THE PLACENTAL TRANSMISSION OF PROTECTIVE ANTIBODIES AGAINST WHOOPING COUGH

BY INOCULATION OF THE PREGNANT MOTHER

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Whooping cough is the dread contagious disease of infancy. During the first two years of life it is the cause of more deaths than measles, diphtheria, poliomyelitis and scarlet fever combined.[1] Against the latter diseases the baby usually is born with a passive immunity transmitted by the mother through the placenta.[2] Since this is a passive immunity it endures for only approximately six months. Such does not seem to be the case with whooping cough.

Pediatrists not infrequently encounter cases of whooping cough in early infancy. The figures on the incidence of whooping cough in the infant vary from 8 to 18 per cent of the total incidence of whooping cough at all ages.[3] This is clinical evidence of the frequent lack of immunity in the newborn.[4] At present there are few data on the humoral immunity of the average adult against whooping cough. This is explainable because it is only in the last few years that proper immunologic tests for whooping cough have been devised. Without proper and sufficient data as to the immunity of the adult female, immunity of the newborn baby against whooping cough in respect both to frequency and to degree can be only conjectured. Thus Holt and McIntosh[3] state that natural susceptibility to whooping cough seems to be equal at all ages and little or no immunity is conveyed in utero, regardless of whether or not the mother is immune. Some believe that natural immunity to pertussis does not exist and that no natural immunity is transmitted from mother to child.[5] On the other hand, Knoepfelmacher,[6] in Pfaundler and Schlossmann's system, states that a congenital immunity to whooping cough can be accepted derived from previous pertussis of the mother. Sauer[1] speaks little of this subject in Brennemann's System of Pediatrics except for quoting Bordet as believing in transient congenital immunity. It seems that there is no unanimity of opinion on this subject.

The human placenta is of the hemochorionic type in which a single layer of chorionic and endothelial cells separates the fetal from the maternal blood.[7] To all intents and purposes, there is here a semipermeable membrane obeying the physicochemical laws of semipermeable membranes.[8] The size of the molecules determines what passes across and what fails to pass the placental barrier.[9] In general, antibodies and not antigens are able to filter through from the mother's blood to the baby's blood.[9] Thus it has been demonstrated that the titer of diphtheria antitoxin is approximately the same in the mother's blood, the cord blood and the placental blood.[10] The same holds true of the other antitoxins such as tetanus.[11] It is well known that the blood group of the baby may not be well established for several weeks because of the passage of the mother's blood agglutinins into the fetal blood.[12] Immunity against scarlet fever, measles and poliomyelitis for the first half of the infant's life is conferred on the baby through the antibodies of the mother's blood by way of the placenta. The newborn baby has also been shown to have, at least in many instances, antistreptolysins,[13] antistaphylolysins and other bacterial antibodies similarly passively transmitted by the mother.[14] The same probably holds true of antibodies against all organisms which are already preformed in the mother's blood during pregnancy.[15]

According to Needham, antigens as a class, unlike antibodies, do not pass through the placental barrier. There are certain exceptions, however, for typhoid, malaria, pneumonia[16] and rheumatic fever, among other diseases,[17] have been described in newborn babies. In these instances we are dealing with a disease process which probably alters the capillaries on both sides of the placenta, effecting an abnormal exchange. Ratner

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and his colleagues,[18] however, have presented evidence that allergenic antigens can traverse the normal placentral membrane and actively induce antibody production. It may be possible, then, for the antigen in the mother's blood to be transmitted to the fetal blood, in which event active immunity will result as well as passive immunity.

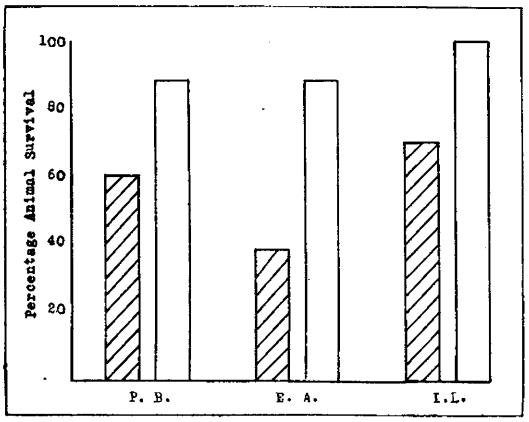

Chart 1.—Showing close correlation of protective titers. The baby's titer is higher in each instance. The shaded column indicates the mother's protective antibodies and the unshaded column the baby's protective antibodies.

As shown earlier, whooping cough in infants is accompanied by a high mortality.[19] It is for this reason—this apparent lack of immunity of any nature against whooping cough—that efforts have previously been made actively to immunize young infants, but the results have been disappointing, for immunity did not result from inoculations with the Sauer vaccine in young infants in the dosage of 80 billion, beginning at 1 month to 2 months of age.[20] The young infant apparently has not the capacity to form antibodies against the whooping cough bacillus antigens. In fact, the most modern opinion is that the very young infant is a poor antibody producer against all antigens.[21] Young infants inoculated with the Sauer vaccine, unlike older infants similarly inoculated, contracted whooping cough on exposure as frequently as those uninoculated. Since active immunity has not been successful in these young infants at this most dangerous age period for whooping cough, the idea came to one of us (P. C.) to create active immunity in the pregnant mother in the last trimester of pregnancy, hoping that the antibodies so formed would pass the placental barrier and induce passive immunity in the baby.

Our idea was to inoculate the pregnant mother with a potent pertussis bacillus vaccine in the fifth or sixth month of pregnancy. The vaccine we chose is one prepared by Mishulow of the New York Laboratories, which has proved potency and which we have used in previous work with satisfactory results.[22] Our plan was to administer the vaccine at intervals of two weeks for six injections, totaling 150 billion organisms. This timing was chosen because it was shown by Mishulow and Wilkes and their associates [23] that the highest titer of protective antibodies was found in the blood of vaccinated children approximately two months after vaccination. In order to minimize reactions, the first dose was 10 billion, the second 20 billion and the other four doses 30 billion, given subcutaneously in one or both arms. In many instances the full dose of 150 billion organisms was not administered either because of the tardy initial presentation of the pregnant mother or because absence from the clinic threw off the timing of our injections, which were aimed to terminate a month or two before the expected date of delivery. At times deliveries occurred earlier than the calculated date, upsetting our time table, but delivery beyond the expected date had little effect on the results.

The reactions of the inoculated mothers were less severe than those obtained when children are inoculated with the Sauer vaccine. Elevation of temperature was encountered only twice in our first hundred cases. Soreness and tenderness in the inoculated area was a feature in almost every case. A persisting lump, sometimes for days, was a common occurrence. There were times when the arms were so sore that the woman could not use them for two or three days. The local reactions were very similar to those generally encountered in children, but the systemic reactions were less frequent and far less noticeable. There were no abscesses and no persistent nodules. It was apparent to us that the inoculations had no effect on the pregnancy or delivery. There were no premature births or postpartum complications which could be attributed to the inoculations. The babies thrived and did as well in the hospital as did the babies of uninoculated mothers serving as a control series.

Before the injections were begun 10 cc. of blood was taken for the titration of antibodies, which also served the purpose of a control measure. These data will be included in a separate article by Mishulow and her co-workers. At the time of delivery 10 to 15 cc. of blood was taken from the mother and the umbilical cord, which represents the baby's blood. These bloods were titrated for immune bodies. At intervals of six to nine months equal amounts were to be taken from mother and baby for a retitration of immune bodies to enable us to study the duration of any immunity

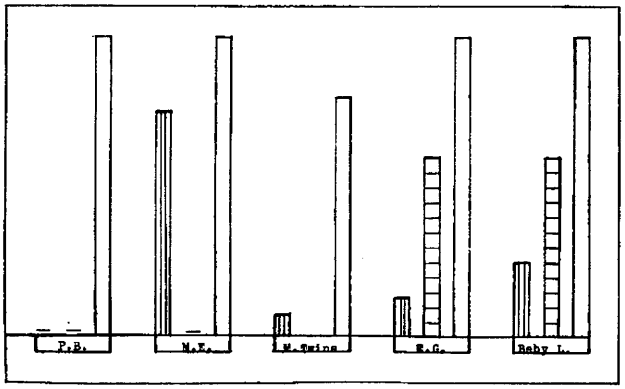

Chart 2.—Illustrating lack of correlation of protective antibodies with agglutinins and complement fixation. Equivalent heights for agglutination 1/200 is indicated by vertical shading, complement fixation 0.01 cc. by horizontal shading and protective antibodies 100 per cent by unshaded column.

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actively or passively induced. A group of uninoculated mothers and their babies were similarly bled and their blood quantitated for the same immune bodies. These served as a control group.

The specific immune bodies studied [24] in this investigation were agglutinins, complement fixing antibodies and protective antibodies. The laboratory tests were carried out by Miss Mishulow and her assistants at the New York City department of health. Her method of testing for these antibodies was the same she used in her studies of the immunologic response in cases of pertussis and in vaccinated children.[25]

TABLE 1.—*Study of Immunity of Mothers Before Vaccination Against Whooping Cough*

Name	Date, 1941	Age	History of Whooping Cough	Agglutination	Complement Fixation	Mouse Protection	
						Survived	per Cent
H. R.	3/27	30	?	0	0	0/9	0
D. B.	4/ 1	27	?	25	0	3/6	50
P. B.	4/ 8	32	Negative	0	0	0/8	0
M. E.	4/16	23	Negative	0	0	2/10	20
F. G.	3/13	24	Negative	0	>0.02	1/8	12.5
E. G.	5/22	29	Negative	0	0	1/10	10
A. M.	5/14	33	Negative	0	0	0/10	0
I. S.	4/ 1	27	Negative	0	0	0/6	0
A. T.	3/27	30	Negative	0	0	10/10	100
P. B.	5/ 1	24	Positive	0	0	9/10	90
R. W.	5/14	26	Negative	75	0.02	4/10	40
S. K.	4/ 3	37	?	0	<0.01	0/10	0
R. W.	5/13	24	?	0	>0.02	2/9	22.2
E. A.	5/13	19	Positive	0	0	0/6	0
R. M.	5/27	19	Negative	50	0	0/9	0
G. S.	5/22	22	?	0	0	1/9	11
L. O.	6/26	25	?	0	0	1/9	11
M. S.	6/10	29	Negative	0	0	4/7	57
G. B.	6/26	22	Positive	50	0	5/9	55.5
V. S.	6/ 4	32	Negative	0	0	7/10	70
C. K.	5/21	31	?	0	0	6/9	66.6
H. L.	5/21	22	?	0	0	3/9	33.3
F. A.	5/21	23	?	0	0	0/8	0
E. B.	6/17	22	Negative	0	0	1/10	10
M. V.	5/20	33	?	0	0	4/9	44.4
S. S.	7/ 3	36	Negative	0	0	0/10	0
I. L.	5/29	32	?	0	0	0/9	0
D. W.	6/12	26	?	0	0	0/10	0
A. S.	5/28	30	?	0	0	1/9	11

In the test for protective antibodies groups of mice were inoculated with 0.2 cc. of the serum intramuscularly nineteen to twenty hours previous to the intraperitoneal injection of a multiple killing dose of virulent Hemophilus pertussis suspended in 1 cc. of 4 per cent mucin. At each test similar groups of mice were inoculated with a known positive serum and with the test doses of the culture without serum; these served as controls on the validity of the test. The serum was considered positive for protective antibodies when 30 per cent or more of the mice survived the seven to eight days. All mice that died during the period of observation were examined post mortem in order to determine the presence of another infection; in the event of such a finding the mouse was eliminated from the calculations. In all mice that were inoculated with the culture H. pertussis was recovered from the heart's blood in the first four days of the test unless the plates were contaminated by other organisms that invaded the blood post mortem when the mice died during the night.

TABLE 2.—*Study of Immunity of Unvaccinated Mothers and Infants at Time of Delivery*

Vaccine Dose	Whooping Cough	Age	Tested	Agglutination	Complement Fixation	Mouse Protection	
						Survived	Per Cent
0	Neg.	22	Mother on delivery	0	0	1/8	12.5
			Baby at birth.....	0	0	2/9	22.2
	Neg.	22	Mother on delivery	0	0	0/8	0
			Baby at birth.....	0	0	0/5	0
	Neg.	19	Mother on delivery	0	0	0/10	0
			Baby at birth.....	0	0	0/10	0

The agglutination results were recorded in terms of the highest dilution of the serum that showed distinctly visible clumps. Indistinct or no agglutination in 1 : 10 dilution of the serum was recorded as negative. Complement fixation was recorded in terms of the smallest amount of the serum that gave complement fixation under standard conditions. Incomplete or no fixation in 0.02 cc. of the serum was recorded as negative.

Because agglutinins and complement fixing antibodies are not necessarily correlated with immunity,[26] special attention was given to the study of protective antibodies. Investigation of other tests which have been used to appraise immunity in whooping cough, such as cutaneous tests,[27] opsonophagocytosis studies,[28] the antitoxin content of the serum [29] and the protection of mice by the serum against a multiple lethal dose of live whooping cough bacilli inoculated into the respiratory tract,[30] led us to choose the mouse protection test as the most searching and convincing available.[31] This test is similar to the testing of antipneumococcus and antimeningococcus serums in mice which have been inoculated intraperitoneally with live pneumococci or meningococci.

TABLE 3.—*Pertussis Antibodies in Infants of Unvaccinated Mothers—Tested at Birth*

Case	Name	Bled	Mother's History of Pertussis in Childhood	Result			
				Agglutination	Complement Fixation	Mouse Protection	
						Survived	Protected, per Cent
1	Baby F.	2/28/42	Positive	0	0	2/6*	?
2	Baby L.	2/27/42	Positive	0	0	5/10	50
3	Baby W.	2/28/42	Positive	0	0	1/10	0
4	Baby C.	3/ 1/42	Negative	0	0	3/10	30
5	Baby G.	2/27/42	Doubtful	0	0	0/10	0
6	Baby Q.	2/27/42	Negative	0	0	0/ 9	0

* One mouse ill at the end of the test.

Agglutination tests were recorded in a figure which indicated the dilution of the serum that yielded distinct clumps. The figure under the column of complement

24. The laboratory immunologic studies were entirely performed for us by Miss Mishulow and her co-workers at the New York City Bureau of Laboratories by permission of Dr. Ralph Muckenfuss.

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fixation indicates the amount of serum needed to produce a 4 plus complement fixation reaction. If 0.02 cc. of serum or less was needed, the test was considered positive. In the mouse protection tests, in almost every case 10 mice were used for each test, but owing to unforeseen and inevitable incidental fatalities this number was at times reduced. If the amount of serum was inadequate, 5 or more mice were employed. The results of these tests are reported in a fractional form; thus 0/9 indicates that 9 animals were used and none survived; 8/10 indicates that 8 out of 10 animals survived. The numerator of the fraction signifies the number of animals that survived and the denominator signifies the number of animals that were used.

Our intention was to use 10 uninoculated women and their infants as control cases. Unfortunately a wave of incidental infection killed most of the animals used for this purpose so that we were left with only three control combinations. The unvaccinated mothers and their babies showed no agglutinins or complement fixing antibodies and little or no protective antibodies against whooping cough. As additional control cases, the cord blood of 6 babies of uninoculated mothers were examined for the same antibodies but their mothers' bloods were not similarly studied. Three of these mothers gave a history of whooping cough in their childhood and the other 3 had a doubtful or negative history of previous pertussis. Of these 6 babies 1 had a fair amount of protective antibodies, 1 had a good titer of such antibodies and 1 had questionable protection. All these bloods revealed no agglutinins or complement fixing antibodies. Thus of 9 babies of uninoculated mothers, 2 or 3 showed some degree of protective antibodies (none with a really high titer) and none of their serums showed the presence of the other antibodies tested for.

TABLE 4.—*Placental Transmission of Pertussis Antibodies to the Newborn*

Lab. No.	Name	Age	Vaccine Dose, Billions	Tested: Date	Tested: Specimen Taken on Day of Delivery	Tested: Period After Vaccination	Result: Agglutination	Result: Mouse Protection: Complement Fixation	Result: Mouse Protection: Survived	Result: Mouse Protection: Protected, per Cent
C-1	H. R.	30	90	6/ 1/41	Mother	1½ wks.	350	0.009	8/10	80
				6/ 1/41	Infant	.....	75	0.01	10/10	100
C-2	D. B.	27	150	7/ 1/41	Mother	2 wks.	650	0.009	8/ 9	88.8
				7/ 1/41	Infant	.....	800	0.004	10/10	100
C-3	P. B.	32	150	8/10/41	Mother	7½ wks.	0	0.02	6/10	60
				8/10/41	Infant	.....	0	0	8/ 9	88.8
C-5	M. E.	23	150	8/ 1/41	Mother	5 wks.	150	0	8/ 8	100
				8/ 1/41	Infant	.....	1,000	0	6/ 6	100
C-6	F. G.	24	150	7/21/41	Mother	6½ wks.	75	0.009	8/10	80
				7/21/41	Infant	.....	75	0	8/ 9	88.8
C-9	E. G.	29	120	7/21/41	Mother	4 wks.	25	0.02	9/ 9	100
				7/21/41	Infant	.....	37	0.01	7/ 7	100
C-12	A. M.	33	90	7/ 3/41	Mother	1 wk.	950	0.02	7/ 9	77.7
				7/ 3/41	Infant 1	.....	0	0	8/10	80
				7/ 3/41	Infant 2	.....	25	0	7/ 8	87.5
C-14	I. S.	25	150	7/30/41	Mother	6 wks.	75	0	6/ 9	66.6
				7/30/41	Infant	.....	100	0	5/ 8	62.5
C-15	A. T.	30	120	6/30/41	Mother	2½ wks.	350	0.02	10/10	100
				6/30/41	Infant	.....	150	0.009	9/10	90
C-18	P. B.	24	150	8/14/41	Mother	5 wks.	700	0.007	8/ 9	88.8
				8/15/41	Infant	.....	200	0.004	9/10	90
C-19	R. W.	26	120	8/ 6/41	Mother	1 wk.	300	0.007	10/10	100
				8/ 6/41	Infant	.....	8,000+	0.005	5/ 6	83.3
C-20	S. K.	37	120	8/ 7/41	Mother	4 wks.	30	0.01	8/ 9	88.8
				8/ 7/41	Infant	.....	0	0.01	9/10	90
C-21	R. We.	24	150	8/31/41	Mother	4½ wks.	250	0.02	8/ 8	100
				8/31/41	Infant	.....	150	0.01	8/10	80
C-25	E. A.	19	150	8/25/41	Mother	5 wks.	450	0.01	3/ 8	37.5
				8/25/41	Infant	.....	500	0.005	8/ 9	88.8
C-26	R. M.	19	120	9/ 2/41	Mother	5 wks.	600	0.02	7/ 8	87.5
				9/ 2/41	Infant	.....	700	0.008	10/10	100
C-30	G. S.	22	150	9/11/41	Mother	4 wks.	900	0.007	7/ 9	77.7
				9/11/41	Infant	.....	900	0.005	8/ 8	100
C-32	M. S.	29	150	9/14/41	Mother	3½ wks.	600	0.006	10/10	100
				9/14/41	Infant	.....	300	0.005	10/10	100
C-33	G. B.	22	150	9/24/41	Mother	3 wks.	900	0.02	9/10	90
				9/24/41	Infant	.....	600	0.007	7/ 7	100
C-34	V. S.	32	150	9/17/41	Mother	5 wks.	800	0.006	6/ 7	85.5
				9/17/41	Infant	.....	400	0.003	5/ 5	100
C-35	C. K.	31	140	9/17/41	Mother	7 wks.	300	0.01	9/10	90
				9/17/41	Infant	.....	100	0.01	N. T.†	..
C-36	H. L.	22	150	9/17/41	Mother	6 wks.	25?	0.01	7/ 9	77.7
				9/17/41	Infant	.....	0	0.01	N. T.	..
C-37	F. A.	23	150	9/29/41	Mother	3½ wks.	200	0	8/10	80
				9/29/41	Infant	.....	25	0.02	8/10	80
C-38	E. B.	22	150	9/24/41	Mother	4 wks.	200	0.02	8/ 8	100
				9/24/41	Infant	.....	0	0.01	9/10	90
C-39	M. V.	33	120	9/22/41	Mother	10 wks.	800	0.02	10/10	100
				9/22/41	Infant	.....	800	0.009	10/10	100
C-40	S. S.	36	120	9/25/41	Mother	4 wks.	25	0	8/ 8	100
				9/25/41	Infant	.....	25	0	10/10	100
C-41	I. L.	32	150	10/ 7/41	Mother*	8½ wks.	50	0.02	7/10	70
				8/28/41	Infant	.....	50	0.02	6/ 6	100
C-42	D. W.	26	120	9/ 4/41	Mother	4 wks.	25	0	6/10	60
				9/ 4/41	Infant	.....	50	0	7/10	70
C-43	A. S.	30	150	10/ 9/41	Mother*	9 wks.	100	0	4/10	40
				9/20/41	Infant	.....	25	0.02	5/10	50
C-44	Mrs. W.	33	...	.....	Mother	.....	6,400	0.009	8/ 8	100
				.....	Infant	.....	9,600	0.01	10/10	100

* This woman was tested after delivery.

† N. T. = not tested; insufficient serum.

We consider protection excellent when the great majority of the mice are protected by the serum. We consider protection good when close to half of the animals are saved by serum. Protection is fair when 30 per cent of the animals survive. Twenty-nine women have thus far been selected for the immunologic studies from a group of 167 women inoculated with the vaccine in doses from 80 to 150 billion. By these standards of immunity, of 29 cases 27 showed a very high titer, all definitely positive results. Of 27 babies tested, including 1 set of twins, the titers were equally high. In the case of E. A. and P. B., the babies had a higher titer than the mother. The babies' figures seemed to indicate a slightly higher titer than the mothers'. This may or may not be significant.

The agglutination and complement fixation reactions did not exactly correspond with the titers of protective antibodies. Thus the serums of 8 subjects were poor in the former antibodies yet yielded high protection. The twin babies, who had high protective antibodies, had little or none of the other antibodies tested. This is in keeping with previous work done on this subject.[25]

The tests were performed at intervals of from one to eight weeks after vaccination. We have some patients with an even longer interval after the last inoculation, but their serums have not yet been studied. The length of the interval seemed to make no difference in the height of immune bodies of the mother and the newborn baby. Whether it will affect the duration and the persistence of the antibodies is a matter for future study. The same probably holds true of the dosage. Although almost all of our patients were vaccinated with 120 to 150 billion organisms, some were vaccinated with only 80 to 90 billion. One woman vaccinated with 80 billion and 2 with 90 billion yielded as high a protective titer as those inoculated with the larger doses. Whether these antibodies will persist as long as in those cases in which the smaller dosage was given is questionable. The ages of our group of women varied from 19 to 36 years of age. The age factor and multiparity seemed not to play a role in the production of immune bodies. The previous history of whooping cough seemed not to play a role in the production of antibodies. Only 3 of the 29 women were sure that they had whooping cough; about a third were doubtful. There was no correlation between their initial titer of antibodies and the antibodies formed by vaccination. There was no difference in the data of this group and of the group who were certain that they had never had whooping cough.

RESULTS AND COMMENT

As far back as 1879 attempts have been made to immunize a newborn baby by inoculation of the pregnant mother against a specific disease.[32] In the case of syphilis, the inoculation of the pregnant mother to prevent or cure congenital syphilis is a universal measure.[33] Lichty, Slavin and Bradford[34] attempted, as they put it, to increase resistance against pertussis in newborn infants by immunizing the mother during pregnancy. They confessed their failure. An analysis of the data revealed the following facts: The injections were given at two week intervals in the last six weeks of pregnancy. The total dose administered was 20 to 25 billion. Thus the dose was inadequate and too late for antibody formation which reaches its climax between one and two months after the last inoculation. The test for immunity which they employed, cytophagocytosis of the blood, has distinct limitations and has been abandoned by them in favor of mouse tests.[35] Their figures showed no increase in cytophagocytosis of the inoculated mother's blood. Granting the validity of the test, they found no increased immunity in the mother, so that there were no antibodies transferable to the baby through the placenta. In rabbits it has been proved, as in babies, that the very young rabbit could not be immunized against pertussis,[36] but by the inoculation of pregnant rabbits antibodies were formed which were transmitted to the newborn rabbit.[37] This would seem to be the animal counterpart and confirmation of our work.

In a recent article it was found with the opsonocytophagic test,[38] that there was a correlation in the opsonizing power of mothers and their infants. This has previously been suggested by Bradford and Slavin;[28] yet Kendrick, Gibbs and Sprick,[28] with the same test, reported that the blood of newborn infants has virtually no phagocytic powers and is not correlated with the mother's reactions. Rambar and his co-workers[38] found that in a large series of premature infants there is a strong reaction up to 2 months of age and then a decline, suggesting a placental transfer of circulating antibodies against whooping cough. Our work is more in agreement with the latter findings. We have found that when a mother has a definite titer of antibodies against whooping cough she transmits it to the baby in about the same titer. This was true of 100 per cent of our series after the mothers had been inoculated with a sizeable dose of vaccine during the last trimester of pregnancy.

Mishulow and her co-workers[39] found that 15.2 per cent of children and adults who had a negative history of pertussis had pertussis protective antibodies. They also found in a study of the preimmunization bleedings of women who were studied in this investigation that 31.2 per cent of them had these antibodies before they were vaccinated.[40] If we can assume, as would seem likely from our investigations, that these antibodies are transmitted from the pregnant adult to the baby, a definite proportion of babies may be born with some immunity against whooping cough. In the few cases that we have studied we have found on two or three occasions protective antibodies in the cord blood, but more investigations are needed to establish percentage incidence. In the meantime, it may be conservative to assume that a small percentage of babies, perhaps 15 per cent to 25 per cent, are born with passive immunity of uncertain duration but that the great majority have no protection against whooping cough. This fits in well with known clinical facts. Sauer's[1] and Top's[3] studies point to no great difference in susceptibility between the younger and the older infants if vaccination has not been performed. This is an important point, for the high mortality in the susceptible infants, which is a

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34. Lichty, J. A.; Slavin, B., and Bradford, W. L.: An Attempt to Increase Resistance to Pertussis in Newborn Infants by Immunizing Their Mothers During Pregnancy, J. Clin. Investigation **17**: 613 (Sept.) 1938.
35. Bradford, W. L.; Scherp, H. W., and Brooks, A. M.: Effect of Refined Antipertussis Rabbit Serum on the Humoral Antibody Titer in Pertussis, Am. J. Dis. Child. **62**: 492 (Sept.) 1941.
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39. Mishulow, Lucy, and others: Am. J. Dis. Child., to be published.
40. Mishulow, Lucy, and others, to be published.

common pediatric experience, was the fact which led us to attempt our prophylactic measure. The need for the protection of the infant against this dread disease is therefore nearly as great as was anticipated.

Recently a similar investigation was performed with diphtheria immunization.[41] Diphtheria lends itself readily to such studies because technics are available for the titration of antitoxin in the blood and there is a good cutaneous test as an index of immunity, namely the Schick test. With such methods past studies of diphtheria have shown a high correlation between the antitoxin content of the bloods of the mothers and their babies.[42] Such studies have revealed also that in large cities close to 90 per cent of mothers are immune to diphtheria, as are their babies.[43] Yet in the recent Chicago study of this subject more than 50 per cent of mothers at term were found to be Schick positive and to have an antitoxin content of blood inadequate to constitute an effective immunity against diphtheria. Because of this, the pregnant mothers were inoculated with diphtheria toxoid in the latter part of pregnancy. There resulted a close correlation between the increased antitoxin titer of the mother's blood, the cord blood and the infant's blood. If this work is verified by further studies, previous estimates of diphtheria immunity in the newborn will have to be revised and measures taken to protect the newborn baby against diphtheria. In a discussion of this paper, mention was made of the great need for a similar project to confer protection on the newborn baby against dangerous whooping cough. Since our work was already in progress, this was an interesting statement to us.

Does the presence of a high titer of protective antibodies in serum signify definite immunity in the human being against whooping cough? While this question cannot be categorically answered in the affirmative, there is much evidence to make this a logical assumption. The convalescent from whooping cough, in most instances, has a serum rich in protective antibodies.[44] After proper immunization with vaccines, the serum becomes rich in protective antibodies.[45] It has been demonstrated that this hyperimmune serum as well as convalescent serum is of great value in preventing whooping cough in unimmunized contacts[46] and is even of great aid if employed in suitable doses in the treatment of whooping cough itself.[47] Small amounts of such serums are remarkably effective in protecting animals against what is otherwise an overwhelmingly fatal infection from live pertussis bacilli injected intraperitoneally.[48] There is ample evidence in the literature now that individuals inoculated with suitable doses of a proper vaccine have a high degree of immunity against whooping cough.[49] Correlated with this immunity is the presence of protective antibodies in the blood of the vaccinated individuals.[50] These facts all point to the conclusion that protective antibodies, if not the sole mechanism of immunity against whooping cough, are a reliable index of immunity. The question can be answered finally only by a follow-up study of the fate of infants and children, vaccinated and unvaccinated, with and without protective antibodies, when actually exposed to intimate contact with whooping cough. We are doing this now, but this is an investigation which will take years and large numbers of cases before an unequivocal answer can be obtained.

What is the nature of this immunity and how long will it last? Judging by the close correlation of the titers between mothers and babies, this transplacental immunity is most likely of a passive nature. On the other hand, the higher titer in a few babies may indicate a passage of antigen, conferring added active immunity on the baby. It must be recalled that there have been several instances in the literature of antigens passing the placental barrier.[51] This is not merely an academic question, for passive immunity will be of short duration—from a few weeks to a few months—while active immunity will last for a much longer time. In addition, boosting doses, which has proved to be a successful technic,[52] is more apt to be of value if the immunity has an active factor. Thus, if one finds that at 6 months of age the baby is rapidly losing his immunity, a further injection of 30 billion bacilli can be given and the dose repeated every six months or yearly. This work we have already begun.

CONCLUSIONS

1. Since whooping cough is such a serious disease in young infants, an attempt was made to immunize newborn babies by vaccinating the pregnant mother with a whooping cough vaccine in the last trimester of pregnancy.

2. In this we have been successful, judging by the presence of immune bodies.

3. The total dose we advise is 150 billion, given at intervals of two weeks beginning at the sixth month of pregnancy. The last injection is to be given six weeks to two months before term.

4. The systemic reactions after vaccination were few and not severe. The local reactions were common, at times very painful, not serious and sometimes lasted as long as a few days.

5. There were no discernible effects on the course of pregnancy, on delivery or on the baby. There were no miscarriages or premature births that could be attributed to the procedure.

6. In 29 instances immunologic studies were performed on the serums of babies and mothers after

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42. McKhann and Chu.[2] von Groer and Kassowitz.[2] Karelitz and Greenwald.[2] Bourquin.[2] Needham.[9]

43. Schick, Bela: Personal communication to the authors. von Groer and Kassowitz.[2]

44. Powell, H. M., and Jameson, W. A.: Further Studies on the Immunology of H. Pertussis, J. Immunol. **32:** 153 (Feb.) 1937. Mishulow, Klein, Liss and Leifer.[25]

45. Lapin, J. H.: Immunity to Whooping Cough as Judged by Skin Test in Rabbits, J. Pediat. **20:** 161 (Feb.) 1942; footnote 50. Mishulow and others (footnotes 23 and 40). Bradford, Scherp and Brooks.[35] Silverthorne (footnotes 31 and 48).

46. Cohen, Philip, and Lapin, J. H.: Prophylaxis Against Whooping Cough in Exposed Children with Special Reference to Serum, J. Pediat. **15:** 78 (July) 1939. Kendrick, P.: A Note on the Use of Reinforced Convalescent or Hyperimmune Serum for Passive Immunization of Infants Exposed to Pertussis, J. Pediat. **9:** 118 (July) 1936. McGuiness, A. C.; Bradford, W. L., and Armstrong, J. G.: The Production and Use of Hyperimmune Human Whooping Cough Serum, J. Pediat. **16:** 21 (Jan.) 1940. Roundtable Discussion on Whooping Cough, J. Pediat. **20:** 244 (Feb.) 1942.

47. Cohen, Weichsel and Lapin.[22] McGuiness, Bradford and Armstrong.[46] Roundtable Discussion on Whooping Cough.[46]

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50. Lapin, J. H.: Combined Immunization of Infant Against Diphtheria, Tetanus and Whooping Cough, Am. J. Dis. Child. **63:** 22 (Jan.) 1942. Mishulow, Klein, Liss and Leifer.[25] Silverthorne (footnotes 31 and 48). Powell and Jameson.[44] Bradford, Scherp and Brooks.[35] Mishulow and others.[40] McGuiness, Bradford and Armstrong.[46]

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52. Wu, J., and Chu, F. T.: Effect of Stimulating Dose of Pertussis Vaccination in Children Previously Immunized, Proc. Soc. Exper. Biol. & Med. **38:** 693 (June) 1938. Lapin, J. H.: The Stimulating Dose in Whooping Cough, J. Pediat. **20:** 18 (Jan.) 1942.

vaccination, with particular emphasis on mouse protection tests.

7. In every case the protective titer was raised to a very high level, which was almost quantitatively transmitted to the baby.

8. We have reason to believe from this evidence that these babies were born with immunity against whooping cough.

9. Further studies are being made as to the duration and persistence of these antibodies in both babies and mothers.

10. A small control series of 9 babies of uninoculated mothers were studied immunologically. None revealed agglutinins or complement fixing antibodies, but 2 or perhaps 3 yielded a fair titer of protective antibodies.

11. There is, then, some evidence that a definite percentage, perhaps between 15 and 25, of babies may be born with some immunity against whooping cough.

12. A biologic follow-up is being carried out to correlate the exposure to and the incidence of whooping cough in the inoculated group as compared with an equally large uninoculated group.

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ABSTRACT OF DISCUSSION

DR. SAMUEL J. SCADRON, New York: Our idea was to inoculate the pregnant mother with a potent pertussis bacillus vaccine in the fifth or sixth month of pregnancy. I want to say a word with regard to the effect of this vaccine on the pregnant mother. We have studied only 29 cases immunologically but we have inoculated 167 mothers; in other words, we immunized 167 mothers. There were 90 multiparas and 77 primiparas. The average dose injected was 120 to 150 billion. Previous history of whooping cough in our patients was unknown to 15. A hundred had whooping cough in early childhood. There were 37 positive histories and 15 were doubtful. The types of delivery were not affected by the pertussis vaccine. We had 2 cases of toxemia, which I did not attribute to the injection of the vaccine. I myself watched these cases ante partum and during the postpartum period and found that the vaccine was absolutely innocuous. But the mothers were protected against whooping cough, and this most likely had a beneficial effect on the babies.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: Several years ago I was interested in the placental transmission of antibodies in pertussis as tested by the opsonocytophagic reaction of the blood. It was observed that in certain newborn infants a high titer existed. When this was true the mother almost always possessed a high titer likewise. Dr. Lichty and Mrs. Slavin were generally able to increase the titer of the baby by injecting the pregnant mother with vaccine during the last trimester of pregnancy. This work was not extended because it did not seem, at the time, to be of practicable application. By using the mouse protective method, Drs. Cohen and Scadron apparently have obtained equally good or better results, suggesting that the opsonocytophagic reaction and the mouse protective antibody may give comparable results as methods of testing humoral immunity to pertussis.

DR. PHILIP COHEN, New York: Owing to limitation of time, I could not go into the presumptive proofs that the protective antibodies in the serums which were induced by inoculation of the pregnant mother conferred immunity. I did mention some of the evidence which Dr. Bradford just presented and some additional evidence in the literature, wherein protective antibodies, if not the chief factor in immunity, is a reliable index of immunity in the newborn baby and in any one who has those protective antibodies. I might add that 29 cases are not a small group to be studied because the number of mice we used in these tests amounted to at least 2,000. At least 30 mice are required for each case, so that the technic is prodigious. Dr. Muckenfuss and Miss Mishulow did this work, without which nothing could have been accomplished.

REPAIR OF TRAUMATIC GAPS IN NERVES

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The requirements for functional regeneration of divided nerves are complex and exacting. This is at once evident when it is realized that under the most favorable conditions of repair, by means of primary suture of accurately approximated stumps, the original function of the nerve is never completely restored. The many problems and clinical difficulties involved in connection with nerve injuries have been the subject of numerous investigations and publications, almost two thousand being cited by Pollock and Davis.[1] Quite recently the experimental data and theoretical considerations on the long investigated problems of nerve regeneration have been reviewed critically and extensively by Young.[2] Since an understanding of the complex series of processes which accompany unaided regeneration of severed nerves is basic for any consideration of methods of closure of gaps too wide to be bridged by the unassisted normal process, a brief summary of some of the essential details, as now understood, may be helpful at this point.

1. Physical union between the separated stumps is accomplished, when the gap is not too great, by proliferating Schwann cells, most of which grow out from the distal stump, and by fibroblastic tissue. The parallel orientation of the elongated Schwann cells and fibroblasts in the union scar is of importance in controlling the direction of growth of fibers regenerating from the central stump, since these fibers may otherwise be lost in futile outgrowth into the collagenous tissue surrounding the nerve. If for any reason the fibroblastic tissue predominates in the union scar or interrupts the continuity of the bands of Schwann cells, such a connective tissue scar as it hardens may form a serious barrier to the regenerating nerve fibers.

2. Although the peripheral stump is capable of receiving new fibers for at least as long as seventeen months after injury, and the central stump retains the power to send out new fibers for much longer periods, the formation of a favorable union scar is prejudiced by delay in approximation of the stumps because of reduced outgrowth of Schwann cells from the cut surfaces, so that fibrous tissue predominates in the union scar.[3] This is one strong indication for primary or early repair as well as the probability that too long a delay in reinnervation of the end organs, especially in muscles, may permit irreversible regressive changes to occur in these end organs.[4]

3. The union scar must supply a full caliber bed of proliferating Schwann cells through which a majority of the regenerating fibers of the central stump, and their branches, may pass to the distal stump. This newly formed bed must allow as much cross sectional space as occurs in the distal stump to permit increase in caliber of the newly formed fibers and their myelination. The "maturation" of the regenerating fibers

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