BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 1 1950

INOCULATION AND POLIOMYELITIS

A STATISTICAL INVESTIGATION IN ENGLAND AND WALES IN 1949

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The immunization campaign which began in 1942 has led, it is well known, to a dramatic reduction in the incidence of and mortality from diphtheria in this country. During its progress, however, there have been reported occasional and sporadic cases of paralysis following the injection of an antigen. This paralysis has sometimes been limited to the limb in which the injection was made; sometimes it has involved other limbs as well. In most cases a diagnosis of poliomyelitis has been made. It is, however, clear that when inoculations are being given to hundreds of thousands of children and when, at the same time, poliomyelitis is endemic or epidemic, then the disease must *inevitably* follow injections in some children without there being any causal relationship whatever between the two events. In other words, children receiving injections might have no more risk of acquiring paralytic poliomyelitis than any other children.

There was in those earlier years no evidence to suggest that they had a greater risk—and, indeed, we do not now know for certain that the danger then existed, though we may well suspect that it did. In the autumn of 1949, on the other hand, it was known that much more incriminating evidence was accumulating in several quarters, evidence which has since been published. J. K. Martin (1950) had collected 17 cases in which paralysis of a single limb had occurred within 28 days of an injection being given. The diagnosis in almost all was poliomyelitis. No statistical proof of the relationship was available, but it appeared very unlikely that the association was wholly fortuitous.

At the same time it was known that observations of the association had been made, and statistical evidence of cause and effect collected, by B. P. McCloskey (1950) working in Melbourne, Australia. Of 340 cases of poliomyelitis investigated by him 31 had received an injection of diphtheria toxoid or pertussis vaccine, alone or in combination, within three months of the onset of their symptoms. In these 31 patients paralysis was distinctly more frequent in their inoculated than in their uninoculated limbs. Likewise in the 17 of them who were under 3 years of age and had received an inoculation within the preceding 35 days, the severity of the paralysis was much greater in the last inoculated limbs than in a comparable group of children not recently inoculated.

Concurrently, D. H. Geffen (1950) had become aware of the occurrence of poliomyelitis in recently inoculated children in the Metropolitan Borough of St. Pancras, an observation which he subsequently extended by the collection of records from other parts of London. Once more the frequency of the occurrence and the tendency for the paralysis to be localized to the limb of injection made it somewhat unlikely that the association was fortuitous.

These reports, at that time incomplete and unpublished, made it essential that a wide-scale statistical inquiry be immediately undertaken, one which could reveal as speedily as possible whether indeed in this country there was a case for believing that paralytic poliomyelitis could be justly attributed to a preceding inoculation.

Mode of Inquiry

For a full answer to the statistical problem the requirements are the numbers of children of given ages injected with defined antigens at given points of time and in specified areas, and then the number of these who develop poliomyelitis within subsequent periods. In relation to the general incidence of poliomyelitis, these figures will accurately measure the probability that an inoculated child will develop poliomyelitis and, likewise, they will show the relative risks at different ages and with different antigens. Such a method is the *only* means by which those risks can be satisfactorily and effectively measured. It is an inquiry, however, that would take a very long time to carry out, since there are no readily available data which give, in the required detail, the numbers of children inoculated. In the circumstances it was essential to use a speedier, even if less comprehensive, approach.

Areas of Inquiry

The method we adopted was to choose deliberately all those administrative areas of the country in which a large number of cases of poliomyelitis had been notified during the three months July, August, and September, 1949 (the number we laid down was 20 of all ages). We then sought the inoculation histories of all the cases of poliomyelitis in which the patient was less than 5 years of age. This procedure led us to seek for returns from 25 areas. It soon, however, became apparent that these areas were unlikely to provide sufficient data for all the subdivisions we wished to make. At the same time, the epidemic of 1949 was unexpectedly prolonged beyond the usual season of poliomyelitis. We therefore sought data from another 14 areas in each of which at least 20 cases of all ages had been notified in the five months July to November inclusive.

From these 39 areas we subsequently eliminated the following: three areas (involving 21 records) which could not provide the detailed data that we essentially needed—the inoculation histories of the children were not known or the site of inoculation or of paralysis was lacking; one area which had had only abortive and doubtful cases (9 records); one area in which the recorded incidence of 20 cases, upon which it was selected, related mainly to cases brought into the town's hospitals from rural areas outside it and which itself had had only a single case in a child under 5 years of age (one record); and one area in which the records of paralysis available related not to the early stages of the disease but to the residual paralysis some weeks later (8 records).*

Excluding these 39 records we were left with 410 records derived from 33 widespread areas (the Metropolitan Boroughs of Battersea, Hackney, Hammersmith, Islington, Kensington, Lewisham, Paddington, St. Pancras, and Wandsworth; the County Boroughs of Birmingham, Bournemouth, Brighton, Bristol, Dewsbury, Hull, Leeds, Leicester, Liverpool, Manchester, Nottingham, Portsmouth, Reading, Salford, Sheffield, Southampton, and York; the Municipal Boroughs of Finchley, Hendon, Hornsey, and Willesden; the Urban Districts of Camborne and Redruth, and Hoyland Nether; and the Rural District of New Forest).

The Protocols

The medical officer of health of each of these areas was asked to provide two series of data, the one relating to the confirmed poliomyelitis cases, limited to children under 5 since inoculation at older ages is less frequent, and the other to a series of "controls." For the former we sought sex; date of birth; date of notification of poliomyelitis and date of onset of symptoms; whether there was paralysis and, if so, which limbs or other sites were affected and whether the attack was fatal; and then the child's full history of inoculations (excluding vaccination) from the time of his or her birth up to September 30, 1949, in the first series of areas and to November 30, 1949, in the second series. Under this history we sought the date of each injection, the dose, site, whether subcutaneous or intramuscular, the nature of the vaccine and its origin.

From these particulars we could see how frequently the site of paralysis coincided with the site of injection at given intervals of time after that injection, and also whether the incidence of paralysis on the various limbs, upper and lower, differed in its distribution between those children (of the same age) who had been recently inoculated and those who had not.

The Controls

As a further standard of comparison we sought a control group of children under 5 years of age—one which would be representative of all such children in the area concerned. By such means we might see whether the poliomyelitis patients had been recently inoculated more often than the general run of children—that is, whether inoculation appeared to be bringing them into the paralytic class. A method of choosing these controls in so many areas and yet by some random process was not easy. We finally determined to ask the medical officer of health to take for each of his poliomyelitis cases a child of the same sex as that case and of closely similar age, but one who was notified at approximately the same date as the poliomyelitis case as suffering from measles. Failing this we asked him to take for each poliomyelitis case a child of the same sex who was born at the same time as the poliomyelitis case, the name to be drawn from the notification of births register.

To the "measles control" there might be objection in that we have to presume that children suffering from measles at ages under 5 are, in relation to the incidence of inoculation, a cross-section of all children of those ages. The "birthday control" presented some difficulty in that the child chosen had to be known to be still living in the area concerned. Difficulty also arose through the dearth of cases of measles at that time of year in 1949. Many such cases we subsequently had to discard since they did not match closely enough in age and date of notification the poliomyelitis case they were supposed to control. We were thus left finally with only 164 controls derived from one or other of the above methods, each of which had been closely "paired" with a corresponding poliomyelitis case.

In obtaining these various data we asked the medical officer of health to take the following precautions: "(*a*) to ensure that the evidence may be wholly objective, and therefore not open to criticism, it is most important that, whenever possible, *the details of the attack of poliomyelitis should be entered before the inoculation history of the child has been determined*; (*b*) the 'control' case of measles to a poliomyelitis case should be chosen to give, as near as can be, equality in sex, age, and date of notification, but otherwise be picked at random and *particularly, if possible, without any* prior knowledge of the child's inoculation history."

The Results

The basic data relating to the 410 cases of poliomyelitis are set out in Table I. They relate, it will be seen, to

TABLE I.—*Number of Children with Poliomyelitis, the Number of Sites of Paralysis, and the Inoculation Histories*

Age at Onset of Polio-myelitis (Months)	No. of Children			No. of Sites of Paralysis and (Mean No. per Child)	Inoculation History		
	M	F	Total		Inoculated at Some Time	Not Inoculated	Not Known
0– ..	32	24	56	103 (1·8)	18	37	1
12– ..	75	44	119	204 (1·7)	82	27	10
24– ..	70	33	103	166 (1·6)	65	27	11
36– ..	45	39	84	123 (1·5)	61	17	6
48–59 ..	26	22	48	49 (1·0)	23	12	13
Total	248	162	410	645 (1·6)	249	120	41

248 boys and 162 girls, with the maximum incidence falling in the second and third years of life. It may also be observed that the number of sites of paralysis in these young children declines steadily with advancing age. This is due, at least in part, to an increasing frequency of non-paralytic cases as age rises—whether as a real phenomenon or through a greater frequency of missed cases very early in life. The incidence of such non-paralytic attacks was 5.4% of all cases in the first year of life, 6.7% in the second year, 11.7% in the third, 15.5% in the fourth, and 25% in the fifth. In total, it will be seen, these 410 children were paralysed in 645 sites.

*We also excluded from the present analysis four records sent to us from Belfast through the kindness of Dr. James Boyd and Dr. F. F. Kane, to whom we express our thanks.

Site of Paralysis and Previous Inoculation

In Tables II and III we turn to the main issue, our first comparison being between the sites of paralysis revealed by recently inoculated children and by others not so recently inoculated. Table II gives the figures for children under 2 years and Table III those for children aged 2–5. Looking first at the younger children (Table II) and at those without any history of previous inoculations, the percentage distribution of paralysis shows (column 4) that the two arms are almost equally affected—11% and 12%—and that the two legs also do not differ greatly—31% and 26%. On the other hand, the legs are paralysed about two and a half times as often as the arms—57% to 23%. Turning next to column 3, it will be seen that children who had been inoculated at least three months before the onset of their attack of poliomyelitis give remarkably similar figures—arms 10% and 13%, legs 25% and 30%, ratio of legs to arms 55% to 23%. There is clearly no indication whatever that an injection three or more months previous to the illness affects the distribution of paralysis.

TABLE II.—*Sites of Paralysis and Previous Inoculation History in Children Under 2 Years of Age*

Site of Paralysis	Interval Between Last Injection and Onset of Poliomyelitis: Less than a Month*	Between 1 and 3 Months	3 or More Months Previous	No Previous Inoculations	Inoculation History Not Known	Total
Right arm	15	1	8	12	2	38
Left arm	23	6	10	14	3	56
Right leg	17	9	20	35	1	82
Left leg	15	5	24	29	1	74
Trunk	9	2	12	10	1	34
Cranial nerves ..	3	0	6	13	1	23
Total No. of (*a*) Sites ..	82	23	80	113	9	307
(*b*) Children ..	35	16	49	64	11	175
Percentages	(1)	(2)	(3)	(4)	(5)	(6)
Right arm	*18*	*4*	*10*	*11*	—	*12*
Left arm	*28*	*26*	*13*	*12*	—	*18*
Right leg	*21*	*39*	*25*	*31*	—	*27*
Left leg	*18*	*22*	*30*	*26*	—	*24*
Trunk	*11*	*9*	*15*	*9*	—	*11*
Cranial nerves ..	*4*	*0*	*7*	*11*	—	*8*
Total sites ..	*100*	*100*	*100*	*100*	—	*100*

* Here and in all tables less than a month means 0–28 days inclusive, between 1 and 3 months is 29 to 91 days inclusive, and 3 or more months is 92 days and onwards.

Turning, however, to column 1 we see a material change. Of the 82 sites of paralysis recorded for these 35 recently injected children the right arm was involved in 18%, the left arm in 28%. Both these proportions are distinctly greater than those shown by the uninoculated or not recently inoculated children (of columns 3 and 4), and together they give to the arms 46% of the paralysis against the 23% in the arms of the latter groups. Also the left arm in these children is affected more often than the right, and the left arm is, it is known, the more usual site of inoculation in this country. (Taking, in fact, these hundred children aged 0–2 as one group we find 85% had been inoculated in an arm against 9% in the leg and 4% in the buttocks (2% unknown site), and the ratio of left arm to right arm is 4½ to 1. The figures for the older children are very similar.) As a corollary of the excess incidence of paralysis in the arms in the recently inoculated group, the legs are proportionately less often affected. In place of the customary ratio of 2½ to 1 for leg paralysis to arm paralysis, we have here a ratio rather less than 1 to 1 (39% legs to 46% arms).

Turning finally to the children injected more than one month but less than three months before the onset of their illness, we have but 16 of these, with 23 sites of paralysis. The number is too small to be convincing. There is perhaps a suggestion of an absence of paralysis in the right arm and an excess on the left, but the arms show 30% in total to the 61% in the legs, a ratio very similar to that found in the uninoculated children.

Turning next to the older children (Table III), we may note once again that those who had been inoculated at least three months before the onset of poliomyelitis reveal almost precisely the same distribution of sites of paralysis as the children who had never been inoculated—arms 20% and legs 54% (column 3), against arms 24% and legs 51% (column 4). The similarity is striking, and confirms the previous conclusion that distant injections produce no changes in the distribution of paralysis.

TABLE III.—*Sites of Paralysis and Previous Inoculation History in Children Between 2 and 5 Years of Age*

Site of Paralysis	Interval Between Last Injection and Onset of Poliomyelitis: Less than a Month	Between 1 and 3 Months	3 or More Months Previous	No Previous Inoculations	Inoculation History Not Known	Total
Right arm	0	1	20	9	5	35
Left arm	2	0	21	9	6	38
Right leg	3	0	52	16	11	82
Left leg	4	2	59	23	10	98
Trunk	1	0	27	14	6	48
Cranial nerves ..	0	0	28	6	3	37
Total No. of (*a*) Sites ..	10	3	207	77	41	338
(*b*) Children ..	7	4	138	56	30	235
Percentages	(1)	(2)	(3)	(4)	(5)	(6)
Right arm	—	—	*10*	*12*	*12*	*10*
Left arm	—	—	*10*	*12*	*15*	*11*
Right leg	—	—	*25*	*21*	*27*	*24*
Left leg	—	—	*29*	*30*	*24*	*29*
Trunk	—	—	*13*	*18*	*15*	*14*
Cranial nerves ..	—	—	*13*	*8*	*7*	*11*
Total sites ..	—	—	*100*	*101*	*100*	*99*

Of recently inoculated children there were at these ages only seven. This is, of course, due to the fact that inoculations are much less frequently performed at these ages, and the few figures we have are clearly of little value.

Sites of Paralysis and Site of Injection

A closer picture of the association between the site of paralysis and the site of recent injection (whether in arm, leg, or buttock) is given in Tables IV and V. Including

TABLE IV.—*Sites of Paralysis in Relation to Site of Last Inoculation. Children Under 2 Years of Age*

Site of Paralysis in Relation to Site of Inoculation	Interval from Last Inoculation to Onset of Poliomyelitis (Months): 0–	1–	3–	6+	Total
Same site*	11	3	1	1	16
Included site* ..	18	1	3	4	26
Different site ..	3	8	10	24	45
No paralysis ..	1	2	1	1	5
No record	3	2	1	3	9
Total No. of children	36†	16	16	33	101†
% of total falling in same and included categories ..	*81*	*25*	*25*	*15*	*42*

* "Same site" denotes that the site of inoculation was the *only* site of paralysis, "included site" that the site of inoculation was *one* of the sites of paralysis but not the only site in which paralysis occurred.

† The total number of children was 100, and the extra one here is due to the fact that one child was given two antigens on the same day, one into the left arm and the other into the right, and developed paralysis in the right arm 10 days later. We have had, here and elsewhere, to include this child twice.

here only those children who had at some time or other been inoculated, we show how often the site of paralysis coincided with the site of injection. Table IV shows that, of the children who had been inoculated in the month preceding their illness, four-fifths (81%) had paralysis in the limb of injection (though not necessary confined to that limb). This proportion is greatly in excess of the figure shown by children whose last injection was more than a month distant. In these groups the limb of injection was involved in 25% when an injection was one to three months before, 25% when it was three to six months before, and 15% when it was six or more months before (proportions which between themselves differ insignificantly).

TABLE V.—*Sites of Paralysis in Relation to Site of Last Inoculation. Children Between 2 and 5 Years of Age*

Site of Paralysis in Relation to Site of Inoculation	Interval from Last Inoculation to Onset of Poliomyelitis (Months)				
	0–	1–	3–	6+	Total
Same site*	1	0	0	4	5
Included site* ..	3	0	0	10	13
Different site ..	0	2	4	88	94
No paralysis ..	2	1	0	17	20
No record	1	1	1	14	17
Total No. of children	7	4	5	133	149
% of total falling in same and included categories ..	*57*	*0*	*0*	*10*	*12*

* " Same site " denotes that the site of inoculation was the *only* site of paralysis. " included site " that the site of inoculation was *one* of the sites of paralysis but not the only site in which paralysis occurred.

The older children of Table V reveal a similar excess in the very small number who had been recently inoculated. Four of these seven children (57%) had paralysis in the limb of injection, whereas of the large group whose inoculation lay more than six months distant only 10% showed an association of these sites of injection and paralysis (a difference which is technically significant; the " exact " probability test gives $P = 0.005$).

Comparison of Antigens

Analysis of the figures according to the antigen last injected gives the results set out in Tables VI and VII. Our numbers are small even at the younger ages (Table VI)

TABLE VI.—*Sites of Paralysis in Relation to Site of Last Inoculation With Specified Antigens. Children Under 2 Years of Age†*

Site of Paralysis in Relation to Site of Inoculation	A.P.T.			Combined A.P.T. and Pertussis			Pertussis		
	Interval in Months			Interval in Months			Interval in Months		
	0–	1–	3+	0–	1–	3+	0–	1–	3+
Same site* ..	2	2	2	8	1	—	1	—	—
Included site*	4	—	3	14	1	3	—	—	—
Different site	1	5	24	1	3	7	1	—	2
No paralysis	1	1	1	—	1	—	—	—	1
No record ..	—	1	3	3	1	1	—	—	—
Total No. of children ..	8	9	33	26	7	11	2	—	3
% of total falling in same and included categories	*75*	*22*	*15*	*85*	*29*	*27*	—	—	—

* " Same site " denotes that the site of inoculation was the *only* site of paralysis, " included site " that the site of inoculation was *one* of the sites of paralysis but not the only site in which paralysis occurred.

† Two children not included here had had other antigens more than 3 months previously.

but there is, we think, a clear association here between site of recent injection and site of paralysis with A.P.T. and with the combined vaccine (A.P.T. and pertussis). With the former antigen six out of eight children (75%) had paralysis in the limb of injection; of the more distantly inoculated the numbers were two out of nine children inoculated between one and three months before (22%), and five out of 33 children inoculated three or more months before (15%). The difference between the recently and not recently inoculated groups (one month or over) is more than would be likely to occur by chance (by " exact " probability test $P = 0.002$).

Similarly with the combined vaccine 22 out of 26 recently inoculated children (85%) show paralysis in the limb of injection, while with more distant inoculations the proportion falls to just under 30% (two in seven and three in 11 children). Again the difference would be unlikely to arise by chance (P less than 0.001). For the pertussis vaccine alone we have no figures of any value. It was clearly not being extensively used in these areas.

At the older ages (Table VII) our data are very few, and the most we can say is that the figures for A.P.T. are in conformity with those for younger children. Of the 115 children who had been inoculated with this antigen three or more months before the onset of their poliomyelitis, approximately one in ten had paralysis in the limb of injection. Of the three children who had been injected within the preceding month all had paralysis in the limb of injection.

TABLE VII.—*Sites of Paralysis in Relation to Site of Last Inoculation With Specified Antigens. Children Between 2 and 5 Years of Age†*

Site of Paralysis in Relation to Site of Inoculation	A.P.T.			Combined A.P.T. and Pertussis			Pertussis		
	Interval in Months			Interval in Months			Interval in Months		
	0–	1–	3+	0–	1–	3+	0–	1–	3+
Same site* ..	1	—	4	—	—	—	—	—	—
Included site*	2	—	9	1	—	—	—	—	1
Different site	—	2	76	—	—	6	—	—	5
No paralysis	—	1	14	—	—	1	2	—	2
No record ..	—	—	12	—	—	1	1	—	1
Total No. of children ..	3	3	115	1	—	8	3	—	9

* " Same site " denotes that the site of inoculation was the *only* site of paralysis. " included site " that the site of inoculation was *one* of the sites of paralysis but not the only site in which paralysis occurred.

† Seven children not included here had had other antigens—six of whom were injected more than 3 months previously and one between 1 and 3 months previously.

To allow comparisons to be made we have in Table VIII put our data on the different antigens into the form adopted by McCloskey which contrasts inoculated with uninoculated limbs in relation to the frequency of paralysis. In this form we observe again a clear association between the site of paralysis and recent injection with A.P.T. and with the combined vaccine. Our four cases of inoculation with pertussis vaccine give no evidence of association.

TABLE VIII.—*Contrast of Inoculated and Uninoculated Limbs in Children Having an Injection Within 30 Days of Onset of Poliomyelitis**

Agent	Site	Inoculated Limbs		Uninoculated Limbs		Total Limbs
		Paralysed	Not Paralysed	Paralysed	Not Paralysed	
A.P.T. (11 cases)	Legs	1	—	11	10	22
	Arms	7	2	2	11	22
Combined vaccine (24 cases)	Legs	4	1	20	23	48
	Arms	19	—	10	19	48
Pertussis vaccine (4 cases)	Legs	—	1	—	7	8
	Arms	1	2	1	4	8

* This table excludes four children in whom the exact site of inoculation was unknown.

Comparison of Poliomyelitis Cases and Their Controls

In Table IX we turn to our control group and contrast the inoculation histories of the children with poliomyelitis with the corresponding histories of their controls. To be sure of this contrast we can take only 164 out of the total 410 poliomyelitis cases, since it was only in these that we had been able to obtain a satisfactorily "paired" control. This "pairing" was made closely for age and sex, while measles cases were accepted only if their date of notification lay *after* the onset of the corresponding case of poliomyelitis. The previous inoculation history was then measured in each such pair from the date of onset in the poliomyelitis case. Eighty-eight of these controls were "measles" controls and 76 were "birthday" controls. This pairing, therefore, seriously reduces the numbers at our disposal, but any less rigorous procedure is in our opinion open to grave objection, since the incidence of inoculation is closely associated with age. Table IX shows

TABLE IX.—*Interval From Last Inoculation to Onset of Poliomyelitis in Cases and in Their Matched Controls*

	Interval from Last Inoculation to Onset of Poliomyelitis Case (Months)						Not Inoculated	Not Known
	0–	1–	3–	6–	12+	All Intervals		
0–23 months of age:								
71 Poliomyelitis cases ..	11	7	7	13	3	41	26	4
71 Controls ..	1	9	7	18	1	36	32	3
24 months of age and over:								
93 Poliomyelitis cases ..	5	1	2	9	38	55	24	14
93 Controls ..	—	1	3	9	34	47	35	11
All ages:								
164 Poliomyelitis cases ..	16	8	9	22	41	96	50	18
164 Controls	1	10	10	27	35	83	67	14

that in each of our age groups rather more of the children with poliomyelitis had had some previous inoculations—41 to 36 and 55 to 47. Division of these figures into the intervals of time that had elapsed between the last injection and the onset of poliomyelitis (in a specified child and its pair) shows a striking result. There is no marked difference in the numbers of distant inoculations, and the excess of inoculations in the poliomyelitis group lies in injections which took place within a month of the onset of the illness.

Time Interval Between Inoculation and Poliomyelitis

Finally, in Table X we set out the intervals of time that had elapsed between the last inoculation and the recorded onset of the illness. In the great majority (26) of the 33 children who had paralysis within 28 days in the limb of injection, the recorded date of onset of symptoms lay in the ten-day interval 8–17 days subsequent to that injection. None fell below eight days, though there were two such cases in which the site of injection was not a site of paralysis. These two cases and others at the upper end of the scale may well have been fortuitous occurrences which must inevitably take place (as Tables IV and V show).

TABLE X.—*Interval From Last Inoculation to Date of Onset of Poliomyelitis in Children who had been Inoculated Within 28 Days of Onset*

Interval from Last Inoculation to Onset of Poliomyelitis (Days)	No. of Children*	
	Under 2 Years	Between 2 and 5 Years
1	*(1)*	
7	*(1)*	
8	4	
9	2	
10	1 *(1)*	1
11	3	1
12	1	*(1)*
13	1	1
14	3	*(1)*
15	3	
16	1	*(1)*
17	4	
18	1 *(1)*	
19	1	1
20	1	
21	1	
22	1 *(1)*	
25	*(1)*	
28	1	
All intervals ..	29 *(6)*	4 *(3)*

* The italicized figures in parentheses are of children who were not paralysed in the limb of injection.

Discussion

Whichever way we choose to set out the statistics collected in this inquiry they reveal clearly an association between recent injections and paralysis. For instance, Tables II and III show that in those inoculated within a month of the onset of their attack of poliomyelitis the distribution of the bodily sites of paralysis is quite abnormal. There is in these cases a high incidence of paralysis in the arms instead of the normal concentration upon the legs, there is an excess in the left arm compared with the right. We know that inoculations are given predominantly in the arms and mainly in the left arm (and the figures of the present inquiry confirm that general knowledge).

Alternatively we may bring the site of inoculation (whatever it may have been) into a more exact comparison with the site, or sites, of paralysis. We then see (Tables IV and V) that the two sites frequently coincide when the inoculation is of very recent date (that is, within the previous month) and come together significantly less frequently when the inoculation is an event of the more distant past.

Lastly, following McCloskey's analysis, we may consider how often, in the same children, their inoculated limbs are paralysed compared with their uninoculated limbs. We find an excess of paralysis in the former.

We must conclude, therefore, that in the 1949 epidemic of poliomyelitis in this country cases of paralysis were occurring which were associated with inoculation procedures carried out within the month preceding the recorded date of onset of the illness. On the other hand, we find no evidence whatever that any inoculations carried out three months or more before the onset of illness have had any such effect. There is not the slightest indication in our figures that such distant injections have localized the paralysis (Tables II and III) or that they have produced paralysis which would not otherwise have occurred (Table IX). On inoculations within one to three months of the onset of poliomyelitis we have very little evidence: what little there is suggests no evil effects—though obviously at the lower end of that period there might be some slight risk. On the other hand, the great majority of the intervals between last inoculation and onset of symptoms that were less than a month lay between 8 and 17 days. Taking a narrower interval, McCloskey reported that 63% of his cases had an interval of 7–14 days. Confining attention to cases with paralysis in the limb of injection, we show a closely similar figure—55%.

With the figures made available by this mode of inquiry we cannot satisfactorily measure the *relative* risks of poliomyelitis following an inoculation, either at different ages or with different antigens. The data do, however, show that the occurrence can (and does) take place in both the age groups we have used—namely, under 2 years and between 2 and 5 years (Tables IV, V, VI, VII, and IX). The smaller number of positive cases in the higher age group is not necessarily due to any lowering of the risk as age advances, for it must be, in part if not wholly, a function of the frequency with which inoculations are carried out. That frequency is, we know, lower in the higher age group.

Similarly, our figures show that paralysis has certainly followed the injection both of A.P.T. and of the combined A.P.T. and pertussis vaccine; for the pertussis vaccine alone we have no convincing data, and presumably it was not being extensively used (Tables VI, VII, and VIII). As stated, we cannot with figures of this kind determine whether one vaccine is more prone to produce paralysis than another. On the present published evidence we can see little support for the belief that the pertussis and the combined antigens are more prone to do this than A.P.T.

It has naturally been suggested that the effect of a recent inoculation is merely to localize the paralysis in the limb of injection in a child already incubating poliomyelitis. In the absence of inoculation the paralysis would not have occurred necessarily in that limb, but it would have occurred in some limb. The comparison of our cases with their paired controls (Table IX) suggests that this argument may not be well founded. The excess of recently inoculated children in the poliomyelitis group—and the equality in other intervals—does, we think, indicate that the group includes cases which would not have been diagnosed as poliomyelitis at all if there had been no previous and recent inoculation. Such children may already have been cases of non-clinically recognizable poliomyelitis, but the data suggest that they have been brought by inoculation into the paralytic class.

Summary and Conclusions

An investigation has been made to determine speedily whether, in the epidemic of 1949 in England and Wales, cases of paralysis diagnosed as and indistinguishable from poliomyelitis were occurring in association with inoculation procedures.

Records of 410 patients aged under 5 years were collected from 33 administrative areas, and in 164 of these cases a record was obtained for a closely paired control child.

The distribution of the bodily sites of paralysis was quite abnormal in children who had been inoculated within the month preceding the onset of their illness. In this group paralysis in the arms was just as frequent as paralysis in the legs, and the left arm showed paralysis more often than the right; in children without recent injections the two arms were equally affected and the legs were affected two to three times as often as the arms. The distribution in the recently inoculated is in accordance with the customary inoculation procedure in this country—that is, use of the arms more than the legs, and predominantly the left arm.

In the recently inoculated children the limb of injection (arm or leg) was a site of paralysis much more frequently than was the case with children not recently inoculated.

There is no evidence whatever that inoculations carried out in the more distant past have any effect at all upon the incidence or localization of paralysis. These effects appear to be confined to injections given within about a month of the onset of poliomyelitis, and after that interval from inoculation has elapsed no risk need be envisaged.

It has been suggested elsewhere that the recent injection of an antigen merely localizes an already developing paralysis in that particular limb of the child. The contrast of the present poliomyelitis cases with their specially collected and paired control children indicates, however, that there may be present in the poliomyelitis group cases which would not have been clinically diagnosed as poliomyelitis at all if their inoculation had not brought them into the paralytic group.

Paralysis in the limb of recent injection was observed to follow both inoculations with A.P.T. and inoculations with the combined A.P.T. and pertussis antigens. Few figures were available for pertussis vaccine, but one case of paralysis following a recent injection was recorded.

The intervals of time less than 28 days that elapsed between the last injection of an antigen and the recorded onset of symptoms of poliomyelitis lay mainly between 8 and 17 days.

The mode of inquiry was such as to give a rapid and sufficiently accurate answer to the problem at issue—were such cases, in fact, occurring more frequently than could be attributed to chance? From the data thus collected it is not possible to determine the *relative* risks of injections either at different ages or with different antigens. For that purpose another, and a very laborious, statistical investigation is required.

We have very gratefully to acknowledge the care and trouble taken by all the medical officers of health who supplied us with the basic data. We are also indebted to Dr. A. H. Gale, who readily gave us much assistance and advice, and to Sir Wilson Jameson, Chief Medical Officer to the Ministry of Health, who suggested that this was a subject upon which inquiry was obviously desirable and gave us encouragement throughout its course.

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CLINICAL POLIOMYELITIS IN ASSOCIATION WITH PERIPHERAL INOCULATION OF PROPHYLACTICS

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Aetiological Investigations

Recent observers in Australia and England have drawn attention to the occurrence, in 1949 in particular, of paralytic poliomyelitis in children who had received prophylactic inoculations within the preceding month. The most striking feature was that the paralysis was either localized to the most recently inoculated limb, or at least was first noticed in that limb, usually the arm. In the article on page 1 Bradford Hill and Knowelden have made a statistical evaluation of data collected in England in 1949 and confirmed the occurrence of such cases in this country.

Without going into the history of paralysis of limbs in association with inoculations of vaccines and sera and with trauma, it may be mentioned that clinical opinion is that two types of syndrome may occur, one of which appears to be associated with a lesion in the anterior horn cells of the spinal cord and the other in peripheral nerves. Therefore it was considered essential to try to determine whether a poliomyelitis virus was associated with the cases occurring in England in 1949, which appeared to be due to a lesion in the anterior horn cells of the cord.

No material has been received from fatal cases in association with the "double event," so that it has not been possible to obtain a histological diagnosis in confirmation of virus studies. However, stools have been obtained less than 21 days after the onset of the illness in a number of children included in some of the recent observations, and the poliomyelitis virus has been isolated by monkey