CLASSIC PAPER

The Relation of Prophylactic Inoculations to the Onset of Poliomyelitis†

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INTRODUCTION

At a time when polio epidemics struck communities causing permanent disability or even death amongst its young victims, public health authorities and concerned parents alike, searched for conditions that might predispose toward the dreaded neurological complications of poliovirus infection. It was realised early in this century that only a fraction of exposed children developed the paralytic syndrome associated with poliovirus infection, whereas the majority of infected peers in close physical and social contact remained unaffected. The identification of factors that might promote the occurrence of paralytic polio was believed crucial for understanding the pathogenesis of poliomyelitis, while preventive measures that could eliminate those factors might potentially decrease the impact of epidemics. Whereas we now know that the invasion of the virus into the CNS is largely a chance phenomenon, risk factors that may increase the probability of neurological complications of poliovirus infections have been debated ever since poliomyelitis took epidemic proportions. The paper by McCloskey added a new dimension to this discussion, namely that during a polio epidemic recipients of prophylactic intramuscular (i.m.) injections had a higher risk of developing poliomyelitis.

Remarkably, as early as 1886, the American physician Mary Putnam Jacobi pointed out that 'traumatisms have a more decided influence (on poliomyelitis) than is generally assigned to them'.[1] Numerous anecdotal reports supported this perception during the next decades, the most widely known case being Sir Walter Scott who developed poliomyelitis after he suffered injuries from a fall. Altogether, these considerations led to the widely accepted wisdom that strenuous exercise may predispose towards polio.[2,3] Consequently, in the climate of despair surrounding polio epidemics, parents and civic organisations occasionally were led to take drastic measures to protect those children thought to be at risk of paralytic disease. Children were instructed to refrain from physical activity, and physical education or organised athletic activities were suspended during epidemic outbreaks of polio.

The report by McCloskey provided the first systematic epidemiologic evaluation of a phenomenon that later became known as 'provocation poliomyelitis'; i.e. poliomyelitis following muscle injury, physical exertion, or prophylactic i.m. inoculations concomitant with poliovirus infection. In their report, a main risk factor associated with provocation poliomyelitis was trivial muscular trauma inflicted through the administration of i.m. inoculations of pertussis/diphtheria vaccine. At the time of publication, public health authorities and the medical community were reluctant to accept the concept of provocation poliomyelitis caused by skeletal muscle trauma and, as pointed out in the report by McCloskey, deferred action until further evidence could be collected.

In the following years, evidence for further occurrences of the phenomenon of provocation poliomyelitis was mainly linked, as in the present paper, to the administration of pertussis/diphtheria vaccines.[4–7] The effect of other forms of muscle trauma on susceptibility to paralytic polio, such as physical exertion, was less obvious. In contrast to the mass pertussis/diphtheria immunisation campaigns subjecting large numbers of individuals to a defined and reproducible form of minor physical trauma, strenuous exercise or accidental skeletal muscle injury were difficult to connect with sporadic incidences of provocation poliomyelitis in an epidemiological survey. The drastic decrease in the occurrence of epidemic poliomyelitis in the industrialised world that followed immunisation with the inactivated (Salk) and oral (Sabin) vaccines, diminished the incidence of cases of suspected provocation poliomyelitis and halted discussion of this phenomenon. In the developing world, however, a preference for invasive routes of administration of prophylactic or therapeutic agents in paediatric practice has contributed towards the continuing occurrence of provocation poliomyelitis.[6,8] Repeated

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appeals to regional health authorities[8–10] as well as mounting epidemiological evidence for the concept of provocation polio had little influence on paediatric practice in endemic areas. Indeed, only with the enormous efforts to increase vaccine coverage in compliance with the WHO plans to eradicate poliovirus, will provocation poliomyelitis cease to claim victims.

THE RELATION OF PROPHYLACTIC INOCULATIONS TO THE ONSET OF POLIOMYELITIS

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An epidemic of poliomyelitis commenced in Melbourne, Victoria, in January of 1949, and later spread to the country areas of the State of Victoria and to the adjoining State of South Australia (July–August). The incidence in the other States of Australia was low during this period. The epidemic in Victoria is now subsiding.

Early in the epidemic, attention was directed to a few patients who had been given an injection of pertussis vaccine, or of a mixture of diphtheria toxoid and pertussis vaccine, shortly before the onset of their symptoms. The parents of these children were naturally inclined to blame the inoculations for the development of the disease, though their medical attendants either dismissed the possibility of any causal relationship or else considered the effects to be due to a radiculitis caused by the vaccine. It was decided to inquire for a history of immunisation in the course of a routine investigation of reported cases; though any real association between inoculation and poliomyelitis infection was then considered highly improbable. Considerable evidence, however, will be presented to show that such an association has existed in this epidemic.

METHOD OF INQUIRY

There were 375 cases of poliomyelitis notified in Victoria from January to August 1949. The parents of 340 of these cases were asked whether the child had even been immunised against diphtheria or whooping-cough, and, if so, the date and the doctor's name. The remaining 35 cases reported during this period could not be similarly investigated, either because of inaccessibility of the patient, or of inability to contact the parents. No selection of cases whose parents were interviewed was made, and every effort was made to interview the parents of every case reported, but in 35 cases this proved impossible.

Of those cases investigated, if any inoculation had been given within three months of the onset, I personally obtained particulars from the parents of the exact dates and of the sites of all inoculations. I then checked the parents' statements with the doctor's records. Occasionally the parents were uncertain of the exact date or site. In only 4 cases confirmation of the parents' statements as to date and site could not be obtained from the doctor. The data of these 4 cases were recorded as doubtful, and they have been excluded from consideration.

DIAGNOSIS

Of the 375 cases of poliomyelitis reported, 340 were investigated : about 250 of them, including every case of which the particulars are presented in the tables, were fully investigated by me personally. Most of them were admitted to the Infectious Diseases Hospital, Fairfield, Melbourne, where the diagnosis was confirmed by the experienced medical staff. Many were also seen by members of the panel of consultant physicians, appointed by the Consultative Council on Poliomyelitis of this State. Clinically, the cases associated with recent immunisation were indistinguishable from the remaining acute cases of paralytic poliomyelitis seen during this period. Of the patients included in table I, only 1 (no. 161) was not paralysed, a female child aged sixteen months. Her clinical picture was consistent with non-paralytic poliomyelitis. On admission to hospital her cerebrospinal fluid contained 65 leucocytes per c.mm. (70% polymorphs, 30% lymphocytes), and its protein content was 60 mg. per 100 ml.

TABLE I. FINDINGS IN 31 CHILDREN INOCULATED WITHIN THREE MONTHS OF ONSET

Case no.	Age in months	Agent	Days between last injection and symptoms	Limb last injected	Paralysis in injected limb	Paralysis in non-injected limbs: RA	LA	RL	LL	Other injections : days before onset and sites of injections
181	54	P	7	LA	***	**	. .	*	0	. .
203	25	P	9	RA	****	. .	**	0	0	16 (LA)
290	15	P	12	LA	***	0	. .	0	0	19 (RA) 35 (RA)
327	24	P	12	RA	**	. .	0	0	0	25 (LA) 35 (RA)
372	54	P	20	RA	***	. .	. .	0	0	41 (LA) 53, 73 (LA)
				LA	**					
56	41	P	26	LL	***	***	**	0	. .	33 (RA)
119	17	PD	4	RL	****	0	*	. .	.	23 (RA) 23 (LA) 9
				LL	****					(♀LL, ♀RL) 45 (LL)
266	67	PD	7	LA	****	***	. .	0	0	
1	12	PD	8	LL	****	0	0	0	. .	. .
178	26	PD	8	LA	****	**	. .	**	0	1, 69 (LA)
358	24	PD	10	LL	****	0	0	0	. .	. .
348	12	PD	11	LA	***	0	. .	0	*	42 (RL)
356	36	PD	11	RL	**	*	0	. .	0	42 (RL) 73 (RA)
161	16	PD	13	RA	0	. .	. .	0	0	46 (LA, RA)
				LA	0					
231	32	PD	13	RL	****	*	*	. .	***	51 (LL)
179	17	PD	14	LL	**	0	0	0	. .	. .
94	18	PD	16	LA	***	0	. .	0	0	. .
222	16	PD	22	LL	***	0	0	0	. .	. .
215	30	PD	27	RL	**	0	*	. .	*	1 (LL)
216	15	PD	28	RL	***	0	0	. .	0	. .
2	18	PD	32	RL	**	0	0	. .	0	. .
85	12	D	5	RA	0	. .	0	***	*	. .
238	84	D	6	RA	0	. .	. .	0	0	29 (RA)
				LA	0					
209	42	D	8	LA	0	0	. .	***	*	. .
211	21	D	8	RA	0	. .	0	*	0	1 (RA)
186	18	D	11	RA	****	. .	0	0	0	. .
259	131	D	12	LA	*	*	. .	****	**	29 (RA)
248	69	D	13	RA	***	. .	***	0	0	41 (LA)
241	180	D	14	LA	**	0	. .	0	0	. .
364	93	D	60	LA	0	0	. .	0	0	(Note : Palate paralysis only)
336	108	D	60	LA	0	0	. .	*	0	. .

**** Very severe.
*** Severe.
** Moderate.
* Mild.
0 Nil.
P, Pertussis vaccine.
PD, Combined pertussis and diphtheria vaccine.
D, Diphtheria toxoid.
RA, Right arm.
LA, Left arm.
RL, Right leg.
LL, Left leg.

ASSESSMENT OF THE SITE OF PARALYSIS AND ITS SEVERITY

The sites of paralysis were determined at the initial examination, or at one shortly after the diagnosis had been made. In the majority of

TABLE II. RELATION OF PARALYSIS TO SITE OF INOCULATION

Agent		Inoculated limbs: Paralysed	Inoculated limbs: Not paralysed	Uninoculated limbs: Paralysed	Uninoculated limbs: Not paralysed	Total limbs
P	Legs	1	. .	1	10	12
(6 cases)	Arms	8	2	2	. .	12
	Total	9	2	3	10	24
PD	Legs	12	2	2	12	28
(14 cases)	Arms	6	1	5	16	28
	Total	18	3	7	28	56
D	Legs	. .	. .	8	12	20
(10 cases)	Arms	6	7	. .	7	20
	Total	6	7	8	19	40

these cases, the extent of paralysis of each extremity was initially assessed by me according to the standard scale of the Australian Association of Physiotherapists. The patients whom I did not initially examine were assessed by members of the staff of the Infectious Diseases Hospital, Fairfield. For the sake of uniformity of presentation, both series have been converted to the following scale :

Very severe	(****)	Complete flaccid paralysis.
Severe . .	(***)	Complete paralysis of at least one muscle group.
Moderate . .	(**)	Partial paralysis of at least one muscle group, sufficient to prevent movement of the involved joint against gravity.
Mild . .	(*)	Lesser degrees of paralysis, permitting movement against gravity.
Nil . .	(0)	No detectable paralysis of an extremity.

These findings were, in all cases whose particulars are included in this paper, compared with those of the physiotherapists treating the cases and were found to correspond exactly.

It is emphasised that the inquiry into the site and degree of paralysis always preceded the inquiry as to the site of inoculation. This procedure seems sufficient to ensure against any possibility of bias on the writer's part in the assessment of the site and severity of the paralysis.

FINDINGS

Table I summarises the relevant data of all 31 patients who have received an injection of diphtheria toxoid or pertussis vaccine, alone or in combination, within three months of the onset of symptoms, for whom exact information on date and site of injection could be obtained. The findings in the 4 patients where some degree of doubt existed as to date and site have been omitted. There were no other cases in the 340 investigated in whom a history of an inoculation of diphtheria toxoid and/or pertussis vaccine within three months of the onset was obtained.

RELATION OF THE SITE OF INOCULATION TO SITE OF PARALYSIS

The data in table I on relation of site of inoculation (at any time up to three months before the onset) to site of paralysis are collected in table II.

Paralysis is distinctly more frequent in the inoculated than in the uninoculated extremities in those cases which received pertussis vaccine either alone or in combination. In the patients given only diphtheria toxoid, a difference in the incidence of paralysis in the inoculated and uninoculated extremities is also evident if we compare the corresponding extremities (the arms), though this difference is not as striking as when pertussis vaccine was used alone.

TABLE III

Agent	Period preceding onset in which incoulation was received (all cases): Under 3 months	Between 3 months and 12 months	More than 1 year
P	6	3	9
PD	15	8	51
D	10	19	61
Unknown	4	0	25
Total	35	30	146

TABLE IV

Agent	Period preceding onset in which last incoulation was received (children under 3): Under 3 months	Between 3 months and 12 months	More than 1 year
P	3	2	1
PD	13	3	3
D	3	10	2
Unknown	2	0	3
Total	21	15	9

Total Inoculated: 45
Uninoculated: 24

The difference in incidence of paralysis in inoculated and uninoculated limbs is so great when pertussis vaccine, alone or combined, has been employed, that an exact statistical assessment of significance, which presents some difficulties, hardly appears to be necessary. The cases involving diphtheria toxoid alone are few and it is doubtful whether their statistical assessment would be profitable.

IMMUNISATION HISTORY OF ALL CASES INVESTIGATED

Of the 340 cases investigated a history of previous immunisation against whooping-cough and/or diphtheria was obtained in 211. Of these, 65 received inoculations within one year of the onset of their poliomyelitis. These results are expressed in table III.

In the remaining 129 cases no history of any immunising procedure against whooping-cough or diphtheria at any period of the patient's life was obtained.

Of the 340 cases investigated, 69 were children under three years of age. The immunisation history of these children regarding pertussis and diphtheria is contained in table IV.

INTERVAL BETWEEN INJECTION AND DEVELOPMENT OF SYMPTOMS

Table I includes all persons who had received a prophylactic inoculation of one of the three agents within three months of the onset of symptoms. It would be expected that the number of inoculations would be the same in each month. That is far from the case, as appears from table V (extracted from table I).

In this table every inoculation received by each subject within ninety days of the onset is included : many patients, of course, received multiple injections in that period.

TABLE V

Agent	Interval between inoculation and onset of symptoms: 1–30 days	31–60 days	61–90 days
P	9	5	1
PD	18	6	2
D	11	3	0
Total	38	14	3

It is clear that the more recent the injection of any agent, the more likely is its association with the onset of poliomyelitis. This association can be assessed by the χ^2 test, and is significant for diphtheria toxoid alone, as well as for pertussis vaccine alone or in combination.

INTERVAL BETWEEN THE LAST INJECTION AND ONSET OF SYMPTOMS AND SITE PARALYSIS

Many patients received more than one injection. Inspection of the data revealed that the last injection before the onset of symptoms was that usually associated with the location of paralysis. The data are arranged in table I to indicate this relationship.

The fourth column in table I shows the intervals, arranged in order of magnitude, between the last injection (excluding three injections given the day before onset) and the onset of symptoms. The incidence of paralysis in limbs receiving the last injection is shown in the sixth, and that in the other limbs in the next four columns. When pertussis vaccine was used, alone or in combination, 22 of 24 limbs receiving the last inoculation were paralysed, and only 16 of the 60 limbs inoculated prior to this or uninoculated were affected. There is less evidence of localisation in the limb last injected when diphtheria toxoid was used ; 4 of 11 of the last inoculated limbs were paralysed, and 10 of 29 of the remainder.

INTERVAL BETWEEN THE LAST INOCULATION AND THE ONSET OF SYMPTOMS

The intervals from the last inoculation before the onset of symptoms to that onset ranged from five to thirty-two days, except in 2 patients in whom this interval was approximately sixty days. These 2 patients received diphtheria toxoid, the limbs injected were not paralysed, and it is quite likely that in them, the injections were not related to the attacks of poliomyelitis but were coincidental.

In poliomyelitis following tonsillectomy, the intervals between the operation and onset of symptoms have ranged from three to thirty days. The literature is summarised by Horstmann and Paul (1947). Leake (1935) reported 12 instances in which an attack of poliomyelitis closely followed administration of a poliomyelitis virus vaccine. Of these 12, 6 children had a single dose two days or less before onset of symptoms. Discarding these very short intervals as unlikely incubation periods, the intervals from injection to onset were seven to fourteen days, as in the majority of cases (19 of 30) in this series. In Leake's series also there was a marked, but not invariable, association between site of inoculation and site of paralysis.

The incubation period of poliomyelitis itself is usually regarded as lying within these same limits, five to thirty days.

RELATION OF INOCULATION TO PARALYSIS IN THE CASES UNDER THREE YEARS OF AGE

In the 17 cases under three years of age receiving pertussis vaccine either alone or in combination within thirty-five days of the onset, full data are available for 16; in 15 paralysis followed in the limb last inoculated before the onset. The paralysis in the limb last inoculated in these cases is shown in table VI.

TABLE VI. SEVERITY OF PARALYSIS IN LIMBS INOCULATED WITH PERTUSIS VACCINE WITHIN 35 DAYS AND IN CONTROLS (CHILDREN UNDER 3)

	Immunised group* (15 cases)					Control group* (48 cases)					Total limbs
	****	***	**	*	0	****	***	**	*	0	
R arm	1	0	1	0	1	0	1	0	3	44	48
L arm	1	3	0	0	1	0	2	1	3	42	48
R leg	2	1	2	0	0	5	3	3	17	20	48
L leg	3	1	1	0	0	3	4	4	13	24	48
All limbs	7	5	4	0	2	8	10	8	36	130	192

*For definition of these groups see text.

By contrast the degree of paralysis in each limb of a control group of all children under three (48 in all), notified during the same period as the above 17 cases, who had not received any inoculation within thirty-five days of the onset, and for whom exact information as to the site and severity of paralysis was ascertained, is also shown in table VI.

It is clear that there is a considerable increase in the severity of the paralysis in the last inoculated limbs of those children under three who received an injection of pertussis vaccine within thirty-five days of the onset of poliomyelitis.

ADMINISTRATIVE ACTION

A report was submitted to the Chief Health Officer (Dr. G. E. Cole) on July 20, 1949, and it was decided to defer action until further evidence had been collected. When this had been done, the Chief Health Officer, in September 1949, invited Prof. F. M. Burnet, F.R.S., Dr. E. V. Keogh, of the Commonwealth Serum Laboratories , and Dr. H. McLorinan, superintendent of the Infectious Diseases Hospital, Fairfield, to confer with him and officers of his department. It was agreed that there was certainly evidence of some association between prophylactic injections and development of poliomyelitis in the epidemic. This raised questions of great importance from the viewpoint of public health administration. It was feared that immunisation, particularly against diphtheria, might be prejudiced if the public were informed. The Chief Health Officer, therefore, laid the facts and the opinions of this expert committee before the Consultative Council on Poliomyelitis of the State of Victoria for an opinion whether or not the medical profession and the public should be informed. The council recommended that doctors be advised to discontinue the use of pertussis vaccine during the currency of the epidemic, just as tonsillectomy had been postponed since it appeared to determine an attack of poliomyelitis in rare instances. They also thought that the public should be informed of the facts in regard to pertussis vaccine, alone and in combination. Similar action as regards diphtheria immunisation was considered unnecessary, (1) because the evidence was less certain, and (2) because temporary cessation of mass diphtheria immunisation could readily be arranged.

On Oct. 4, 1949, the Commonwealth Government and the Department of Health in each State were informed of the Victorian findings by the Chief Health Officer acting on the advice of the council. A circular letter was also addressed to all doctors in Victoria, informing them of the position, and a brief statement was issued to the press. The announcements caused no unfavourable press comment ; so there is no reason to suppose that the future of immunisation in Victoria has been prejudiced.

DISCUSSION

Evidence has been presented which indicates that an injection of pertussis vaccine, given during an epidemic of poliomyelitis, may determine the onset of paralysis in the immunised child. The evidence that an injection of diphtheria toxoid may have similar effects is, perhaps, less conclusive.

In discussing various possible explanations of this phenomenon, attention will first be directed to those instances in which localisation in the inoculated limb was the prominent feature, following administration of pertussis vaccine, alone or combined.

Any suggestion that the prophylactic agents, on release by the makers, were contaminated with poliomyelitis virus seems highly improbable. No single batch of any one product could be incriminated. The products were made by three different firms—one English, one American, and one Australian. The same immunising agents have been used throughout Australia, but their injection was followed by paralysis only in Victoria, during a severe epidemic of poliomyelitis. Any harmful effects were therefore associated, not with their origin, but with the epidemic prevalence of poliomyelitis.

The chances of syringe transmission have to be considered. The possibility exists of contamination of the hypodermic needle with virus from the doctor's hands or the patient's skin. Or a syringe used to give, for example, penicillin to a child with an undiagnosed fever, which was in reality a non-paralytic attack of poliomyelitis, might later be employed without adequate sterilisation to give a vaccine to another child. But it has also then to be assumed, either that a viræmia occurs in non-paralytic cases, and that the injection of pencillin or other drugs coincides with the viræmia, or that virus is present for a longer or shorter time in the subcutaneous tissues. And since these injections are not intravenous, the chances of contamination of the interior of the syringe would be relatively slight, even if the needle did pierce tissues in which virus was present.

Allowing that local tissue damage caused by the vaccine might favour the successful implantation of a very small dose of virus, these foregoing assumptions are not in harmony with current views of poliomyelitis.

It is conceivable that, in a subject suffering a non-paralytic infection, circulating virus might be arrested and concentrated in tissue damaged by the vaccine, and then travel, perhaps after multiplication, via the peripheral nerves or some other channel, to the corresponding areas in the cord. Again it is necessary to postulate a viræmia and also that the injection itself is given during the period of viræmia, or that the viræmia occurs before the damage done by the vaccine has been repaired.

The final hypothesis to be considered is that proposed by Horstmann and Paul (1947) in explanation of the effect of exercise and other traumata on the development of paralysis. They suggest that local trauma may be reflected in corresponding areas in the cord in the form of central changes, which favour activation of virus already present in the central nervous system. Although the nature of the presumed mechanism is somewhat obscure, the suggestion seems applicable to the present observations, since it merely adds injection of pertussis vaccine to the list of known traumata which influence unfavourably the course of an infection with poliomyelitis virus. But Levison et al. (1945), in experiments on rhesus monkeys, found that trauma to the muscles of an extremity did not influence the site or extent of paralysis, though exercise to the fatigue-point and chilling in the prodromal period had a pronounced effect. These workers injured the tissues by bruising with hammer blows ; it is possible that the type of injury may be decisive, and that pertussis vaccine may specifically favour localisation.

None of the hypotheses considered provides a convincing explanation of the observations. Further information, some of which should be obtainable by experimental procedures, is required. It would obviously be of interest to determine whether pertussis vaccine introduced intramuscularly can modify the course of the experimental infection in the monkey. Two lines of inquiry might be profitable : (1) to see whether, in monkeys infected by the intranasal or oral routes, a subsequent or coincident injection of pertussis vaccine can determine paralysis of the infected limb; and (2) to determine whether a minimal dose of virus, non-infective by the intramuscular route, may become infective if given mixed with pertussis vaccine.

The differences observed between the effects of pertussis vaccine and diphtheria toxoid are in harmony with the presumption that local damage to tissue is a determining factor. Since the local damage following the injection of pertussis vaccine, or combined pertussis-diphtheria prophylactic, is much more severe than that usually following diphtheria toxoid alone, one would expect more striking and frequent effects to follow administration of pertussis vaccine, even if, as is the case in Victoria, many more children are immunised against diphtheria.

In considering, however, the frequency and severity of the effects of pertussis vaccine, in comparison with diphtheria toxoid, it should be remembered that pertussis vaccine is usually given early in the child's life, while diphtheria prophylaxis is often postponed until the child is four or five, and about to enter school. The average age of the children in this series given pertussis vaccine, alone or in combination, was 2·4 years, and of those receiving diphtheria toxoid 5·1 years. Location of the paralysis in the injected limb may be, therefore, a phenomenon more likely to occur in younger children, irrespective of the nature of the prophylactic agent.

One further point remains to be mentioned. A nursing sister developed typical poliomyelitis after an injection of typhoid-paratyphoid vaccine into the left upper arm. Ten days after the injection she felt unwell and remained in bed for two days. She returned to duty, but on the thirteenth day developed general muscle pains and vomiting. She developed considerable weakness in the injected left arm and in both legs. Another nursing sister who received a similar inoculation at the same time became ill after the same interval and was diagnosed as suffering from poliomyelitis. She was not, however, reported as a case, and no further details are available.

SUMMARY

Evidence is presented that in the current epidemic of poliomyelitis in Victoria there has been a relation, in a number of cases, between an injection of an immunising agent and the subsequent development of paralytic poliomyelitis.

I am indebted to the Chairman of the Health Commission of Victoria, Dr. G. E. Cole, for permission to publish this paper.

I wish to acknowledge gratefully the encouragement and guidance given me by Dr. E. V. Keogh throughout this investigation, and his help in the preparation of this paper. Also I wish to thank Dame Jean Macnamara (who is a constant inspiration to workers in the poliomyelitis field in Australia) ; Dr. H. McLorinan for his courtesy in giving me access to the patients, and their records in the Infectious Diseases Hospital, Fairfield ; Mr. Alwyn Matthew of the Commonwealth Serum Laboratories, Melbourne ; and Dr. H. O. Lancaster of the School of Public Health and Tropical Medicine, University of Sydney, for statistical advice. Finally, I wish to thank the staff of the Health Department in Victoria who have so willingly assisted me in my investigations.

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COMMENTARY

This classic paper describing a link between trauma and polio was followed by a large number of epidemiological

studies solidifying the concept of provocation poliomyelitis. These reports linked the administration of i.m. inoculations (most commonly for immunisation purposes) with an increased susceptibility toward neurological complications of concomitant poliovirus infection.[8] Most recently, a cluster of cases of vaccine-associated paralytic poliomyelitis in Romania has been linked to the common practice of administering excessive numbers of i.m. injections of various therapeutic agents to infants who had received oral polio vaccines.[14] This alarming report showed that poliomyelitis may not only be provoked by muscle injury incurred concomitant with wild-type poliovirus infection but that it can also occur after vaccination with the live-attenuated (Sabin-) strains of poliovirus (oral polio vaccines, OPV). Furthermore, the number of i.m. inoculations administered was correlated with the likelihood of provocation poliomyelitis.[14] Whereas the report by Strebel *et al.*[14] complemented the epidemiological data supporting the concept of provocation polio induced by i.m. injections, the pathogenic mechanism that could provide a scientific explanation for this phenomenon remained unknown.

For decades numerous explanations had been put forward to account for provocation poliomyelitis. Mechanisms thought to contribute towards increased incidence of polio amongst children treated with i.m. inoculation included (i) contamination of administered agents or equipment with poliovirus, (ii) genetic predisposition, (iii) autoimmune reactions elicited by local trauma, (iv) alterations induced within the CNS by trauma in the periphery (either regional changes in vascular permeability within the spinal cord,[11] or alterations within the spinal cord parenchyma itself[12]), (v) retrograde axonal transport of infectious polio particles, (vi) non-specific membrane destabilisation. In the original report of McCloskey as well as in later investigations, it was determined that contamination of administered agents and equipment with poliovirus was unlikely.[13] Furthermore, epidemiological analyses of the effect of i.m. injections of a wide variety of unrelated agents suggested that the procedure of the i.m. injection itself, rather than the nature of the administered agent, carried the risk to provoke poliomyelitis.

Experiments to shed light on the problem of provocation poliomyelitis were first conducted by Bodian *et al.*[11,15] who studied the relation of onset of paralysis to muscle injury in primates. In his studies, Bodian was particularly interested in the phenomenon of localisation of paralysis in children. It was observed that i.m. injections seemed to precipitate initial paralytic symptoms in precisely that limb where the injection ('provocation') had occurred. This localisation was described by McCloskey and constituted one of the hallmarks of iatrogenic poliomyelitis. The correlation between injury and localisation of paralysis was later found in victims of the 'Cutter incident'; children vaccinated with i.m. injections of improperly inactivated Salk vaccine developed poliomyelitis with initial paretic symptoms in the inoculated limb.[16]

Obviously, the circumstances that determine the anatomical site within the CNS initially affected by poliovirus are key to solving the contentious question of how poliovirus could enter the CNS. At the time, the mechanism of CNS invasion was fiercely debated[17,18] and remains a matter of discussion even today (recently, evidence for passage of the brain/blood barrier by poliovirus[19] as well as for retrograde axonal transport has been presented[20]). In his studies Bodian distinguished between neurotropic and pantropic poliovirus strains; neurotropic strains seemed to invade the CNS through peripheral nerves whereas pantropic strains appeared to gain access to the CNS through passage of the blood/brain barrier. Curiously, he failed to observe the localisation effect that seemed to define provocation polio in affected patients with the latter.[11] Furthermore, blocking of the nerve supplying the inoculated muscle only affected the localisation after infection with neurotropic poliovirus strains in monkeys whereas it had no effect on pantropic strains.[11] To accommodate the pathogenic properties of all poliovirus isolates in primates, Bodian proposed a model for provocation poliomyelitis that implied regional alterations in vascular permeability to account for preferential CNS invasion of poliovirus in certain segments of the spinal cord. These vascular effects were supposedly induced by the local injury caused in conjunction with i.m. injections.[11,16,21]

New insight into the pathogenic mechanism of provocation poliomyelitis stemmed from studies using a novel model for poliomyelitis in mice transgenic for the human poliovirus receptor (CD155). CD155 is an immunoglobulin superfamily cell surface protein whose non-pathogenic function is currently under investigation.[22,23] CD155 transgenic mice, when infected with poliovirus, develop a paralytic disease, clinically and histopathologically identical to primate poliomyelitis.[24–26] This experimental animal model for poliomyelitis has proven to be invaluable to the study of provocation poliomyelitis because the characteristic features of this phenomenon can be readily reproduced in transgenic mice.[27] Mice were made viraemic with neurovirulent poliovirus by intravenous administration. Those viraemic mice treated with repeated i.m. inoculations of physiological saline developed paralytic disease after a shortened incubation period compared with control viraemic mice. This included a pronounced localisation effect to the inoculated limb[27] and a significantly accelerated rate of progression toward respiratory involvement. Early onset and accelerated progression of paralytic symptoms in mice treated with i.m. injections were the consequence of elevated regional virus titres in precisely those segments of the spinal cord that harbour the motor neurons innervating the injected limb.[27] This increase of virus titres correlated with the acceleration of the pace of spinal motor neuron destruction.[27] Provocation poliomyelitis in these animals could be prevented by ipsilateral sciatic nerve transection in poliovirus-infected animals that were treated with multiple i.m. inoculations into the gastrocnemius muscle.[27]

These studies provided a pathogenic mechanism for provocation poliomyelitis based on a route of CNS invasion of poliovirus that seems to short-cut a more general pathway. A simple explanation for direct invasion of the CNS would be retrograde axonal transport induced by local skeletal muscle injury stemming from i.m. inoculations. In his experiments in monkeys, Bodian had studied the provocation effect of i.m. injections, but he evaluated only the site of initial symptoms. This may have led to an experimental bias, since the appearance of signs of paralysis not only reflects the site of incipient intraspinal virus replication but also varying clinical reponses according to the spinal segment affected. It appears that varying degrees of clinical symptoms (extent of paralysis) develop even if the virus load is very similar in different regions of the spinal cord. Intravenous poliovirus infection of CD155 transgenic mice induces even levels of virus propagation in cervicothoracal and lumbosacral segments of the spinal cord, whereas the onset of clinical symptoms almost invariably is located to the lower extremities.[27] The evaluation of the kinetics of virus replication in the spinal cord in parallel with the progression of spinal motor neuron damage and clinical symptoms allowed a more inclusive analysis of the provocation effect.[27] It led to the definitive conclusion that retrograde axonal transport accounts for an increased susceptibility toward neuroinvasion of poliovirus, a shortening of the incubation period, and the localisation effect.[27]

Retrograde axonal transport as a route of CNS entry for poliovirus has been shown to be operational in transgenic mice as well as in monkeys after i.m. virus deposition.[11,20] We have linked the role of retrograde axonal transport to the pathogenesis of provocation poliomyelitis, making use of skeletal muscle injury inflicted during viraemia in experimental animals. This model implies that skeletal muscle trauma incurred in the presence of viraemia (i) favours virus uptake into the peripheral nerve and thus induces retrograde axonal transport, (ii) leads to increased local virus replication within injured skeletal muscle in close proximity to the neuromuscular junction, (iii) increases the pace of retrograde axonal transport (the effect of peripheral nerve injury on the efficiency of retrograde axonal transport has been observed previously[28]). Several mechanisms may be activated by i.m. injections to promote poliovirus retrograde axonal transport. Upregulation of the expression of the poliovirus receptor CD155 in nerve endings upon peripheral nerve trauma may favour virus uptake (upregulation of expression on peripheral nerves has been reported for the immunoglobulin superfamily molecule L1[29]). Similarly, upregulation of CD155 in injured myocytes or in invading macrophages or lymphocytes may lead to an increase of local virus replication in skeletal muscle induced by trivial injury.

The Classic Paper presented here provided the first solid epidemiological documentation for a causal link between skeletal muscle injury and enhanced susceptibility toward paralytic polio. The concept of provocation poliomyelitis was never fully acknowledged by the medical community[30] and, accordingly, awareness of the increased risk of polio through administration of i.m. injections in regions endemic for poliomyelitis, was low. In the industrialised world, provocation polio ceased to be a problem with the advent of extensive immunisation. Tragically, despite the well documented epidemiology of the provocation phenomenon, iatrogenic poliomyelitis as a consequence of a preference for i.m. injections in paediatric practice (that is frequently inappropriate[31]) has continued to be a source of childhood paralysis in the developing world. This relates not only to those few regions where poliovirus may still be endemic, it also applies to those populations that receive oral polio vaccines. Finally, the possibility should not be ignored that provocation poliomyelitis may play a role also in paralytic disease caused by enteroviruses other than poliovirus, such as coxsackieviruses A7 and -A9 or enteroviruses 70 and -71.

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