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IMMUNIZATION AGAINST DIPHTHERIA WITH ALUM-PRECIPITATED TOXOID*

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During recent years evidence has gradually been accumulating to suggest that the best and most economical method of immunizing children against diphtheria is by two suitably spaced doses of alum-precipitated toxoid (A.P.T.). Experience, however, of this method has so far been very limited. The great immunizing campaigns in the United States, Canada, and France have been carried through mainly with toxin-antitoxin mixture and with formol toxoid. Most of the early trials of A.P.T. were made by the one-dose method, which is now generally recognized to be unsatisfactory. The number of careful observations made on the two-dose method is small, and nearly all of the published records differ in either the dosage used or the interval between the doses, or both. We therefore make no apology in presenting our figures, which refer to the production of immunity, as judged by the Schick-conversion rate, in children inoculated with doses of 0.1 and 0.3 c.cm. of A.P.T. at four to six weeks' interval. If we did need an excuse, we could not do better than quote from Sir John Ledingham's address to the British Medical Association at Aberdeen in 1939, in which, discussing the antigenic value of different prophylactics, he stated: "There is no doubt that it is highly expedient that comparative trials should still go on, for it is desirable in planning extensive crusades to determine what form of antigen and what scheme of administration are best calculated to yield the most lasting immunity, due consideration being always given to the tolerability of the antigen or antigens in the interest of acceptable propaganda."

The Primary Schick Test

During the course of inoculating about 30,000 school children against diphtheria in the past two years we took the opportunity of judging the efficacy of our method by Schick-testing a proportion of the children before and after their immunizing injections. Our observations, which cover the period November, 1939, to November, 1941, were made on children in residential and non-residential schools in Oxfordshire, Berkshire, Buckinghamshire, and Wiltshire. A few pre-school children and a few adults were included, but approximately 95% of the subjects were between the ages of 5 and 16 years. The majority of the schools were of the elementary or secondary type and were situated in urban or rural districts. No large towns were visited, but most of the schools contained a proportion of evacuees from London. Apart from the evacuees,

very few children had been previously immunized against diphtheria. The Schick test was carried out by inoculating 0.2 c.cm. of toxin intradermally into the left forearm and 0.2 c.cm. of heated toxin as a control into the right forearm. All reagents used for this test were prepared at the Wellcome Physiological Research Laboratories and conformed to the requirements of the regulations made under the Therapeutic Substances Act, 1925. Readings were made three to five days later. The diameter of the reaction was measured with callipers, and usually a note made of the degree of redness. Negative reactions were taken as those which, even after rubbing, showed no evidence whatever of erythema. Reactions of 1 to 5 mm. were classified as $\pm$ and, in accordance with O'Brien's (1929) recommendations, were regarded as negative. Reactions of 6 to 10, 11 to 20, 21 to 30, and 31 to 40 mm. were classified as $+$, $++$, $+++$, and $++++$ respectively, and were regarded as positive. Table I sets out the primary Schick reactions according to age and sex.

TABLE I.—Frequency of Positive Reactors at Primary Schick Test according to Age and Sex

Age in Years	Boys			Girls			Boys and Girls		
	No. Tested	No. Pos.	% Pos.	No. Tested	No. Pos.	% Pos.	No. Tested	No. Pos.	% Pos.
1 & 2	7	7	100.0	14	14	100.0	21	21	100.0
3	13	11	84.6	15	15	100.0	28	26	92.9
4	25	24	96.0	15	15	100.0	40	39	97.5
5	90	72	80.0	69	64	92.8	159	136	85.5
6	109	93	85.3	91	79	86.8	200	172	86.0
7	114	100	87.7	110	101	91.8	224	201	89.7
8	229	184	80.3	169	145	85.8	398	329	82.7
9	282	223	79.1	161	137	85.1	443	360	81.3
10	272	224	82.4	184	160	87.0	456	384	84.2
11	373	292	78.3	312	261	83.7	685	553	80.7
12	383	295	77.0	397	308	77.6	780	603	77.3
13	361	285	78.9	367	299	81.5	728	584	80.2
14	122	78	63.9	131	100	76.3	253	178	70.4
15	118	61	51.7	57	48	84.2	175	109	62.3
16	106	48	45.3	27	19	70.4	133	67	50.4
17	62	22	35.5	18	15	83.3	80	37	46.3
Over 17	85	31	36.5	13	7	53.8	98	38	38.8
Total	2,751	2,050	74.5	2,150	1,787	83.1	4,901	3,837	78.3

Difference between boys and girls: $\chi^2 = 52.488$. $P = < 0.000001$.

The average Schick-positive rate was 78.3%. This figure resembles that of 76.4% for children of 5 to 14 years of age at Croydon given by Lewis (1941a), but is considerably higher than that of 64.4% recorded by Ker and McGarrity (1924) for children aged 5 to 14 years in the Edinburgh City Hospital, and very much higher than that of Zingher (1923)—namely, 32.9%—for children in New York City. There were too few observations in our series to show a regularly decreasing proportion of positive reactors with

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increasing age, though the trend was obviously in this direction. It will be noted that during the statutory school age of 5 to 14 years there appeared to be very little change in the reaction rate. At 14 years and later the rates showed a rapid fall, but undue importance should not be attached to these figures, since they were heavily weighted by the inclusion of a training colony in which a considerable proportion of the boys had been previously immunized and in which diphtheria had been occurring during recent months.

Like Zingher (1923), we found that the Schick-positive rate was higher in girls than in boys. The difference in our series, as shown by the χ^2 test, was highly significant.

Intensity of the Schick Reaction

It was thought that the progressive diminution in the proportion of Schick-positive reactors with age might be reflected in a corresponding diminution in the intensity of the reactions given by those who were still Schick-positive. For this reason the intensity of the Schick reaction in relation to age has been worked out in Table II.

The number of observations made was rather smaller than in Table I, owing to the absence of accurate measurements for the first three schools we visited. The proportion of $\pm$ reactors did not seem to differ significantly in the different age groups, the average being 3.4% of the total

Frequency of Pseudo-reactions

Reactions to the heated toxin used as a control were very few and rarely gave rise to trouble in reading the result of the Schick test. Records were available for eighteen schools. In ten of them no pseudo-reactions were observed. In the other eight schools the proportion varied from 0.2 to 6.1%. The total number recorded was 40 out of 3,392 persons tested—i.e., 1.2%. Of these, 6 were noted in children under 10 years of age and 34 in children over this age. There was no appreciable difference between the sexes. When pseudo-reactions did occur they were usually small and rarely exceeded 20 mm. in diameter. For practical purposes it seems doubtful whether it is worth while carrying out a control test on children under 10 years of age. In our experience the error introduced by such an omission would have been less than 0.2%.

Reactions to A.P.T.

Owing to pressure of other work very few observations were made on the degree of reaction following inoculation with A.P.T. into the deep subcutaneous tissue. The few opportunities we did have showed us that about half the children receiving 0.1 or 0.3 c.cm. developed some degree of redness or swelling at the site of injection within the

TABLE II.—Intensity of Reaction at First Schick Test in Relation to Age. Schools 4 to 22

Age in Years	Diameter of Reaction in Millimetres												Total		
	—		±1-5		+ 6-10		++ 11-20		+++ 21-30		++++ 31 and over				
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No. Tested	No. Schick-positive	% Schick-positive
1-4	2	3.2	—	—	1	1.7	38	63.3	21	35.0	—	—	62	60	96.8
5-8	94	11.8	19	2.4	26	3.8	333	48.8	305	44.7	19	2.8	796	683	85.8
9-10	107	14.3	30	4.0	21	3.4	309	50.7	253	41.5	26	4.3	746	609	81.6
11	113	18.6	19	3.1	25	5.2	256	53.7	187	39.2	9	1.9	609	477	78.3
12	137	19.7	36	5.2	19	3.6	260	49.6	237	45.2	8	1.5	697	524	75.2
13	137	18.8	24	3.8	18	3.7	267	55.2	191	39.5	8	1.7	626	484	77.3
14-17	118	18.8	24	3.8	18	3.7	267	55.2	191	39.5	8	1.7	626	484	77.3
	62	20.1	4	1.3	6	2.5	132	54.3	104	42.8	1	0.4	309	243	78.6
Total	633	16.5	132	3.4	116	3.8	1,595	51.8	1,298	42.1	71	2.3	3,845	3,080	80.1

Percentage figures in — and $\pm$ columns refer to percentage of total tested.

Percentage figures in +, ++, +++, and ++++ columns refer to percentage of Schick-positive reactors only.

number of children tested. Of the Schick-positive reactors 93.9% fell into the ++ and +++ groups. The number of + reactors was very small, the average being only 3.8%. If the ++, +++, and ++++ reactors are added together the following figures are obtained: 1-4 years, 98.3%; 5-8, 96.3%; 9-10, 96.5%; 11, 94.8%; 12, 96.3%; 13, 96.4%; 14-17, 97.5%. There appears to be practically no difference between the different age groups in the proportion of moderately, strongly, and very strongly positive results. In other words, a decrease in the proportion of positive Schick reactors with age did not seem to be accompanied by a corresponding decrease in the intensity of the positive reactions. The numbers, however, may have been too small to reveal such a difference, if it did exist.

next two days. In a small proportion a widespread area of erythema appeared, accompanied by swelling, stiffness, and tenderness. Occasionally the whole of the upper arm was affected, and very occasionally the forearm also. We ourselves met with only one subject in which a sterile abscess developed, but the medical officer of health of a district where a number of schools were immunized reported that several children had developed sterile abscesses, some of which required opening. Confidential information received from other parts of the country suggests that such an occurrence seemed to follow the use of a particular batch of A.P.T. Similar observations are recorded by McGinnes, Stebbins, and Hart (1934) and Harrison (1935) in the United States of America. Comparisons between

TABLE III.—Comparison of Local Reactions following Inoculations of (a) 0.1 c.cm. of A.P.T. into Schick-negative Reactors; (b) 0.1 c.cm. of A.P.T. into Schick-positive Reactors; (c) a Second Inoculation of 0.3 c.cm. of A.P.T. into Schick-positive Reactors

Group	Dose of A.P.T.	Intensity of Local Reaction										Total Showing Reactions	
		—		±		+		++		+++			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Schick-neg.	0.1 c.cm.	8	14	3	5	29	52	15	27	1	2	48/56	85.7
Schick-pos.	0.1 c.cm.	138	57.8	37	15.5	54	22.6	8	3.3	2	0.8	101/239	42.3
" " " " " " " "	0.3 c.cm.	106	56.1	55	29.1	19	10.1	9	4.8	—	—	83/189	43.9

— : No local reaction.

$\pm$: Area of redness not greater than 10 mm. with or without swelling.

++ : " " " 11 to 20 mm. with swelling and tenderness.

+++ : " " " 21-60 mm.

++++ : " " " 61 mm. and over " " "

TABLE IV.—*Schick-conversion Rates in Relation to Make and Dosage of A.P.T.*

No.	School	A.P.T.			First Schick Test			Second Schick Test				Conversion Rate %
		Maker	Dosage in c.cm.	Interval between Doses in Weeks	No. Tested	No. +	% +	Time after 2nd Dose of A.P.T. in Weeks	No. Tested	No. +	% +	
1	R.M.N.S. . . .	A	0.1	5	238	139	58.4	8	133	4	3.0	97.0
2	Turner's Court . .	A	0.3	6	314	112	35.7	8	86	1	1.2	98.8
3	Chadlington and Spelsbury	A	0.1	4	114	87	76.3	11	57	2	3.5	96.5
4	Sutton Benger and Christian Malford	A	0.3	5	139	105	75.5	9	83	6	7.2	92.8
5	Hilmarton . . .	A	0.1	4	56	45	80.4	12	38	0	0.0	100.0
6	Maidenhead . .	A	0.3	5	326	291	89.3	8	278	3	1.1	98.9
7	Queen's Park, Aylesbury	A	0.1	5	350	324	92.6	8	226	5	2.2	97.8
8	Wokingham . .	A	0.5	5	188	179	95.2	12	90	1	1.1	98.9
9	Purton . . .	A	0.1	4	104	96	92.3	12	66	0	0.0	100.0
10	1 Summerfields . .	A	0.3	4	46	41	89.1	9	31	0	0.0	100.0
11	2 Summerfields . .	A	0.1	4	44	32	72.7	8	27	0	0.0	100.0
12	Cothill . . .	A	0.3	4	80	49	61.3	8	40	0	0.0	100.0
13	Charlbury . . .	A	0.1	4	266	197	74.1	9	47	1	2.1	97.9
14	Chesham . . .	B1	0.3	5	348	279	80.2	8	104	14	31.1	68.9
15	Amersham . . .	A	0.1	6	368	279	75.8	8	103	2	1.9	98.1
16	Chalfont St. Giles . .	B1	0.3	4	255	202	79.2	8	112	34	33.0	67.0
		A	0.1	4					106	1	0.9	99.1
			0.3						0	0	0.0	100.0
			0.2						63	2	3.2	96.8
			0.4						77	37	48.1	51.9
17	Kidlington . . .	A	0.1	4	603	509	84.4	8	67	0	0.0	100.0
		D	0.3						143	3	2.1	97.9
18	Thame . . .	E	0.3	4	326	288	88.4	16	144	0	0.0	100.0
		A	0.1	4					78	9	11.5	88.5
		B1	0.5						75	22	29.3	70.7
			1.5									
19	Slough . . .	A	0.1	5	247	151	61.1	16	28	2	7.1	92.9
		C	0.3						22	3	13.6	86.4
		D	0.3						23	0	0.0	100.0
		E							23	1	4.3	95.7
20	Grammar School, Aylesbury	A	0.1	4	240	211	87.9	8	71	0	0.0	100.0
		F	0.3						77	20	26.0	74.0
21	Sunninghill . . .	A	0.1	4	225	202	89.8	8	52	1	1.9	98.1
		B2	0.3						89	2	2.2	97.8
22	Wychwood and Wychlea	A	0.1	4	33	25	75.8	8	9	0	0.0	100.0
		B1	0.3						9	2	22.2	77.8
Total . . .					4,910	3,843	78.3		2,722	178	6.5	93.5

Note.—All schools were mixed except Nos. 2, 10, 11, 12, and 19, which were for boys only, and No. 22, which was for girls only. Nos. 1, 2, and 3 were given combined active and passive immunization. The slight discrepancy between Tables I and IV in the numbers given for the primary Schick test is due to imperfect records of the age of the children.

the products of different manufacturers did not reveal any great difference in the reactions caused, though on the whole the A.P.T. prepared by maker B was less irritant than that prepared by maker A, but it was also a less efficient immunizing agent. General statements in this connexion, however, are dangerous, since there is often more difference between successive batches from a given maker than between any two individual batches of different makers.

In one school we made the observation that local reactions following the injection of 0.1 c.cm. of A.P.T. were much commoner in Schick-negative than in Schick-positive subjects. It was our usual practice to give all Schick-negative reactors a single dose of 0.3 c.cm., but in this particular school they were given 0.1 c.cm., the same dose as that received by the Schick-positive reactors. Table III records the proportion of reactions, graded according to the degree of intensity, in the two groups.

In the Schick-negative group 86% of children experienced some degree of reaction, as against only 42% in the Schick-positive group. The proportion of moderate reactors to A.P.T. was about eight times as high in the Schick-negative group. These findings are in general harmony with those of Paschla (1939), who found that the severity of the reaction to A.P.T. corresponded fairly closely with the antitoxin titre at the time of inoculation, and with those of Jensen (1937), who states that among a group of children in Mattersburg, Austria, reactors to a single dose of A.P.T.

were more than twice as frequent among those who had suffered from diphtheria as among those who had not.

Table III also contains a comparison between the reactions observed in the same group of Schick-positive children after their first dose of 0.1 c.cm. and their second dose of 0.3 c.cm. Though approximately the same proportion of children reacted to each dose, the proportion of very mild reactions was higher after the second than after the first dose.

These two sets of observations taken together seem to indicate that the severity of the reaction to A.P.T. is determined more by the degree of sensitivity of the subject than by the size of the dose used. The work of Park (1922), Zingher (1923), Zoeller (1925), and Moloney, Fraser, and Fraser (1929) suggests that reactions to heated Schick toxin, formol toxoid, or A.P.T. are usually due to the sensitization of the subject to products of the diphtheria bacillus, presumably of protein nature, other than the specific toxin itself. Thus reactions are commoner in Schick-negative than in Schick-positive subjects, in those with a history of diphtheria than in those without, and in older than in younger persons.

The conclusions to be drawn from these findings and from those recorded in the literature are that (1) in Schick-positive children under 10 years of age very few severe reactions are likely to follow a small initial dose of A.P.T.; (2) in Schick-positive children of 10 years of age or over

severe reactions will be more frequently encountered; (3) in Schick-negative children of any age and in children with a history of diphtheria severe reactions, even to 0.1 or 0.3 c.cm., are likely to be fairly common. It follows that in practice large initial doses of A.P.T. should not be given to a population without previous Schick-testing. If Schick-testing is impossible it is probably wiser to give a small initial dose, such as 0.1 or 0.2 c.cm., followed by a second dose of 0.3 to 0.5 c.cm. if the reaction to the first is comparatively mild.

Schick-conversion Rates

With the exception of the children in school No. 7 and of approximately half the children in schools Nos. 16 and 18 who received larger doses as part of a special investigation, all Schick-positive children were inoculated with 0.1 c.cm. of A.P.T. followed four to six weeks later by 0.3 c.cm. In the first five schools the inoculations were made into the same arm, but after the publication of Lewis's (1940) recommendation they were given into opposite arms. The deep subcutaneous method was chosen throughout, the left arm being used for the first dose, the right arm for the second. Children in schools Nos. 1, 2, and 3 were also inoculated with 350 to 400 units of refined antitoxin at the time of their first dose (see Fulton *et al.*, 1941). Schick-negative children were given one dose only, usually of 0.3 c.cm., of A.P.T., though, in view of the findings recorded in Table III, it might have been wiser to use a dose of only 0.1 to 0.2 c.cm. Doubtful reactors in the $\pm$ class were treated for *practical* purposes as positive, and were given two doses. Seven preparations of A.P.T. from six different makers were employed. Twelve schools were inoculated exclusively with A.P.T. supplied by maker A. In the remaining ten schools other preparations were tried, but preparation A was always given to a proportion of the children as a control. It was uncommon to use the same batch of A.P.T. from any given maker for more than one school.

Schick-testing was repeated as a rule eight to nine weeks after the second injection, but in a few schools it was delayed to twelve or sixteen weeks. The results are recorded in Table IV. In compiling this table all reactors giving a $\pm$ reaction have been counted as negative. Those at the first Schick test have therefore been omitted from the table altogether, and those at the second Schick test have been included.

Though 4,910 children were Schick-tested originally and though 3,843 of these reacted positively and were immunized, the number coming to their final Schick test was only 2,722. This fall was attributable largely to transference of children to other schools and to intercurrent disease, particularly measles and whooping-cough, not to reluctance on the part of the parents to have their children immunized or re-Schicked.

The Schick-conversion rate varied considerably with the preparation used, and to some extent with the time elapsing between the second dose and the final Schick test. There was no obvious relation between the primary Schick-positive rate and the Schick-conversion rate, as might have been expected from Dudley, May, and O'Flynn's (1934) so-called "law of immunizability." This, however, may merely mean that the stimulus we were applying was great enough to overcome any minor differences in the ability of the tissues to form antibody.

Schick-conversion Rate in Relation to Make of A.P.T.

Table V analyses the results of Table IV in relation to the preparation of A.P.T. employed.

These figures are very striking. Four preparations, A, C, D, and E, stand out prominently as giving Schick-

TABLE V.—*Figures extracted from Table IV comparing the Antigenic Value of A.P.T. prepared by Different Makers given in Two Doses of 0.1 and 0.3 c.cm. at 4 to 6 Weeks' Interval, as Tested by the Schick-conversion Rate 8 to 16 Weeks after the Second Injection of A.P.T.*

No. of Schools	Maker	Approximate Lf Units per c.cm.	Second Schick Test		Schick-conversion Rate %
			No. Tested	No. +	
22	A	50	1,786	40	97.8
3	B1	13	157	50	68.2
1	B2	42	89	2	97.8
2	C	23	128	3	97.7
2	D	30	166	3	98.2
2	E	47	167	1	99.4
1	F	15	77	20	74.0

One school inoculated with A was given 0.5 c.cm. for the second dose; the Schick-conversion rate of this school was 97.8%.

conversion rates of 97.7 to 99.4%. B1 and F, on the other hand, proved unsatisfactory, the corresponding Schick-conversion rates being only 68.2 and 74%. When the results with B1 were first obtained it was thought that the failure might be due to insufficient dosage. Two further series of observations were therefore made to test this. In school No. 16 (Table IV) the doses were increased to 0.2 and 0.4 c.cm., and in No. 18 to 0.5 and 1.5 c.cm. The fact, however, that the Schick-conversion rates were only 51.9 and 70.7% respectively showed that not the dosage but the antigenic quality of the product was at fault. Examination revealed an Lf value of only about 13 units per c.cm. as opposed to 50 Lf units for product A. The attention of the makers was drawn to this deficiency, and they thereupon prepared a fresh product, B2. This was found to contain about 42 Lf units per c.cm. and to give a Schick-conversion rate of 97.8% when used in a dosage of 0.1 and 0.3 c.cm. (school No. 21). Further experience, however, of this product suggested that it was not altogether satisfactory and that, in spite of a relatively high initial Lf value, its mode of preparation was such as to lead to its progressive antigenic deterioration. Preparation F, like B1, had a low Lf value, and also behaved poorly in the field.

Schick-conversion Rate in Relation to Age and Sex

To find out whether there was any apparent difference in immunizability according to the age and sex of the subjects, Schick-conversion rates were worked out for the twenty-two schools enumerated in Table IV. Children immunized with preparations B1 and F, which gave unsatisfactory results, were omitted, since unless their age and sex distribution had been identical with that of the other children, any difference in immunizability might have been due not to a difference in age or sex response but merely to the fact that certain children had been inoculated with a product of lower immunizing efficiency. The results are recorded in Table VI.

No obvious difference was discernible between the Schick-conversion rates in girls' and boys or between children of ages up to 18 years. Above this age the number of subjects tested was too small to enable a reliable figure for the Schick-conversion rate to be obtained. Reference may, however, be made to the observations of Downie and his colleagues (1941), who recorded a conversion rate of 95.7% for a group of 115 university students receiving the same dosage. On the assumption that there is a constant dose: weight ratio for optimal response, it might be argued that though 0.1 and 0.3 c.cm. are large enough for children they are too small for adults. We have no figures of our own to disprove this argument, but the observations of Zingher (1923), Anderson (1937), and Bunch, Morrow, Timmons, and Smith (1940) all suggest that adults are on the whole more difficult to immunize than children.

TABLE VI.—Schick-conversion Rate in Relation to Age and Sex

Age in Years	Boys			Girls			Boys and Girls		
	No. Tested	No. +	Schick-conversion Rate %	No. Tested	No. +	Schick-conversion Rate %	No. Tested	No. +	Schick-conversion Rate %
5-6	109	0	100.0	91	0	100.0	200	0	100.0
7-8	177	3	98.3	157	1	99.4	334	4	98.8
9-10	268	2	99.3	194	2	99.0	462	4	99.1
11-12	339	8	97.6	300	3	99.0	639	11	98.3
13-14	161	0	100.0	173	1	99.4	334	1	99.7
15-17	63	0	100.0	34	0	100.0	97	0	100.0
18 and over ..	20	0	100.0	1	0	(100.0)	21	0	100.0
Total	1,137	13	98.9	950	7	99.3	2,087	20	99.0

Incidentally it may be pointed out that our figures lend no support to the contention of Lewis (1941a) that children over 8 years of age, as the result of latent infections, are more readily immunizable than younger children and therefore require a smaller dosage of diphtheria prophylactic.

Schick Tests a Year after Inoculation with A.P.T. (Preparation A)

Examination of Table IV shows that with preparations A, C, D, and E the Schick-conversion rate eight to twelve weeks after the second dose of A.P.T. was almost uniformly between 97 and 100%. In a small series of children, however, in schools Nos. 18 and 19, in which re-Schicking was delayed till sixteen weeks, the conversion rates with preparations A, C, and E were rather lower, suggesting that Schick-negative reactors were beginning to relapse towards the positive state. In order to see whether this suspicion was correct, or whether the results were merely fortuitous, the children in school No. 17 at Kidlington were re-Schicked 5½ months after their second dose of A.P.T., with the following results:

Of 55 children inoculated with preparation A, 96.4% were Schick-negative
Of 111 " " " " " " D, 74.5% " " "
Of 110 " " " " " " E, 96.4% " " "

The conversion rates for children inoculated with preparations A and E were not significantly different from those recorded eight weeks after the second dose, but the rate for D was manifestly lower, indicating that this preparation was antigenically less potent.

Further observations were therefore made on children who had been inoculated with preparation A. Schick

TABLE VII.—Schick Reactions 12 to 14 Months after Second Dose of A.P.T. (Preparation A). The First Three Schools had been Schick-tested before Immunization and again 8 to 12 Weeks after the Second Dose; the Remaining Schools, all of which were at Chippenham, had never been Schick-tested

School	Interval in Months after 2nd Dose of A.P.T.	Schick Reactions		
		No. Tested	No. +	% Schick-negative
A Aylesbury*	14	124	0	100.0
B Wokingham	13	47	0	100.0
C Purton	13	39	2	94.9
Total		86	2	97.7
D Westmead: Infants	12	57	5	91.2
E Westmead: Mixed	12	94	11	88.3
F St. Paul's: Infants	12	138	12	91.3
G Ivy Lane	12	181	18	90.1
H Senior	12	163	15	90.8
I Secondary	12	294	22	92.5
J Wanstead	12	39	1	97.4
Total		966	84	91.3

* Received 0.5 c.cm. for second dose.

Observed difference between schools B and C and schools D to J = 6.4%
Standard error of this difference " " = 1.9%
Observed difference divided by its standard error " " = 3.4

tests were repeated thirteen to fourteen months after the second dose of A.P.T. in three schools that had been Schick-tested twice previously—once before immunization and once eight to twelve weeks after the second dose of A.P.T. The children at Aylesbury had been given doses of 0.1 and 0.5 c.cm. of A.P.T., those at Wokingham and Purton doses of 0.1 and 0.3 c.cm. The results are shown in Table VII.

At Aylesbury and Wokingham none of the children was Schick-positive, and at Purton only two—one of whom was a very weak reactor. The figures are small, but they indicate that the Schick-relapse rate a year after inoculation with doses of 0.1 and 0.3 c.cm. of A.P.T. at four to six weeks' interval is of the order of 2%.

Since it might be argued that the children in these three schools had received the additional antigenic stimulus of two previous Schick-test doses of toxin, the effect of which has been shown by previous workers (O'Brien, 1926; Parish and Okell, 1928; Parish and Wright, 1938) to increase antitoxin production in sensitized persons, it was decided to examine schools that had never been previously Schick-tested. Observations were therefore made on children in seven schools at Chippenham, all of whom had received 0.1 and 0.3 c.cm. doses of A.P.T. at four weeks' interval twelve months previously. The results, which are also recorded in Table VII, show that an average of 8.7% of the children tested were Schick-positive. The reactions on the whole, however, were very weak. There were no +++ reactions among them, and 66% of the reactions that did occur were pale or very pale. Many of them had to be inspected in different lights to make sure that there was any difference at all between the toxin and the control arms, and would probably have been read by most observers as negative. It may be objected that the 91.3% Schick-negative rate obtained with children who had not been previously Schick-tested is not strictly comparable with the 97.7% Schick-conversion rate obtained with the children at Wokingham and Purton, since a certain proportion of the children at Chippenham were presumably Schick-negative at the time of inoculation. This is true, but if the proportion of initially Schick-negative children had been no greater than at Wokingham and Purton—namely, 5.8%—and if, in fact, these children had not been inoculated, then the observed Schick-negative rate of 91.3% would have been replaced by a true Schick-conversion rate of 90.8%.

Since no cases of diphtheria had occurred in any of these schools for some time prior to immunization, and since only six cases had been notified in the whole of Chippenham during the twelve months following immunization, it is probable that the immunizing effect of the A.P.T. had not been augmented by that resulting from latent infection.

These results must be regarded as very satisfactory. So far as the products of maker A are concerned, they lend no colour to the implication of Table IV that the level of immunity was falling seriously between eight and sixteen

weeks after the second dose of A.P.T. The fact, however, that the Schick-positive rate a year after inoculation was rather higher in schools which had not been previously Schick-tested than in those which had suggests that a larger second dose of A.P.T. might have given an even more favourable result.

(The second half of this paper will appear in next week's issue.)

WAR NEUROSIS

A YEAR IN A NEUROPATHIC HOSPITAL

BY

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(Concluded from page 285)

Aetiological Factors : Quantitative Estimate

The psychoneuroses may be defined as those disorders, mental and physical, which are primarily psychogenic. But it is generally agreed that other factors may play a part in their aetiology. We therefore made a quantitative estimate* of the aetiological factors to determine the proportion of (a) physical, (b) constitutional, (c) psychological predisposition, (d) psychological precipitating causes, on a percentage basis : e.g., physical, 20 % ; constitutional, 30 % ; psychological predisposition, 40 % ; psychological precipitating causes, 10 %.

In a total of 100 cases investigated the following were the percentage scores† : physical, 9.9 ; genetic, 20.6 ; psychological predisposition, 34.5 ; psychological precipitating, 35. From these figures we may assume that the physiogenic factors amounted to 30 % and the psychogenic to 70 %. This preponderance of the psychogenic factors in itself means very little, as it was mainly the psychoneuroses we were investigating ; we did not include any con-

TABLE IV

	Physical	Genetic	Psychological Predisposition	Psychological Precipitating
100% ..			1	6
90% ..			5	7
80% ..			2	6
70% ..			9	11
60% ..		1	13	7
50% ..	3	24	13	24
40% ..		9	16	18
30% ..	1	26	24	17
20% ..	22	19	3	4
10% ..	40	21		
0% ..	34			
Total ..	100	100	100	100

dition in which either the physical or the genetic factor amounted to over 70 %, since we did not regard such cases as primarily psychoneuroses. Some cases, for instance, were purely neurological (100 % physical), and it would have been misleading to include them. The numbers of patients in each percentage group are shown in Table IV.

* It will be noted that this does not represent the absolute amount of each factor in our cases, but only the ratio between the various aetiological factors, since one patient may be much more ill than another, and his 20 %, shall we say, of psychological predisposition may represent the same amount of illness as the 30 % of a man less ill. But the relative amount will remain the same, and it is precisely this relative estimate of the part played by the various factors which is here under review. It is also admittedly difficult to compare the amount of a psychological as compared with a physical factor, since the basis of comparison cannot be the same. But as a rough estimate the figures are not without significance.

† These figures were taken in two groups, in each of which the percentages were almost identical, thus confirming their accuracy.

The following comments may be made on these figures :

1. In no case was there only one factor present—e.g., none was marked 100 % psychological precipitation, as we might have expected if the traumatic experience had been considered to be the only one operative. One case, however, came near to it with 95 % psychological predisposition—obviously an old chronic neurotic. Eight had over 70 % psychological predisposition, and nineteen had over 70 % precipitating factor. These may, then, be regarded as the effective cause in each of these cases.

2. The most important conclusion to be drawn from these figures is the multiple nature of the aetiology. In more than a third of the cases all four factors played a part ; in only three were there psychogenic factors alone. This supports the view of those who hold that in considering the psychoneuroses we must take into account the whole personality in all its aspects—physical, constitutional, and psychogenic. In practice, however, one or another of these factors may be so important that to treat it alone may be enough to produce a "cure."

3. *Physical*.—In more than a third (34 %) of the cases there was no physical contributing factor (and all our cases were examined by the medical specialist). Where it did exist it was small, for in 74 out of 100 cases the physical factor was 10 % or under, and in total amount it represented only 9.9 % of the whole. This suggests that the physical factor plays but a small part in the aetiology of the psychoneuroses. Obviously the toxic theory of the neuroses does not gain much support from these figures.

4. The constitutional factor was a more important one than the physical in the aetiology of these conditions—namely, 21 %. In only 21 out of 100 cases was it absent. This figure is surprisingly large, but it may be accounted for by the fact, already mentioned, that there were included in the investigation not only the psychoneuroses, which in terms of the definition are psychogenic, but also a few cases of psychopathic personality, in which the constitutional element plays a prominent part. These cases would account for some of the higher percentages in the genetic scale—e.g., 25 cases were 40 % and over.

5. The predisposing psychological factors were important, constituting 34 % of the whole. They were found in all but 3 cases out of 100. These figures, together with the fact that in only 21 out of the 100 cases was no genetic or constitutional predisposition recorded, substantiate the conclusions already drawn from the larger group of 326 cases (in which only 18 % showed no predisposition) as to the significance of the predisposing factors in these cases. If we add the genetic and psychological predisposition together they amount to 55 % of the whole aetiological causes (i.e., in quantity, not number of cases).

6. The precipitating psychological factors constituted 35 % of the whole, and formed the highest group of all. They were concerned in the aetiology of 96 out of the 100 cases, and were completely absent in only 4 ; but in some of them the precipitating factor was nothing else than being in the Army. But the figures also show that the precipitating factor, though the largest, cannot be regarded as the only or all-important one, for the predisposing psychological factor was nearly as great (34 %), and the whole predisposition—constitutional and psychological (55 %)—was considerably greater. This is also proved by the fact that in 63 % of the cases the precipitating factor was 30 % or under, suggesting only a mild aggravation.

Onset and Precipitating Factors (262 Cases)

These cases were divided into those with :

(a) *No definite precipitation* ; cases in which the patient was no worse than when he came into the Army or developed his illness without ascribing this to any specific condition in Army life. (18 % of cases.) They were mostly cases of chronic neurosis.

(b) *Gradual onset* ; those which were due to specific conditions in Army life, to conditions of service such as strain in the retreat from France, coast-watching, etc., but which took some time to develop (more than two or three days). (41 %.) These may be regarded as *subacute*.