body. For the will to execute the simplest movement leads to physico-chemical change in the nerves and muscles taking part, and chemical change, the body being basically a physico-chemical machine, is structural change. Further, we now know of three physiological mechanisms through which mental states can exert an influence on the body: the autonomic nervous system, the pituitary-thyroid mechanism, and the pituitary-adrenal mechanism. And it would be unscientific to expect consistency. All experience suggests that one man's psychosomatic constitution is such that his body can stand up to mental stress, while another man's is such that under the same circumstances he inevitably succumbs. One is like a castle built on sand and another like a house built on rock.

There remain, therefore, a group of diseases associated with structural change in the body for which at present no certain cause can be found, and in which the part played by the mind cannot as yet be assessed. It may well be very important. True that some of these—disseminated sclerosis and diabetes, for instance—may prove to be somatic only; that is, due to some combination of genetic predisposition and adverse factors acting on the body. Others—for example, duodenal ulcer and malignant hypertension—may well prove to be in part psychogenic in the sense that the psychosomatic constitution of the individual was such that he was predestined to succumb in this way when exposed to mental stress of that type or of that degree of intensity, while another person of different constitution under similar circumstances would have stood the strain.

The Future

What, therefore, of the future? For modern medicine, with its emphasis on the prevention of disease rather than on the treatment of the established condition, now that the age of materialistic optimism is past, can no longer ignore the psychosomatic concept or the part played by mental states in the pathogenesis of structural disease. Short of eugenic control of human mating we have no power (and one can hardly see how we could ever gain it) to alter the plan whence the individual is derived, and, although we should theoretically be able to modify its execution by controlling the environment in which it is carried out, the plan laid at the conception is hidden, so that, even if we could modify it in its execution, indications for the attempt are always wanting. We can, however, by controlling environment minimize the risks to which body and mind are exposed. But how is environment controlled? That depends on teaching the patient how to live, the doctor how to work, and the State its responsibilities (and the limits of its responsibilities) in this direction.

Lastly, will it ever be possible to alter the psychosomatic constitution of the individual so as to reduce the risks to which he is peculiarly exposed in one direction without increasing them in another? To give one example to indicate my meaning. Maleness is one form of psychosomatic development, as I have already pointed out, and femaleness another, while it is well known that men are predisposed to certain diseases and women to others by virtue of their constitution. If the female constitution could be converted into the male, and vice versa, it seems reasonable to suppose one would alter the diseases to which that person was liable to succumb by virtue of his or her sex. Whether in the future this will become possible is one question. Whether, if it ever does become possible, it will be wise or justifiable to do it, is, however, another.

Conclusion

One thing is certain. Our power over body and mind has increased, is increasing, and is likely to increase still further, and, as our power increases, it becomes more and more important that it should be used in the right way in the interests of society. This depends on a proper understanding of the nature of disease and on establishing the right relationship between the potential patient, the doctor, and the State.

IMMUNIZATION OF YOUNG BABIES AGAINST DIPHTHERIA

BY

N. R. BUTLER, M.D., M.R.C.P., D.C.H.

MOLLIE BARR, M.Sc., A.R.I.C.

AND

A. T. GLENNY, B.Sc., F.R.S.

(From the Obstetric Hospital of University College Hospital, London; the L.C.C. Infant Welfare Clinic of University College Hospital Medical School; and the Wellcome Research Laboratories (Biological Division), Beckenham, Kent)

This paper records some of the first results obtained with one prophylactic in an investigation of the methods of immunizing young babies against diphtheria. The whole work includes a comparison between the efficiency of different prophylactics, and a consideration of the effect of age at the time of the first injection and of the interval between injections on the levels of immunity produced.

Immunization against diphtheria is usually started during the second half of the first year of life. It is now generally recognized that immunization can be carried out successfully in the great majority of babies if the first dose of prophylactic is given earlier than this. Immunization against diphtheria has not the same appeal to mothers as protection against whooping-cough. Their eagerness for immunization against whooping-cough, however, can be used to include early immunization also against diphtheria: work on early protection against whooping-cough is being carried out by one of us (N. R. B.) in conjunction with other workers.

Although diphtheria is not at present a danger to young babies there are several advantages in early immunization. Large doses of prophylactic can be given without fear of undue reaction, and injections can be made at the same time as those of *H. pertussis* vaccine, which should be given as early in life as possible. The chief disadvantage lies in the possibility that inherited passive immunity may interfere with active response by neutralizing some or all of the injected prophylactic. The extent to which such interference may occur may increase as the proportion of immunized mothers increases. It is therefore important to employ methods of immunization that are effective in the presence of considerable passively acquired antitoxin. At all times there is also the question of post-inoculation poliomyelitis, and it would seem that the incidence of poliomyelitis in very young babies is not so low as had been supposed (Wright and Owen, 1952).

Barr, Glenny, and Randall (1950) found that babies in whom the maternally conferred antitoxin had fallen below 0.04 unit per ml. at the time of the first injection could be successfully immunized by two doses, each of 0.5 ml. (25 Lf) of A.P.T. When, however, the passive antitoxin was in higher concentration, immunization was unsatisfactory as judged by antitoxic response two months after the second injection. Barr *et al.* (1952) have shown that babies with low maternally conferred antitoxin titres can be successfully immunized by two doses of 0.5 ml. of A.P.T. even when the first dose is injected at the age of 6–10 days. They also found, however, that a high proportion of failures could be

expected if, instead of two doses of A.P.T., three doses of purified toxoid were injected at monthly intervals, the first dose at the age of 6–10 days. They suggested that very young babies might not respond well to unprecipitated prophylactics, or that the intervals between the injections might have been ill-chosen.

Bousfield (1951) used a mixture of P.T.A.P. with additional fluid toxoid for the immunization of older babies. He thought it possible that the free toxoid in this preparation, which he named F.P.T., might neutralize circulating passive antitoxin, so that interference with the action of the P.T.A.P. would be reduced or abolished. He employed a mixture containing 100 Lf toxoid plus 25 Lf of P.T.A.P. per ml. and stated that a "reasonable proportion" of the toxoid remained unadsorbed on the phosphate: no figures were given.

Present Investigation

The results here recorded have been obtained with a preparation of F.P.T. This material contained a total dose of 145 Lf of purified diphtheria toxoid per ml., of which 75 Lf was unadsorbed a few days after preparation. This prophylactic was made for us by Dr. F. V. Linggood, who kindly retested the flocculation values after three months' storage at 4° C., and found that a further 15 Lf had been adsorbed during this time. The composition at the beginning of the work on babies was 60 Lf free plus 85 Lf adsorbed per ml. of prophylactic: 11 months later the composition was 52 Lf free plus 93 Lf adsorbed. The dose injected into babies on each occasion was 0.5 ml. (72.5 Lf), and the schemes used in this work are shown in Table I.

TABLE I.—Schemes of Injection of Babies with F.P.T.

Age	Scheme		
	A	B	A and B
1 week	F.P.T.	F.P.T.	<i>H. pertussis</i> vaccine
6 weeks	"	"	" " "
14 "	"	"	" " "

Of the babies in scheme A 96% received the first injection when between 6 and 9 days old (72% of the total were within the narrow limits of 7 or 8 days) and the remainder when from 9 to 15 days old. The variation in the length of time between the two injections in individual babies can be seen in Table VII; for practical administrative reasons few babies were injected at the exact ages shown in Table I. Blood samples were taken from the babies by jugular venepuncture, the first being taken eight to nine weeks after the second injection of F.P.T. in 90% of cases.

The children were consecutive babies born in the obstetric department of University College Hospital. Samples of cord blood were collected in every case for estimation of the diphtheria antitoxin content. The nature of the immunization scheme was explained to each mother personally or by pamphlet on or about the fifth day of the baby's life, and it was pointed out that most of the injections would be given at the time of routine hospital attendance. Premature babies weighing less than 5½ lb. (2.5 kg.) at birth were excluded, as were babies suffering at the end of the first week from congenital malformations, effects of birth trauma, or infections; a few others were excluded because their homes were so far from the hospital as to preclude further attendance. The parental response was excellent, for out of the first 250 births of all weights 209 (83%) received a first injection in hospital and 195 completed the primary course of diphtheria and whooping-cough immunization.

An autoclaved all-glass syringe was used for each injection; after the prophylactic had been drawn up, the needle was changed to a No. 20 for the injection. The route and site of the injection were varied, and included subcuticular

or deep subcutaneous in the leg and deep subcutaneous in the deltoid area: this route gave the lowest reaction rate to injections either of diphtheria prophylactic or of *H. pertussis* vaccine. Both local and general reactions to the first injection of F.P.T. were very slight, and no reaction was complained of after the second injection, given at either 6 or 14 weeks. Table II shows the incidence of local reactions

TABLE II.—Incidence of Local Reactions to First Injection of F.P.T. Given at Age of About 1 Week

Group	Site	Route	No. Showing Erythema				Total	No. Showing Induration				Total
			0	1–25	26–50	>50 mm.		0	1–25	26–50	>50 mm.	
1	Thigh	Subcuticular	11	70	12	1	94	41	46	2	0	89
2	"	Deep subcutaneous	38	41	4	1	84	59	24	0	0	83
3	Deltoid	"	50	47	1	0	98	85	12	0	0	97
All groups			99	158	17	2	276	185	82	2	0	269
Percentage			35.9	57.2	6.2	0.7		68.8	30.5	0.7		

in 305 consecutive babies given the first injection of F.P.T. in the hospital nursery during the first two weeks of life: 99 (35.9% of the 276 examined) showed no erythema, and 185 (68.8% of 269) had no induration at the site of injection 24 hours after the first injection. Only 19 babies (6.9%) showed areas of erythema or induration of more than 2.5 cm. diameter, and none of these progressed to local abscess formation. There were 14 babies showing small nodules five weeks after the first injection, but none of these was still present at the age of 3 months.

We are indebted to Mr. P. A. Young, of the Wellcome Research Laboratories, for making a statistical analysis of the figures given in Table II. From this analysis he has drawn the following conclusions.

Erythema is significantly more frequent and more extensive after subcuticular injection than when it occurs after subcutaneous injection.

Erythema occurs with equal frequency on thigh and deltoid after deep subcutaneous injection, but when it does occur it tends to be more extensive on the thigh.

After deep subcutaneous injection induration is significantly more frequent on the thigh than on the deltoid.

Induration on the thigh is significantly more frequent after subcuticular injection than after deep subcutaneous injection.

Determination of Antitoxin Titres

The antitoxin titres of sera from cord blood and from the babies after immunization were determined by a modification of the Römer and Sames (1909) guinea-pig intracutaneous method (Glenny and Llewellyn-Jones, 1931). Tests were made at approximately twofold differences; the lowest level tested was 0.001 unit per ml. Since only small amounts of serum were available from some of the babies, a dilution 1 in 5 was made, and the lowest titre measured, in terms of undilute serum, was therefore raised to 0.005 unit. When serum was plentiful tests were made at lower levels, but for the purpose of analysis of results such low titres were included as under 0.005 unit: this figure corresponds roughly to the Schick level. Diluted sera were tested at the same levels as the undilute cord sera, but the multiplication of the titre by five brings some recorded values to slightly different figures. For example, cord blood titres are recorded as 0.004 (above 0.004 and below 0.01), 0.01, 0.02, and 0.04 unit per ml., but tests on diluted material at the same levels represent titres of 0.02, 0.05, and 0.1, etc., after correcting for dilution. The form of the histograms in Figs. I, II, and III shows the limiting values for all the recorded titres; The geometric means in the tables are calculated from the geometric means of the limiting titres; thus a recorded titre of 0.01 is regarded as 0.014 for the purpose of such calculations. Values recorded as under 0.005 are taken to be 0.002.

Antitoxin Titres of Babies in Scheme A

Fig. I shows the distribution of antitoxin titres of babies at the age of 3 months, about eight weeks after the second injection of F.P.T. The results have been arranged

FIG. I.—Distribution of diphtheria antitoxin titres in the serum of babies when 3 months old after immunization under scheme A.

- (1) 110 babies with cord blood titre of 0.01 unit per ml. or less
 (2) 21 " " " " " " " 0.02 or 0.04 unit per ml.
 (3) 34 " " " " " " " 0.1, 0.2, or 0.5 unit "
 (4) 12 " " " " " " " 1, 2, or 10 units "
 Broken lines show the distribution of residual passive antitoxin titres.

into four groups according to cord blood titre. In diagram 1, which shows the titres of babies for whom the cord blood had contained 0.01 unit or less, the great majority were between 0.1 and 1 unit per ml. Only four babies had titres below 0.05 unit.

In diagram 2 (cord blood titres between 0.01 and 0.1), there is a suggestion of two, possibly three, populations. Two babies out of 21, both with the higher cord blood titre of 0.04 unit, failed to produce 0.005 unit per ml.; 12 babies produced over 0.01 but under 0.1 unit; and only five reached 0.2 or 0.5 unit per ml. There is thus a clear dividing line at 0.02 unit between the cord blood titre which seldom interfered with and that which often reduced active response to injection. With lower cord blood titres (diagram 1) only 10 among 110 babies failed to produce 0.1 unit, compared with 14 of 21 shown in diagram 2.

Diagram 3 deals with babies whose cord blood titres were between 0.1 and 1 unit per ml. Such babies would have measurable amounts of residual passive antitoxin at the age of 3 months. Calculations from the formula of Barr, Glenny, and Randall (1949) show that slightly less than one-tenth (7.8%) of the cord blood titre would still be present in the serum of babies 3 months old. Babies with cord blood titres recorded as 0.1 unit per ml.—that is, between 0.1 and 0.2 unit—would thus be expected still to have titres between 0.0078 and 0.0156 unit. Such titres would be recorded as either 0.005 or 0.01. By assuming an even distribution of titres between the various limits, it is possible to work out the distribution of passive titres to be expected at 3 months (and also at 6 months as shown in Fig. II)

if no active antitoxin production had occurred as a result of the injections of F.P.T. This distribution is shown in Fig. I as a broken line, and corresponds fairly closely to the distribution actually found. There was thus little active response in these babies, though there is a suggestion from both diagrams 3 and 4 (babies whose cord blood titres were 1 unit or more) that a few babies may have produced some antitoxin actively. In diagram 4 the agreement between the distribution of calculated passive titres and those found is not so good as that in diagram 3, but the figures for both diagrams seem to provide confirmation of the formula of Barr, Glenny, and Randall.

Fig. II shows the distribution of antitoxin titres of the babies when 6 months old. The titres of those with low cord blood initially had mostly fallen to about one-half the titre found at 14 weeks (diagrams 1 and 5). A comparison of the titres in diagrams 2 and 6 shows that a few of the higher titres at 14 weeks had fallen, but that there was an increase in some of the lower ones. Diagram 7 shows that the passive titres of babies with cord blood values over 0.1 and under 1 were almost negligible at the age of 6 months, and that nearly all the babies had responded actively by this time. A number of the babies in the highest cord blood group (diagram 8) had also shown an active response by this time. Thus a delayed response, the "intermediate response" of Glenny and Südmersen (1921), may occur in babies with a high level of circulating passive antitoxin at the time of injection of prophylactic. Barr, Glenny, and Howie (1953) found a close inverse correlation between passive titre and response to the first and to the second injection of A.P.T. in lambs that had acquired diphtheria antitoxin from the colostrum of their actively immunized mothers. Even very high passive titres that

FIG. II.—Distribution of diphtheria antitoxin titres in the serum of babies at the age of 6 months after immunization under scheme A.

- (5) 38 babies with cord blood titre of 0.01 unit per ml. or less
 (6) 17 " " " " " " " 0.02 or 0.04 unit per ml.
 (7) 30 " " " " " " " 0.1, 0.2, or 0.5 unit "
 (8) 8 " " " " " " " 1, 2, or 10 units "
 Broken lines show the distribution of residual passive antitoxin titres.

prevented any detectable antitoxin production after two injections of A.P.T. did not prevent the development of basal immunity, so that considerable antitoxin production occurred after a third injection. It is therefore possible that some antitoxin would be actively produced by all babies if given a third injection at the age of 6 months.

TABLE III.—*Changes in Antitoxin Titres in Serum of Babies Injected under Scheme A and Bled when 3 Months and 6 Months Old*

Cord Blood Titres		No. of Babies Whose Titres			Total
Over	Under	Increased	Remained the Same	Decreased	
—	0.004	1	4	25	30
0.004	0.1	6	10	5	21
0.1	0.2	9	2	1	12
0.2	1.0	4	3	8	15
1.0	—	0	0	8	8
Total	...	20	19	47	86

Table III shows the changes in antitoxin titres of all babies injected under scheme A and bled when 3 months and 6 months old: the responses are divided according to cord blood titre, but in different groups from those in Figs. I and II. Twenty-five of the 30 babies whose cord blood titres were below 0.004 unit showed a fall in antitoxin between the third and sixth months, and only one increased. This suggests that nearly all the babies in this group had given a secondary response to the second injection of F.P.T. Only two out of six with cord blood titres of 0.004 or 0.01 decreased in titre during the third to sixth months of life; these results are therefore included in the second group in Table III. Those with initial titres of 0.1 unit per ml. formed the only group in which more than half the titres increased during the third to sixth months; this group is therefore recorded separately. Those babies with higher cord blood titres—0.2 and 0.5—were almost equally divided between those who decreased in titre and those who either increased or remained the same. All with an original value of 1 or more decreased in titre during the third to sixth months.

Table IV gives a comparison of the distribution of antitoxin titres of those babies who were bled on two occasions, together with the average passive titre expected to be present in the higher groups at the time the blood samples were taken. These figures were calculated from the formula of Barr *et al.* (1949), and, by subtraction from the total titre found, the average active titre for each group has been calculated. Babies in the first group must have reached their maximum antitoxin titre at or before the time of their first bleeding when 3 months old, and their titres had fallen considerably when bleedings were taken three months later. The second group consisted of two populations irrespective of the cord blood titres within the recorded limits; 10

babies had responded by three months as well as those in the first group, and those had mostly fallen in value by 6 months, although the reduction in titre was not so great as that in the first group. The other population had responded badly by 3 months and mostly increased in titre by 6 months. As a result of this delay in reaching the maximum titre the average titre at 6 months of the second group was higher than that of the first group. The third group, consisting of those babies whose cord blood titre was 0.1 unit, included only one whose titre at 6 months was lower than that at 3 months. As this baby reached 0.2 unit at 3 months it can be concluded that all had been actively immunized.

It can be concluded, therefore, that all babies with cord blood titres of 0.1 unit or less per ml. were actively immunized by scheme A. This would apply to 766 of the first 1,000 at U.C.H. whose cord blood titres were tested.

The results given in the last two groups in Table IV are not so definite. In the fourth group the geometric mean of the titres found at 3 months is almost identical with the expected passive contribution, but at 6 months the mean titre found was 3.7 times the expected passive titre; some at least of the babies must have responded actively. It seems reasonable, therefore, to accept as actively immunized the 7 out of 15 recorded in Table III as at least maintaining their level of total antitoxin content from the third to the sixth month, although their passive antitoxin content fell by 0.03 unit per ml. This would bring the estimated number of babies immunizable under scheme A to at least 84%. The figures given for the fifth group in Table IV suggest that at least one of the seven babies was actively immunized, although the cord blood titre was 1–2 units per ml.

TABLE V.—*Comparison Between Titres at 3, 6, and 9 Months of Babies Injected under Scheme A. Cord Blood Titres were all 0.01 Unit or Less per ml.*

Antitoxin Titre (Unit/ml.)	No. of Babies Possessing the Stated Antitoxin Titre when Aged		
	3 Months	6 Months	9 Months
Under 0.005	..	1	1
0.005	..	1	1
0.01	..	0	1
0.02	2	3	3
0.05	2	7	5
0.1	27	10	9
0.2	34	12	7
0.5	36	4	4
1.0	3	1	..
Total	109	39	30
G.M. (unit/ml.)	0.298	0.150	0.136

Further data have been collected on later blood samples from some of these babies with low cord blood titres who were bled at the age of 9 months. Table V shows the distribution of all such babies immunized under scheme

TABLE IV.—*Comparison Between Titres at 3 and 6 Months of Babies Bled on Both Occasions After Immunization under Scheme A*

Antitoxin Titre (Unit/ml.)	No. of Babies with Cord Blood Titres of									
	< 0.004		> 0.004 < 0.1		> 0.1 < 0.2		> 0.2 < 1.0		> 1.0 < 5.0	
	Passing the Antitoxin Titre Stated when Aged (Months)									
	3	6	3	6	3	6	3	6	3	6
Under 0.005	..	..	1	..	2	..	1	..	..	..
0.005	..	..	0	..	4	..	2	..	..	..
0.01	..	..	1	2	0	1	5	3	1	1
0.02	1	3	6	3	3	0	5	7	0	3
0.05	..	..	7	3	2	2	4	1	3	1
0.1	..	..	9	0	0	3	1	1	2	0
0.2	..	..	7	3	1	..	..	..	0	1
0.5	..	..	3	2	..	..	..	..	1	..
1.0	..	..	7	1	..	..	..	..	..	..
Total	..	30	22	12	15	7	..	..	..	..
G.M. of titres	..	0.327	0.133	0.117	0.147	0.023	0.046	0.033	0.022	0.200
Passive contribution	..	Nil	Nil	Nil	Nil	0.011	0.002	0.036	0.006	0.155
Active production	..	0.327	0.133	0.117	0.147	0.012	0.044	Nil	0.016	0.045
										0.081
										0.026
										0.055

A and bled at 3 months and at 6 or 9 months. The figures come from a dwindling and mixed population, and few of those bled at 9 months had been bled at 6 months, but it is important to note that, whereas the geometric mean titre of those bled at 6 months was about half that at 3 months, the mean titre at 9 months was only 10% lower than that at 6 months. This suggests that babies in whom the maternal antitoxin was insufficient to interfere with active immunization gave secondary responses, and that the flattening out of the curve of loss, typical of such responses, occurred at about 6 months.

TABLE VI.—Comparison Between Antitoxin Titres of Babies about 8 Weeks After the Second of Two Injections of F.P.T. under Scheme A Divided According to Route of Injection. Cord Blood Titres were all 0.01 Unit or Less per ml.

Route	No. of Babies with Antitoxin Titres (Units/ml.)							No.	G. Mean Titre
	0.01	0.02	0.05	0.1	0.2	0.5	1.0		
Subcuticular									
Deep subcutaneous (arm and thigh)	2	1	1	7	22	23	0	56	0.377

It is perhaps of interest to record the antitoxin titres in babies immunized by subcuticular and by deep subcutaneous injections of F.P.T. A comparison is given in Table VI, relating to babies injected in scheme A whose cord blood titres were 0.01 unit per ml. or lower. Although there is

a suggestion of better results with deep subcutaneous injections, the differences between the means of the logarithms of the two sets of titres is not significant.

Antitoxin Titres of Babies in Scheme B

Babies injected under scheme B were bled for the first time at the age of 6 months. Antitoxin titrations were therefore made about 12 weeks after the second injection, compared with eight to nine weeks in scheme A.

The distribution of antitoxin titres of these babies at 6 months is shown in Fig. III. The results are grouped according to cord blood titre as in Fig. I, so that diagrams 1 and 9, 2 and 10, 3 and 11, and 4 and 12 show titres of babies with the same ranges of cord blood values. It is at once evident on comparing diagrams 1 and 9 that babies born with little maternally conferred antitoxin were better immunized under scheme B than under scheme A. There is a very small scatter of titres in diagram 9, in contrast to the wide scatter and the poor titres of some babies in diagram 1. We are of the opinion that a small scatter provides evidence of satisfactory immunity in a population as a whole (see Barr, Glenny, and Randall, 1950). The same improved response is shown in all groups under scheme B except those with cord blood titres of 1 unit or higher. The improved response of babies receiving the second injection at the longer interval after the first, recalls the finding of Barr *et al.* (1950) that young babies immunized with two doses, each 0.5 ml. of A.P.T., responded better if the interval between the injections was 10–18 weeks than if it was 6–9 weeks.

It is probable that, when a potent prophylactic such as F.P.T. is used, intervals between injections could be extended even further in babies with low passive titres at the time of the first injection. It is, however, of interest that those with high cord blood titres responded less well when the interval between injections was 13 weeks than when it was five weeks. This result suggests that the potential immunity conferred by the first dose of F.P.T., injected at a time when the circulating passive antitoxin was considerable, had been largely lost by the 13th week. The presence of considerable passively conferred antitoxin reduces the amount of effective prophylactic available to act as a stimulus. When very small dosage is used the degree of potential immunity established by the first injection is insufficient to provoke a good antitoxic response if the second injection is delayed unduly (Barr and Glenny, 1945). Although the babies whose titres are shown in diagram 12 may subsequently show delayed production of antitoxin, they seem to be less effectively immunized than those in diagram 4.

The effect of interval between injections upon response is shown in Table VII. The titres are those of babies for whom the cord blood titre was 0.01 unit or less per ml., and babies who received the second injection after eight

FIG. III.—Distribution of diphtheria antitoxin titres in the serum of babies when 6 months old after immunization under scheme B.

(9) 43 babies with cord blood titres of 0.01 unit per ml. or less
 (10) 18 " " " " " " " 0.02 or 0.04 unit per ml.
 (11) 26 " " " " " " " 0.1, 0.2, or 0.5 unit "
 (12) 7 " " " " " " " 1 or 2 units "
 Broken lines show the calculated distribution of residual passive antitoxin titres.

TABLE VII.—Distribution of Antitoxin Titres in Serum of Babies Taken about 8 Weeks After Second of Two Injections of F.P.T. under Schemes A and B Divided According to Interval Between Injections. Cord Blood Titres were all 0.01 Unit or Less per ml.

Interval Between Injections (Weeks)	No. of Babies with Antitoxin Titres (Unit ml.) of								Total	G.M. (Unit/ml.)
	0.01	0.02	0.05	0.1	0.2	0.5	1.0	2.0		
4 to 5 ..	2	1	1	19	14	12	1	0	50	0.24
5 " 6 ..	0	1	4	7	17	7	0	0	46	0.31
6 " 8 ..	0	0	0	1	3	17	2	0	13	0.58
12 " 15 ..	0	0	0	0	3	21	9	2	35	0.86

weeks or less (scheme A) were bled and tested eight to nine weeks later, while those in scheme B (12–15 weeks interval) were bled about 12 weeks after the second injection. It is clear from the distribution of titres, the smaller scatter, and the geometric mean values that the response of these groups of babies improved as the interval between injections was increased.

Table VIII compares the distribution of titres of babies with higher cord blood values immunized under schemes A and B. This table shows in addition the average passive titre to be expected in each group at the time the blood samples were taken. It is clear that much greater active antitoxin production occurred in babies immunized under scheme B than scheme A, except those with cord blood titres of 1 unit or more.

It is perhaps of interest to consider these results in relation to the distribution of 1,000 cord blood titres from this particular population. Only 7.4% of this large sample had cord antitoxin titres of 1 unit or more per ml., and it would therefore appear that over 90% of the babies would be immunized more satisfactorily by two doses of F.P.T. given at the ages of 1 and 14 weeks than by two similar doses given at the ages of 1 and 6 weeks. There was, however, one other point of difference between the injection procedures in schemes A and B. Whereas group A received

suitable, not necessarily optimal, interval for P.T.A.P., but a much longer interval, such as that in scheme B, was necessary for uniformly good results when F.P.T. was used.

Summary

Further evidence is given that active production of diphtheria antitoxin in babies is greatest in those with little or no antitoxin in their cord blood. The interference with active production caused by higher passive titres does not appear to be reduced by the use of F.P.T.—that is, P.T.A.P. to which additional unprecipitated purified toxoid has been added.

Babies whose cord blood titres were below 1 unit per ml. and who were immunized with two doses of F.P.T., each of about 70 Lf, gave better antitoxic responses if injected at the ages of about 8 days and 14 weeks than

TABLE VIII.—*Distribution of Antitoxin Titres in Serum of Babies Given Two Injections of F.P.T. Under Schemes A and B Divided According to Cord Blood Titres*

Cord Blood Titres (Units/ml.)	Scheme	No. of Babies with Antitoxin Titres (Units/ml.) of									Total	Geometric Mean	Passive Contri- bution	Active Response
		Under 0.005	0.005	0.01	0.02	0.05	0.1	0.2	0.5	1.0	2.0			
0.02, 0.04	A	2	0	2	4	6	0	3	4	0		21	0.074	Nil
0.02, 0.04	B	0	0	2	0	0	1	3	11	1		18	0.380	..
0.1, 0.2, 0.5	A	4	0	11	9	7	2	1	0	0		34	0.026	0.021
0.1, 0.2, 0.5	B	0	0	3	6	6	5	1	4	1		26	0.094	0.005
1, 2, 5, 10	A		0	0	1	2	3	4	0	1	1	12	0.228	0.174
1, 2, 5, 10	B		1	2	2	1	1	0	0	0	0	7	0.028	0.026

two injections each of F.P.T. and of *H. pertussis* vaccine given at the same times but in a different site, group B received an injection of *H. pertussis* vaccine alone between the injections of F.P.T. and vaccine. The effect of the introduction of injections of one antigen alone in a course of combined prophylaxis has not received much investigation. It has been recently shown by Barr and Llewellyn-Jones (1953a) that a preliminary injection of typhoid-paratyphoid vaccine before the first of two injections of this vaccine in combination with tetanus toxoid may bring about interference with the response to the tetanus toxoid in guinea-pigs. The same workers (1953b) have found that in certain circumstances an injection of a vaccine in between two injections of a combined prophylactic containing the same vaccine and a toxoid may improve the response to the toxoid. It is possible that the injection of *H. pertussis* vaccine given to the babies of scheme B between the two injections of the same vaccine and of F.P.T. contributed in some measure to the better response of the majority of this group. We are, however, of the opinion that the superiority of results in scheme B to those in scheme A was due chiefly to the longer interval between the injections of F.P.T.

P.T.A.P.—A few babies, including 25 with cord blood titres of 0.01 unit or less per ml., were injected with 0.5 ml. of P.T.A.P., given at the same time as in scheme A. The responses of this group were far better than those injected with F.P.T. in scheme A, and approached the results of scheme B. The total antigen content in the dose of F.P.T. was slightly more than double that in the dose of P.T.A.P. Thus, babies with no circulating passive antitoxin at the time of the first injection of F.P.T. received twice as much total antigen as similar babies injected with P.T.A.P. In babies who had maternally conferred antitoxin the free toxoid in F.P.T., though it might neutralize this antitoxin, would be expected also to have an antigenic effect if gradual dissociation of the toxoid-antitoxin complex took place. It is therefore to be expected that the optimum interval between the two injections of this potent prophylactic would be longer than that for the weaker preparation, P.T.A.P. It is probable that five weeks between two injections was a

if injected at the ages of about 8 days and 6 weeks. When the cord blood titre was 1 unit or more, responses were poorer in the group receiving injections at the longer interval.

In the short-interval group, comparison of the antitoxin levels of babies at the ages of 3 and 6 months suggested that many with cord blood titres above 0.004 unit per ml. had given an intermediate, not a secondary, response to the second injection of prophylactic. This was shown as a delayed production of antitoxin, due to reduction in the effective first dose of F.P.T. because of neutralization by passively conferred antitoxin. A few babies with low cord blood titres gave better responses to two doses, each of about 25 Lf of P.T.A.P., given at the ages of 8 days and 6 weeks, than similar babies receiving two doses of F.P.T. at the same ages.

The general reaction rate was negligible after injections of F.P.T.: local reactions were also very slight, and were less after deep subcutaneous than after subcuticular injection

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