

THE EPIDEMIOLOGY AND CONTROL OF  
POLIOMYELITIS

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Poliomyelitis has probably taken its toll of life and left its scars through man's history, for the stigmata of the disease are found in Ancient Egyptian mummies and are depicted in the painting of Hieronymous Bosch and Bruegel. It was a disease of childhood and was described first by Underwood in 1784. The first clinical record of the disease in England is a series of four cases among young children in Worksop, Nottinghamshire described by Badham in 1834 and in the same year an outbreak was recorded in St. Helena. Until 1911-13, when the first widespread epidemics occurred in Great Britain, scattered cases and small groups only were reported, and Creighton (1894) gives it no mention in his exhaustive survey of epidemic diseases.

In recent years in Britain, as in some other parts of the world, the disease has undergone a change in pattern and the popular name of "Infantile Paralysis" is no longer comprehensive.

In 1908 a causal virus was demonstrated by transmission of the disease to monkeys and by neutralisation tests three distinct immunological types can be recognised, type I being responsible for 80% of cases, type II is associated with endemic infection usually and type III is occasionally incriminated in epidemics.

#### PATHOGENESIS:

The enteroviruses have a common mechanism of pathogenesis and studies in the last few years have led to a complete change in thought on this subject. In the extensively studied rhesus monkey the virus is a

neurotrope and travels to the brain from the point of entry in the pharynx or olfactory mucosa by the peripherae nerves, and as this animal cannot be infected by the oral route, more support was given to the then popular theory of respiratory infection with nerve spread.

The current conception of the pathogenesis of the polio virus has developed from work on chimpanzees and man and according to this hypothesis there are four stages in the spread of the virus in the body (Rhodes 1960).

Stage I. The virus is inhaled or ingested and proliferates in the lymphoid tissue in the pharynx and intestine, in the Tonsil and Peyer's patches in particular.

Stage II. The virus passes to the regional lymph nodes where further multiplication takes place and then passes into the blood stream via the thoracic duct .

Stage III. Viraemia which lasts 4-5 days and may be accompanied by fever and non-specific illness (the minor illness).

Stage IV. The virus enters the target organ, the central nervous system (C.N.S.) and attacks the ganglionic nerve-cells and anterior horn cells.

Other views are also currently held. Sabin (1956, 1958) believes that the modification of paralytic poliomyelitis by  $\gamma$  globulin, killed virus vaccine, and previous experience with a different strain is more rationally explained by assuming the virus multiplies in the epithelial cells of the alimentary tract and drains to the lymph nodes from which it spills over into the blood stream. It is then taken up by the reticulo endothelial

system and travels to the C.N.S. by the peripherane nerves in various organs. His views on the all or none effect of a viraemic infection of the C.N.S. are, however, subject to much criticism, and it seems likely that in the presence of low titres of antibody a smaller number of particles may reach the brain with a resultant modification of the outcome.

The virus multiplication in the pharynx and intestine is of great epidemiological significance as the virus is excreted in the pharyngeal exudates and faeces. It can be isolated from the oropharynx for 3-7 days after the onset of the major illness and for 3-5 days before it and from the faeces for as long as 21 days before the onset of the major illness and at least 14 days after it.

Three weeks after the onset of the major illness 50% cases are still excreting the virus in their stools and after 5-6 weeks the number has fallen to only 25%, and even after 12 weeks a small proportion may still be excreting the virus. There is no evidence of chronic excretion (W.H.O. Tech. Rep. Series No. 81, 1954).

Recognition of these figures is of vital importance in any attempt to control the spread of the disease by the isolation of cases and contacts.

#### Forms of Poliomyelitis:

The polio virus may infect man causing -

1. No symptoms whatsoever - inapparent infection, but the figures quoted above for virus excretion are valid. The inapparent case is, therefore, an important potential disseminator of the virus in the community.

2. Minor illness which is the accompaniment of viraemia. Pyrexia, headache, malaise and gastro-intestinal symptoms are present lasting 1-2 days. The significance of this is usually unrecognised unless it occurs during an epidemic. The disease may proceed no further or after an interval of 3-7 days the patient may develop -
3. Major illness which may be divided into two distinct stages:-
  - (a) Preparalytic in which a fever develops, frequently with great rapidity, accompanied by headache, malaise and often vomiting, anorexia and diarrhoea. There may be signs of meningeal irritation and tenderness in the muscles. At this stage the patient is characteristically restless. Such cases may subside in 24-48 hours without further development (non-paralytic polio) or may proceed to the
  - (b) paralytic stage (bulbar or spinal) either directly or after an apparent improvement for 24-48 hours.

The disease can be halted at the various stages above by the body's defence mechanisms, and even if the C.N.S. is invaded it is only when certain critical areas are involved that paralysis appears.

#### Modes of Spread and Methods of Entry into the Body:

Man is the only natural host of the poliovirus and is therefore the ultimate source of infection. The virus is excreted in the pharyngeal secretions and faeces of infected persons whichever course the disease may take, and the greatest danger is the clinically inapparent case.

Sabin (1956,1959a) disputes the importance of pharyngeal infection in the spread of the disease maintaining that most viruses are swept down into the stomach leaving insignificant quantities in the mouth. He claims that the high incidence of pharyngeal infection in the natural disease is more readily explained on the basis of secondary localisation from the blood than on primary infection after ingestion, for it found that high doses of attenuated vaccine are necessary to produce carriage. However, it may be that the virulent viruses responsible for epidemics multiply quite readily in the pharynx.

Equal levels of virus are found in the oropharynx in those with and without tonsils and these organs are therefore not to be regarded as the primary source of multiplication (Sabin 1956).

Dick and Dane (1959) maintain that quite significant amounts of virus are isolated from the saliva and that there is a very good chance of transfer occurring especially in young children. This is reinforced by descriptions of cases by Sweetnam (1947) which seem likely to have occurred as a result of the transfer of pharyngeal secretions. It has been shown that spread of an attenuated virus fed for immunisation purposes can occur in the absence of pharyngeal infection, and that close contacts of an adult excreting the virus from the pharynx may not become infected (Gelfand et al. 1959). These findings indicate that although pharyngeal infection may be an important factor in virus dissemination especially in children, it is by no means an essential prerequisite.

Spread from faeces, which may contain one million infective doses for monkey per gram, is easy to visualise and occurs particularly in the

lower socio-economic classes in which the standards of hygiene are frequently low. (Gelfand et al. 1959). For spread to occur intimate relations are usually necessary and for this reason there is usually a focus of the virus in the community. The incidence of the disease in contacts is lower than in the afflicted family and in non-contacts it is still lower. The infection tends to follow the lines of human movement and the distance travelled depends on the immunity of the exposed persons. Dick (1959) claims that children in certain families excrete more viruses than other children and this may indicate an increased familial susceptibility to multiplication and possibly to viraemia and paralysis.

The means of transfer are quite apparent, for instance, hand-shaking, food, eating utensils and other fomites, although the virus does not resist drying well. Kissing young slobbering children would appear a potent source of transfer to adults. Although the virus is excreted for many weeks in the faeces, there is some evidence that cases are infectious for a rather shorter period.

Sewage presents a very rich source of the virus and ungrounded suspicions arose that it was able to multiply in the protozoa present. The virus may survive several stages of sewage purification and may indeed be present in the effluent as a source of infection to those bathing in rivers or drinking the water. If the water were used for irrigation, fruit and vegetables might constitute sources of the virus.

Water supplies, milk and food are potential but unproven sources of the virus and the widespread immunity in underdeveloped areas suggests these as forms of transfer. Milk exerts a protective effect on the virus and although pasteurisation at 62°C destroys it, the safety margin is small and the flash method at 72°C is preferable.

Flies are readily contaminated with the virus but seem to play little part in its spread, as their suppression with D.D.T. has had no abortive effect on epidemics.

Viruses have been isolated from cockroaches but not from biting insects and they are not considered as modes of transmission. Cuts may become infected, and injections made through contaminated skin must be considered potentially dangerous.

Faecal contamination of swimming baths constitutes a risk/<sup>but</sup>with adequate chlorination this is small.

#### Factors Predisposing to Paralysis

Estimates vary, but for every case of paralytic polio in Britain there are probably about 1000 non-paralytic ones, but figures based partly on clinical diagnosis are unreliable due to the similarity of certain other enterovirus infections to polio, paralytic and non-paralytic.

In a family it is unusual for more than one member to be paralysed and there are many possible factors predisposing to paralysis. Shope goes so far as to say that host factors are more decisive in the outcome than the virus.

It might be mentioned that a virus isolated from a contact has been found to have less neurovirulence than that isolated from the paralytic case, and this might account for inapparent infections in some instances. (Dick and Dane, 1958).

A genetic predisposition has been postulated by some workers and Dick's (1959) observation on the familial variation in virus excretion may bear this out. The apparent polio attack rate of the indigenous populations of tropical countries is much lower than that of visitors and settlers, and this was thought to be due to genetic differences, but differences in immunity have been shown to account for this.

The effect of exercise was studied by Horstmann (1950). It was found that no correlation existed between the subsequent outcome and amount of exercise performed 3 days before and 2 days after the onset of the minor illness, nor was there any correlation between the exercise performed 3 days prior to the major illness and the outcome. However, the greater the amount of exercise performed after the onset of the major illness, the greater the chance of paralysis.

Activity on day of onset  
of major illness

	Full	Minimum
Paralytic	74%	9%
Non-paralytic	45%	35%

Exercise immediately before the onset appeared to have no effect on whether or not paralysis occurred. There was some tendency for the muscles used most after the onset to be paralysed preferentially as shown by the slightly higher incidence of right-sided paralysis in right-handed people (and therefore R. footed) and vice versa.

It may be that exercise does not bring about paralysis but that it is associated with it as part of the symptomatology, for it has been suggested that those cases which become paralysed may feel compelled to exercise and there is some indication that exercise is frequently performed to relieve low back-ache of which adult patients often complain at the onset.

There is some evidence that physical activity at a crucial time exerts a deleterious effect directly or indirectly on the anterior horn cells and the observation that intense muscular work depletes the anterior horn cells' proteins may be relevant in this context. It is suggested that the virus is in the C.N.S. before the onset of symptoms of the major illness and the physical activity of the patient determines whether or not the destructive processes continue.

The age of the individual seems to influence the course of the disease to a great degree. After the maternal antibodies have disappeared from the circulation and till the age of about 4 years, children tend to have mild or inapparent infections and the severity of paralysis tends to increase with the age of the child. In adults, the major illness frequently appears quite gradually and the individual tends to continue

his full activities, thus predisposing himself to paralysis, but whatever the mode of onset of the disease adults carry on with their daily routine more resolutely than children (Horstmann 1955). The peak incidence of paralysis and of the bulbar form occurs in children about 10 years old and the greatest incidence of non-paralytic polio in the civilised world occurs in older persons who usually have some degree of protection due to the presence of heterogeneous antibodies (vide infra). In virgin populations with almost complete absence of antibody to any of the three types of polio virus, the incidence of paralysis rises with age quite steadily.

Intramuscular injections of certain vaccines have been found to have a definite effect in provoking poliomyelitis (Wellcome Foundation 1960, Lancet 1956, 2, 1223). 1 in 37,000 inoculations of the prophylactics studied were found to have resulted in paralysis and the risk, which varied with the prophylactic given was greatest in the second quarter of the year and lasted for about a month. Alum precipitated diphtheria-pertussis vaccine carries the greatest risk (1 in 15,000 injections) with A.P.T. P.T.A.P. and mixed diphtheria-pertussis without alum following in that order. A minimal risk was found with T.A.F. and F.T. injections. 13% of paralytic cases between the ages of 6 months and 2 years could be causally related to inoculations, and reinforcing doses at 5 years of age were responsible for 2% of the total.

A clear relationship was shown between the site of inoculation and the site of paralysis and paralysis is definitely provoked by these prophylactics, not transmitted nor merely localised. Other

intramuscular injections particularly organic arsenicals and heavy metals carry a clear risk of provoking paralysis as was demonstrated in Tahiti in 1951, when the islanders were being treated for spirochaetal infections (Horstmann, 1955).

As with the prophylactics above there is much doubt about the manner of this action. Bodian (1955) showed that the incubation period in monkeys was longer after intramuscular injection of the virus than after intravenous administration with an intramuscular injection of irritant into one limb. It seems hardly likely, therefore, that localisation of the virus at the injection site is the mode of action, at least in monkeys. Trueta (1955) investigated the variation in calibre of the vessels in the spinal cord of mice and found dilatation after ipsilateral i.m. injection and suggested this as the basis of the increased susceptibility. Sabin (1956) points out that this theory is not supported by the observation that the virus is in the blood stream for some days before it can be demonstrated in the C.N.S. and after i.m. injection of diphtheria toxoid in monkeys the virus is found first in the sciatic nerve. It may be that the cells in the corresponding segment of the cord are rendered more susceptible to virus invasion.

A significantly higher incidence of cases of polio are found among tonsillectomised people than average and most cases so provoked are bulbar in type (Paffenbarger and Wilson 1955). The duration of risk may be many months. Adenoidectomy and even tooth extraction are said to carry a risk of provoking paralytic poliomyelitis and in these cases the mechanism is obscure but it may be that the virus spreads up the nerves exposed at operation.

Susceptibility to paralytic polio is enhanced by pregnancy, due possibly to the influence of endocrine glands (Paffenbarger & Wilson 1955) in a role similar to cortisone in experimental animals and the disease near term tends to be bulbar in form.

Injury is claimed to increase susceptibility but the case is not proven.

Bacterial and viral infections of the throat and alimentary tract may predispose to poliomyelitis. Sometimes a patient is found to have a double enterovirus infection and viruses in Coxsackie gp. A. occur with significantly greater frequency than those of group B for it to be suggested that infection with group A virus predispose to paralysis (Stern 1961). It is interesting to note that the group B viruses, in contrast to group A, have an interfering action which spares the mouse from the effects of experimentally induced polio, and epidemiological studies in man have shown that during epidemics of Coxsackie type B infections, paralytic poliomyelitis is uncommon (Stern 1961).

#### Immunity and Age Distribution of the Disease

Resistance to infection by viruses depends on the same defence mechanisms which operate against bacteria. Infection is usually followed by the development of antibodies which combine with the invading micro-organism and prevent it gaining access to the host's cells.

However, in the condition of congenital agammaglobulinemia, although children do not develop antibodies after recovery from measles, mumps or chickenpox, the disease is no more severe than usual and they are

resistant to reinfection. Viral immunity must therefore rest on other factors besides antibodies, and it seems probable that cellular resistance together with interference by interferon production by other viruses may be of importance. The role of phagocytes and non specific factors such as properdin has not been elucidated.

After natural infection with one type of polio virus, type specific antibodies are developed and are present in the circulation, and in addition there develops a degree of resistance in the alimentary tract to reinfection with the same type of the virus. It has recently been shown that the antibodies are of two types, low avidity which develop rapidly and are easily reversible and high avidity which develop later and are less readily reversed. At the beginning of the disease there may be a 50-100 fold difference in titre (Sabin 1958).

Some respond to the infection with a high titre of antibody and some with a low titre and the level drops between 4 and 20 fold in 1 or 2 years. In addition low titres of heterologous antibodies may be present transitorily (Lennette and Smith 1957). It was found studying the antibody levels in different age groups in different populations that the titres decline over the years even in unsanitary areas where the opportunities for reinfection are excellent. This suggests that in such communities the alimentary tract resists the infection altogether after a certain period of years (Sabin 1959a).

Persistence of this naturally acquired antibody is not dependent on its original level and the resistance of the alimentary tract is unrelated

to the titre. Indeed, the alimentary tract may be very susceptible to infection in the presence of high titres of antibodies as after vaccination with killed virus vaccine and be totally resistant in the absence of demonstrable antibodies. Furthermore, Sabin found no evidence of specific antibodies or neutralising factors in the alimentary tract although these had been reported by Steigman & Lipton (1959) in cases of polio. This points to the resistance being of a cellular rather than humeral nature (Sabin 1959a).

The persistence of natural antibodies is uncertain although Paul et al (1951) gave convincing evidence of antibodies being present after 50 years. He investigated the antibodies to all three types of poliovirus in a township of Eskimos which had experienced an epidemic with a type II strain in 1930. Antibodies were found only in those who were alive at this time and in no children under 18 years, apart from 5 who had visited outwith the community. The serological pattern suggested, for similar reasons, a type I epidemic in 1915 and a type III epidemic in 1905. In the absence of infection, antibodies are thus known to persist for nearly 50 years in some cases but whether this can be generally accepted or reinfection is usually superadded is uncertain.

The durability of the alimentary tract resistance seems to be variable and it is likely that repeated reinfection is required to maintain it, for it is possible to re-establish the same strain in the gut after immunisation with live vaccine and second paralytic attacks are reported although the virus types involved are unknown.

The pattern of the disease in the different age groups reflects fairly closely the immunity of the population. In an endemic area such as Casablanca, the paralytic attack rate over the age of 2 years is negligible and in the age group 0-2 yrs. is very low. Serological studies reveal a sharp rise in antibody titres after the decline of the transplacental antibodies so that 75% children in the 12-23 months age group have titres of at least one antibody type and by 5-9 years 80% have antibodies to all 3 types of virus.

The low susceptibility to paralysis between the ages of 0-2 yrs. accounts for the low paralytic rate in that age group and almost all persons older than this are immune to a greater or lesser degree (Horstmann 1955). This state of affairs reflects the wide dispersal of the virus in the community and is due primarily to the low standard of hygiene.

In the endemic areas which are now mainly tropical and sub-tropical this is the typical pattern of the disease and it was probably valid for W. Europe and North America as they existed before the great advances in hygiene took place. Infantile paralysis is a true description under these conditions.

However, a tropical climate per se is no guarantee of freedom from epidemic polio, as was seen in St. Helena in 1945, the Nicobar Islands in 1947 and Tahiti in 1951. These islands had very severe epidemics and this may have been due to their being isolated communities and which having had virtually no experience of the virus for some years, had built up a large young non-immune population.

The first widespread epidemics occurred in countries with high standards of living - U.S.A., Scandinavia, Australia and New Zealand. The spread of the virus being severely limited in such communities large numbers of susceptible people were built up and the introduction of a virulent, fast-spreading virus led to wide dissemination particularly in schools with large numbers of paralytic cases occurring in the older age groups.

In the towns the opportunities for virus spread are better than in the country and immunity is gained earlier in life. Within one town the age distribution of paralysis in the upper and lower socio-economic classes reveals that the lower standards of hygiene found in the lower classes results in earlier immunisation. This is confirmed by serological studies (Gelfand et al. 1959).

Although in any one year one enterovirus type seems to predominate in each locality (Rhodes 1960), the three types of antibody are acquired usually at approximately the same age in the town, but in the country there is evidence of different serological waves. The presence of antibodies to type II virus tends to reflect immunity to the other two types and because of sharing of antigenic contents among the types, antibodies to type II are of more than type specific significance.

It may be said that the poorer the standard of living and sanitation, the more extensive is polio virus dissemination and the lower is the apparent incidence of paralytic polio (W.H.O. Tech. Report Series 1954 No. 81). This is the explanation of the apparent but spurious race differences mentioned

above, and the danger of this apparently low incidence must be emphasised in relation to visitors and settlers.

#### Influence of Climate

Climate has a marked effect on the incidence of polio, for in temperate zones the epidemic and non-epidemic forms are most common in the summer although winter epidemics are by no means unknown. Peart (1950) reported an outbreak among Eskimos in midwinter but this may have been due partly to genetic factors created by inbreeding (Horstmann 1955).

In the endemic areas the disease appears to be uniformly distributed throughout the year although there is some evidence that it occurs in waves. The relative infrequency of paralytic cases makes this difficult to verify without serological surveys. It would seem that either the spread of the virus is facilitated in summer or that the resistance of the host is reduced, but there is no definite information on this subject.

#### Virus Survival in Inter-Epidemic Periods

In the intervals between epidemics there are usually sporadic cases and a resurgence may be caused by reactivation and spread of viruses already present in the community. There is evidence of the virus undergoing a favourable change in neurovirulence (Dick & Dane, 1958) and Sabin (1959a) cites this as a possible means by which epidemics die down and suggests that changes in the virus are quite as likely to be responsible for epidemics as changes in the immunity of the population.

Alternatively, a recrudescence of the disease might be due to the introduction of exogenous strains into the community and there is some

evidence that the large number of outbreaks after World War II were attributable, at least in part, to personnel returning from endemic areas.

In this context extra-human reservoirs are of great importance and most of these have been considered under modes of spread. However it is worth emphasising that man is the only known natural harbour of the virus and that birds, upon which certain suspicion fell at one time, have not been successfully inoculated with the virus nor has it been isolated from them. With reference to contaminated irrigation, tomatoes grown in solutions containing the virus have never been found to be infected.

Before discussing control it is appropriate to consider the size of the problem and whether the enormous sums of money spent are justified. Some diseases, although lethal, are so rare as to make protection unnecessary and others are so common and have effects so mild as to make protection not worth while. In between the extremes of psittacosis and the common cold lies a wide belt of diseases with varying virulence and incidence and the majority view is that polio lies here and calls for protective treatment. Paralytic cases may be comparatively few but the effects are peculiarly poignant if only because they occur chiefly in children.

Cases of Polio Showing Age Distribution over 50 years (E. & W.)

	%	%	%	%	%
0 - 1	6.3	10.1	( 39.0	( 26	3.9
1 -	51.2	60.8	(	(	26.9
5 -	25.6	18	31.3	37	20.7
10 -	7.5	5.1	16.2	15.2	14.3
15 -	2.6	2.1	5.8	13.0	16.9
20 -	2.8	2.1	7.0	6.5	16.5 (25+)
30 +	4.0	1.7	0.7	2.2	
DATE:	1908/11	1912/13	1926	1938	1947

This shows the changing age distribution discussed above; the cases in older persons increasing at the expense of the young children.

The notifications for England and Wales 1950-59 give some indication of the size of the problem.

	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959
Paralytic	5,565	1,529	2,747	2,976	1,319	3,712	1,717	3,777	1,419	739
Non-paralytic	2,195	1,085	1,163	1,571	641	2,619	1,483	1,667	575	289
<u>Deaths</u>	755	217	295	338	134	270	137	255	154	87

C O N T R O L

The control of an infectious disease embraces an assault on morbidity or attack rate and the care and cure of the infected person with consequent reduction in mortality. It prevents all damage whether physical, economic, social or psychological to the human host as a result of the disease (Cruickshank 1942).

The control of poliomyelitis can be considered under three major headings:

1. General control methods for infectious diseases.
2. Active immunisation with killed vaccine.
3. Active immunisation with live virus vaccine.
- (4. Medical and surgical treatment are not considered in this essay).

In the early days the general control methods were considered to be of little use due to the huge number of inapparent cases disseminating the virus. However, more recent knowledge suggests that owing to focal outbreaks, isolation is valuable particularly for the first cases in the community.

It is to be hoped that the high level of protection afforded by the vaccines will be extended to all people and that the disease will soon be eliminated. Until such time, however, general control measures have a part to play in protecting the public.

Notification is particularly useful to the epidemiologist in tracing the development of an epidemic. Owing to the clinical picture of other enterovirus infections frequently being indistinguishable from non-paralytic polio, it is recommended that cases be grouped into paralytic and non-paralytic

and much more reliance may be placed on the figures for paralytic polio although some residual palsies may occur after Coxsackie and E.C.H.O. virus infections (Stern 1961).

The principles of isolation are based on our knowledge of the epidemiology of the disease. A suspected case of polio must therefore be isolated for at least 3 weeks and ideally until virological examination of the stools for the polio virus is negative. Isolation may be effected in the home or in special hospital units where suspected cases should be kept separate from confirmed ones.

Great care must be taken over the disposal of throat secretions and faeces and the use of individual bedpans is recommended. Maximum hygienic precautions must be observed by the staff. The virus is resistant to the action of many disinfectants and the use of oxidising agents such as potassium permanganate or hypochlorites is recommended.

It must be borne in mind that although swimming may be desirable in convalescence, patients may still excrete the virus 12 weeks after the onset, but chlorination of the water will obviate any danger (2 parts per million). The room which housed the patient should be thoroughly disinfected after convalescence.

The contacts of paralytic cases are statistically unlikely to be similarly affected but they are very likely to become infected and children being the most ready virus disseminators should be isolated for 21 days, should avoid exertion and pay particular attention to the factors predisposing

to paralysis. It is not considered essential to isolate adults but they should observe maximum hygiene and avoid exertion. Association with children is undesirable as is the preparation of foodstuffs for people other than those within their own family.

Children's nurseries have a characteristically high infection rate due to the close contact of naturally unhygienic children and for this reason should be closed.

Residential institutions present a rather different problem as if they are closed, any virus present may be spread over a wide area. It is therefore recommended that 21 days isolation be observed with attention being paid to the factors predisposing to paralysis. There should, of course, be no new admittances.

The public should be educated in the spread of the disease and in brief should:

1. Observe maximum hygiene.
2. Regard all febrile illness as potentially dangerous and take bedrest or minimum exertion for 1 week.
3. Avoid over-exertion particularly if not feeling well.
4. Avoid association with the family of a suspected or proven case for 3 weeks. This includes handshaking!
5. Protect food from flies and wash uncooked food.
6. Avoid travel in or out of epidemic areas.
7. Delay opening schools in severe epidemics and close unchlorinated swimming pools.
8. Avoid public gatherings.

Isolation on a national level with restrictions on international travel have been proposed but it is hoped that widespread active immunisation will never render this necessary.

In an attempt to reduce the paralytic rate, attention should be directed towards those factors which have been shown to predispose to paralysis and which can be controlled.

1. Tonsillectomy and adenoidectomy should be avoided during times when polio is prevalent.
2. The activity of people feeling unwell should be restricted.
3. Contacts of cases who might develop the disease in 5 - 21 days should avoid undue fatigue.
4. Diphtheria-pertussis vaccination should continue except in very severe epidemics. Adsorbed combined vaccine should, of course, be avoided.
5. Intra-muscular injections of irritants such as organic arsenicals and heavy metals should be avoided.
6. Skin contamination should be remembered when giving injections and careful skin cleaning with a suitable agent is recommended.

These general methods of control are a natural development from what is known about the epidemiology of the disease. They were of particular value when there was no available active immunisation but they still have a part to play in preventing epidemic flaring up particularly in view of how disappointing the numbers accepting vaccination have been in some countries.

Passive Immunisation

For many years  $\gamma$  globulin or convalescent serum was the only form of prophylactic available. It had a very limited usefulness in that its half life was little more than 10 days. In a control trial in U.S.A. in 1952 it was found to give protection for 5-6 weeks with little apparent effect for the week in which it was given, for once the stage of viraemia is passed the virus multiplies within the cells of the C.N.S. and is inaccessible to the neutralising effect of the antibodies.

Although this form of prophylactic has been largely superseded by active immunisation, there seems to be some place for it still in certain cases.

1. For contacts of diagnosed cases - if the contact was exposed to the same source of infection as the case, the disease due to early C.N.S. invasion, would probably develop before the  $\gamma$  globulin could exert its effect ; it might, however, modify its course. If the contact was still liable to infection or the virus was still multiplying in the gut, the  $\gamma$  globulin should abort the disease and in this might be profitably helped by a live virus vaccine.

For contacts of cases, therefore, particularly when it is not known whether cross infection has occurred, a combination of  $\gamma$  globulin and live vaccine seems to offer the best prospect of protection.

2. To cover operations during epidemics. Since killed vaccine has a delayed effect due to the necessity for antibody formation it is of no value for immediate protection and as there is some potential danger in using live vaccine to cover operation,  $\gamma$  globulin is the prophylactic of choice.

Before the era of widespread use of the two other types of prophylactic, there were other categories of people who might benefit from  $\gamma$  globulin, but active immunisation now affords more effective protection.

#### Active Immunisation with Killed Virus Vaccine

"Until evidence is produced to the contrary, it must be assumed that killed poliomyelitis vaccine protects only as long as antibody remains in the circulation and it is generally agreed that this is the object of vaccination" (Wellcome Foundation 1960).

Immunity does not signify a state of absolute resistance to infection, and the protection afforded by the circulating antibody is only relative. This was demonstrated in Israel in 1960 when children aged 0-5 months with high levels of transplacental antibodies accounted for 98 out of 405 cases in an epidemic (Horstmann 1955).

The vaccine is manufactured from attenuated strains of polioviruses which are killed by formalin. There are a number of rigorous tests to be carried out including tissue culture and monkey inoculations to ensure that no active virus particles are included with vaccine. Safety precautions have been made more stringent after the occurrence of several deaths in the U.S.A. directly attributable to the inclusion of live virus particles in several lots of vaccine produced in one laboratory. It is for this reason that strains of low virulence are used in Britain.

Apart from those unfortunate accidents, reported reactions from the use of these vaccines are very few. Allergic reactions would be expected to occur in a few cases to the monkey protein or antibiotics included in

minute proportions in the vaccine, and indeed a few cases of urticaria and anaphylaxis have been reported. Local irritation and pain are the most frequent complaints and neurological signs such as meningeal irritation and encephalitic convulsions have been recorded. Christensen (1959) analysed the complaints about Lilly's vaccine and calculated a complaint rate of only 1/1,200,000 inoculations.

The aetiology of cases of polio occurring within one month of inoculation is difficult to assess. The following possibilities must be considered.

1. The infection had no connection with the disease.
2. It had a local provocative action.
3. It produced a short lasting phase of increased susceptibility.
4. A trace of active virus was included in the vaccine.

Active virus in the inoculum and a local provocative action are likely to lead to paralysis in the inoculated limb but the figures for such cases are not statistically significant. However, if paralysis in any limb is considered significant, as might be produced by increased susceptibility, the figures of cases occurring during epidemic periods are suggestive of a possible causal relationship. It is therefore possibly advisable to withhold vaccine from a crowded epidemic area until the epidemic is waning, by which time, in all likelihood, the vaccine would just be beginning to take effect.

It would be of great value to inoculate peripheral areas before the disease reached them.

### Efficacy

Tests of antigenicity can be performed in the laboratory in guinea pigs with a good measure of reproducibility. Monkeys were found to give inconsistent results.

Reports from field trials are quite encouraging although a great deal of variation is found. Dramatic reductions in incidence can occur without any interference by man and controlled trials are essential to establish the efficacy of the vaccine.

A serological response in persons with no demonstrable antibodies to any of the three types of virus is considered more reliable than a response in people with one or two antibody types present owing to heterologous responses (see below). The methods used are to take paired sera, one just after the first injection and the other after 2-3 weeks and a positive result is recorded if new antibody production or an increase in titre is found. The other method used is to study the incidence of paralysis in the different age groups in the population and compare the figures with those gathered over the decade. This is only possible, of course, in certain relatively advanced countries.

In U.S.A. in 1956 70 million inoculations were given and a shift in the distribution of the disease was noted as well as an alteration in frequency. The frequency of paralysis in reported cases in people under 20 years was 34% in those vaccinated and 60% in those unvaccinated. 21% of the paralytic cases in those younger than 20 years occurred in the vaccinated group which comprised approximately 50% of the population studied

and the reduction in cases was estimated at 73%.

The effectiveness of the vaccine in the U.S.A. has been estimated:

	<u>0 - 14 years</u>	<u>15 - 39 years</u>
3 inoculations	90%	82%
4        "	96%	86%

It is noteworthy that the vaccine is more effective in the younger age group.

In Canada 98% reduction in cases with 96% effectiveness was reported.

Russia records less satisfactory results and has turned to live vaccine. No apparent protective effect was noted against type III strains in Massachusetts in 1959. The type III vaccine was said to be antigenically poor.

The duration of the protection is a matter of great importance and is considered to be identical with the persistence of the antibodies. Kendall et al (1960) found that in adults and adolescents after 2 doses 4 weeks apart, the antibody levels fell at widely different rates and that the persistence was largely determined by the initial level. Furthermore, the response to the 3rd or booster dose was dependent on the level of antibodies when this was given, for a very low or undetectable level of antibody was followed by a poor and short-lasting response.

The average fall in titre for all types was from 76-81% in 18-24 months which is similar to that observed after natural infection. Antibody

decline varies considerably from one individual to another and for a 4th dose to be guaranteed success it should be given within 2 years of the 3rd. More potent vaccines producing better antibody levels would allow a greater interval between the 3rd and 4th doses.

Similar persistence was noted by Logan et al. (1960) in children aged between 1-10 years. The response to a 4th dose 2 years after the 3rd was satisfactory in all children who had detectable antibodies before inoculation. Even after only 2 years some children had very low titres of type I antibody.

Salk (1960) has shown that the mass of antigen is the factor controlling the initial levels of antibody and therefore their persistence. The number of persons protected by successive doses of antigen is related to the number protected by the first so that successive doses of vaccine reduce the number of susceptibles by the same proportion as did the first; poor potency vaccines thus become less and less efficient with multiple doses.

There are indications that induced immunity may be irreversible and that a critical event occurs; whether or not the persistence of antibodies is necessary is discussed below. Salk believes that lasting protection may be afforded by one dose of potent vaccine. The level of antibody one year after 3 injections gives a good guide to the levels in the following 6 years for there is little drop in titre.

Polio vaccine prepared in monkey-kidney tissue cannot be concentrated by the simple method of centrifugation owing to the small size of the particles and the potency depends largely on the initial titre of virus in

the fluid before inactivation. Since the accidents which occurred as a result of the incomplete inactivation of the virulent strains used, attenuated and less antigenic strains have been included in the vaccines. However, recent lots have been more potent.

A new purified and concentrated vaccine is being studied at present. It is prepared by a chemical process. Tests show it to have much greater seroconverting powers in children and to produce better antibody levels. It has two major advantages. Firstly it is able to overcome the effect of maternal antibodies more easily. Perkins et al. (1958) showed that maternal antibodies interfered with the production of homotypic antibodies by the child and that vaccination was rarely successful before 6-9 months after birth. It was noted that this effect could be overcome in some instances. Infants normally receive 3 doses of the triple diphtheria-pertussis tetanus vaccine in the first 6 months of life and in the absence of good transplacental antibodies this may involve some risk of acquiring poliomyelitis. This may be overcome by immunising the mother during pregnancy and thus raising her antibody titres or with this new potent vaccine there is a prospect of an effective quadruple prophylactic.

The second advantage is that the vaccine being purer, fewer toxic reactions may be expected.

Salk (1955) believes that for effective immunity detectable levels of antibodies in the circulation may not be necessary. It has been shown that viruses of one type have antigenic components that characterise the predominant antigen in 1 or both of the other types.

Different patterns of response to vaccination with killed virus vaccine occur according to whether the individual is serologically triple negative or has had previous contact with one or two types, for higher levels of antibodies are more rapidly obtained if there has been a previous heterologous response. Thus if type II antigen is given to a person who has had previous experience with a type I strain, higher levels of type II antibody are obtained more rapidly than in a person with no previous polio virus experience. Type III antibodies make little difference. Similar differences have been noted after inoculation with types I and III antigen.

In summary there is little antigenic sharing between types I and III but there is a large amount of type I antigen in type II virus and a little of type II antigen in viral types I and III and type III antigen in virus type II.

The sensitising effect of type II infection has been shown to result in a reduced risk of paralysis due to a type I infection. This is due to hyperactivity with a very rapid outpouring of antibody and not to heterologous antibody (Salk 1955). Heterologous antibody has been detected in low titre in polio patients, but it is transient (Lennette and Schmidt 1957).

Sabin (1958, 1959a) has shown that no accelerated reaction occurs on feeding attenuated strains to people with prior experience with another type or after Salk vaccination and claims that the effect of reducing paralysis is due not to hyperreactivity, which he denies exists, but to undetectable levels of antibodies in the circulation. He believes that the incubation

period may be much shorter than previously thought and has seen slight viraemia occurring on the third day - this would hardly allow mobilisation of antibody even in a hyperreactive state.

From this evidence it would seem that Balk vaccine is effective only for as long as there are circulating antibodies. The question is to what level it is safe to let them fall.

Effect of vaccine on virus excretion and epidemics

Type-specific polio virus antibodies have been found in the stools of patients suffering from the disease (Steigman and Lipton 1959). They were heterotypic to the current infection and were found transitorily in the serum at the same time. It is suggested that alimentary exposure to a single serotype sensitises the local cells to type and species specific antigens and that heterotypic antibodies are more readily produced if a heterotypic virus has been experienced previously.

Logan et al. (1960) found no faecal inhibitors after killed virus vaccine and it appears that a natural infection is necessary although Sabin (1959a) failed to demonstrate any after live polio virus vaccination.

In the presence of very high titres of antibodies in the circulation, the oropharyngeal secretions may contain a detectable amount and Kendall et al. (1960) found the homotypic titre in the circulation was over 2,000 when this occurred. These antibodies may prevent pharyngeal infection and if the throat is the major source of the virus, then killed virus vaccine will influence its spread in sanitary populations. However, as it appears from Kendall's figures that the circulating antibodies must be <sup>in</sup> exceptionally

high titre before they are detectable in the mouth, an increase in the antigenicity of the vaccines will be a prerequisite to their having much effect on virus dissemination. However, Sabin (1959a) considers the pharyngeal infection is secondarily produced by blood spread and much lower antibody levels would therefore suffice to suppress this.

Dick and Dane (1959) point out that high levels of antibodies produced by more potent vaccines may have an effect in suppressing alimentary tract infections, although Sabin (1959a) concluded that the resistance was essentially cellular rather than humoral in nature. The killed virus vaccines used till now have been shown to have no modifying effect on the alimentary tract infections produced by live vaccines apart from suppressing the pharyngeal infection.

It is therefore not surprising that it has been found in the field that killed virus vaccines have no effect in halting an epidemic and poliomyelitis spread in the community must be combatted by the adequate immunisation of each individual.

In the U.S.A. the disease is concentrated in well-defined areas which correspond closely with the regions inhabited by poorly vaccinated lower socio-economic classes (Alexander 1961). Although according to many authorities polio cannot be eradicated by killed vaccine without continuous 100% immunisation of the population, these islands of infection are said by others to represent effective control despite only 32% of the population having received the recommended 4 doses of vaccine (Langmuir 1961). It

seems a dangerous and unethical experiment not to continue pressing for further vaccination.

With the protection afforded by the killed vaccine tonsillectomy in epidemic periods is still contra-indicated because the virus may spread up the nerves uninfluenced by circulating antibodies. Any increased susceptibility due to alum containing and other infections should be adequately covered by the antibodies and these are not contra-indicated.

#### ACTIVE IMMUNISATION WITH LIVE VIRUS VACCINE

"Attenuation of the polio virus can most easily be defined as loss of pathogenicity for man, but retention of all antigenic qualities for immunisation purposes". (Korpovoski 1960).

In the early days repeated passages through animals and chick embryos were the only means of attenuating the virus, but tissue culture systems rapidly gained favour after their introduction. The advent of monolayers in 1954 allowed selection of the progeny of a single virus particle and all strains used today for the oral immunisation of man have been selected by this method.

Tests of pathogenicity are of obvious importance before a strain is fed to man and monkey neurovirulence has been used as the yardstick on the assumption that a valid relationship exists between monkey/man neurovirulence. It should be remembered that there is no direct evidence that polio strains isolated from human paralytic cases are all virulent for the C.N.S. of monkeys and the monkey neurovirulence of strains isolated from asymptomatic children varies very greatly.

The neurotropism of a virus particle is a measure of its capacity to multiply sufficiently in a given neurone to be able to spread and destroy the large number of other neurones required to produce clinical manifestations (Sabin 1959a).

In testing the neurotropism of a particle, therefore, the number injected is of obvious importance as is also the position into which they are placed, for in intraspinal inoculation it is possible to damage anterior horn cells with the needle so that paralysis is very readily induced by the destruction of the limited number of cells left intact. Furthermore, results are comparable only when techniques are standardised and it is the lack of standardisation which accounts for many of the inconsistencies in the literature.

It has been found that the thalamic neurones of monkey are more resistant to invasion than the neurones in the lumbar enlargement and the lumbar neurones of chimpanzees are markedly more resistant than those of monkeys. The neurones in man are believed to be still more resistant.

Intracerebral inoculation is more reliable than intraspinal but there is the danger that trauma produced by the needle allows direct spread of the virus down the motor tracts without previous multiplication. Even two consecutive tests with the same lot of vaccine may show widely differing results and this is attributable often to the differing physical states of monkeys. (Cabasso 1960b). In interpreting the results of inoculations into monkey CNS it should be borne in mind that it is a selective

medium for the more neurotropic particles and that mutants may arise in the course of multiplication, and furthermore, that however attenuated a poliovirus may be found to be in the laboratory, its safety is ultimately established in man (Cabasso 1960a). All strains used show some activity on intraspinal inoculation and there is some variation in the results of intracerebral inoculation, Sabin's strains being most favoured.

Sabin (1959a) has laid great emphasis on the technique of intraspinal inoculation and claims that some laboratories have made their injections/<sup>too</sup>low in the cord. The inoculum must be placed in anterior horn in contact with the anterior horn cells and if the needle track is in the white matter with the neurones intact, the test is discarded. Cabasso et al. (1960a) questions the virulence of a strain which in such a case cannot bridge the gap of a few millimetres to the neurones.

In vitro markers have received much attention recently, in relation to the neuropathogenicity and the recognition of oral strains in the field. Markers d, rct, MS, cy, t and others have been studied. The d (bicarbonate) markers have been shown to correlate poorly with monkey neurovirulence and of the markers studied so far, t (temperature sensitivity for inactivation) seems to correlate best but discrepancies have been found (Cabasso 1960b). Many markers tend to change simultaneously in the same event (covariation) but no pair has yet been found in which covariation always occurs in both possible directions.

This indicates that other unknown factors play a part in neurovirulence and it is to be expected that a multitude of environmental factors, intra- and extracellular are involved.

Elaborate precautions are necessary to exclude bacterial and fungal contaminants, Simian viruses and other human pathogens (Coxsackie, E.C.H.O. herpes and others) and a series of in vivo and in vitro tests are designed for the purpose (Cabasso 1960a).

#### Administration and manner of action

A known quantity of the attenuated virus, standardised usually by the tissue culture inoculation dose method (TCID<sub>50</sub>), is fed by mouth in a variety of forms ranging from syrup to the candy administered by the Russians, with the aim of initiating an alimentary tract infection. Each type is usually given separately at approximately 3-4 week intervals and Sabin (1959b) suggested feeding the different types in a particular sequence, namely in the reverse order of their dominance so that they supplement each other most easily, reducing the chances of interference. Others have found no significance in the order of administration and suggest feeding them in the order in which virulent strains most frequently cause paralysis. Interference by other enteroviruses causes poor sero-conversion rates in some parts of the world, particularly in the endemic areas and winter feeding, when the enterovirus infections are minimal, is suggested.

Triple virus type vaccines have been studied and Sabin (1959b) considers them only of value when there are conditions conducive to extensive secondary spread because the seroconversion rates after one feeding are not usually as high as with single spaced feedings.

This has been confirmed by recent experience in Hungary (Dömök et al 1961) where single spaced feedings seemed to be more effective.

Cox et al.(1959) record excellent conversion rates in adults with types I and III after feeding triple vaccine in U.S.A. and rather less good results with type II. They consider that due to the cheapness of production and ease of administration triple vaccine will find a place in prophylaxis in epidemic areas.

In the trial in Toluca, Mexico, Sabin (1960) found a very high rate of enterovirus infections in the population beginning a few days after birth and reaching a peak of 72% during the first year of life. In order to overcome this interference he fed triple vaccine to large numbers of children over a short period of time and the conversion rates indicated marked interference and also dominance of the type II strain used. However, the results (see below) upheld the use of triple vaccine in endemic areas.

After the virus has been fed it is excreted in the faeces for a varying length of time up to a recorded period of 171 days and it may spread to others giving more widespread immunisation. Those strains of virus showing greater monkey neurovirulence show great infectivity and powers of spreading than more attenuated strains. There is greater spread after administration to infants and to the lower socio-economic classes which is probably associated with lower levels of hygiene (Gelfand et al. 1959). However, these attenuated strains do not spread far beyond the household contacts and soon disappear from the community. In the Toluca trial (Sabin 1960) where the conditions greatly favoured the spread of the virus, there was a very rapid decline in the level of infection in the community, so that 3 months after the mass feeding the isolation rate of the virus was

lower than before it. It fell from 11% before the feedings to .7% three months afterwards.

#### Repeated passage in humans

The spread of the attenuated virus beyond the recipient has caused much interest and alarm. Although widespread virus dissemination is associated with a more virulent and more antigenic virus and can therefore be expected to produce a wider and more satisfactory degree of immunity, it may also be associated with a dangerous increase in virulence. Sabin (1959a) claims that by careful technique all strains show slight increase in spinal neurotropism after passage through the human alimentary tract, but strain T.N. II is the only one which so far has shown marked change and has been withdrawn (Dick and Dane 1958). Care must be taken that the culture of the virus prior to monkey inoculation does not induce a change in virulence.

The alimentary tract does not selectively favour strains of greater neurotropism, they arise by chance. For a range of attenuated strains is found naturally in the population and indeed the virus isolated from a contact has been found less virulent than that causing paralysis of the patient (Dick and Dane, 1958). It is worth repeating that the C.N.S. of monkeys is selective for any virulent particle in the inoculum and that the virulence may change in the course of multiplication within the C.N.S. Although no progressive increase in neurotropism has been found, this potential danger will have to be closely watched, but there is no indication at present that fears are justified.

### Results of feeding

The antibody response resulting from the multiplication of an attenuated strain in the alimentary tract varies with the individual, his age and the strain of the virus. As in natural infection some respond with a high, some with a low titre, and the persistence of the antibody does not appear to be dependent on its level as it does with killed virus vaccine.

The nature of the resistance of the gut following infection has been discussed above and it is noteworthy that it is unrelated to the antibody titre. It was noted by Sabin (1960) in the Toluca trial with triple vaccine that many children who developed antibodies did not excrete the virus in sufficient quantity to be detected on rectal swabbing and that some children with no demonstrable antibody at 10 weeks excreted sufficient virus to be detected in the first 4 weeks.

It seems possible that limited alimentary tract infection resulting from interference between strains in the triple vaccine may produce a poor degree of alimentary resistance to further infection although the antibody levels are satisfactory.

This assumes, of course, that the extent and duration of the multiplication of the virus in the walls of the alimentary tract is related to the degree of resistance produced. There is some evidence for this supported by the recent findings from Hungary (Dömök et al. 1961) that reimplantation of a strain occurs most readily after a short period of virus excretion.

This may mean that the control of the virus in the community may be little better than with the killed vaccine and in the face of large numbers of the population having poor gut resistance an epidemic of polio could occur and the protection of the individual by triple vaccine would be less comprehensive than with the single spaced feedings. This seems to demand further investigation.

There is some evidence that after natural disease and feeding with attenuated strains there is a greater measure of gut resistance against type I virus than II and III. Type III virus is said to produce the least degree of resistance (Dömök et al 1961).

The susceptibility of the host to the virus infection varies at different ages and for the first 1-2 months of life the child is rather more resistant than older children to the same dose of virus (Koprowski 1960). This may at first be due to the presence of transplacental antibodies in the gut for the antibody response is inversely proportional to the level of maternal antibody (5th Internat. Conference, Lancet 1960). However, these very young children usually develop an intestinal infection if the dose is increased 10 or 100 fold and those who fail to be immunised at the first feeding can be successfully refeed when somewhat older. It has been shown that the ability of the antibody-forming tissues to react depends on their being presented with antigen at a time when they are mature, and antigen tolerance can be induced by their experiencing the antigen in immaturity. This has been suggested as the basis of the connective tissue diseases. However, the successful immunisation of children immediately after birth has excluded this possibility. Children older than two months

establish an infection in the alimentary tract as readily as adults.

There is therefore much to recommend the immunisation of children shortly after birth (with a second dose at 6 months) or perhaps at 2 months of age when the seed virus is almost certain to multiply in the gut. Triple or single spaced methods may be tried.

The advantages may be summarised:

1. The virus can be administered to all children when they are still under medical care.
2. There are less likely to be interfering enteroviruses.
3. The result will be a wide population coverage.
4. Immunity may be long lasting, although this is uncertain.

(Koprowski 1960).

#### DANGERS

No cases of major illness nor of paralytic polio have been definitely ascribed to the vaccines although reliable markers are desirable before any final verdict is given on their safety. All cases occurring within 30 days of vaccination are carefully investigated, although the Russians assume that cases of polio developing within 21 days after feeding the vaccines are examples of infection with wild viruses before the vaccine virus has had time to create immunity.

The potential danger of the attenuated virus showing a reversion to virulence has been discussed and the Russians consider this an academic problem. (5th Intern. Conference).

Some strains give rise to a minimal degree of viraemia and although the comparison of results is unreliable owing to differences in technique,

the Sabin strains seem least frequently incriminated. When there are no maternal antibodies this may be a source of danger to the foetus although no effects have been noted; the abortion rate is unaltered. In these circumstances it is probably desirable to give killed vaccine 2 weeks before the live vaccine so that any viraemia will be suppressed.

Triple negative adults are particularly susceptible to paralysis and although no cases have been recorded as a result of the live vaccine, very large numbers of immunisations may have to be performed to produce a case. Any slight risk would be nullified by the previous administration of killed vaccine, although in epidemics the risk of paralysis from a virulent strain is greater and live vaccine should be fed. When children are fed the live vaccine unimmunised parents may be running a slight risk of contracting paralytic polio and should be immunised with killed vaccine. This may, of course, be followed by live vaccine.

The occurrence of viraemia and multiplication in the gut contraindicates the use of live vaccine before surgery, particularly on the oropharynx.

In the U.S.S.R. the only contraindications are -

1. Acute febrile states or other evidence of acute illness for 2 weeks previously.
2. Diarrhoea, intestinal disorders, T.B. and cardiac failure.

In view of the animal experiments mentioned, care should be exercised in the administration of the vaccine to subjects undergoing steroid therapy, and agammaglobulinaemia although very rare should be remembered.

The previous administration of  $\gamma$ globulin or 3 or 4 doses of killed virus vaccine has no effect on the establishment of the alimentary tract infection

although the infection in the pharynx may be suppressed (Koprowsky 1960). More potent vaccines may be found to have some effect (Dick and Dane 1959).

The persistence of antibodies has not yet been fully investigated although there seems no reason why the decay should be difficult from that found after natural infection, the levels dropping between 4 and 20 times in 1 or 2 years. Koprowski (1960) reports the persistence of type II antibodies for 8 or 9 years, the longest yet recorded.

#### Protective effect

There are several reasons why the controlled prophylactic trial, which has been so useful with other vaccines is not readily applicable to this particular problem. In the first place, many of the countries which experienced high morbidity from poliomyelitis in the past have used Salk type vaccines on a large scale, and it would not be easy to allocate individuals in a population randomly to receive either inactivated or live virus vaccine. Secondly, due to the great reduction in morbidity in the countries, very large populations would have to be studied to give any chance of seeing sufficient paralytic polio to provide an assessment. Thirdly, because there is the possibility of the vaccine spreading to contacts, an unknown number of those protected ostensibly only by killed vaccine, would in fact harbour the live vaccine as well. This would, of course, invalidate any comparisons.

As an alternative to the controlled trial as a method of assessment reliance has been placed either on the comparison between areas in which attenuated virus vaccines have or have not been used, or on the trend of

morbidity, before and after the use of such vaccines. Past experience of this disease has, however, been so unpredictable in both time and place that such comparisons cannot indicate immediately whether a specific prophylactic is responsible for any change in pattern. Repeated demonstrations of the association of vaccination with reduced morbidity would carry more conviction, but such evidence would not provide a quantitative assessment of protective effect. Laboratory tests of potency, such as the measurement of the ability to produce antibodies may not be a valid method of comparing inactivated and attenuated vaccines because the former do not aim to produce alimentary resistance (Knowelden et al. 1961).

Field results have followed two rather different patterns one being representative of the findings in endemic areas and the other in epidemic areas.

In endemic areas the vaccines have been used with less success due largely to the degree of interference by other enteroviruses. The spread of the attenuated viruses in the community has been less than expected and this has resulted in rather poor population coverage.

In the Belgian Congo a Koprowski type I strain achieved only 60% seroconversion.

In Toluca, Mexico, where 90-100% of the children gain antibodies to all three types of virus in the first 4 years of life at the expense of approximately 14 paralyses per year, there was a very high level of enteric infection beginning a few days after birth and reaching a peak of 72% during the first year of life. In an attempt to overcome these natural enteric viruses, Sabin (1960) fed triple vaccine to a large proportion of the

children under 10 years over a very short period. As a result of this blanketing effect the polioviruses quickly became dominant and then rapidly declined (see above).

The conversion rates for types I and III varied according to whether the people were serologically single, double or triple negative.

Conversion Rates

<u>Serotypes</u>	<u>Single</u>	<u>Double</u>	<u>Triple</u>	<u>Overall</u>
I	100	88	55	68
II	82	80	83	82
III	59	42	37	43

This demonstrates clearly the occurrence of interference and the dominance of the type II strain used.

After 2 feedings the overall conversion rates were 96%, 96%, 72% for types I, II, III respectively, thus effecting in a few months a degree of immunity with no deaths nor palsies which would, in the course of nature, have taken 4 years at the cost of 56 cases of paralysis.

The virus depends on the balance between the susceptible and the immune for survival and was almost eliminated after these feedings. These children now have little chance of gaining natural immunity in this environment and must be vaccinated in the first 6 months of life or a potentially epidemic population will grow up.

The results from epidemic areas, when single serotypes are fed in sequence in the winter months, are more encouraging. Under these conditions conversion rates of nearly 100% for all types are claimed.

A striking reduction in incidence was observed in Estonia and Lithuania in 1959 where mass vaccination was completed by June of that year (Mass Immun. with Live Vaccine in Soviet Union).

	<u>1955</u>	<u>1956</u>	<u>1957</u>	<u>1958</u>	<u>1959</u>
Estoria	180	213	102	963	8
Lithuania	411	247	124	264	17

These results must be viewed with caution as no control trial was carried out and dramatic reduction in incidence can occur without the agency of man.

#### Effect on Epidemics

The killed virus vaccine takes several weeks to confer protection and is of little value in an emergency. However, the immediate interference of one virus with another is less type specific than the more slowly produced lasting immunity and may have an aborting effect on an epidemic.

Hale and his colleagues (1959) were faced with an epidemic in Singapore caused by a type I virus in the latter part of 1958 and they fed almost 200,000 children a Sabin type II virus vaccine. This epidemic was preceded by the two warning signs (Paul 1958); for the infant mortality fell from 215/1000 live births in 1945 to 41/1000 live births in 1957 and a case of polio occurred in an 8 year old child.

Six cases of paralytic polio caused by type I virus occurred in those inoculated and none of these occurred within 10 - 20 days after vaccination which was the period of maximum interference. 179 paralytic cases caused

by type I virus occurred in approximately 300,000 unvaccinated children in the same age group. There were no type II cases in the vaccinees.

The peak of the epidemic was reached before inoculation was initiated. In the early part of the vaccination period, when the incidence of poliomyelitis was high, the unvaccinated group was large and the vaccinated group small. By the end of this period, the vaccinated group was relatively large, but the whole population, vaccinated and unvaccinated, was subject to a small risk. Even if the vaccine had been completely valueless the attack rate, counting cases since vaccination started, would appear to be far smaller in the vaccinated group than in the remainder who were never vaccinated. The interpretation of the findings is therefore difficult. After a reanalysis of the results (Knowelden et al 1961) it is concluded that the type II vaccine afforded considerable protection.

A similar situation was described in Mauritius by Teelock (1960) where both killed and live vaccines were used.

#### Salk or Sabin?

After touching briefly on some of the features of both vaccines and the results they have achieved, it is pertinent to consider their relative merits.

1. Cost and ease of manufacture. The attenuated vaccine was originally manufactured with much less labour than the killed vaccine but great trouble is now involved in testing for and eliminating adventitious agents. As no inactivating procedure is used, any adventitious agent can multiply as well as poliomyelitis virus.

2. Ease of administration. An oral vaccine obviously involves the administrative staff in less work and is less unpleasant for the recipient. This may have a favourable effect on the numbers coming forward for vaccination; in the U.S.A. only 32% of the population under 40 years of age have received the recommended 4 doses of killed vaccine and in the age group 5 to 9 only 50% (Langmuir 1961).

3. The oral vaccine spreads to others in some measure and this confers a wider immunity among the population. The vexed question of increased virulence after human passage has been mentioned. Although the spread is less than originally thought and no marked increase in virulence has been noted, it is often thought advisable to feed a large proportion of the population at the same time and thus reduce the risk of causing poliomyelitis due to the spread of viruses of increased virulence. This presents certain administrative problems.

4. The live vaccine may have an aborting effect on epidemics not shared by killed vaccine. This may prove to be of great value.

5. There are indications that immunity conferred by Sabin's vaccine is the longer-lasting and it has the advantage of providing two lines of defence - gut resistance and antibodies.

For reasons explained above it is very difficult to obtain a comparison of their effectiveness.

6. Disease eradication. By conferring gut resistance, there is a good chance of banishing virulent strains entirely from the community with the Sabin vaccine. It is doubtful if this end is attainable with Salk vaccine.

The advantages seem to lie with a Sabin type vaccine but it is not without its dangers. Many countries have decided to combine the two courses and this is theoretically safer (see above).

Britain is withholding the live vaccine at present and this seems a wise step, for a number of questions on dosage, spacing of doses and length of immunity remain to be answered in the context of the British environment.

#### Signs of epidemics

Paul (1958) showed convincingly that when the 5 year average infant mortality fell below 70-80/1000 live births, there was a danger of an ensuing poliomyelitis epidemic. The numbers dying in the first year of life /1000 live births is an index of sanitation and reflects the prevalence of these serious infections which are apt to attack infants. The occurrence of cases of poliomyelitis in older children is also a pointer to the presence of a non-immune population.

The epidemiology of poliomyelitis held the key to its successful control. As great material advances are made in Africa and Asia the disease will rapidly alter in character as it did in the Western world, and it is imperative that the signs of an impending epidemic be looked for and appropriate measures be taken. There will be an increasing demand for vaccines and for the programmes to be a complete success full vaccination of the population at no risk must be sought. The safety of any vaccine will ultimately be confirmed in man not monkey and with live vaccine programmes there is a very real chance that this scourge will be annihilated.

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