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THE EPIDEMIOLOGY AND CONTROL OF POLIOMYELITIS.

Peter G. Rose,
The Island of St. Helena, 1834.

"... An epidemic spread among all the children on the island about three or five years of age .... all the children who had the fever were .... affected with a want of growth in some part of their body or limbs."

(Sir Charles Bell, 1836.)

The elucidation of the epidemiology of Poliomyelitis has been hampered since the time of Bell both by its complexity and, no less important, the failure to recognise the disease when it occurs.

In its epidemic form the disease is new, for it is extremely unlikely that outbreaks of the size recently experienced in the U.S.A. and elsewhere would have gone unnoticed in the past. No reports of a disease resembling epidemic poliomyelitis can be found prior to that of Sir Charles Bell in 1836, and indeed the first description of any form of polio was only made in 1789 by Underwood, a London physician.

Poliomyelitis did not attract the attention of physicians until the end of the 18th. century, but by the beginning of the 19th. century the disease was geographically widespread. 'Teething Fever' and 'Foul Bowels' were common diagnoses, and North American Orthopaedic surgeons in the 1830's referred to club-foot following such 'Teething troubles'. Other, more recent, diagnoses have been 'Radiculitis' (34), Dengue or Sandfly fever, (46)

After the St. Helena epidemic of 1834, Scandinavia and the U.S.A. were affected and by 1900 the disease was a periodic scourge. It was about this time too that a change in the age incidence was noticed. Infantile paralysis grew into Poliomyelitis, a disease of many forms and a wide age incidence.

Before any attempt to unravel the epidemiology can be made, a reliable notification system must be introduced and here it is that a major difficulty is found. The disease exists in both endemic and epidemic forms, and within each of these it may manifest itself in any of the following ways:

1) Subclinical, Asymptomatic or 'Silent' polio.
2) Abortive: 24 to 48 hours duration and showing the typical symptoms and signs of a febrile illness.
3) Non-Paralytic: Symptoms similar to the above but with additional paraesthesia resembling 'Virus' or 'Abacterial' meningitis. Duration: 4 - 7 days.
4) Paralytic Poliomyelitis: Spinal or Bulbar or both.
5) Additional encephalitic manifestations: Coma, Tremors etc.

The diagnosis of any but stage four is no easy matter without the help of a virologist, and even today there is no rapid, reliable test for the presence of poliovirus generally available.

The situation is further complicated by cases of 'Polio' due to other viruses. Schär, (56) reports that 65% of non-paralytic cases in Switzerland during 1958, were caused by ECHO virus and Coxsackie viruses have been isolated from fatal cases of paralytic poliomyelitis. (74) In one recent experiment conducted on 24 cases of paralytic polio, (Virus tests being made on 21), 19% were due to Coxsackie B2 or B5. (59)

Other errors, primarily in the existing forms of notification, will be mentioned as the need arises, and their possible influence on the validity of any quoted results will be discussed.
The following factors must be considered in the description of the epidemiology of Poliomyelitis:

a) What is the causative organism, and to what extent do the individual characteristics of that organism contribute to the spread and mode of expression of the disease?

b) Since the disease exists in several forms, do any of these forms show a relationship to the incidence of infection?

c) How does the disease spread in the infected host? How does it spread on a world-wide scale?

d) Does any degree of immunity exist toward infection by the organism, and if so, what form does this immunity take? Does immunity have any effect on the spread of the disease?

e) Are there any non-specific factors which affect either host resistance or the virulence of the organism; which facilitate spread of the organism?

The control of the disease must be aimed at the eradication or improvement of any or all these factors, at the same time bearing in mind that the method of control must be reliable and effective.

Causative organism.

The Poliovirus was discovered by Landsteiner and Popper in 1909 at the same time as Wickman was laying the foundations of the epidemiology, basing his theories simply on the infective nature of the disease. The virus was later isolated from stools by Kling in 1912 and Sawyer in 1915.

The virus is now known to exist in three distinct serological forms of which the prototypes are known as Brunhilde, (Type I), Lansing II, and Leon III. By filtration methods the virus was known to be less than 27 millimicrons in diameter and electron microscopic work has since shown it to be between 10 and 20 millimicrons in diameter. It is thus the smallest known human pathogen. Spherical in shape and containing about 25 to 30% RNA, it is one of the most stable organisms known, being active over a pH range of 2 to 11 and resistant to dry heat alone up to 57 - 60 degrees C. The virus may remain viable over a wider range still if it is suitably protected by animal tissue or faecal matter.

In general, Type I is responsible for most epidemics and approximately 85% of paralytic cases, and Type II for endemic poliomyelitis but with the advent of rapid, long distance transport, any type may be incriminated as the causative organism in a given epidemic. Type III epidemics have occurred in some parts of the world.

Several in vitro characteristics are known and will be mentioned later in relation to the testing of vaccine strains for neurovirulence. Serological characteristics are no longer believed to as distinct as was formerly supposed since Salk has demonstrated a certain degree of cross protection between types II and I. (55)

The viruses are of world-wide distribution and there is no proven association between strain, locale and mode of expression other than that which can be accounted for on the basis of immunity.

It is suspected by some workers that there may be an interaction of some form between the polioviruses and certain other enteroviruses. Stern, (59) comments on the prevalence of Coxsackie virus infections when paralytic polio is uncommon and vice versa. These viruses are notable for confusing the non-paralytic polio notifications since they often produce a meningo-encephalitis, (B series only).
Ratio of apparent to sub-clinical/silent infection.

This is a question of considerable importance because in many instances, the quoted incidence of poliomyelitis is based on notifications of paralytic poliomyelitis alone, no mention of non-paralytic incidence being given unless they were in great numbers.

Until serological typing became possible on a wide scale, it was not possible to ascertain whether there was any statistical relationship between the incidence of paralytic disease and the overall case incidence. One estimate carried out on the sewage from a New York drainage area, (Four notifications; 625,000 people), gave a Silent/Paralytic ratio of 1000:1. (36)

The ratio is now known more accurately and Paul, (36) quotes the following results:

<table>
<thead>
<tr>
<th>Frank/Abortive</th>
<th>Paralytic/Silent</th>
<th>Age Range</th>
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</thead>
<tbody>
<tr>
<td>1: 5.2</td>
<td>1: 175</td>
<td>0 - 1 years.</td>
</tr>
<tr>
<td>1:7.7</td>
<td>1: 62</td>
<td>1 - 4 &quot;</td>
</tr>
<tr>
<td>1:7.5</td>
<td>1: 95</td>
<td>5 - 9 &quot;</td>
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</table>

Unfortunately the validity of these figures is questionable since they are the results of epidemic studies carried out in two places at wide intervals. Each column of results is valid for the epidemics in question but would probably be erroneous if applied to other epidemics in other regions or to endemic polio in the same region. Such figures cannot be universally applied and merely serve as a general indication as to what these ratios are likely to be. The presence of paralytic polio in a community can only be regarded as the clinical manifestation of the spread of virus strains through that community.

The death rate is even less reliable in assessing the severity of an outbreak or its dissemination throughout the community since it depends on the quality of group immunity and individual host susceptibility more than on the virulence of the invading strain.

One can indeed give the mortality rate for a given community during an epidemic, but it is of little value if the immunity status is not also taken into account. The civilian mortality rate during the 1942/43 epidemic in Malta was 3.5% of all notified cases, whereas among Service personnel it was 19%. (5; 35; 62) These figures alone are meaningless until the age distribution and factors of immunity are also considered. As will be seen later, these values take on a different light when it is found that out of the 426 civilian cases, no fewer than 422 were among children, with only one fatality.

Mode of spread in the infected person.

It is now generally accepted that primary infection begins with the ingestion of the virus. From initial experiments in cynomolgus monkeys it was thought that infection occurred following the inhalation of droplet nuclei. The virus was then believed to travel along the nerves, particularly the Olfactory nerve, to the Central Nervous System whence they spread to eventually localise in the anterior horn cells of the Spinal Cord. (36)

Since that time, and especially since experiments with live virus vaccines, it has become known that the primary infected site is the lymphatic tissue of the alimentary tract. (52; 71) Here the organism multiplies, setting up a local infection in the gut wall, before passing through the lymphatic system, via the Thoracic Duct, into the systemic circulation where there is a resulting viraemia.
The organism can be isolated from the blood 4 - 6 days after exposure to the disease; from the fauces and pharynx from 4 - 14 days and from the faeces from 4 days to a maximum of 20 weeks after the initial infection. Most people however stop excreting the virus after the fourth week. No long term carriers have been found and the Typhoid fever type of carrier has never been demonstrated.

The first week after infection seems to be the most infective period probably being due to the large quantities of virus excreted during this time and also to the host's continued association with other people before the prodromal fever is experienced. The incubation period varies from 4 to 28 days following exposure to infection, the former period being the most common, and there is no guarantee that the victim will go to a doctor if he feels unwell. (24)

The degree to which the individual is affected probably depends more on his own resistance than on the virulence of the prevailing strain, and depending on the degree of his resistance, he may show one of the clinical appearances mentioned above, ranging from the vague 'Abortive' to a full bi-phasic disease culminating in bulbar paralysis and death.

Once an individual has been infected, he is a source of the virus for all his acquaintances, the members of his own family, (12) and other intimate associates being in the greatest danger. Melnick; and Horstman, (35) in experiments on a nursery school population, showed that spread of the virus was up to 35% greater at home than at school where more rigid control of dissemination is possible.

The spread from one individual to another is by direct contact as is well shown by the results of Peart's work during the 1948 epidemic among Canadian Eskimos, (41) and may be by faecal contamination or possibly by droplet spread. This last is a debatable point and Sabin, (46) discards droplet nuclei as a mode of spread and suggests that only in the case of nasal carriers, e.g. in pyogenic streptococcal infections, is droplet spread of any importance. No other droplet spread infections have the same seasonal incidence as is shown by Poliomyelitis.

As mentioned above, the victim's own family should be in the greatest danger but the actual number of multiple cases of paralysis occurring during an epidemic is surprisingly small. In the 1957/58 epidemic in Mauritius, there were no multiple cases in families despite overcrowding, yet in the 1945 epidemic there were 24 multiples in 1018 cases.

Spread on a world-wide scale.

It is now well established that polio is a highly contagious disease spread by intimate contact and often by unwitting carriers. It follows that the degree and rapidity of spread will follow lines of human movement and will be dependent on the prevailing local, national and international modes of transport. This is demonstrated well by the trans-European spread of the disease during and after the Second World War. In this spread from the Eastern Mediterranean countries in 1941 to Malta, 1942 and 1943; South Africa and France, 1945; Africa, Italy and France in 1946; and Britain, Germany and Austria in 1947. (71)
Other vectors are involved in the transmission of the disease, and this discussion must include the following possible means of transfer:
1: - Direct human contact i.e. with known infected persons.
2: - Direct contact with carriers of the virus.
3: - Transmission via fomites, this in turn being related to the social status of the population and hygienic standards of the community.
4: - Role of animal vectors.
5: - Role of insect vectors.
6: - Water-borne infection and its importance in any of the above groups.
7: - Possible long term reservoirs.

It must be remembered that all these factors give no guarantee that any one individual will be infected. As noted before, this depends almost entirely on the status of that individual's immunity. This topic will be fully dealt with under the section concerning Host/Group immunity.

Contact with infected persons.

Spread from infected persons may be by direct transfer of pharyngeal secretions, though Sabin considers this to be possible only in cases where disphagia may result in an excessive localisation of the virus in the oropharynx. (46) It may also be facilitated by simple mechanical transfer or, more important, by faecal contamination. This last is of particularly great importance in poor communities where overcrowding is common and sanitary facilities are limited or non-existent. The disease is spread as easily as Bacillary Dysentery and an estimated 1 Million Monkey-Lethal doses of the virus per gramme of faeces may be found in the faeces from an infected person. (36) This is demonstrated by the lower incidence among extra-household contacts than in the family, and the still lower incidence among non-contact persons in the area.

The age groups primarily affected by all factors mentioned here will be discussed in detail under the section on immunity.

Another means of direct infection which is of great immunologic importance is infection in utero, which may occur during the viremic phase of a polio infection in the mother. The end result of this is not that the child may be still born but that the maternal infection results in a depletion of the maternal antibody level. The new born child is therefore without its normal, passive placental immunity to polio which results from maternally transmitted antibody, and may succumb to infection shortly after birth. There is also a high rate of paralysis and death among women during pregnancy.

The evidence for the theory of direct spread is considerable, and a few reports are worthy of mention. Paul, (36) draws attention to the relative rates of spread of measles and polio from Tahiti to the Marquesas on two separate occasions, (1950 and 1951). The time of appearance of both diseases in outlying areas was almost identical. The same authority also quotes a rate of spread of 0.1 to 0.5 miles per day in certain states of the U.S.A. depending on the local transport and the 'Hot' or 'Cold' nature of the contacts. (10)
Carrier contact. Human.

The importance of carriers in poliomyelitis cannot be overemphasised since they are a source of potential danger to the whole community, and, as often as not, are unaware of their infective state. Following any inapparent or overt infection the person must be regarded as a carrier for a period of up to 17 weeks or until excretion of the virus ceases, as indicated by virologist's reports.

The danger here is that the disease is widely disseminated throughout the community before it is realised that polio is epidemic in the region, and no Public Health control measures are of any avail in restricting the spread once this stage has been reached. The advent of serological typing has improved the possibility of diagnosing carriers, but until these facilities are universally available, large scale diagnosis of the carrier state is not a practical proposition.

A carrier state may result from any degree of infection with the virus and its importance in the epidemiologic spread of poliomyelitis is brought out in this report by Peart. (41)

In the July of 1948, an Eskimo hunter was in contact with two cases of polio in the town of Churchill. This hunter then travelled, during September, to the settlement of Nuneau, where two cases were reported in the first week of October. He then travelled to Eskimo Point where three cases occurred, one of these being a policeman, who later went to Padlei, and the other being a missionary, who was confined, but permitted visitors including a fellow missionary, who went on to Chesterfield Inlet. By the beginning of the following year there were seven cases of polio in Padlei and fifty-four at Chesterfield, with a total of sixteen fatalities. During the whole of this epidemic no less than 60% of the Eskimo population was paralytically affected, the lowest attack rate being among infants, the reverse of the usual epidemic appearance.

The 1954 St. Helena epidemic has been mentioned already. A further epidemic occurred there in 1945 among a virgin population. It is interesting to note that the last ship to call at the island before the onset of the epidemic had called at Durban and Capetown where an epidemic had just occurred. (16)

The value of carriers in the dissemination of virus throughout a community is reflected in the rates of spread quoted above and by the frequent inability of investigators to find any connection or history of exposure to infection. As recently as 1959, in the epidemic on the island of Mauritius, the whole island was affected with a case rate of 15/100,000, yet, in all reported cases but one no connecting link could be found and, even more strange, there were no multiple cases. (60) Even Paul et al. could find no evidence of patient contact in Cairo in 1943. (38)

The rate of spread during a particular epidemic also has a bearing on this question. The weekly case notification rates commonly show a rise from week 3 reaching a maximum in the region of the 7th. to 8th. weeks, thereafter regressing until the end of the epidemic, usually about the 15th. week.

Reference to the results from several epidemics in Mauritius, (1945; 1948/49; 1950; 1959), show that in each epidemic year the weekly case rates were parallel to a great extent, and the duration of each epidemic was approximately the same, despite the use of Salk vaccine throughout 1957; 1958 and 1959.
This would suggest that from the earliest weeks, the virus is spread through the population in ever increasing waves, on the principle that 2 people will infect 4; 4 will infect 8, etc., until the number of susceptibles remaining is less than the number infected. This is when the peak of the epidemic is reached, the remainder of the population being immune to the circulating virus strain. This is further borne out by Seddon’s, report on the 1945 outbreak in Mauritius, when it was noticed that the incidence of double limb paralysis decreased as the epidemic progressed, whereas that of single limbs increased, particularly after the peak of the epidemic. This might indicate that at the peak, the virus was attacking people with only a minor degree of immunity but who were able to localise the lesion. The principal mode of spread thus also, to a large extent, accounts for the self-limiting nature of the disease.

Virus characters change during the course of an epidemic so that a strain of weaker neurotropism results. This is possibly the cause of cases showing only paralysis of the Masseter which often herald the end of an outbreak. This may be seen in up to 24% of cases. (3; 53; 62)

To summarise, it may be said that the disease shows a wave like advance from some focus as yet undetermined and that the spread often occurs via mild or sub-clinical cases, all of which may carry the virus for up to a maximum of twenty weeks. The appearance of paralytic cases is the clinical evidence of the spread of the virus strain through the community, and the rate and degree of the dissemination is dependent on the mode, or modes, of human movement within that community. The spread often follows lines of communication with such regularity that some workers are now attempting to plot the currents in the sea of spread. (14)

**Influence of Fomites.**

As the poliovirus can remain viable under a wide range of adverse conditions, provided it is suitably protected e.g. by faecal matter, it is reasonable to propose that it may be transferred by means of some inanimate intermediary. These fomites might also serve as reservoirs for the virus during inter-epidemic periods as well as being ever present sources of the virus to anyone who might handle them.

Anything coming into contact with faecal matter is open to suspicion, and even the outflow of otherwise efficient sewage works has been found to be heavily contaminated with poliovirus during epidemic periods. (71) This in turn raises the possibility of a role for insect and animal vectors in virus transmission.

Anything which has been in the hands of a carrier may act as a fomite and for this reason it is inadvisable to have suspected carriers engaged in the preparation or packing of foodstuffs, infant teaching, or child nursing, especially in relatively closed communities.

The renowned hand-to-mouth transfer of S. sonnei is duplicated by that of polio. Toilets, towels, door knobs, kitchen utensils and cutlery, children’s toys, any school equipment and anything used by children, particularly infants, may be a source of potential infection to others. Such fomite spread is practically impossible to detect except in very rare cases and is equally impossible to control. The situations where control might be effective is in the removal of large reservoirs of the virus e.g. the removal of all open latrines such as still exist in many regions in Britain.
The poor standard of sanitation on the railways has also been accused of making railway tracks a source of virus available for mechanical transfer by flies. This has not been proved to have any effect on the spread of polio virus but it is certainly possible for the virus to be transferred by flies and other insects. (71; 36; 46)

Hospital wards which have been used for the isolation of infective cases may also serve as a focus of spread for this disease throughout a hospital. This question of fomite spread will again be mentioned under the discussion on Public Health measures in the control of polio.

As mentioned above, one gramme of faecalmatter may contain up to 1 million M.L.D. of virus, therefore the degree of fomite spread within a community is related to the social level of that community and hence to its hygienic standard. This is reflected by case incidence and immunity status of populations with high social/low hygienic; restricted social/high hygienic standards. This topic is again more conveniently dealt with under the heading of immunity.

**Rôle of Animal vector.**

The rôle of animals in the epidemiology of poliomyelitis is still a doubtful entity and, if polio does in fact occur in animals, is the virus involved transmissible to man? Is the virus then capable of causing the disease in man and if so, are its characteristics modified in any detectable manner?

The Java monkey, (Macaca cynomolgus), has long been used as an experimental test animal in the testing of virus strains for neurovirulence and has also been used to a great extent in epidemiologic studies relating to the spread of the poliovirus through the host animal. (71; 52)

Indeed these animals still remain the most reliable test of poliovirus pathogenicity available. (74; 7; 40)

So far as is known, none of the animals with which man usually surrounds himself is susceptible to polio and it is therefore unlikely that they could serve as a silent source of disease for man. There have however been reports of spontaneous infection of chimpanzees by humans. (71)

It has also been reported that human outbreaks are preceded by a paralytic disease, occasionally epidemic in nature, in fowl and some mammals. (71)

Even budgerigars have been incriminated. (10) These have not been verified either by isolation of the virus or by demonstrating experimental infection in these animals. Sera from domesticated animals is occasionally found to neutralise poliovirus but it is not conclusive evidence of these animals being infective. In spite of domestic animals being in such close contact, especially in primitive regions, there is no concrete evidence for supposing them to be involved to any great extent in the spread of poliovirus.

Attempts have also been made to isolate the virus from animals which might become infected after contact with water contaminated with sewage, treated or otherwise. Transfer of the virus by Protozoa has been investigated but has given negative results as have similar experiments on fish found in contaminated waters. (46)

Some rodents can be shown to carry polioviruses, but all strains so far isolated are non pathogenic for monkeys and apparently non pathogenic for man although they can be successfully innoculated with human strains. (46; 71)
Insect vectors.

The importance of insect transfer in the epidemiology of polio is again doubtful but since such transfer is definitely possible and often suggested in the absence of more reliable causative factors, the various forms of transfer must be considered here.

Mechanical transfer by flies and other insects has long been recognised and Sabin proved this by causing paralysis in chimpanzees fed with food contaminated by house and Blow-flies caught during the height of an epidemic. His results were supported by those of Ward et al in 1945. With this evidence available it was then suggested that flies were responsible for the seasonal incidence of polio in temperate countries and were important in the spread of virus during a polio outbreak. No supporting evidence for this view has been found and indeed the removal of much of the fly population from cities during the course of an epidemic has had no observable effect on the case incidence, though this is not valid evidence against fly spread since by the time such measures are put into operation the virus is probably widely disseminated throughout the community. The question of seasonal incidence and fly spread is as difficult to refute as it is to prove since so many factors are involved, not the least of which is the increase in the number of people who visit doctors during the summer months through fear of developing polio. Such an increase in 'patient density' invariably leads to an increased notification rate of 'non-paralytic polio'.

Repeated attempts have been made to implicate blood-sucking insects but again there is no proof that the virus can be transferred by insect bite since no virus multiplication can be demonstrated in these insects. Some Japanese workers did find that the virus could survive in artificially infected mosquitoes, (Culex pipiens), for periods up to three weeks. (56)

We are therefore left with only the proven possibility of mechanical transfer by insects. How may such transfer effect human infection by the virus?

The only route by which an infection may be thus acquired, is oral so any materials which may be put in the mouth, mainly food, can act as fomites.

Food is the principal item to be implicated and many cases are reported in which food is the suspected, but not proven, aetiological factor. (51)

Elimination of transfer by flies is hardly feasible and in the few instances where it has been attempted, no beneficial effects have been noticed.

Water borne infection.

The treated sewage from otherwise efficient plants may be heavily contaminated and in this condition is often discharged into rivers and other natural water systems. Since most sewage systems are of the water-carriage type, there is a possibility that the virus may be spread throughout the community by faults in the sewage system. The primitive sanitary measures used in many parts of the world, particularly where the majority of the people are maintained by their own farming, also provide a potent source of water borne virus.

This then raises the possibility of animals and plants, protozoa and insects, as well as man becoming carriers of the virus. So far there has been no report of virus isolation from protozoa or plants even in those growing on infected sewage.
Localised outbreaks of polio among fruit workers occurring during the season are often attributed to eating cultivated strawberries which are grown on irrigated plots. There is no confirmatory evidence for this.

Fish, sea-birds and cattle have all been investigated without any success and, in general, it would appear that infection of man via water and intermediate animals is unlikely.

Man himself can be infected directly by contaminated water and he in turn may contaminate water that others use and facilitate spread in that way. Unchlorinated swimming baths, fresh water used for bathing and polluted sea water may become involved in this Man...Water...Man cycle of infection. Cases of multiple polio within a family after swimming in polluted pools, are difficult to assess, since most members of a family become infected at about the same time. The effect of a crowded household is, in all probability, of more aetiological significance than the pool.

Contamination of fresh water supplies does not appear to play any part in virus spread and has not been demonstrated.

Long term reservoirs.

There are several possible long term reservoirs for the polio virus but no single one will account for the great variability in both the intervals between outbreaks and the extent of those outbreaks. The epidemiology is such that, in temperate countries, the disease only becomes epidemic during the summer months and few cases occur in winter. It is probable that the few sporadic cases found in winter are the clinical manifestation of the persistent, inapparent infected state of the community i.e. the endemic form of the disease is shown as it would be if there were no facilities for epidemic spread. The principal reservoir is therefore human and, since any form of polio infection results in the excretion of the virus for any period up to 20 weeks, (Average 5 weeks), only six successive subclinical or clinically undiagnosed infections are required to carry the virus through the winter season. The size of this reservoir is impossible to determine without an extensive serological survey covering the whole of any isolated community. Surveys on a small scale have been carried out in many parts of the world, preparatory to the testing of polio vaccines but in most of these surveys only the immunity status has been determined and tests for the faecal excretion of virus are usually only made during the course of epidemics.

In the absence of true endemic polio, the continued presence of the virus throughout the winter may be due to the continued existence of untreated sewage, in which the virus may remain viable for several years, or to the existence of an animal ingestion/excretion cycle as yet undiscovered.

Since major epidemics seldom occur in the same region in successive years and are often separated by an interval of three to seven years, (14; 36), affecting the same group of countries in a similar pattern during individual outbreaks, it would seem likely that the virus is dependent principally on human carriage for its long term propagation. The disease becomes prominent only when a series of other factors conducive to spread and infection are present in a suitable pattern for the regions involved in the outbreak.
Some of these factors related to dissemination of the virus have been mentioned above. Other factors related to host and group immunity will be discussed later as will several non-specific aetiological agents whose rôles in host immunity and virus spread are complex and, in many cases, not proven.
Immunity to the infection: In the individual.

A detailed description of the various forms of immunity would be out of place here but in any one community there may exist, according to the age of the individuals concerned, either immunity due to previous exposure to the disease or that resulting from vaccine administration.

A further immunity exists in the youngest age groups which is due to the presence of maternally transmitted antibody. The importance of group and ethnic immunity is discussed separately.

In any person the manner by which immunity is achieved is difficult to determine. Immunity is produced by at least two separate components: cellular and humoral mechanisms both being involved. Other agents are probably involved as well but the two mentioned above are the most important in recovery from a virus infection and, of the two, cellular immunity probably has the more important role. Non-humoral mechanisms are undoubtedly involved since children with agammaglobulinaemia will show immunity to the measles virus after infection yet they have no antibody system.

Cellular immunity.

The intracellular growth of viruses is dependent on the pH, temperature, suitable cell receptors and the availability of proper enzyme complexes among other things. This growth may be intranuclear or simply in the cytoplasm. It is possible for two viruses to multiply within the same cell, one in the nucleus and another in the cytoplasm e.g. measles and polio, without interference occurring between the two.

The phenomenon of interference is of great importance in cellular resistance and also intrudes in the field of control by live-virus vaccine.

Interference is the action of a virus on cells as a result of which the cells are rendered unable to support fully the growth of immunologically related or unrelated viruses. (25)

An animal inoculated with one virus may become temporarily resistant to infection by another and perhaps more virulent virus.

There have been several theories as to the mechanism of viral interference but it is now known that when viruses are incubated on various tissue cultures a protein-like substance with all the interfering activity of the original virus is produced. This compound has been partially purified and has been called Interferon. The mode of action of Interferon is believed to be by uncoupling of enzyme systems associated with oxidative phosphorylation within the cell, thus limiting the amount of ATP available for viral synthesis. This also accounts for the lack of action of Interferon in cancer cells which can produce all the ATP required by anaerobic means. (27)

Formaldehyde inactivated viruses cannot produce Interferon but viruses inactivated by other means can induce Interferon formation which is effective only against further doses of inactivated vaccine but not against live virus. Cells stimulated to produce live virus cannot make Interferon therefore the ability of a cell to produce live virus is inversely proportional to the Interferon production. (25)

The role of Interferon in recovery from a virus infection is shown by experiments where both Interferon and antibody titres are taken throughout the course of a virus infection e.g. Influenza, following exposure to the virus. It was found that the Interferon titre paralleled accurately the antibody titre but more important, the peak virus and Interferon titre occurred between days 3 - 5 whereas the antibody only attained detectable proportions by the 14th day. By this time, the virus titre was well on the decline. (26)
It would appear from these results that, at least in the case of a first infection, cellular resistance is more important than antibody in recovery from that infection. This phenomenon of interference may also account in part for the importance of maternal antibody levels in the newborn child since tissues which show active glycolysis are less sensitive to Interferon than are adult tissues. (27)

At present Interferon is only used to prolong and maintain latent virus infections, (57) but the possibility of there being a therapeutic or prophylactic potential must not be discarded.

Role and importance of Antibodies.

Antibodies as mentioned above, seem to play but little part in the recovery from an initial virus infection but their protective effect in the event of a second infection is of particular value. Following infection there is a considerable time lag before any antibody is detectable in the blood stream, but once the disease process has finished, the antibodies may remain in the blood for a varying length of time - in some cases, for the whole life of the patient.

For the purposes of discussing the epidemiology of polio, the following features must be investigated: How may an individual acquire immunity by means of antibody? Are there any factors related to ease of acquisition of immunity? Are there any variations in the immunity which can be related to the virus type or strain involved? Lastly, how long, considering the above, may this immunity last?

Acquisition of Immunity.

This is most easily discussed on the basis of age of the immune individual. The situation is complicated by the change in the epidemiology of the disease whereby the age incidence has been showing a progressive rise hand in hand with improvements in the standards of living. It is to be assumed that as other, at present less well developed countries, approach more to the high standards of, for example, Sweden, then they too will begin to experience epidemic rather than endemic poliomyelitis.

The social status of any country or close social group is reflected by the infantile mortality rate and in endemic polio regions the link between the rate and polio incidence is such that Paul states that once the infantile mortality rate falls below 60 - 80/1,000 the polio incidence will show a tendency to change towards epidemic proportions. This has been amply demonstrated in many countries showing rapid hygienic and economic growth. (20)

If a baby is born of a mother who has at some time been infected with polio, provided it was not during the third trimester of pregnancy, that child will possess a form of immunity to the poliovirus due to the presence of maternal antibody acquired in utero. This antibody shows a progressive fall-off from birth to nine months and is not usually demonstrable after this time. (9) It will be remembered that the half life of maternally transmitted antibody is the same as normal gamma globulin and has been estimated to be 18 days. (31)

The proportion of children possessing such antibody is dependent on the immunity status of the population in general.
In Israel, 90% of the neo-nates possess maternal antibody but by the age of six months 90% are no longer immune.(9)

It has been suggested that the child may also acquire antibody by drinking breast milk which contains anti - polio antibody. Observations have been carried out, (16) where the children have been under continuous supervision. In one group of Bantu, comprising 16 babies and their mothers, no clinical signs of polio were seen, but within one year, four of the sixteen had been infected while still being nursed; three of them by type II immune mothers.

This would seem to indicate that it is impossible for a child to get antipolio antibody by any means other than transplacental transfer. There seem to be no variations in the quality of the immunity acquired which are related to the type of virus causing the infection in the mother.

Once the child is no longer protected by maternal antibody, it is available for infection by the virus, and, depending on the social, hygienic and general living standards of the community, this may occur at any age four months, if possessing maternal antibody, to the last years of life.

In an area where the disease is endemic i.e. exists as a 'silent' and not an overt infective cycle, the average age at which immunity is acquired tends to be much lower than in a region where the disease is more epidemic in its mode of expression.

The earliest age at which infection may occur would appear to depend on the time at which a balance or minimal active infection point is reached between the infective virus and the waning passive immunity level.

Once this passive form of immunity has been lost, only infection or vaccination can produce immunity and the individual will remain non-immune until one or other of these events takes place. In the same way that person may remain non-immune to either one, two or all three types of the virus or become immune to one, two or all three. So far as is known, it is not possible for immunity to one strain to cover against infection by another, even closely related strain although Salk has shown that some degree of protection to type I virus is conferred by previous infection by type II. (53)

In a country of poor socio-economic standing, and where the disease is also endemic, or rather hyperendemic, there are many opportunities for a child to become infected. It is one of the unusual features of polio that it often appears in children as a very mild and often clinically unrecognisable disease with no after effects. As the age of the infected person rises however, the disease expresses itself in a more and more serious manner, and one of the main causes for worry about poliomyelitis is that the age incidence shows a progressive increase towards a more adult range as the standard of living of a country rises. The case fatality rates show a parallel rise as also does the Paralytic/Non paralytic ratio.

Thus it is that in an endemic polio region, immunity is acquired early in life. In Israel 90% of children are non-immune at the age of six months but by the age of four years between 86 - 95% have antibody to the three serotypes. The predominantly infantile nature of poliomyelitis in this country is further indicated by the results for the epidemics occurring between 1957 and 1960. Nearly 90% of cases were in the under fives and 80% were in children less than three years of age. (9)

In a truly endemic region where the age incidence is infantile, the disease may circulate among the lowest age group in so silent a manner that otherwise experienced clinicians may say that polio has never been known in that region.
A very good example of this situation occurred in the Philippine Islands during the last war. (36; 46) It was said by many that the disease was never seen in the Islands, yet when U.S troops were stationed there, they showed a polio attack rate that was ten times that of U.S. troops at home. The actual attack rate was probably considerably higher since many cases were misdiagnosed as Dengue or Sandfly Fever. In a later investigation it was found that 90% of Filipinos had got polio neutralising antibodies.

This sort of situation is so characteristic that it might almost be called the hallmark of true endemic polio. Similar occurrences have been noticed all over the world especially where large population movements have taken place. The endemic nature of the disease in many countries was only brought to light during the course of the Second World War, when large numbers of troops were moved from home stations into overseas service. (33; 36; 46; 38) The situation was aggravated in most cases because the service personnel were being transferred from areas where the disease had a seasonal incidence, to more tropical regions where it was present in equal intensity throughout the year. (36; 64; 71) All the Middle East stations were affected to some extent by polio epidemics among the servicemen, although polio was not obviously epidemic in nature among the civilian population of those areas.

The obvious conclusion to draw is that the more primitive the community, the greater the proportion of immune individuals. This does not hold true except within very narrow limits since there must also be in such a community, continued contact with the disease before any degree of immunity at all can be achieved. Among societies which are relatively isolated, there may be little or no possibility of contact with the virus and although their living conditions are primitive, they are non immune to the disease. Good examples of this are found among islanders and other groups with few contacts outside their own society. Most island communities have in their time, shown how susceptible they can be to the poliovirus. The case of St. Helena has been mentioned twice in this respect and the 1945 epidemic, (16) gives a clear picture of an outbreak affecting a virgin community. The overall attack rate was high at 5.4/100; paralysis, (including deaths), was 1.92/100 of the islanders. The age range was from 1 - 19 years. There were no cases in children less than one year old and only 4/1000 of the children between 1 - 4 years contracted the disease. Children aged 5 - 19 were equally affected but the majority of deaths were in the 15 - 19 year old age group. The important point here is that the disease was more severe than usual with a higher incidence of paralysis and death in older children and young adults than in infants. This is the reverse of the endemic appearance of the disease in other similar poor societies where it is predominantly the infant population which is affected.

A similar situation has also occurred among equivalent populations in other parts of the world. The epidemic among Alaskan and Canadian Eskimos during the winter of 1948/49 demonstrated an even greater lack of immunity among Arctic dwellers. Children, parents and grandparents were infected; in all 60% of the population was affected to some extent, the lowest attack rate being in the youngest age group. (36; 41)

The basis for such severe outbreaks among these primitive societies is lack of communal contact with the virus over a long period of time. The same condition can be applied to other epidemic regions if one considers the length of each inter-epidemic period.
The longer the period, the greater the number of susceptible children and young adults there are available and hence the disease will probably be of greater severity when it next returns. This argument may be brought to bear on the year to year variations of the disease in any one area if the disease is endemic there. If a severe epidemic year occurs in one area where there are a regular number of notifications each year, then the majority of the population will, by the end of the year, have developed antibodies to the epidemic strain. By the following summer there will be a large new susceptible group within that community i.e. the children born during the winter and so a further epidemic due to the previous years strain may occur.

It must be realised that if, on three separate occasions, a group is infected with three different strains then there are likely to be three years of severe epidemics since immunity to one strain does not give any certain degree of immunity to the other two main strains.

The association between socio-economic standards and age at which immunity is achieved is so strong that the results of serological surveys have been presented in the form of a table: (73)

<table>
<thead>
<tr>
<th>GROUP</th>
<th>AGE AT WHICH:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% have antibodies.</td>
</tr>
<tr>
<td>I</td>
<td>0 - 2 years.</td>
</tr>
<tr>
<td>II</td>
<td>3 - 5 &quot;&quot;</td>
</tr>
<tr>
<td>III</td>
<td>6 - 9 &quot;&quot;</td>
</tr>
<tr>
<td>IV</td>
<td>10 - 15 &quot;&quot;</td>
</tr>
<tr>
<td>V</td>
<td>15 + &quot;&quot;</td>
</tr>
</tbody>
</table>

All the countries and cities investigated have been put into these groups:

I: Brazil; Chile; Cuba; All French Oceania; Mauritius; India; Southern U.S.A.; Belgian Congo; Uruguay; Turkey; Glasgow; Belfast; Israel.
II Japan; Korea; Australia, (Aboriginal population), Liverpool.
III Germany; Iceland; Hungary; Roumania; Czecho-Slovakia.
IV Finland, (Kuhmoinen); Northern U.S.A.; Australia; New Zealand; Sweden, (Rural)
V Sweden, (Urban); Canadian/Alaskan Eskimos; Australia, (Melbourne); Serbia.

Much interesting information can be obtained from the few facts quoted above. The list shows quite clearly the relation of immunity to primitivity not only on an international scale but on a national one also. The various parts of the U.K. are spread through groups III & IV but the largest cities in the country are shown to provide greater opportunities for spread of the virus since Belfast, Glasgow and Liverpool come into groups I & II. Most other countries also show this to a greater or lesser extent according to the size of the nation; size and degree of over-crowding of its cities and the relative proportions of the population living in cities or rural districts.

So far as can be judged, there are no differences in the degree of immunity given by one strain or another, and little cross cover has been demonstrated. In the section on control of this disease by vaccination, it will be seen that variations in the quality of immunity conferred are demonstrable, but it is not known whether these variations occur among strains which are of natural occurrence.
Variations in the conversion rates for the many virus strains used in the practical control of polio are of importance in the assessment of the efficacy of a particular strain which is used for vaccination, but the application of these facts to naturally occurring virus strains is not feasible since, on the results of serological surveys, it is not possible to discover whether lack of type I antibodies in a test group is due to non-exposure to that type of infection or to a shorter duration of immunity. This question cannot be satisfactorily answered at the moment, and full serological investigations must be carried out over a long period of time before any valid answer may be given.

The observation of endemic and naturally arising epidemics of poliomyelitis may soon become impossible, since most of the countries with facilities for work of this kind are carrying out large immunisation campaigns, often with live virus, with the result that the true endemic and epidemic forms of the disease are rapidly disappearing from those countries.

Since in many cases it is not possible to obtain a reliable estimate of the number of doses of vaccine that have been given, it is during the course of a vaccination programme, the size of the theoretically immune population cannot be calculated. This leads to errors in the evaluation of the efficacy of a particular vaccine and more stringent control of vaccine use is necessary.

It has often been suggested that some degree of ethnic immunity may be present among certain groups and such races, if removed from their countries of origin, would be expected to show at least some indication of natural immunity if resettled in other endemic countries.

Large scale experiments of this kind have not been performed on such populations and the only evidence available is that obtained from immigrants. The long association of some such people with a foreign land together with the racial intermarriage that often occurs, results in a 'dilution' of the immigrants' initial racial characteristics. In other words this theory has not yet been subjected to rigorous testing in these ethnic groups in their racial habitat.

Sabin noted variations in the incidence of polio according to ethnological groups in some places but not in others, and concluded that this variation was not solely due to economic factors.

Gear, (16) summarised the results of several series of experiments on this question. In the Northern U.S.A., the incidence of paralysis in whites is four times that in negroes, but in the poorer Southern states, there is little difference between the two. After the 1930 San Francisco outbreak, it was found that the incidence among Chinese was twice that in whites and Japanese, and, in the 1955 - 1959 epidemics in Mauritius, the Chinese and Indians had a higher incidence than the other races.

In 1959 a type I epidemic occurred in Singapore with this comparative incidence: (20)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases / 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malays</td>
<td>23</td>
</tr>
<tr>
<td>Chinese</td>
<td>29</td>
</tr>
<tr>
<td>Indians, Ceylonese etc</td>
<td>33</td>
</tr>
<tr>
<td>Eurasians</td>
<td>35</td>
</tr>
<tr>
<td>Europeans</td>
<td>74</td>
</tr>
</tbody>
</table>

This is the reverse of the situation found in the U.S.A. and elsewhere although it must be remembered that economic status of the above examples shows great variation.
This particular example brings to notice how difficult it is to distinguish between racial immunity, if any, and environmental factors. Europeans, as is to be expected, have a far higher incidence than any other group. Native Malays have the lowest incidence again to be expected since they are on the whole living in conditions eminently suitable for rapid dissemination of the poliovirus, and hence, have a better immunity status than the Europeans. The interesting group here is that comprising the Chinese, Indians and Eurasians who show a better immunity level than Europeans, but one which is a little worse than that of the Malays.

In view of the rarity of polio among indigent Chinese, it is strange that the results of the surveys quoted above show a fairly high incidence among Chinese in other lands. National characteristics of a different sort must be taken into account. The Malays in general show a considerable acquiescence as to the nationality of their commercial rulers and the majority of the traders and shopkeepers are Chinese, Indian and Eurasian. The same is true of Mauritius. This results in the Chinese living in a very similar environment to that of the native population, and hence their immunity status approximates to that of the natives.

It would appear that in countries with mixed populations there are differences in racial incidence, but they are probably due to social, environmental and economic conditions.

In some closed, medically supervised communities such as those found in the mining areas of South Africa where all are living in close contact, there are still differences in race incidence which cannot be ascribed to other factors and so there is still the possibility of some form of race immunity probably based on inherited variations in cellular immunity. (71)

As a summary, it may be stated that at present our knowledge of group immunity and the variations which occur in its degree throughout the world, is still very limited and, until serological surveys have been conducted over most of the populated regions of the world, it will not be possible to lay down any laws as to what the immunity status of a community should be, or why.

The importance of group immunity is that it governs the spread of poliovirus through that community no matter what strain is prevalent, and prevents the expression of the disease process on a large scale.

Individual immunity depends to a large extent on group immunity but the whole environment of the individual colours the presence or lack of resistance to the virus.

The family group is the centre of both forms of immunity and the spread of a 'new' strain of polio through a community can be related to the number of 'hot' or 'cold' families.

In the case of endemic poliomyelitis the disease follows a more or less silent course through all sections and ages of the population, and its existence may only be revealed when susceptibles are brought into the endemic region.

Epidemic polio on the other hand, is the representation of passage of the virus through a population with a relatively high proportion of non immune individuals.
Non - specific factors affecting either Host resistance; Spread or pathogenicity of the virus.

These factors are, to a certain extent, bound up with the question of reservoirs and the spread of the virus on a large i.e. subcontinental or climatic scale. Whether any of these factors do play any part in the appearance of the virus is, in many cases, uncertain. As so often happens, there is very little experimental evidence for the theories which are put forward.

Under this heading may be included the possibility of effect by climate; temperature; humidity and rainfall; predisposing/precipitating factors such as bacterial or virus infections, pregnancy, exertion, previous inoculations, and trauma other than that due to the above. Whether the effect of these factors is due to an increased host susceptibility or to changes in the pathogenicity of the virus strain and its facility for spreading, is not known. The factors in which some form of human observation is possible, (Pregnancy, Innoculations etc.), have a good amount of proof, but the role of uncontrollable factors, (Weather), is very difficult to evaluate and the consideration of these as separate factors without involving all agent mentioned previously is impossible.

Climate.

The disease occurs throughout the whole world but there are general variations in its appearance that might be ascribed to climatic differences. In temperate climes the disease is more prevalent, in both its endemic and epidemic forms, in the summer months rather than in the winter whereas, in the tropics it tends to occur with a uniform intensity throughout the whole year. (60) It has however been noticed that even in tropical regions there is some seasonal variation with a slight increase in the number of reported cases during the summer season. (16)

In an examination of the sewage of Johannesburg, the virus was not present in demonstrable amounts during inter epidemic periods, and the inference was drawn that polio was therefore a truly seasonal disease and not maintained during these periods by human carriage. The fault here lies in the fact that the disease is endemic among the Bantu and not the White population who have a higher social and hygienic status than the Bantu, and who show the disease only on epidemic form. The sampling of what is predominantly 'white' sewage will not give a true picture of the nature of the disease in such a mixed community.

These months are those usually associated with the rains in tropical and subtropical regions and it is interesting to note that the most severe outbreaks in South Africa and India, (1949; 1954; 1956), have occurred in years of high rainfall and that epidemics in Mauritius have followed in the wake of severe rain seasons.

Temperature plays an unknown part in the seasonal incidence but many observers comment on the parallellism between the mean temperature and the case notification rates throughout the year. In the report on the 1957 - 59 Israel epidemics, the two curves are parallel, each reaching their respective peaks at an interval of three or four weeks, the case incidence lagging behind the temperature curve. Epidemics in all parts of the world tend to show some dependence on the temperature but whether this is due to temperature alone or to other factors conducive to better spread, and diagnosis of the disease remains to be determined.
The virus itself shows changes in virulence as shown by histological methods and other in vitro techniques which are used to mark experimental virus strains. (6; 67; 74) If viral characteristics can be altered under experimental conditions by temperature changes, then it is feasible for similar changes to occur in more natural circumstances. Proof of such changes in epidemic strains is not available.

It may be that a combination of two or more of these climatic factors has an effect on the spread of the virus and, there is some evidence that the actual agent may be the relative humidity. It has been mentioned above that epidemics often occur in tropical regions when temperature and high rainfall coincide and, it has recently been reported, (68) that, in experiments on the poliovirus type I in aerosol, there is a correlation between humidity and virus survival. At relative humidities greater than 50% there is good survival, but when the humidity falls below 40%, the virus was so rapidly inactivated that no virus could be recovered from an aerosol 30 seconds after spraying.

In temperate climates, the relative humidity is less than 40% during the colder months of the year and it seems likely that it is involved, at least to some extent, in the seasonal nature of the appearance of poliomyelitis.

Whether any bacterial or virus infections predispose to poliovirus infection is not known but in view of the results of some animal experiments, (44) it is conceivable that chronic suppurative infections may intensify the body reaction to the poliovirus. The oscillation through several years between polioviruses and Coxsackie group B viruses may be an indication of an interaction between these two groups but whether this has any part in predisposing to the paralytic disease is not known. (59)

There are several special groups of any society who are more susceptible to the polio virus than others. Pregnancy and traumata of several kinds are the basis of this decreased resistance. Surgery, some inoculations and minor accidents also result in the presence of susceptible groups within a community. It is of great importance that the existence of all such groups is recognised, since the danger to them during epidemics and during vaccination programmes is quite high.

Polio in the pregnant tends to show as a more dangerous form than in the non pregnant. There is a high paralytic/non paralytic ratio, and there is a much higher mortality rate than usual. The danger is proportionately greater the nearer term the woman is, there being a very large number of cases of bulbar paralysis in the last trimester. The frequency of infection is highest in women with large families, as would be expected.

Grelland, (19) gives the results of a series of observations on polio in pregnancy. Of women infected during the first six months, there were 29 cases of acute anterior polio with 1 fatality. A further 29, infected during the last trimester were acute cases and 14 died. In both groups the deaths were due to respiratory paralysis.

A more recent report shows how short the progress of this disease towards a fatal conclusion may be. (61)

The danger of polio in late pregnancy is not only to the mother but also to the child, since infants born of women with polio are deficient in anitbody and have a high infantile mortality. This, in a country where the disease is endemic, and hygienic standards generally low, results in a very high infantile mortality rate and adds weight to Paul's dictum, (Page 13).

Many operative procedures have been incriminated in the provocation of polio, those involving the oro-pharynx in particular, shown a definite relationship.
Although the theory of polio infection via the oro-pharynx has been disproved, it is apparent that if the integrity of the paryngeal wall is disrupted, then it likely that the poliovirus can enter the body there and travel along the nerve sheaths, particularly if there has been damage in this region, and set up an infection in the brain stem. The proportion of cases of bulbar polio in those who contract poliomyelitis following tonsillectomy and other E.N.T. operations, is high, and multiple cases within families have been known to occur. (12; 15) Throughout the period covering 1944 - 1949, the percentage was 56.7% among those who had undergone operations, whereas the overall rate for the epidemics was 25.5% (12) Similar high rates are also associated with dental extractions, and some authorities think that these rates may be affected by the type of surgical procedure adopted during Tonsillectomy.

**Provocation polio: prophylactic immunisation.**

This had long been a subject for debate, although the possibility of a connection between the two had long been recognised, but it was not until serious assessment of the relationship was attempted that the extent of the danger was realised.

The danger is that a person exposed to infection who has recently been inoculated with a prophylactic vaccine shows a higher incidence of paralysis than those who have not. The site of the paralysis is related to the limb which has been inoculated. Many vaccines have been suspected of this, but the main ones are those which include heavy metal or arsenicals. Diphtheria, Diphtheria/Pertussis, Pertussis vaccines are most often involved.

McCloskey carried out a detailed investigation during the 1949 outbreak in S. Australia, in which 340 child cases were checked for date and site of inoculation. 31 had had one of the three vaccines within the three months prior to onset of symptoms. (34) The results are summarised below:

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Innoculated limbs</th>
<th>Non Innoculated limbs</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paralysis</td>
<td>non-P.</td>
<td>Paral.</td>
</tr>
<tr>
<td>D/P.</td>
<td>18</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>P. Only</td>
<td>9</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D Only</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

The combined vaccine is shown to hold more dangers than the separate vaccines, but for all three types there is some association between the site of inoculation and that of the subsequent paralysis. There was also an increased severity of paralysis when compared to that of a control group.

Probably the most important result of McCloskey's work was that in the three month period, the later injections were those usually concerned with localisation of the paralysis. Many other observers have come out with similar results and drawn the same conclusions. (22; 63)

The danger period following such injections is estimated to be about four weeks, and then only when the disease is prevalent in the region.

The other injections mentioned, heavy metals etc., also have evidence of sufficient danger to warrant their abolition during epidemic periods. During the 1951 epidemic in Tahiti, the children who had had weekly intramuscular injections of Neoarsphenamine had a far higher paralytic rate, (81.2/1,000), than comparable children.
As long ago as 1932, clinicians noted that 138/1766 cases in Western Samoan children of less than 5 years of age had been receiving neosarsphenamine i.m., but those who had been given i.v. injections showed no provocative results. (16; 71)

In general it seems that the phenomenon of paralysis in the injected limb may be restricted to the younger age groups. (34)

The term provocation may also be applied to results of poliomyelitis vaccination but because of their variable nature and age spread they will be mentioned in the discussion of the control of polio.

**Trauma as a provocative agent.**

Trauma is a word of very wide application and under this heading are included the effects of injury, both mild and severe; of varying degrees of exertion prior to the second phase of the disease and even down to the effect of using one limb, by habit, more than another. Trauma will be discussed here under these main divisions.

**Injury:** Horstman, (23) investigated a large group of polio cases for an association between previous trauma and site of subsequent paralysis. 22 gave a history of injury about the time of onset of the disease. 12 were paralysed; 10 showed slight or no paralysis. Some of the investigated cases, though not of sufficient number to be of any statistical significance, show this supposed correlation to a remarkable extent. One case had osteomyelitis of the left femur and developed paralysis only in the muscles of the left thigh. Another who had received a chest injury was paralysed only in the intercostals.

The effects of surgical treatment have already been mentioned, but they are also examples of traumatic provocation.

The theory behind this predisposing effect of trauma is that the damage may result either in the admission of the virus directly into nervous tissue, whence it may spread to the spinal cord, or, that the trauma in some way decreases the resistance of the lower motor neurones in the cord to infection by the virus. (23; 45) In support of this is the finding by Hyden, that muscular work depletes the anterior horn cells of protein. (23)

It has also been suggested that peripheral trauma may be reflected in the cord and act as a stimulant to the activity of a virus already present. This has been disproved by experiments on Rhesus monkeys although the effect of exertion was not tested. (24)

**Exercise:** Experiments have been carried out on large numbers of polio cases to ascertain the effects, if any, of exercise on the severity of paralysis. Russell, (45) made observations on degree, duration and time of exercise before the onset of meningeal symptoms, and the extent to which residual impairment was affected. The results of one small survey are shown below:

<table>
<thead>
<tr>
<th>Type of exercise after onset of Symptoms:</th>
<th>Light</th>
<th>Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full recovery expected:</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Patients</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

His conclusions were that physical activity in the pre-paralytic stage gravely increases the danger of impairment following infection and that the critical period for such activity is the first 24 - 48 hours of the major illness. It is not feasible to give any ruling as to the type of exercise which is most dangerous since individual variations are so great. It is likely that long ambulance journeys are as bad in some cases as heavy labouring would be in others.
Seddon et al, in 1945 carried this a stage further and determined which limbs were most commonly affected in cases of one sided paralysis. While the number of lower limbs affected was almost equal for each side, (169 left, 103 right), there was nearly a two fold difference between right and left arms, (21:11). The same investigators however found no association between more serious trauma and the site of paralysis, (57). Seddon also related site of the cord lesion to the activity of the area supplied by that section of the cord:

<table>
<thead>
<tr>
<th>Site</th>
<th>Lumbar</th>
<th>Lumbar/cervical</th>
<th>Cervical</th>
<th>Medulla</th>
<th>(Uncertain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>64.3%</td>
<td>22%</td>
<td>9.5%</td>
<td>2.5%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

There are no doubt, other aggravating factors involved and whether these provoking effects are due solely to these suspected agents or are actually the result of combinations of other variable factors e.g. Host resistance or virus strain variations, cannot at present be determined.
THE CONTROL OF POLIOMYELITIS.

Until the turn of the century poliomyelitis was a disease whose existence was well recognised but which was impossible to limit. Its appearance in any country was apparently a haphazard affair and no underlying principles seemed to govern its spread which was again irregular. Once serious efforts were made to establish the epidemiology of the disease it was soon realised that it was progressing to affect older age groups and that the severity in these older groups was much greater than in the young. The disease was apparently also singling out those countries with the most rapid social and economic growth, in particular the New World and the Scandinavian countries.

Polio became feared as a paralytic disease leaving a high proportion of its victims permanently incapacitated, and its control became a question of great importance.

Before any attempt at controlling the disease is possible, it is essential to have an accurate knowledge both of the infecting organism and its cycle of existence in man and his environment. The method of control is usually applied to the eradication of some accessible part of this cycle. The aim of control is then either to remove the organism, or prevent it from infecting man.

The removal of the organism from the world scene is not practicable by ordinary methods so attention is usually turned to the sources of the organism in the environment which can best be destroyed, or, to the investiture of man with the means by which he may resist attack.

From the epidemiology of polio it is known that the disease is of world wide occurrence and the virus is disseminated throughout most of the world's population to such an extent that a large proportion of the world's children are immune to one or other of the virus strains by the age of ten years. The reservoir of the virus is mainly human and is so vast that its removal is not feasible. The spread of the virus through a community can be checked to a very limited extent, but the results of travel restrictions etc, bear so little benefit in return for the expenditure and effort involved that they are frequently not attempted or the effort is half-hearted.

The only method of approach to the question of control is by providing man with some degree of immunity to the virus.

The whole system of control can be divided therefore into palliative and preventive measures, with the ultimate objective of total eradication of the disease.

Palliative measures:- General Public Health measures.
  Treatment of the disease in the affected persons.

Preventive measures:- Removal of non-human reservoirs, (If any)
  Provision of active, artificial immunity:
  1) Cellular.
  2) Humoral.
  on a group basis by one of the following methods:
  1) Use of a killed vaccine which retains its immunologic characteristics.
  2) Use of an attenuated, live vaccine.

The choice of preventive measure is a matter to be discussed at some length but at first sight it would seem preferable to choose one which will provide both humoral and cellular immunity if possible. Palliative operations are equally useful no matter which method is adopted, and these will be considered first.
Palliative measures: 1) Treatment of the disease.

At present there is no effective treatment of the patient with polio, and the outcome of the disease process in any one patient is dependent simply on the numerous factors mentioned in the preceding section. Much of the work in treatment of polio is devoted to the amelioration of the lives of those who are permanently paralysed.

The administration of preformed antibody to the patient is of little value on the disease process is under way and is not used to any great extent now. Experimental work on Interferon shows that there may be some hope of its having therapeutic applications, but this is, at the moment, surmise. (25; 26; 67; 69)

Further work is being done to find an anti-viral therapeutic agent, and it has recently been reported that Tamm has found that the Hydroxy-benzyl derivative of Benzimidazole has anti viral activity limited to the Polio, ECHO and Coxsackie viruses. This work has been done in vitro and in animals, and although it is still at an early stage, it bears some promise for the future. (69)

2) Public Health measures, (General).

Control of the patient by means of vaccination is to be discussed later. Simple control measures may be applied if one considers the regional epidemiology of polio. (39; 71)

1) Control of infection in the environment.

   Elevation of the existing hygienic level in the community. This is essential despite the paradoxical appearance of more clinical disease as the hygienic status of countries is raised.

2) Control based on the existing social system:

   3) Quarantine and isolation of patients and contacts.

4) Control, if possible, of non specific factors.

These measures can therefore be subdivided into those aimed at the reduction of spread of the virus, and those effecting a reduction of paralysis.

Reduction of spread:

The first essential is early and accurate diagnosis, but without good laboratory facilities this is difficult if not impossible since the milder forms of the disease often fail to reach the doctor. This can only be rectified by the introduction of compulsory examination of the whole population, and the development of a means of rapid detection of the poliovirus. Rapid identitication is becoming a practicable technique based on Precipitin type tests, but they are not universally available.

The situation with regard to diagnosis has improved over the last two decades as is shown, to a certain extent, by the yearly notification rates. Since the recognition of the existence of several forms of polio the number of diagnoses of that disease has risen steadily and not a small proportion of this increase is due to the increased alertness of the clinicians, and also to the increasing number of patients who visit their doctors through fear of polio.

Once the diagnosis is established, the patient should be isolated if possible and have regular laboratory checks of virus excretion until the excretion ceases. This may be anything from 5 - 20 weeks but 75\% stop excreting the virus after 5 - 6 weeks. This is a measure which has had little effect so far, but with the advent of better laboratory facilities may be of some benefit.
During the period of isolation, concurrent disinfection of all fomites and excreta should be maintained, and, at its termination full disinfection of the room must be done.

Contacts should be reduced to a minimum, and the family of the index person must be regarded as having been infected. Laboratory checking and restriction of the family's movements should also be considered since they may serve as an infective focus for the rest of the community.

If, after these measures have been taken, the incidence of the disease is still rising, then the whole population should be warned that the disease present.

Suspected contacts should not be allowed to handle food or come into contact with young children, and all should be reminded that it is not advisable to attend large social gatherings; games; unchlorinated swimming baths and other public fomites, and if necessary, baths should be closed. They must be warned of the dangers of any unnecessary exertion if they feel at all unwell. Nurseries and schools however need not be closed since there is often less opportunity for spread at school than there is at home. (35) Holiday camps and other closed communities should be isolated to prevent spread to uninfected communities and, if possible, ingress and egress to any area, particularly isolated, heavily affected townships, should be restricted.

Such measures have never been applied on a large scale since they are difficult to put into action and and almost impossible to enforce. Yet their possible effect on the spread of polio could be highly restrictive.

The last word here is as given in one report at the Fourth International Poliomyelitis Conference:— "While it was felt that what was being done was logical, the results did not seem to be impressive".

Reduction of paralysis.

This is attempted by controlling, as far as possible, the non specific factors mentioned previously. If these can be minimised during an outbreak, then the paralytic/non paralytic ratio should show a decrease.

The ill must be confined to bed as soon as diagnosis of polio is made, and all contacts should be warned of the dangers attendant on fatigue following infection.

All clinicians should be notified when polio is reaching epidemic proportions and that the injection of arsenicals, heavy metals and the Piphereria, D.P., and Pertussis vaccines is to be avoided throughout the period. Clinicians should also be reminded of the necessity to ensure that there is no possibility of syringe contamination, since it has been suggested, but not proved, that the polio virus as a skin contaminant, may be pricked through the skin during injections and may be transferred by the syringe if it is not adequately sterilised.

In view of the association between surgical treatment and paralysis, all elective operative procedures, especially those involving the nasopharynx, should be avoided. If surgical treatment is essential then great care is required to prevent the patient from coming into contact with the disease.

Preventive measures.

Removal of non-human reservoirs—In the light of the evidence available it appears that non of the non human reservoirs which is involved in the dissemination of the virus can be adequately controlled. The complete eradication of all virus particles from sewage is not practicable both from the point of view of cost and from that of efficiency and maintenance.
The spread of the virus from the faecal reservoir can be limited by the general public health measures indicated above.

The eradication of the insect vectors has been unsuccessfully attempted during epidemic periods without any noticeable effect on the progress of the disease. Large scale spraying from the air in an attempt to reduce the fly population was attempted in South America without success, but there is the possibility that, if such measures were rigorously applied, there would be a beneficial effect in the long run. This again would be expensive and difficult to operate.

This leaves only the human reservoir which obviously cannot be eradicated as such, but if the whole world population were to be rendered immune to the virus, then there might be a progressive regression of this disease through the lack of susceptible individuals. The end result would be the complete removal of the virus from the world.

The aims of any form of preventive vaccination are therefore:
1) To give all susceptible individuals some form of immunity
2) To provide the whole population with the same immunity.
3) The development of world wide immunity to the virus with the ultimate objective of forcing a regression of the disease by the removal of all susceptibles. The virus type might then die out completely.
It has long been known that following a virus infection, the individual remains immune to re-infection by that virus for a variable period of time and the means by which this immunity is attained has already been mentioned in some detail.

In providing some form of artificial immunity therefore, it is necessary to decide what form the immunity should take and what its duration must be. Other criteria of safety and effectiveness must also be considered.

Two types of vaccine have been developed and are at present in use in many parts of the world. Each of these vaccines has been shown to provide adequate degrees of immunity in the vaccinees, but their modes of action and their administration differ in many respects.

The first type to be used on a large scale consists of a suspension of killed poliovirus whereas the second is a live, attenuated virus vaccine. It is interesting to note here that, after the isolation of the virus by Lansteiner and Popper in 1909, Dr. Flexner expressed the hope that the development of a vaccine to prevent the disease would only take a matter of months. More than five hundred months were to elapse before any real progress was made.

Before any attempt is made to evaluate the efficacy of these two vaccine types, there must be established a number of criteria by which each type may in turn be judged:

1) Since there is no certain cross protection given by any one strain of the polio virus, any vaccine must contain all three virus types. Failing this it must be possible for it to be given in three distinct forms corresponding to the virus strains.

2) If possible the vaccine should induce both cellular and humoral immunity toward the virus.

3) It must provide a high degree of immunity which is of long duration.

4) There must be no possibility of the vaccine causing, or predisposing to, the disease. Side effects should be minimal.

5) The vaccine must be safe to administer not only to the general population, but also to those groups requiring extra care e.g. triple negative adults; pregnant women; premature infants and the new-born; those undergoing certain forms of medical or surgical treatment.

6) It is preferable that the vaccine should be easy to administer.

7) The vaccine must be stable and show no radical potency changes.

8) The cost of the vaccine and its ancillary requirements should be as low as possible to enable countries of poor economy to make use of the vaccine.
FORMALIN INACTIVATED VIRUS VACCINE.

It is a little known fact that as long ago as 1910 attempts were made to induce immunity with both killed and live virus preparations. None of these experiments was successful. Numerous killed vaccines have been used prophylactically in the past, either alone or in conjunction with others, against a variety of diseases and the development of killed polio vaccines is largely due to the wide range of experience gained from the use of similar vaccines, against other diseases. There is nothing new in the use of such vaccines and it is for this reason that I propose to deal in less detail with the Salk type of vaccine than with the live-virus type which is a radical departure from standard medical prophylactic measures.

Interest in an anti-polio vaccine waned during the inter war period and it was not until the immediate post war years that experiments with killed vaccines were begun. This was largely a result of experience with formalinised influenza virus vaccine during the second world war. By 1954 the Salk vaccine was ready for large scale field trial. This was what is now known as the Francis Trial. The results of the trial were favourable and, since that time, the Salk vaccine has been used in many parts of the world and, within certain limits, has been successful.

The theory behind the use of a killed vaccine is that when viral nucleic acid or any other specific antigen is injected into the body, there is a body reaction of antibody formation which is specific for the antigen injected. In the presence of any other forms of body/tissue resistance, the circulating antibody level effectively counteracts the spread and development of infection within the body.

Salk vaccine consists of a suspension of Formalin treated virus particles in a nutrient medium. The three strains used in the U.S.A. are the Mahoney(I); M.E.F.1(II); and Saukett(III). The nutrient medium is an admixture of a suitable medium e.g. Connaught 199, and animal serum. Streptomycin, Penicillin and other antibiotics have also been included in the suspension to prevent bacterial contamination of the vaccine. Modifications of this vaccine are used in many parts of the world and, less virulent derivatives, usually of the I strain, of local isolation are substituted for the more virulent Mahoney.

In Britain the Brun-Enders variant of Brunhilde I, and a strain of M.E.F.1 adapted to suckling mice have replaced the more virulent Mahoney and M.E.F.1 strains. In Canada and Australia, the Mahoney strain is still used. South Africa has also used the Brun-Enders variant with local strains: Collans II and Templeon III. Denmark uses the Brunhilde type I. (72; 73)

We must now consider the merits of such a vaccine against the criteria established above.

1) The vaccine contains all three virus types in a triple vaccine which is administered as a 1.0 ml intra-muscular injection. The number of booster doses given has now reached three and many countries using Salk have opted for a four course schedule. The number of doses actually required by any one person is of course very variable.

2) The achievement of both cellular and humoral immunity would be the optimum. Salk type vaccine cannot provide both forms of immunity. Humoral resistance can be induced by the formation of specific antibodies to the polioviruses. This can be checked by serological determinations, and the rate of fall-off, if any, can be estimated. Cellular immunity cannot be induced by killed vaccines. The evidence for this is both experimental and practical. In the preceding section on immunity, the phenomenon of interference and Interferon production was mentioned.
Theoretically a killed virus should result in the production of Interferon without having either the upset of cellular metabolism, or, the cytopathic effects of a live virus. This does not in fact occur with many viruses but not with inactivated polio viruses. Interferon is not produced by formalin inactivated viruses and therefore cannot protect against live polioviruses. (25; 26) The results of numerous experiments have shown that a previous Salk vaccination does not prevent the establishment of infection by the oral administration of live, attenuated vaccine, since this infection is located in the wall of the gut where antibodies are ineffective and only cellular mechanisms are of value. Some experimental results however throw some doubt on this question. (31) Thus it is apparent that the use of Salk vaccine will not prevent reinfection of the alimentary tract, although it will prevent passage through the human body from such a focus. The resulting situation is that the vaccinated individual is immune to the virus but may still remain as a potential source of virus for the whole community since infection of the gut can occur and excretion of the virus continue in that individual.

The failure of inactivated vaccine to produce cellular and alimentary tract resistance to infection is a disadvantage in some respects since the immune person may be reinfected by natural means. In other ways this is theoretically advantageous since the Salk vaccine is open to numerous 'natural' booster doses resulting from intestinal infection.

3) It must provide a high degree of immunity which is of long duration.

The theory that Salk worked on was that any one person could be regarded as having a fixed number of antibody producing cells. If this number of cells could be saturated by antigen there would be an extremely high antibody level. The development of a good antibody titre is dependent on vaccine potency, the number and spacing of inoculations and the response of the individual to the antigen. Also the time elapsed since the last inoculation. (53)

This theory has been borne out by serologic determinations on individuals given graded doses of vaccine from 1/16 dilution to x2. The results showed a progressive mean titre rise, as the vaccine dilution was decreased from 1/16 to 1, but there was little improvement in the titre if 2 ml vaccine were given instead of 1. (53)

Booster doses of 1 ml given within one year produced a response dependent on the initial dose given. Those given the highest initial dose showed the highest final titre of antibody i.e. the hyper-reactivity is not an all or none response. Numerous small scale trials were carried out using the vaccine but the numbers involved were small. Initially triple negative individuals showed, as a group, a lower mean titre after booster doses. Too many of these trials before and since the 1954 field trial were done in groups that had already had antibodies to one or more types of the polio virus. The proportion of tests done on triple negative individuals was small and so were the numbers tested. A true picture of the efficacy of a vaccine can only be obtained from triple negatives since Salk himself demonstrated considerable boosting effect and degree of cross boosting, (Mainly of the type I component by prior type II infection), due to previous infection. (53)

Many commercial vaccines leave triple negative children immune to type II only, even though the paralytic incidence is reduced, but a third dose usually provides all three types and a fourth dose almost invariably does.
In 1954, the U.S. authorities decided on a large scale trial, and public opinion seemed to be in favour of such a trial. The results were given in the now famous Francis Report,(13) which warrants attention. The intention was to immunise all second grade schoolchildren in the study areas. Nearly 70% of the group were involved and 65% of these children were vaccinated. The total number of children being 1829,916.

Two major groups were established: 1) A placebo controlled trial in which two sections of the child population were injected, the one section with vaccine and the other with a placebo.

2) Observed trial in which only vaccine was injected.

A thorough investigation of all cases of poliomyelitis was carried out on the following basis:

a) Clinical report.
b) Laboratory specimens,(Stool, paired serums).
c) Examination by a Physical Therapist on two occasions: 10 - 20 days. 50 - 70 "  
d) Full autopsy of all fatal cases.

The result of the trial was given in the report on April 12th, 1955. The assessment of the level of immunity on a serologic basis is difficult and the correlation in any group is complex. The assessment of vaccine effectiveness is more epidemiologic than immunologic.

The ratio of the number of cases of poliomyelitis in the placebo and vaccinated groups was:

<table>
<thead>
<tr>
<th>Ratio of Total cases:</th>
<th>Placebo</th>
<th>Vaccinated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Paralytic cases:</td>
<td>3.5</td>
<td>1</td>
</tr>
<tr>
<td>Non paralytic cases:</td>
<td>1.0</td>
<td>1</td>
</tr>
</tbody>
</table>

There were no fatal cases among those given vaccine and only 2/38 cases of bulbo-spinal polio had been vaccinated. If the figures are broken down further and the percentage effectiveness* of the vaccine ascertained, we get the following figures:

Effectiveness against spinal paralysis: 82%
" " bulbo-spinal " 91%
" " of type I vaccine: 62%- 65%
" " type II " 80%
" " type III " 78%

There was no evidence of any cases of polio developing as a result of the vaccination. As a result of this trial, in particular the effectiveness of the vaccine against the more severe forms of the disease, full scale use of vaccine was established in the United States.

The experience in the U.S.A. before and since the Francis report, is interesting when viewed overall. Figures for the total incidence,(Paralytic and Non paralytic notified), of the disease prior to the Second World War are difficult to assess due to irregularities in diagnosis and notification. From 1945 however, the case incidence rose from 10/100,000 to 37/100,000 in 1952. The years 1953 - 55 were mild and by 1956 the incidence had reverted to the 1947 level.(See over).

* = percentage of the reduction in number of actual cases from the expected. Thus: Placebo cases - Vaccinated cases x 100%
Placebo cases.

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951</td>
<td>10,037</td>
</tr>
<tr>
<td>1952</td>
<td>21,269</td>
</tr>
<tr>
<td>1953</td>
<td>15,648</td>
</tr>
<tr>
<td>1954</td>
<td>18,308</td>
</tr>
<tr>
<td>1955</td>
<td>13,850</td>
</tr>
<tr>
<td>1956</td>
<td>7,911</td>
</tr>
<tr>
<td>1957</td>
<td>2,499</td>
</tr>
<tr>
<td>1958</td>
<td>3,697</td>
</tr>
<tr>
<td>1959</td>
<td>6,289</td>
</tr>
<tr>
<td>1960</td>
<td>2,265 (Estimate)</td>
</tr>
</tbody>
</table>

The vaccine was still in short supply during 1955 and only the first and second grade schoolchildren (6 - 8 years), were vaccinated before the peak of the season. The resultant attack rate for this group was significantly lower than in any other age group from 0 - 14 years. A notch in the incidence curve corresponded to a large group of 2 - 3 year olds, who had been vaccinated in clinics through 1955. By 1956, an estimated 50% of 0 - 19 year olds, had received one or more doses and the peak incidence showed a shift that year from the 2 - 5 year age group to the 0 - 1 years. This is the expected first phase of the forced regression of poliomyelitis and indicates a return, under pressure, to being a more infantile disease. Of 3,198 acute admissions:

59% were paralytically affected in the non vaccinated group.
47% 1 dose
32% 2 dose
23% 3+ dose

Reference 32.

This in itself is strong evidence for the necessity of giving three doses.

By 1959, the effectiveness ratios by age group in triple vaccinated persons were:

3 Doses: 0 - 14 year olds = 90+%; 15 - 39 yrs. = 82%
4 Doses: do. = 96%; do. = 86%

Reference 74.

Many other countries soon followed the lead of the United States and the experiences of some of them with this vaccine will be mentioned at the end of this section.

The vaccine was thus proved to be effective in protecting the majority of the vaccinees against the more severe forms of polio but how long could this immunity be expected to last. The experience with Yellow Fever vaccine was such that certificates of vaccination were valid for only three years.

Work by Salk indicated that adequate antibody levels would persist for at least two and a half years if the inoculations were complete, but since the duration of persistence is related to the initially induced antibody titre, it follows that variations in vaccine potency will not only result in variations in the degree of protection achieved, but will also vary the length of time over which protection can be expected.

Work on antibody persistence following a third dose of vaccine, (28) has shown that the rate of decline in polio antibody is considerably reduced during the nine month period commencing two years after the injection, and the opinion of Kendall et al. was, that good, persistent antibody levels could be obtained if the material used was of adequate potency. In common with other investigators they noted almost equal antibody responses to the type II and III components, but a lower and more variable level with the type I.
It is for this reason that the Australian workers altered the Tissue Culture/Liquid volume ratio for the type I component resulting in a I : II : III ratio of 2 : 1 : 1 and this was used as the vaccine. Tests on triple negative children resulted in equal antibody responses to all three types. (2)

The consistently low incidence figures for the U.S.A. since 1956 would seem to emphasise the durability of the immunity gained.

4) There must be no possibility of the vaccine causing or acting as a precipitating agent for the disease or producing any undesirable side effects.

It will have been noticed from comments made on variations in potency, that the battle for safety and potency of vaccine is one likely to be fought out in the laboratory. The need for extreme delicacy of control was brought home to all associated with the Salk vaccine only a fortnight after the Francis Report was published in 1955. The Cutter incident as it was called, showed that the Mahoney strain could be as virulent in man as in monkey. Six cases of poliomyelitis occurred in children who had received vaccine produced in the Cutter Laboratories. This incident led to a temporary suspension of vaccine production and halted the whole vaccination programme.

Whether vaccine induced polio has occurred or not is judged on the basis that 1) There would be an increased frequency of cases associated with the use of certain vaccine lots, this being independent of the prevalence of natural polio,

2) There would be a concentration of cases during the 4 -- 11 day period in vaccinees and the 8 -- 22 day period in their contacts,

3) There would be a correlation between the site of inoculation and the site of subsequent paralysis.

Reference 32.

All these were fulfilled in the Cutter incident but have not been since, although well over 300 Million doses have been given in the United States.

The degree of certainty of control must be extremely high when dealing with a vaccine designed to protect against a disease of low incidence. Not only must the inactivation be complete but the vaccine must be of adequate potency. It is worth while considering some of the difficulties which had to be overcome, some still remain before the vaccine could be considered for general use.

Suitable virus strains must be produced which have low virulence associated with high immunogenic qualities. The initial cultures were from M.K. monolayers but minced kidney cultures are now commonly used since filtration is more easily effected. Here is a difficulty already, for how is the neurovirulence of a strain to be measured? With Salk vaccine, the strains were chosen primarily as a result of cynomolgus monkey inoculations and, to a certain extent, the suitability of the strain to the manufacturing process. With a killed vaccine the problem is not of such great importance but the question of choice of strains for live virus vaccines will be dealt with later at some length.

Many countries have however used different strains in their own inactivated vaccines, (See above).

The general scheme of production is as shown on the accompanying sheet. (33a)
Schema of Production Process for Formaldehyde Inactivated Vaccine.

M.K. cell) *
culture )Store/F/ 'Formalin' Inactivation: 7 - 12 days/F/Store **
fluid: } 4°C/F/ 72+ hrs. +F/ 4°C. ++
Type I ) Pool equal lots of all three types.
Type II . . . . . . . .   As above
Type III . . . . . . .   As above

To the pool may be added preservative which has its own Mouse safety test. Container sterility checks are performed before and after bottling.

F Indicates Seitz filtration. Additional 'in Process' filtration may be done.

* Safety tests for Sabin B virus; ECHO; Coxsackie viruses.
+ Tissue Culture safety tests. 500 ml. (1500 if a triple pool is used).
** Monkey/Guinea pig; Potency Test.
++ Monkey safety tests.

'Formalin' is a 1 : 4,000 Formaldehyde solution. Processing is done at 37°C, and pH 7.0
Seitz filtration has been proved superior to the sintered glass type, (4) in the filtration of untreated virus although when two filtration steps are used, there is often depression of potency particularly with type III.

The inactivation process was initially thought to be a straight line Rate/Time reaction, but it is now known that the inactivation process proceeds most rapidly during the first few hours following the addition of Formalin. 10 - 12 days are the usual inactivation times adopted. In South Africa, Ultra Violet irradiation supplements the Formalin process. With such a reaction the complete inactivation of all particles present is impossible and filtration is essential.

The question of potency is perhaps the most difficult problem of all, since there is no standardised antigenicity test available, and the tests that are available are incapable of detecting changes in antigenicity with any degree of accuracy. Antibody combining tests are in use but not on a large scale and the animal tests are always open to error. The technique most commonly used is the antigenic extinction method, developed by Gard in Sweden, in which the lowest concentration of vaccine producing an antibody response in Guinea Pigs is used as the measure of potency. Results by this method correlate reasonably well with vaccine efficiency in the field.

Safety of vaccines is estimated in two ways:- a: monkey sensitivity test; b: Tissue Culture tests.

The monkey sensitivity test has been proved satisfactory if several routes are used instead of simple intra-cerebral inoculation. Many of the strains now used are so highly attenuated for neurovirulence and production methods so good that this test has, to a large extent lost its initial sensitivity. Techniques for improving sensitivity are in use, in particular concentration of the vaccine before injection. (74) Injection of Cortisone with the vaccine has also been tried but without consistent results.

Tissue Culture is preferable, but is much more expensive and takes considerably longer. Their prime advantage is that the cytopathic effect of the virus is more easily noticed and larger inocula may be used. The value of any negative test is enhanced if other lots in the series are also negative. Tissue culture also avoids confusion between poliovirus and simian viruses such as the Sabin B virus.

With prolonged experience of inactivated vaccine production, many of the difficulties have been satisfactorily overcome, and since the Cutter episode there have been no cases of poliomyelitis in vaccinees which could be attributed to the vaccine used.

Provocation Polio.

Many queries have been raised as to whether provocation of the disease may occur following vaccination. The theory of a negative antibody phase for 24 hours after injection gave rise to great concern even though such an occurrence had never been noticed and the existence of such a phase is not regarded seriously. (54)

The Francis Report made special note of the lack of evidence of selective localisation of paralysis or of disproportionate frequency of paralytic poliomyelitis in vaccinees.

The vaccine has been used successfully in the face of epidemics. A vaccination programme was carried out in South Africa in the face of the worst epidemic they had experienced, with no serious reactions. (17) An epidemic occurred among Naval dependents at Pearl Harbour in 1955. 80% of the population was vaccinated and the epidemic slowed down after only four weeks. Subsequent notifications were from among new arrivals at the base.
Careful supervision failed to demonstrate any provoking effect. (32) Similar circumstances prevailed in Chicago in 1956, 1,750,000 doses were given in the area most severely affected, 300 cases with a history of vaccination were reported but none were proven to be related to the vaccine, (According to the criteria on p. 35). (32) Other theoretical complications to the use of Salk vaccine are:

1) Sensitisation to one of the vaccine constituents especially to antibiotics and to the contents of the animal serum that forms the basis of the nutrient fluids.

2) Rh sensitisation against vaccine antigens.

3) Renal damage due to the development of anti-renal antibodies by vaccine antigens derived from monkey kidney cells.

4) Neurological sequelae.

5) Allergic reactions to vaccine contents.

In general, vaccine reactions of all types have been rare and are, at most, as infrequent as those associated with any other immunising agent in common use. Here again the Francis Report is revealing in the relative frequency of reactions among vaccinated and placebo groups. (13)

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Rash</th>
<th>Poison Ivy</th>
<th>Asthma</th>
<th>Others</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacc. gr.</td>
<td>17</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0.004%</td>
</tr>
<tr>
<td>(27:12)</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>1</td>
<td>0.006%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Placebo gr.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003%</td>
</tr>
</tbody>
</table>

It is apparent that in any community, a certain number of people will show some mild illness during the observation period and the assessment of their relationship to the vaccine is extremely difficult.

Some reactions have undoubtedly occurred, many being due to the Penicillin content of the vaccine. In Penicillin sensitive individuals, anaphylactic shock has followed vaccine administration, but the possibility of vaccinees being unwittingly sensitised to Penicillin by the vaccine is probably an even greater danger. The Penicillin content of the vaccine is extremely low and anaphylactic reactions are rare at an estimated 1 per 300,000 inoculations.

Rh sensitisation to vaccine contents has not been demonstrated in small scale tests on Rh (-)ve children even in markedly reactive individuals. No signs of renal damage have been demonstrated in vaccinated individuals under continuous assessment of renal function.

Mild allergic reactions are infrequent and never serious and occur with a frequency of roughly 0.4%. Whether these are true allergic reactions to the vaccine is difficult to say.

Neurological sequelae have never been reported, but the danger does exist of an allergic reaction, taking the form of encephalo-myelitis, resulting in post vaccinal epilepsy or psychic changes. This has occurred in experimental animals, after a third dose, which were also suffering from a chronic infectious disease. The antibody titre was also far higher in these than in comparative animals. This would suggest that some care should be taken in innoculating children with such infections. (44)

Once again it must be emphasised that reactions are few and far between and in practice, the inactivated vaccine is safe.
5) Safety of administration to special groups.

These groups are: 1) Triple negative adults,
2) Pregnant women,
3) Children who have lost maternal antibody and show no antibodies to any poliovirus type. This includes premature infants,
4) Patients undergoing certain forms of medical and surgical treatment,
5) Those suffering from chronic infectious diseases.

Reference 74. (SEE ABOVE)

1) There is no evidence to suggest that triple negative adults are in any danger from the vaccine although they may require more booster doses than persons showing antibody to one or more of the various poliovirus types. Antibody levels following the first dose are low and levels are frequently only detectable against type II. By the third booster dose most of this group shows good antibody levels to all three types. A fourth dose is usually required to cover all non-immunes.

2) The vaccine may be given to pregnant women without any harmful effects either to the mother or the foetus.

3) Neo Nates and premature children form a highly susceptible group and although there are difficulties involved, there are no dangers attached to inactivated vaccine inoculation. Protection can be given to the child in utero by successful inoculation of the mother. This immunity lasts for approximately four months depending on the maternal antibody titre.

Inoculation of neo nates and children possessing maternal antibody is more difficult and the resultant antibody response is inversely proportional to the maternal antibody level at the time of inoculation. We have noted above how the boosting effect of a second dose of vaccine is dependent on the antibody level achieved by the first, and a vaccine of high antigenic potency is required. (42) Perkins et al., (42; 43) tested Pfizer vaccine on three groups of children aged 1 week; 4 months; 6 - 9 months, each child being given three doses at four week intervals. A booster dose was given 12 - 16 months later. The booster response in the 4 month children was considerably better than in the 1 week group and the best results were with the 6 - 9 month group. All three age groups showed a better response than similar children who had been given only two primary doses. These workers commented on the lower antigenic potency of the type I component and concluded that the earliest age when satisfactory immunity could be achieved was 6 - 9 months the vaccine was sufficiently potent. (43)

It is therefore clear that successful inoculation of this group is difficult unless they are provided with what Dr. Francis called, "A prenatal, amniotic cocktail". There are however no dangers associated with vaccination.

In association with child immunisation, we might also consider the use of killed vaccine in association with other antigens. A number of multiple antigen preparations are in use now especially in the U.S.A. Since many of these include Diphtheria and Pertussis antigens also, there is a high rate of reaction. (Up to 20%). (74) These products also raise manufacturing and testing difficulties. The polio vaccine must be tested both separately and in combination with the other antigens since the adjuncts used in their preparation often depress poliovaccine potency. In spite of the increase in time and labour involved, it would seem preferable to adhere to a suitable vaccine schedule. (63) since experience with multiple antigen vaccines is still limited.
4) Patients undergoing dental or E.N.T. surgery are not subject to any
dangers due to vaccination provided there is no risk of any live virus re-
main ing in the vaccine. The principal danger in this group is infection
by live virus.

5) The vaccine should be easy to administer.
   The reason for this requirement is that it controls, to a large
extent, the efficacy of the vaccine in large scale use. How may a
population be induced to accept the vaccine to the required level for the
complete control of the disease?

In most countries, four doses of inactivated virus vaccine are given
over a period of 16 months or more. Injections are not the most pleasant
way an individual can be vaccinated and a large proportion of the population
of any country consists of those who would do without vaccine rather than
be put to trouble. This applies particularly to the adult population who
take confidence from the name 'Infantile Paralysis'. With the Salk vaccine
it is often difficult to approach the pre-school age children who are most
in need of the vaccine.

It has been well established that the degree of protection against
the severe forms of polio, is greatest where the degree of vaccination
has been high. (74) It is apparent that a vaccine should be acceptable by
the public. Salk vaccine, unfortunately, is not. An indication of the problem
is given in the data based on immunisation survey and questionnaire results
in the U.S.A. The immunity status shows a gradual decline from 90% vaccin-
ated in the upper social groups (0 - 14 years mostly), to less than 25% among
adults in the lower socio-economic group.

This has been observed under the epidemic conditions that occurred
in Chicago in 1955/56. (32) In 1955 the upper and middle class North and
South parts of the city were heavily affected. By 1956 vaccine was available
in larger quantities and the vaccination programme was progressing, but
there was another severe epidemic affecting mainly the Central, Negro
quarter of the city. This area had been poorly innoculated numerically and
there was little opportunity of obtaining vaccine, whereas the upper
and middle class population, who are served mainly by private physicians,
have every opportunity of being vaccinated.

Similar situations have occurred in Detroit (1958), Kansas City and
Des Moines in 1959. (74)

Lack of acceptance by the public is the stumbling block to fully
effective use of inactivated virus vaccine. There seems to be no method of
over coming this obstruction.

7) Vaccine stability and persistence of potency.

There are no standardised methods sensitive enough to determine
changes in vaccine potency, and frequently the efficacy of a vaccine can
only be estimated retrospectively. Under ideal conditions the vaccine shows
only 'slight' loss of potency after nine months refrigerated storage but
several failures with vaccine have occurred, notably in Hungary, which may
be attributed to loss of antigenic titre. The experience in Sweden was
that serological conversion rates of less than 35% were obtained for imported
vaccine as against 65 - 100% with national vaccines. The observed/Expected
case ratio was also much lower with domestic vaccine.

With the development of vaccines of greater potency and more rapid
distribution methods, it should be possible to reduce potency depreciation
to a minimum, but it will not be until a satisfactory antigenicity test can
be selected that any reliable information can be obtained. (74)
8) Cost of Vaccine and Programme.

Salk vaccine is expensive to produce. Considerable material and a large working force is required to maintain a vaccination programme of any size. Now that the vaccine is being produced in large quantities, the only barriers to full utilisation are economic considerations, (And currency problems re. distribution to many countries), and lack of acceptance by the general public.

EXPERIENCE WITH KILLED VACCINE.

U.S.A.: By the end of 1956, more than 70 Million doses had been distributed primarily among the 0 - 19 age group. There were 7,911 reported cases that year with an over all paralytic rate of 58%. Of 3,198 acute admissions from this age range, 60% of the non vaccinated cases were paralytically affected but in the groups vaccinated 1,2 or 3 times, the corresponding rates were 17% ; 32% and 23%. (73; 32) The age incidence peak was shifted from the 2 - 5 year olds to the 0 - 1 year group.

The notification rates for the years 1951 - 60 are given on p. 32. It is seen that there was an increased incidence in 1959. How much this is due to better diagnosis or to a decreased incidence of aseptic meningitis due to other enteroviruses is difficult to say. The preliminary 1960 figures however are the lowest yet for the U.S.A. (37)

Major epidemics have occurred however in well vaccinated communities: Massachusetts, Pearl Harbour, Chicago, (1955); Chicago again in 1956; Detroit, Kansas City and Des Moines in 1958/59.

United Kingdom: In 1947, Britain was caught in the trans European spread of the virus. The whole country was severely affected with an overall notification rate of 30.2/100,000 and a case fatality rate of 10.4%. (14) Further epidemics were experienced in 1949, 1950 and 1952. (71)

Early in 1956, a vaccination programme was established for children born between 1947 and 1954 and a trial was carried out on 150,000 children aged 1 - 9 years. The results were encouraging. In two age group, 1 - 5; 5 - 9, the effectiveness ratio vaccinated/nonvaccinated children were: 1:5:1:16, indicating an effectiveness of better than 80%. (5) It was again noted that vaccination had no effect on the number of paralytic cases reported.

By 1958, 1,500,000 children 0 - 15 years, had been given two doses. The ratio of incidence of all forms of the disease in vaccinated,(2 doses); and non vaccinated groups was 3.4:21. (70) A more detailed analysis in the age group 0 - 15 was presented by Geffen and Spicer. (13)

<table>
<thead>
<tr>
<th>Paral.</th>
<th>Non Par.</th>
<th>Ratio P/NP</th>
<th>Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacc. 1 dose:</td>
<td>829</td>
<td>321</td>
<td>2.64</td>
</tr>
<tr>
<td>&quot; 2+ doses:</td>
<td>42</td>
<td>19</td>
<td>2.21</td>
</tr>
<tr>
<td>NON vaccinated:</td>
<td>83</td>
<td>83</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Here the vaccinated,(2 doses)/non vacc. ratio was better than 1:6.

By 1959, this ratio had been improved to 1:8, (70). By 1960, 75% of the 0 - 15 age group and 40% of the 15 - 25 group had been vaccinated, (74) and this year showed the lowest incidences but there are signs that 1961 will show a considerable increase over the low 1960 level. Notification for all parts of Great Britain and Eire were 23 for the week ending April 29th, this year as against 5 for the same week in 1960.

Australia: Between June 1956 and May 1957, 2,012,000 out of a possible 2,470,000 children aged 0 - 14 years were given two doses of vaccine. Serological tests indicated that 10% of these were triple negative.
The incidence of polio in this period was the lowest for 12 years being a reduction of over 90% on the number of expected cases.\(^{(73)}\)

<table>
<thead>
<tr>
<th></th>
<th>Expected</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>July '56-June '57:</td>
<td>2,253</td>
<td>224</td>
</tr>
<tr>
<td>Jan. '57-May '57:</td>
<td>1,224</td>
<td>71</td>
</tr>
<tr>
<td>Polio within 7 days of vacc:</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>&quot; 7 - 28 &quot;</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>&quot; after 2nd. dose:</td>
<td>400</td>
<td>9</td>
</tr>
</tbody>
</table>

No cases were reported in triple vaccinated persons up to June 1958. Protection was estimated at over 90\%.\(^{(74)}\)

U.S.S.R.: Vaccination of 2 - 5 Million persons was studied during 1957 with an effectiveness of 70%. By October 1958, 15 Millions had been vaccinated. Overall incidence fell from 20,000 p.a. to 12,000. Live virus vaccine trials were begun and Salk vaccine eventually discarded.\(^{(58; 74)}\)

Czechooslovakia: Killed virus vaccines have been used since 1957 and by the end of 1959, 80% of the 0 - 15 age group had received 2 or 3 doses. Serological investigation carried out 1 year later showed that 40% of these children had no antibodies to types I and III and that spread of the virus through the country was unrelated to vaccination history.\(^{(74)}\)

Despite the low morbidity during these years, nearly 50% of notified cases of polio in the under 16 age group, had been vaccinated. Comparative tests were carried out with live virus vaccine and a fourth dose of Salk vaccine. The normal seasonal increase still occurred in the Salk vaccinated regions but not in those where live virus had been given to less than 6% of the population.\(^{(50)}\)

Hungary: In spite of intensive vaccination,\(^{(70\% \text{ of the 6 month - 19 year old age group), with three doses intradermally during 1957/58 an epidemic occurred in 1959 with a case rate of 24/100,000. Polio occurred in both immunised and non immunised children.}\(^{(74)}\)

Israel: Most of the 6 month - 3\(\frac{1}{2}\) years age group were vaccinated,\(^{(2 \text{ doses) before June 1957. They were given a third dose early in 1958. In March and April, 85\% of the 1957 born children were given two doses. During the May of that year, a type I epidemic gained impetus and it was the 1957 born children who were mainly affected. 80\% of cases were in the 0 - 3 age range.}\(^{(9)}\)

Summary: Salk vaccine has proved itself to be a safe and effective vaccine and is widely used in many parts of the world. With the progressive improvements in vaccine potency that could yet be made, such a vaccine would, under suitable circumstances, produce a high degree of protection in the vaccinated community.

Some countries, Hungary and Israel particularly have experienced failure with this vaccine. The explanation of this could be vaccine of low potency and/or differences in route of administration, dosages and intervals between doses.

Evidence as to the duration of protection bestowed by killed vaccine is often highly contradictory. In general it seems that the type I and III antibodies are readily lost if booster doses are not given at regular intervals.

Degree of protection with the vaccine is highest in areas where the degree of vaccination is high. This is difficult to achieve for reasons given above.

The vaccine is expensive to produce, distribute and administer.
In practice the vaccine does not immunise the port of entry of the virus i.e. the alimentary tract, and provides humoral immunity only. Since this takes a minimum of 7 - 10 days to develop, the vaccine cannot be used to terminate an epidemic outbreak. Such action has been tried in the United States,(32) and South Africa,(17) but not even the most optimistic can say that the course of these epidemics was altered.

Many countries have carried out comparative tests with inactivated and live virus vaccines and the results, in many cases, have swung the balance in favour of live vaccines.
LIVE VIRUS VACCINE.

If the natural process of infection could be imitated in some way, not only would there develop humoral immunity but also the alimentary tract would be rendered highly insusceptible to further infection.

The first virus strain to be used for live vaccine purposes was a type II, (T.N.) which, after 35 cotton rat passages, was fed to a 6 year old boy who showed no antibodies to the type II virus. Intestinal infection was established and the 15 day blood sample showed specific neutralising antibodies. The child showed no signs or symptoms of illness. (30) This same strain was later fed to a further 18 children and was shown to be harmless.

In a similar experiment in 1952, two children were given vaccine. One child was fed a mouse adapted mixture of the Sickle and Mahoney, (S.M.) type I strains. The second child was given a SM/TN mixture. Neither of these children was ill and both were later shown to have developed immunity to the strains with which they had been fed. (30)

These were the first human tests of live attenuated virud vaccine, since then an immense amount of work has been done in the development of suitably attenuated virus strains and, the practical and theoretical problems involved in the administration of live virus vaccines.

Three names; Cox, Koprowski and Sabin are associated with the development of the types of live vaccine at present in use and the strains used are shown below:

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lederle Labs., (Cox):</td>
<td>Lederle SM</td>
<td>Lederle MEF</td>
<td>Lederle Fox.</td>
</tr>
<tr>
<td>Koprowski:</td>
<td>Wistar CHAT</td>
<td>TN(P712)</td>
<td>Wistar Fox.</td>
</tr>
<tr>
<td>Sabin:</td>
<td>L, Sc</td>
<td>P 712</td>
<td>Leon.</td>
</tr>
</tbody>
</table>

The SM, TN and MEF & Leon strains have already been mentioned previously. The two J.P. Fox variants are identical are an isolated monkey avirulent substrains. CHAT is a substrate of SM; L Sc is a substrain of Mahoney I derived from mouse passage by Li and Schaeffer in 1954. (30) Of these three, the Sabin vaccine has had most use, with well over 50 Million doses given and much of the following information pertains to this vaccine.

Again it will be helpful to consider the efficacy of such a vaccine in reference to the criteria on p. 28.

1) The vaccine is produced in trivalent and separate strain forms and is administered orally in capsules or as a syrup, or again, as in U.S.S.R. as candy. In the youngest age groups it may be given in liquid form with fruit juice or milk.

2) Live attenuated virus vaccine will provide both cellular and humoral immunity since it establishes an infection in the intestinal wall as does the naturally occurring virus. There may or may not be a viraemia but this will be discussed later.

Humoral immunity is undoubtedly induced and is demonstrable by antibody determination. Intestinal immunity may also be demonstrated up to 3 years after the initial feeding with types I and II. (30) In addition to this, or more likely as part of the same mechanism of resistance, there is the interference phenomenon.

3) The vaccine must provide a high degree of immunity which is of long duration. Since the objective of any vaccination programme is to immunise the whole community, a consideration of the immunity levels produced must include any groups within that community who are likely to at special risk from the disease.
We must also consider whether vaccination of these groups can be performed with satisfactory results.

In some vaccination programmes in the U.S.S.R. in 1958/59, the vaccine was administrated in several combinations: 1) 3 x Trivalent vaccine; 2) Monovalent I followed by Divalent II + III; 3) Mono, I, Divalent II + III, Trivalent. All doses were given at one month intervals. The serological conversion rates for these regimes were:

<table>
<thead>
<tr>
<th>Schedule</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>100%</td>
<td>100%</td>
<td>87%</td>
</tr>
<tr>
<td>2)</td>
<td>77%</td>
<td>91%</td>
<td>72%</td>
</tr>
<tr>
<td>3)</td>
<td>96%</td>
<td>99%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Reference 58.

In the Baltic republics, using monovalent vaccine only, in the order I; III, II ; in a community with an estimated 10 - 14% triple negative individuals, the conversion rates ranged from 91 - 98% for I and II; and 88% to type III. Three months later there was a response to all three types of 94 - 98%. (74)

The effect of this vaccination programme, covering over 1½ Million people was striking. There was no seasonal rise and poliomyelitis almost disappeared. Shown below are the notifications in Estonia and Lithuania through the period 1955 - 1959.

<table>
<thead>
<tr>
<th>Year</th>
<th>Estonia</th>
<th>Lithuania</th>
</tr>
</thead>
<tbody>
<tr>
<td>'55</td>
<td>180</td>
<td>411</td>
</tr>
<tr>
<td>'56</td>
<td>213</td>
<td>247</td>
</tr>
<tr>
<td>'57</td>
<td>102</td>
<td>124</td>
</tr>
<tr>
<td>'58</td>
<td>963</td>
<td>264</td>
</tr>
<tr>
<td>'59</td>
<td>8</td>
<td>17</td>
</tr>
</tbody>
</table>

The estimated protection is well over 90%. Similar results were obtained in other parts of the U.S.S.R.

In Czechoslovakia a trial of Sabin vaccine was carried out in 1959 against a control group of children who were given a fourth dose of Salk vaccine. By the September of that year it was apparent that the usual seasonal rise of case notifications was present in the Salk vaccinated region but not in the live vaccine population. (50) Conversion rates were 95; 93 and 94 to types I; II and III. (74)

These countries however are all in temperate climes but since this vaccine is live and given orally it will be subjected to varying degrees of interference both from other enteroviruses and from its own component strains. (30) The Sabin strains show decreasing capacity for interference in the order II; III, I. (50) It has also been shown that this interference is best overcome by sequential administration of these strains, in the reverse order to that given above, at intervals of not less than 4 weeks. A single dose of trivalent vaccine is considerably less effective than three monovalent doses. The question of simultaneous versus sequential feeding is still unsolved but the conversion rates given by Smorodintsev for the third schedule indicate that this method of giving the vaccine is preferable to the others mentioned.

Interference between the vaccine strains is thus fairly easily overcome, but interference of vaccine strains by other enteroviruses poses a different question particularly in tropical and subtropical regions where 72% and more of the child population are harbouring enteroviruses other than and in addition to, polioviruses. (51) There is little point in having a vaccine efficacious only in temperate climes.

If vaccination programmes in tropical regions are spread over several weeks and cover only a small proportion of the susceptible population, there is invariably failure to immunise a proportion of those vaccinated and there is no effect on the dissemination of natural paralytogenic strains.
These were the findings after trials in Mexico City, Monterrey, Guadalajara and Puebla in 1959. (74)

In such communities where polio is endemic, the most susceptible group is the 0 - 3 year olds. In preliminary investigations at Toluca, natural virus infection of the alimentary tract was noted during the first days after birth and by the end of the first month of life, 90 - 100% of children became triply immune by their fourth year. The cost paid for this protection is an average of 14 paralytic cases per year. This was the scene then for the experiment conducted in Toluca, Mexico, in the August of 1959 using the city of Queretero as a control. The total child population was over 30,000. Of these 86% were involved in the experiment and 97% of the group were fed triple vaccine mixture in a period of four days. Throughout the experiment, isolates of non polio virus remained at about 50%, whereas the polio isolates showed, after a slight initial rise, a fall from 11% to 0.7% in a period of three months. The overall antibody response was compared with that in Queretero. For types I, II and III the levels were 69%, 87%, 50% for Toluca, and 62%, 10% and 13% for Queretero. The non-polio/ poliovirus ratio in Toluca's children had been reduced from 4.6:1 to 72.3:1.

The antibody response after 10 weeks is shown below:

<table>
<thead>
<tr>
<th></th>
<th>Single(-)</th>
<th>Double(-)</th>
<th>Triple(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100%</td>
<td>88%</td>
<td>55%</td>
</tr>
<tr>
<td>II</td>
<td>82%</td>
<td>80%</td>
<td>83%</td>
</tr>
<tr>
<td>III</td>
<td>59%</td>
<td>42%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Reference 51.

Some children with no detectable antibody were excreting the virus. 44 children who did not develop antibody at 21 weeks were fed a second time with responses of 96% to I & II; and 78% to type III.

It is apparent that with a rapid mass vaccination of the susceptible population even in such conditions, there is a possibility of eradicating the poliomyelitis virus from the community.

The only other group requiring special consideration with regard to administration is the 0 - 6 month age range which, may be difficult to immunise owing to the presence of acquired maternal antibody. Several vaccination schedules have included vaccination of children from 2 days old onwards. The newborn population is the ideal one for receiving the live virus since the vaccine can be given within a few hours of birth when there is little likelihood of interference by other enteroviruses. There are however some unusual aspects to this point. In an experimental vaccination programme on 96 infants, aged from a few hours - 140 days, Koprowski et al. (51) found that the ability to support the multiplication of attenuated viruses in the intestine appeared to vary with the age of the child at the time of vaccination. At the same time they found the expected variation in antibody response with age: only 53% of the youngest children developed a positive antibody response as against 90% in the oldest group. The results for the whole group were:

<table>
<thead>
<tr>
<th>Age</th>
<th>Infection:% of cases</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 7 days</td>
<td>94</td>
<td>88</td>
<td>100</td>
<td>160%</td>
</tr>
<tr>
<td>8 - 35 &quot;</td>
<td>73</td>
<td>81</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>36 - 70 &quot;</td>
<td>73</td>
<td>68</td>
<td>58</td>
<td>87</td>
</tr>
<tr>
<td>71 - 140 &quot;</td>
<td>90</td>
<td>89</td>
<td>88</td>
<td>93</td>
</tr>
</tbody>
</table>
It can be seen that immediately after birth infants are fully susceptible to intestinal infection but this is followed by a long period of relative resistance. This period is not relatad to maternal antibody level and the reason for this phenomenon is unknown. It has been suggested that the effect is due to the presence of Gram (-)ve bacteria, whose endotoxins have a suppressive effect on the growth of attenuated polioviruses in tissue culture. (31) In general, intestinal infection was fairly easily established no matter what the maternal antibody level had been, but the frequency of positive antibody response was inversely related to the prevaccination titre of amternally acquired antibody in the child. It may be that a response does develop in time. Conversion rates in Costa Rican new born children, measured 8 months after vaccination, were 70%, 32% and 85% for types I, II and III, (Lederle). (74) One other fact of interest resulted from these experiments; children who had a good antibody response to the vaccine resisted reinfection with the vaccine better than those children who had a poor initial antibody response. This indicates that furthervaccination of an immune child while doing little good, can do no harm. It also suggests that humoral antibody plays some role in the maintenance of intestinal immunity. In most countries where the vaccine is in large scale use, refeeding of the vaccine is a standard procedure and the immunity, so far as can be judged in the short time that has elapsed, is of long duration. In the above experiment, antibodies have persisted for 3½ years at a minimum titre of 1:16. Earlier work by Koprowski showed good antibody levels 8 - 9 years after vaccination with the TN strain and more than four years with the SM. Sabin also noted intestinal resistance to types I and II in both adults and children when re exposed after a two year interval. As with the Salk vaccines it would appear that reinfection can occur most frequently with the type III component. (30) 

4) The vaccine must be free from suspicion of causing or precipitating the disease and side effects should be minimal. 

With a live virus vaccine the situation is quite different from that with Salk vaccine, for the virus can be spread from the vaccinee in the same way as a naturally infected person acts as a focus of infection and distributing centre for the virus in his own community. The spread of the virus may take place by any of the means mentioned in the section on epidemiology. Such spread cannot be controlled and the live virus vaccine must be proved safe in the following respects:

a) It must be suitably attenuated as shown by laboratory investigation.
b) The virus strains must be genetically stable on human passage.
c) There must be no opportunity of the vaccine becoming contaminated by potentially harmful, adventitious agents.
d) There must be a decreased capacity to invade tissues other than the alimentary tract, (As shown by the presence or absence of a viraemia).
e) Restricted capacity for spread.

(40; 74) 
a :- Attenuation implies that an agent, in this case the poliovirus, has undergone changes in its characteristics. These changes are loss of pathogenicity yet retention of the antigenic qualities for immunisation purposes. There is a danger that a strain is developed which retains its virulence for mice yet loses its immunogenic properties in man. This happened with the 17D strain of Yellow Fever. 

Variants of all strains used in live vaccine have been selected by the Dâlbecco and Voght tissue culture technique of progressive isolation and purification of the less pathotenic virus strains.
The assessment of pathogenicity is performed in two ways; the tissue culture technique mentioned above resulted in the possibility of marking of viral characteristics to distinguish attenuated strains from those of high pathogenicity. Neuro-pathogenicity tests in monkeys are still standard practice and although doubts exist as to the validity of applying results of animal experiments to human use of the viruses, experience has shown that monkey neurovirulence tests correlate quite well with the effects of the vaccine in the field.

It is important to note that if cynomolgus monkeys are fed with standard monkey passage virus, no paralytic manifestations occur but, if fed with human passage virus, these animals develop a paralytic form of the disease. (46) This raises the possibility that monkey passage strains which are of low neurovirulence for monkeys, may still cause polio if ingested by humans.

It is important to draw a distinction between cerebral and spinal neurotropism because a strain showing a high degree of spinal neurotropism may have a very low degree of cerebral neurotropism and vice versa. Secondly, there is a 'scale of susceptibility' in which man and monkey are at two different levels, This may be represented diagrammatically:

Susceptibility<------------------------>Resistance.
Neurone: Monkey(LMN)......Monkey(Brain).....; Chimp, LMN, Man.-...Man.
Gut: Man .................Chimp .............cynomolgus/rhesus.

Reference: 49; 72.

Also it should be remembered that for the sake of convenience, many animals used in these experiments are not infected by natural routes, resulting not only in the local application of high concentrations of the virus but also in mechanical damage to highly susceptible tissues. This has an adverse effect on cell and host resistance.

All the virus strain mentioned show neurovirulence by intraspinal inoculation but vary considerably when given by the intrathalamic route. All three Sabin strains show no clinical signs or histological lesions via the thalamic route but do so when given intraspinally. Intramuscular inoculations also are used but the dosage required to produce lesions or paralysis is high. (74) Errors may occur due to the development of mutants arising in the monkeys, but such occurrences can frequently be distinguished by one - sided nature of the paralysis and failure to recover cytopathogenic viruses from the brain stem and cord. (49)

Monkeys and Guineas Pigs are also used to determine antigenic potency as they are for Salk vaccine.

It is obvious that these procedures involve a great deal of time, work, (Especially histological assessment), and expense. Attempts are being made to determine the association between certain genetic markers and neurovirulence/antigenic characteristics. Some of the markers studies in detail are 'd', (+ indicating ability to grow in presence of reduced, 0.05%, concentrations of Bicarbonate); MS, (+ indicating ability to grow on the MS stable line of monkey kidney cells); T or rect = reproduction capacity at a given temperature, (+ or - ). Others used are Bovine or Horse serum inhibitor resistance; Temperature sensitivity for inactivation; Cystine requirement or inactivation, and others.

Cabasso et al. (7) carried out experiments of 8 type I, II and III vaccine lots, to determine the association between MS; d and T markers and monkey neurovirulence.
They found that if the T marker was retained with a change of d- to d+, there was no change in neurovirulence. T- to T+ was associated with a sharp increase in neurovirulence as shown by histological sections. MS- was associated with decreased neurovirulence, but this has been left unaltered by changes in d and T. T+ was assumed to indicate increased neurovirulence but this has been disproved by isolation of T- strains from paralytic children. (7; 74) Difficulties encountered are due to covariation of d and T in an irregular and unpredictable manner and the MS marker is also subject to variation. Because the marking of in vitro characteristics are not definitely established as being useful criteria, the monkey neurovirulence test is still the most reliable indication of neurovirulence.

Such tests would however be of great use in the development and testing of new vaccine strains and, probably more important, would be used for screening polio cases in vaccinated persons. Their epidemiologic value would also be considerable. As yet unfortunately, there are no reliable markers in use.

b) Genetic Stability. A great deal of apprehension has been caused by reports of increased neurotropism of vaccine strains following human passage. Since the vaccine virus can spread throughout the non vaccinated portion of the community, there is a grave risk of these nonvaccinated contacts becoming infected with the passage strain and developing a severe form of the disease. Such a situation as believed to have occurred in some regions. Smorodinskev,(58) noted a fairly high incidence of paralytic polio in Russian 'Internal Control' groups i.e. those who were potentially in contact with the vaccines and he suggested the mass, compulsory vaccination was the only solution.

 Highly attenuated viruses multiply as vigorously as highly neurotropic viruses as detected by virus/gramme stool estimations. If such multiplication is prolonged it is possible to produce viruses of increased neurotropism. This modified virus can then be excreted. Assessment of the neurotropism of human passage vaccine virus has been done. For type I, the neurotropism has been found to be less for the passage virus than for that fed. (49) Russian experiments have reaffirmed this and have also shown that slight increase in the neurotropism of type II and III occurs during the first four and five passages respectively. By the 5th. and 6th. passages, the increased neurovirulence was not found. There is no progressive intensification but the minor oscillations mention d above do occur. (74; 58)

Sabin has failed to recover virus particles of high neurotropism when they have been administered with normal vaccine. These viruses were not excreted and not absorbed, and Sabin suggests that they are unable to compete with the large population of the original virus in the gut.

Obviously, if such highly virulent strains were selectively absorbed and excreted during intestinal infection, all the polioviruses occurring in nature would show very high neurovirulence. (49) It is impossible to say that such preferential excretion of viruses of heightened neurotropism does not, or will never, occur and continued observation of the virus strains at present in use is essential.

c) Vaccine Contamination. Filtration and tissue culture/monkey safety tests are carried out on each batch of vaccine. Since the vaccine virus is live, no sterilisation procedures can be performed and the prevention of contamination lies in the careful preparation of the cultivation medium before seeding takes place. Contamination by Simian viruses does occur but of the many types so far isolated, none has shown pathogenicity for man.

Footnote: Ret/40 studies have been performed in field trials in Hungary: Domok; B.M.J., 1961, I, 1411.
There is no guarantee that these contaminants will not show pathogenicity. For this reason 30% or more of tissue culture bottles are specially set aside to allow the growth of any contaminants to be observed. (74)

The presence of a viraemia. The amount of information available on this point is very limited and its importance is doubtful. Evidence of viraemia in field trials is only found when large innocula are used and the percentage of inoculated individuals showing a viraemia is about 1% and then only to certain strains. In the Third Report of the Expert Committee, (74) several suggestions are made as to standardisation of viraemic tests but no satisfactory results are yet available.

Spread of the Virus. The two modes of excretion of the virus by the vaccinated person are via the stool and the pharyngeal secretions. Their relative importance in the spread of polio virus has been dealt with at length elsewhere. It must be mentioned however that pharyngeal excretion may play a greater role here since many children are given the vaccine in liquid menstrua. It has been noted that this only occurs frequently if very high doses of liquid vaccine are given. (51; 8) The danger of spread is primarily related to the possibility of the vaccine strain showing increased neurotropism after passage.

Spread throughout a circle of vaccinee contacts is related to the infective capacity of the strain involved and to the age of the vaccinee. Children of less than 6 months of age are less efficient disseminators than three year olds. Dissemination also depends on the duration of virus excretion following infection, which has been shown to be the same as for natural infection.

Cabasso et al., (8) investigated the spread of live virus in sibling and family contacts. 7,000 individuals were tested. It was found that type I spread to 32% of intrafamilial contacts, type II to 35% and type III to 35%. Extrafamilial contacts were tested on a group of 148 families; one group of 74 receiving vaccine, and the second group a placebo. Type I spread to 12%, type II to 8.1% and III to 14.3% of the placebo families within each of which the spread was similar following vaccination of the index child in a family. This bears good comparison with the investigations of Melnick and Horstman. (35) The tendency to spread is of course, dependent on all epidemiologic factors previously considered.

Is spread dangerous? In the event of increased neurotropism it certainly could be dangerous, but this has not been adequately demonstrated. Spread of the virus can be beneficial and several worker have carried out vaccination programmes relying on rapid dissemination of the vaccine virus to cover a greater proportion of the community. (Toluca (51); Singapore (20); Baltic, states (74)). Here again there is room for further investigation, but from available evidence it would appear that the tendency to spread decreases with the number of contacts, and that spread across international borders from countries where live vaccination programmes are established, is minimal. (74)

Field Evaluation of Safety.

Numerous large scale vaccination programmes are being carried out in many parts of the world and there have been no cases reported yet where paralytic polio has been produced by the vaccine. 65% of cases of paralytic polio are due to the type I virus. If 1 Million people were vaccinated with type I, then approximately 5,000 might be expected to develop paralytic manifestations.
By the end of 1960, more than 77 Million people had been vaccinated in the U.S.S.R. with no proven cases of resulting paralytic disease. Certain reservations must be made however since the statement that,'No paralytic disease has occurred due to the vaccine', is meaningless unless it is also specified on what grounds it was decided whether or not to implicate the vaccine.

A stringent test of live virus vaccine would be its use in the face of a rising epidemic and this has been done on several occasions. The Lederle vaccine has been used during type I and II epidemics,(Sequential feeding I, II, III; II, III, I), in Colombia and Nicaragua without ill effects.(8; 74)

The assessment of the effectiveness of a vaccine and its possible dangers is extremely difficult under such circumstances and cannot be effectively determined without the aid of in vitro markers.

Hale et al, faced with a type I epidemic in Singapore in 1958, decided to use the Sabin type II vaccine on children aged three months to 10 years with these points in mind:

a) To demonstrate the safety of the vaccine in both vaccinees and contacts since a type II infection would be quickly shown up against a type I epidemic background.

b) Interference of the type I virus might be effected.

c) The vaccination would ensure that all vaccinated persons, and probably many contacts had antibodies.

d) The administration of large quantities of type II attenuated virus might interfere with the natural spread of the epidemic strain.

198,965 children were vaccinated over a period of 12 weeks. 6 children later developed a type I paralysis as compared with 179 paralytic cases in the 500,000 non vaccinated children. None of the vaccinees developed a type II paralysis. One case of type II paralysis occurred in a non vaccinated person but was proven to be due to a 'wild' strain.

The experiences of other countries will be briefly mentioned in the summary to this section.

Side effects due to the vaccine are uncommon, 3/100,000, and when they do occur are mild in character. Usually they take the form of transitory intestinal tract disturbances.(64) Feverish reactions are no more frequent among vaccinees than among the non vaccinated population under normal circumstances. Urticarial reactions have been inconsistently reported and appear to have no significance. (74) The dangers mentioned in connection with Salk vaccine due to contaminants, monkey kidney antigens etc., apply in the case of live vaccine also but no serious reactions have been reported. There has been no evidence of accumulation of cases within the 5 - 20 day period and no unusual age distributions of paralysis have been observed.(40)

It is unlikely that the attenuated viruses will never cause any illness since the ability to 'Take' and induce immunity is inevitably associated with the capacity to injure some cells in the course of the infection, however minor that injury may be.(37) The lack of close observation in mass vaccination programmes with regard to minor reactions, still leaves considerable doubt as to the frequency and degree of reactions to the vaccine.

*Footnote:* A second report on this epidemic has just been published: Knowelden and Hale: B.M.J., 1961, 1, 1418.
5) Safety in administration to special groups.

a) Triple negative adults: An estimated 10 - 14% of vaccinated persons in the U.S.S.R. were triple negative but there has been no apparent difficulty in immunising these people and the complete absence of a seasonal rise in regions where mass vaccination has been carried out, is indicative of the high level of immunity which can be attained with this vaccine. There is perhaps greater danger to this group than others, but under epidemic conditions of polio, the risk of infection and paralysis by a naturally occurring strain far exceeds the hazard to the small proportion of non immune adults from the use of attenuated vaccine. Further investigation is required into this question, but the danger could be reduced by primary vaccination with inactivated vaccine.

b) Pregnant Women: Here again there is some theoretical danger but there is no evidence of harmful effects to the mother or foetus. If the mother shows no antibodies before vaccination, there is a danger to the foetus from the possibility of a viraemia. No increase in the abortion rate following vaccination of the mother has been found. Experience is still limited and the reservations made regarding safety in triple negative adults, apply equally well here. Primary vaccination with Salk vaccine is again indicated.

c) Premature and new born Children: These form the ideal population for live virus vaccination and, although their immunisation raises certain practical problems, there are no dangers involved.

d) Patients undergoing certain forms of medical and surgical treatment. Patients receiving Corticosteroids could be in danger from the vaccine and primary vaccination with Salk vaccine is again indicated.

In view of the danger to persons undergoing ENT surgery, where damage to cranial nerves is possible, the use of oral vaccine is not recommended. The danger is increased if the patient is also triple negative.

e) Provocation: Polio due to injection with Biphtheria and Pertussis vaccines and other antigens after oral vaccination, has not been reported but it is suggested, that such vaccinations and elective operative procedures should not be performed during mass vaccination programmes.

In the U.S.S.R., the only contraindications to live vaccine use are acute febrile states within the two weeks prior to vaccination, T.B., (44), intestinal disorders and decompensated cardio vascular disease.

6) Live vaccine is easy to administer and has proved to be acceptable by the general population. There are no injections required, a great advantage in the eyes of many potential vaccinees, and children of any age can be vaccinated by means of vaccine syrup, fruit juices or dragees. The importance of ease of administration cannot be over-emphasised. A high level of communal immunity depends on a high proportion of that community being vaccinated. All ages and socio economic groups can be easily reached and there are few who would avoid second and third vaccinations by the oral route. This is probably one of the foremost recommendations for live virus vaccine.

7) Stability of potency is difficult to assess and there are no sufficiently sensitive tests generally available to assess this factor.
Sabin reports, (49) that live vaccine bottled at room temperature and maintained at 20°C. for two years, shows 'very little' change in potency. From field tests it would appear that minor variations in potency are of little consequence and resulting conversion rates are dependent more on the degree of interference by other enteroviruses in the vaccinated persons. (51; 6)

8) The vaccine is cheap to produce, distribute and administer. There are no injections required which eliminates the necessity for skilled workers, sterilising equipment and numerous other ancillary requirements being mobilised for a large scale vaccination programme. The overall cost of such a programme is considerably lower than it would be with Salk vaccine. This means that countries of poor, or unstable, economy can make use of the vaccine.

Ease of production is being facilitated by investigation into the use of stable human cell lines for the tissue culture of polio viruses. Such a development would obviate the need for testing for simian viruses and other contaminants and also be cheaper to prepare than monkey kidney cultures. The danger with such lines is that they are potentially malignant. (74)

Experience with live vaccine.

A great deal of difficulty is encountered in attempting to assess the effects of live virus vaccine, since so many countries have made use of Salk vaccine. This means that the true epidemiologic status of a country is frequently impossible to determine. This raises problems regarding future assessments following the use of Salk, Sabin, or both vaccines.

In the U.S.A. trials have, in the main, been done on a small scale. Some results show that good conversion rates among triple negative adults can be obtained. From February to May 1960, Lederle triple vaccine was given to 412,000 people under 40 years of age, and the triple negatives in the group showing conversion rates, to types I, II and III of 88%, 62% and 90%.

The U.K. has, as yet, done no large scale trials of live vaccine although the vaccine is now being produced by Glaxo, following recommendations for trials made during April, 1961.

Experiences in Czechoslovakia have been mentioned already, and very favourable results have been obtained using the Sabin vaccine. (50; 74) No side effects were experienced and the usual seasonal rise failed to develop in the vaccinated regions. In 1960, a live virus vaccination programme covered 93% of the two months to four years, age group, without bringing any adverse side effects to light.

The U.S.S.R. has had the greatest experience with live vaccine, and an estimated 80 Million people had been vaccinated before the epidemic season started in 1960. In all areas where vaccination was completed before the anticipated seasonal increase, no increase occurred. Vaccination has been used to effect in epidemic conditions, resulting in a four fold decrease in incidence among vaccinated persons. Salk vaccine is no longer used.

Similar vaccination programmes are in progress in Hungary, Germany, Bulgaria and China and no complications have been reported.

* See footnote on page 46.
Mauritius in 1959, experienced a type II epidemic, case rate 15/1,000, although the island had been well vaccinated with inactivated vaccine. Sabin type I vaccine was given to 195,000 children of less than 10 years of age, beginning at the 11th week of the epidemic. The total number of cases reported was 97, but only 4 of these were notified after the 11th week. The epidemic was already waning however, (Weekly case incidence reaching a maximum during weeks 7 and 8), and the effect of the vaccine is difficult to determine. There were no fatalities. (60)

Colombia had had Lederle vaccine given under epidemic (Type I) conditions during 1958. Vaccine was fed in the order I, II, III at 3 - 4 week intervals. 90% of the 2 month - 6 years age group was vaccinated and 4 cases, in non vaccinated, non contact children, were subsequently reported. Immunisation with triple vaccine is now performed on neonates in Medellin. In one study, in the same area, 8 children who had been vaccinated, developed paralytic poliomyelitis. None were due to vaccine virus.

Nicaragua and Costa Rica have also made use of Lederle vaccine, but, as in Colombia, a sequential feeding system was adopted. As we have seen, this is not conducive to developing a high level of immunity. The optimum system would be simultaneous administration of vaccine to all susceptible groups. In Nicaragua, 12% of subsequently notified cases were in people who had received one or more virus types. In Costa Rica, the corresponding figure was 4%. In neither country could the paralysis be associated with the vaccine.

Mexico has had large comparative trials done with Sabin vaccine and the results have already been mentioned. Despite a very high infection rate with enteroviruses, successful vaccination with live virus was performed.
Sabin or Salk or Both?

The advantages of live vaccine over the inactivated type are:
1 It is easily administered and acceptable by the populace. Vaccinees will return for a second dose since there are no injections involved.
2 It provides both long lasting humoral immunity and insusceptibility of the intestinal tract.
3 It does not multiply in people who have gained solid immunity.
4 It can be given as a booster to Salk vaccine. Transfers of vaccination programmes from Salk to live vaccine are easily carried out.
5 Absence of general/local reactions.
6) May be used to halt the progress of an epidemic.
7 Immunity up to 100% is possible.
8 It is cheap to manufacture and apply in the field.

Potential disadvantages:
1 Spread of the virus to contacts is a potential danger.
2 Possibility, not demonstrated, of reversion to a more virulent form of the virus.
3 Possible dangers attached to its use in certain special groups especially those undergoing surgical treatment.
4 Interference by enteroviruses. This may however be counteracted in temperate regions by winter feeding, (67) and in the tropics by rapid, mass inoculation, (51; 74)

Salk vaccine has in its favour:
1 Its safety has been established.
2 There are no dangers attached to its use in the special groups mentioned above.
3 Immunity up to 95% is possible.
4 Absence of general reactions.

Disadvantages:
1 Lack of acceptance by the populace.
2 Degree of immunity provided is not reliable due to variations in potency, and rapid loss of antibody to some antigenic components.
3 Only humoral immunity is provided.
4 Expensive to produce and administer.
5 Has no effect on the progress of an epidemic.

The occurrence, in several parts of the world, of epidemic poliomyelitis in communities who have received inactivated vaccine, indicates that while Salk vaccine has undoubtedly prevented a great degree of paralytic poliomyelitis, it is inadequate in eliminating the disease or providing full protection.

In considering this undoubted prevention, it is worth while considering whether Salk vaccine alone has been responsible for this decline. Has the disease been regressing naturally since the introduction of these vaccination programmes? This is a difficult question to answer since epidemiologic study in countries using Salk vaccine has been pushed off balance by the introduction of this vaccine, with the resultant situation of a false epidemiologic status. The situation is further confused by the introduction of live, attenuated virus which can spread virtually without limit under suitable circumstances. Natural regression may have been involved although I would think this is unlikely.
Since accurate records, and improved methods of diagnosis have been introduced, all countries plagued by epidemic poliomyelitis have shown a steady rise in the minimum number of notifications during each inter-epidemic period. (14) Epidemics on a large scale still occur among well vaccinated communities, (viz. Chicago 1956; Massachusetts 1959), and in instances where Salk vaccination has failed e.g. Israel and Hungary, there has been no evidence of natural regression.

Forced regression has occurred and followed the expected stages i.e. a shifting of the peak incidence to a younger age group; decrease of the paralytic/non paralytic ratio, but this regression has occurred during the course of less than four years. (viz: 1954 - '57; U.S.A. notifications) in some countries. This would be an unprecedented change if natural regression had occurred at such a rate. The rest of the world however still suffers from epidemic and endemic poliomyelitis and the regression, if natural, might have been expected to show up in countries of lower economic standing than the U.S.A.

Elimination of wild viruses from the world scene is, although remote, conceivable with the use of live vaccine; but the little time that has elapsed since the introduction of this vaccine is not sufficient to make a full assessment of its safety in all portions of the community.

What of the future? The trend is towards the use of live virus vaccine alone, but it is more likely that a compromise will be reached.

The combination of a primary dose of Salk vaccine followed by booster doses of live virus would seem to be the best combination for use with triple negative adults, pregnant women and other susceptible groups of the population. For the present, Salk vaccine is assured of a prophylactic niche in this field by reason of its proven safety.

Improvements in both forms of vaccine will be made in the future, and the full control of poliomyelitis will rest, probably, on a combination of both vaccines. Once the adult population of any country is immune, the vaccination programme can be limited to the 0 - 3 year old age group. The concept of poliomyelitis eradication could become reality.

Much more work is still to be done before a choice is made between these two vaccine forms and the final programme adopted could be, as visualised by Dr. Francis, "......giving antibody in the form of pre-natal amniotic cocktail, a course of Salk vaccine, and live virus in candy for dessert".
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