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THE PREVENTION OF WHOOPING-COUGH BY VACCINATION

A MEDICAL RESEARCH COUNCIL INVESTIGATION*

Since 1942 investigations have been in progress under the direction of the Whooping-cough Immunization Committee of the Medical Research Council to assess the prophylactic value of pertussis vaccines. From 1942 to 1944 controlled trials were made in Oxford City with children attending welfare clinics and day nurseries, and also in Oxfordshire, Berkshire, and Buckinghamshire with children in residential nurseries. A report of this work was published by McFarlan, Topley, and Fisher (1945). No significant difference was observed in the incidence or severity of the disease between the vaccinated and unvaccinated groups. In the Oxford City trial 12.5% of 327 vaccinated and 14.1% of 305 unvaccinated children developed pertussis, while in those residential nurseries in which whooping-cough occurred 55% of 33 vaccinated children and 63% of 30 unvaccinated children were attacked. Similar unfavourable results have been reported by others. Doull and his colleagues (1939) described a trial, comprising 479 vaccinated and 496 unvaccinated children who were the older siblings of the former, in which the numbers of cases of pertussis in the two groups were 74 and 94 respectively. Siegel and Goldberger (1937), in a trial in a tuberculosis sanatorium, reported attack rates in children exposed to the disease of 53% in the vaccinated and 58% in the unvaccinated groups.

On the other hand, the majority of vaccination studies, most of which were made in the United States of America and Canada, indicated that pertussis vaccine produced a significant degree of protection. Many of these studies were reviewed by Felton and Willard (1944) and by Tudor Lewis (1946). The first hopeful results were observed by Zachariassen (see Madsen, 1933) in two epidemics in the Faroe Islands. A plain vaccine was used prepared from freshly isolated strains of *Haemophilus pertussis*. In the first epidemic, vaccination was begun during the outbreak and was found to have no effect on incidence, although it was reported to have reduced the severity of the disease. In the second epidemic, vaccination was completed shortly before the outbreak occurred, and of the 1,832 vaccinated children 75% contracted pertussis, compared with 98.2% among the 446 unvaccinated children. Encouraging results were later obtained by Sauer (1937), who used a plain vaccine prepared from strains which fulfilled the criteria for phase I *H. pertussis* described by Leslie and Gardner (1931). In this investigation Sauer vaccinated 1,122 children, and reported that of 128 who were subsequently exposed to pertussis, 94 in their own homes, only six developed the disease. Of the many studies made with plain vaccine the best known are those conducted by Kendrick and Eldering (1939). These studies comprised a total of 4,212 children, divided into vaccinated and unvaccinated groups which were similar in a number of respects. Of children exposed to infection in the home 34.9% in the vaccinated group contracted pertussis compared with 89.4% in the unvaccinated group.

In the majority of studies with plain vaccine the total dosage was relatively large in volume (sometimes 7 ml.) and in numbers of organisms (70 to 120 thousand million), and was given in three to five injections. More recently investigations have been made to determine whether effective protection could be obtained with alum-precipitated pertussis vaccine when given in smaller doses than those used with plain vaccines. Bell (1941, 1948) made two well-controlled trials, the first with alum-precipitated vaccine alone and the second with alum-precipitated combined pertussis vaccine and diphtheria toxoid. In each trial the total dose of vaccine was 20 thousand million organisms, given in two inoculations at an interval of four weeks. The incidence of the disease among the unvaccinated children was three to four times greater than that among the vaccinated. Kendrick (1942, 1943) also obtained good results with an alum-precipitated vaccine which was given in three doses.

In view of these favourable reports the Whooping-cough Immunization Committee concluded that the vaccines used in their trials in 1942–4 differed in some material though unknown way from those vaccines which had been shown to give protection. The Committee therefore decided to carry out a new series of

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Medical Officers of Health: The late Dr. G. C. Williams (Oxford); Dr. C. Metcalfe Brown (Manchester); Dr. F. Roy Dennison (West Ham); Dr. G. Hamilton Hogben (Tottenham); the late Dr. A. G. Morison and Dr. E. Grundy (Wembley); Dr. J. Johnstone Jervis, Dr. J. F. Warin (Deputy M.O.H.), and Dr. I. G. Davies (Leeds); Dr. D. Regan (Edmonton).

Field Workers: Dr. M. Fisher and Miss C. Rudkin (Oxford); Dr. A. V. Magee and Miss O. I. Howell (Manchester); Dr. W. C. Cockburn, Miss M. A. Massey, and Miss M. M. Wall (Wembley, Tottenham, and Edmonton); Dr. G. R. Baxter and Mrs. E. R. Beard (Leeds); Dr. F. Barasi and Mrs. L. J. Bunch (West Ham).

Laboratory Workers: Dr. R. Knox (Oxford); Dr. H. W. Clegg, Dr. H. R. Cayton, and Dr. M. T. Parker (Manchester); Dr. A. J. H. Tomlinson and Dr. H. D. Holt (Colindale); Professor J. W. McLeod, Mrs. E. H. Farnworth, and Dr. B. Dawson (Leeds); Dr. W. W. Walther (West Ham).

The trials were planned with the advice of the Statistical Research Unit of the Medical Research Council and were arranged and supervised by Dr. W. C. Cockburn.

The results were analysed and the report prepared by Dr. W. C. Cockburn, Dr. D. G. Evans, and Dr. J. Knowelden.

field trials with a number of vaccines prepared in different laboratories and to include vaccines of American origin which in previous studies had been reported to give substantial protection.

The first trial in this new series was in Oxford City. Three batches of Sauer vaccine, prepared by Messrs. Parke Davis & Co., of Detroit, were tested. In all, 1,530 children between the ages of 6 months and 5 years were inoculated, 785 with pertussis vaccine and 745 with "anticatarrhal" vaccine containing no *H. pertussis*. After inoculation the children were observed for a period of two to three years. The total number of definite cases of pertussis diagnosed in those children who received pertussis vaccine was 113 and in those who received "anticatarrhal" vaccine 165, giving attack rates per 1,000 child-months of observation of 5.28 and 8.17 respectively. In addition to these definite cases there were 143 doubtful cases—80 in the group which received pertussis vaccine and 63 in the comparative group. This trial was begun during the war, in 1944, when it was impossible to obtain adequate staff to deal with intensive follow-up investigations. Further, the staff necessary and the number of visits required to ensure the standard of accuracy needed in these trials were, at this early stage, underestimated by the Committee. The follow-up studies, therefore, were in many cases incomplete. For this reason the Committee does not propose to draw any firm conclusions from the results of this early trial, though it appears unlikely that the vaccines were highly effective. The trial, however, provided invaluable information regarding the problems associated with organization, and the subsequent trials, reported below, were planned in the light of experience gained in the Oxford investigation.

General Plan of Investigation

In all trials a uniform plan was followed. Children between the ages of 6 and 18 months, whose parents agreed that they should be inoculated, were divided by the method of random sampling into two groups of approximately equal size. *The children in one group were inoculated with pertussis vaccine and are referred to subsequently as "vaccinated." Those in the other group were given a similar dose of "anticatarrhal" vaccine which contained no H. pertussis and are referred to subsequently as "unvaccinated."* After inoculation each child was visited at frequent intervals for a period of two to three years by a nurse-investigator. Neither the parents nor the observers knew whether a child was in the vaccinated or the unvaccinated group.

Five batches of pertussis vaccine from three manufacturers—Messrs. Parke Davis & Co., of Detroit, the Michigan Department of Health, and Messrs. Glaxo Laboratories Ltd.—were used in ten separate field trials in Leeds, Manchester, Tottenham and Edmonton, Wembley, and West Ham. Information on the nature and dosage of the vaccines and the areas to which they were allocated is given in Table I. The "anticatarrhal" vaccine was prepared specially for the inquiry by Messrs. Burroughs Wellcome & Co. It contained killed suspensions of *Staphylococcus aureus, Streptococcus pneumoniae, Corynebacterium hofmannii, and Neisseria catarrhalis,* and was similar in turbidity to the plain pertussis vaccines. It was dispensed in the same type of bottle as that used for the pertussis vaccines.

Procedure in the Field

In each trial area a "pertussis team" was appointed comprising a full- or part-time medical officer, a nurse-investigator for each group of 400–500 children, and a full- or part-time clerk. The members of the teams in most areas were appointed from the staff of the local health department who had had close associations in their routine work with mothers of young children and experience in the administration and day-to-day work of diphtheria immunization schemes. Where it was not possible to make such arrangements the teams were appointed by the Committee in collaboration with the medical officer of health.

Propaganda

Parents with children aged 6–18 months were given a pamphlet, to which was attached a parent's consent form, explaining the scheme. The pamphlet was either sent by post, distributed at welfare centres, or handed to the mothers by a health visitor on her routine visits. In the pamphlet it was made clear that the vaccines were being tested, that it was necessary to inoculate some of the children with a substance which was not whooping-cough vaccine, and that parents and observers would not know until the end of the investigation whether a child was in the vaccinated or the unvaccinated group. In addition, posters were displayed in welfare centres and nursery schools, and in some areas the medical officers of health publicized the scheme with the help of the Press, the cinema, and the radio. A letter was sent to all general practitioners in the area giving them details of the plan and inviting them to co-operate by giving advice on the scheme to parents and by informing the health department of suspected cases of pertussis among trial children under their care.

TABLE I.—*Trial Areas, Vaccines, and Dosage Schedules*

Trial Area	Vaccine				Dosage Schedule	
	Batch	Manufacturer	Description	Conc. in Millions of Organisms/ml. (American Count)*	Doses at Monthly Intervals (ml.)	Total Dose in Millions of Organisms
Manchester	Sauer 087860	Parke Davis & Co., Detroit	Plain suspension	15,000	1, 2, 3	90,000
Manchester, Tottenham and Edmonton, Wembley	Michigan D231	Michigan Dept. of Health	,, ,,	10,000	1, 2, 3	60,000
Leeds	Glaxo 61	Glaxo Laboratories	Alum precipitated	50,000	0·75, 0·75, 0·75	112,000
Leeds	Glaxo 174	,, ,,	,, ,,	50,000	0·75, 0·75, 0·75	112,000
West Ham	Glaxo 174	,, ,,	,, ,,	50,000	0·5, 0·5, 1	100,000
Manchester, Tottenham and Edmonton, Wembley	Michigan A236	Michigan Dept. of Health	Plain suspension	10,000	1, 2, 3	60,000

* Concentrations of all vaccines are given in terms of the American count, as British and American vaccines, with the same labelled concentration, differ considerably in density (see McFarlan, Topley, and Fisher, 1945).

Allocation of Children to the Vaccinated and Unvaccinated Groups

On receipt of signed consent forms from the parents, children with no previous history of pertussis or of previous inoculation with pertussis vaccine were classified by sex and placed in one of the following age groups: 6–8, 9–11, 12–14, and 15–17 months; a few children were accepted just after they had reached the age of 18 months. For each age and sex group, sheets were previously drawn up on which vaccine letters A, B, C, and D in random order were repeated a sufficient number of times to deal with all expected volunteers in the appropriate age and sex group. As each child's name was received it was written in the first vacant space on the appropriate sheet, and the vaccine letter opposite the child's name determined what it should receive and was inserted on the child's record card.

Although four vaccine letters were used, two of them in fact indicated the pertussis vaccine being tested in the trial and the other two the "anticatarrhal" vaccine. It was thought that by employing this method field-workers would be less likely to distinguish the pertussis vaccine from the "anticatarrhal" vaccine. As the early trials progressed it became evident that more cases of pertussis were occurring in children inoculated with vaccines A and C—the "anticatarrhal" vaccines—than in children with vaccines B and D—the pertussis vaccines. There was also some difference in the incidence of slight inoculation reactions between the pertussis and "anticatarrhal" vaccines. To ensure, therefore, that follow-up observations remained unbiased, the vaccine letter on each record card was covered by a thick label until the end of the investigation or until the duration and severity of an attack of pertussis had been recorded on the card.

Inoculation of Children

When sufficient names had been obtained, clinic sessions were arranged on an appointment system. On arrival at the clinic the children were inoculated with vaccine from the bottle labelled with the appropriate vaccine letter. Three inoculations were given at monthly intervals. In general the inoculations were given intramuscularly, although in some areas at the beginning of the trials they were given subcutaneously. One child in every five was visited 24–72 hours after each inoculation to determine the severity of the reaction.

If a child failed to attend for the first inoculation, a second and, if necessary, a third appointment was arranged, and if these were not kept, no further steps were taken and the child was excluded from the trial. Further appointments were also made for those children who failed to attend for the second or third inoculation, and if they still failed to attend they were visited to ascertain the reason. In most cases a satisfactory reason was obtained.

When each child received the last inoculation the mother was given a report slip in a stamped envelope addressed to the health department and was instructed to post this slip if the child had been in contact with whooping-cough or had developed suspicious symptoms.

Follow-up Observations

When the course of inoculations was completed each child was visited monthly by a nurse-investigator until the end of the investigation or until it was excluded from the trial. On the first visit the information already entered on the record card was checked and notes were made of the duration of breast-feeding and of the number of other children under 14 years of age living in the house. On subsequent monthly visits information was obtained on exposures to pertussis, the incidence of upper respiratory-tract infections, the history of diphtheria immunization and smallpox vaccination, and the incidence of measles, chicken-pox, bronchopneumonia, and diphtheria.

When it was found, either on a routine visit or by receipt of the report slip from the parent, that a child had been exposed to pertussis or had developed suspicious symptoms, repeated visits were made to determine the diagnosis and to assess the severity of the attack if it proved to be pertussis. So far as possible these special visits were made by the senior nurse-investigator or by the medical member of the pertussis team. During the special visits a detailed history of the intimacy and duration of exposure was obtained and, where possible, nasopharyngeal swabs were taken. Sometimes swabs were also taken from the presumed infecting case. The mother was asked to make notes of the number of paroxysms during each 24 hours at the height of the disease. Notes were also made by the observers of the nature and severity of complications. At the end of the illness the degree of severity of the attack (see footnote to Table VII) and the duration of the cough were recorded.

Once children who had developed pertussis were considered to have made a complete recovery, nurse-investigators were not required to visit them more often than every three months, although in fact in most areas it was found convenient to continue the monthly visits. These visits were necessary to obtain information on diphtheria immunization, on smallpox vaccination, and on the incidence of other infectious diseases.

Number of Children and Duration of Trials

The number of children whose parents agreed to take part in the investigation was 8,927, of whom 4,515 were allocated to the vaccinated and 4,412 to the unvaccinated group (Table II). Of these, 7,558 completed the course of inoculations—3,801 in the vaccinated and 3,757 in the unvaccinated group. Most of the remainder, 1,369 in all, were children whose parents repeatedly failed to

TABLE II.—*Numbers of Children in All 10 Trials*

	Vaccinated (Inoculated with Pertussis Vaccine)			Unvaccinated (Inoculated with "Anticatarrhal" Vaccine)			Total
	Male	Female	Both Sexes	Male	Female	Both Sexes	
Total children entered for inoculation	2,182	2,333	**4,515**	2,273	2,139	**4,412**	**8,927**
Excluded before completion of inoculations*	359	355	**714**	341	314	**655**	**1,369**
Total number given 3 inoculations	1,823	1,978	**3,801**	1,932	1,825	**3,757**	**7,558**
Excluded during follow-up period†	218	225	**443**	213	192	**405**	**848**
Total number remaining at end of follow-up period	1,605	1,753	**3,358**	1,719	1,633	**3,352**	**6,710**

* Persistent defaulters; developed or were in contact with pertussis; moved from area; illness or death not associated with pertussis or inoculation.
† Moved from area; reinoculated by private doctor; death not associated with pertussis or inoculation; uncooperative parents. Observations on these children, up to the time when they were lost from the investigation, were included in the analysis.

keep appointments for the first inoculation. After the first inoculation few parents defaulted, and those that did had good reasons, such as prolonged illness in the child or removal from the trial area. The period for observation began as soon as each child received its third inoculation. After the completion of inoculations, 848 children were lost from observation at varying intervals, in most cases because they left the area. Other reasons for withdrawal are given in the footnote to Table II. Observations on these children, up to the time when they were lost from the investigation, were included in the analysis. At the end of the investigation 6,710 children remained; 3,358 were in the vaccinated and 3,352 in the unvaccinated group.

Trials were begun between November, 1946, and April, 1948, and were completed during 1950. In all trials, except that in West Ham, the inoculations were given within a period of three to six months; in West Ham most of the children were inoculated during the first year of the investigation. On the average, each child was observed for 27 months after its third inoculation; the average period varied from 23 to 30 months in the separate trials. The period of each trial in relation to the incidence of notified cases of pertussis in the general population is shown in the Chart.

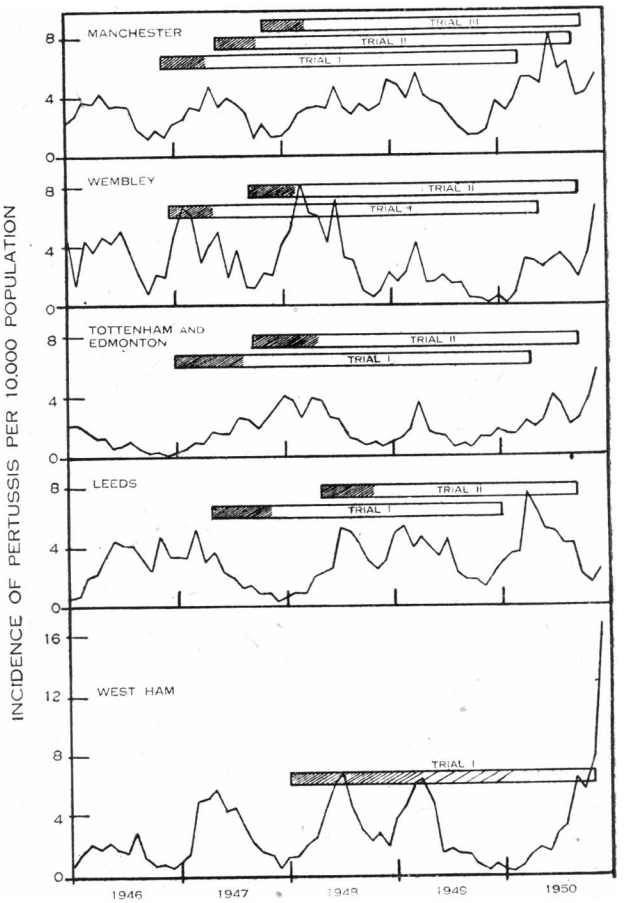

Chart showing notified incidence of pertussis per 10,000 population (all ages), from 1946 to 1950, in the trial areas. The horizontal blocks indicate the period of the trials and the shaded areas the period during which the inoculations were given. In the West Ham trial the densely shaded area indicates the period during which the majority of children were inoculated.

Similarity of Vaccinated and Unvaccinated Groups

The method of allocation of the children to vaccinated and unvaccinated groups was found, by examining certain relevant attributes of the children, to give two groups of closely similar character. It is clear from Table III, which relates to all 10 trials, that the two groups were similar in the number of children, their average age, the average number of children (including the trial child) under 14 years of age in the families, and the average duration of the period over which they were observed. Furthermore, the similarity of the two groups was evident from the information relating to breast-feeding, infectious diseases other than pertussis, immunization against diphtheria, and vaccination against smallpox. In each separate trial also, the two groups were similar in character.

Reactions to Inoculations

One child in every five in the vaccinated and unvaccinated groups was visited 24–72 hours after each inoculation. With the plain vaccines no severe local or general reactions were observed, although a number of children developed a rise in temperature within 24 hours of inoculation, and in some the site of inoculation was red and swollen for one to two days. In only a few instances were the reactions such that the mother refused to co-operate further. There was no apparent increase in the incidence of reactions after the second

TABLE III.—*Similarity of Vaccinated and Unvaccinated Groups in All 10 Trials*

	Vaccinated			Unvaccinated			Grand Total
	Male	Female	Total	Male	Female	Total	
Total No. of children given 3 inoculations	1,823	1,978	**3,801**	1,932	1,825	**3,757**	7,558
Average age (months)	12·1	12·3	**12·2**	12·2	12·2	**12·2**	12·2
Average duration of observation per child (months)	26·9	27·2	**27·1**	27·2	27·2	**27·2**	27·1
Average No. of children under 14 years per household	1·8	1·8	**1·8**	1·8	1·8	**1·8**	1·8
Breast-feeding:							
No. breast-fed	1,457	1,575	**3,032**	1,540	1,471	**3,011**	6,043
Average duration of breast-feeding (months)	5·4	5·3	**5·3**	5·3	5·4	**5·4**	5·4
No. not breast-fed	321	350	**671**	344	308	**652**	1,323
No. where history not known	45	53	**98**	48	46	**94**	192
No. of cases of certain other infectious diseases in children during the trial:							
Measles	440	480	**920**	471	420	**891**	1,811
Chicken-pox	138	151	**289**	139	141	**280**	569
Bronchopneumonia	50	45	**95**	53	41	**94**	189
Diphtheria	0	1	**1**	1	0	**1**	2
Total	628	677	**1,305**	664	602	**1,266**	2,571
No. known to be:							
Immunized against diphtheria	1,592	1,736	**3,328**	1,716	1,609	**3,325**	6,653
Vaccinated against smallpox	1,151	1,240	**2,391**	1,205	1,141	**2,346**	4,737

and third inoculations. In trial areas where alum-precipitated vaccines were used, six children developed sterile abscesses.

Byers and Moll (1948), Toomey (1949), and others, in the United States of America, and Anderson and Morris (1950), in this country, reported the occurrence of convulsions and encephalopathies as rare complications of pertussis vaccination. Martin (1950), McCloskey (1950), Geffen (1950), and Bradford Hill and Knowelden (1950) drew attention to the occurrence of poliomyelitis in which the paralysis affected with undue frequency the limb which had recently been injected with diphtheria or pertussis or with the combined prophylactic. These reports were made while the present studies were in progress, and the records of all children who had completed the course of inoculations were carefully scrutinized and most of those children who had not completed the course were revisited. None of the children had a history of convulsions, and in none did poliomyelitis develop within the arbitrarily chosen period of two months after inoculation. In only two trials—Manchester II and Leeds I—were the children inoculated during periods of high incidence of poliomyelitis, and as the numbers of children were relatively small the risk of any one child developing poliomyelitis was remote.

Incidence and Severity of Pertussis

Attack Rates Per 1,000 Child-months of Observation

In all ten trials the total number of cases of pertussis diagnosed in the vaccinated groups was 149 and in the unvaccinated groups 687 (Table IV). The corresponding attack rates per 1,000 child-months of observation were 1.45 and 6.72—a ratio of 1:4.6. This difference in attack rates is clearly significant. In both vaccinated and unvaccinated groups the attack rates in females were higher than in males, an observation in agreement with previous epidemiological studies.

It is also evident (Table V) that in each separate trial the attack rate in the vaccinated was substantially less than in the unvaccinated group, but the ratio of the attack rates was not the same for all trials. These differences in ratios are taken into account when comparing the potency of vaccines (Table XIV).

Attack Rates in Children Known to Have Been Exposed to Pertussis

Analysis of information on the exposure of the children to pertussis showed that such occurrences could be conveniently divided into two categories: (1) "Home exposures"—children exposed in their own homes to infection in one or more siblings; (2) "other exposures"—children exposed to infection in day nurseries, in nursery schools, at parties, in cinemas, in buses, and while playing outside the home with other children. The figures for each of these categories are given for each trial and also for all 10 trials (Table VI). In the table the number of exposures to pertussis is recorded, not the number of children exposed, as some children were exposed on more than one occasion. Exposure to infection could also occur *after* a child in the trial had developed pertussis, but such exposures were not recorded.

The average attack rate in the "home exposures" for all 10 trials was 18.2% in the vaccinated and 87.3% in the unvaccinated groups. A high incidence of pertussis occurred in the unvaccinated group of each trial; in only one trial was the attack rate less than 75%. The attack rates in the vaccinated groups varied considerably with the different trials, and this variation is considered when comparing the potency of the vaccines (Table XIV).

With the "other exposures," the average attack rate for all 10 trials was 8.3% in the vaccinated and 38.0% in the unvaccinated groups. In this category the attack rates in both groups varied, but the variation was not as great in the unvaccinated as in the vaccinated groups.

A history of exposure was not obtained for every case, and 65 children in the vaccinated and 323 in the

TABLE IV.—*Number of Cases of Pertussis and Attack Rates per 1,000 Child-months of Observation in Vaccinated and Unvaccinated Groups in All 10 Trials*

	Vaccinated				Unvaccinated			
	No. of Children given 3 Inoculations	Duration of Observation* (Child-months)	Cases of Pertussis	Attack Rate per 1,000 Child-months	No. of Children given 3 Inoculations	Duration of Observation* (Child-months)	Cases of Pertussis	Attack Rate per 1,000 Child-months
Males	1,823	49,105	**68**	**1·38**	1,932	52,472	**327**	**6·23**
Females	1,978	53,856	**81**	**1·50**	1,825	49,708	**360**	**7·24**
Both sexes	3,801	102,961	**149**	**1·45**	3,757	102,180	**687**	**6·72**

* Observation began from the date of the third inoculation.

TABLE V.—*Number of Cases of Pertussis and Attack Rates per 1,000 Child-months of Observation in Vaccinated and Unvaccinated Groups in Each Trial*

Trial Area	Area-trial No.	Vaccine	Vaccinated				Unvaccinated			
			No. of Children given 3 Inoculations	Duration of Observation (Child-months)	Cases of Pertussis	Attack Rate per 1,000 Child-months	No. of Children given 3 Inoculations	Duration of Observation (Child-months)	Cases of Pertussis	Attack Rate per 1,000 Child-months
Manchester	I	Sauer 087860	415	12,125	32	**2·64**	449	13,241	89	**6·72**
Tottenham and Edmonton	I	Michigan D231	167	4,394	3	**0·68**	183	4,726	33	**6·98**
Wembley	I	Michigan D231	142	3,680	2	**0·54**	144	3,828	33	**8·62**
Manchester	II	Michigan D231	321	9,522	12	**1·26**	328	9,762	63	**6·45**
Leeds	I	Glaxo 61	489	13,392	27	**2·02**	464	12,864	85	**6·61**
Leeds	II	Glaxo 174	484	11,488	25	**2·18**	425	10,215	97	**9·50**
West Ham	I	Glaxo 174	727	16,768	29	**1·73**	771	17,464	92	**5·27**
Manchester	III	Michigan A236	460	13,445	11	**0·82**	458	13,828	94	**6·80**
Tottenham and Edmonton	II	Michigan A236	306	9,307	5	**0·54**	257	7,471	49	**6·56**
Wembley	II	Michigan A236	290	8,840	3	**0·34**	278	8,781	52	**5·92**
Totals			3,801	102,961	149	**1·45**	3,757	102,180	687	**6·72**

TABLE VI.—*Number of Cases of Pertussis and Percentage Attack Rates by Type of Exposure in Vaccinated and Unvaccinated Groups in Each Trial*

Trial Area	Area-trial No.	Vaccine	"Home Exposures"						"Other Exposures"						No. of Cases with no History of Exposure	
			Vaccinated			Unvaccinated			Vaccinated			Unvaccinated				
			No. of Exposures	No. of Cases	% Cases/ Exposures	No. of Exposures	No. of Cases	% Cases/ Exposures	No. of Exposures	No. of Cases	% Cases/ Exposures	No. of Exposures	No. of Cases	% Cases/ Exposures	Vaccinated	Unvaccinated
Manchester..	I	Sauer 087860	36	8	**22·2**	20	17	**85·0**	100	15	**15·0**	73	24	**32·9**	9	48
Tottenham and Edmonton	I	Michigan D231	12	0	**0**	15	14	**93·3**	20	1	**5·0**	21	9	**42·9**	2	10
Wembley ..	I	Michigan D231	9	1	**11·1**	12	8	**66·7**	33	0	**0**	42	12	**28·6**	1	13
Manchester..	II	Michigan D231	20	2	**10·0**	12	9	**75·0**	78	5	**6·4**	65	26	**40·0**	5	28
Leeds ..	I	Glaxo 61	23	7	**30·4**	21	19	**90·5**	69	6	**8·7**	71	29	**40·8**	14	37
Leeds ..	II	Glaxo 174	29	7	**24·1**	24	21	**87·5**	60	9	**15·0**	72	28	**38·9**	9	48
West Ham ..	I	Glaxo 174	18	7	**38·9**	19	18	**94·7**	23	4	**17·4**	36	22	**61·1**	18	52
Manchester..	III	Michigan A236	26	3	**11·5**	21	19	**90·5**	112	6	**5·4**	90	35	**38·9**	2	40
Tottenham and Edmonton	II	Michigan A236	14	2	**14·3**	16	15	**93·8**	26	1	**3·8**	22	12	**54·5**	2	22
Wembley ..	II	Michigan A236	16	0	**0**	13	11	**84·6**	45	0	**0**	69	16	**23·2**	3	25
Totals ..	..	.. ..	203	37	**18·2**	173	151	**87·3**	566	47	**8·3**	561	213	**38·0**	65	323

unvaccinated groups developed pertussis without the source of infection being known.

It is of interest that in the "home exposures," the "other exposures," and in children with no history of exposure the ratios of the incidence of pertussis in the vaccinated to that in the unvaccinated children was almost identical—namely, 1:4.8, 1:4.6, and 1:5.0.

Severity and Duration of Attack

The assessment of the degree of severity of attack was based, in general, on the parent's record of the number of paroxysms in 24 hours during the height of the disease (see footnote to Table VII). Parents varied in their ability to keep accurate records of the number of paroxysms and, in any event, no record could be made of the severity of each paroxysm. As a general guide to severity of attack, however, the method was valuable, particularly as neither parents nor members of the team knew whether any one child suffering from the disease was in the vaccinated or the unvaccinated group.

TABLE VII.—*Degree of Severity of Attack in Diagnosed Cases of Pertussis in All 10 Trials*

	Vaccinated (149 Cases)					Unvaccinated (687 Cases)					
	Degree of Severity*					Degree of Severity*					
	1	2	3	4	5	1	2	3	4	5	Not Stated
No. of cases..	32	77	29	9	2	17	148	281	212	28	1
Percentage	21·5	51·7	19·5	6·0	1·3	2·5	21·6	40·9	30·9	4·1	
	73·2		**26·8**			**24·1**		**75·9**			

* 1 = An abortive attack, with or without occasional paroxysms confirmed bacteriologically. 2 = Fewer than 10 paroxysms in 24 hours at height of disease. 3 = 10–20 paroxysms in 24 hours at height of disease. 4 = More than 20 paroxysms in 24 hours at height of disease. 5 = Attack complicated by bronchopneumonia, atelectasis, etc.

The severity of attack for cases in both the vaccinated and the unvaccinated groups for all 10 trials is given in Table VII. Degrees of severity of 1 and 2 may be considered as mild, and 3, 4, and 5 as moderate, severe, and complicated attacks. In the vaccinated 73.2% of cases were mild compared with 24.1% in the unvaccinated groups. Two complicated cases occurred in the vaccinated, compared with 28 in the unvaccinated. There were no deaths in either group.

An additional indication of severity was obtained by recording the duration of the cough (Table VIII). By this method also, a difference between the two groups was observed: 44.3% of cases in the vaccinated had a cough for less than six weeks, compared with 14.4% in the unvaccinated groups.

Similar differences in severity and duration of attack between vaccinated and unvaccinated children were observed when each trial was considered separately.

TABLE VIII.—*Duration of Cough in Diagnosed Cases of Pertussis in All 10 Trials*

	Vaccinated (149 Cases)					Unvaccinated (687 Cases)					
	Duration (Weeks)					Duration (Weeks)					
	Under 4	4–	6–	8–	10+	Under 4	4–	6–	8–	10+	Not Stated
No. of cases..	20	46	47	15	21	15	82	178	159	240	13
Percentage	13·4	30·9	31·5	10·1	14·1	2·2	12·2	26·4	23·6	35·6	
	44·3		**55·7**			**14·4**		**85·6**			

Duration of Immunity

An analysis was made which indicated that during the period of observation there was no waning in the degree of protection afforded by the pertussis vaccines. Attack rates at intervals after inoculation are given in Table IX for those vaccinated and unvaccinated children who were exposed to infection in their own homes. It is evident that the attack rate in the unvaccinated children was almost constant during the whole period of observation, and it is therefore justifiable to compare the corresponding attack rate in the vaccinated children. Throughout the period of observation the attack rate in the vaccinated children remained at approximately 20% and showed no evidence of increasing even two years after inoculation.

TABLE IX.—*Percentage Attack Rates in "Home Exposures" at Intervals After Inoculation in Vaccinated and Unvaccinated Children in All 10 Trials*

Period after Third Inoculation (Months)	Vaccinated			Unvaccinated		
	No. of Exposures	No. of Cases	% Cases/ Exposures	No. of Exposures	No. of Cases	% Cases/ Exposures
0–5 ..	54	8	15	49	44	90
6–11 ..	50	10	20	45	38	84
12–17 ..	36	6	17	41	39	95
18–23 ..	36	8	22	22	18	82
24 and over	27	5	19	16	12	75
Totals ..	203	37	18	173	151	87

A further analysis was made for each of the five vaccines separately, and for none of them, within the limits of the small numbers of cases involved, was there evidence of waning immunity during the period of observation.

Occurrence of Coughs not Diagnosed as Pertussis After Exposure to Infection

After reported exposure to pertussis particular attention was paid to all children for a period of 42 days. During this period a number of children developed a cough which was not paroxysmal in character. Most of those in whom the cough lasted for more than a week were swabbed. The average number of swabs taken from each child was 1.5. From some of these cases *H. pertussis* was isolated, and they were recorded as cases of pertussis with a degree of severity of 1, but in the majority no bacteriological evidence of pertussis infection was obtained.

The duration of the cough in these cases is given in Table X. It is evident that in 90% of the children the cough was of short duration, lasting for less than four weeks, and that there was no pronounced difference between the vaccinated and unvaccinated groups in its average duration. Further, from Table XI it is evident that the incidence of this type of cough in those who were exposed to pertussis but did not develop it was similar in both groups. For these reasons it was considered that most of these cases were not due to infection with *H. pertussis*.

TABLE X.—*Duration of Cough in Children Who Did Not Develop Pertussis but Who had a Cough which Began Between 7 and 42 Days After Known Exposure to Pertussis*

	Vaccinated (231 Children)					Unvaccinated (129 Children)				
	Duration (Weeks)					Duration (Weeks)				
	Under 2	2–	3–	4–	5+	Under 2	2–	3–	4–	5+
No. of cases	111	61	29	20	10	45	46	27	5	6
Percentage ..	48·0	26·4	12·6	8·7	4·3	34·9	35·6	20·9	3·9	4·7
	87·0			13·0		91·4			8·6	

TABLE XI.—*Incidence of Cough in Children who Did Not Develop Pertussis After Exposure*

	Vaccinated	Unvaccinated
Total No. of "home" and "other" exposures	769	734
No. of exposures followed by pertussis ..	84	364
No. of exposures not followed by pertussis ..	685	370
No. of cases of cough not diagnosed as pertussis	231	129
Percentage of cases of cough in exposures not followed by pertussis	34	35

Bacteriological Observations

Swabs were taken from 806 (96.4%) of the 836 clinically diagnosed cases (Table XII). Postnasal swabs were used in the early stages of the investigation, but later it was found that pernasal swabs gave better results (Cockburn and Holt, 1948) and these were then used in all areas. So far as possible the swabs were obtained in the first two weeks of the disease and the average number of swabs per child was 1.85 for all trials; the figures for the separate trials are also given in Table XII. *H. pertussis* was isolated from 59.8% of the cases which were swabbed and from 57.7% of all cases diagnosed. The proportion of clinical cases confirmed bacteriologically varied from area to area, but the percentage in the vaccinated was similar to that in the unvaccinated group for each trial and for all trials together (Table XIII).

TABLE XIII.—*Number and Percentage of Bacteriologically Confirmed Cases in Vaccinated and Unvaccinated Groups in All 10 Trials*

Vaccinated			Unvaccinated		
Cases of Pertussis	Confirmed Bacteriologically		Cases of Pertussis	Confirmed Bacteriologically	
	No.	%		No.	%
149	83	55·7	687	399	58·1

Haemophilus parapertussis was isolated from 24 children with clinical symptoms of pertussis. None of these cases occurred in Tottenham and Edmonton, nine were in West Ham, and the remainder were distributed in the other trial areas. There were 10 cases in the vaccinated and 14 in the unvaccinated group. Nearly all were mild; in 21 the degree of severity was 3, and in 18 the cough lasted less than six weeks. *Haemophilus bronchisepticus* was isolated from one case with clinical symptoms of pertussis which occurred in Leeds. The child had a cough for six weeks and the degree of severity was estimated as 3. There have been previous reports of the isolation of *H. parapertussis* from cases clinically diagnosed as pertussis (Bradford and Slavin, 1937; Eldering and Kendrick, 1938; Miller *et al.*, 1941; Cruickshank and Knox, 1946; Sohier and Fauchet, 1949), and a case, with symptoms of pertussis, from which *H. bronchisepticus* was isolated has also been described (Brown, 1926).

Serological tests were made in a number of children in both the vaccinated and unvaccinated groups at varying intervals after inoculation and the results will be referred to in a later report.

Comparison of the Prophylactic Potency of the Vaccines

It is not possible from the results of these trials to make a direct comparison of the prophylactic potency of the vaccines, as they were not tested in the same area

TABLE XII.—*Number and Percentage of Cases From Which H. pertussis was Isolated by Swab Culture in Both Vaccinated and Unvaccinated Groups in Each Trial*

Trial Area	Area-trial No.	Vaccine	Cases of Pertussis	No. of of Cases Swabbed	Average No. of Swabs per Swabbed Child	No. of Cases giving Pos. Swab	Percentage of Total Cases giving Pos. Swab	Percentage of Swabbed Cases giving Pos. Swab
Manchester ..	I	Sauer 087860	121	119	2·26	76	62·8	63·9
Tottenham and Edmonton	I	Michigan D231	36	36	1·67	18	50·0	50·0
Wembley ..	I	,, ,,	35	35	2·03	24	68·6	68·6
Manchester ..	II	,, ,,	75	72	2·14	43	57·3	59·7
Leeds	I	Glaxo 61	112	104	1·63	67	59·8	64·4
Leeds	II	Glaxo 174	122	113	1·37	79	64·8	69·9
West Ham ..	I	Glaxo 174	121	121	1·94	44	36·4	36·4
Manchester ..	III	Michigan A236	105	104	2·00	75	71·4	72·1
Tottenham and Edmonton	II	,, ,,	54	48	1·52	23	42·6	47·9
Wembley ..	II	,, ,,	55	54	1·85	33	60·0	61·1
Totals			836	806	1·85	482	57·7	59·8

and at the same time. In Table XIV, however, the attack rates in children have been compiled for each vaccine and the corresponding attack rates in the unvaccinated children are also given. It is evident that the

TABLE XIV.—*Attack Rates in Vaccinated and Unvaccinated Groups for Each Batch of Vaccine Tested*

Vaccine	Attack Rate per 1,000 Child-months		% Attack Rate in "Home Exposures"		% Attack Rate in "Other Exposures"	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Sauer 087860 ..	2·64	6·72	22·2	85·0	15·0	32·9
Michigan D231 ..	0·97	7·04	7·3	79·5	4·6	36·7
Michigan A236 ..	0·60	6·48	8·9	90·0	3·8	34·8
Glaxo 61	2·02	6·61	30·4	90·5	8·7	40·8
Glaxo 174 ..	1·91	6·83	29·8	90·7	15·7	46·3

attack rate per 1,000 child-months of observation in the unvaccinated children for each of these vaccine groups was almost constant, varying only from 6.48 to 7.04. This was no doubt due to the fact that the incidence of pertussis in the general population, over the whole period of the investigation, was alike in each trial area and that no large epidemic occurred (see Chart). There was only slight variation also in the attack rate in the unvaccinated children exposed in the home—from 79.5% to 90.7%—and considerable uniformity was evident in the attack rate in the unvaccinated children in the "other exposures" category—from 32.9% to 46.3%.

It is justifiable, because of these similarities in the incidence of pertussis in the unvaccinated groups, to compare the prophylactic value of the different vaccines. Each vaccine gave substantial protection. It is evident that for the trial with the Sauer vaccine the ratio of the attack rate per 1,000 child-months of observation in the vaccinated to that in the unvaccinated group was 1 : 2.5. There was a slightly greater degree of protection with each of the two Glaxo vaccines, where the corresponding ratios were 1 : 3.3 and 1 : 3.6. The two Michigan vaccines, however, gave a considerably greater degree of protection than any of the others; the ratios with these were 1 : 7.3 and 1 : 10.8. Similar differences in the degree of protection are revealed by the rates of attack in "home exposures" and "other exposures."

Further Studies

It is evident from the results of these field trials that pertussis vaccines may vary considerably in their protective property. This variation in potency is possibly related to the many variables concerned in the preparation of vaccines, such as the selection of strains, the composition of the medium on which the organisms are grown, the method of harvesting the growth, and the nature of the killing and preservative agents. In these trials the vaccines prepared by the Michigan Department of Health proved to be more potent in the field than any of the others tested, and full details of the method of preparation have been made available to the Committee. Vaccines prepared in this country by the Michigan method are now being tested in the field in comparison with a new batch of Michigan vaccine with the object of ascertaining whether the method, in the hands of British manufacturers, gives vaccines of high potency. Some of the field trials with these new vaccines have already been begun in Manchester, Oxford, Cardiff, Poole, Leeds, Tottenham, and Wembley.

Although the Michigan method of preparation may, in the hands of others, prove to give vaccine of high prophylactic potency, it would not be advisable to adopt the method as a standard procedure, as other methods may be equally satisfactory or even better. The ideal method of controlling the prophylactic activity of pertussis vaccine would be to adopt a reference vaccine which has been shown to give substantial protection in the field and in terms of which the potency of other vaccines could be assayed by means of comparative tests made in the laboratory. Such a procedure is being investigated in the United States of America by the Biologics Control Laboratory of the National Institutes of Health and the Michigan Department of Health (Pittman and Lieberman, 1948; Kendrick *et al.*, 1947, 1949), and a provisional reference pertussis vaccine has been adopted (United States Biologics Control Laboratory, 1948).

The method of comparative testing employed by these workers necessitates the immunization of mice with pertussis vaccine and the determination of the level of immunity by the intracerebral challenge injection of virulent *H. pertussis*. It is, however, not yet known whether there is a correlation between this laboratory test and the ability of vaccines to induce immunity in children. It was therefore decided to investigate this problem by testing the prophylactic property of a number of vaccines in children and comparing the results with those obtained by laboratory tests. With this aim in view, trials were begun in Manchester, Oxford, Cardiff, Poole, Walthamstow, and Leyton, and have now been in progress for two years. The results will be reported later.

Summary and Conclusions

Controlled trials were made to assess the prophylactic value of pertussis vaccine in children. Those between the ages of 6 and 18 months whose parents consented to take part in the study were divided by the method of random sampling into two groups of equal size. The groups proved to be strikingly similar in the average age of the trial children, the average number of children in the families, and the average duration of observation. The close similarity of the groups was also evident from a comparative history of breast-feeding, infectious diseases other than pertussis, immunization against diphtheria, and vaccination against smallpox.

The children in one group (referred to as the vaccinated group) were inoculated with pertussis vaccine and those in the other (referred to as the unvaccinated group) with "anti-catarrhal" vaccine containing no *H. pertussis*. Each child was visited at frequent intervals for a period of two to three years by a nurse-investigator. Neither parents nor observers knew to which group a child had been allocated.

Five batches of pertussis vaccine from three manufacturers—Parke Davis & Co., of Detroit, the Michigan Department of Health, and Glaxo Laboratories, Ltd.—were tested. Ten separate field trials were made in five different areas. In all, 7,558 children were inoculated and followed up—3,801 in the vaccinated and 3,757 in the unvaccinated group. With only a few exceptions there were no severe local or general reactions after inoculation. None of the children had convulsions and in none did poliomyelitis develop within two months of inoculation.

In all the trials, 149 vaccinated and 687 unvaccinated children developed pertussis. The corresponding attack rates per 1,000 child-months of observation were 1.45 and 6.72, giving a reduction in the incidence of the disease of 78%. Among children exposed to pertussis in their own homes the attack rates were 18.2% in the vaccinated and 87.3% in the unvaccinated groups. The cases that occurred in the vaccinated were on the average less severe and of shorter duration than those in the unvaccinated children. During the two- to

three-year periods of observation there was no evidence of a waning in the degree of protection afforded by the pertussis vaccines.

Swabs were taken from 96.4% of all clinical cases, and in 59.8% a bacteriological confirmation was obtained.

Each batch of vaccine gave substantial protection, but the two batches supplied by the Michigan Department of Health gave a considerably greater degree of protection than the others.

Vaccines prepared in this country according to the method used by the Michigan Department of Health are now being tested in similar field trials. An investigation is also being made in which the immunizing properties of vaccines as indicated by laboratory tests are being compared with their prophylactic value in the field.

The Whooping-cough Immunization Committee and the medical officers of health concerned wish to record their gratitude to the many parents who, in the full knowledge that their children would not necessarily receive pertussis vaccine, consented to take part in the investigation. They also wish to thank Messrs. Parke Davis and Co., of Detroit, the Michigan Department of Health, and Messrs. Glaxo Laboratories Ltd. for the free supply of pertussis vaccines, and Messrs. Burroughs Wellcome and Co. for the free supply of "anticatarrhal" vaccine.

REFERENCES

Anderson, I. M., and Morris, D. (1950). *Lancet*, **1**, 537.
Bell, J. A. (1941). *Publ. Hlth Rep., Wash.*, **56**, 1535.
—— (1948). *J. Amer. med. Ass.*, **137**, 1276.
Bradford, W. L., and Slavin, B. (1937). *Amer. J. publ. Hlth*, **27**, 1277.
Brown, J. H. (1926). *Johns Hopk. Hosp. Bull.*, **38**, 147.
Byers, R. K., and Moll, F. C. (1948). *Pediatrics*, **1**, 437.
Cockburn, W. C., and Holt, H. D. (1948). *Mon. Bull. Minist. Hlth, Lond.*, **7**, 156.
Cruickshank, R., and Knox, R. (1946). Ibid., **5**, 233.
Doull, J. A., Shibley, G. S., Haskin, G. E., Bancroft, H., McClelland, J. E., and Hoelscher, H. (1939). *Amer. J. Dis. Child.*, **58**, 691.
Eldering, G., and Kendrick, P. (1938). *J. Bact.*, **35**, 561.
Felton, H. M., and Willard, C. Y. (1944). *J. Amer. med. Ass.*, **126**, 294.
Geffen, D. H. (1950). *Med. Offr*, **83**, 137.
Hill, A. Bradford, and Knowelden, J. (1950). *British Medical Journal*, **2**, 1.
Kendrick, P. L. (1942). *Amer. J. publ. Hlth*, **32**, 615.
—— (1943). *Amer. J. Hyg.*, **38**, 193.
—— and Eldering, G. (1939). Ibid. (Sect. B), **29**, 133.
—— —— Dixon, M. K., and Misner, J. (1947). *Amer. J. publ. Hlth*, **37**, 803.
—— Updyke, E. L., and Eldering, G. (1949). Ibid., **39**, 179.
Leslie, P. H., and Gardner, A. D. (1931). *J. Hyg., Camb.*, **31**, 423.
Lewis, J. Tudor (1946). *Med. Offr*, **76**, 5.
McCloskey, B. P. (1950). *Lancet*, **1**, 659.
McFarlan, A. M., Topley, E., and Fisher, M. (1945). *British Medical Journal*, **2**, 205.
Madsen, T. (1933). *J. Amer. med. Ass.*, **101**, 187.
Martin, J. K. (1950). *Arch. Dis. Childh.*, **25**, 1.
Miller, J. J., Saito, T. M., and Silverberg, R. J. (1941). *J. Pediat.*, **19**, 229.
Pittman, M., and Lieberman, J. E. (1948). *Amer. J, publ. Hlth*, **38**, 15.
Sauer, L. (1937). *J. Amer. med. Ass.*, **109**, 487.
Siegel, M., and Goldberger, E. W. (1937). Ibid., **109**, 1088.
Sohier, R., and Fauchet, S. (1949). *Bull. Acad. nat. Méd., Paris*, **133**, 202.
Toomey, J. A. (1949). *J. Amer. med. Ass.*, **139**, 448.
United States Biologics Control Laboratory, National Institutes of Health (1948). "Minimum Requirements for Pertussis Vaccine."

The World Health Organization is helping the Indian Government take preventive action against possible outbreaks of cholera and malaria in the famine-stricken area of Bihar. An appropriation of $30,000 was made to purchase bleaching powder to sterilize drinking-water as a measure against cholera, and proguanil tablets to prevent malaria. In presenting the Indian request for aid, the W.H.O. regional director for South-east Asia stated that the area affected, with a population of about 20 million people, is normally subject to outbreaks of cholera and malaria, and that the famine conditions that now exist are bound to aggravate the situation.

PROGNOSIS AND TREATMENT OF CARDIAC INFARCTION

A SURVEY OF 200 PATIENTS

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The mortality in untreated series of myocardial infarction has been extensively reviewed in recent publications (Tulloch and Gilchrist, 1950 ; *Lancet*, 1950). The figures given in different statistics vary between 20 and 40% for the first four weeks following cardiac infarction. About 25% of the patients die either in the seizure or within two months of it, 50% by the end of the first year, 75% by the end of the third year, and 80% by the end of five years (Katz, Mills, and Cisneros, 1949). The average period of survival after the appearance of coronary artery disease, estimated at three and a half years by Levine and Rosenbaum (1941), is now said by McCain, Kline, and Gilson (1950) to be only one and a half years. Cardiac infarction is not a disease of uniform severity, and statistics, however large in number, give only a rough average of the variants encountered in cardiological practice. Although the prognostic significance of the individual symptoms was subjected to painstaking analysis by Rosenbaum and Levine (1941) and by Mintz and Katz (1947), it is rather the grouping of symptoms into clinical features which determines the degree of gravity and the outcome of the disease.

We were impressed by the fact that in a survey comprising 109 cases of cardiac infarction, mostly untreated by anticoagulants, there were 33—almost one-third—in which shock and cardiac failure were absent and in which prolonged cardiac pain accompanied by conclusive electrocardiographic changes were frequently the only diagnostic features (Papp and Shirley Smith, 1951). All these patients survived the two-months period of close observation. Post-mortem evidence has since proved that these slight coronary attacks correspond to subepicardial cardiac infarctions rarely reaching the endocardial surface. Others in our series were unmistakable examples of severe cardiac infarction showing the critical combination of persistent circulatory shock and early congestive heart failure. A middle group of moderate cases could be formed of those in which the ominous symptoms of the severe group appeared only for a short time, in which shock did not outlast the pain, and in which signs of left ventricular failure did not go beyond fleeting basal crepitations.

It seemed worth while, therefore, to investigate separately the prognosis of patients afflicted with slight, moderate, and severe infarctions ; to review the complications in the different groups and the ensuing disabilities ; and to correlate the clinical and electrocardiographic findings. It was hoped that this study might help to define the treatment of the individual case and lend some precision to prognosis. Patients who had full anticoagulant treatment were considered separately.