PAPERS AND ORIGINALS

Reactions after pertussis vaccine: a manufacturer's experiences and difficulties since 1964

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Summary and conclusions

Pertussis vaccines vary in quality, safety, and efficacy according to the production strains of *Bordetella pertussis*, the method of manufacture, and quality control procedures. It is therefore not justifiable to combine information on the incidence, nature, and severity of reactions after all manufacturers' pertussis vaccines as if they were a single product. Attempts were made to collect information on all suspected cases of severe reactions that occurred after administration of about 15 million doses of Wellcome pertussis vaccines in the United Kingdom and Northern Ireland from 1964 to mid-1977. Altogether six deaths, six neurological reactions with sequelae, and 17 convulsions without sequelae were reported, but some were clearly not attributable to the vaccine, while, in other cases, the available information was inadequate for assessing the role of vaccination. Neurological disorders, similar to those reported in a few children after pertussis vaccination, occur unexpectedly in apparently healthy infants at the recommended age for immunisation, so chance association between vaccination and these events can be expected in some children. The Joint Committee on Vaccination and Immunisation has made several recommendations aimed at reducing severe reactions after pertussis vaccination. These include replacing plain vaccine with aluminium-adsorbed vaccine, but there is no clear evidence that the aluminium-adsorbed vaccine produces fewer reactions than the plain.

There are difficulties enough in deciding the cause of events that occur after vaccination, since these reactions often occur naturally in children of vaccination age. The task is made even harder by the assumption that

various manufacturers' vaccines are the same and the lack of information available to manufacturers about cases in which their vaccine has been implicated. Information on vaccines administered is entered on immunisation records cards; it should be used and referred to if reactions occur.

Introduction

Vaccine manufacturers have an obligation to collect and consider information on reactions after administration of their products. To meet this obligation they rely on doctors to provide full case reports on adverse clinical events after vaccination. With pertussis vaccines there is a prevailing assumption that all manufacturers' preparations are so similar in quality, safety, and efficacy that there is no need to distinguish between them or acknowledge the possibility of differences in their effects on children. Consequently, public discussions of reactions pay little or no regard to individual manufacturer's products, whereas there may be substantial differences between them. Further difficulties arise from the fact that pertussis vaccines are routinely administered to infants at an age when serious clinical disorders of unknown cause are particularly likely to occur or become evident.

Allegations that pertussis vaccine might be causing permanent brain damage to 60 to 80 children a year, or 1 or 2 per 100 000 children, in the United Kingdom¹⁻⁶ stimulated investigation into the incidence of brain damage and other adverse reactions after Wellcome pertussis-containing vaccines. The incidence of these reactions was considered against the background of serious clinical conditions of unknown cause that occur in infants of vaccination age. Information was sought from publications, hospital discharge records, and the Committee on Safety of Medicines.

Case tracing through publications

Dick based his initial estimate of 80 permanently brain-damaged children a year on private information received on 16 cases in city A during 1956-62¹⁻⁵ and two cases in city B in 1966-7.²⁻⁶ He did not respond to requests^{7 8} for information on the cases in city A, and his

informant in city B had not seen the children's case records.⁹ Dick later referred to two patients he had personally seen in Northern Ireland, but it was suggested⁹ that these had been described in previous publications^{1,10} as having transient neurological complications after an early batch of diphtheria, tetanus, pertussis, and poliomyelitis vaccine. That vaccine had not been prepared by Wellcome, but no information was available on the source of the vaccines given to other children.

Kulenkampff *et al* reported in 1974¹¹ that about 50 children had been seen at the Hospital for Sick Children, London, from January 1961 to December 1972 because of neurological illness thought to be due to diphtheria, tetanus, and pertussis (DTP) vaccine. Although these children were seen months or years after the event, the authors claimed that they had adequate data on the time between vaccination and onset of symptoms in 36 cases. There was no indication whether Wellcome vaccines were implicated in any of the cases; none had been reported to the manufacturer and the authors did not supply information on request on the manufacturers of the vaccines, normally recorded on children's immunisation cards.

In 1977 Stewart¹² asserted that a strong relationship existed between pertussis vaccination and neurological reactions in 79 of the 160 cases he had investigated. He was able to identify Wellcome vaccine in three patients: one had had a convulsion three hours after vaccination, one had an encephalopathy already known to the manufacturer and included in table III, and the third had what appeared on further inquiry to be a mild, transient reaction.

Hospital discharge records

In October 1973 senior administrative medical officers of regional hospital boards in England and Wales were asked for information from hospital discharge records on children admitted to hospital since January 1972 for treatment after pertussis vaccination. Their records or Hospital Activity Analysis provided a varied amount of information (table I). One hospital board gave the names of three consultants who could be contacted for further information. Nevertheless, a request for information, provided Wellcome vaccine was implicated, brought no response from two and a reply from the third that the child had been given measles vaccine, not DTP.

Cases notified to the Committee on Safety of Medicines

The Wellcome Foundation reports severe reactions after vaccination to the Committee on Safety of Medicines irrespective of the extent to which Wellcome products may be implicated. Since the committee also receives reports direct from doctors, Wellcome periodically

requests information on all cases notified to the committee and receives a summary of notified cases, which gives the number and nature of reactions without any appraisal of the extent to which the vaccines may be implicated.

About 25% of the reports do not identify the manufacturer, but this information is later obtained in all cases of severe reactions. Because of the need to maintain confidentiality, clinical information provided by the committee is usually sparse and insufficient to allow the manufacturer to appraise or, in some instances, identify cases he originally notified to the committee. Nevertheless, it appears that the Wellcome Foundation had obtained some information, mainly from community physicians, on all the deaths and all but one of the severe neurological reactions that had occurred after administration of its DTP vaccines and which had been reported to the Committee on Safety of Medicines.

Summaries of deaths and severe adverse reactions reported after Wellcome pertussis-containing vaccines during 1964 to mid-1977 are given in tables II and III.

Discussion

DIFFERENCES BETWEEN MANUFACTURERS' PERTUSSIS VACCINES

It is commonly assumed that there is no need to discriminate between manufacturers' pertussis vaccines because they have closely similar effects on infants,^{2-6,11-16} but this assumption is not scientifically or clinically supportable. For example, contrary to recent generalisations on British vaccines by the Joint Committee on Vaccination and Immunisation,¹⁶ Wellcome pertussis vaccine has consistently been shown to contain agglutinin^{3,17-20}; it has met the World Health Organisation's potency requirements, even when they were higher than British requirements²¹⁻²³; and it has been found to be more protective than another manufacturer's vaccine.²⁴

There are sound reasons why differences between various manufacturers' vaccines could be expected. Production strains of *Bordetella pertussis* are selected by each manufacturer according to representation of major serotypes, growth characteristics in the culture medium of choice, toxigenicity and ease or speed of detoxification, and potential protective qualities as assessed by the mouse potency test. There is strain variation in agglutinability, growth requirements, haemagglutination, mouse toxicity, alum precipitability, and protective properties, and these characteristics are readily lost, independently of each other, on subculture.²⁵ The mouse pathogenicity of a strain seems to be

TABLE I—Details of cases obtained from regional hospital boards and Hospital Activity Analysis (HAA)

Regional hospital board	No of cases	Nature of reaction	No of days in hospital	Sequelae	Comments
A	3	Fever, screaming (1 case)	2	?	Period covered 1972, first quarter 1973
B	10	No information (2)	1, 1, 1, 2, 2, 3, 3, 4, 5, 13	?	HAA covering 75% discharges in 1972
C	2	?			
D	None	Convulsions		?	HAA covering 50% discharges in 1972 HAA covering 75% discharges in 1972; most discharges of children under 3 years were covered
E	4	Sweating, twitching attacks Convulsion	3 1	Fits again from 11th day; family history of fits	
		Severe reaction	4		
		Pyrexia, vomiting, convulsion	2		
		Fits one week later	?	Progressive; severe mental subnormality	Total 34 vaccine reactions: 18 DTP, of which 8 were regarded as serious
		?	?	Severe abnormality-hydrocephalus	
F	8 (severe)	Pyrexia	?	Improved slowly	
		Photophobic encephalopathy	?	Recovered slowly	
		Acute encephalopathy, hypersarrhythmia	?		
		Convulsion	?		
		Encephalitic convulsions	?		
		Swelling of trunk and left hand	?		
G	1	?	2		
H	? None				8 vaccine reactions (5 vaccinia, 1 measles vaccine encephalopathy, 2 unidentified vaccines)
I	? None				HAA identified 1 post-immunisation encephalitis 1971-2; vaccine not identified
J	? None (but MOHs knew of 2)	Fever and collapse	1	Recovered	HAA identified 1 post-immunisation encephalitis, 1 anaphylactic shock, and 7 other serum reactions in children under 10 years
		Major convulsion, cardiac arrest	?	Recovered	

TABLE II—Deaths and cases of persistent neurological damage reported after Wellcome pertussis-containing vaccines in 1964 to mid-1977

Case No	Year	Age (months)	Interval from vaccination to onset of reaction	Clinical summary
<i>Deaths</i>				
1	1968	3	3 days after 1st DTP	Died 3 days after vaccination; at necropsy child weighed 9 lb, had early bronchopneumonic changes; certified cause of death was pneumonia
2	1969	7	8 days after 2nd DTP	Had haematemesis and melaena, became comatose and died 2 days later; initial diagnosis of pertussis vaccine encephalopathy later changed to Reye's syndrome, the certified cause of death
3	1970	5	1 day	Pyrexial illness treated with antibiotics; sudden deterioration on 4th day; died before admission to hospital; necropsy did not show cause of death
4	1970	5	Few hours after 2nd DTP	Convulsion, admitted to hospital; had a lumbar puncture, appeared fully recovered but later found intensely cyanotic, face downwards; necropsy showed acute tracheobronchitis, adhesions between frontal lobes and base of skull; death attributed to cerebral anoxia during a convulsion after administration of triple antigen
5	1974	6	1 day	Health deteriorated; on the 10th day child had convulsions and was admitted; deterioration ended in coma and death after a few days; diagnosis of post-pertussis vaccination encephalopathy changed at necropsy to primary tuberculosis of lung with tuberculous meningitis
6	1976	10	7 days after 2nd DTP	Admitted to hospital with pyrexia, signs and symptoms of meningeal irritation; transferred after 3 days with provisional diagnosis of encephalomyelitis but died 30 days after vaccination; necropsy showed no specific changes; recorded cause of death: encephalopathy due to injection of triple vaccine
<i>Cases of persistent neurological damage</i>				
7	1971		Day after 1st DTP	Convulsions for over two months; cytomegalovirus isolated from urine; developed antibodies to virus
8	(reported 1974)		5 days	Convulsion with considerable residual brain damage
9	(reported "months" later)		3 days after 3rd DTP	Prolonged convulsion with intense cyanosis and upper respiratory tract infection and fever
10	1974			Vaccinated 3 days after discharge from hospital after treatment of pharyngeal herpetic infection; developed encephalopathy; mentally retarded
11	1975		2 days after 2nd DTP	Became lethargic and had convulsion on 4th day; admitted to hospital on 5th day with total left hemiplegia and partial paralysis of the right; became quadriplegic for 6 weeks; residual moderate left hemiplegia and mental retardation

TABLE III—Severe reactions without sequelae reported after Wellcome pertussis-containing vaccines in 1964 to mid-1977

Type of reaction:	Convulsion	Transient encephalopathy	Infantile spasms	Persistent screaming	Collapse
No of cases	17	2	1	9	2

Interval between vaccination and convulsion: up to 4 hours in 5 cases; about 24 hours in 4 cases; no information in 8 cases.

inversely correlated to its ability to yield highly protective vaccine.²⁶ Since bacterial strains lose protective antigenicity on subculture,²⁷⁻²⁸ all vaccines have to be prepared from freshly isolated strains. The antigenic profile of *Bordetella pertussis* strains varies continuously with environmental conditions of growth.²⁹ *Bordetella pertussis* is difficult to isolate, slow growing, and fastidious, but it can adapt rapidly to grow profusely on media unsuitable for primary isolation and on a large scale in media which will not support growth of small numbers of organisms.³⁰ Rapid growth of Gram-negative organisms can increase cell wall endotoxin, an important cause of toxicity in mice.³¹ Such variability in biological, immunological, pharmacological, and growth profiles has long been troublesome to vaccine manufacturers and accounts for the inclusion of up to six strains of *Bordetella pertussis* in their vaccines. For commercial manufacture, the organisms are grown either dispersed in liquid medium in large tanks or on the surface of a solid medium containing charcoal instilled in numerous glass bottles. The solid medium with charcoal is purported to absorb the bacterial toxins from the surface cultures,³² but for large-scale production it is more tedious and expensive than the tank deep culture method.³³ Wellcome pertussis vaccine has been produced on solid medium containing charcoal for the last 25 years with little variation in procedure and with only one change in production strains of *Bordetella pertussis*, which was deemed desirable to enhance the agglutinin 3 component of the vaccine.

Batch quality control testing is particularly important in

pertussis vaccine manufacture. The only obligatory specific tests for batch safety and efficacy are the opacity and mouse potency tests, but manufacturers usually apply additional in-house quality tests. Since reactogenicity of pertussis vaccine in children is related to the number of organisms injected,³⁴⁻³⁸ the World Health Organisation and the European Pharmacopoeia have set a limit of 20 000 million organisms per 0.5-ml dose.³⁹⁻⁴⁰ The number of organisms is assessed by photometric means whereby the density of bacterial suspensions is compared with that of an opacity standard. In the United States the stated maximum number of organisms per dose is 16 000 million, but the US opacity standard is denser than that of the World Health Organisation, and the actual number of killed organisms per dose is therefore nearly twice that of non-American vaccines.⁴¹ Even when a common opacity standard is used, differences in size, shape, and colour of different manufacturers' vaccines result in discrepancies in actual number of organisms per dose.⁴¹⁻⁴² The addition of aluminium hydroxide to bulk vaccine does not allow a check to be made on the number of organisms per dose in final containers. The mouse potency test⁴²⁻⁴³ correlates well with protection against whooping cough in infants,⁴⁴ but it is an expensive and protracted test with inherent peculiarities and difficulties.³⁰⁻⁴¹⁻⁴⁵ Nevertheless, contrary to commonly held assumptions,¹⁶ the potency of released batches of Wellcome pertussis vaccines has consistently exceeded 4 International Potency Units per dose and thereby met World Health Organisation requirements, even when British potency requirements were only 2.1 units per dose.²¹⁻²³ The mouse weight test for abnormal toxicity, purported to reflect reactogenicity in infants,⁴⁶⁻⁴⁹ and obligatory in the United States, is used for batch testing by most manufacturers, but it is subject to vagaries,⁴¹ is not internationally standardised, and can provide conflicting results according to whether readings are taken after 24 hours or seven days.³⁸ In practice, each manufacturer standardises and applies his own mouse weight test.

The eventual quality, safety, and efficacy of a pertussis vaccine depend on the manufacturer's choice of production strains of *Bordetella pertussis*, on production technology, and on

application of meaningful quality control tests. Nevertheless, the variability in manufacture of vaccines from manufacturer to manufacturer is usually not appreciated.⁵⁰ For example, Preston¹⁷ found that all five production strains of *Bordetella pertussis* used by one manufacturer were devoid of agglutinin 3 and four of the five were low in agglutinogens 1 and 2. This vaccine was later reported to give poor protection in infants^{51 52} and was said to account for "much of the pertussis vaccine" used in Britain.⁵² From this statement it was deduced¹⁶ that most if not all other manufacturers' vaccines were similarly poorly immunogenic, even though Preston reported that all their vaccine strains had adequate amounts of agglutinogens 1 and 2 and that one of the three strains used in the production of Wellcome pertussis vaccine had an adequate amount of agglutinin 3.

DIFFICULTIES IN OBTAINING ADVERSE REACTION REPORTS

Published reports on severe neurological damage after pertussis vaccination are noted for sparseness of clinical information and absence of reference to the origin of the vaccines.^{1-3 11 12} This is difficult to understand, since the name of the manufacturer and the vaccine batch number are usually recorded on vaccination record cards. Published reports on the high incidence of severe non-neurological reactions—shock, collapse, extreme pallor, persistent screaming—were mainly related to quadruple vaccines^{34 53} with a liquid-culture pertussis component at about the time when quadruple vaccines in the United States were also causing problems due to instability of the pertussis components.⁵⁴⁻⁵⁷

The regional health authorities and the Committee on Safety of Medicines hold or receive case reports on serious clinical events occurring soon after administration of pertussis-containing vaccines, while manufacturers are expected to provide the medical profession with information on the incidence, nature, and severity of adverse reactions associated with administration of their particular products. But manufacturers do not have access to those case reports and may be denied an opportunity of investigating the cases. Resources available to the Committee on Safety of Medicines for investigating these cases may be limited and manufacturers have no means of assessing the interest and experience of the committee's investigators. But were the Health Boards or the Committee on Safety of Medicines to forward copies of case reports to manufacturers it might be regarded as a breach of confidence. Manufacturers in some other countries have access to patient records in cases of severe adverse reactions and can undertake their own investigations.⁵⁸⁻⁶⁰ In the United Kingdom there seems to be a multiplicity of expert committees, officially appointed to investigate various aspects of reactions after pertussis immunisation, but manufacturers are not informed of the number of such committees, their composition, terms of reference, activities, or progress made by them in their investigations.

NEUROLOGICAL REACTIONS

About 18 million doses of Wellcome pertussis-containing vaccines were distributed in the United Kingdom and Northern Ireland from 1964 to 1977, and about 15 million of those doses were probably given to infants. During that period eight reports of neurological reactions with sequelae, including two deaths, and 17 of convulsions without sequelae were received, giving a combined incidence of 1.7 reports of neurological reactions per million doses used. That incidence is lower than that of various neurological disorders after smallpox vaccination in infants under 1 year of age, which is estimated to be 15.8 per million in 1951-7 in the United Kingdom⁶¹ and 2.9 per million in the United States in 1968.⁶² The incidence of 1.7 reports per million used doses of pertussis vaccine refers to unappraised cases, and it is

noteworthy that some reactions originally attributed to pertussis vaccination were, on further investigation such as necropsy, found to be due to other factors. During 1964-76 about 35 million doses of pertussis-containing vaccines were used in this country, and, according to the Joint Committee on Vaccination and Immunisation,³⁴ the Committee on Safety of Medicines received during that time 32 reports of illnesses described as encephalopathies and 142 reports of convulsions, but it is not clear whether spurious association with vaccination had been considered.

The first report of serious reactions after administration of a pertussis vaccine did not appear until 1933,⁶³ although workers in many countries had administered various preparations of killed *Bordetella pertussis* to some thousands of children during the previous 20 years, and whooping cough vaccines had been on the list of new and non-official remedies in the USA from 1914 to 1928.⁶⁴ Since then there have been sporadic reports on series of infants with serious neurological disorders arising soon after pertussis vaccination.^{1-3 11 13 65-74} Pertussis vaccines from eight different manufacturers were implicated in the series of Byers and Moll⁶⁶ and from six manufacturers in Toomey's series.⁶⁷ After the Medical Research Council trials Cockburn concluded that neurological reactions could occur after any injection of any batch of any pertussis vaccine.⁷⁵

Published reports on neurological disorders arising after pertussis vaccination have been devoid of clinical information¹⁻⁵ and lacked perspective on incidence,¹¹ for which they have been criticised,⁷⁶ or have omitted relevant clinical information^{72 73} that could have absolved the vaccines.^{77 78} Some severe neurological conditions, which on clinical and temporal grounds seemed to be due to pertussis vaccination, were shown on further investigation to be due to innate factors.^{79 80}

Neurological disorders reported after pertussis vaccination do not conform with any consistent pattern but tend to represent the spectrum of neurological conditions that develop spontaneously among unvaccinated infants. Immunisation schedules require at least three doses of pertussis vaccine to be given to infants when they are between 3 and 18 months of age—a period when first convulsions are not uncommon in the previously healthy. Some 5% of children have a convulsion by the age of 5 years^{81 82}; 2 to 4% have a febrile convulsion⁸²⁻⁸⁵ more commonly between the ages of 6 and 24 months⁸³ and most prolonged between 9 and 15 months. Griffith⁸ estimated that the incidence of first convulsions in children aged 6 to 18 months was between 1 and 3 per 100 000 children per day, basing his estimate on the results of a survey by general practitioners⁸⁶ and from surveillance of unvaccinated controls in the pertussis vaccine trials of the 1950s⁴⁴ and in the measles vaccines trials of the 1960s.⁸⁷ Epilepsy follows a febrile convulsion in about 2% of the children,⁸³ the risk of sequelae depending on the duration of the fit.⁸¹ After administration of some 15 million doses of Wellcome vaccine, the expected number of first convulsions occurring by chance within 24 hours of any of the three injections was about 250, with 5 to 10 cases of permanent brain damage. The fact that only 25 cases of neurological reactions, with or without sequelae, were reported may have been due partly to administration of some doses of vaccine to children under 6 months of age, who have a lower background incidence of first convulsions; partly to precautions taken not to vaccinate children not in good health; and partly to some degree of under-reporting. The results of a recent epidemiological survey in the Oxford area confirmed the view that febrile convulsions are uncommon after pertussis vaccination.⁸⁵

In the Medical Research Council's whooping cough vaccines trials 56 000 doses were administered and 15 children were reported to have had convulsions during the ensuing 28 days, six during the first 72 hours. The incidence of convulsions during the first three days was therefore about 4 per 100 000 children per day, somewhat higher than the background incidence. Fever commonly occurs during the first 12 hours after vaccination, and although it may not exceed that recorded after smallpox vaccination,⁸⁸ it might be sufficient to affect infants with a

particularly low threshold for febrile convulsions, irrespective of the cause of the fever. Pollock was recently reported to have encountered six cases of convulsions, five during the first 24 hours, after administration of 80 000 doses of an undisclosed DTP preparation, whereas no convulsions occurred after 73 000 doses of a diphtheria-tetanus vaccine.⁸⁹ Brody and Sorley⁹⁰ described a child who was vaccinated, possibly during an attack of whooping cough, and had a mild encephalitis a fortnight later. Three further doses of pertussis vaccine were given, each followed by progressively more severe exacerbations of the encephalitis, but an encephalitic episode also occurred unrelated to vaccination. It is also noteworthy that twins feature in several reports of neurological reactions after pertussis vaccination.^{10 11 91-94}

No significant progress seems to have been made in unravelling the problem since an annotation on encephalopathy and pertussis vaccination was published in 1950.⁹⁵ It stated that 4 to 7% of apparently normal children have a convulsion, mostly associated with pyrexial illnesses, before they are 5 years old, that 5 to 10% of these convulsions are followed by epilepsy in later life, and that violent and local convulsions often leave cerebral sequelae, especially if the child is aged under 12 months. The annotation stated that the most puzzling are those encephalopathies encountered after prophylactic inoculations, which sometimes occur by chance, since there is at least one case of a child having a severe convulsion a quarter of an hour before a dose of vaccine was to have been given.

INFANTILE SPASMS

Infantile spasms have been reported after smallpox and poliomyelitis vaccines⁷¹ as well as after pertussis-containing vaccines.^{69 71 96} An association between vaccination and onset of infantile spasms was noted in Danish children,⁹⁷ but subsequent epidemiological investigation showed that the association was entirely fortuitous,^{98 99} a finding which has recently been confirmed in Japan.¹⁰⁰

SHOCK, COLLAPSE, EXTREME PALLOR, PERSISTENT SCREAMING

Shock, collapse, extreme pallor, and persistent screaming are alarming reactions that have periodically been reported after administration of pertussis-containing vaccines.^{34 53 58 59 74 101 102} They are probably attributable to vaccination since they usually occur two to 12 hours later and are otherwise rare in well children, and observers give consistent accounts of these types of reactions. Incidence can vary considerably according to vaccine manufacture and storage; it may be unrelated to the incidence of neurological reactions after the same pertussis vaccine. The quadruple vaccines used by Dick *et al*³⁴ and Hannik⁵⁸ caused an alarming number of such reactions, but some manufacturers' DTP preparations have also been reported to give such reactions.^{34 53} Nevertheless, only nine cases of persistent screaming and two of shock or collapse were reported after Wellcome pertussis vaccine from 1964 to mid-1977, but some of these reactions may have been disregarded or missed.¹⁰³ They may be due to sensitivity to free endotoxin, the amount of which may depend on choice of vaccine strains of *Bordetella pertussis*; methods of culture; inactivation or stabilisation; or, more commonly than is realised, inappropriate storage conditions for the vaccine. The possibility of unintended intravenous inoculation cannot be discounted.

RECOMMENDATIONS OF THE JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

The Joint Committee on Vaccination and Immunisation has issued revised recommendations on the use of pertussis vaccine in the United Kingdom, with the aim of reducing post-

vaccination reactions.^{13 16 104 105} The joint committee emphasised contraindications to the use of pertussis vaccines, recommended aluminium-adsorbed vaccines in place of plain, and revised immunisation schedules.

Those responsible for vaccination are asked to pay scrupulous attention to contraindications to pertussis vaccine, which include personal or family history of seizures, convulsions, or cerebral irritation in the neonatal period, neurological defects, or a family history of epilepsy or other diseases of the central nervous system.^{13 16 106} These are longstanding contraindications, initially introduced on the empirical grounds that children with suspected neurological deficit were particularly susceptible to any encephalopathogenic factor that may be present in pertussis vaccines. They are not universally accepted contraindications,¹⁰⁷⁻¹¹² and they do not appear in recommendations of the American Public Health Advisory Committee on Immunisation Practice¹¹³ or the report of the Committee on Infectious Diseases of the American Academy of Pediatrics.¹¹⁴ Cockburn¹¹⁵ remarked on the absence of evidence supporting these contraindications, Illingworth¹¹⁰ found no reason for adhering to them, and Livingston¹⁰⁷ vaccinated thousands of children with seizure disorders or brain damage without encountering more reactions than expected in a normal infant population. It is generally held, however, that a neurological reaction after a pertussis-containing vaccine is a contraindication to further administration of a pertussis vaccine.

The joint committee's statement^{13 106} that aluminium-adsorbed pertussis vaccines produce fewer systemic reactions than plain vaccines is based on assessment of minor systemic reactions in children.^{38 116-119} Dick¹²⁰ has pointed out that there is no good evidence of a lower incidence of serious reactions after adsorbed vaccines, and in Sweden the replacement of adsorbed by plain vaccine in 1967 coincided with the cessation of adverse reaction reports relating to pertussis vaccine.¹²¹ Aluminium-adsorbed pertussis vaccine should be injected intramuscularly¹²² or deep subcutaneously¹²³ to reduce the risk of persistent injection site nodule or abscess.

The Department of Health and Social Security published a report by the Standing Medical Advisory Committee in 1968¹⁰⁴ advising that the first dose of DTP vaccine be delayed until the age of 6 months, when fewer severe reactions to the pertussis component could be expected. In 1977 health authorities and general practitioners were informed that the first dose of triple vaccine should be given at the third month of life. The main reasons given for earlier vaccination were the need to protect very young infants, who are particularly vulnerable to whooping cough, and the reduced risk of febrile convulsions in those under 6 months of age. While the recommendation that immunisation should start at the third month is supportable, it should be appreciated that the incidence of sudden, unexplained death or "cot death" is between 2.5 and 3.0 per 1000 live births,¹²⁴⁻¹²⁷ and, according to data from the Oxford area in 1966-70, 50% of these deaths occur during the first three months of life and 25% during the second. The risk of sudden, unexplained death occurring fortuitously within 24 hours of administration of any vaccine, whether diphtheria-tetanus, pertussis, or a bacterial meningitis vaccine, at 3 months of age is in the region of 0.5 per 100 000 doses administered.

DIFFICULTIES ENCOUNTERED BY MANUFACTURERS

It is rarely appreciated, even by those with special interest in the safety and efficacy of pertussis vaccination, that various manufacturers' products may differ substantially. Consequently, allegations may be made against pertussis vaccines in general without providing opportunities for manufacturers to examine and appraise any data that may relate to their own particular products. It should be emphasised that information on administered vaccines must be entered in the infants' vaccination records, must remain retrievable for many years, and must be referred to in all reports relating to those vaccinations. Serious

clinical events in recently vaccinated infants should be reported without delay to the Committee on Safety of Medicines and, whenever possible, to the manufacturers so that they can participate early in discussions and investigations; otherwise they may be left to learn of the event only through a summary statement months or years later.

The various expert committees appointed to investigate or advise on the use of pertussis vaccines rarely communicate or consult with manufacturers, possibly because they believe that the manufacturers do not have unique knowledge, experience, or investigative capacity relevant to the committees' activities. In few other fields of high technology production is advice issued to all potential users of a product without prior consultation with the manufacturers.

Perhaps the greatest difficulty encountered by manufacturers of pertussis vaccine results from the administration of their products on three separate occasions to 70 or 80% of all apparently healthy infants, a significant proportion of whom are likely at that age to have a sudden, unexpected, and serious disorder of unknown cause. Should that tragedy occur within a short period of vaccination, how is it to be decided whether it was chance or a vaccine-provoked phenomenon?

References

- 1 Dick, G W A, *International Symposium on Combined Vaccines*. Basle, Karger, 1967.
- 2 Dick, G W A, *Proceedings of the International Conference on the Application of Vaccines against Viral, Rickettsial and Bacterial Disease of Man*, p 418. Washington, DC, Pan American Health Organisation, 1971.
- 3 Dick, G, *Community Medicine*, 1972, **127**, 73.
- 4 Dick, G W A, *Proceedings of the Royal Society of Medicine*, 1974, **67**, 371.
- 5 Dick, G, *Update*, 1974, **9**, 39.
- 6 Dick, G, *British Medical Journal*, 1975, **4**, 161.
- 7 Griffith, A H, *Community Medicine*, 1972, **127**, 77.
- 8 Griffith, A H, *Proceedings of the Royal Society of Medicine*, 1974, **67**, 16.
- 9 Griffith, A H, *British Medical Journal*, 1975, **4**, 347.
- 10 Dick, G, *Canadian Journal of Public Health*, 1966, **57**, 435.
- 11 Kulenkampff, M, Schwartzman, J S, and Wilson, J, *Archives of Disease in Childhood*, 1974, **49**, 46.
- 12 Stewart, G T, *Lancet*, 1977, **1**, 234.
- 13 Joint Committee on Vaccination and Immunisation of the Central Health Services Council and the Scottish Health Service Planning Council, *British Medical Journal*, 1975, **3**, 687.
- 14 Miller, C L, Pollock, T M, and Clewer, A D E, *Lancet*, 1974, **2**, 773.
- 15 Noah, N D, *British Medical Journal*, 1976, **1**, 128.
- 16 Joint Committee on Vaccination and Immunisation of the Central Health Services Council and the Scottish Health Service Planning Council. *Review of the Evidence on Whooping Cough Vaccination*. London, HMSO, 1977.
- 17 Preston, N W, *British Medical Journal*, 1965, **2**, 11.
- 18 Preston, N W, *British Medical Journal*, 1965, **2**, 1001.
- 19 Preston, N W, *British Medical Journal*, 1973, **2**, 485.
- 20 Abbott, J D, Preston, N W, and MacKay, R I, *British Medical Journal*, 1971, **1**, 86.
- 21 Perkins, F T, *British Medical Journal*, 1969, **4**, 429.
- 22 Griffith, A H, *British Medical Journal*, 1969, **4**, 689.
- 23 Griffith, A H, *Public Health*, 1972, **87**, 17.
- 24 Public Health Laboratory Service Whooping Cough Committee and Working Party, *British Medical Journal*, 1973, **1**, 259.
- 25 Standfast, A F B, *Journal of General Microbiology*, 1951, **5**, 531.
- 26 Cameron, J, *Journal of Pathology and Bacteriology*, 1967, **94**, 367.
- 27 Leslie, P H, and Gardner, A D, *Journal of Hygiene*, 1931, **31**, 423.
- 28 Kendrick, P L, Updyke, E L, and Eldering, G, *American Journal of Public Health*, 1949, **39**, 179.
- 29 Lacey, B W, *Journal of Hygiene*, 1960, **58**, 57.
- 30 Parker, C, *Advances in Applied Microbiology*, 1976, **20**, 27.
- 31 Pearson, A D, and Ellwood, D C, *Journal of Medical Microbiology*, 1974, **7**, 391.
- 32 Cohen, S M, and Wheeler, M W, *American Journal of Public Health*, 1946, **36**, 371.
- 33 Anderson, G R, *Advances in Applied Microbiology*, 1976, **20**, 43.
- 34 Haire, M, Dane, D S, and Dick, G, *Medical Officer*, 1967, **117**, 55.
- 35 McFarlan, A M, Topley, E, and Fisher, M, *British Medical Journal*, 1945, **2**, 205.
- 36 Bousfield, G, *Medical Officer*, 1952, **87**, 265.
- 37 Perkins, F, *Medical Officer*, 1967, **117**, 97.
- 38 Butler, N R, et al, *British Medical Journal*, 1969, **1**, 663.
- 39 World Health Organisation Expert Committee on Biological Standardisation, *16th Report*, p 25. Technical Report Series No 274. Geneva, WHO, 1964.
- 40 *European Pharmacopoeia*, 1971, **2**, 409.
- 41 Cameron, J, *Advances in Applied Microbiology*, 1976, **20**, 57.
- 42 Kendrick, P L, et al, *American Journal of Public Health*, 1947, **37**, 803.
- 43 Pittman, M, *Journal of Pediatrics*, 1954, **46**, 57.
- 44 Medical Research Council, *British Medical Journal*, 1959, **1**, 994.
- 45 Muggleton, P, *Public Health*, 1967, **81**, 252.
- 46 Pittman, M, and Cox, C, *Applied Microbiology*, 1965, **13**, 447.
- 47 Perkins, F, et al, *Symposia Series in Immunobiological Standardisation*, 1970, **13**, 141.
- 48 Hilton, M, and Burland, W, *Symposia Series in Immunobiological Standardisation*, 1970, **13**, 150.
- 49 Barnes, J, and Hilton, M, *Symposia Series in Immunobiological Standardisation*, 1970, **13**, 180.
- 50 Manclark, C R, *Advances in Applied Microbiology*, 1976, **20**, 1.
- 51 Bury, H S, *Medical Officer*, 1966, **115**, 187.
- 52 Public Health Laboratory Service Whooping Cough Committee and Working Party, *British Medical Journal*, 1969, **4**, 329.
- 53 Hopper, J M H, *Medical Officer*, 1961, **106**, 241.
- 54 *New England Journal of Medicine*, 1960, **263**, 656.
- 55 *New England Journal of Medicine*, 1961, **264**, 1214.
- 56 Pittman, M, *Journal of the American Medical Association*, 1962, **181**, 25.
- 57 Edsall, G, et al, *New England Journal of Medicine*, 1962, **267**, 687.
- 58 Hannik, C A, *Symposia Series in Immunobiological Standardisation*, 1970, **13**, 161.
- 59 Christensen, P E, *Ugeskrift for Laeger*, 1969, **131**, 741.
- 60 Galazka, A, and Andrzejczak-Kardymowicz, B, *Epidemiological Review*, 1972, **26**, 411.
- 61 Wynne-Griffith, G, in *Proceedings of a Symposium on Immunisation in Childhood*. Edinburgh, Livingstone, 1960.
- 62 Lane, J M, et al, *New England Journal of Medicine*, 1969, **281**, 1201.
- 63 Madsen, T, *Journal of the American Medical Association*, 1933, **101**, 187.
- 64 Felton, H M, and Willard, C Y, *Journal of the American Medical Association*, 1944, **126**, 294.
- 65 Doull, J A, Shibley, G S, and McClelland, J E, *American Journal of Public Health*, 1936, **26**, 1097.
- 66 Byers, R K, and Moll, F C, *Pediatrics*, 1948, **1**, 437.
- 67 Toomey, J A, *Journal of the American Medical Association*, 1949, **139**, 448.
- 68 Globus, J H, and Kohn, J L, *Journal of the American Medical Association*, 1949, **141**, 507.
- 69 Baird, H W, and Borofsky, L G, *Journal of Pediatrics*, 1957, **50**, 332.
- 70 Berg, J M, *British Medical Journal*, 1958, **2**, 24.
- 71 Bower, B D, and Jeavons, P M, *British Medical Journal*, 1960, **2**, 1453.
- 72 Strøm, J, *British Medical Journal*, 1960, **2**, 1184.
- 73 Strøm, J, *British Medical Journal*, 1967, **4**, 320.
- 74 Forrester, R M, *British Medical Journal*, 1965, **2**, 232.
- 75 Cockburn, W C, *British Medical Journal*, 1959, **1**, 1343.
- 76 Premsky, A L, *Developmental Medicine and Child Neurology*, 1974, **16**, 539.
- 77 Malmgren, B, Valquist, B, and Zetterstrom, R, *British Medical Journal*, 1960, **2**, 1800.
- 78 Langercrantz, R, *Symposia Series in Immunobiological Standardisation*, 1970, **13**, 168.
- 79 Ounsted, C, *Lancet*, 1977, **1**, 419.
- 80 Stephenson, J B P, *Lancet*, 1977, **1**, 357.
- 81 Ounsted, C, in *Recent Advances in Paediatrics*, 4th edn, ed D Gairdner and D Hull, p 363. London, Churchill, 1971.
- 82 Ross, E M, *Proceedings of the Royal Society of Medicine*, 1973, **66**, 703.
- 83 Nelson, K B, and Ellenberg, J H, *New England Journal of Medicine*, 1976, **295**, 1029.
- 84 Van Den Berg, B J, and Yerushalmy, J, *Pediatric Research*, 1969, **3**, 298.
- 85 Harker, P, *British Medical Journal*, 1977, **2**, 490.
- 86 College of General Practitioners, *British Medical Journal*, 1960, **2**, 416.
- 87 Medical Research Council, *British Medical Journal*, 1966, **1**, 441.
- 88 Ruuskanen, O, et al, paper presented at Scottish-Scandinavian Conference on Infectious Diseases, Uppsala, June 1977.
- 89 *Lancet*, 1977, **2**, 50.
- 90 Brody, M, and Sorley, R G, *New York State Journal of Medicine*, 1947, **47**, 1016.
- 91 Werne, J, and Garrow, I, *Journal of the American Medical Association*, 1946, **131**, 730.
- 92 *British Medical Journal*, 1949, **2**, 1478.
- 93 Miller, H G, and Stanton, J B, *Quarterly Journal of Medicine*, 1954, **23**, 1.
- 94 Anderson, I M, and Morris, D, *Lancet*, 1950, **1**, 537.
- 95 *Lancet*, 1950, **1**, 630.
- 96 Gordon, N, *Neuropädiatrie*, 1970, **2**, 119.
- 97 Melchior, J C, *Ugeskrift for Laeger*, 1969, **131**, 746.
- 98 Melchior, J C, *Neuropädiatrie*, 1971, **3**, 3.
- 99 Melchior, J C, *Archives of Disease in Childhood*, 1977, **22**, 134.
- 100 Fukuyama, Y, Tomori, N, and Sugitate, M, *Neuropädiatrie*, 1977, **8**, 224.
- 101 Parish, H J, *Bacterial and Virus Diseases. Antisera, Toxoids, Vaccines and Tuberculin in Prophylaxis and Treatment*, 2nd edn. Edinburgh, Livingstone, 1951.
- 102 Laurent, L J M, *British Medical Journal*, 1959, **1**, 1343.
- 103 Baines, J H E, *British Medical Journal*, 1965, **2**, 592.
- 104 Standing Medical Advisory Committee for the Central Health Services Council and the Secretary of State for Social Services, *Immunisation against Infectious Disease*, p 3. London, HMSO, 1968.
- 105 Chief Medical Officer, Department of Health and Social Security, Letter 17/74 to General Practitioners and Regional and Area Health Officers, 11 June 1974.
- 106 Chief Medical Officer, Department of Health and Social Security, Letter CMO(77)7CNO(77)3 to General Practitioners and Area Medical and Nursing Officers, 31 March 1977.

- ¹⁰⁷ Livingston, S, in *Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence*, p 159. Springfield, Illinois, Charles L Thomas, 1972.
- ¹⁰⁸ Melin, J, *Journal of Pediatrics*, 1953, **43**, 652.
- ¹⁰⁹ Veeder, B S, *Journal of Pediatrics*, 1953, **43**, 746.
- ¹¹⁰ Illingworth, R S, *British Medical Journal*, 1965, **1**, 1124.
- ¹¹¹ Stephenson, J B P, *British Medical Journal*, 1977, **3**, 261.
- ¹¹² Krugman, S, *Journal of the American Medical Association*, 1977, **237**, 2228.
- ¹¹³ Public Health Service Advisory Committee on Immunisation Practices, *Morbidity and Mortality Weekly Reports*, 1972, **21**, 4.
- ¹¹⁴ American Academy of Pediatrics, *Report of the Committee on Infectious Disease*, 7th edn. Evanston, Illinois, AAC, 1974.
- ¹¹⁵ Cockburn, W C, *Bulletin of the World Health Organisation*, 1958, **19**, 109.
- ¹¹⁶ Burland, W, *et al*, *Medical Officer*, 1968, **119**, 17.
- ¹¹⁷ Griffith, A H, *Medical Officer*, 1970, **123**, 97.
- ¹¹⁸ Rodgers, J, *Medical Officer*, 1970, **123**, 153.

- ¹¹⁹ Williams, R M, *Medical Officer*, 1969, **122**, 274.
- ¹²⁰ Dick, G, *Lancet*, 1976, **2**, 1239.
- ¹²¹ Tiru, M, *WHO Informal Consultation on Immunisation against Whooping Cough*. Utrecht, December 1974.
- ¹²² Sauer, L W, and Tucker, W H, *American Journal of Public Health*, 1954, **44**, 784.
- ¹²³ Snell, E S, and Burland, W L, *Medical Officer*, 1970, **123**, 36.
- ¹²⁴ Fedrick, J, *British Journal of Preventive and Social Medicine*, 1973, **27**, 217.
- ¹²⁵ Froggatt, P, Lynas, M A, and MacKenzie, G, *British Journal of Preventive and Social Medicine*, 1971, **25**, 119.
- ¹²⁶ Peterson, D R, *American Journal of Epidemiology*, 1966, **84**, 478.
- ¹²⁷ Richards, I D G, and McIntosh, H T, *Archives of Disease in Childhood*, 1972, **47**, 697.

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SIDE EFFECTS OF DRUGS

Severe lithium toxicity with "normal" serum concentrations

The severity of intoxication from lithium treatment has been thought to vary with the serum concentrations. Thus anorexia, diarrhoea, vomiting, loss of weight, and tremor are common findings when concentrations exceed 1.5 mmol(mEq)/l; and generalised coarse tremor, hypertonia, and hyperactive reflexes, epileptiform seizures, and coma have been described in patients with concentrations exceeding 4 mmol/l.¹ We, however, report a case of severe central nervous system (CNS) toxicity that went unrecognised for many weeks because the serum concentrations of lithium were in the normal therapeutic range.

Case report

A 26-year-old gardener had a 10-year history of admissions for manic depressive psychosis. He required considerable supervision in his work and was a shy, dependent, immature man with difficulties in social skills. For four years he had been taking 100 mg phenytoin sodium and 30 mg phenobarbitone three times a day after several episodes of loss of consciousness. He continued with this treatment throughout. Electroencephalography (EEG) showed 4-6 cps theta rhythm with occasional left-sided emphasis, especially in the frontal area.

In September 1973 he was admitted to hospital with hypomania and stabilised with lithium carbonate (Priadel) 1200 mg by mouth daily. Morning serum concentrations were initially in the therapeutic range but then began to fall, though the dosage remained constant (table). Over the next few months stepped increases in dosage to 2400 mg daily produced only a moderate response in serum concentrations.

He was readmitted on 19 June 1974 with a further hypomanic episode. During the previous two months he had developed a coarse regular tremor, mainly in the legs. He looked generally unwell and had been losing weight. His appetite was poor but he did not have diarrhoea, abdominal pain, nausea, or polyuria. On 2 July his serum lithium concentration was 1.2 mmol/l (table), but in view of his clinical state the dosage was reduced to 2000 mg daily. Physical examination showed no other abnormality and all routine blood test results were normal. Within three weeks his hypomanic state had resolved; he was continuing with 2000 mg daily and his serum

concentration was 0.8 mmol/l. By this time the tremor had become very coarse and was affecting his whole body. On 26 July the lithium was stopped but he continued to deteriorate; he became restless, shaking all over and sweating profusely. Muscle tone became hypertonic and reflexes hyperactive. One week after the lithium was stopped he became drowsy and drifted into coma. He was deeply unconscious and unresponsive to painful stimuli for five hours.

During the coma he was given only intravenous fluids. Results of investigations were: plasma sodium 139 mmol(mEq)/l, potassium 3.8 mmol/l, bicarbonate 30 mmol/l, urea 4.6 mmol/l (28 mg/100 ml), and protein 66 g/l; packed cell volume 0.41 (41%); white cell count 9×10^9 /l (9000/mm³), normal differential; erythrocyte sedimentation rate 1 mm in first hour; midstream specimen of urine, no pathogens; EEG, 4-6 cps theta activity with proximal bursts of 1-2 cps throughout and no focal features; chest radiograph normal.

Two days later he was up and about. Tremor was still pronounced, however, though less coarse. He made steady progress and was followed up regularly as an outpatient. Phenytoin sodium 100 mg and phenobarbitone 30 mg three times daily were continued but he was not given lithium. The fine tremor took about six months to disappear, and two years after the episode he was well and had needed no further admissions.

Discussion

This patient had a history suggestive of chronic brain damage or epilepsy or both and was taking phenytoin sodium. The case raises several questions.

(1) Why was there a gradual fall in the serum lithium concentrations despite steady dosage after treatment was first begun? Eventually the patient's requirements for lithium doubled, though his serum concentration remained in the therapeutic range (see table).

(2) Why did his serum lithium concentration not correlate with the degree of clinical toxicity?

(3) Is there any interaction between lithium carbonate and phenytoin sodium that could account for the severe CNS toxic reaction despite a normal blood concentration?

The patient's parents were confident that he had been taking the lithium tablets while being treated as an outpatient; during the last month, when he was an inpatient, this was supervised. Lithium was estimated with a standard flame photometer to within 0.1 mmol/l. There is no reason to believe that this was inaccurate.

Lithium is usually measured in serum with the assumption that dynamic equilibrium is established between tissues and blood stream. Red blood cells (RBC), however, concentrate lithium and there may be important interindividual differences in RBC:plasma ratios. These differences are partly genetic² but may be related to depression³ and manic depressive psychosis.⁴ The RBC:plasma ratio in any one individual appears to be stable over time.⁵ An important factor in lithium toxicity in some patients may be the RBC lithium concentration or the ratio of this to the plasma lithium concentration. It would be well if these determinations could be made in patients with toxic symptoms in the absence of high serum lithium concentrations.

Another explanation is suggested by the work of Graham-Smith and Green,^{6,7} who investigated CNS hydroxytryptamine function in rats. They found that lithium and phenytoin sodium have several similar pharmacological properties. In a series of controlled investigations they observed that hyperactivity was significantly enhanced when a

Dosage and serum concentrations of lithium from time of first admission with hypomania

Date (1973)	Dose (mg/day)	Serum lithium concentrations mmol(mEq)/l	Date (1974)	Dose (mg/day)	Serum lithium concentrations mmol(mEq)/l
24 Sept	1200	1.2	4 Jan	2000	0.9
8 Oct	"	0.9	7 Feb	"	1.0
12 "	"	0.4	16 May	2400	1.1
18 "	1600	0.4	13 June	"	1.3
24 "	"	0.4	19 "	"	Admission to hospital
8 Nov	2000	0.8	2 July	2400	1.2
15 "	"	1.1	25 "	2000	0.8
28 "	"	1.3	26 "	Lithium withdrawn	
13 Dec	"	1.0	15 Aug	Nil	Nil

Conversion: SI to traditional units—Lithium: 1 mmol = 1 mEq.