Diphtheria is caused by a bacillus, Corynebacterium diphtheriae, which is spread by dust or secretion droplets. Having infected a subject, usually through inhalation, the bacilli remain localised around the nasopharynx and tonsils, with the formation of a grey patch of inflammatory exudate, known as the false membrane. A powerful exotoxin, first demonstrated by House and Yersin in 1888, is released by the organisms and produces widespread systemic effects, often leading to a fatal termination.

In 1890, the antitoxin was discovered and its disabled patients to be treated with convalescent serum. Experimental prophylactic immunisation was carried out by Rabold Smith on guinea-pigs in 1907, but the toxin-antitoxin mixtures used were regarded as too toxic for human subjects; in addition there was no method available to determine the required immunising or toxic effective the procedure had been. These difficulties were overcome in 1912 when Schick introduced his test for detecting the presence or absence of immunity, and Bock, working in the United States, carried out experiments on the composition of T.A. and started the new standard procedure of testing the safety of prophylactics on animals. In England, prophylactic immunisation against diphtheria was carried out to a limited extent as early as 1921; but, though good results were obtained, recommendations for extension of this work were not followed.

Advances in the production of prophylactic antigens have been outstanding, with the result that...
modern products have a high antigenic activity and little or no toxicity. The different types will be discussed later.

During 1941 a National Immunisation Campaign was launched by the Ministry of Health in Great Britain; the increasing proportion of immunised persons has been accompanied by a decrease in both morbidity and mortality figures for diphtheria. Similar reports have been received from Canada and the United States, where prophylactic immunisation had been introduced earlier. These findings will be subjected to certain statistical analysis towards the end of this essay.

**Immunity**

Immunity may be defined as the power which an individual sometimes acquires to resist or overcome an infection to which most or many of its species are susceptible.

Active immunity may occur naturally after a clinical or subclinical attack of a disease or it may be induced artificially by the injection of a suitable antigen. It is with the latter that this account is mainly concerned. Passive immunity may also be acquired naturally (e.g. from mother to offspring) or by artificial means, as in the treatment of diphtheria with immune serum.

Active and passive immunisation against diphtheria will be discussed with reference to the graphs on Page 3. Graph I shows the effect of intravenous injection of immune serum on the antitoxin concentration of the blood. This is a rapid test, since the full dose of antitoxin reaches the circulation immediately, but the duration of immunity is short due to the elimination of foreign protein by the body. Passive immunisation is thus an emergency measure used only for the immediate protection of contacts or the treatment of cases.
As seen in Graph II, one injection of antigen stimulates little antibody production (primary response) and no immunity results; however, it prepares the body so that a second inoculation some weeks later may produce large amounts of antibody rapidly (secondary response) (Graph III), depending on various factors such as the nature and dosage of the antigen and the state of the body cells. Active immunity is therefore slow in onset but it is also very steady, and even if antibody is no longer detectable in the serum the body retains its capacity to respond rapidly to a stimulus with the production of further antibody.

Graph II shows the second injection acting as an intermediate stimulus, in contrast to the usual short rise associated with the secondary response. This sometimes occurs with children in whom the antibody-producing mechanism has not fully developed four weeks after the first inoculation.

Dear and Gilmore (Lancet 1947, ii, 647) have shown that the maintenance of antibody production long after the cessation of injections can be explained on the basis of two different responses. During the ten days after the second injection of antigen a rapid rise in antibody values occurs, but this may be followed by a decline over the next two months. Then the antibody titre may steadily regain its former values, a delayed response. If the two processes overlap, a steady level will be maintained.

These workers tentatively suggest that two types of cell are involved. Temporary cells give rise to antibody corresponding to the secondary stimulus response; as these cells disappear there is a decrease in the amount of antibody formed. Under certain conditions, more permanent cells are stimulated and these account for the delayed response so that a more lasting immunity is attained. This is clearly a need for antigens which...
will evoke this delayed response and so produce lasting immunity.

Various sites of antibody production have been postulated, amongst them the cells of the reticulo-endothelial system, lymphoid tissue and, in the rabbit, immunized with alum-halogenated toxoids, adipose tissue and voluntary muscle. Evidence for the different hyphomycetes cannot be examined here. Having briefly reviewed the mechanism of artificial immunization, Schick’s test for determination of immunity to diphtheria may now be considered.

The Schick Test.

The Schick reaction is a biological test used to detect those who are susceptible to diphtheria and need immunization, to confirm a useful degree of immunity after immunization and to indicate any sensitivity to bacterial proteins.

Schick Test toxin is a sterile filtrate from a culture of Corynebacterium diphteriae, diluted before use with a bovine buffer solution. It remains stable for up to six months at room temperature, but should be stored at 4° C.

The standardization of Schick toxin is regulated by the Therapeutic Substance Test which states certain limits of activity as determined by intracutaneous injection into guinea pigs with and without antitoxin.

When the Schick Test is performed in man, a local skin reaction occurs in those with less than a certain level of circulating antitoxin. On the other hand, if the circulating blood contains more than this level of antitoxin no reaction is produced. There is considerable individual variation in the amount of antitoxin necessary to insure neutralization of the test dose of toxin, but the average value is 200 units per ml. of blood.

The neutralization of toxin and toxoid in the Schick Test fluid by the subjects' antitoxin does not affect
other substances, such as bacterial proteins present in the fluid, to which some white cells react (pseudo-reactors). It is therefore necessary to use a control in which the tissue has been destroyed by heat. This control prevents false elevation of the reaction due to reactivity of the proteins contained in the Schick test fluid.

All glass 1 ml. syringes with needles of fine gauge are preferable for the injections. It is important to keep the syringes used for toxin injection separate from those used for the control fluid. The skin and the platen surfaces of both jorums should be cleansed with methylated spirit and allowed to dry. The test is carried out by the intradermal injection of 0.2 ml. of Schick test toxoid into the left jorum and 0.2 ml. control fluid into the right.

Readings may be made after forty-eight hours from the time of injection, at that time pseudo-reactors will be detected quite easily, but a number of late reactors may be missed. If the readings are made after a week Schick positive reactions will be seen but pseudo-reactors will usually have faded. The few possible results will now be discussed.

Negative: If only the needle marks are visible on both arms, it indicates that the subject possesses a variable amount of circulating antitoxin in the blood, usually over 20 milliunits per ml. and that the is immune to diphtheria.

Positive: If the control arm shows nothing and the test arm a patch of erythema up to 20 millimeters in diameter, it indicates insufficient circulating antitoxin and susceptibility to diphtheria.

Reads and negative: If identical areas of erythema occur on both arms in twenty-four hours and disappear after a further twenty-four, it indicates sensitivity to bacterial toxins but the absence of immunity.

Reads and positive: When areas of erythema occur on both arms, but in the test arm being larger and there is
The Schick test was once regarded as fundamental but it is now much less widely used for several reasons. The antigens employed today are far more reliable than formerly so that tests for immunity are no unnecessary. In addition several Schick negative reactions have contravened the theory of specific reaction, and this has detracted greatly from the reputation of the test; it is now universally accepted that a negative reaction is no guarantee against infection. Since the test has wide limits its use in research has been abandoned.

The accurate quantitation estimation of antitoxin concentration in the blood is of great practical value in this respect. In addition it is known that practically all young children prior to immunisation are susceptible to diphtheria and sensitivity to bacterial protein is uncommon at that age, so that the Schick test is no longer used in children's clinics.

In older children and adults it is important to detect sensitivity to toxin before immunisation and here the Schick test is valuable and is still used. If less reliable byphlogisticus such as Tocciid-antitoxin titer (C.A.T.) are administered the Schick test is again used to confirm the presence of immunity. Finally the test may be retained for checking the efficiency of alum-acpliated Tocciid (A.P.T.) in random samples of the population.

Phosphorhetic Antigens:

The antigens used for producing immunity to
diphtheric have varied in nature, toxicity, and efficiency since the early days of immunization. The first toxoid to be used was a toxin-antitoxin mixture (T.A.). The preparation of such mixtures was difficult, since the proportions of toxin and antitoxin had to be adjusted so that there was a small excess of toxin neutralized to act as the antigen, but insufficient to cause severe toxic reactions. Thus, over-neutralization would lead to loss of antigenic activity while under-neutralization might well prove toxic or fatal, if excessive. T.A. is now of historical interest only.

A definite advance over T.A. was made when formal toxoid (F.T.) was introduced as a toxoid antigen. It had been discovered in 1891 that toxins could be detoxified by incubation with formalin, but only later was it discovered that this toxoid retained the antigenic properties of the original toxin. The advantages of F.T. were its easy preparation, its lack of virulence, live serum or specific toxicity and its comparatively simple estimation by flocculation tests. It was widely used in the United States and France. In Great Britain severe local reactions occurred, especially in adults, which were not encountered in other countries and which suggested a possible cause might be found in the type of medium on which the organism was cultivated. These toxic effects at least served the purpose of stimulating British workers to develop other and more perfect antigens.

Toxoid-antitoxin mixtures (T.A.M.) were prepared quite simply by incubating toxin with formalin for a given period and adding antitoxin to the toxoid so produced. This, any toxin which escaped detoxication by the formalin was effectively neutralized by the relative excess of antitoxin. No great accuracy was, therefore, required in preparation of the mixture; in addition it had a low toxicity, those reactions which occurred were thought to be due to
specific substances derived from the breath constituents, from products of metabolism and from live serum used in the preparation of antitoxin. T.A.F. has been prepared in various forms, but its use was limited to local use in the mouth and it was not used after the introduction of specific toxoid antigens.

In 1927, Chum and Perez introduced Toxoid-antitoxin Hocules (T.A.F.) by the following method. The precipitate of undenedioidal toxoid-antitoxin mixture was allowed to sediment; it was then collected and washed several times to remove impurities, and finally emulsified in saline forming about 10 times the original volume. T.A.F. produces few, local or general reactions, since most contaminants are removed in washing; but it contains sensitizing live serum, which accounts for the occasional toxic effects which are encountered. Absorption from the site of injection in dogs and this probably leads to a higher antibody efficacy than with the other toxoids, as far as known.

95 per cent become Schick-negative after immunization with T.A.F. These doses of 1 ml. each intramuscularly are necessary, the second injection being administered at least four weeks after the first, and the final injection after a further two weeks.

Plumb toxoid precipitated Toward (P.T.A.T.) was prepared by pluming from a high grade toxin, prepared as a special medium containing 0.01 per cent and a strictly controlled quantity of iron. The plumb was then joined and purified with charcoal, finally it is precipitated with a known amount of lead chloride. Further purification was effected by washing with a solution of calcium hydroxide and sodium chloride. P.T.A.T. has a very high antigenic activity, it is relatively free and totally free from sensitizing live serum. Like T.A.F. it is slowly absorbed and produces local reactions on intramuscular injection very rarely.

Recently, Protein Toxoid Aluminum Phosphate Preparations (P.T.A.P.) have been developed by Holt in London.
He prepared a high grade toxin on a carefully adjusted semi-synthetic medium, extracted it with toluol under optimum conditions, then treated it with compounds of magnesium and cadmium and finally fractionated it with ammonium sulphate. The use of pathogenic is still very much in the experimental stage clinically, but Bensfield has used it and states that it has a high antigenic activity, which is believed to be increased on storage, and produces no local reaction. Large quantities of the highly purified toxin can be stored in the dry state, the use of the antigen being provided by the addition of a solution of inorganic salts as required. It is hoped that the efficiency of P.T.A.P. will be proved sufficiently great that biological assay, which has always presented immense difficulties to manufacturers, will be unnecessary.

Choice of pathogenic antigens made around the late 1930s included (T.A.P., A.P.T., P.T.A.P.). Since these injections are required with T.A.P., its use is nowadays limited to adults, in whom A.P.T. is more likely to produce fewer effects. Both A.P.T. and P.T.A.P. can be administered in two doses of 0.5 ml each, separated by an interval of at least four weeks. The fewer number of injections makes these antigens particularly suitable for children and in these reactions with A.P.T. are almost inert.

P.T.A.P. may prove to be the pathogenic of choice for both children and adults, then most useful to the joined.

Immunization of Infants.

Children and adults are at every day coming in contact with each other obviously run the risk of contracting diphteria unless they have been adequately immunized, but the disease has also been reported in young infants who are relatively sheltered from infecting sources (schools, cinemas etc.) and who were previously thought to have an adequate degree of naturally acquired immunity.

The following figures show that diphteria is fairly common
in children under three months of age.

<table>
<thead>
<tr>
<th>Total No. of Cases</th>
<th>No. under 12 months old</th>
<th>%</th>
<th>Source of Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,337</td>
<td>102</td>
<td>4.5</td>
<td>Murray (1943) in South Africa</td>
</tr>
<tr>
<td>921</td>
<td>46</td>
<td>5</td>
<td>Hiatt (1947) in Finland</td>
</tr>
</tbody>
</table>

Local epidemics have been reported in remote and running infants from Scandinavia with a mortality rate of 20 percent; as the disease was often of the initial type it was frequently misdiagnosed. Only six deaths, under the age of one year, from whooping cough were reported in Great Britain in 1948; so that we deserve further scrutiny at present, though it is a high proportion of the total number of deaths from the disease. The situation should be watched carefully and it is essential that the optimum time for vaccinating these very young infants should be studied.

The idea that infants during the first few months of life possess an adequate degree of inherited immunity has been fostered extensively in many areas. However, as pointed out above, it is true that such children are less exposed to infection; and in addition their mucous membranes are believed to be in the most resistant. It is also believed that antibody producing mechanisms are fully developed before the age of six months. This is probably untrue; the poor response to tetanus toxoids at this age is partly due to the "blocking effect" of the inherited antibodies derived from the mother. The improved response which occurs in rather older children is no doubt due to the building up of local immunity in the same form stimulating the injecting dose of the organisms, and to any development of the antibody producing mechanisms for so.

Since the yolk sac content, which gives an indication of antibody concentration, is similar in the yolk and maternal blood, it may be concluded that antibodies from the mother are passed to the child via the placenta.
salarium contains a large, but with a relatively low titre of 
plasminogen, and it is thought that these play little or no part 
in the transmission of immunity in the human subject. Though 
the amounts in the mother with any help to maintain the 
early protection afforded through the placenta.

Wright and Clark in 1946, compared the Schick reaction in 
human and the infant in 270 cases. In 101 cases both 
were Schick negative, but in the remaining 99 the mother was 
Schick positive and the children Schick negative. Thus one third of 
the infants failed to respond to the Schick test. It has been suggested 
that the skin of infants is suffused with a rich endothelial network, 
which acts as a barrier against the toxins from the mother and no reaction 
occurs. The Schick test in the first few days of life is of no value for 
determining the presence of passive immunity (naturally acquired) in these subjects.

Randall has suggested that two factors must be taken 
into consideration when studying the immunity response of infants to A.P.T.
They are (a) the amount of circulating passive antibody present in the 
blood at the time of the first injection, and (b) the age of the baby 
at that time. He concluded that infants of eight weeks and below 
should be injected with A.P.T., and would produce antibodies as 
well as those over nine months old, and that a reasonable response 
could be obtained provided that not more than 0.05 units of passive 
antibody were present at the time of the first injection. If samples 
of cord blood were analyzed it would be feasible to predict (a) 
the immunization would be effective and (b) when the passive antibody 
content would be reduced to such levels that passive immunity could occur 
since the antibodies, inherited from the mother, would affect 
subsstantially. Two simple methods are available. Either a 
sample of cord blood from each child can be obtained at birth 
and the child’s immunization period (i.e. post injection) or 
a representative sample of cord blood could be taken and the ideal 
age for immunization of the majority of infants could be 
estimated. The first method is the ideal, but would be at 
out of the question with the present laboratory facilities.
The second procedure, on the other hand, would result in infants
receiving their first injection before their third and fourth month of life. Not only will a number of attempts be inevitably unsuccessful due to the absence of passive antibodies, but also 20 to 30 per cent of the infants will react to a greater extent than their first months are sufficient to the disease.

The most practical method of dealing with the cases described above, infants should, therefore, receive their first injection at about the third month, in the unsuccessful cases not less than six hours of ART will be necessary. Should the infant be likely to come into contact with carriers or persons having subclinical infections, a Schick test may be performed on the mother before the birth of the child to detect immunity and whether or not the infant will be infecting much earlier. However, the Schick test will slightly alter the result that ready an infant by stimulating some antibody formation in the mother. It should be noted that injections at the age of three months are far less shocking to a child than one month later. The red solution, however, is to increase the number of mothers who have been actively immunized and has retained their immunity, then the danger to the child during the first few months before its first injection will be reduced considerably.


dilution of immunity

The maintenance of antibody production and a high titer is just a small part of the subject. It has already been discussed (p. 14), the present material in clinical evidence on the duration of immunity in school children as detected by the Schick Test. The limitations which have been set forth have been determined upon.

Duke and Scott performed Schick Tests on children at varying intervals from the time of the first successful immunization as detected by the Schick Test. The areas under investigation were urban but included large cities, where natural immunity to diphtheria is common, and cases 0 in the general population are rare.

The results of the investigation are recorded in the following table (p. 14), from which conclusions may be drawn.
<table>
<thead>
<tr>
<th>Poliomyelitis</th>
<th>Years after</th>
<th>Total Told</th>
<th>No. falc.</th>
<th>% falc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.A.F.</td>
<td>6</td>
<td>579</td>
<td>105</td>
<td>18</td>
</tr>
<tr>
<td>T.A.F.</td>
<td>5</td>
<td>164</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>T.A.F.</td>
<td>4</td>
<td>588</td>
<td>91</td>
<td>15</td>
</tr>
<tr>
<td>A.P.T.</td>
<td>3</td>
<td>522</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>T.A.F.</td>
<td>2½</td>
<td>1039</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>A.P.T.</td>
<td>2</td>
<td>354</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

(Duke-Wilkins O.M.T. 1902, 3, 710.)

The total told of the "Five-Year Group" was statistically insignificantly, so that the high protection of which anterior results is not to be taken into account. However, it can be seen that the great majority of children have maintained their immunity for six years and that the loss is gradual during that time. For the benefit of the profession who will test immunity, testing should be given to children who have been immunized, at regular intervals. They are usually given just prior to starting school, about the age of ten and probably a final test or leaving school at fifteen, assuming that the child has been immunized during its first three years of life.

Carriers:

Immunization is directed against the action of diphteria, and actual infection is not prevented so that a large number of potential carriers are built up. This has led to criticism of immunization on the grounds that these new carriers act a menace to those who have not been immunized. It may be pointed out to the critics that children may develop antibody immunity with their own resources, and is especially so in city children, so that there are likewise potential carriers. In any case a high carrier rate will result in better maintenance of immunity level by the action of continued subclinical infections.

It may be necessary to isolate carriers if they are in contact with susceptible children, but it is quite unnecessary if the majority of contacts are immunized.
Practical Procedures.

It is of prime importance to avoid septic injection in the process of immunization. This can best be achieved by attention to proper sterilization of instruments, protection from infection after sterilization, the wearing of masks by the doctor and assistants, and avoiding contamination of the sterile portion of instruments with the hands. Serious accidents have occurred due to lack of attention to these points.

The sterilization of instruments is such an important subject that methods will be described, as briefly as possible. All-glass syringes should be used as they are easier to handle and sterilize than those made of glass and metal, and if properly cleaned they may be assembled tight sterilization. New syringes should be washed with soap and water. Used syringes should first be washed with 2 per cent lye, which facilitates the removal of toxic matter adherent to the glass. They are then rinsed and dried. The assembled syringe may be wrapped in kraft paper and sterilized in a hot-air oven or autoclave or it may be boiled in water, if these facilities are not available. Different sterilized needles should be sterilized to allow a separate one for each injection.

The doctor and nurse caring at the injection should see that their hands are scrupulously clean before commencing. Masks should be worn if there is any sign of respiratory injection. It is essential to have the child, who is to be injected, in the optimum position and so held that even a sudden movement will not touch the needle. Young children are usually held seated on their mother's knee with the arm extended and the mother holding the hand. The fingers of the operator's hand are arranged to hold the syringe in a firm grip and the needle inserted deeply into the anterior muscle just above the insertion of the deltoid. After removing the needle, the arm should be massaged for a moment or two. All the adjuvants should be given while the needle remains in the ductus, or adjuvants along the track of the needle, has been the cause of local reaction.

To read the details of immunization, separate
cards shall be provided for each individual. On these are
written essentials such as the name, sex, date of birth, date
and place of immunization, with details of the inoculation,
antigen used and finally the signature of the doctor.

Local reactions which may occur include: oedema,
redness and tenderness and general reactions usually manifest
themselves as headache, malaise or fever. The frequency
increases with age being very rare under the age of five. Slight
irritation to toxin in adults will be encountered from time to
time as matter has been the antigen may be.

The administration of large doses of diphtheria
antitoxin to a child with some allergic condition is often
undesirable. It is therefore important to immunize tetanically
This may be carried out with small repeated doses of A.P.T.
or P.T.A.P., until the effects are produced.

It has been reported that anterior toxicotic effecting the injected limb may occur with
tetanus toxin, more especially at the height of en
siveness. There is lack of sufficient material for statistical
support or otherwise of this claim, but it is perhaps wise
in the meantime to discontinue immunisation during the
epidemic season (late summer and autumn) in an affected locality.

Diphtheria Antitoxin Postphtysalactic (B.P.P.) is a combined
antigen used for immunising young children against diphtheria
and whooping cough. Unfortunately, in a proportion of cases,
whooping cough still occurs and thus the whole idea of
immunisation tends to become discredited. It is also said
that the paralytic form of diphtheria, mentioned above is
associated with this combined immunisation rather than
diphtheria prophylaxis alone, but again there are insufficient data

Some Administrative Methods

It is essential that, if a high proportion of
immune persons is to be maintained, the public should be
well informed and encouraged to have their children immunised
against diphtheria. Many methods of publicity have been
tried and the relative efficiency of these was investigated
and reported upon by a Social Medicine Committee in
1942 (Lancet 1942, ii, 642). The most sure and effective
way of influencing a mother to have her children
immunised is through personal contact, directly by the
family doctor or welfare officer, or indirectly from
the school. Two main difficulties face the social worker in
this field today; the virtual disappearance of
diphtheria has led to some degree of complacency and
has made it harder to convince parents of the necessity
for continued immunisation, this problem will persist,
and the second difficulty is to influence mothers to
have their newly-born infants immunised in the first few
months of life.

There is no doubt that the family doctor can
bring a very great influence to bear on his patients, so
that they will respond to his advice, whereas they would
ignore it coming from a 'lower source'. Efforts are being made
to include immunisation against diphtheria as a subject
in ante-natal clinics; it is already emphasised to parents
attending child welfare clinics and local authorities have taken
up 'the cause' enthusiastically in many areas.

No satisfaction can be felt until the time is
reached, when having her child immunised is as natural
and important to a mother, as adequate preparation for
its arrival is, before birth.

Results of Prophylactic Immunisation.

The graph on page 18 represents the incidence of
diphtheria in England and Wales for the thirty year period
(1921-1951). From the figures of incidence of the disease
prior to the start of immunisation in 1941, the mean
was obtained (\(= 55,000 \pm 1250\)); the standard deviation
If the figures from the mean were also calculated (≈ 9500), horizontal lines representing these values were drawn on the graph and extended (by dotted lines) into the 1941-51 period. The majority of incidence figures from 1921 to 1940 fell between the two lines, representing the fiducial limits; if the same is true of the fort 1941 figures then no significant alteration in the area incidence of diphtheria can be considered to have occurred. If, on the other hand, the majority of readings fell on one side of the area enclosed by the fiducial limits then some significant change has taken place; and as can be seen quite clearly from the graph, this has indeed taken place.

It can be concluded that the introduction of prophylactic immunisation against diphtheria in England and Wales in 1941 was accompanied by a significant drop in the incidence of diphtheria.

The graph in figure 20 shows the death rate from diphtheria in England and Wales for the sixty-year period (1891-1951). An exponential curve was drawn representing the trend of the 1891-1940 figures for mortality. The curve was extended by interpolation into the 1941-51 portion. It has been shown by Burnet et al. that such an extension does not always give a true forecast of future trends; it is preferable to extend into the future along the tangent to the curve at some recent point. By studying the graph it will be seen that the death rate has declined steadily over fifty years as represented by the exponential; if the National Immunisation Scheme of 1941 and subsequent immunisation can be considered to have had any effect on the death rate from diphtheria the slope of the actual values must descend more steeply than that of the tangent drawn, and this is seen to be the case.

Although conclusions about death rate are subject to variable factors such as antibiotic treatment, there can be little doubt that the beneficial effect of immunisation is
clearly demonstrated by the graph.

For the incidence of diphtheria in the cities of New York and Toronto are plotted on the graph of Fig. 23. In this case exponential curves were drawn, the values being calculated from the actual figures, as shown, but the

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DEATHS</th>
<th>YEAR</th>
<th>DEATHS</th>
<th>YEAR</th>
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<td>936</td>
<td>1910</td>
<td>384</td>
<td>1920</td>
<td>510</td>
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**MORTALITY RATE 1891 - 1920 (ENGLAND & WALES)**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DEATHS</th>
<th>YEAR</th>
<th>DEATHS</th>
<th>YEAR</th>
<th>DEATHS</th>
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<td>1951*</td>
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<td>1952</td>
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<td>1953</td>
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<td>266</td>
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<td>190</td>
<td>1956</td>
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<td>1929</td>
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<td>92</td>
<td>1958</td>
<td>3.6</td>
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<td>1950*</td>
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<td>1964</td>
<td>3.6</td>
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</table>

*Subject to correction

**MORTALITY AND MORBIDITY 1921 - 1951 (ENGLAND & WALES)**
They represent figures covering the whole period (1941-51). They are
necessary since no fixed date for the commencement
of intensive immunisation could be fixed as with Britain.
That says nothing about a decline and the actual values are
well below the calculated values from 1931 onwards. It can be
concluded that a significant decrease in diphtheria incidence has
accompanied the increased intensity of immunisation and the
successive higher proportion of immunised persons in Toronto and
New York.

**Diphtheria in Scotland, (1941-1951)**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Total Number Immunised Persons</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>610,705</td>
<td>11,199</td>
<td>518</td>
</tr>
<tr>
<td>1942</td>
<td>706,387</td>
<td>9,750</td>
<td>290</td>
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<tr>
<td>1943</td>
<td>780,173</td>
<td>7,146</td>
<td>230</td>
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<tr>
<td>1944</td>
<td>841,060</td>
<td>6,152</td>
<td>163</td>
</tr>
<tr>
<td>1945</td>
<td>919,282</td>
<td>4,631</td>
<td>124</td>
</tr>
<tr>
<td>1946</td>
<td>992,145</td>
<td>3,446</td>
<td>91</td>
</tr>
<tr>
<td>1947</td>
<td>1,066,967</td>
<td>1,096</td>
<td>44</td>
</tr>
<tr>
<td>1948</td>
<td>1,176,137</td>
<td>722</td>
<td>31</td>
</tr>
<tr>
<td>1949</td>
<td>1,259,878</td>
<td>333</td>
<td>14</td>
</tr>
<tr>
<td>1950</td>
<td>1,328,653</td>
<td>134</td>
<td>3</td>
</tr>
<tr>
<td>1951</td>
<td>1,411,375</td>
<td>128</td>
<td>3</td>
</tr>
</tbody>
</table>

The morbidity and mortality figures for Scotland (1941-51)
are shown in the table above. In the second column the estimated
number of immunised persons resident in Scotland in the year is
shown. The correlation coefficients between the total number immunised
and the number of cases, and the total immunised and the number
of deaths were calculated by the following formula:

\[ r = \frac{\sum (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum (X_i - \bar{X})^2 \sum (Y_i - \bar{Y})^2}} \]

The coefficient of correlation, X and Y, the variables, \( \bar{X} \) and \( \bar{Y} \),
the mean of the variables, N the total number of variables, and
$\sigma_x$ and $\sigma_y$ the standard deviations. The coefficient of correlation between the number immunised and the number of cases $= -0.91$ and that between the number immunised and the number of deaths $= -0.89$. These calculations show that there is almost complete negative correlation between these sets of figures and indicate that the morbidity and mortality of diphtheria have shown a most definite improvement with increased proportion of immunised persons.

It may be concluded after analysis of various morbidity and mortality figures for England and Wales, Toronto, New York and Scotland by different statistical methods, that prophylactic immunisation has brought about outstanding improvements, so that diphtheria has become a relatively rare disease in these places.

Summary.

After a short account of the mechanism of immunity, the ease and limitations of the Schick Test were discussed.

The development of prophylactic antiparas, with a note on the indications for their use, was described.

Various factors governing immunity in infants were outlined and two methods for determining the ideal age for immunisation were mentioned.

A recommended technique for immunisation was described, bearing in mind possible dangers during an epidemic of infantile paralysis. The importance of disseminating knowledge about immunisation amongst the public was stressed.

Finally, the results of immunisation were subjected to various statistical analyses.