chest wall. His pain was relieved immediately by this operation, and, should it recur, treatment by percussion is now much more likely to be successful, as the neuromata are easily reached.

In conclusion it should be emphasized that treatment by percussion has not on any occasion in our experience done harm. In some cases benefit has been apparent almost from the first treatment, but in others considerable perseverance has been required to get the desired relief.

Summary

The treatment of painful amputation stumps by repeated percussion to the neuromata has proved successful in most cases.

Of 33 cases considered suitable for percussion treatment, 19 reported good or excellent results and 5 were improved. There was only one failure in the first 15 cases treated, but in the last 18 cases, some of which were especially difficult, there have been eight apparent failures.

Methods of applying the treatment are described. The neuromata are located as accurately as possible. If they are very tender the arterial supply to the stump is occluded by a sphygmomanometer cuff, as anoxaemia renders them less sensitive. Percussion is done with a mallet and an applicator about 15 cm. long. After several minutes the cuff is removed and percussion continued for 20 minutes. An electrical vibrator may be used in place of the mallet, and is of particular value in treating areas beyond the patient's reach. Cases with cold and diffusely tender stumps should be treated by sympathetic block or section rather than percussion.

Illustrative case histories are given.

We are specially indebted to Dr. E. J. H. Schuster for designing and constructing apparatus, also to several members of the Ministry of Pensions staff for their encouragement with this study, and to Miss Ruth Hurst for her assistance with the treatment of many of these cases at Headington Hill Hall Rehabilitation Centre, Oxford.

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Another highly successful year's working was announced at the annual general meeting on June 6 of the Medical Sickness, Annuity, and Life Assurance Society, Ltd. The chairman, Mr. R. J. McNeill Love, said that when he last addressed the members he had reported on improvements in the policies and policy conditions, and he was now pleased to say that these had produced most satisfactory results. It had been hoped that the new life assurance business might pass the £1,000,000 mark for the first time, and it was gratifying to find that the amount actually achieved was £1,420,734. The figures for the current year indicated that this progress had been fully maintained. A subsidiary company, Medical Sickness Finance Corporation, Ltd., appeared for the first time in the accounts. By the end of last year it had assisted members of the medical and dental professions in the purchase of cars and equipment to the extent of about £100,000. The directors were convinced that this would be a satisfactory investment, especially when there was an increase in the number of cars for the home market. The increase in life assurances effected during the year amounted to £649,614. Claims had increased by £14,646, but were well within the amount expected. The amount paid in sickness benefit was £77,448. The funds of the Society stood at £4,371,026, an increase of practically £330,000.

P.T.A.P.

DETERMINATION OF THE ESSENTIAL Lf DOSAGE

BY

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P.T.A.P. is an integrated diphtheria prophylactic prepared by the adsorption of highly purified toxoid on to pure aluminium phosphate—each prepared separately. Because of this it is possible not only to duplicate accurately any given composition but also to alter, at will, the amounts of both, as well as their ratios. In this we have a means of answering a number of important questions in diphtheria prophylaxis which previously could not be reliably investigated at all.

Of the several questions that required an accurate answer three have now received attention: (a) How much mineral carrier is required to produce the maximal anti-toxin response? (b) What is the route of choice for inoculation? (c) What is the essential or optimum quantity of toxoid necessary?

An account of work done to determine the correct dosage of aluminium phosphate carrier for young children has already been described (Bousfield, 1947a, 1947b; Holt and Bousfield, 1949). This amount was found to be not less than 5 mg. of $AlPO_4$, determined by observing the Schick conversion rate following a single injection. The conversion rate obtained, using 5 or 7.5 mg. of $AlPO_4$, was of the order of 97%; and this was found to persist for at least 15 months in 95% of the children examined. These figures bear interesting comparison with those of Faragó (1935), who, by using a 1-ml. dose of large-precipitate A.P.T., obtained an overall S.C.R. of 93.5% (4,297 cases) following one inoculation, and furthermore reported no significant decline in the S.C.R. after one year.

We have found the route of choice to be intramuscular, in that the relative effectiveness of the intramuscular route to the subcutaneous is 2.6—that is, in order to obtain the same results, 2.6 times as much $AlPO_4$ carrier must be used by the subcutaneous route as by the intramuscular.

Included in these same reports were the results of preliminary attempts to determine the essential toxoid dosage. No statistically significant differences were obtained when the $AlPO_4$ carrier was maintained constant at 7.5 mg. injected, and the amount of toxoid varied from 30 to 5 Lf per dose; the S.C.R.s were determined three months after a single intramuscular inoculation (Holt and Bousfield, 1949, Tables III and IV).

As the solution of this question is one of no small importance or interest the experiment has now been extended. For purposes of accurate comparison it is not a reliable procedure to compare uncritically one set of clinical results with another made at a different time or place. Because of this it is a minimum precaution always to arrange that new materials should overlap, in terms of the variable under investigation, with former preparations used in previous experiments.

It is of some importance also to describe the exact procedure used in making the Schick tests. Schick control was invariably used in all work carried out since

midsummer, 1948 (Bousfield, 1948). Burroughs Wellcome Schick toxin and control were used, 0.2 ml. being inoculated intradermally on the flexor surface of either forearm. The tests were read seven days later without any knowledge of the treatment the child had received. The readings are recorded in such a way that negative results are entered only when the reaction, if any, does not exceed approximately 5 mm. in diameter. For the purpose of this work any reaction greater than this is recorded as positive. This routine is exacting, but is fully justified by the quantitative work of Vahlqvist and Högstäd (1949) on the relationship between circulating antitoxin and the Schick-test result.

Investigation of Minimum Amount of Toxoid which will Produce a Reasonable S.C.R.

A series of preparations was made in which the aluminium phosphate content was maintained constant at 10 mg./ml., and the contents of purified toxoid (1,900 Lf/mg. of protein nitrogen) varied from 10 to 1 Lf per ml. These preparations were made from a sample of P.T.A.P. of exactly known titre and one which had matured at room temperature for nine months; this was appropriately diluted with a 10-mg./ml. suspension of AlPO_4 , to give the desired concentrations of toxoid.

As in previous work, Schick-positive children between their first and second birthdays were employed. A uniform dose of 0.5 ml. was used, the inoculations were made into the deltoid muscle, and two time intervals of observation were adopted. Four weeks after their single inoculation 494 cases were post-Schick tested, and a further 192 two months after injection. The details of the results are shown in Table I.

TABLE I.—Schick Conversion Rate in Children (aged 1 Year) Using Samples of P.T.A.P. Containing a Constant Amount of AlPO_4 Carrier (10 mg./ml.), but Decreasing Amounts of Purified Toxoid (Intramuscular Inoculation, dose 0.5 ml.)

Time	Dose of Toxoid (Lf) Injected	Post-Schick Test Result			S.C.R. (%)
		+	—	Total	
1 month after injection	5	11	105	116	90.5
	2.5	11	116	127	91.4
	1	37	98	135	72.6
	0.5	45	71	116	61.2
2 months after injection	5	1	50	51	98.0
	2.5	2	49	51	96.1
	1	6	38	44	86.4
	0.5	19	27	46	58.7

The results of work of this kind may be examined in two ways.

First Examination of Results

The easiest and perhaps slightly naïve way is to present them in graphic form, using percentage S.C.R. on one ordinate and dosage of toxoid on the other. This method of presentation is shown in Fig. 1, supplemented by all previous results obtained, working on the same lines. These latter results are given in Table II.

TABLE II

Dose of Toxoid (Lf)	Post-Schick Results			S.C.R. %
	+	—	Total	
5	20	452	472	95.76
10	6	244	250	97.60
15	51	1,677	1,728	97.05
20	5	251	256	98.05
30	9	244	253	96.44
Total ..	91	2,868	2,959	96.92

χ^2 , 5 Lf/the rest = 3.33. $P = <0.1$

FIG. 1.—Schick-conversion rate in Schick-positive children, aged 1 year, to single inocula of P.T.A.P. containing a constant amount of AlPO_4 (5 mg.) and varying amounts of purified toxoid. — = previous results Table II. x—x = current results after two months. o—o = current results after one month.

From the graph (Fig. 1) it would appear that the S.C.R. is substantially constant between dosages of about 3 Lf and 30 Lf. If it be conceded that the S.C.R. definitely declines when less than 2.5 Lf of toxoid is used, an approximate evaluation may be made of the critical ratio of toxoid to AlPO_4 carrier, which, with those figures, becomes 2.5 Lf/5 mg. of AlPO_4 , or 0.5 Lf/mg.

These findings—the result of a clinical experiment in immuno-physiology—show an excellent agreement in character with a similar experiment performed in guinea-pigs, in which the critical ratio of toxoid to mineral carrier was found to be approximately 0.2 Lf/mg. of AlPO_4 (Holt, 1949). But there seems to be a difference in the amounts of toxoid in the two instances—0.5 Lf/mg. of AlPO_4 for children and 0.2 Lf/mg. for guinea-pigs. Although it is difficult to be certain that the difference in these critical ratios is a real one, it would seem that the amount of specific antigen required to convert a normal globulin-producing cell to an antitoxin-producing cell may vary from one animal species to another. Even so, these findings do reveal how very great is the physiological activity of the antigen proper (toxoid protein) when it is administered in this form.

It may be of some interest, at this point, to mention the results obtained in immunizing an exceedingly sensitive adult (combined Schick result) with preparation C (P.T.A.P. Lf 2 and 10 mg. of AlPO_4 /ml.). This subject tolerated 0.2 ml. of the prophylactic (0.4 Lf). Her antitoxin titre before treatment was <0.005 u./ml. of serum, and four weeks after the one inoculation <0.01 u./ml., but four months after a second 0.2 ml. it rose to 0.2 u./ml. This subject, a difficult one, was therefore adequately immunized with a total of 0.8 Lf of purified toxoid, with no more than a transient (48 hours) feeling of slight local discomfort and malaise. The possibility must be admitted, however, that in view of the combined reaction shown there existed the possibility of contact with *Corynebacterium diphtheriae*, although probably not a virulent strain.

These observations do emphasize how appallingly inefficient and inexpertly prepared some samples of A.P.T. obtained from unusual sources must have been in the early days of the war. Even two doses of such material sometimes failed to give a 50% S.C.R. On the other hand, the law governing the amount of toxoid in present-day prophylactics (A.P.T. or P.T.A.P.) demands a minimum

of 50 Lf/ml. From this we see that there is approximately a tenfold margin of safety (against deterioration) in respect of P.T.A.P. as issued for general use.

Second Examination of Results

A more refined analysis is possible by applying statistical methods which permit an examination of the data in several ways and by using devices for checking the accuracy of hypotheses.

For the purpose of a complete-as-possible analysis of the results described above, it was found best to use all the relevant available data; this was done, and the results are given in Table III.

doses) is 20.151 with 17 degrees of freedom; this indicates a satisfactory homogeneity.

In view of its homogeneity this material seemed to provide a particularly reliable body of data for use (at least in a first-stage analysis) of the Lf-dose-response curve. This curve is plotted as probits of the percentage S.C.R. against log. dose of toxoid (see Carlinfanti, 1948), and is shown in Fig. 2. It will be seen from this curve that there is a tendency towards a maximum response and one that is less than 100%.

An assumption, and one not unreasonable from a biological point of view, is that a small proportion of the child population just does not react demonstrably—

TABLE III.—Showing all Available S.C.R. Data Following a Single 0.5 ml. Intramuscular Inoculation of Different Samples of P.T.A.P. (All Cases are Children Between Their First and Second Birthdays)

Dose Toxoid (Lf)	Dose AlPO ₄ Carrier (mg.)	pH	Time Interval (Months)	Post-Schick Result		S.C.R. (%)	Total Cases	Probit % S.C.R.	χ^2 *	d.f.	P
				+	—						
0.5	5	5.2	1	45	71	60.49	162	5.266	0.0143	1	0.9-0.95
			2	19	27						
1.0	5	5.2	1	37	98	75.98	179	5.776	2.735	1	0.05-0.2
			2	6	38						
2.5	5	5.2	1	11	116	92.70	178	6.454	0.609	1	0.3-0.5
			2	2	49						
5.0	5	5.2	1	11	106	94.84	639	6.629	7.963	6	0.2-0.3
	5	5.2	2	1	50						
	5.5	5.2	1	4	51						
	6.5	5.2	1	3	81						
	7.5	5.2	1	2	86						
	7.5	5.2	3	6	114						
	7.5	5.2	6	6	119						
	7.5	5.2	3	2	123						
10	7.5	5.2	6	4	121	97.60	250	6.977	0.171	1	0.5-0.7
	7.5	5.2	1	28	883						
15	5.0	5.2	1	2	206	97.05	1,728	6.888	7.934	5	0.2-0.3
	5.0	5.2	1	4	167						
	7.5	5.2	3	5	118						
	7.5	5.2	6	2	122						
20	7.5	6.5	1	10	181	98.05	256	7.064	0.724	1	0.3-0.5
	7.5	5.2	3	1	124						
30	7.5	5.2	6	4	127	96.44	253	6.804	0.001	1	0.95-0.98
	7.5	5.2	3	4	120						
	7.5	5.2	6	5	124						
									20.151	17	0.2-0.3

* χ^2 indicates homogeneity within toxoid doses. All χ^2 s with one degree of freedom have been corrected for continuity (Yates's correction).

Although these data are of heterogeneous origin, the materials having been used at different times of the year, and were different, apart from the variable under investigation—namely, a slight variation in the amount of AlPO₄ injected, some prepared at pH 5, others at pH 6.5, and the observations made one, two, three, and six months after inoculation—the results are fairly homogeneous. In fact, all internal analyses show no appreciable differences between these variations. If, therefore, there are differences due to the above-mentioned variations, they must be very small, as the total χ^2 between experiments (within toxoid

namely, show circulating antitoxin—to any single inoculum, whatever the dose. A similar observation was made by Scheibel (1943) in guinea-pigs, also using diphtheria toxoid. This worker observed that the “non-immunizability” was inherited and in a nearly typical Mendelian manner. It seems, therefore, not unlikely that a similar situation might exist in man, although for the purpose of mass-immunization it does not matter whether the lack of responsiveness in a proportion of the total population is determined genetically or not. It does not follow that the same proportion of refractory subjects will be found following a two-dose system of immunization.

Two well-spaced injections of P.T.A.P. containing 15 or 25 Lf of toxoid with 5 mg. of AlPO₄ are now being found to yield virtually 100% S.C.R. two or three months after the second injection.

A study of the responses in individual guinea-pigs to one injection and to two spaced injections of toxoid has revealed that most of the poor antitoxin producers—as judged by their responsiveness to a single inoculation—do respond satisfactorily to a second injection (unpublished work). The adult clinical example referred to above may be quoted as a case in point for man.

If we accept the assumption that a proportion of the child population does not respond to a single inoculum, we may try to estimate this proportion, and test whether this hypothesis fits the whole body of data.

From the point of view of statistical analysis this is a problem closely related to one solved by Finney and by

FIG. 2.—Probit % S.C.R./log dose toxoid. $C = 0.027$. 97.3% convertible, 2.7% non-convertible.

Fisher for the treatment of dose-response curves in the presence of natural mortality. In our present case the situation is reversed in that instead of a lower asymptote we have an upper one. The method of dealing with this problem statistically is by substituting the residual percentage of Schick positives for the natural "mortality," and then working on the decrease of positives with increasing dosage of toxoid—that is, with a negative regression coefficient. The "maximum likelihood" estimate obtained with Finney's (1949) improved method is $2.7 \pm 0.5\%$ of "non-convertible" children, and the fit of hypothesis obtained by accepting this figure is very good: χ^2 with five degrees of freedom gives a probability of $>50\%$. The curve corresponding to this hypothesis is shown in Fig. 2. Briefly, this analysis suggests, and supports the suggestion, that when an infinite quantity of toxoid is used with 5 or 7.5 mg. of AlPO_4 carrier the maximum S.C.R. obtainable (single dose) is 97.3% ($\pm 0.5\%$ standard error), and when 10 Lf are used the expected S.C.R. will be 96.8% and with 5 Lf 95.25%.

This statistical analysis confirms the conclusions drawn from the simple % S.C.R./dose toxoid curve in that there is a maximum ($<100\%$) S.C.R. for P.T.A.P. The maximum is reached asymptotically, and in such a way that the advantage of using more than 10 Lf per dose is negligible.

Summary

Schick-positive children in the London area aged 1 year were given one intramuscular inoculation (0.5 ml.) of samples of P.T.A.P. containing 10 mg. of AlPO_4 per ml. and decreasing amounts of purified toxoid.

With an inoculation of only 0.5 Lf a S.C.R. of 60% was obtained, and with 5 Lf one of 93.8%.

By employing all relevant data previously obtained, it appeared that a maximum S.C.R. of about 97% was obtainable using a single 5–10 Lf dose, and that this S.C.R. was not exceeded (on the average) if more toxoid were used.

A special statistical examination of all the results also showed that a maximum S.C.R. of $<100\%$ is obtainable with a single inoculation of P.T.A.P. (10 or 15 mg. of AlPO_4 per ml.). Using an infinite quantity of toxoid this maximum S.C.R. was calculated to be $97.3\% \pm 0.5\%$; using 10 Lf per dose, the expected S.C.R. is 96.8%, and with 5 Lf 95.25%.

These maximum conversion rates for a single inoculation are most probably significantly below those following a two-dose method of immunization.

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Dr. Angeliki Tsaona, gynaecologist and obstetrician, and president of the League of Women Scientists of Salonika, is visiting the United Kingdom under the auspices of the British Council. She is studying gynaecological and obstetrical methods in British hospitals, and is particularly interested in the use of anaesthetics in childbirth.

ILL EFFECTS OF THE RADIUM MENOPAUSE*

BY

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Induction of the menopause for non-malignant uterine bleeding is a safe and effective method of treatment, and is much used in the Birmingham School, but the resultant improvement in the patient's health may obscure certain immediate and remote sequelae. In this review attention has been paid to flushing and sweating, loss of libido, and premature senile changes in the genital tract.

In all, 118 cases were examined at an average interval of two years after receiving intrauterine radium (2,400 mg.-hours). The ages of the patients varied from 33 to 58 (average 45). The outstanding symptom after irradiation was flushing, and the cases were grouped according to the following definitions:

(a) *Mild Flushing* (commonest).—An occasional sensation of heat and sometimes sweating with an obvious flush of the face and neck. Normal duties are not disturbed and the patient is seldom inconvenienced.

(b) *Moderately Severe Flushing*.—From 12 to 20 or more flushes by day severe enough to cause temporarily listlessness and a sense of fatigue. Generalized sweating usually accompanies flushing, and this often causes the patient to waken from sleep with her night attire uncomfortably wet.

(c) *Severe Flushing* (rare).—A severe disability causing insomnia, listlessness, and fatigue (20 cases from b and c were already under stilboestrol therapy in this series).

The results after radium were: severe flushings, 5 (4%); moderately severe flushings, 53 (45%); mild flushings, 51 (44%); and flushings absent, 9 (7%).

The incidence of serious and persistent attacks of flushing after irradiation is three times the normal, or approximately the same as that following surgical castration (Table I).

TABLE I.—Comparison of Menopausal Flushing*

	Pre-menopausal	Post-menopausal	Radium	X rays	Castration	Hyst. Only
No. of cases	74	78	118	17	43	67
Incidence of severe or moderately severe flushing	7 (9%)	13 (17%)	58 (49%)	10 (59%)	20 (46%)	1 (1.5%)

* Comparative figures from previous report (McLaren, 1941).

On the other hand, simple hysterectomy with conservation of ovarian tissue is not followed by the immediate onset of these symptoms. Moreover, the reservation of radium for patients nearer to 50 than 40 years of age does little to alter the incidence of severe flushing (McLaren, 1941).

Spontaneous Cure of Flushing.—It is commonly held that the passing of a few months will cure flushing, and that a little encouragement is all that is required from the doctor. With this in mind we carefully investigated 71 patients who had completed the radium menopause for periods up to four years (average two years), to find that a spontaneous cure had resulted in only 13 cases, while four appeared to be more seriously affected with the passage of time. The remaining 54 cases (76%), however, continued to have flushing of unabated severity, so that "radium" flushes are by no means transient.

* A postgraduate lecture delivered at the Royal College of Obstetricians and Gynaecologists on November 18, 1949.