DIPHTHERIA PROPHYLAXIS WITH ALUM PRECIPITATED TOXOID.

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DIPHTHERIA - THE DISEASE AND ITS CONTROL.

Diphtheria is still a disease which kills children and especially young children. For the past ten years in England and Wales the annual average has been 57,500 cases and 3,100 deaths from diphtheria. London alone has had 11,000 cases and 400 diphtheria deaths annually (Forbes 1937). Practically all these deaths have occurred in children under 10 years old and the greater number in the pre-school child. Apart from whooping cough and measles, diphtheria causes more deaths annually than any other infectious disease.

Although diphtheria cannot be prevented entirely the fatality rate can be reduced to nil (Deadman and Elliott 1933, McKinnon and Ross 1935, May and Dudley 1932). This fact was also most strikingly illustrated in the 13th Annual Report of the Journal of the American Medical Association. Very occasionally, however, severe cases and even deaths occur amongst immunised children but usually these children have not been proved to be immune e.g. Dewsbury 1933 and 1934. But, as Benson (1932) stated - "To no disease may the aphorism 'Prevention is better than cure' be more aptly applied."

Friedmann/

Friedman (1928) considers that diphtheria epidemics are not due to fluctuations in the virulence of C. Diphtheriae but to variations in 'latent epidemisation'. So that after several decades arises a generation with a low heredited basal immunity and accordingly the diphtheria morbidity rises. Natural resistence probably also plays its part. Thus it appears that the best method of wholesale diphtheria prophylaxis is to maintain the basal immunity of the population by artificial latent epidemisation in the form of active immunisation.

In Berlin, of those children reaching the age of 10 years only 3.3% have had diphtheria but 70.7% are Schick negative due to latent epidemisation by virulent carriers. The majority of such carriers are very transient and only 'carry' for an average of about four weeks annually. It is therefore estimated that about 30% of school children are virulent carriers at some time during the year. In only 3.2% of actual cases could contact with another case be proved.

It is hopeless, therefore, to fight against carriers by virulence tests and isolation. Also it is probable that removal of virulent carriers from circulation would lower the basal immunity in the long run (Dudley 1928, Bessimans 1926). Indiscriminate isolation/

isolation of carriers is very expensive as avirulent strains are 2-3 times more common than the virulent strains (Doull 1932, Christison, Wright and Shearer 1936). Accordingly the only successful preventive measure is Active Immunisation.

ACTIVE IMMUNISATION.

In Canada and the United States of America diphtheria immunisation is an ordinary event in a child's life (Hutt 1934). Although this is not yet the case in Great Britain there is a definite demand for immunisation as a preventive measure. But in this important branch of preventive medicine the benefit to the individual, although important, is outweighed by the effect on the community. And here there are differences of opinion.

Friedberger (1931) maintained that active immunisation was not having any effect on diphtheria epidemics. He considered that statistical evidence overlooked the fact that the disease was itself definitely showing a tendency to abate. This view was not held by von Drigalski (1931) who considered active immunisation well worth while because scores of lives were being saved annually. Saunders (1937) has drawn up a graph to show the marked fall of the diphtheria morbidity figures in Cork since the introduction of active/

active immunisation. Also during this same period the basal herd immunity of the population, as evidenced by routine Schick testing, has risen. New York results are very similar. In Edinburgh, active immunisation has been rather spasmodic and cannot be said to have influenced the trend of diphtheria especially as the field of the pre-school child has hardly been touched.

THE PROPHYLACTIC - ITS DEVELOPMENT.

Although the majority of observers are in favour of diphtheria immunisation on a large scale, opinions vary on which is the most efficient prophylactic and how it should be employed. The governing factor here is the basal immunity of the population to be immunised.

This problem of basal immunity has been in evidence since the early days of diphtheria immunisation with Toxin Antitoxin mixture and is even more prominent when alum precipitated toxoid is employed as the antigen.

The discovery of Toxoid to replace toxin antitoxin mixture was a great advance. Ramon (1924) enumerates its several advantages as follows:-

(1) As an antigen toxoid is 20-30 times more powerful.

(2) It contains no horse serum and accordingly does not sensitise.

(3)/

(3) It is more stable.

(4) It produces less local and general reactions.

As a result of various investigations it was decided and generally agreed that the best prophylactic for a population of average basal immunity was three well spaced injections of either Toxoid Antitoxin floccules or formol toxoid in order to obtain an adequate degree of immunity.

It became apparent however that the necessity of three injections was a serious drawback to the general acceptance of diphtheria immunisation. Accordingly an endeavour was made to find a prophylactic which would produce an adequate and lasting immunity after one injection.

O'Brien (1934) states that before such an ideal prophylactic could be obtained three substances have to be dealt with:-

(1) The toxin which can be turned into harmless but antigenic toxoid.

(2) Non-specific bodies - i.e. proteins, amino-acids and salts etc. which can be dealt with by precipitation, dialysis etc. and modification of the alum precipitation technique.

(3) A heat resisting substance closely allied to the production of pseudo-reactions in sensitive persons (as shown by the Moloney Test). It is in such/

such persons that reactions will continue to occur unless this substance can be eliminated.

During a discussion on diphtheria immunisation at the British Medical Association meeting in Belfast (1937) Chesney(1937b) summarized the requirements of the ideal prophylactic from the clinical point of view. It should have:-

(1) Entire freedom from toxicity.
(2) Freedom from the liability to produce sharp reactions.
(3) Capability of consistently producing a high grade of Schick immunity.
(4) Capability of rapidly developing this immunity with a minimal number of injections.
(5) Capability of producing an immunity which will last from infancy to adolescence.

Up to the present no 'ideal' prophylactic suitable for all purposes has been produced. Each group of children and sometimes each child has to be considered on its own merits as a result of variations in the basal immunity from place to place. A good indication of the degree of basal immunity may be obtained from the number of Schick positive reactions present in the different age groups and the morbidity rates taking into consideration the prevalent type of C. Diphtheriae.

BASAL IMMUNITY - ITS DEVELOPMENT AND MEASUREMENT.

The great majority of children are born with a natural immunity to the disease, i.e. they are Schick negative. This means that from 1/30th - 1/50th of an antitoxin unit is present per c.c. of circulating blood. Park and Williams (New York) suggest that the Schick negative level indicates only 1/250th - 1/500th of an antitoxin unit in some people which is hardly sufficient to protect against clinical diphtheria. Occasionally this amount of circulating antitoxin is insufficient to protect against a severe infection with the gravis or intermediate strains of C. Diphtheriae. (Robinson & Marshall 1934, Underwood 1935(b), Parish & Wright 1935).

Under most circumstances, however, the Schick negative person is not susceptible to the disease. This is especially true if the multiple Schick tests devised by Glenny and Waddington (1929) are employed. It must be remembered that the Schick positive or susceptible individual may have almost sufficient circulating antitoxin to render him Schick negative or he may have none at all and no power to produce it. This is the factor which governs the severity with which a person will take the disease, i.e. it is his basal immunity. Naturally when the basal immunity is high in a susceptible individual very little stimulus/

stimulus is needed to complete his immunity. An essential factor in the production of basal immunity is the opportunity for latent immunisation with minimal doses. When this is good the basal immunity of the community will be high and the majority will be Schick negative.

Basal immunity is not such an important factor when the older prophylactics e.g. T.A.F. and F.T. are being employed for active immunisation.

COMMON PROPHYLACTICS IN USE.

Toxoid antitoxin floccules (T.A.F.) given in three injections of 1 c.c. at fortnightly intervals is the immunising antigen which is most suitable for general use. It is safe and gives a sufficiently high protection to about 95% of all age groups. Its one fallacy, which it shares with Formol Toxoid (F.T.) is the necessity of three injections. Many parents are swayed by this factor into not having their children immunised at all. Often the first injection is safely carried out but the child absolutely refuses any more (several annual reports reveal this state of affairs.)

Alum precipitated toxoid (A.P.T.) was introduced with the intention of employing one injection only. The alum aimed at holding the toxoid in the tissues over a longer period than the previous immunising agents. Small amounts of toxoid were to be disseminated/

disseminated from the site of injection thus gradually stimulating the formation of antibodies (Glenny, Buttle and Stevens 1931). By this slower dissemination and elimination from the body it was hoped that a second and third injection would be unnecessary. Other substances were used in animal experiments instead of alum but were not so successful. Glenny (1930) found that the addition of alum to toxoid when immunising horses and guinea pigs increased its antigenic power even up to a thousand-fold.

Before such a substance as A.P.T. could be universally recommended much experimental work had to be carried out. Burroughs Wellcome & Co. must be congratulated on introducing A.P.T. as a commercial prodoct and not placing it on the market until they were satisfied with both its antigenic properties and its safety as regards reactions in human beings.

EARLY INVESTIGATIONS WITH A.P.T.

Several large scale investigations were carried out with A.P.T. in America but in a considerable number the children were not Schick tested before being immunised (Volk 1935, White & Schlageter (1934). This is a most important preliminary as it reveals the basal immunity of the community and permits the results to be used for comparative purposes. The results in most/

most areas were encouraging (McGinnes, Stebbings & Hart 1935) and some even rose above the height attained by three injections of T.A.F. or F.T. (Walker 1934, Keller & Leathers 1934). Many of these brilliant results were obtained in 1934 and as a result New York introduced A.P.T. on a large scale. 1936, however, saw the return to the older prophylactics (Health Quart. Bull. 1936).

These good results were, however, not universal e.g. Lai (1935) in China and Underwood in this country (1935(a)). Tests were carried out on guinea pigs and the results with the prophylactic (A.P.T.) used in America and Great Britain turned out identical. Thus it became apparent that the response to A.P.T. depended on the basal immunity of the population.

Thus it seemed probable that reports on A.P.T. from other countries did not necessarily apply to Edinburgh children. Therefore before a large scale immunisation drive could be instituted an investigation on a limited number of children was necessary. It was also thought that if the claims of the much advertized 'one shot immunisation' could be substantiated then diphtheria prevention would be simplified.

TABLE I.

Age periods.	Number Schick tested.	Number Schick positive			
0 - 2	36	23	- 64%		
2 - 3	99	69	- 69%		
3 - 4	101	61	- 61%	65%	
4 - 5	138	89	- 64%		
5 - 6	207	113	- 55%		54%
6 - 7	187	76	- 41%		
7 - 8	170	83	- 49%		
8 - 9	131	66	- 50%	49%	
9 - 10	99	60	- 60%		
10 - 12	132	60	- 45%		
	1300	700			

IDENTIFICATION OF SUSCEPTIBLE CHILDREN.

In order to investigate the properties of A.P.T. it is absolutely necessary to employ Schick positive children so that the basal immunity of the population and the true success of the antigen may be judged.

Every child under 12 admitted to the Edinburgh City Hospital notified as scarlet fever was Schick tested on admission. The Schick test was carried out 1-2 hours before any scarlet fever antitoxin was administered because the latter contains small quantities of diphtheria antitoxin due to the horse's natural immunity to diphtheria (Mayfield 1934, O'Brien 1932). It has been found that this length of time is sufficient to obtain accurate Schick test readings. In order to overcome personal difference of opinion all the tests were both performed and read 7 days later by the author. The results are tabulated in Table I.

This table compares favourably with others brought out under similar circumstances. (Ker 1922, Ward 1921) It shows that by the age of 2 years 2 out of 3 children have lost their inborn immunity and are susceptible to diphtheria. From that age onwards as a result of latent immunisation the immunity gradually rises. This development depends on environmental factors (being slower in rural areas - Bessiman 1926, Benson 1924). It is this gap in a child's life before latent immunisation effects the change from the Schick positive/

positive to the Schick negative state that active artificial immunisation attempts to bridge.

During this series of 1300 children no allergic phenomena, as reported by Parish (1936b)were encountered. Considering the number of Schick tests performed annually no undue concern need be caused as these phenomena are extremely rare. As the cause may have been a peptone which is used as a stabilizer Glenny and Stevens (1937) suggest that human serum be used instead as it is successful in animal experiments.

A point noted throughout, even amongst the 600 re-tested children, was the marked absence of pseudo reactions and no difficulty was encountered on reading the test at 7 days. It is therefore suggested that the control can be safely dispensed with in young children with considerable saving of time.

These Schick tests were carried out over a period of over 2 years (1934-36). Some of these children had been immunised against diphtheria at school. Exact figures were difficult to obtain. A few were still Schick positive and if further permission was granted these children were included in the investigation.

It was noticeable that the number of Schick positive children amongst the scarlet fever admissions varied with the school and district of the City from which they came. Some schools enjoyed a high basal immunity/

immunity whilst others (usually of a better type) were not so fortunate. Similar findings are reported by Lavan & Black from Kansas City (1927) and by Bessimans in Belgium (1926).

Two facts emerge from Table I.

(a) The pre-school child, being more susceptible, is more important from the immunisation point of view than the school child.

(b) There are a considerable number of school children susceptible throughout their school life even while active immunisation is taking place in their midst.

For the purpose of investigating the properties of A.P.T. it was thought that such a varied group would give better and more valuable results than an isolated community because all types as well as all ages are included. As a comparison three residential schools were Schick tested. (Royal Blind School, Widowers Children's Home and Crippled Children's Home). These children showed a higher degree of basal immunity as evidenced by (a) the greater number of Schick negative reactions; (b) the better response of the Schick positives to the antigen. These facts illustrated the danger of employing isolated communities for such investigations. Elementary school children are used very often for similar investigations but even here the basal immunity varies considerably from school to school.

A PRELIMINARY INVESTIGATION.

When this investigation was started A.P.T. was not on the market in Great Britain and its safety as regards reactions was not definitely known. A preliminary investigation on Schick positive children of varying ages was therefore carried out. 50 children were given doses by subcutaneous injections from 0.1 cc. of A.P.T. to 1 cc. by gradually increasing amounts. At least 12 children were given 1.0 cc. without any untoward effects before the investigation proper was started.

THE METHOD OF INVESTIGATION.

On permission being granted by the parents each Schick positive reactor was given its injections personally by the author and inspected 24 and 48 hours later.

Throughout the series the same technique was employed. The injection was given, after skin sterilization with ether, into the postero-lateral aspect of the left arm about 2-3 inches above the elbow. An attempt was made in each case to put the A.P.T. into the deep subcutaneous tissues so that absorption might be as slow as possible. Naturally no injection was given to any child not truly convalescent from scarlet fever. If two injections were given care was taken/

taken to avoid the previous injection site owing to the very minute possibility of an Arthus phenomenon developing. Not a single case of sepsis occurred either in the scarlet fever patients or in the residential schools.

THE INVESTIGATION PROPER.

After preliminary trials two injections of 1 cc. of A.P.T. were given to a group of 85 Schick positive children with an interval of a fortnight between them (Group I).

As the results were fairly satisfactory and good results were being published by other observers (especially abroad) it was decided to try 'one shot immunisation' with 1 cc. A.P.T. A group of 298 Schick positive children of varying basal immunity were employed for this purpose. 213 were in hospital and 85 in residential schools (Group II).

The results in Group II were not entirely satisfactory therein agreeing with other observers in Great Britain. O'Brien suggested the employment of two small doses of A.P.T. as he had found that in guinea pigs 5-10 times more antitoxin was formed than with one single dose. A group of 310 children (Schick positive) were given a 'detector' dose of 0.2 cc. A.P.T. This enabled children sensitive to A.P.T. to be singled out/

out. The next dose (0.5 cc.) was given a fortnight later.

A total of 597 were immunised with A.P.T. in the three groups and may be summarized as follows:-

	Dose of A.P.T.	Interval.	Hospital patients.	Residential School Children.	Total.
Group I	1 cc x 2	14 days	85	-	85
Group II	1 cc.	-	213	85	298
Group III	0.2 cc. & 0.5 cc.	14 days	299	11	310

THE MATERIAL USED.

The A.P.T. used for the investigation was supplied by Messrs Burroughs Wellcome & Co. In Groups I and II different batches contained slightly different percentages of alum. In Group III only the standard product as marketed was employed.

As exactly the same material was not used throughout the three groups they are not strictly comparable. But on examining the failures no one batch could be held responsible. Another factor enters in here, i.e. the basal immunity of the children immunised by each batch (usually over 50 in number). Naturally this factor varied from time to time according to the type of/

of child being admitted to hospital and so the chance which each batch of A.P.T. had to produce good results varied. Saunders (1933) and Chesney (1933) found the same difficulty in assessing both the results and reactions of different batches of A.P.T.

DEVELOPMENT OF IMMUNITY.

Whichever antigen is used as an immunising agent a period of time elapses before full immunity has developed. 2-3 months is an average length of time. It has been generally agreed that the so-called 'negative phase', during the development of immunity, does not exist (Quart. Bull. of League of Nations Health Organisation 1932). Once developed this artificial immunity should last until the natural immunity of later life develops.

In animals it was shown that an even greater antibody response might be expected with A.P.T. as the immunising stimulus (Glenny, Buttle & Stevens 1931). It was speculative, however, how long this immunity would take to develop and how long it would last.

Throughout this investigation whenever the opportunity presented itself an attempt was made by repeated Schick testing to try to determine when a satisfactory immunity developed. Unfortunately the number of children remaining under supervision for a sufficient length of time were few. However, a number of/

of Schick positive children who were re-Schick tested in hospital 3-4 weeks after 1 cc. of A.P.T. had become Schick negative. And it was noticed that when tested again 8-12 weeks afterwards they all remained Schick negative and some of those Schick positive at the end of 4 weeks had then become Schick negative.

A group of 74 Schick positive children out of Group II (1 cc. A.P.T.) were re-tested 4 weeks after their injection and 65 (86%) had become Schick negative. This may appear at first sight to be a rather conflicting result as it is almost as good as the total results for this group (see later). The reason is, however, that the majority of these 74 children were in the residential school section. These residential schools had a high basal immunity to begin with as may be judged from the fact that in the Royal Blind School there were only 50 Schick positive amongst 160 children (under 15) tested.

This small interim group brings out two points, however:-

(1) Immunity does develop rapidly with A.P.T. especially where the initial basal immunity is high.
(2) In such localised communities 'one shot immunisation' produces good and rapid results.

So far it has not been possible to do any further tests to see how the immunity is lasting in all groups.

In/

In the majority of reports by other investigators re-testing has been carried out from 2-3 months after immunisation. Underwood (1935), however, reports that 83.6% ± 2% of 152 Schick positive children became Schick negative in 4 weeks after 1 cc. of A.P.T. Graham, Murphy and Gill (1933) using a similar dose obtained better results in 185 children, 96% of whom became Schick negative in 2-6 weeks. Parish (1936), in drawing attention to the basal herd immunity and its effect on A.P.T. immunisation, only got 51% of 165 Schick positive children Schick negative in 5 weeks and 64% in 15 weeks after 1 cc. of A.P.T. Better results followed two small injections (0.1 cc. and 0.2 cc.) i.e. 89% and 100% of 35 children became Schick negative in 5 and 15 weeks respectively. Keller and Leathers (1934) reported a very quick development of immunity amongst a small group of children in Alabama.

Thus as a period of 2-3 months might be expected to elapse before a satisfactory immunity developed in all cases it was decided to recall all immunised children in convenient batches after they had left hospital. This procedure meant, of course, a distinct falling off in the number retested but was expected to give more accurate results in the long run. The response was good in all groups except towards the end of the experiment/

experiment when very inclement weather conditions resulted in poor attendances at the re-test clinic.

The results of the investigation are set out in Table II, the retest being carried out 2-3 months after the children were immunised. The age groupswill be considered later.

TABLE II.

	Number immunised.	Number re-tested.	Number Schick negative.
Group I.			
2 x 1 cc. A.P.T.	85	65	57 (87.7%)
Group II.			
1 cc. A.P.T.	298	245	213 (87%)
Group III.			
0.2 cc. & 0.5 cc. A.P.T.	310	208	198 (95.2%)

For reasons already stated re-testing in Group III was not so satisfactory as in the other two groups, but it includes over two-thirds of those immunised. Other observers are of the opinion that at least 60% of a group must be retested for the results to be conclusive.

CONCLUSIONS/

CONCLUSIONS TO BE DRAWN FROM THE FOREGOING RESULTS.

It is rather remarkable that the results of Groups I and II are almost identical. Group II, however, contains 40% of residential school children among those retested. The residential school children (85) accounted for 8 failures (9.4%) whilst the hospital children (160), not having such a high basal immunity, accounted for 24 failures (15%).

The results of Group III are extremely gratifying because these children were immunised with a stock antigen and were of average basal immunity. They are superior to the two dose (2 x 1 cc.) method employed in Group I although the groups are not quite identical in numbers and age. Group III was composed almost entirely of hospital children and its results are much better (by almost 10%) than the 15% failure experienced amongst hospital children in Group II. Group III has the one disadvantage of two injections but on these lines compares very favourably with the three injections of T.A.F. or F.T. (Lavan & Black 1927, Saunders 1933, Chesney 1933) which vary from 90-95%.

FURTHER/

FURTHER CONCLUSIONS AFTER DIVISION OF THE GROUPS INTO PRE-SCHOOL AND SCHOOL CHILDREN.

After division the numbers in Group I are too small for any definite conclusions to be drawn.

In Group II amongst those hospital children re-tested there were 55 under 5 and 105 of school age. 9 (16.3%) failures occurred in the pre-school group and 15 (14.3%) amongst those of school age.

Amongst the 85 residential school children in Group II there was 1 failure in 22 pre-school children (4.5%) and 7 failures in the remaining 63 (11.1%).

Thus the results in Group II show the danger of one shot immunisation unless the basal immunity is high. Although the greatest number of diphtheria cases occur in the 5 year olds (when the child goes to school) the disease is relatively more killing at an earlier age. So by employing one dose of A.P.T. these children are left with an insufficiently high immunity when they require it most. Again their parents are liable to consider that the child is fully protected and therefore cannot take diphtheria - in this way tragedies occur.

In Group III there were no failures amongst the 11 children from residential schools. Amongst those resident in hospital only 1 out of 75 under 5 (1.33%) and 9 older children (7.4%) still remained Schick positive/

positive at the end of 2-3 months. One fact stands out clearly in comparison with Group II, i.e. the much higher immunising power of two small doses especially amongst younger children. In comparison with the three injection methods employing T.A.F. and F.T. only two injections of smaller bulk are required and the cost of the antigen is much less (see later).

COMPARATIVE RESULTS BY OTHER INVESTIGATORS.

It is difficult to obtain results from other observers which can be truly compared with Groups II and III. As Saunders (1937) remarks, the reason may be put down to (a) differing natural basal immunities, (b) differences in quality of the preparation and in the strength and purity of the antigen. For these reasons observers in Great Britain, U.S.A. and elsewhere have found very variable results. A great many unfortunately have not proved their children Schick positive before immunisation and their results are therefore useless in this case for comparative purposes. Also others have waited for considerable periods before re-testing.

Table III sets out some results published employing 1 cc. of A.P.T.

TABLE III./

TABLE III.

Author.	Schick positive children immunised & retested.	Interval before retest.	Result % Schick negative.
McGinnes & Stebbings (1934)	2000 (approx.)	2-3 months	99%
Graham, Murphy & Gill (1933)	185	2-6 weeks	96%
Walker (1934)	165	2-6 months	100%
Farago (1936)	3468	2 months 1 year (retested) again	93.3% 93.3%
Isobolinski, Judenitsch & Lewzow (1935)	245	6 weeks	96.8%
Baker & Gill (1934)	197	2-3 months	100%
Underwood (1935)	152	1 month	83.6%
Lai (1935)	359	3 months	62.6%
Kosita (1935)	175 335	2 wks.- 3 mths. 8-9 weeks	91.4% 86.3%
Pansing & Shaffer (1936)	462 445	1 month 2 months	84% 86%
	(549 still Schick negative	2 years later)	
Parish (1936(a))	165	15 weeks	64%

The age group varies but the majority of the results apply to school children. These results only bear out the fact too clearly that the success of one shot immunisation depends on the local basal immunity.

Table IV sets out the results which may be compared with Group III of this series. It is unfortunate that the results published by Chesney & Powell omit the pre-Schick test as they are remarkably good.

TABLE IV.

Author.	Schick positive children.	Period.	Retest results.
Parish (1936(a))	35	15 weeks	100%
Chesney (1937(a))	162	2 months	100%
	(112 re-Schick tested 18 months later - 100% still negative.)		
Chesney (1937(b))	1200	2 months	Almost 100% (fourfold Schick test)
Powell (1935)	100	?	99%

McSweeney (1935) gave a divided dose of 2 cc. to 78 Schick positive children and when tested one month later 77% were Schick negative.

Good results from other countries are really only useful from the point of view of stimulating workers at home to confirm them. After all it is the 'home'/

'home' results which must be considered before instituting a wholesale immunisation scheme. Thus when results of investigations in this country showed that 'one shot immunisation' was not going to have the success anticipated for it Parish and O'Brien suggested the two small dose method (Group III). This method was for use where the basal immunity was low. Apart from Parish's own results truly comparative evidence is difficult to obtain owing to the absence of the pre-Schick test. It seems probable,however, that in the two small dose method of using A.P.T. we have an adequate substitute for the older three injection methods. Group III results bear out this statement which was also advocated by O'Brien, Park & Bonsfield at the Second International Congress for Microbiology held in London in 1935. Another point worth noting is that Dudley (1936) maintains that the two small dose method gives greater protection against 'gravis' diphtheria. Whilst the number of true gravis strains has steadily risen in Edinburgh so far no child in Group III has taken diphtheria.

Chesney (1937(a)), using the fourfold and standard Schick tests, retested two groups of children after immunisation with A.P.T. and F.T. and concluded that two small doses of A.P.T. gave a higher degree of immunity than three injections of F.T.

CONCLUSIONS/

CONCLUSIONS FROM ALL RESULTS.

(1) The success of A.P.T. depends on the basal immunity of the population being immunised.

(2) 'One shot immunisation' is quite successful in some closed communities of high basal immunity but it fails in this country at any rate amongst the more susceptible communities. Its place can be taken by the two small dose method with very satisfactory results.

RESULTS OF IMMUNISATION SCHEMES.

It is interesting to note at this point the effect of diphtheria immunisation not on the individual but on the community as a whole. Whatever method has been employed provided the scheme succeeded in immunising one half of the pre-school children and at least two-thirds of the school children the results all reveal lowering of the morbidity and mortality rates of diphtheria (Bauer, 1932). This fact, as far as it concerns American cities, was most strikingly shown by the 13th Annual Report of the Journal of the American Medical Association (1936). In New York, for example, 93% of diphtheria cases occur amongst non-immunised children (Wynne 1931) and these children suffer a 13-17 times higher mortality rate.

In/

In Edinburgh, although immunisation has been rather sporadic in character, only 100 true cases of diphtheria have occurred amongst over 20,000 immunised children (1923-36). There were 2 deaths - one within two weeks of the last injection and the other after 2 complete courses of injections. During the same period there were 530 deaths in over 9,000 cases amongst non-immunised children.

Farago (1936) claims that in Hungary as a result of active immunisation the incidence of diphtheria has fallen since 1933 whilst rising in other European states.

As a contrast, in Detroit, Newark and Buffalo there was no appreciable decline in morbidity and mortality rates until immunisation of the pre-school child was properly established.

Further it has been suggested that immunisation increases the carrier rate with greater risk to those children not immunised (Dudley, 1932.) This position is most likely to arise in closed communities such as residential schools (Dudley, 1935.) While it may be dangerous to the non-immunised it seems the best method of maintaining the immunity of those artificially immunised. It is unlikely that any severe effect will manifest itself on the general population as statistics show that if the campaign is adequate both morbidity and mortality rates fall.

REACTIONS.

There is one factor which almost every parent inquires about, i.e. how much reaction will the injection cause? At the present time many parents permit a child to be vaccinated against an extremely rare disease (i.e. Smallpox in Scotland) but will not run the risk of a local reaction to prevent a disease which kills thousands of children annually. The widespread fear of an injection is very noticeable to all who have interviewed many parents on this subject.

Broadbent (1932) summarizes a small number of tragedies which occurred in China, Texas, Vienna and Moscow in the early stages of diphtheria prophylaxis. Fortunately there have been none in this country. The employment of a reliable antigen from a reputable firm considerably diminishes such risks.

The reaction caused by amy of the diphtheria prophylactics must be considered along with their immunising power. The older established prophylactics T.A.F. and F.T. cause very few local reactions and very rarely any general reaction amongst children. As alum is a tissue irritant a considerable amount of experimental work had to be done to find the optimum percentage of alum from the point of view of both reaction and immunising power. Much of this work/

work was carried out in the Burroughs Wellcome Laboratories on guinea pigs. The initial part of this experiment formed part of the early trials in the human being. It is worth noting that Paterson (1935), after using various types of A.P.T. found that those with the best antigenic power produced the most reactions.

All the 597 children immunised in hospital were under ideal conditions for observing both local and general reactions. Also all the injections were given and the reaction, if any, noted by the same observer. Most of these children received their injection while convalescent and so hardly undergoing the complete rough and tumble of everyday life. Each child was inspected 24 and 48 hours after the injection and again if complaining. The findings in this investigation agree with Paterson (1935), who inspected his children for 4 days afterwards and concluded that if any reaction was going to occur it would be present within 24 hours.

As the Moloney Test does not lend itself for use during a wholesale immunisation scheme it was not employed for any children immunised in hospital. In fact no discrimination was used, A.P.T. being given to all Schick positive children from whose parents permission was obtained unless immunisation was contra-indicated by a complication of scarlet fever.

A general reaction occurred in only one of all the children immunised in hospital. It took the form of general malaise, headache, temperature 99° with local swelling and redness. Recovery was complete within 24 hours apart from some local induration.

Local reactions were more common and took the form of redness round the injection site accompanied by a tender induration. 10 children (2.5%) from Groups I and II (i.e. receiving 1 cc. injections) experienced some local induration and stiffness but only in the child mentioned was the temperature elevated. These reactions all subsided in the course of 2-4 days. No abscess formation took place. In a considerable number of all the children immunised, however, a very small indurated nodule at the site of injection was found on inspection - rarely was it tender and it usually subsided within a week or so. One point is worth noting - the older the child the greater the chance of reactions.

When using the smaller two injection method (Group III) no general reactions occurred amongst the 299 children immunised in hospital. Also no complaints were made of stiffness and swelling locally. Some redness was occasionally noticed round the injection site accompanied by slight induration which soon subsided. One child, however, developed a minute/

minute sterile abscess after the 'detector' dose, although there had been only a slight local reaction after the injection. The same sequence of events followed her second injection given into the other arm a fortnight later. On being incised both wounds healed rapidly.

In the residential schools the Moloney test was employed on Schick positive children over 10 years of age. Only Moloney negative children were given A.P.T. Results bore out the fact that even Moloney negative children may suffer reactions (Shafton 1936). These children were under the observation of a trained nurse and were inspected personally 24 hours after the injection.

In Group II two children experienced a slight general reaction and 8 (9.4%) complained of some local pain and stiffness. No abscess formation took place. The greater number of reactions among these children was attributed to the higher average age and the fact that they were leading on the whole a more active life (except at the Crippled Children's Home.).

No reactions were experienced in Group III.

As a contrast and in order to see how the adult reacted to A.P.T. a batch of a dozen Schick positive medical/

medical students were given 1 cc. A.P.T. The reactions both local and general as described by the students compelled the next batch to ask for the three injections of T.A.F.

All nurses on the staff of the Edinburgh City Hospital receive a yearly injection of diphtheria prophylactic to maintain their immunity at as high a level as possible. During one year (1935-36) each nurse was given 0.2 cc. of A.P.T. instead of the usual 1 cc. of T.A.F. both to test the potency of A.P.T. and its reactions in the adult (18-21 years). Amongst 64 nurses who received this injection there were 4 general and 20 local reactions (37.5%), - some of the latter being of considerable severity. No abscess formation took place. In view of these findings a return to T.A.F. took place although no case of diphtheria had occurred.

With the above in view it cannot be too strongly emphasized that A.P.T. is a prophylactic to be used only in children under 10 years old with safety.

The experiences of other observers agree with the number and degree of reactions which follow A.P.T. McNaughton, White and Foley (1935) using Burroughs Wellcome A.P.T. in 130 institutional children (84% of which were over 10) found diffuse erythema in 10%, brawny/

brawny induration with stiff joints in 6 children lasting 6 days and one sterile abscess. These are almost similar results to the residential school children in Group II.

Parish (1936a)found that reactions with the two small dose method were less severe and fewer in number. Group III agrees with this finding.

Saunders (1937) was not satisfied with the Burroughs Wellcome A.P.T. during its experimental stage in 1931-32 and accordingly carried out further tests with the marketed product (1934-36). Using a community with an already high and still rising basal immunity reactions occurred in 14.5% of which 3% were severe. He noted that even Moloney negative children over 7 years old were prone to reactions.

Shafton (1936) records, however, 25% of reactions but as these results are much higher than the average a non-specific irritant may possibly have been present in the material.

Waterfield (1935) makes a point which was noted in hospital as well as in residential school children i.e. those taking most exercise were more liable to reactions. He recommends that no exercise be allowed following immunisation.

Ichard (1934) records reactions like serum sickness and even haemorrhagic purpura and nephritis following/

following diphtheria prophylaxis - fortunately such findings are unknown in this country. Care was taken in all scarlet fever convalescents and in no case which subsequently developed nephritis could the A.P.T. be blamed. The nephritis complication rate did not increase during this investigation.

Although it is important that weakly children should be immunised against diphtheria it must be remembered that activation of both pulmonary and surgical tumberculosis has been noted following protective injections in France (Mozer, M. & G.) Accordingly all suspicious children should be examined before being immunised.

CONCLUSIONS.

Four facts stand out from these results:-

(1) A.P.T. can be employed in children and especially young children with little fear of anything worse than a slight transitory reaction at the injection site.

(2) The younger the child when the injection is given the less the chance of reaction - the Moloney test is rarely positive under 5 years old (Saunders 1937).

(3) The employment of the two small dose method permits a smaller injection with less reaction and also reveals the child sensitive to A.P.T.

(4)/

(4) Restriction of the child's activities for 24 hours or so after the injection lessens the chance of a reaction occurring.

THE AGE TO IMMUNISE.

It is generally agreed that the best age to immunise a child is soon after its first birthday. When younger a certain proportion of children still possess some inborn passive immunity which may inhibit the development of their artificial active immunity (Blum 1932, Debre 1932). If immunisation is delayed until these children grow older they run the risk of taking diphtheria sometimes with fatal results.

DURATION OF ARTIFICIAL ACTIVE IMMUNITY.

The main object of immunising the pre-school child is to fill in the gap during which it is susceptible to the disease in its deadliest forms and while latent immunisation is taking place.

Re-tests following immunisation with the older prophylactics are on the whole satisfactory. A return to the Schick positive state takes place in about 5-10% of immunised children who have been proved Schick negative following immunisation (Dudley, May and O'Flynn 1934, Parish and Okell 1928). It is quite possible/

possible that the artificial immunity is not so lasting as results might suggest but its place is being taken by latent immunisation (Underwood 1934).

As yet it is too soon to form a definite opinion on the lasting properties of A.P.T. immunisation. Park (1936) thinks, however, that the duration will be long. Chesney (1937) when he re-tested 112 children immunised 18 months previously with two small doses of A.P.T. found the immunity maintained in all cases. Pansing and Shaffer (1936) also found good results 2 years after 1 cc. of A.P.T. had been used in 549 susceptible children.

As A.P.T. gives a good initial immunity which lasts for a short period there does not seem any reason why this immunity should not be maintained at least as well as that resulting from the older prophylactics. Jones (1937) finds even less reversion with A.P.T. than T.A.F.

THE RESPONSE TO IMMUNISATION SCHEMES.

The parental response to such an investigation is better than the response to an ordinary immunisation scheme because the children were either in hospital or in residential schools.

Reference to Table I, which includes only hospital children, shows that during this period (1934-36) there were 700 Schick positive children admitted to the scarlet fever wards. Of these children 501 were used/

used in the investigation proper and at least 50 for the preliminary tests. This leaves about 150 Schick positive children not available. Only 125(approx.) could not be immunised owing to the parents refusing permission. The remainder were not done on medical grounds.

Benson (1934) estimated that an 80% permission rate could be attained in hospital practice. In this case it is over 80%. The response was even better in the residential schools (over 90%). As a contrast during the same period less than 50% of the children entering school at the age of 5 were immunised and very few pre-school children at all. Gundel (1935) however, obtained full permission from the parents of 90% of 170,000 children by well organized staff work and suitable propaganda. This is an illustration of what can be accomplished and although it is unlikely that such success will attend schemes in this country much remains to be done.

RECOMMENDATIONS FOR THE ORGANIZATION OF IMMUNISATION SCHEMES.

It is of little use finding the most satisfactory prophylactic if the facilities for immunising considerable numbers of both school and pre-school children are lacking. In Great Britain the majority of local/

local authorities are only playing with diphtheria prophylaxis.

In certain European countries compulsory immunisation has been introduced with satisfactory results i.e. Russia and Hungary, the latter with A.P.T. Other States may follow but it seems unlikely that such legislation will come about in this country.

It is very unlikely that the general public will bring their children to be immunised unless properly stimulated. For the past few years diphtheria has been mild and accordingly it has not seemed necessary to the lay mind to immunise. Even the rising number of true gravis cases, which lately in Edinburgh reached nearly 30%, has failed to stimulate immunisation appreciably. When an epidemic occurs it will then be too late to immunise.

Broadbent (1932) suggests that for immunisation purposes the population be divided into:-

(1) Staffs of hospitals who should be immunised before commencing their duties (Benson 1934, Harries 1930.)

(2) Isolated communities, i.e. Institutions and residential schools because as Dudley has pointed out the isolation of carriers fails to control the disease under these conditions. Dudley at Greenwich and Fraser (1931) in Liverpool have produced good results to prove this.

(3)/

(3) The general public divided into:-

(a) The pre-school child should be immunised either by its family doctor or at the Child Welfare Clinic at one year old or at the latest before going to school.

(b) Any remaining school children on entry. When the basal immunity is low and opportunity for latent immunisation poor as in rural communities it may be advisable to give a maintenance dose when the child enters school (Fraser & Brandon (1936). Once a scheme is running properly the number of children requiring immunisation at school will be much smaller as the majority will have been done at an earlier age (Russell 1935).

A larger immunisation scheme will probably be more successful under the direction of an Immunisation M.O. responsible to the M.O.H. than, as at present, when each department carries out its own ideas.

The wholehearted cooperation of the general practitioner is, of course, essential as public advisers and for carrying out immunisation amongst better class children.

The most important items to be considered before putting a scheme into operation are:-

(1) The most successful prophylactic to be employed for each section of the population.

(2)/

(2) Suitable propaganda to stimulate the general public to submit their children for immunisation.

The results obtained with A.P.T. in adults compel the employment of T.A.F. for all persons over 10 years old, i.e. hospital staffs etc. Anderson's results amongst the Nurses in Ruchill Fever Hospital, Glasgow, suggest that it may be possible to find a method of using A.P.T. in adults. The investigation is still proceeding.

Isolated communities respond well to A.P.T. provided their basal immunity is high. 'One shot immunisation' can be safely employed under these circumstances.

From the point of view of the general public the question now arises - 'Is the parental response likely to be as great if the two small dose method is employed instead of the now established 'one shot immunisation'?' Or to put it in another way - 'Will we obtain a higher percentage of successfully immunised children by accepting the failures of one shot immunisation or the probably poorer response to the two injection method? The answer to this question seems to lie with the basal immunity of the child population. One shot immunisation will be satisfactory up to a point in Child Welfare Centres and schools in densely populated/

populated areas. But for rural areas and better class children either two small doses of A.P.T. or three injections of T.A.F. or F.T. will give the best results. If 1 cc. of A.P.T. is used as the antigen then post-Schick testing is advisable to prevent a valuable prophylactic falling into disrepute and disuse.

In order to be successful all propaganda must be as pithy and to the point as possible. Long explanations are neither read nor understood.

It is inadvisable to promise either complete protection or freedom from reactions. In fact, it is better to prepare the way for an occasional mild case or a fairly severe reaction. This is especially advisable in districts where there is no difference in the lay mind between cases and carriers.

THE COST OF IMMUNISATION.

When protecting a small number of children the difference in cost between the various prophylactics matters little. However, when a large scheme is put forward by a local authority the cost of the prophylactic, although not the only factor, must be considered.

The cost of the prophylactic varies slightly according to the manufacturing firm from which it is obtained. The difficulty of using a supply of materials at intervals has been largely overcome by fitting rubber caps to the vials which can be penetrated by/

by a hypodermic needle without being removed. 10 cc. vials are a useful size to employ unless large numbers of children can be immunised at once.

Both T.A.F. and F.T. require 3 cc. for a course of injections and their respective costs are about 3/6 and 3/- per course. Employing one shot immunisation with A.P.T. (1 cc.) a course costs about 1/6 and two smaller doses (0.2 and 0.5 cc.) slightly less. If smaller vials are used the cost increases rapidly. Thus an immunising course with A.P.T. is only half as expensive as the older prophylactics.

When a scheme for wholesale immunisation of the pre-school and school population is being worked out other factors have to be considered, i.e. the cost of additional personnel and propaganda.

Against these expenses must be put the loss of child life from diphtheria as well as the cost of each case requiring hospital treatment (often £10-20 on the average). There is also the loss of education fees to be considered.

If it is possible to lower the morbidity rate of diphtheria, beds in infectious diseases hospitals will become available for complicated cases of measles and whooping cough with further saving of child life. So the results of intensive diphtheria immunisation are likely to be more far-reaching than would appear probable at first sight.

SUMMARY.

(1) Active immunisation is the best prophylactic measure we possess against diphtheria as the isolation of cases and carriers has proved a failure in preventing the spread of the disease.

(2) The success of the various prophylactics depends on the basal immunity of the child population (especially A.P.T.).

(3) T.A.F. is widely used in both children and adults. F.T. and A.P.T. should be confined to children.

(4) It is unwise to employ 'one shot immunisation' with A.P.T. except in closed communities of high basal immunity.

(5) The 'detector' dose method of using A.P.T. seems likely to give as good results as T.A.F. and perhaps may be an even better prophylactic in combating 'gravis' diphtheria.

(6) The best time to immunise is as soon as possible after a child's first birthday.

(7) Reactions are not likely to occur if the child is immunised before going to school.

(8) The pre-school child should receive almost as much attention as the school child.

(9)/

(9) The general public should be educated to receive diphtheria immunisation as a natural event in a child's life.

(10) When an epidemic occurs it is too late to immunise.

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