical and mental deterioration (Brody, 1947; Byers and Moll, 1948)—this despite the fact that earlier inoculations had not been thought to have had consequences serious enough to contra-indicate subsequent ones.

Past Personal and Family Histories

An analysis of these data is difficult to interpret because in many instances no information is given, and when it is given the amount varies greatly from author to author.

TABLE V

	Personal History No. of Cases	Family History No. of Cases
Neurological abnormalities	7	6
Allergic manifestations	1	5
Normal	48	16
Not stated	51	80

Such an analysis is shown in Table V. It may be presumed that considerably more of the personal and family backgrounds were normal than is indicated by these figures, and this is often implied. Table V records only the instances where this was actually stated.

Clinical Features of Acute Illness

Time Interval Till Onset of Symptoms.—The early onset of neurological symptoms was characteristic, though not invariable. Table VI shows the time interval from inoculation to the onset of symptoms in the 63 instances in which it was recorded.

TABLE VI

Time interval in hours	Up to 12	13–24	25–36	37–48	49–72	Over 72
No. of cases	39	9	4	3	2	6

State of Consciousness.—In all instances where this is mentioned changes varying from listlessness to deep coma occurred.

Convulsions.—These, ranging from mild localized episodes to severe generalized ones, were an almost invariable and striking feature. There were, however, several notable exceptions: In one case reported by Brody (1947), four different inoculations (the last an intradermal one) between the ages of 6 and 41 months were associated with severe neurological sequelae at progressively shorter intervals, culminating in complete paralysis and death, apparently without associated convulsions; in Sutherland's (1953) case, listlessness and weakness of the limbs appeared some five to seven days after a third inoculation, with evidence of bilateral pyramidal-tract dysfunction about one month later, and apparent complete recovery within seven months, with no mention of convulsions; and in one of Miller and Stanton's (1954) cases neurological signs (drowsiness and right hemiplegia) were delayed for about a week after a third inoculation, with right hemiparesis still present two years later—here, too, convulsions are not mentioned.

Pareses or Paralyses.—These were specifically stated to have occurred in 19 cases.

Other Features.—Besides the above neurological signs, occasional cases presented additional features such as cyanosis, hiccups, diarrhoea, and vomiting. In 39 cases where the temperature is mentioned, it was elevated in 35. Pyrexia is, however, a not infrequent transient concomitant of immunization in which no question of neurological sequelae arises.

Mortality.—In 8 cases death was reported within 48 hours of inoculation, 7 of them within 24 hours.

Progress

Complete Recovery.—This was specifically reported in 41 cases, including 23 of Toomey's (1949) 38, and 11 of Halpern and Halpern's (1955) 15, and presumably occurred in at least nine other instances.

Persisting Morbidity.—Follow-up of the affected children for varying periods revealed evidence of persisting abnormality (Table VII). So far as could be determined from the case reports, in a number of cases in which absence of details makes a fuller analysis of the above signs somewhat hazardous, these signs were distributed as follows: A only, 9 cases; B only, 8; C only, 1; A+B, 2; A+C, 2; B+C, 3; A+B+C, 6. Thus a total of 31 children were specifically

TABLE VII

Major Signs	Follow-up Period	No. of Cases in Which Actually Reported
A=Recurring convulsions	2 months—5½ years	19
B=Pareses and paralyses *	1 month—3 years	19
C=Mental retardation	2 months—5½ years	12

* Varying from slight hemiparesis to gross crippling.

reported as having physical and/or mental signs of cerebral involvement one month to five and a half years after immunization.

Mortality.—Fifteen deaths (seven of them within 24 hours) were reported at varying time intervals since inoculation (Table VIII). Thus, an analysis of the available data indicates a recovery rate of about 50%, a persisting morbidity rate of about 30%, and a mortality rate of about 15%. The small percentage of cases unaccounted for because of lack of information in the reports would not significantly alter these figures.

TABLE VIII

Time interval since inoculation	½–48 Hours	1–2 Months	6 Months	20 Months	Unspecified
No. of deaths	8	2	1	1	3

Aetiological Considerations

Various hypotheses to account for the complications discussed have been advanced from time to time, but each is open to objection and there is still no unanimity of opinion. Among the suggested causes are the following.

1. *A Sensitization Phenomenon.*—Miller and Stanton (1954) considered that "most neurological illnesses which follow prophylactic inoculation are manifestations of hypersensitivity," and Brody (1947) favoured a sensitization phenomenon as an explanation in the two cases reported by him, pointing out that both had a family history of allergic disturbances. However, allergy was recorded in only two other instances in the reviewed cases: the father of twins reported by Werne and Garrow (1946) as having died within 20 hours of a second diphtheria–pertussis inoculation had had two episodes of angioneurotic oedema of the lip; and one of Köng's (1953) cases had a personal and family history of asthma and eczema. An antigen-antibody response to previous specific sensitization has been suggested as a possible cause, but this is difficult to reconcile with the relatively large number of children who developed neurological sequelae following a first inoculation. It could well account, however, for some of the other cases—for instance, those of Werne and Garrow (1946), where necropsies "disclosed lesions consistent with death in anaphylactic shock."

2. *A Specific Toxin or Toxins Produced by H. Pertussis.*—Toxins have been isolated from *H. pertussis* cultures (Byers and Moll, 1948); and Miller (1951), who favours this view of the aetiology, points out that they are known to be neurotropic in experimental animals. However, Byers and Moll (1948) have raised the serious objection that as these toxins are unstable they can hardly survive in properly aged vaccines.

3. *Some Constitutional Predisposition in Affected Children.*—The sex ratio in Byers and Moll's series has been thought to suggest this possibility (*British Medical Journal*, 1950), but it is difficult to know what is meant by the term "constitutional predisposition." Certainly a large proportion of the patients reviewed were regarded as normal in all respects prior to their inoculations.

4. *Pyrogens Contaminating Vaccines.*—While this hypothesis has sometimes been postulated, there appears to be no definite evidence in favour of it.

5. *Accidental Intravenous Injection of Vaccine.*—As Faber and Miller (1948) have pointed out, this could be a factor only in reactions occurring almost immediately after injection. In the reviewed cases, reactions within half an hour were reported only six times.

Contraindications to Immunization

Though complications following pertussis immunization may be serious and even fatal, they are extremely rare, and it is generally conceded that such immunization is undoubtedly worth while. It is well known that whooping-cough itself may produce serious complications, neurological and others, and the opinion of Brody and Sorley (1947) that "the risks of not immunizing against whooping-cough are vastly greater than the risks of immunizing" probably reflects the general view. Byers and Moll (1948) found that, in the same 10-year period during which their 15 cases of pertussis vaccine encephalopathy were admitted to the Boston Children's Hospital, 26 children suffering from the effects of encephalopathy complicating pertussis itself were admitted to the same hospital. Of these 26 children seven died during their acute illness, six had mental retardation, three had chronic convulsions, and one had cerebral palsy.

Opinions differ, however, on what constitute the contraindications to immunization. Some have regarded a personal or family history of convulsions or other neurological disorders as a definite contraindication (for instance, Cockburn, 1951; Tudor, 1951; Escardo and Vazquez, 1950; Köng, 1953; Sutherland, 1953). Others, while tending towards this viewpoint, have been less emphatic. Both Toomey (1949) and Grace (1950), for example, suggest a decreased dosage in these circumstances. As analysis of the reviewed data does not indicate any tendency for reactions to be associated particularly with larger doses, decreased dosage would not seem helpful, besides creating the problem of possible inadequate immunity. On the other hand, Melin (1953), basing his views on experience with epileptic children in Stockholm, actually recommends pertussis vaccination for children with convulsive disorders because he considers that "the risk of a seizured child contracting pertussis and eventually developing complications is more pronounced than the risk involved in the immunization procedure itself." Peterman (1953), Livingston (1953), and Byers (1953) have agreed with Melin.

The small number of reported suspect nervous systems, based on personal and family histories, in the cases reviewed would seem to bear out Livingston's (1953) doubt about children with convulsive disorders or tendencies being more likely to develop cerebral complications from pertussis immunizations than other children. The whole question depends on whether a child, in any given circumstances, both personal and environmental, is more likely to contract pertussis with serious complications therefrom than he is to develop serious sequelae from pertussis inoculation, and this is a matter not easily settled. On one point, however, there appears to be no room for controversy, and this is that *any* suggestion of a neurological reaction to a pertussis inoculation should be an *absolute* contraindication to further inoculation. This is forcefully illustrated by the fact that of the seven patients who had neurological sequelae after more than one injection two died and four were left with grave complications.

Allergy is sometimes considered a contraindication to inoculation. Köng (1953) lists allergic diseases among his contraindications, and Miller (1951) considers fractional doses advisable in asthmatic children. Halpern and Halpern (1955) feel that it may be advisable to administer smaller doses more frequently in older, highly allergic children. The few cases among those reviewed where a personal or family history of allergy was reported suggest that it is perhaps over-cautious to consider this as a contraindication.

Some authors, amongst them Miller (1951), Cockburn (1953), and Sutherland (1953), have recommended that inoculations should not be undertaken while a child is unfit or suffering from acute illness of any sort. While there appears to be no direct evidence that reactions are more likely under such circumstances, it seems a reasonable

precaution to avoid provoking a possible reaction at a time when resistance is likely to be relatively low.

Summary

A case is reported of an 8-months-old normal child who, within 24 hours of a combined diphtheria–pertussis inoculation, became pyrexial, drowsy, and hypotonic. Convulsions and evidence of mental deterioration followed rapidly. At 3 years of age convulsions still persisted and mental retardation was gross (I.Q.=23).

Review is made of 107 cases of neurological complications of pertussis inoculation reported in the literature. Males predominated; reactions occurred in all age groups in which immunizations were done, irrespective of the dosage used, and followed first or subsequent inoculations. A wide variety of vaccines, single and combined, were implicated. Past personal and family histories indicated relatively few instances of neurological or allergic abnormalities. The early onset of neurological symptoms was characteristic, with changes of consciousness and convulsions as the most striking features. Pareses or paralyses were not infrequent, and eight children died within 48 hours of inoculation. Follow-up revealed a recovery rate of about 50%, a persisting morbidity rate (physical and/or mental) of about 30%, and a mortality rate of about 15%.

The question of aetiology is considered and contra-indications are discussed. The value of pertussis immunization is emphasized, as is the grave danger of further inoculations when a previous one has produced any suggestion of a neurological reaction.

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THE NEUROLOGICAL COMPLICATIONS OF MUMPS

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The neurological complications of mumps have been recognized since the eighteenth century, and a number of reports have appeared in the European and American literature describing various forms and the frequency with which they occur. Thus in 1911 Doptor reviewed 1,700 cases of mumps and estimated that 9.8% showed meningeal symptoms. Laurence and McGavin (1948) found 60 cases in an epidemic involving 208 New Zealand Service men; and Frankland (1941), in discussing an outbreak of 234 cases, put the incidence of meningitis as high as 30%. On the other hand, Paddock (1932) and Coe (1945) found neurological involvement in only 0.15–0.5% of their series, which were less selective and covered a wider age range.

It has been suggested that differences in frequency of meningitis in various epidemics are due to variations in resistance to infection, perhaps due to racial factors or to an altered virulence of the mumps virus leading to an increased affinity for nervous tissue. It is partly accounted for by the different criteria which have been used in the diagnosis of meningitis, some authors relying on symptoms, others on symptoms and physical signs, and some on the alterations in cerebrospinal fluid. To add to the confusion, it has been repeatedly confirmed, since Lavergne's observation in 1938, that cerebrospinal pleocytosis may occur in uncomplicated cases of mumps (Finkelstein, 1938) or even in contacts showing no signs of mumps (Frankland, 1941), and that meningeal symptoms may precede parotitis by as much as ten days (Bedingfield, 1927; Frankland, 1941).

These facts led Doptor and others to the view that the mumps virus is primarily neurotropic and that involvement of the parotid glands occurs as a secondary and not invariable complication. The existence of a separate neurotropic strain of the virus has not received much support (Macrae and Campbell, 1949), and Gordon (1927) was able to produce a fatal meningo-encephalitis in a monkey by intracerebral inoculation of material from throat-washings of uncomplicated cases. No correlation has been found between the occurrence of nervous complications and the severity of parotid disease or of epididymo-orchitis (Holden, Eagles, and Stevens, 1946).

Mumps meningitis is a remarkably benign condition usually appearing within a few days of the parotid enlargement and recovering without complications in three to four days; occasionally it may precede parotitis or occur alone. The cerebrospinal fluid contains a variable number of lymphocytes (10–1,000 per c.mm.) with slight increase in protein and normal values for chloride and glucose. Mumps virus has been isolated from the spinal fluid (Henle and McDougall, 1947).

The major neurological complications are much less common (approximately 1 in 6,000) and have been