# Provocation of poliomyelitis by multiple injections

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**Abstract**

Injections of vaccines provoked paralytic poliomyelitis in children in the UK and elsewhere. The effect of multiple injections has not been recognized previously but could be important in the tropics where children receive many injections. A number of epidemics of poliomyelitis between 1914 and 1962 are related to children with congenital syphilis or yaws under treatment with arsenicals or penicillin.

Rates of 25% of children with paralysis occurred in epidemics while in non-epidemic periods the increase in susceptibility was about 25 fold. Other possible cases of provocation are discussed. Although in the tropics injections before paralysis may be causal, it will be difficult to prove that they are not coincident. The very high rate of paralysis following multiple injections is powerful evidence that injections in the tropics are often causal.

## Introduction

In 1950, poliomyelitis following prophylactic injections was recognized in Australia, the UK and later in the USA (WYATT, 1981). Epidemiological analysis showed a causal relationship which was later confirmed by animal experiments (BODIAN, 1954). By giving the injections to children in the winter months, provocation poliomyelitis was reduced to a minimum. The original investigations had shown that a single injection could increase the risk of paralysis by about five fold but the following questions were not answered: (i) What was the greatest possible increase in risk for a single injection? (ii) Did the injection only increase the risk with a virus of low virulence or was the risk with a virus of high virulence also increased by the same amount? (iii) Was there an upper limit to the percentage of exposed non-immune children who could have paralysis after an injection? (iv) was penicillin a provoking agent? (v) Would multiple injections only increase the time that a child was at risk or would multiple injections also increase the risk for a particular agent?

In this paper, I examine these questions by referring to a number of previously neglected epidemics. The questions are of great practical importance as children in the tropics are given many injections and poliomyelitis is a serious health problem (WYATT, 1980). Many parents associate paralysis with previous injections yet proof may be very difficult (WYATT, 1980).

### *Provocation Poliomyelitis*

Provocation poliomyelitis following injections was recognized because: (a) there was a high incidence of initial paralysis in the injected limb; (b) the first symptoms of paralysis occurred 7 to 18 days after the injection; (c) there was both higher incidence and more severe residual paralysis among those given injections than in those not injected.

Epidemiological analysis showed that injections could increase the risk of paralysis by up to five fold and that the more immunogenic the injected agent, the greater the risk (MRC, 1956). The enquiry used data from wide areas and nothing is known of the virulence of the polio-viruses involved, the proportion of children already immune or how many children were infected. We therefore do not have a baseline of the real risk of paralysis. The animal experiments do not help us to answer questions (i), (ii) and (iii) because the highly virulent Mahoney strain injected into the heart of monkeys gave a control rate of 48% (BODIAN, 1954), many times greater than the rates in the children studied by the MRC Committee. Bodian was able to increase the rate to between 70 and 90% with provocation. The mechanism of provocation in children is similar to that in animal experiments but the assessment of maximum risk in children can only be made when the base rate in children is known (see below).

## Increased Risk Following Injections

In non-epidemic years in Rome and London very young children receiving injections for congenital syphilis had a 25 fold increased risk (Table I), about five times as great as any previously reported. For a group of children of similar age in an epidemic on the island of Taravao in Tahiti, there was a similar increased risk. However, on Taravao, the paralytic rate increased with age as noted previously in many epidemics among non-immunes (ROSEN & THOORIS, 1953; WYATT, 1975b). Among those injected at Taravao, the rate was between 6·9 and 9·7% in the three age groups, with the increased risk following injections falling with age from × 25 to × 5·5. One explanation of this could be that the total number of those susceptible to poliomyelitis increases with age to a maximum of 25% and that provocation converts what would have been a non-paralytic attack to a paralytic one and an abortive to a non-paralytic attack. The virus causing the Taravao epidemic was probably one of moderate virulence as it is most unlikely that there was any significant number of immune children in the age-groups. It has been shown previously that for many epidemics caused by highly virulent strains the greatest incidence among

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**Table I—Rates of paralysis in those receiving injections and those not**

| Poliomyelitis | Place | Age (years) | Paralytic rate % no injections | Paralytic rate % injections | Ratio | Reference |
|---|---|---|---|---|---|---|
| Non-endemic | Rome | 0-2 | 0·19 | 5·3 | × 28 | MENICHELLA, 1950 |
| | London | 0-2 | 0·02[a] | 0·5[b] | × 25 | BRINKER & MITMAN, 1939; NABARRO, 1954. |
| Epidemic | Taravao, Tahiti | 0-4 | 0·4 | 9·7 | × 25 | ROSEN & THOORIS, 1953 |
| | | 5-9 | 0·7 | 6·9 | × 10 | |
| | | 10-14 | 1·6 | 8·6 | × 5·5 | |
| | | 15+ | 0·34 | 1·15 | × 3·4 | |

[a] cases 0-5 yr, poliomyelitis and polioencephalitis 1926-1937 for London. Non-paralytic cases are included.
[b] About 900 children treated with Salvarsan for congential syphilis between 1917 and 1939.

**Table II—Paralytic poliomyelitis in children given multiple injections**

| Disease and Treatment | Place | No. of children | Age (years) | Poliomyelitis | % cases of poliomyelitis | Ref. |
|---|---|---|---|---|---|---|
| Congenital syphilis: | | | | | | |
| Salvarsan, etc. | Berlin 1913 | 22 | 0-3 | epidemic | 23 | KERN, 1914 |
| Salvarsan, bismuth | Rome 1936-47 | ? | 0-4 | epidemics | 25+ | MENICHELLA, 1950, 1955. |
| Penicillin[a] | Rome 1949 | 50 | 0-4 | epidemic | 26 | |
| Yaws: | | | | | | |
| acetylarsan, bismuth subsalicylate, mercuric iodide | Tahiti 1951 Afaahiti | 40 | 0-15 | epidemic | 25 | ROSEN & THOORIS, 1953 |
| | Taravao | 468 | 0-15 | epidemic | 8·1 | |
| neo-arsphenamine | W. Samoa 1932 | 1766 | 0-4 | epidemic | 7·8 | LAMBERT, 1936 |

[a]Dr. V. Menichella, personal communication.

the one to two-year-old age group was about 2% (WYATT, 1975 a & b). The incidence in a number of epidemics in children's homes among children receiving injections was about 25% (Table II). This would indicate that for a virus of high virulence, the maximum increase in risk with provocation was about twelve-fold. The data again shows that 25% is the highest incidence of paralysis reached.

*Penicillin*

Although penicillin was a provoking agent in monkeys (BODIAN, 1954), evidence in children suggested otherwise (PEACH & RHODES, 1954). This was because in the latter study the penicillin had been given in the febrile stage of the illness, before paralysis occurred. An epidemic which occurred in a home for children with congenital syphilis shows that penicillin can be a provoking agent. From 1936 to 1947 treatment was with Salvarsan and bismuth but in 1947 was changed to twice daily intra-gluteal injection of penicillin (Dr. Menichella, personal communication). In 1949 there were 13 cases of paralysis of whom four died, among 50 children treated with penicillin who had not been present at the previous epidemics. In nine of these children, the first paralysis was in a leg (MENICHELLA, 1950, 1955). There were similar epidemics of poliomyelitis affecting mainly the congenital syphilitics at homes in Novara and Naples (Dr. Menichella, personal communication).

Multiple injections of penicillin can therefore increase the paralytic rate to 25% and can be as effective provoking agents as the arsphenamines. Whether the provocation was caused by the penicillin itself or by impurities is not clear.

## Effect of Multiple Injections

If a child received multiple injections over some weeks then that child would be at increased risk for a longer time than a child given a single injection. Children given multiple injections should therefore have had a higher incidence of paralysis when poliomyelitis was endemic and this was so in London (Table I). In schools, institutions and hospitals for children, epidemics are short as most or all children are very rapidly infected. The effect of injections should be two-fold: more children should be affected and there should be more epidemics. However, multiple injections might have a further effect: the injections might be cumulative and the provocation risk of a particular substance might be increased with multiple injections. Bodian showed that a single injury with a needle did not provoke but that two needle injuries did (BODIAN, 1954). The interval between injections might also be important: injections at 17-day intervals might simply prolong the period of provocation whereas injections at more frequent intervals would presumably be equivalent, at least during the overlap period, of a double dose and so give an increased risk.

The Instituto per l'Assistenza all'Infanzia della Provincia di Roma housed about 1000 children, about one tenth of whom had congenital syphilis. These luetic children were housed in the main institute at some periods and in a separate villa 500 m away in

1937-39 and 1942. From 1936 to 1950 there were 11 outbreaks among the luetic children and eight among the others (MENICHELLA, 1950, 1955). There were 53 cases of paralysis among 1000 luetic children but only 17 among 9000 others. There were, therefore, not only more epidemics but also more children affected. This seems to show that multiple injections are much more provocative than smaller numbers of injections of penicillin.

It is difficult to assess directly the effect of multiple injections. The greatest number of epidemics associated with one have resulted from the use of arsphenamines. In Samoa, almost all of the group received two injections one week apart in the buttocks (LAMBERT, 1936); in Tahiti the children received weekly injections, possibly about four to six in most cases (ROSEN & THOORIS, 1953). In both Samoa and Taravao, Tahiti, the paralytic rate was 8%, although the ages were different. In a small group of children in Berlin, given combinations of Salvarsan, Neosalvarsan, Hg-salicyl-Kur, etc., either subcutaneously or intravenously, there was a 23% case rate (KERN, 1914).

These figures indicate that multiple injections of arsphenamines and particularly of penicillin can considerably increase the rate of paralysis beyond that caused by single injections or injections given weekly. In general, only intramuscular injections will provoke and there is no evidence of provocation by subcutaneous injections (PEACH & RHODES, 1954). However, the determining factor will be how much of the underlying muscle is involved in the inflammation following the injection (WYATT, 1976). This will depend on the nature and amount of the material injected and whether there is seepage towards the muscle. A very inflammatory material such as Salvarsan would probably provoke even if given subcutaneously. All drugs which cause peripheral motor neuropathies (ARGOV & MASTAGLIA, 1979) will promote an increase in poliomyelitis, whether the drug is injected or taken by mouth (WYATT, 1976, 1983).

## Other Epidemics

Epidemics in homes for children and schools were frequent but accounts were seldom published (SMITH, 1939) and publicity about children with syphilis would be avoided. Two epidemics are, however, suggestive. In 1923 there were 10 cases of paralytic poliomyelitis in three wards of a 12-ward home for infants. The cases were all between six months and two years, giving a case rate in the three wards of 12%. In the home there were 300 children aged from a few days to five years so the over-all rate of over 3% was unusually high (BLOOMBERG & BARENBERG, 1924). The onset of paralysis was sudden and in eight cases the right deltoid muscle and shoulder were affected—the only paralysis in two cases. The two oldest cases had bulbar paralysis with the right shoulder and arm affected. This concentration of paralysis suggests that the children had received injections in the right arm and that two might have had tonsillectomies. 34 cases of poliomyelitis occurred in a leprosarium in the Philippines (CDC, 1962) among 142 children up to two years old, some of whom were given DPT inactivated poliovaccine in the early stages of the outbreak. There were 21 cases of paralysis including four deaths and 14 cases of non-paralytic polio, a rate suggesting provocation.

## The Paralytic Rate

The highest rates in these epidemics of 23 to 26% (Table II) are very similar to the 26% supposed to be genetically susceptible over the age of 10 years (WYATT, 1975a, b; 1976; 1978a).

This figure was obtained from two epidemics and tested with over 40 others (WYATT, 1975b). In New York City in 1916, nearly 2% of the children two to three years old were paralysed; among the Eskimos at Chesterfield Inlet in 1948, only two of 53 children were paralysed, but 25% of 222 persons over five years were paralysed. These two epidemics can be explained if there is a dominant gene $p^+$ for susceptibility, with homozygotes $p^+p^+$ and heterozygotes $p^+p^-$ becoming susceptible at different ages. The proportions are consistent with a Hardy-Weinberg equation

$$p^+p^+ + 2p^+p^- + p^-p^- = 100\%$$

where $p^+p^+$ is 2% and $2p^+p^-$ is 24% giving a total of 26% susceptible over the age of 10 years.

I suggest that multiple injections convert the heterozygotes phenotypically to full susceptibility for as long as the inflammation caused by the injections.

**Table III—A model for provocation poliomyelitis in children 0-2 yr**

| | Virulence of virus | | | | | |
|---|---|---|---|---|---|---|
| | Low | | High | | | |
| | normal | provocation | normal | provocation | multiple provocation | % of children |
| heterozygotes | — | abortive[1] | abortive | NP[2] | P[2] | 18 |
| | abortive | NP | NP | P | P | 6 |
| homozygotes | NP | P | P | PP | PP | 1·8 |
| | P | PP | PP | F[2] | F | 0·2 |
| % of children with paralysis | 0·2 | 2 | 2 | 8 | 26 | |

[1] see WYATT, 1978b.
[2] NP, non-paralytic; P, mild paralytic; PP, severe paralytic; F, paralysis followed by death.

By comparing the rates among those with and without injections, an increase of about × 25 occurred in those between nought and two years receiving injections (Table I). This is about the ratio expected from the genetic model: an average of about 1% between nought and two years and 26% at age 10 and above. A model for the effect of injections on infections with polioviruses of different virulence is shown in Table III.

## Discussion

Islands, isolated communities and schools have suffered many epidemics of very high incidence. These epidemics are experiments of nature and are particularly valuable for the interpretation of the epidemiology (WYATT, 1975b). In the same way, the epidemics among children receiving injections provide data which may never occur again.

That many of these epidemics occurred when modern methods of virology were not available, should not lead us to dismiss the high incidence of paralysis. Doctors were familiar with poliomyelitis and were able to make clinical judgements: there is no reason to doubt these figures any more than the incidence of poliomyelitis in the tropics based on lameness surveys (WYATT, 1980, 1982).

Paralytic poliomyelitis in the tropics is often associated with injections but it is difficult to determine whether this is causal or coincident (WYATT, 1980). The study by GUYER *et al.* (1980) showed that children with poliomyelitis had received many more injections before the onset of paralysis than had a control group. While this is an important step forward it leaves more questions than before. In particular, it is unlikely that in the tropics, where injection-giving is prevalent, children who are paralysed have more injections in the first five years of life than others. In Guyer's study, 67% of all the injections given were quinine and penicillin for clinical reasons other than poliomyelitis. Such a study simply shows that some of these children would also suffer from a later attack of poliomyelitis. Where poliomyelitis is endemic, other diseases are prevalent and injections are frequent; proof of the causal effect of injections will be extremely difficult or impossible. Instead, we must seek to convince by other methods.

The effect of multiple injections provides a reasonable explanation of the prevalence of poliomyelitis in the tropics (WYATT, 1980) we must act accordingly.

A preliminary report of this work has been published as an abstract (WYATT, 1978c).

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