The Lewis Cameron Undergraduate Prize
in Bacteriology, 1960.

IMMUNIZATION IN CHILDHOOD.

Ann M.R. Black.

May, 1960.
SUBJECT MATTER.

Introduction.

I. Immunity - Natural and Acquired.

2. Individual Diseases - Diptheria.
   Tetanus.
   Whooping Cough.
   Tuberculosis.
   Smallpox.
   Poliomyelitis.
   Other Diseases.

3. Practical Aspects - Complications.
   Precautions.
   Immunization Programmes.
   Administration.

4. Comments and Conclusions.
INTRODUCTION.

We wish to immunize the child in order to protect him against certain diseases to which he may be particularly prone or to induce a harmless immunity to prevent him from succumbing to other diseases when he is older. Immunization in Childhood is essentially a weapon of preventive medicine for the benefit of the whole community. It is a vast subject with a complex theoretical and experimental basis, fascinating history and promising future — and we shall be considering the subject in the light of these aspects in the following pages.
IMMUNITY.

This term is used to denote the resistance offered by an organism to a parasite; such resistance may vary from complete susceptibility to an infection to complete immunity and is determined by a number of factors. We shall first outline those defensive mechanisms which do not depend on any previous contact with the organism.

Normal Defence Mechanisms:

The skin and mucous membranes lining body entrances have means of ridding themselves of contaminants. When a micro-organism breaches these defences, for instance through a cut, the process of inflammation begins. The mobilized polymorphonuclear leucocytes bring into play the most formidable mechanism of defence - that of phagocytosis. Both the fixed phagocytes and these wandering phagocytes of the blood are capable of ingesting and digesting organisms. The fact that the natural or acquired properties to which a micro-organism owes its invasiveness are essentially anti-phagocytic ones indicates how important the phenomenon is.

One of the non-specific immune substances in the serum is termed opsonin; this seems to adhere indiscriminately to many bacterial species rendering them much more vulnerable to phagocytosis by modifying their surfaces in some way. Again, so-called "normal" antibodies are said to enhance the phagocytosis of particular organisms. In addition to aiding phagocytosis, normal serum possesses a direct bactericidal action; several such immunologically non-specific substances
have been named including β lysin which, however, has a limited range of activity. But the most important constituent discovered so far is Pillemer's properdin which is considered largely responsible for the bactericidal power of such serum and participates in such diverse activities as the destruction of bacteria, the neutralization of viruses and the lysis of certain red cells. It is a large euglobulin molecule and amounts to 0.03% of the total serum proteins. Properdin, however, requires another component of normal serum for its bacteriolytic action. This is called "complement" and is a complex group of substances; four components have been determined and appear to be protein in nature. Complement mediates also the defensive activity of leucocytes, is essential for the lytic action of certain antibacterial antibodies, and may aid the opsonizing action of antibodies. Other antibacterial substances have been found in normal serum but those considered are the most important.

Many other factors influence the existence of natural immunity, for there are species, racial and individual differences in resistance. Species differences are mainly due to variations in the receptivity of the tissues of the different species; racial differences are only relative and in most cases are not due to any essential genetic peculiarity; individual differences in the case of a virgin population are influenced by age, sex, hormonal status, state of nutrition and environment. People in good health, well-nourished and in good surroundings are generally more
resistant than those without these advantages; vitamin deficiency, especially A or C, also tends to lower resistance.

**Acquired Immunity:**

This is the state of resistance which is engendered by an attack of infectious disease - in clinical, subclinical or atypical form - or by injection of a vaccine.

**Historical aspects:** The fact that recovery from infectious disease may confer resistance to another infection of the same kind - from a few months to a lifetime - has been known for centuries - very old records refer to the immunity to smallpox acquired by survivors and it was common practice in some regions to immunise healthy people by inoculating the skin with pustular material from known mild cases of the disease. This practice "variolation" was brought to Britain from the Middle East by Lady Mary Wortley Montagu in 1718 but it was considered too dangerous to be very widely accepted. Edward Jenner turned his attention to the problem; in 1796 he found a modified infectious agent in the form of cowpox pustular material which had the power of invasion but did not produce dangerous disease. When he inoculated his subject with virulent smallpox material some months later, he found him to be completely immune. This discovery remained an isolated observation for 83 years though the method was universally practised.

Immunization to other diseases was not applied until 1879 when Pasteur accidentally found a modified agent which
prevented chicken cholera. Cultures which had been left over the summer vacation had lost their virulence for the chicken; he inoculated the same chickens with freshly isolated virulent strains and found that they were immune although the bacterium was fully virulent for chickens not treated in this way. Pasteur at once saw the similarity between this and Jenner's observation; he had thus discovered the rationale of vaccination and a formula for possible protection of man against disease. He next produced attenuated vaccine deliberately for anthrax, swine erysipelas, and finally for the virus of rabies.

But, long after immunization had become widely used as a prophylactic measure there was still little knowledge of the mechanisms of acquired immunity. The first steps in this direction were taken by Behring and Kitasato, in 1890, who demonstrated that such immunity was a function of a protective agent in the blood. They injected serum from an animal who had received serial small doses of diphtheria toxin into a susceptible animal, together with a lethal amount of toxin; the animals did not die but those control animals who received toxin and no serum did die. Furthermore only serum from immune animals was protective and this protection was found to be highly specific for the particular toxin. This was an example of passive immunity conferred from an animal with an actively developed immunity; the specific substances in the blood were termed "antibodies".

Theoretical Aspects:

Antitoxic immunity: It gradually became clear that
antitoxin was not so much a new substance as a modification of existing material; it is made up of molecules of gamma and $\beta_2$-globulin. This antitoxic immunity to tetanus, diphtheria and others is highly effective; it is direct in its action not depending on the efficient functioning of a complex system of phagocytic cells. The increased resistance afforded by this kind of immunity is determined almost entirely by the interception and neutralization of the toxin before it reaches the susceptible cells and causes irreversible damage.

**Anti Bacterial Immunity:** We can summarise the difference between an actively immunized and a normal animal very briefly by saying that an immunized animal behaves towards a virulent strain of a particular bacterium in the same way as a normal animal to a non-virulent or only slightly virulent strain. This change in behaviour is again largely a function of blood antibodies, which are globulins; they react with the antigen and make the bacterium more phagocytosable i.e. they have an opsonizing action. In some cases this antibody coating makes the bacteria sensitive to lysis by the normal blood components.

Metchnikoff conceived that the phagocytes themselves possessed enhanced activity in the immune animal; Kahn and Lurie have experimental evidence that this is so. Leucocytosis in the actively immune animal is also more marked than in the non-immune. Finally, a specific tissue immunity has been postulated but this has been explained by many on the production of intracellular antibodies.
AntiViral Immunity: In most viral diseases lasting immunity follows an attack. Because people with the rare disease agamma-globulinaemia constantly succumb to bacterial infection but resist and even develop immunity to viral diseases it is argued that antibodies are unimportant in resistance to virus diseases. However, though there are no doubt other important factors, antivirus antibodies capable of protecting against many viral diseases have been found in the gammaglobulin separated from plasma. Knowledge of in vitro reactions of filterable viruses and their antisera is sufficient to show that there is no essential difference between antibodies developed against bacteria and those against viruses. Opsonins have not been found nor is there convincing evidence that phagocytosis plays an essential part. Sabin has suggested that antibody might act by uniting with the susceptible cells of the host somehow rendering them resistant to infection. Viruses demand an intracellular environment; once a virus has reached a cell antiserum can do little for the cell walls seem to be impermeable to it.

Antibodies:

Nature of antibodies: Blood antibodies can be sharply specific; they can distinguish minute spatial and chemical differences in the configuration of the antigenic substances and only a limited portion of the surface of the antibody molecule can come into effective contact with the surface of a molecule of antigen. Since antibodies are chemically little different from other serum globulins the
chemical modifications which give them specific combining power with antigen are limited and at present the combining group is said to consist of a local arrangement of amino-acids differing from normal globulin and from other antibodies. One antibody can combine with two or three antigen molecules and vice versa. Antibody cannot be identified chemically; it is identified by such antigen antibody reactions as neutralization, precipitation, complement fixation and agglutination.

There is considerable evidence that the site of formation of antibodies is in the reticulo-endothelial system and lymphoid tissues. The weight of evidence at present also suggests that the plasma cell is the main source of antibody production though the lymphocyte is also concerned with the process of manufacture.

Evidence has also shown that the longer persistence of antibody in the actively immunized as compared with that in the passively immunized is due to the continued production of antibody. Isotopic studies have shown that antibodies are rapidly destroyed and rapidly formed and in the actively immunized the level depends mainly on the rate of production. Persistence of immunity varies in duration with different diseases; artificially induced immunity tends also to be shorter - lasting than that naturally induced.

Theories of Antibody Production: The theory most frequently referred to is "the direct template theory" which is particularly associated with the names of Haurowitz and
Pauling (1940). They assume that the high degree of specificity of the antibody is determined by its synthesis against a "template" which is an "innate pattern of the body cell adapted to direct synthesis of molecules like itself but modified by the presence of some antigen." One of Burnet's objections to this theory was that it implied persistence of antigen in the body for the duration of the immunity, however long. He proposed an "indirect template theory" in which antibodies could be formed long after the disappearance of antigen. Antigen induced a heritable change in the antibody forming host cells. (1949). Jerne developed a different conception of antibody production (1955)-the so-called "natural selection theory" - which contributed somewhat to the "clonal selection theory" proposed by Burnet in 1959. The fundamentals of this theory are that antigen plays no part in impressing a pattern on the antibody producing cell; such antibody production is a genetically determined quality of certain groups or clones of mesenchymal cells the function of antigen being to stimulate these clones to proliferate and subsequently to produce antibody.

Burnet's theory is held in a largely biological framework; that of Haurowitz is more in line with classical chemistry. It is impossible here, to discuss the relative merits and demerits of each; we may note that it is difficult to prove either complete absence or presence of antigen or its determinant groups partly because of lack of sufficiently sensitive test methods.
Factors Influencing the Antibody Response:

Following exposure of the animal to antigen there is a latent period during which the immune mechanism is probably elaborating the antibodies which will appear later. When antibody does appear it increases in concentration for a time, reaches a certain point and then begins to decline - at first rapidly and then gradually until zero is reached. The actual concentrations and time intervals depend on many varying factors e.g. host variations, antigenic variations and variations in technique.

If, however, there is another exposure to antigen before zero is reached then the antibody response is quite different. This time there follow a more rapid rise, a higher peak and a longer-lasting high level of antibody. This immunological characteristic is of importance in both immunity from natural exposure and in that induced artificially and forms the rationale for the "recall" or "booster" dose in immunization procedures. The most advantageous time for such secondary stimulation is arrived at from careful experiment and we shall be considering this question later.

Other important influences include the actual dose of antigen to which the animal is exposed and its chemical and physical state. In general it is found that increasing amounts of antigen increase the measurable blood antibody level - up to a point - and when antigens are being used in immunization the necessary dose must obviously be determined. Different methods of preparation of antigens may induce
chemical changes which affect quantitatively the antibody response; physical adjuvants are employed in some cases to affect this response advantageously. These adjuvants may be antigenic, like killed micro-organisms, or non-antigenic - as are alum and mineral oil; though the mechanism of their action is not entirely understood it has been postulated that the antigen is retained longer at the injection site and provides a longer lasting stimulus, and that there is an enhancing effect of irritation and hence inflammation at the site of injection.

Little study has been made of host variations in relation to antibody production; there is some evidence of family and strain differences in experimental animals but these are difficult to estimate since individual responses followed a normal Gaussian curve of distribution. However, it is known that young animals are generally poor antibody producers but, except in certain cases, there is not adequate proof that immunization neonatally is ineffective and numerous studies have shown that effective immunization to certain diseases can be achieved in infants of 2 to 3 months provided they do not possess maternal antibody.

Artificially Increased Immunity:

Non-Specific: From a brief review, such as we have made, of these normal defence mechanisms it is obvious that adequate diet and good surroundings raise resistance to disease - but this does not really enter our present domain. However, there may be a possibility of increasing artificially the amount of
properdin, complement or opsonin in the blood or perhaps of enhancing the efficiency of phagocytosis. One never knows what the future holds and the development of biochemistry and bacteriology may reveal new approaches to the question of immunity and its applications.

**Specific:** At the moment we take the highway which follows the natural processes of actively acquired immunity; our methods and understanding have developed greatly from their earlier stages but even now there is much to be learned and the potentialities are not fully explored. Immunological procedures are more successful with some diseases than with others; their success tends to be greater in those diseases which are naturally followed by a high degree of immunity. Difficulty may be encountered in those diseases which are caused by more than one infectious agent or by different strains of this agent since only one of the antigenic types may be present in the vaccine (e.g. influenza). Immunization is generally more successful, too, in those diseases in which antibodies play a relatively important role.

There is no one method of preparing immunizing agents - the right one is found by trial and observation; for many reasons we wish to produce only those antibodies to an infectious agent which will aid in resistance - and we shall see later the various forms of antigen used to this end.

But the preparation of antigen is only a beginning. We must know the most efficient route of inoculation; we must also know
that a given immunological procedure is a success – this knowledge can only be gained by strictly controlled field trials on a large number of children divided into test and control groups. All possible means to randomize the conditions of the test i.e. to distribute the children between the two groups so that differences between these due to heterogeneity are kept to a minimum – are essential parts of a good experimental technique. We also want to have some correlation between resistance and antibody level in the individual; this may be done directly by titrating specific antibodies or using an indirect method and measuring rates e.g. in the Schick test. There must be accurate statistical analysis of data and the closest cooperation between field and laboratory; in most cases these observations will continue for a number of years and we shall see some examples later when we consider specific diseases.

The extent to which immunizing procedures will be adopted will usually depend on the prevalence and severity of the disease in question and in temperate climates mass immunization in childhood has been recommended or adopted against diptheria, tetanus, whooping cough, tuberculosis, smallpox and poliomyelitis; there are other diseases which it may be necessary to immunize against in certain situations.

In the light of what we have already reviewed, we shall first examine some of the more experimental and theoretical aspects of active and also passive immunization against these diseases, in childhood.
INDIVIDUAL DISEASES.

Diptheria:

The seriousness of this disease is due to the liberation of toxin and its effects on many organs. The organism is spread by droplets and is highly infective; the gravis and intermedius type of bacillus tend to be associated with a higher case fatality rate than the mitis type.

Before mass immunization was introduced the disease had an age incidence which was always highest in the pre-school child; it was uncommon in the first year of life, became increasingly frequent in the second year and had a maximum incidence between two and five years; the incidence tailed off after this until there was little probability of contracting the disease after the age of fifteen. Of the 5-10% of children who contracted diptheria in pre-immunization days there was a 7% case fatality. Others might have virulent diptheria bacilli in the throat and thus acted as "carriers". Nowadays, because of early immunization the incidence has shifted to the higher age - groups, and as many as 25% of cases are in adults.

Diagnosis of Susceptibility: The Schick test which consists of the intradermal injection of 0.2 ml. of standard toxin is of great aid in experiments e.g. measuring Schick conversion rates of various toxoids. For practical purposes, children under ten years are not usually tested; in adults and children over this age prophylaxis should not be carried out without a Schick test since those with a negative and pseudo-reaction may react severely to it. The best time for
reading results and avoiding false positives is on the fifth to seventh days. A positive reaction is uncommon with an antibody titre of 1/100 unit/ml or more and rare with 1/30 unit/ml or more. A negative reaction seldom occurs with less than 1/500 unit/ml. There is no doubt that a negatively reacting person is comparatively immune to all ordinary risks but this degree of immunity is far from absolute.

**Active Immunization: Choice of Prophylactic:** Though experiments had been performed on animals since the 1890's it was not until 1913 that Von Behring reported the successful use of toxin-antitoxin mixtures in children. It is now possible to treat toxin in such a way that it loses its poisonous properties but retains its antigenicity - the main preparations are Formol toxoid, Toxoid-antitoxin mixture (mainly displaced because it contains horse serum), Toxoid-antitoxin floccules (from which much non-specific protein and bacillary products have been eliminated), Alum precipitated toxoid (A.P.T.), Purified toxoid aluminium phosphate precipitated (P.T.A.P.).

Several careful studies have been made on the different types of diptheria prophylactic and it has been found that A.P.T. and P.T.A.P. in 2 doses of 0.2 ml. and 0.5 ml. spaced at four weeks or more gave an average Schick conversion rate of about 98% whereas with others this high rate may be approached but not equalled. A.P.T. and (latterly) P.T.A.P. are, indeed, considered largely responsible for the virtual disappearance of diptheria in this country between 1941 and
1951. However these tend to have undesirable side effects; the incidence of paralytic poliomyelitis after inoculation appears to be higher with the use of such adjuvants than with Formol toxoid alone, as we shall see in more detail later. Accordingly, further trials with Formol toxoid in children under two years, showed that the Schick conversion rate in those given two doses of 0.5 ml. at monthly intervals was 98% and in those given three such doses, so spaced, it was 99.4%. The addition of 20,000 million H. Pertussis organisms/ml. raised the Schick conversion rate of one dose of Formol toxoid from 50% to 95%; the addition of 5 L.f. Tetanus toxoid reduced this to 83%. Unfortunately the combination of Formol toxoid and Pertussis seems to be incriminated almost as much as A.P.T. alone in the provocation of poliomyelitis. Among these prophylactics Formol toxoid is now preferred by the Ministry of Health in London; the smaller risk of poliomyelitis is an advantage which is considered to outweigh that of somewhat decreased antigenicity and stability. Two standardised doses of loc. separated by at least four weeks are officially recommended for primary immunization; injections are given subcutaneously or intramuscularly.

**Age at Immunization:** Since the highest incidence of the disease is from two-five years primary immunization is recommended at between six and twelve months. Sometimes this is done earlier, mainly for the convenience of combining it with pertussis vaccine but if it is given too early it will not be as effective because of "neutralization" by maternally
transmitted antibodies. The body of opinion is now in favour of giving the first booster dose at 18 months and another at pre-school age. Dr. Bousfield experienced two severe allergic reactions when giving reinforcing doses of 0.5 ml. F.T. at school entry; he favours reinforcement with P.T.A.P. and A.T.P. in winter (when there is less danger of polio-provocation than in summer) and T.A.F. throughout the year.

**Protective Effect of Active Immunization:** A number of trials in different countries have demonstrated that prophylactic inoculation confers substantial immunity judging from the incidence of infection and case-fatality on exposure to natural infection. In this country in 1913 - of 1,097 children immunized - 4.8% contracted diphtheria; and of 3,275 non-immunized 15.1% contracted it. The following is a later example of good results:— in England and Wales 4,829,115 children under 15 years were immunized between 1940 and 1943 - the estimated child population under 15 years in 1943 being 8,583,000. Analysis of the 1943 returns showed the following annual rates of incidence per 1000 child years.

- a) in immunized children 1.16) a:b = 1: 3.5
- b) in non-immunized 4.06)

and annual rates of death per 1000 child years

- a) in immunized children 0.0104) a:b = 1: 26
- b) in non-immunized 0.260 )

These results show that, while diphtheria immunization did not always prevent a child getting the disease or even from dying as a result of it, it did substantially reduce both incidence and case-mortality.
The Results of Mass Immunization: There has been a precipitous fall in the death rate since the introduction of immunization. The death rate was, however, already declining before this which might indicate that other factors, such as a natural "change" in virulence were operating; but notifications of the disease from 1938-40 to 1949 fell by 91% and so it can be assumed that the decrease was largely due to the introduction of mass immunization. When comparisons of divergent results were made in some American cities it was found that when 50% of the 5-14 years age group was immunized there was no evidence of a fall of incidence in the community as a whole; but when 30% of the 1-5 years age group was immunized as well as the later groups, then there was a striking decline in the prevalence of the disease.

Passive Immunization: Antitoxic serum prepared commercially by the injection of horses with increasing doses of toxoid, and then "purified", is the best available method of treatment for diptheria and should be given as early as possible in the disease before the toxin has had time to injure the cells irreversibly ($\approx 50,000$ units). Passive immunization may be employed prophylactically to meet particular emergencies e.g. the introduction of an infected child into a children's ward. ($\approx 500-1000$ units).

Tetanus:

This disease results from contamination of a wound or raw surface with the tetanus bacillus, a spore-forming organism which germinates in the tissues and elaborates a
The death rate per 100,000 from diphtheria in New York and in England and Wales over the last fifty years. The arrows mark the year when immunization of 50% or more of children against diphtheria was first attained. [Burnet]

Diphtheria in England and Wales (immunization, incidence, deaths).

Symposium on immunization.
lethal toxin; this affects the anterior horn cells causing muscular spasm and convulsions.

It is comparatively uncommon in this country. There are no more than 200 cases a year in civilian practice and these are mostly in people of rural areas. It is very rare in children under five, increases during the years of "cowboys and indians" and decreases again between 20-30 years. The case fatality was 85% in pre-serum days; is now approximately 27%. In the tropics, where hygiene is more primitive the disease is more widespread and in French West Africa 80% of the deaths are neonatal.

No skin test of susceptibility and immunity is available.

Active Immunization: Choice of Prophylactic: Behring and Kitasato discovered that injection of filtered culture bacilli into an animal stimulated the production of antibody which could neutralize the toxin. Since then other prophylactics have been developed but plain fluid tetanus toxoid appears to be adequate.

The injection into man of two to three doses of toxoid at properly spaced intervals raises the antitoxin content of the blood in a few months to a level usually obtained with a prophylactic dose of antitoxin. Proof that the antitoxin level is raised on a later stimulating dose has been given by many experimenters; sometimes these titres reached levels 100 times higher than the primary ones though there were great variations; effective levels were maintained for a
longer period. The effect of simultaneous immunization with other antigens, for administrative convenience, is apparently not of much import with regard to tetanus antibody response.

**Dosage and Interval between Injections:** The usual method is to inject deep-subcutaneously or intramuscularly two doses of 1 ml. standardised toxoid separated by an interval of six weeks followed by a boosting dose of 1 ml. after twelve or eighteen months. In very young children these dosages may be halved. This results in a high level of antibody which does not reach the danger-line for some years — which for the purposes of civilian immunization, is usually taken as five years. Immunization is begun in childhood, with diptheria for convenience, and because of the high incidence at 5-14 years.

**Protective Effect of Active Immunization:** Almost all our knowledge was gained from studies made during the second world war. At the end of the 1914-18 war the incidence was 1/1000 casualties. In the British Liberation army in the 1939-45 war the incidence was 0.06/1000 casualties; of the six cases three were in those who were not actively immunized. These figures give undisputable proof of the efficacy of active immunization in the prevention of tetanus.

**Passive Immunization:** The antitoxin is prepared on the same lines as that against diptheria; it is used as a prophylactic in the case of contaminated wounds. Usually 1500 units are given into the subcutaneous tissues as soon as possible after injury. For treatment, 100,000 units intravenously repeated in one or two days, followed by 25,000 units weekly are administered.
**Protective Effect of Passive Immunization:** The effectiveness of tetanus antitoxin is best illustrated by figures from the 1914-18 war. Tetanic complications of wounds fell from 10 per 1000 wounds in the first six months to 1 per 1000 in the last year of the war.

**Whooping Cough:**

This is a highly infectious disease of the respiratory tract caused by Bordetella pertussis which is spread by droplets. It has an incubation period of 7-14 days which is followed by catarrhal and paroxysmal severe coughing phases. Complications are bronchopneumonia with segmental or lobar collapse, predisposing to bronchiectasis.

It is mainly a disease of infancy and childhood - 97% cases are in children under 10 years of age. Mainly 4/5 of all deaths however, are in children under 1 year and over half the deaths in children under 6 months - the case fatality in this age group being 1-2%. Only a small proportion of the cases occurred in this age group (1957). The disease is widespread; 95% of the world population is attacked by it, in some form, at some time in their lives. After the illness there is usually a lifelong immunity. There is no skin test of susceptibility and immunity.

**Active Immunization:** Much research has been expended on this disease in an attempt to produce a good vaccine. The development of vaccines is intimately related to experiments designed to define protective power and the two
will be considered concurrently here.

Protective power appears to be associated with the somatic antigen which was extracted by Cruickshank and Freeman and injected into mice; the mice later resisted a challenge with living, virulent organisms.

Clinical Trials: There have been many large scale trials in all parts of the world but the results conflicted a great deal. In some of the studies there was no control group and in others not enough care was taken to ensure that the treated and control groups were similar in every respect.

In 1942 the Medical Research Council began a series of investigations which were designed to assess the value of pertussis vaccines in protecting children against the disease and to determine whether their prophylactic value could be assessed by a laboratory test. Three trials were organised with pertussis vaccines prepared by different laboratories including vaccines of British and American origin. In all, 19 vaccines were used and 36,000 children inoculated and followed up. The best comparative index was the attack rate among children under 14 exposed to the risk of infection in their own homes. The results showed that protection varied from 87% attack rate (the worst) to 4% (the best). It was thus demonstrated that vaccination could produce a high degree of protection. The trial also proved that dip-pertussis vaccine was as effective as pertussis alone.

Pillemer's soluble antigenic fraction, which is closely
associated with the bacterial cell and is prepared by absorbing sonically disintegrated bacteria with human red cell stromata, was found to be antigenically more potent in these trials but had a higher incidence of side effects, both local and general. It has not, therefore, been adopted.

A British standard vaccine has been selected from one of the batches giving good protection in the field trial. This is a whole bacterial vaccine, strains of B. pertussis being selected for optimal growth properties; they are killed with a bactericide which does not destroy the antigens. By employing this standard in comparative mouse protection tests — by the intracerebral inoculation method — we should be able to ensure that vaccines used for immunization will produce substantial immunity but there have apparently been some striking exceptions and the comparison is not infallible.

**Dosage:** For Primary Vaccination 3 doses of 1 ml. (20,000 organisms) at four-weekly intervals, are recommended. It is better to lengthen the intervals if they cannot be rigidly adhered to than to shorten them.

**Age at Vaccination:** It is obvious that vaccination must be carried out as early as it is effective. In a recent study only 20% of cord blood samples showed measurable levels of pertussis agglutinin; we have already stated that little is known of the efficiency of the antibody forming apparatus in the very young. So far not much evidence has been produced for the protection of three doses given early. Bell found that two doses of alum containing vaccine protected children from 2–4
months and Bousfield and Holt have evidence that three doses of non-alum precipitated vaccine were effective in protecting children from 2-5 months. How long this effectiveness lasts cannot be sure; since there is a high incidence of the disease in later childhood - with attendant complications - it would seem a necessary safety measure to give a reinforcing dose again at about 1 year. Though Burnet in Preston suggests that another "booster" be given at 5 years it is probably wiser at this stage to let the child acquire a natural immunity. There are obviously still many unsolved problems in the practice of vaccination against whooping cough.

**Results of Mass Immunization:** In Britain the number of deaths due to pertussis fell from 4,401 in 1920 to 678 in 1940 in spite of increasing population. The total deaths fell from 678 in 1940 to 394 in 1950. The death rate is still markedly decreasing (see Table P.236).

It would appear that some change has been occurring in the behaviour of pertussis in the community and that we are enjoying a "trough" in the virulence of the organism. There are now longer gaps between epidemics. The fact that treatment was gradually improved has, no doubt, played a part in decreasing the severity of disease and immunization has helped, particularly latterly, in reducing the severity.

However the figures given for a decrease in incidence since 1953 have to be examined in a sceptical light. Two fallacies are probably inherent in them: a) the vaccine certainly modifies the disease so that it is often unrecognisable.
### Pertussis 1953-1957
Deaths by ages.

<table>
<thead>
<tr>
<th>Year</th>
<th>Less than 3 mos.</th>
<th>3-5 mos.</th>
<th>6-11 mos.</th>
<th>12-35 mos.</th>
<th>36 and more</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>54</td>
<td>54</td>
<td>59</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>1954</td>
<td>40</td>
<td>29</td>
<td>26</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>1955</td>
<td>20</td>
<td>23</td>
<td>17</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>1956</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>1957</td>
<td>22</td>
<td>23</td>
<td>23</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

1957 deaths as a % of annual average: 70 77 79 50 25 63.

### Pertussis 1953-1957
Cases notified by age

<table>
<thead>
<tr>
<th>Year</th>
<th>Less than 1</th>
<th>1-4</th>
<th>5-9</th>
<th>10 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>13,978</td>
<td>81,694</td>
<td>37,243</td>
<td>4,425</td>
</tr>
<tr>
<td>1954</td>
<td>9,438</td>
<td>52,448</td>
<td>40,003</td>
<td>3,656</td>
</tr>
<tr>
<td>1955</td>
<td>7,043</td>
<td>39,094</td>
<td>29,930</td>
<td>2,716</td>
</tr>
<tr>
<td>1956</td>
<td>8,466</td>
<td>43,720</td>
<td>30,551</td>
<td>3,416</td>
</tr>
<tr>
<td>1957</td>
<td>7,604</td>
<td>38,148</td>
<td>34,453</td>
<td>4,563</td>
</tr>
<tr>
<td>1953-57</td>
<td>48,579</td>
<td>255,104</td>
<td>198,179</td>
<td>18,776</td>
</tr>
</tbody>
</table>

1957 cases as a % of the annual average: 82 75 87 122.
b) notifications represent only a fraction (probably only 10%) of the cases of whooping cough.

**Tuberculosis:**

The primary infection in this disease, which is spread by droplets, usually occurs in the lung and in most people this and the associated glandular lesion heal and calcify. In a few, healing may be incomplete and, at some later date there may be a discharge of bacilli into the blood stream with the production of lesions in many body sites. Secondary infection may also be from an exogenous source. The human type bacillus is responsible for almost all cases of pulmonary tuberculosis; the bovine type causes an infection of lymph glands and bone in children; it enters in milk and infects via the intestine.

Tuberculosis spares neither age, sex, race or nation. There is a genuine difference in the susceptibility of different races to T.B. depending, to some extent, on the length of time they have been in contact with the disease. There appear also to be hereditary and genetic predispositions. Tuberculosis, though now declining, is still a major problem in adolescents and young adults. In 1958, 2,501 new cases were notified among those aged 15-19 years and 3,414 in those aged 20-24 years in England and Wales. Until recently a high rate of childhood infection has been the rule in most European countries but this is now much less frequent and many individuals are becoming infected for the first time in adult life.
Immunity in Tuberculosis: There is little doubt that as a result of tuberculous infection a specific immunity is developed but there is considerable dispute as to the mechanism responsible. The balance of evidence is in favour of the view that although the allergic reaction can contribute to resistance there is, in addition, a specific immunity which may be due to some as yet unrecognised form of humoral antibody. There is a "fixation" of organisms that occurs at the site of infection in the allergic subject; this prevents rapid lymphatic dissemination and enables the sensitized mononuclear cells to ingest and destroy the invading tubercle bacilli more quickly than in the non-allergic subject. This "sensitization" of the body cells allows us to determine whether or not an individual has been infected with tuberculosis.

The Tuberculin Test: Tuberculin, which has been extracted from the bacillus is injected intradermally into the forearm. Three tuberculin units (T.U.) are used; if the test is negative then the test is performed again with 100 T.U. A positive reaction is characterised by the development in 12-72 hours of an area of oedema and induration; if the diameter of this area is less than 5 mm. then the reaction is regarded as negative. In some countries sensitization to tuberculin may result from other infections but this is unimportant in Britain. This test is exceedingly important in differential diagnosis; it determines earlier than other procedures when bacilli have invaded the body and determines the effectiveness of control methods far earlier and more
accurately than other criteria. Vaccination should always be preceded by the tuberculin test except in the first two months of life as unpleasant Koch phenomena can occur in tuberculin positive people.

**Active Immunization:** **Prophylactic:** It used to be claimed that old tuberculin had protective value but this claim has no supporters nowadays. In 1906 Calmette and Guerin of the Pasteur Institute in Paris advocated the use of B.C.G. – a living attenuated variant of a bovine strain of the tubercle bacillus. It was first introduced in 1922 as a means of protecting infants born into tuberculous families. A vole bacillus vaccine has now also been prepared.

**Age at Vaccination:** B.C.G. can be given at any age but the incidence of troublesome complications in infants with the present intradermal method is higher than in older children. We have noted too that the problem of tuberculous infection of adolescents and young adults is of greater import, at least in this country; tuberculous infection of infants is rapidly declining and, while vaccination of this group is still practised in Scandinavia, the authorised scheme in Britain concentrates its energies on protecting 13 year old school children (and certain other special categories). The Symposium on Immunization (May 1959) advised vaccination at 10-earlier 15 years – at the stage fewer children will already have been infected and more could be protected during adolescence.

**Methods of Vaccination:** The various methods of intradermal inoculation are preferred now to the oral or subcutaneous
0.1 ml. vaccine of strength 0.5 to 1.0 mg/ml. is injected intradermally. The multiple puncture and scarification methods may also be used.

Protective Power of Vaccination: There has been much dispute as to the efficacy of B.C.G. in producing immunity to tuberculosis. The French results over the period 1922-23 appeared to show great decrease in mortality amongst vaccinated infants - but statistically there was much to be desired.

The Scandinavians claimed very encouraging results from the use of B.C.G. during the war and, indeed, later introduced compulsory mass immunization in childhood. This, they claim, has been largely responsible for the marked fall in incidence.

But the attitude in the U.S.A. has been more critical; an article "The Case against B.C.G." published in the British Medical Journal last year by a group of American doctors and professors, condemned the vaccine on many counts - they pointed out that in countries which have employed B.C.G. extensively, concomitant developments could equally well have been responsible for the fall. They also complained that the use of B.C.G. meant that the diagnostic and epidemiological value of Tuberculin Testing would be lost - a complaint which has been reiterated in many quarters. Among many other objections in a rather biased article they also considered that B.C.G. was not even safe. However, S.R. Rosenthal in the U.S.A., states that changes in the strain of B.C.G. are those tending to further attenuation rather than further virulence and he states furthermore "Of the numerous reports cited where
B.C.G. vaccination was part of an overall tuberculosis control programme and where the vaccinated and non-vaccinated groups were comparable it can be stated unequivocally that B.C.G. affords a decided protection against virulent super-infection."

There have been many other reports which gave "highly suggestive" evidence that B.C.G. reduced incidence and mortality but it was left to the Tuberculous Vaccines Clinical Trials Committee of The Medical Research Council to carry out a well controlled clinical trial of B.C.G.; this began in 1950.

The vaccine used in the trial was Danish liquid vaccine. The trial was rigorously controlled; it involved approximately 56,700 children in urban and suburban English areas aged between 14½-15 years at its commencement. Those with active T.B. were excluded; those with negative radiographs but positive tuberculin test were followed up along with tuberculin negative vaccinated and tuberculin negative unvaccinated (CONTROL) groups. Great efforts were made to avoid prejudice including the use of an independent assessor who, unaware of data on Tuberculin Testing and B.C.G., decided whether a disease which might possibly be T.B. was to be regarded as such. The highest incidence of tuberculosis in the observation period was in those tuberculin positive on entry which is not surprising since tuberculin sensitivity indicates that the disease is present even if there are no other observable manifestations. In the vaccinated group not only was the incidence of pulmonary T.B. greatly diminished but there was also some evidence that in the cases which did
occur it was less severe; the small numbers of cases of miliary T.B. and T.B. meningitis all occurred among unvaccinated individuals.

An estimation of the benefits of vaccination stated that "the percentage reduction in the incidence of tuberculosis, in the B.C.G. vaccinated group, compared with the incidence in those concurrently admitted to the negative unvaccinated group was 83% for the five year period following vaccination. It is possible to say that protection afforded by the vaccine in the tuberculin negative section of the population studied lay between 71% and 90%." The vole bacillus vaccine gave equally good protection but at present there is little suggestion that its use would confer any great advantage.

**Results of Mass Immunization:** Sutherland has estimated the reduction in incidence of T.B. in those 15-19 year olds which resulted from local authority vaccination schemes. In 1958 though the reduction in notifications was 241 this would have been 1,440 if all children eligible had been vaccinated.

**Smallpox:**

This viral disease is characterised by acute prostrating fever and headaches followed by a severe rash particularly on the face and hands. It is spread by droplet infection and has an incubation period of about 12 days.

The disease is of great antiquity, wide distribution and
affects both sexes at all ages. It is endemic in most tropical countries and from time to time Europe is infected by the importation of cases from these areas. There are two forms of the disease and both breed true. Variola Major has a case fatality of 10-30% and Variola Minor one of 0.25%.

Immunity to smallpox lasts for life after an attack.

**Active Immunization: Choice of Prophylactic:** Attenuated virus is still employed, as it was in Jenner's day. The virus is not a descendant of Jenner's cowpox but one more closely related to the smallpox virus i.e. the vaccinia virus. The method of preparation of vaccine lymph has remained unchanged in principle for the last seventy years; it is prepared from blisters of vaccinia rash on shaved areas of calf or sheep skin. Two other vaccines have been prepared, one by growth of the virus in a chick embryo tissue culture medium (Rivers, 1931), the other by cultivation on the chorio-allantoic membrane of the developing chick embryo. These were prepared to avoid the reactions sometimes occurring with calf lymph, to provide a bacteria-free product and because it was hoped to prepare a vaccine of more constant virulence. But they have not been given sufficient trial to assess their value realistically.

**Method of Administration:** Scarification is employed. Thirty or forty applications of the needle to the skin are made through a drop of lymph over an area \( \frac{1}{4}-\frac{1}{2} \)" diameter. A lesion develops - the more immunity present, the smaller and shorter lasting the reaction.
Age at Immunization: It is preferable to give primary vaccination between the ages of 1 and 4 years, - severe reactions are less common in this age group as we shall see later. The effect of vaccination appears to wear off with increasing age; in countries where smallpox is rife it is advisable to reinoculate every two years, but in other countries a five to ten year interval should suffice.

Protective Effect of Vaccination: It decreases the case fatality due to smallpox. The case fatality in 1901-4 in a group of hospitals showed that in the unvaccinated it was three times greater than in the vaccinated. Again, in 1921-26 of 4,406 cases of smallpox in vaccinated persons in England and Wales only three were under 12 years of age which is explicable on the hypothesis that vaccination in infancy confers a large measure of protection against the disease. These are randomly selected results - there are many more which prove the efficacy of the vaccine.

Results of Mass Immunization: The incidence of smallpox has become infinitesimal in the Western world. This is due both to improved living conditions, to strict enforcement of shipping regulations and to the prophylactic procedures outlined above.

Poliomyelitis:

This is a common virus disease which usually runs a mild course characterised by upper respiratory or gastro-intestinal symptoms. Occasionally the picture is complicated by invasion of the central nervous system. When this happens
there is wide dissemination of the virus throughout the neuraxis and flaccid paralysis of voluntary muscles resulting from destruction of motor neurons in the spinal cord.

There are three main antigenic types - Brunhilde, Lansing and Leon. The virus is spread by human contact though it is not clear what the nature of this contact is.

The disease is of world-wide distribution and occurs sporadically and epidemically. In the 1947 epidemic here, the attack rate was 18/100,000. Several people have estimated that, under endemic conditions there are something like 100 latent cases to every paralytic one. The case fatality of the declared disease is usually 10-15% and probably only 15-40% cases show residual paralysis.

In countries with a low level of sanitation the disease, mainly non-paralytic, is seen in infants and young children. In those with a high level of sanitation the infection is in the older age group because little subclinical immunization occurs in early life; because the incidence of paralysis increases with age the paralytic form is seen more frequently.

Immunity: On the whole the evidence is that a type specific immunity to central nervous system involvement develops as a result of exposure to infection; this is dependent, to a large extent, on the production of neutralizing antibodies. The level of antibody necessary for immunity is not known; there may not even be such a fixed level. After natural infection there is also an alimentary immunity which
may depend on the circulating antibody level but is suggested to be local.

**Immunization:** The preventive effects of gamma globulin against experimental and natural poliomyelitis was a strong indication that vaccination could be effective.

**Active Immunization:** There are two types of vaccine currently in use. We shall describe these separately.

**Killed vaccine:** Attempts were made as early as 1934 (Brodie) to produce a satisfactory killed vaccine. In 1953 Salk reported the first major field trial on children using a vaccine composed of a mixture of three types of formaldehyde inactivated virulent, poliomyelitis viruses grown on monkey kidney cells in tissue culture. This country is now employing Salk's vaccine but a less virulent strain (Brunenders) of the type I virus, than the original Maloney, is used. There is now a British Standard Poliomyelitis Antisera types 1, 2 and 3 (June 1959) and 10 units per ampoule (1 ml.) is the value assigned to each.

**Dosage and Administration:** At present, from antibody studies in children, adolescents and adults, it would appear that two primary doses of the vaccine - 1 ml. intramuscularly or subcutaneously with an interval of three to six weeks - establish a good antibody level. Though it is not known how long immunity lasts after primary vaccination a third reinforcing dose is usually given not less than seven months later.
Age at Immunization: Perkins, Yetts and Gaisford have contributed much experimental evidence on antibody levels in children. They found that, in only a small proportion of infants under ten weeks could a satisfactory antibody level be established by the injection of two doses of poliomyelitis vaccine - because of the inhibiting effect of maternal antibody and the necessity for highly potent antigenic stimuli in early infancy. They could not overcome these difficulties in one-week old infants but were able to show that in sixteen-week old infants a more satisfactory level followed primary immunization, with three doses though maternal antibody in some still inhibited the response to Type I. However, placentally transmitted antibody had decreased to non-inhibitory levels in almost all six-months and all nine-months infants tested. These workers recommended three doses at monthly intervals as the primary course at this age.

Protective Power of killed vaccine: In 1954 the Poliomyelitis vaccine Evaluation Centre (U.S.A.) carried out a controlled field trial on the Salk Vaccine. In the second part of this 200,000 volunteer children randomly allocated from the 1st-3rd grades of school were vaccinated; very nearly the same number received "placebos". It was calculated that the vaccine was 72% effective against paralytic disease; at worst the true protectiveness was unlikely to be less than 61%. Other trials in the U.S.A. demonstrated a similar effectiveness. In Britain an assessment was made on paralytic polio occurring among about 150,000 children from
1½-9 years who received vaccine compared with that in 1,500,000 children of the same age who received none. The apparent protection was 84% in the 5½-9½ years group and 80% in the younger group. But, because the number of cases was so small the true degree of protection could have been only 39% in the younger and only 6% in the older. Further trials may need to be instituted.

It is important to note that vaccination with killed virus vaccine does not prevent natural infection of the alimentary canal with polio viruses.

Results of Mass Immunization: Despite the widespread use of the vaccine there have been several substantial outbreaks of poliomyelitis especially in the U.S.A. Apparently the paralytic rate in 1956 and 1959 was almost the same. This has been blamed on faults in the immunization programmes. As usual time will tell.

Live Vaccine: Even before the results of the Salk vaccine tests were available, some workers were advocating the development of attenuated live virus vaccines, the intention being to give it by mouth to children so that it would induce an immunizing infection of the intestinal tissues without risk of paralysis—a less equivalent to the normal process.

Each type of virus is separately prepared and, after serial passage in monkeys, hamsters and/or chick embryos or chick tissue culture it is plaqued out on monkey-kidney tissue cultures. Specific production and testing standards for it
have not yet been established. Much work on this aspect is in progress in the Lederle laboratories.

**Field Trials:** Large and small scale trials have been carried out all over the world to gather knowledge both as to the efficacy of the vaccine and to its safety.

It has been found by Sabin and confirmed by workers in the U.S.S.R. that antibody response to the feeding of live virus depends on the dose, strain and extent of multiplication in the intestinal tract; the persistence of antibody is not dependent on the titre achieved and the resistance of the alimentary tract is not related to the level of antibody, being present even in its absence, in some cases. Sabin also found that the neurotropism of the virus excreted in the stools was increased but this increase was small even, as Smorodintseff has shown, after serial passage through a number of children. It is also known that the vaccine virus spreads to others by natural means.

In the U.S.S.R. thousands of children have been fed with Sabin's vaccines of all three types. By the end of July 1959 it was estimated that six million had been vaccinated. Svonranek in Czechoslovakia had fed vaccine to 150,000 by the end of June. Safety of the vaccine is being judged chiefly by the overall incidence of polio in the populations concerned - and these workers are convinced that it is very safe. Live vaccines made by Lederle Laboratories have been given to hundreds of thousands in Central and South America and reports of large trials of Sabin's or Lederle's vaccines are coming in
from Mexico, Costa Rica, Poland, Finland and Africa. So far, the protective effect has not been estimated though there is presumptive evidence that this may be high.

In August 1958 an epidemic of polio due to type 1 virus began in Singapore. Eleven or twelve weeks after the first cases had been reported vaccination with Sabin's type 2 vaccine was begun. It was believed that the presence of type 2 virus in the alimentary tract would interfere with the establishment of type 1 virus causing the infection and it was hoped that the type 2 would invoke heterologous protection against type 1. 198,965 children received the oral vaccine and 6 of these developed the disease; of 300,000 unvaccinated, 17 developed it; taking the results at face value it can be claimed that vaccination with type 2 gave substantial protection against an epidemic of type 1 strain.

So far there has been little published work in Britain.

Other Diseases:

**Measles:** This is a highly infectious viral disease which spreads by droplets causing a generalised infection with clinical evidence mainly in respiratory tract, skin, mouth and conjunctivae. It is a serious disease in very young and debilitated children; fatalities are usually due to secondary bronchopneumonia to which it strongly predisposes; another important complication is meningoencephalitis. Children between three and five years are mainly affected. Immunity to measles lasts for life and a mother who has had the disease
confers passive immunity on the infant which lasts for six months.

**Immunisation:** The imminent introduction of vaccination against measles seems assured. Passive immunization is employed in the prevention of measles in certain groups of exposed children. These are

1) infants less than six months whose mothers have not had the disease.

2) children under four years ill with other diseases particularly T.B., rheumatic fever or otherwise in poor physical condition and healthy children of this age whose siblings are ill with other diseases.

3) when it is considered necessary to abort an epidemic. This protection is accomplished by giving children 0.12 ml. of 12.5% (per lb. of body weight), of gamma globulin prepared from pooled human plasma which contains antibodies to the virus. It must be given within five days of contact.

Successful prevention means that no active immunity results in the protected child; if a protective dose is not indicated then a "modifying" dose (0.028 ml. of 12.5% solution per lb. body weight) is given to children under four years and to those over four years in poor physical condition. In this way, a mild attack of measles is allowed to develop, the child produces antibodies and active immunity results.

**Mumps:** The administration of convalescent serum or gamma globulin prepared from such serum to contacts gives some
degree of protection - it is claimed that, if given early, it diminishes considerably the risk of developing orchitis as a complication.

**Influenza:** Vaccines have been developed and trials carried out; the difficulty here is that one does not know the variant which may cause the next epidemic. However, trials have shown that the corresponding vaccine does reduce incidence in an epidemic. As far as children are concerned the immunization of community groups e.g. in boarding schools may be useful; it is unlikely that mass immunization is a prospect of the near future.

**Worms:** Human infestation by helminths is world wide. Previously the problem has been tackled mainly with drugs and better sanitation. But hopes are now held out that immunization is a possibility. Workers at the Glasgow Veterinary School have been able to immunize calves against husk with oral doses of irradiated larvae. They have also shown that it is possible to immunize against the stomach worm of sheep and a hookworm of the dog. If this method of using irradiated larvae could be extended to man it would be extremely useful; by blocking the original penetration or attachment of the larvae the number of carriers could be reduced and the general health of the community improved. There is an interesting challenge here to the enterprise of the immunologist.
Complications:

Provocation poliomyelitis: A Medical Research Council Committee sponsored a large investigation of this problem in Great Britain and on the basis of information during 1951-54 confirmed observations of earlier workers that sometimes there was an association between the site of injection and the limb paralysed in children who developed poliomyelitis within four weeks of inoculation with immunizing agents. Taking all prophylactics together there was one associated case of polio for every 37,000 inoculations given. The rate was different for different antigens (please see Table 7). The mixed-antigens-with-alum prophylactic was the most dangerous but it is really impossible to point out a significant difference between mixed-without-alum, P.T.A.P. and A.P.T. Pertussis Vaccine, F.T. and T.A.F. were the safest. Dr. Cockburn has shown that in a further study by the Epidemiological Research Laboratory the same picture was coming to light; mixed diphtheria and pertussis without alum was no better than mixed with alum. Studies in Canada where alum free diphtheria-pertussis-tetanus is used failed to show an association with poliomyelitis. It must be noted that, although the M.R.C. rates are based on experience of three million inoculations the provocation rates were quite small and the total number of children developing paralysis within 1-28 days of injection was only 68; divided into separate prophylactics it can be seen that the numbers were far too
### Paralytic Poliomyelitis After Inoculation

E. B. Clinics in England and Wales

1951 and 1953

<table>
<thead>
<tr>
<th>Prophylactics</th>
<th>Rates 1/00,000 per month</th>
<th>Incidence to produce one case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed with alum</td>
<td>4.0 days</td>
<td>6.7 days</td>
</tr>
<tr>
<td>Mixed without alum</td>
<td>6.0 days</td>
<td>5.2 days</td>
</tr>
<tr>
<td>P.T.A.P.</td>
<td>6.0 days</td>
<td>4.7 days</td>
</tr>
<tr>
<td>A.T.</td>
<td>3.4 days</td>
<td>2.1 days</td>
</tr>
<tr>
<td>Pertussis vaccine</td>
<td>1.9 days</td>
<td>0.6 days</td>
</tr>
<tr>
<td>F.T. and T.A.F.</td>
<td>1.4 days</td>
<td>0.1 days</td>
</tr>
<tr>
<td><strong>ALL PROPHYLACTICS</strong></td>
<td><strong>4.0 days</strong></td>
<td><strong>2.7 days</strong></td>
</tr>
</tbody>
</table>

### Provocation Poliomyelitis

Rate per 100,000 inoculations. E.B. Clinics 1951-1953

![Graph](image-url)
small to give precise estimates of the risk involved.

The most characteristic pattern in cases with provocation polio was complete paralysis of muscles around the shoulder, slightly less severe for the elbow region and less severe again for the wrist and finger movement. The mechanism of action may be that local trauma induces vascular changes in the corresponding part of the spinal cord which increase the permeability of the blood-brain barrier and facilitate entry of virus into the cord direct; it may be that virus damages the motor nerve endings at the site of injection – or it may even be a local hypersensitivity reaction.

Hazards of Whooping Cough Vaccination: Encephalopathy. Reports on convulsions and coma sometimes going on to hemiplegia, severe mental deterioration and death have totalled 100 (7 in Great Britain) up to May 1959. It was not possible to calculate the risk; however, it is clear that it is very small indeed. Febrile Convulsions, have also been associated with the vaccine.

Sometimes B.C.G. can cause a regional suppurative adenitis.

Hazards of Smallpox Vaccination: Complications occur less often on revaccination than on primary vaccination at every age. The risk of encephalitis and generalised vaccinia was lowest in the 1-4 years age group and rose with increasing years. In 1951-5 in Britain some rates of generalised vaccinia were: 51/million procedures with 5 deaths in children below one year, and 23/million procedures with no
deaths in children one to four years of age. For post-
vaccinal encephalitis the corresponding rates were 15.8/million with 8.7 deaths in children under one year and 2.1/million with no deaths for the one to four age group.

Generalised vaccinia is serious. Persons with chronic skin lesions are the most susceptible. It varies from a mild rash to severe variola disease and rapid death. Post-
vaccinial encephalomyelitis may be caused by some latent infection with a neurotropic virus which is stimulated into activity by vaccination; the latest theory (Hurst and Fairbrother) is that it is an allergic manifestation and this has some experimental support.

Other reactions are suppuration - one of the commonest, and tetanus - one of the most serious. Because calf lymph is used the introduction of micro-organisms in very small amounts is inevitable but it is very difficult to say how often calf lymph and how often uncleanliness of the operator or the person vaccinated is responsible. Tetanus is never a complication in those who leave the scarified area uncovered.

When vaccinating against influenza or any other egg-
prepared vaccine, enquiries must be made about any history of hypersensitivity to egg because reactions can occur.

Sometimes on polio vaccination penicillin reactions are encountered - the vaccine contains traces of penicillin and streptomycin which are incorporated as bactericidal agents. These reactions are rarely serious.
Serum Hepatitis: Between two and five months after inoculation with a syringe or needle that has been used previously for someone else without subsequent sterilisation, a person may develop virus hepatitis; this virus apparently exists in the blood of a number of people without clinical manifestations and can be transmitted to a needle and syringe on inoculation. The hepatitis induced can be fatal or can leave serious liver damage and there is no specific remedy. Though the incidence of the disease is unknown it is probably very small; the connection has not been explored too deeply partly because prophylactic immunization may be discredited and litigation encouraged.

Non-specific: Other non-specific bacterial or viral reactions may occur due to negligence in the technique of the operator.

Precautions:

Careful asepsis must be observed all the time during immunization procedures.

Syringe Sterilisation: It is seemingly quite common practice in some centres to fit a clean sterile needle for each patient to a syringe used for a much greater number. Evans and Spooner have shown that aspiration of tissue fluids from a needle into the nozzle of a syringe can contaminate the whole contents of the syringe. It was advised at the Symposium in May 1959 that a separate syringe and needle should be provided for each person. This involves slightly
greater cost (6d. for each syringe and needle) and more work. In France this is law.

sterile syringe i.e. one free from all contaminating micro-organisms, spores or otherwise can be obtained by a) boiling in water. This is preferred in General Practice but it has many disadvantages. The World Health Organisation recommends at least ten minutes boiling as a safeguard against serum hepatitis; but even at its best boiling does not kill all spores. In practice other disadvantages are encountered — often the time is not rigidly adhered to, syringes and needles often not cleaned properly and not assembled by full non-touch technique, keeping them sterile for future use is difficult and inconvenient. b) Autoclaving (120°C for ½ hour). In this case syringes cannot be fully assembled or lubricated if sterilisation is to be guaranteed. In practice faults arise through packing in such a way that steam cannot reach all the syringes. c) Dry Heat—oven (160°C for 1 hour). This method permits the sterilisation of fully assembled lubricated syringes which can be sealed in a container and stored for future use. Sometimes faults arise from uneven heating in the oven or, again, from bad packing of syringes.

The latter method is considered the most reliable. In some cities (including Edinburgh) there is a central syringe service using dry heat. But disposable plastic syringes are now also being employed in Edinburgh and a few other centres. These syringes — 2 ml. capacity — cost 3½d. and the needles
lid. each. They are provided sterile in transparent plastic coats. They are proving their worth and may replace the all-glass syringe in the near future - that is, in Public Health Departments. But such facilities are not available for every doctor engaged in immunizing procedures; one can only hope that the doctor concerned will see to it that the facilities he does command, are used to best advantage, whatever they are.

**Inoculation Techniques:** This has been fully described by H.J. Parish. Only the main points will be outlined here. The hands of the operator must be thoroughly clean and the site of injection prepared with swabs soaked in methylated spirit; it is then painted with iodine and should be dry before puncture is made. The label on the ampoule should be read; after dislodging liquid in the neck it is filed open - the neck must previously be "sterilised" with alcohol. If a rubber-capped bottle contains the vaccine this cap must be sterilised too before plunging the needle in. Different routes of injection are employed as we have noted throughout, but there is not space to describe them here.

**Immunization Programmes:**

Obviously there are many procedures to be carried out and a generally applicable programme is required. In any mass immunization programme we are aiming to immunize as many infants as possible against diptheria, tetanus, whooping cough, polio and smallpox - and tuberculosis in later childhood. We want to give the injections at the optimum age taking into
consideration all the factors influencing our choice of an optimum age, and we want to give the injections in the form least likely to injure the child and to maintain immunity indefinitely.

Many immunisation programmes are in existence in different countries and in different parts of this country, but, judging from correspondence in The British Medical Journal, particularly that in the early months of 1959, there was much doubt and confusion among Medical Officers and General Practitioners as to what was the best approach. Accordingly, at a Symposium on Childhood Immunization in May 1959 two programmes were carefully prepared after much discussion. These are suggested as alternatives.

<table>
<thead>
<tr>
<th>Programmes:</th>
<th>Age (weeks)</th>
<th>Visit</th>
<th>Vaccine</th>
<th>Injection Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>3</td>
<td>1</td>
<td>OPV</td>
<td>4 weeks or more</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>2</td>
<td>Poliomyelitis</td>
<td>4 weeks or more</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3</td>
<td>Diph. and Tetanus</td>
<td>Same Visit</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>4</td>
<td>OPV</td>
<td>Same Visit</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5</td>
<td>Diph. and Tetanus</td>
<td>Same Visit</td>
</tr>
<tr>
<td></td>
<td>9-10</td>
<td>6</td>
<td>Smallpox</td>
<td>Same Visit</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>7</td>
<td>Diph. and Tetanus</td>
<td>Same Visit</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>8</td>
<td>Smallpox</td>
<td>Same Visit</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>9</td>
<td>B.C.G.</td>
<td></td>
</tr>
</tbody>
</table>

| B.          | 2-3         | 1     | Diph.   | 4 weeks or more   |
|             | 4-5         | 2     | OPV     | 4 weeks or more   |
|             | 6           | 3     | Poliomyelitis | 4 weeks or more |
|             | 7           | 4     | Diph. and Tetanus | Same Visit |
|             | 8           | 5     | Smallpox | Same Visit       |
|             | 9-10        | 6     | Diph. and Tetanus | Same Visit |
|             | 11          | 7     | Diph. and Tetanus | Same Visit |
|             | 12          | 8     | Smallpox | Same Visit       |
|             | 13          | 9     | B.C.G.  |                   |

There is no doubt that a full dose of polio vaccine will be necessary, but the exact timing of this dose has not yet been decided.
The difference between them is that triple or mixed antigens are advised in one and separate antigens in the other. Scientifically the ideal scheme must be Scheme A for at once we have avoided the risk of polio which we have seen to be inherent in the combined vaccines; this scheme also allows us more leeway in choosing the optimal age for each separate immunizing agent.

The question of combined vaccines arises out of a number of considerations a) to reduce the attendances. In fact the use of Scheme B only reduces attendances from eight to six in the first 2 years. b) to prevent the child acquiring injection terror. The number of injections falls from 10 to 7 in the first two years, by the use of Scheme B.

Dr. Kelman of Perth commented on what might be a baby's attitude to immunization –

"I was only born six months ago
But I wish I hadnae come
Its been naethin' but injections
Since I parted from my mum."

We do not profess to know anything of child psychology and we do not know how much mental trauma injections inflict on a child but it seems to have been rather exaggerated and there have been one or two slightly hysterical letters, mainly from women doctors, published in the B.M.J. on the subject of a child's sufferings at the hands of medicals. It is more likely that the mother "feels" the injection more than the child and it is even more likely, in the majority of cases, that a mother is more influenced by the number of attendances.
It is left to the Local Authority or General Practitioner to decide whether the increase in practicability of Scheme B makes it socially more desirable than Scheme A. The opinions are varied.

Edinburgh's Public Health stopped using Triple Antigen in 1957 because of its alleged dangers. The department now feels that there is a definite tendency for mothers to miss out the later injections and wonders if it was altogether wise to abandon triple antigen. One of our main aims, that of maintaining immunity indefinitely, may thus be thwarted.

At the moment, research into quadruple antigen (Diptheria, Tetanus, Pertussis and Polio) is continuing. This is used in some countries already. Its advantages are that it cuts down the number of attendances yet again and helps to ensure protection against diptheria and tetanus which are "less popular" measures than those for polio and whooping cough. The quadruple antigen given at 3 and 6 months produces good antibody levels for diptheria, tetanus and pertussis but is not reliable in protecting against polio. Though its polio-myelitis antigenic potency may be improved, it seems unlikely in spite of its practical advantages, and in view of the cloud over triple antigen, that it will be accepted here.

A suggested Schedule for areas with inadequate medical services - to be modified to suit local conditions was outlined at a W.H.O. Symposium in Rabat 1959.

3-6 months. Small pox + 1st triple vaccine + alum
2nd dose triple 1-3 months after.
5-6 years: Booster dose diptheria-tetanus vaccine
Smallpox revaccination.

Administrative Problems:

Publicity: Though we have indisputable proof of the
efficacy of immunizing procedures we are no further ahead unless
we can also convince the public; a great deal of responsibility
for this publicity rests on the Regional Public Health
Departments and much of it is carried out personally by the
Health Visitor who is employed by the Public Health. Each
visitor is assigned a specific area in the city and, among
other duties, it is her responsibility to explain to a young
(or old!) and possibly ignorant mother the benefits of
immunization, the best age for it and where to go to have
it done. The Health Visitor, usually a public spirited
individual, who does not need any bullying, is made to feel a
sense of personal responsibility; the Public Health
Department is quick to remind her, or him, if a particular
child in her area has not been immunized.

When the father of the child registers its birth he
receives a letter from the department. This explains to him
the need for vaccination and tells him where he should take
the child. It also informs him that he does not have to pay
for it! Dissemination of knowledge is aided by the offering
of free lectures and films to youth and church groups and other
societies. Occasional advertisements appear in the press and
large, colourful notices advocating immunization are displayed
in prominent places - e.g. in public transport vehicles and
dance halls. The department here has even gone to the length of visiting that hive of entertainment the "Palais de Danse" and explaining to some of the teenagers there why they should be immunized against poliomyelitis.

Of course the family doctor can probably do more than anybody to influence his patients on such an important matter as this; many people will listen with more respect and attention to what their family doctor might advise. It is important that the public should have an idea of the possible hazards and limitations of immunization as well as the potential benefits.

Organisation:

Usually the Central Health Authority is responsible for large-scale organisation and the local authority executes its plans. The actual immunization procedure is nearly always done by a physician, either a General Practitioner or one attached to the Local Authority, or by a trained nurse under a physician. The Symposium in Rabat suggested that it might be useful to train auxiliaries who could take over a large part of the injecting; this sounds a very sensible idea for areas where the medical personnel are over-burdened and understaffed; it might meet with substantial resistance in this country, where things work quite smoothly at present and where there is no real need for others to do the doctor's work.

It has been advised that a Central Advisory Body be set up to examine problems requiring further study and "so ensure reasonable uniformity of immunization schedules". This body
might report on such aspects as for example whooping cough antigens, quadruple antigens and changes in the epidemiological characteristics of a disease, such as tuberculosis.

**Recording:** A system of collective and personal recording of inoculations is desirable. Collective recording enables an estimate to be made of the success of publicity, organisation and immunization programmes, from the number of children immunized. In most places the Local Authority keeps the record cards for each child and, when the inoculation is performed by the General Practitioner he receives 5/- (per child) for informing the Public Health of completed procedures. Doctors, as a rule, also make records for their own reference.

Various suggestions on personal recording have been forwarded. Such readily available records of previous inoculations may be of help in making a diagnosis and may obviate unnecessary inoculations. People are usually vague about previous procedures and it has been known for a child actively immunized against tetanus to be given a dose of antitoxin, which caused a dangerous serum-sensitivity anaphylactic reaction. This antitoxin need not have been given if it had been known that the child was already immune. Numerous other cases could be cited. The Tattooing of a "T" on the ileal region to denote active protection against tetanus was suggested at the Symposium in May - this could be extremely useful but there then enters the question of when the last recall injection was given and therefore whether an adequate degree of immunity is actually present. Dr. Parish has suggested the use of three metal discs; a "motto" could
be engraved on the outer two faces and the necessary data engraved on the inner four faces. These discs could be attached to wrist bands or to a key ring - or any other article, which is easy to carry. Other suggestions have included one advocating the use of a locket but boys are likely to object to this and girls usually find something prettier to hang around their necks. Though cards have been used these are liable to become frayed and torn and some form of more permanent record is preferable. Doctor Parish's discs seem to be the neatest and most acceptable.

Cost and Legislation: In this country the National Health Service pays for these immunization procedures. In some countries they are paid for by central or local authorities and in others by the individual.

No immunization procedure is compulsory in the United Kingdom but in most other countries smallpox vaccination is compulsory and in some diptheria and tetanus are also compulsory. In Norway and in France B.C.G. is compulsory and in these countries typhoid, paratyphoid and typhus are compulsory for certain susceptible groups.

Britain has always hesitated to introduce legislation into such an area as immunization in childhood, mainly on the grounds that it is not democratic. One wonders, especially when Scandinavian countries which are by no means undemocratic have enforced immunization against some diseases in childhood, whether this is really a cogent argument; does it;avour too much of state control to give the child a valuable start
in life, in the face of ignorant, lazy or unwilling parents. When the experience of countless immunologists, bacteriologists etc. is considered for a moment one would think that such legislation could be nothing but democratic; why go half measures in something which does not (except in a very few cases) infringe on deep moral convictions; the minority who do object morally however unreasonable they may appear would be allowed to exert their democratic rights. Of course it would really be ideal not to enforce these procedures and yet be able to guarantee a high level of immunization in the community.
COMMENTS AND CONCLUSIONS.

Although we have been free from significant diptheria for many years in this country and have accepted that this is due in large part to our programmes of active immunization we must beware of complacency. To keep herd immunity at such a high level it has been calculated that 70% of school and pre-school children must be immunized and kept immune by reinforcing injections. The situation now is that some children are being given primary immunization but that less are being given booster doses because of general apathy on the part of the public and even some of the medical profession. In Edinburgh 51% of children under five years were primarily immunized against diptheria and (no figures available) considerably less were given reinforcing doses. Here, at least, we are not near the 70% target. One of the results of mass immunization is that we have more immune children and a shift of susceptibility to adults; we may expect and indeed experience sporadic outbreaks of the disease in the present situation and it may degenerate markedly should a particularly virulent strain of gravis enter the community. Britain is still a centre of world traffic and cases, in some instances with high fatality, are still arising in many countries including Germany, Italy and the Union of South Africa. The large number of non-immunes means that the bacillus will spread rapidly from a few infected persons and a catastrophic situation might arise. Even those we consider at the moment to possess a good immunity may succumb; Professor O'Meara of Dublin has said that the present prophylactics are
incomplete, although possibly adequate, for protection against current strains. He states that current prophylactics contain substance A but not enough substance B, which is responsible for most of the toxaemia in hypertoxic cases of diphtheria. All these remarks point to the one conclusion that even though our methods are not foolproof we should employ active immunization to the hilt as the most potent weapon possessed by Preventive Medicine against the disease.

There are many objections to the present routine method of passive immunization against tetanus. It has been estimated that \( \frac{3}{4} - 1 \) million doses of antitoxin are given annually with some thousands of attacks of serum sickness. 16 deaths due to antitoxin reactions have been notified from 1945-57. Another potent reason for the use of toxoid is that many fatal cases of tetanus result from wounds which have not been regarded, either by patient or doctor, as serious enough. Moynihan (1956) estimated that in 15% of cases of tetanus the original injury was trivial while in 35% it was unknown, so that even the most efficient use of antitoxin would only prevent half the cases and maybe even less because the formation of antihorse serum antibody after one administration could "mop" up antitoxin given subsequently. Passive immunization usually gives protection for only one week. There is good reason to suppose that immunity is greater for a given blood level of antitoxin in the actively immunized than in passively immunized persons, probably due to better distribution of antitoxin in the actively immunized animal and
to the fact that the antibody mechanism has "learned" to make antibodies so that further antigenic stimulus increases the level of circulating antitoxin. Dr. Edsall has said that in those in whom a protective level of antibody is not considered to be present a booster dose of toxoid would induce a marked rise in circulating antitoxin in 4–6 days which would prevent all but the most fulminating cases of tetanus. However toxoid is not totally reliable. Cases have occurred in the actively immunized and, if there was any delay in treating an injured person who has an inadequate antitoxin titre, then antitoxic immunization must be employed.

One survey showed that only about 1/5th of the population studied had already been actively immunized mostly in the Forces and, since National Service is ceasing, our reservoir of actively immunized will decrease. The case for the routine active immunization of children in areas where incidence may be low must be weighed against the advantages and disadvantages of antitoxin prophylaxis and against the disadvantages, which is very slight, of imposing one more injection on the child or risking decreasing the effectiveness of other antigens when mixed with these — again not of much import. It has been generally concluded, that active immunization of all children against tetanus is the goal in our community but probably a 100% immunization could only be achieved through legislation. At present there is a tendency for doctors to "play-safe", administering antitoxin in cases of doubt; this is because of the small numbers of actively immunized and because of the lack of a method of portable recording.
It remains to be seen whether or not it will be necessary to vaccinate children against whooping cough, earlier than was recommended in the schedule - the decision will likely devolve on whether or not the disease disappears from the community or merely becomes modified, so that cases shed virulent bacilli into the environment, exposing the neonatal child to great risk; it will also be taken in the light of further investigations on antigens and their immunizing efficacy in the very young. If, of course, the incidence falls to a low level then the occurrence of even one or two cases of encephalopathy might well turn the general opinion against vaccination.

In assessing the value of B.C.G. in the community we have to consider the risk of infection after vaccination and the proportion of children who will already have been infected by the time vaccination is offered to them. I. Sutherland has estimated the value of B.C.G. at the present day in England and Wales and found that the percentage of preventable cases in 15-19 year olds, if all who had been tuberculin negative at the age of 14 had been vaccinated, dropped from 60% to 52% between 1953 and 1958. The scope for B.C.G. will decline as the risk of exposure decreases and apparently B.C.G. vaccination of all tuberculin negative 14 year olds will reduce the incidence of tuberculosis in the next five years by less than 50% - there may soon come a time when mass vaccination of school children will prevent only a few cases of tuberculosis. The tuberculin positive proportion of 13
year olds is diminishing each year. We already noted, under "Results of Mass Immunization" that the number of cases prevented should have been six times greater than the actual number and this has been blamed on the Local Authorities who are either inefficient or still unconvinced, even after the M.R.C. trials.

B.C.G. vaccination will not eradicate tuberculosis though it has been very effective in Scandinavia and is a weapon of which every advantage should be taken; it is and has been used in conjunction with methods of hygiene and improved sanitation and, particularly in the last ten years, with new chemotherapeutic measures.

The case for early vaccination against smallpox and frequent revaccination in countries where it is endemic is obvious. The situation is, and has been more difficult in Western Countries. At one time vaccination was compulsory in Britain; nowadays the value of vaccination must be measured against the side reactions and the degree of supposed risk. During the ten years 1948-1957 there have been 26 deaths from smallpox and 34 attributed to the vaccine in England. However apparently only 20-40% of children are vaccinated in infancy now, and it is possible for an un-immunized community to develop under such conditions - introduction of virulent viruses into the population may have serious consequences; this latter event is more probable today with the increase and development of air transport; it is easier, in spite of stringent port regulations, for individuals
incubating the infection to gain entrance to the country. Several such outbreaks have occurred and the disease developed in persons not vaccinated for some time, the fatal cases being mainly in those not previously vaccinated; whenever the scare of smallpox is around, people converge in masses on the clinics and on their doctors - many of them demanding primary vaccination at an age when there is considerable risk. The balance appears to swing definitely in the direction of employing vaccination in the 1 to 4 years age group and maintaining this immunity by revaccination when necessary.

The argument against poliomyelitis live virus vaccine is cogent if its prophylactic efficiency is unknown; if the vaccine were known to be highly effective there would be little argument. On the other hand we do not know whether naturally occurring strains alter their neurotropism in the field; the genetic behaviour of polio virus is not yet perfectly understood nor is its natural history. If living attenuated virus can be guaranteed to remain safe in spite of its passage through a series of human intestines, then the fact that it can pass by natural means to contacts may be a useful characteristic in increasing the number of artificially immunized people without their knowledge or even their consent. Because of "Medical Ethics" disapproval of the vaccine has been expressed since compulsory vaccination plays no part in the control of infectious disease in this country at the present day. However, the fact that there is alimentary resistance to reinfection with attenuated virus vaccines gives hope that a similar resistance to virulent virus might be produced;
and this vaccine might also be used to stop an actual or
threatened epidemic, as we have seen. Of course it may be
possible to control an epidemic with inactive virus vaccines -
as Dane, Dick et al have shown using single large doses in
cynomologous monkeys. In spite of its effectiveness formolized
vaccine also has its drawbacks. It produces little, if any,
immunity to alimentary infection, so that vaccinated people
are as effective sources of infection to their associates as
are the unvaccinated, and because we are unlikely to reduce the
reservoir of poliovirus in the community the programme would
have to be maintained indefinitely. The vaccine probably
does not give a very durable immunity unless vaccination
is repeated often and, added to this, it has been estimated
that it is more expensive to make and administer on a large
scale than is the live virus vaccine. If the large scale
trials of live virus vaccine fulfil their promise and are
associated with a substantial fall in the incidence of polio,
then there must be a careful appraisal of the merits and
demerits of both killed and live (Cox, Sabin or Koprowski) in
this country. This appraisal will include further
investigation of the already mentioned gaps in our knowledge
and of the antigenic effectiveness of live vaccine at
different ages, dosage and persistence of immunity.

Because the percentage of paralytic polio increases with
age and because children do not acquire subclinical immunity
in a society such as ours there is an obvious need for
immunization in childhood - with whatever vaccine. The
problem of paralytic polio is not one of numbers and our aim
is to produce a high level of herd immunity to protect the few. Perhaps, in the future, when host factors and virus behaviour are better understood, we may be able to control the spread of the disease in the community and in the individual in some other way.

While we have chosen to study this subject from the standpoint of patterns of disease in "civilized" countries many of the procedures we have outlined are in use in less civilized areas. Smallpox springs immediately to mind but diphtheria, tetanus and pertussis antigens are employed in places. B.C.G. is coming into use and may be given at an earlier age than it is here because the epidemiological situation means that infection occurs earlier; since the child population of tropical countries has a high level of subclinical immunity against polio, mass immunization is largely a luxury. In general, other preventive procedures such as yellow fever, typhoid and paratyphoid immunization take precedence over both those we have considered as regards time, personnel and economy. The problem of infectious diseases in these countries is numerically greater than and qualitatively different from the situation here; general improvements in sanitation, hygiene and living conditions and measures such as malaria control with D.D.T. make the role of Immunization in Childhood a relatively less vital one.

Finally, though its importance in medicine is established and undisputed it is a subject which is in all stages of development - depending on the aspect taken and the disease
studied. There is, as yet, much to conquer and explore; but it is pertinent to add the warning that unless what has been proved effective is used to the hilt, vigorously and conscientiously by medical men and women and, unless, either by legislation or, better, by publicity and education, we can achieve an effective degree of immunization in childhood, the fruits of our further endeavour cannot hope to thrive.
BIBLIOGRAPHY.


"Fundamentals of Immunology." Boyd. 1956.

"The Natural History of Infectious Disease." Sir MacFarlane Burnet. 1954.


"Bacterial and Mycotic Infections of Man." Dubas.
From "The Lancet."

Pillemer, Blum, Lepow. 1954. I. 1257.
"Public Health" (Influenza). 1959. II. 661.
Professor O'Meara. 1959. II. 737.
Leading Article: (Specific Tuberculin Reactions) 1959. II. 834.
Leading Article: (Serum Hepatitis) 1960. I. 532.
Leading Article: (Immunization against Helminths) 1960. I. 685.

From "The British Medical Journal."

Perkins, Yetts, Gaisford: 1958. 2. 68
Perkins and Yetts: 1959. 1. 680
Spiller, Groarke, Barnes, Holt. 1959. 1. 618.
Professor Dick. 1959. I. 96.
Dr. Knowelden. 1959. 1. 620.
Editorial "Vaccination against Worms." 1959. 1. 637.
Dr. H.J. Parish. 1959. 1. 640.
Sabin. 1959. 1. 663.
Anderson et al. 1959. 1. 1423.
Lorber and Menner. 1959. 1. 1430.
Hale et al, Monteiro. 1959. 1. 1541.
Perkins and Evans. 1959. 1. 1549.
Spiller and Holt. 1959. 2. 174.
Cox, Cabasso et al. 1959. 2. 591. 592.

Medical Research Council:
1958. B.M.J. 1. 1206) killed Polio Vaccine.
1959. B.M.J. 1. 609)
1959. B.M.J. 1. 1150. Tetanus spores from wound material. B.C.G.
1958. B.M.J. 2. 79)
1959. B.M.J. 2. 379)
1959. B.M.J. 1. 994)


Personal Communication from -

Dr. Mair - Chief Immunologist. Edinburgh P.H.D.

Dr. S.F. Bervell - Bacteriologist. Oslo.