A RE-ASSESSMENT OF THE RISK OF PROVOKING PARALYTIC POLIOMYELITIS BY MAKING PROPHYLACTIC INOCULATIONS AGAINST DIPHTHERIA AND PERTUSSIS

By LEWIS B. HOLT

The Wright-Fleming Institute, St Mary's Hospital Medical School, London, W. 2

INTRODUCTION

Immunization procedures that involve the injection of antigenic substances into the tissues always carry some potential risk of an untoward effect. In general, these risks are very small and are outweighed by the advantage of the inoculation concerned. There are, however, certain conditions under which the injection of a particular immunizing preparation can constitute a greater risk than a different preparation of the same essential antigen or antigens. Recently a Medical Research Council Committee on Inoculation Procedures and Neurological Lesions (Report, 1956) examined in considerable detail the available evidence relating to the provocation of paralytic symptoms in patients, infected with the virus of poliomyelitis, by immunization procedures designed to protect such individuals against diphtheria, whooping cough and small-pox. The Report in question deals with two investigations, the first covering the years 1951–53 and the second 1954–55. There is abundant evidence from the former, which is considered in detail, that prophylactics combining diphtheria toxoid and pertussis vaccine with 'alum' constituted a very much greater risk of provoking paralytic poliomyelitis than similar prophylactics that did not contain alum.

The burden of the present communication is concerned with a re-examination of the M.R.C. Report and to plead the case of reduced risk of provocating paralytic poliomyelitis if certain combined diphtheria-pertussis prophylactics are used for the mass immunization of children early in life.

Reference is made in the M.R.C. Report to the experimental work of Bodian (1954), relating to the phenomenon of provocation of paralytic poliomyelitis. Since data obtained from Bodian's experiments are employed in the analyses presented in this communication it seems appropriate to give a brief summary of these experiments and the results.

Bodian showed that if Cynomolgus monkeys were inoculated intracardially with carefully adjusted doses of the Mahoney strain of poliomyelitis virus some 50 % of the animals would develop paralytic symptoms. Employing this technique, approximately 500 Cynomolgus monkeys were inoculated with the virus. About 160 of these animals served as controls to record the normal pattern of paralysis developing after the experimental infection. The remainder, the test animals, received intramuscular injections in the *right leg* of various preparations and the pattern of paralysis that developed in the different groups was duly recorded. The results may be summarized as follows. Right leg paralysis only: controls 4 %, test

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animals 25%. Lower limb paralysis, right, left or both: controls 14%, test animals 46%. Upper limb paralysis: controls 26%, test animals 19%. Upper and lower limb paralysis: controls 8%, test animals 8%. Facial paralysis: controls 15%, test animals 19%. The normal pattern of paralysis as seen in the controls was predominantly of the upper-limb type, whereas the superimposed provocation paralysis, as seen in the test animals, was confined to the lower limbs. Further, provocation paralysis would seem to be related anatomically to the spinal segments corresponding to the site of the intramuscular injections; it was confined to the injected limb, its opposite fellow or to both the injected and the opposite limb. Excluding the figures for this type there is virtual uniformity of the site-rates in both the control and test animals. The method of analysis presented here arose out of the author's observations, following a close study of Bodian's work, that provocation paralysis is superimposed on the normal pattern of paralysis. The results provide a means of obtaining quantitative 'built-in' control data.

Analysis of the nature of 'risk'

In the absence of poliomyelitis in a child community there can be no risk of provocation paralysis: in a heavily infected population the risk may be very great. The number of cases of provocation paralysis will depend on the number of children inoculated and the type of prophylactic (relating to its paralysis-provoking properties) used for immunization.

In a normal child population for every one that shows symptoms of paralytic poliomyelitis it is estimated (Melnick, 1954) that about 100 contract the disease but do not develop paralytic symptoms. The provocation index of a prophylactic is, therefore, taken as the number of cases of paralysis following the inoculation of 100 such infected children with that particular prophylactic. This number can only be determined indirectly.

The total number of cases of paralytic poliomyelitis following the inoculation of a number of children with a prophylactic may be expressed by the simple equation:

$$No = NPR,$$

where

No = number of cases of paralytic poliomyelitis;
N = number of child-inoculations (one injection, unit of time one month);*
P = probability that a child is infected when inoculated;
R = the provocation index of the prophylactic used, and possibly the type of poliovirus present in the child population and other unknown factors—*vide infra*.

From this we see that the number of cases of provoked poliomyelitis paralysis following, say, 100,000 injections of prophylactic A is not fixed but dependent on the values of P and R. P and R are strictly independent.

R or the provocation index is defined here as the number of children who, having a latent poliovirus infection, develop paralysis within 28 days of receiving one

* The restriction of time to 1 month is because no evidence has been found associating provoked paralysis beyond 28 days, this is also the basis for obtaining control data.

injection of a prophylactic compared with an identical uninoculated population and in which one case only of paralysis occurs.

A. *Overall estimate of R*

In the following calculations use is made of the information provided in tables IX and XI of the M.R.C. Report, reproduced here in Table 1 by kind permission of the editor of the *Lancet*, and the Medical Research Council.

The basis for calculation is: (*a*) a unit of time of 4 weeks, (*b*) the occurrence of paralytic poliomyelitis 0–28 days after inoculation, and (*c*) the 4-week average number of cases occurring 29–84 days after injection (see Table 1). The method of calculation is to compare (*a*) the total of all cases occurring within 29 days of injection to the 4-week average* occurring 29–84 days after inoculation (control data), and (*b*) to compare the totals of 'same' (paralysis at site of inoculation only) and 'included' (paralysis at site of inoculation and other sites) only in both categories. The figures provided reduce to:

Overall estimate of R

	Period 1951–53		Period 1954–55	
$\frac{0\text{–}28}{29\text{–}84}$	(i) $\frac{153}{29} = 5{\cdot}29$;	(ii) $\frac{224}{114} = 1{\cdot}96$	(i) $\frac{38}{25} = 1{\cdot}52$;	(ii) $\frac{78}{79} = 0{\cdot}95$

(i) = 'same' + 'included' only; (ii) = totals.

If we accept the thesis that the paralysis-provoking effect of an inoculation is anatomically related to spinal segments corresponding to the site of inoculation, then ratios (i) are the more informative.

B. *Use of ratio of 'same' and 'included' paralysis to 'different'*

It is assumed that the paralysis-provoking effect of the injection is strictly confined to the anatomical region injected, as is accepted clinically and found in the experimental work of Bodian (1954). Therefore the 'different' paralyses are unrelated to provocation and may be used as 'built-in controls' to the 'same' and 'included' paralyses. Any increase in the ratio of $S+I$ to D, (S (same) plus I (included) to D (different)), is then a direct measure of provoked paralysis. This method of examination has the advantage of including, and giving weight to, both any cross-over of provoked paralysis in arms and provoked arm paralysis occurring with unprovoked paralysis elsewhere.

The normal ratio of D to $S+I$ was calculated from the control (29–84 day) data from both surveys as follows:

Calculations of $D/(S+I)$ or K from the control data: arms only. Totals for 29–84 days over period 1951–53 and 1954–55, see Table 1.

	S	I	D	
1951–53	9	13	73	$K = 73/22 = 3{\cdot}3$
1954–55	5	11	52	$K = 52/16 = 3{\cdot}25$
Total	14	24	125	$K = 125/38 = 3{\cdot}28$

* This amalgamation of the number of cases, per 8-week interval, has already been made in the tables quoted.

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Table 1. *Data taken from the M.R.C. Report* (Lancet, 1956, ii, 1223)

Table IX—1951–53 England and Wales: paralytic cases—association between site of inoculation and site of paralysis at different intervals between inoculation and onset of poliomyelitis.

Interval (days) and prophylactic	Arm inoculations				Leg inoculations			
	Same	In.	Diff.	No. of patients	Same	In.	Diff.	No. of patients
1–28 days								
APT	24	19	28	71	9	2	3	14
PTAP	9	2	9	20	—	—	—	—
TAF and FT	2	1	4	7	—	—	1	1
Plain pertussis	3	4	4	11	2	1	2	5
Mixed, with alum	24	2	4	30	24	12	4	40
Mixed, without alum	5	2	5	12	3	—	2	5
Smallpox vaccine	—	3	5	8	—	—	—	—
All prophylactics	67	33	59	159	38	15	12	65
29–84 days								
APT	4	6	32	42	—	4	2	6
PTAP	—	—	9	9	—	—	—	—
TAF and FT	1	3	12	16	—	—	—	—
Plain pertussis	—	1	9	10	—	—	1	1
Mixed, with alum	3	—	2	5	1	—	5	6
Mixed, without alum	1	2	3	6	1	1	4	6
Smallpox vaccine	—	1	6	7	—	—	—	—
All prophylactics	9	13	73	95	2	5	12	19

Seventeen cases are excluded from this table because either sites of inoculations or sites of paralysis were not accurately recorded. Same: paralysis at site of inoculation and at no other site. In., included, paralysis at site of inoculation and at other sites. Diff., different, paralysis at sites other than sites of inoculation.

Table XI—1954–1955. England and Wales: paralytic cases—association between site of inoculation and site of paralysis at different intervals between inoculation and onset of poliomyelitis.

Interval (days) and prophylactic	Arm inoculations				Leg inoculations			
	Same	In.	Diff.	No. of patients	Same	In.	Diff.	No. of patients
1–28 days								
APT	8	5	12	25	1	—	—	1
PTAP	—	1	3	4	—	—	—	—
TAF and FT	—	—	2	2	—	—	—	—
Plain pertussis	1	2	4	7	—	3	1	4
Mixed, with alum	—	—	—	—	—	—	—	—
Mixed, without alum	6	3	11	20	3	3	2	8
Smallpox vaccine	—	2	2	4	—	—	—	—
All prophylactics	15	13	34	62	4	6	3	13
29–84 days								
APT	1	4	22	27	1	2	—	3
PTAP	1	3	2	6	—	—	—	—
TAF and FT	—	—	5	5	—	—	1	1
Plain pertussis	1	2	3	6	—	—	—	—
Mixed, with alum	—	—	—	—	—	—	—	—
Mixed, without alum	1	2	16	19	2	4	1	7
Smallpox vaccine	1	—	4	5	—	—	—	—
All prophylactics	5	11	52	68	3	6	2	11

Ten paralytic cases were excluded from this table because either sites of inoculation or sites of paralysis were not accurately known.

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Thus when there is no provocation then $(S+I)/D \times K$ = unity and when there is provocation the formula gives R (the provocation index) anatomically controlled.

The two estimates of K agreed closely and for the purpose of calculating the values of R for the individual prophylactics (0–28 day data) was adopted as 3·3.

C. *Use of ratio of 'same' and 'different'*

A variation of this method, but weakened as the quantity of usable data is greatly reduced, is to use only 'same' and 'different' site of paralysis. The values of the normal ratio of D/S or K' from the first and second surveys are 73/9 or 8·1 and 52/5 or 10·4, respectively, giving a mean value of 9, in which case $R' = S/D \times 9$.

In any form of analysis it is important to have some index of the reliability of the data being examined. In this case it is the uniformity of the control data that is important in that this corresponds to 'stability of rates' in other methods of analysis. We have already seen that for both surveys the value of K, or $D/S+I$, for the entire control data was approximately 3·3, and therefore

$$S+I/D \times 3{\cdot}3 = \text{unity},$$

and correspondingly in the case of R', $K' = 9$ and $D/S \times 9 = 1$. It follows that an evaluation of the values of $D/S+I \times 3{\cdot}3$ and $D/S \times 9$ from the control data of each prophylactic would provide an index of the stability of rates in each particular group being examined.

In order to transform the M.R.C. Committee's estimate of relative provocation into provocation indices their estimated rates per 100,000 injections have been divided by 1·3 as this value is their control rate, e.g. rate in the absence of provocation.

Examples, employing APT

(*a*) The M.R.C. method (see Table IV, Report, 1956) 0–28-day paralysis rate per 100,000 injections = 3·38. $R = 3{\cdot}38/1{\cdot}3$ or 2·6.

(*b*) Method using $R = S+I/D \times 3{\cdot}3$.

	0–28-day data	29–84-day data	
1st survey	$43/28 \times 3{\cdot}3 = 5{\cdot}06$	$10/32 \times 3{\cdot}3 = 1{\cdot}03$	Table 1
2nd survey	$13/12 \times 3{\cdot}3 = 3{\cdot}57$	$5/22 \times 3{\cdot}3 = 0{\cdot}75$	
Totals	$56/40 \times 3{\cdot}3 = 4{\cdot}62$	$15/54 \times 3{\cdot}3 = 0{\cdot}967$	

(*c*) Method using $R' = S/D \times 9$.

1st survey	$24/28 \times 9 = 7{\cdot}7$	$4/32 \times 9 = 1{\cdot}03$	Table 2
2nd survey	$8/12 \times 9 = 6{\cdot}0$	$1/22 \times 9 = 0{\cdot}41$	
Totals	$32/40 \times 9 = 7{\cdot}2$	$5/54 \times 9 = 0{\cdot}87$	

The results of the three methods of estimating R for all the prophylactics tested, with the appropriate control data estimate of R, are given in Table 2.

The importance of this tabulation is that it reveals the site of main discrepancy emerging from the two methods of analysis. By the M.R.C. method the value of R for pertussis vaccine alone is very small, and that for vaccine plus toxoid large,

indeed almost as large as for APT plus vaccine; whereas by the frequency of site of paralysis method the value of R for vaccine alone is much higher and scarcely—if at all—altered by the addition of the fluid toxoid.

While the site-frequency method of analysis began with the assumption that a given type of prophylactic, inoculated into poliovirus-infected children, would not only increase the rate of paralysis but do so uniformly, there is evidence that this is not so. This is seen in the analysis shown in Table 2, where the values of R for the

Table 2. *Estimates of R (provocation index) of different prophylactics using different methods of calculation*

(a = 0–28 day data, b = 29–84 day or control data. Arms only.)

	M.R.C. method (1951–53 only)		$R = S+I/D \times 3{\cdot}3$ method: both surveys		$R = S/D \times 9$ method: 1951–55 combined	
Prophylactic	*a*	*b*	*a*	*b*	*a*	*b*
APT	2·64	1·075	4·62 (5·06, 3·57)*	0·917 (0·75, 1·0)	7·2	0·83
PTAP	4·6	0·92	3·3 (4·03, 1·1)	1·2	6·75	0·82
TAF and FT	1·075	0·77	1·65	0·776	3	0·53
Pertussis vaccine	1·46	0·92	4·125 (5·78, 2·48)	1·1	4·5	0·75
Mixed, with alum (1951–53 only)	6·15	1·38	21·4 (30 cases)	4·95 (5 cases only)	54	13·5 (5 cases only)
Mixed, without alum	5·0	2·07	3·3 (4·62, 2·7)	1·04	6·2	0·95
All prophylactics	—	—	4·5 (5·6, 2·7)	1·0	8·0	1·0

* First number within the brackets from 1951–53 survey, second number from 1954–55 survey.

individual prophylactics are all greater for the 1951–53 survey than in the 1954–55 investigation—the reduction is to about half the 1951–53 values, and again in the figures for the overall estimate of R, being 5·27 for the first survey, and 1·52 for the second.

The reason for this reduction in provocation for the same materials in the second of the two surveys is obscure: the average paralytic poliomyelitis attack rate is virtually the same for the two time intervals (see Table 3). Three possibilities were investigated to try to account for the difference: (1) variations in sunlight and temperature, (2) variations in rainfall, and (3) variations in the predominant type of poliovirus occurring during the time intervals of the two surveys. No apparently useful correlation appeared between the average quarterly or yearly variations in temperature, hours of sunlight or rainfall except a very rough one that hot, dry years were associated with an increased attack rate.

Table 3. *Age-frequency distribution of paralytic poliomyelitis: England and Wales* 1950–55 *inclusive*

Year	Age (years) 0–	1–	3–	5–	10–15	Total 0–15	15+	Total (all cases)
1950 *a*	256	1,037	821	1,130	555	3,799	1,733	—
b	6·74	27·61	21·61	29·79	14·61	100	(+23	5,555
c	—	—	—	—	—	68·39	unknown)	—
1951 *a*	61	267	227	291	136	982	545	—
b	6·21	27·91	23·12	29·63	13·85	100	—	1,572
c	—	—	—	—	—	64·3	—	—
1952 *a*	108	490	397	619	220	1,834	906	—
b	5·88	26·72	21·65	33·75	12·0	100	—	2,740
c	—	—	—	—	—	67·0	—	—
1953 *a*	110	407	387	733	266	1,903	1,067	—
b	5·87	21·39	20·34	40·62	11·87	100	—	2,970
c	—	—	—	—	—	64·0	—	—
1951–53 *a*	279	1,164	1,011	1,643	622	4,719	2,518	—
inclusive *b*	5·91	24·67	21·42	34·82	13·18	100	—	7,273
c	—	—	—	—	—	65·21	—	Mean 2,424
1954 *a*	49	253	183	353	96	934	379	—
b	5·25	27·09	19·59	37·79	10·28	100	—	1,313
c	—	—	—	—	71·1	—	—	—
1955 *a*	158	545	502	954	347	2,506	1,205	—
b	6·31	21·75	20·03	38·07	13·85	100	—	3,711
c	—	—	—	—	—	67·5	—	—
1954–55 *a*	207	798	685	1,307	443	3,440	1,584	—
inclusive *b*	6·02	23·20	19·91	37·99	12·88	100	—	5,024
c	—	—	—	—	—	68·47	—	Mean 2,512
1950–55 *a*	742	2,999	2,517	4,080	1,620	11,958	5,835	—
inclusive *b*	6·205	25·08	21·05	34·12	13·55	100	—	17,816
c	—	—	—	—	—	67·00	—	—

a = number of cases; *b* = % 0–15 years total; *c* = % total all cases.

The available information on the epidemiology of the three types of poliovirus for England and Wales is as follows:

	Virus types			
Year	1	2	3	
1951–52	7 (46·7 %)	1 (6·6 %)	7 (46·7 %)	Goffe (1955)
1953	46 (44·66 %)	45 (43·69 %)	12 (11·65 %)	
1954	46 (92 %)	4 (8 %)	Nil	
1955 (pooled data)	83 (60·14 %)	9 (6·52 %)	46 (33·3 %)	Payne & Freyche (1956)

It will be seen that the major difference in the frequency of types, in so far as the data will show, is the low rate of Type 2 for the years 1954–55 and the very high rate for 1953. From this it may, tentatively, be concluded that for a given type of prophylactic the value of R is greatest when the child is infected with Type 2 virus. This conclusion would be much stronger—or discounted altogether—if the epidemiological data for 1951–52 were more substantial. Even so, there may be some support for this tentative conclusion in that (*a*) Rhodes (1953) and Peach & Rhodes (1954) could find no evidence of provocation in Canadian children, and (*b*) by far the most dominant type of poliovirus in Canada between 1948 and 1955 was Type 1, Type 2 being very rare (Rhodes quoted by Payne & Freyche, 1956). In Ontario in 1955, however, Type 2 was much less rare.

Again, in table V of the M.R.C. Committee's Report it will be seen that the ratio of incidence of paralytic poliomyelitis 0–28 days after inoculation to the 29–84-day incidence is much greater for 1953 than 1952: 1952, 5·2/2·1 = 2·48; 1953, 3·6/0·8 = 4·5.

The 1951 data cannot reliably be used as the virus-type data are inadequate. One further point, in table VI of the same Report is recorded the incidence rates for 0–28 days and 29–84 days per 100,000 inoculations for each quarter of the year—1952–53 inclusive. The ratio of rates for the second quarter is outstandingly severe:

1st quarter	1·1/0 —
2nd quarter	5·6/0·4 = 14·0
3rd quarter	8·1/4·5 = 1·8
4th quarter	2·6/1·3 = 2·0

Goffe (1955) found that during 1953 there was a rapid increase in the proportion of Type 2 virus from January to July followed by its displacement by Type 1 during November to the following year. Although the evidence is small in quantity and restricted to the south of England, it does show the possibility for an 'explosive' predominance of Type 2 in the first half of 1953 which might account for the marked differences in the ratio of rates described.

Analysis of P

Three main factors would seem to contribute to the probability that a child is infected by poliovirus in any unit (1 month) of time. These are: (1) the overall severity of the disease in the child population, (2) the time of the year and (3) the

age of the child. In respect of the mass inoculation of children, advantage may be taken of factors (2) and (3) in order to help minimize the risk from the paralytic poliomyelitis provocation action of the prophylactics used.

Time of year variable

The pattern of the paralytic poliomyelitis incidence rates for each quarter of the year is, by and large, uniform over the years having their highest values during summer and autumn. Restriction, national or regional, to those quarters of low incidence is, of course, clearly to be recommended, particularly in times of severe epidemics.

The age-risk variable

Since the purpose of this communication is to plead the case for the use of combined antigens early in life, and the age interval 3–4–5 months is a very suitable one, the point at issue is to estimate the relative probability of injecting an infected child during the age interval 3–6 months compared with another aged 1–3 years. For the present purpose it is assumed that the rate of paralysis attack is uniformly related to infection rate.

For this aspect of the analysis it is necessary to know to what extent the age-frequency distributions of paralytic poliomyelitis vary during epidemics of different severity. In Table 3 is shown the age/frequency analysis for the years 1950–55 inclusive, where in 1950 the epidemic was severe and in 1951 and 1954 relatively mild (data taken from Registrar General's Statistical Reviews of England and Wales). It will be seen that the frequency/age as a percentage of the total frequency is, in every year, remarkably uniform, and that the frequency of paralytic poliomyelitis during the first 12 months of life is 6·2 % of the total for the interval 0–15 years, with a maximum frequency between 1 and 3 years of age.

Advantage is taken of this uniformity of frequency/age distribution and the fine analysis of the frequency 0–12 months of age provided by Logan (1952), to make an estimate of the relative risk (or relative probability) of injecting a polio-virus-infected child *once* between its first and third birthday to the total relative risk involved in giving three injections at ages 3–4–5 months of age. The frequency of paralytic poliomyelitis for the time interval 3–4–5 months from Logan's figures is $4{\cdot}72 + 5{\cdot}90 + 7{\cdot}48 = 18{\cdot}1\,\%$ of the total for the first year of life. Whence for every 100 cases of paralytic poliomyelitis occurring per year in the 0–15-year age group, 6 will be less than 1 year old, 46 between 1 and 3 years of age, and 52 between 3 and 15 years. The average monthly risk for the 1–3 year olds is therefore 46/24, or 1·9 % of the total and the cumulative 3-month risk at age 3–4–5 months is $6 \times 18/100$ or 1 % of the total, namely, the entire risk taken in giving a three-dose course at 3–4–5 months of age is less than the average risk taken in giving one dose between the first and third birthday.

These calculations are based on the assumption that there is a uniform rate of paralysis to infection; there is, however, some good evidence that this is not so. This is provided by Melnick (1954) who determined—by means of sampling—the virus antibody titres of groups of children before and after the severe poliomyelitis

epidemic that occurred in Winston-Salem in 1948. This epidemic followed 4 years of very low incidence of poliomyelitis. By knowing the number of cases of paralytic poliomyelitis in each age group, the total number of children in each group, and the percentage that developed virus antibodies consequent on the epidemic, Melnick was able to estimate the degree of infection in each age group and the rates of paralysis to infection. He found a remarkable uniformity of infection rate in the several groups, but the rates of paralysis per 1000 infections were different in different age groups. The lowest paralysis rate was in the 0–1 year group being 6/1000 and highest in the 5–9 year group at 16/1000. Unfortunately for the present purpose the 0–1 year data were not broken-down to 0–6, 7–12 months of age. Even so, should Melnick's findings be generally true then the same overall conclusion is arrived at, since the evidence shows that the very young are more able to escape paralysis, when infected, than when only a few months older. Furthermore, if the indicated tendency holds, then the paralysis rate per 1000 infections would be reduced to about one at 3–4–5 months of age. And finally, Payne & Freyche (1956) have drawn attention to the scattered indications that whooping cough itself is a predisposing factor for paralytic poliomyelitis, from which it would follow that not only does early immunization with pertussis vaccine protect against whooping cough directly but against paralytic poliomyelitis indirectly.

DISCUSSION

Martin (1950), Geffen (1950), and McCloskey (1950) each brought forward evidence to show that the poliomyelitis paralysis attack rate was increased in children as a result of prophylactic inoculation against whooping cough and diphtheria. This naturally evoked serious anxiety in those concerned with the preservation of an efficiently immunized child population against the two latter diseases. The findings of these early workers have been confirmed, and in addition it has been shown that alum-containing toxoid plus pertussis vaccine is outstandingly the most dangerous preparation, followed by precipitated toxoids and plain pertussis vaccine, all of which had approximately equal paralysis-provoking effect. Plain or fluid toxoid and TAF were the least provoking. A return to the use of liquid diphtheria toxoid, first suggested in 1951—as the sole diphtheria prophylactic—seemed retrograde in that it would probably result in a far less efficiently immunized child population than that prevailing. Formol toxoid is a very weak antigen compared with APT or PTAP and since the disease has virtually disappeared from the country mothers are becoming increasingly indifferent to its dangers.

Bousfield (1951), who had already been working on the responses of very young infants to different forms of diphtheria and diphtheria-pertussis antigens, suggested that the poliomyelitis paralysis provocation risk could be greatly reduced by inoculating infants at 3–4–5 months of age, and showed that the use of combined fluid toxoid and pertussis vaccine was indeed a very efficient procedure, both on long- and short-term ratings. The immunological advantage of the combination lay in the fact that the vaccine acts as a powerful adjuvant to the toxoid; the further advantage was related to the three spaced injections of this prophylactic

that were recommended. Spiller, Barnes, Holt & Cullington (1955) who, by bleeding infants aged 15 months—some 9 months after their last inoculation—found that immunization with three doses of combined fluid toxoid and pertussis vaccine resulted in a geometric mean titre of 0·54 u./ml. (units of diphtheria antitoxin per ml. of serum). This may be compared with 0·27 u./ml. following the two doses of APT measured under roughly similar circumstances (Barr, Glenny & Randall, 1950). In the opinion of the present author a geometric mean titre of 0·54 u./ml.—a Schick failure rate of about 6/10,000—at age 15 months and measured 9 months after the last injection is more than adequate for protection up to 5 years of age—when the pre-school booster dose is given. By contrast two doses of 30 Lf of purified toxoid result in a Schick Conversion Rate (S.C.R.) of about 96·6 % (Bousfield & Holt, 1954) or a geometric mean titre of 0·06 u./ml. of antitoxin (Holt, 1955). It is estimated that to double the Lf dosage (to 60 Lf) would not increase the geometric mean titre by more than 50 %, and such a figure is but one-sixth of that resulting from three doses of the combined prophylactic.

Because the mortality from whooping cough is greatest during the first year of life it is important to immunize children in early infancy, and for effective prophylaxis three spaced inoculations of the vaccine are required. By doing this the infant is protected against whooping cough and at a time of extremely low risk of being inoculated while also infected with poliovirus. Mothers will bring their infants to Immunization Clinics for protection against whooping cough and be quite willing to have them at the same time immunized against diphtheria, but are less likely to return at a later date for a separate course of inoculations against diphtheria. The vital issue is, therefore, whether the admixture of fluid toxoid to the pertussis vaccine does or does not significantly increase the paralytic poliomyelitis provocation risk. The method of analysis of the available data, described above, does not support the contention that there is an increased risk with this particular preparation in early infancy.

The suggestion that provocation is more closely associated with Type 2 poliovirus infections is of considerable interest and it is possible that an appropriate re-examination of the finer details of the M.R.C. Committee's data would reveal information of value on this point.

SUMMARY

The variables operating in respect of the risk of provoking paralytic poliomyelitis by inoculating children with different prophylactic reagents have been analysed.

It is concluded that the use of combined diphtheria fluid toxoid and pertussis vaccine, administered in early infancy, incurs a minimal risk and is to be recommended because of its immunological efficiency, its unquestionable value in helping to maintain a high immunization rate against diphtheria in the child community and for its marked administrative convenience.

REFERENCES

BARR, M., GLENNY, A. T. & RANDALL, K. J. (1950). *Lancet*, i, 6.
BODIAN, D. (1954). *Amer. J. Hyg.* **60**, 358.
BOUSFIELD, G. (1951). *Lancet*, i, 1028.
BOUSFIELD, G. & HOLT, L. B. (1954). *Med. Offr.* **92**, 289.
GEFFEN, D. H. (1950). *Med. Offr.* **83**, 137.
GOFFE, A. P. (1955). *Proc. r. Soc. Med.* **48**, 937.
HOLT, L. B. (1955). *Biometrics*, **11**, 83.
LOGAN, W. P. D. (1952). *Mon. Bull. Minist. Hlth Lab. Serv.* no. 147.
MARTIN, J. K. (1950). *Arch. Dis. Childh.* **25**, 1.
MCCLOSKEY, B. P. (1950). *Lancet*, i, 659.
MELNICK, J. L. (1954). *Amer. J. publ. Hlth*, **44**, 571.
PAYNE, A. M. M. & FREYCHE, M. J. (1956). *Bull. World Hlth Org.* **15**, 43.
PEACH, A. M. & RHODES, A. J. (1954). *Amer. J. publ. Hlth*, **44**, 1185.
REPORT OF THE MEDICAL RESEARCH COUNCIL'S COMMITTEE ON INOCULATION PROCEDURES AND NEUROLOGICAL LESIONS (1956). *Lancet*, ii, 1223.
RHODES, A. J. (1953). *Canad. med. Ass. J.* **68**, 107.
SPILLER, V., BARNES, J. M., HOLT, L. B. & CULLINGTON, D. E. (1955). *Brit. med. J.* ii, 639.

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