K. M. Lewis[2] refers to reports of localized manifestations of allergic reactions, and presents a case-report of a severe anaphylaxis in one of his cases, and notes similar experiences in three other instances among his colleagues. All of the cases occurred in persons who had received injections of sodium morrhuate at a preceding interval of a year or more. He concludes that one should proceed with caution in using it in patients who have previously received the same solution if a sufficient time has elapsed to allow for the development of a foreign protein sensitiveness, on the theory that the reactions are due to some protein liver radicle to which the patient becomes sensitized.

N. J. Simmons[3] reports 2 cases of severe anaphylaxis attending the use of sodium morrhuate for injection of hæmorrhoids. In the one the shock followed a second injection of 1 c.c. one week after the first injection. In the other, the shock followed a second injection of 1 c.c. two weeks after the first injection. He advances three theories: (1) An allergic reaction to the saponified fatty acids, or to an admixture of liver proteins. (2) An hæmolysis, the contact with the patient's blood resulting in the liberation of protein substances which are responsible for the reaction. (3) Sodium morrhuate acts as a hapten, and sensitizes susceptible individuals.

The lesson is one of caution in the use of the mixture of saponified fatty acids of cod liver oil known as sodium morrhuate at the beginning of treatment, but especially in patients who have previously received the same solution, if a sufficient time has elapsed to allow for the development of a foreign protein sensitivity.

Of interest is the note of a "bad reaction" (how bad is not definitely known) to monolate in one of the subjects of this report. (Monolate is monoethanolamine oleate 5 per cent, benzyl alcohol 2 per cent—an attempt to replace the unknown and variable quantity which is sodium morrhuate by a standardized product of known and invariable composition which will produce the "morrhuate action").

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ACTIVE IMMUNIZATION AGAINST WHOOPING-COUGH*

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IN recent years a number of publications have appeared on the use of fresh strain pertussis vaccine in the immunization of children against whooping-cough. Madsen,[1] Sauer,[2] Macdonald and Macdonald,[3] Park,[4] Kendrick and Eldering,[5] Daughtry-Denmark,[6] Kramer,[7] Howell,[8] Singer-Brooks,[9] Miller,[10] Silverthorne, Fraser and Brown,[11] and Silverthorne and Fraser[12] have reported results which suggest that children may be successfully immunized. On the other hand, Doull, Shibley and McClelland[13] and Siegel[14] in their studies show little if any difference between the incidence of whooping-cough in control and vaccinated children.

The present communication may for convenience be divided into two parts: Part I.—A progress report on the use of fresh strain pertussis vaccine in active immunization against whooping-cough. Part II.—A preliminary report on the minimal protective dose of fresh strain pertussis vaccines in mice.

PART I.

Clinical material.—Over the course of six years an opportunity has been afforded to follow a control and a vaccinated group of children. A questionnaire was sent to mothers as to contact, exposure, and clinical course of the disease when the latter developed. Similarly, a questionnaire was sent to a group of physicians. This has been the only practical way in which we could assess the results of a trial of the vaccine, and we believe from the reports received

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that information of a reliable nature has been obtained.

Since our last report the vaccine used in these studies was made according to the method outlined in Part II of the article by Silverthorne and Fraser.[12] The total dosage over a 4-week period was approximately 120,000 million bacilli (Gates turbidometer density of vaccine used 2 cm.) In addition, the vaccine has been tested for its protective effect in mice according to the method reported by Silverthorne.[15]

Results.—Up to the present time 288 control and 1,007 vaccinated children have been followed in order to obtain a history of direct indoor exposure. It will be observed (Table I)

TABLE I.

WHOOPING-COUGH
ANALYSIS OF CONTROL AND VACCINATED CHILDREN

	Controls	*Vaccinated*
Total followed	288	1,007
Total direct contacts	52	97
Total developing whooping-cough	43	10
Percentage contacts developing whooping-cough	82	10

that 52 of the control group have come in direct house contact with patients suffering from clinical whooping-cough and 43 of these have contracted the disease, in which whooping and vomiting of some weeks' duration occurred. In the 1,007 vaccinated children there have been 97 similar direct house contacts with clinical whooping-cough and only 10 children have developed the disease. In the control group an opportunity was afforded of examining 14 of these cases by means of the cough plate, and these 14 showed positive cultures. In the vaccinated group 4 patients were examined by means of the cough plate, and positive cultures were obtained in two of them.

Discussion.—Of 97 contacts in the vaccinated group there were 23 direct exposures to brothers or sisters with whooping-cough. In the 23 instances the nature of contact was intimate and continuous (often kissing, drinking out of the same glass, or sleeping in the same bed). None of the 23 developed the disease from their brothers or sisters. This fact is very strong evidence of the protective value of the vaccine, since one would not expect all of 23 children continuously and intimately exposed to whooping-cough to escape the disease. Further, it has been stated by the physicians who assisted in this study that they had either no whooping-cough in children vaccinated in their practices or at most one or two cases, compared with from 6 to 20 cases in unvaccinated children in their private series. Such reports are obviously of no statistical significance. However, it is noteworthy that all of this group of physicians report similar results. In Table I it will be noted that the percentage of contacts developing whooping-cough in the control group was 82. This figure is similar to that reported by other investigators. The percentage of contacts developing whooping-cough (10 per cent) in the vaccinated group is significantly lower and strongly suggests that the vaccine used in this study has conferred protection against whooping-cough on a large number of the children.

Summary.—Of 52 control-children coming in direct contact with children with whooping-cough, 43 developed the disease, a morbidity of 82 per cent, whereas of 97 vaccinated children only 10 developed the disease after similar direct exposure, a morbidity of 10 per cent.

PART II.

In 1938 the author[15] reported the technique of experimental infection with freshly isolated strains of *H. pertussis* injected with mucin intraperitoneally into mice. It was shown that fresh strain pertussis vaccines were effective in protecting mice against a fatal septicæmia induced by this method of infection. During the last few months an attempt has been made to obtain a minimal protective dose of the phenolized vaccine used in our studies. This was done in an attempt to evaluate the protective value of vaccines killed by phenol, formalin, Merthiolate, ether and heat respectively.

Experimental.—One batch of a heavy suspension in saline of *H. pertussis* was prepared from a 72-hour growth on Bordet medium enriched with 33 per cent citrated sheeps' blood. Five lots of vaccine were made from this suspension, killed, and standardized at a Gates turbidometer density of 2 cm. The vaccines were killed with phenol (0.5 per cent), formalin, (0.2 per cent), Merthiolate (1 in 5,000), ether (5 per cent), and heat (1 hour at 56° C.), respectively. Each lot of vaccine (both diluted and 1 in 10 dilution) was injected subcutaneously into groups of 10 mice. At intervals mice were tested for protection. Thus, one week after the third injection of 0.1 c.c. three mice were tested, three after the fourth injection and four after the fifth injec-

tion. In the case of the phenolized vaccine (undiluted) it was found that protection occurred with 0.4 c.c. one week after the fourth injection. None of the mice with any of the five lots of vaccine survived after 0.4 c.c. of 1 in 10 diluted vaccine, and therefore served as adequate controls. In Table II are shown the results of the experiments.

TABLE II.

PROTECTION OF MICE WITH VARIOUS PERTUSSIS VACCINES

Vaccine	*Protection in mice with*		
	0.3 c.c.	*0.4 c.c.*	*0.5 c.c.*
1. Phenol 0.5%, undiluted	0	+	+
" 0.5%, 1 in 10 dilution	0	0	0
2. Formalin 0.2%, undiluted	0	0	0
" 0.2%, 1 in 10 dilution	0	0	0
3. Merthiolate 1 in 5,000, undiluted	0	0	0
" 1 in 5,000, 1 in 10 dilution	0	0	0
4. Ether 5%, undiluted	0	0	0
" 5%, 1 in 10 dilution	0	0	0
5. Heat 1 hour, 56° C., undiluted	0	0	+
" " " 1 in 10 dilution	0	0	0

+ = protection. 0 = no protection.

It will be observed from Table II that vaccine killed by phenol and injected into mice protects them in doses of 0.4 c.c. and 0.5 c.c. given by injecting 0.1 c.c. at weekly intervals. Vaccines killed by formalin, Merthiolate, or ether have not protected when injected into mice in similar amounts. Experiments previously carried out and not reported in this communication have shown that fresh strain vaccines prepared with phenol, formalin, Merthiolate, ether and heat protect mice when given in higher dosage. Vaccine killed by heat begins to protect mice after 0.5 c.c. has been given.

DISCUSSION

It would appear from these experiments that 0.4 c.c. (0.1 c.c. at weekly intervals) of the undiluted product of pertussis vaccine (density of Gates turbidometer 0.2 cm.) is a fairly large dose to be administered to mice in order to obtain protection. It would require an exceedingly large dose in the human subject if a similar amount of vaccine per pound of body weight were required for protection against whooping-cough. On the other hand, it may be emphasized that in the case of the mouse protection is obtained against an overwhelming septicæmia by literally millions of living virulent pertussis bacilli. It is unlikely that relatively similar amounts are necessary for protection against the disease as it occurs in the respiratory passages of man.

SUMMARY

1. It has been established that 0.4 c.c. of a 0.5 per cent phenolized fresh strain pertussis vaccine is the minimal protective dose against a fatal septicæmia produced in mice by the intraperitoneal injection of fresh strains of *H. pertussis* in mucin.

2. Preliminary experiments show that vaccines killed by other methods do not protect mice in similar dosage.

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PROBABLE ERROR OF BLOOD-PRESSURE MEASUREMENTS.—When the effects of temporal differences and differences between the two arms are eliminated systematic differences between observers are insignificant. Significant differences in the variability of determinations made by different observers are found. The probable error of measurement of a single blood-pressure observation is 1.2 to 1.8 mm. for systolic pressures and 1.8 to 2.0 mm. for diastolic pressures when readings are made under conditions of rest and adequate time is permitted for the establishment of postural equilibrium. An average of more than five observations of blood pressure does not result in a useful gain in precision.—W. Nathan and E. Ogden, *Quart. J. Exper. Path.*, 1939, **29**: 49. Abs. in *Brit. M. J.*