In preventive medicine it is difficult to think of any opinion which is not based on groups rather than on individual patients. If there were such a thing as a universal malady then it might be argued that one person who escaped the disease after being given a supposed prophylactic had shown evidence of its effectiveness. In real life, however, this one person may have remained in good health as much because he was never at risk of illness, or being at risk was naturally immune, as because of the prophylactic. The freedom from illness of one individual cannot show that a prophylactic worked. Also, since no preventive measure is likely to be completely successful, the failure of prophylaxis in one individual does not prove that the measure was valueless.

The effectiveness of preventive measures in patients is assessed in answer to the question: 'Do patients given the prophylactic have less illness than those who do not get it?' There is no counterpart to the question we put in curative medicine: 'Does an individual patient get better when he is given a particular remedy?' Instead, a comparison is made between the experience of illness of a group with and a group without the prophylactic.

**ASSESSMENT BY TIME TRENDS**

The comparisons of this nature on which our judgement of prophylaxis rests have been made in several ways. Commonly a prophylactic is proposed and introduced and the incidence of illness subsequently is compared with the incidence beforehand. The freedom from scurvy among Captain Cook's ships in the voyages of 1772, in which he used antiscorbutics such as inspissated juice of wort, were in sharp contrast to the unhappy experience of earlier travellers, and Cook seems to have regarded
this as of great importance as his geographical discoveries. Although his conclusion that antiscorbutics were effective was almost certainly valid, many other before-and-after comparisons have had less justification. An excellent controlled trial of an oral vaccine against the common cold illustrates the dangers perfectly (Diehl et al., 1938). Volunteer students reported an average of 5.6 colds each in the year previous to the experiment and only 1.8 in the year following vaccination. This would suggest good protection were not almost identical figures, 5.5 in the previous year and 1.7 in the year of study, obtained for a control group who swallowed dummy capsules.

The interpretation of time trends as indicators of effective prophylaxis can be particularly hazardous for diseases whose mortality and morbidity have been declining already in response to a number of general factors, such as improved hygiene and sanitation and changing social and family conditions, as well as to improved treatment. Nearly all the infectious diseases of childhood have shown substantial falls in their mortality in the last 50 years, so that the existence of a further reduction in diphtheria mortality in Britain since 1941, when the large-scale immunisation campaign was started, cannot of itself be taken as evidence of effective prophylaxis. Three special features make this particular time trend significant. From 1942 onwards the rate of fall became much more rapid and has continued at this accelerated rate since then; this abrupt change in trend was not shared by other diseases, such as measles and whooping cough; the reduction affected both the notification and death rates, i.e., the lowered mortality was not largely a reduction in case fatality as in these other two diseases of childhood.

In such isolated cases, where there is good corroboratory evidence, time trends may indicate the value of a prophylactic measure. It is paradoxical that although the object of prophylaxis is the elimination of a hazard, the historical evidence of its disappearance can only rarely be taken to indicate the value of the measures employed.

ASSESSMENT BY GEOGRAPHICAL COMPARISONS

A second method of measuring prophylaxis has been the comparison between areas in which the prophylactic is employed
and those in which it is not. The low mortality from tuberculosis in some Scandinavian countries compared with the rest of Europe, for example, has been attributed to the widespread use of B.C.G. vaccine. Such geographical comparisons are, however, as unreliable as the study of time trends in judging effective protection, as it is always difficult to be certain that there are not other factors beside the use of the prophylactic which might account for the mortality differences between areas. The Scandinavian tuberculosis experience is difficult to attribute to B.C.G. vaccine since Holland has notably low mortality and morbidity from the disease without the general use of this vaccine.

Once again there are situations in which, if geographical comparisons are made carefully, and as part of a planned experiment, much of the objection to using them as methods of measuring prophylaxis disappears. The American studies of fluoridation of water supplies in attempts to reduce the incidence of dental caries are good examples. In one such study (Arnold et al., 1956) two cities in Michigan, Grand Rapids and Muskegon, were selected because they both had a low natural fluoride content in their water supplies, and had similar caries rates as measured by the average number of decayed, missing or filled permanent teeth per child.

In the first five years of the study sodium fluoride was added to the Grand Rapids water supply only. A subsequent fall in caries rate was observed in young children there, but no change in Muskegon children. Fluoride was then added to the Muskegon supplies as well. In the next few years caries rates for young children living in Muskegon began to fall; at the same time the decline already apparent in Grand Rapids continued, so that after 10 years' fluoridation it began to affect older children whose permanent dentition was established early in the study period. Such a carefully planned combination of time and geographical comparisons is good evidence of a prophylactic effect.

**ASSESSMENT BY COMPARING VOLUNTEERS WITH NON-VOLUNTEERS**

A third approach to estimating prophylaxis is to compare the experience of a group of people who have accepted the agent with the general population at large who have not, a comparison
between volunteers and non-volunteers. The literature on every prophylactic inoculation abounds with arguments of this kind. In a large statistical investigation of cholera vaccine it appeared that the attack rate in unprotected persons was over 10 times that in the vaccinated. A more rigorous assessment, however, reduced the contrast to just over twice the risk in the unprotected group (Chandra Sekar, 1947); and even then, although it was said that there was no known selection for inoculation, there was no way of determining why some were vaccinated when others were not. Greenwood and Yule (1915), discussing the statistical assessment of antityphoid and anticholera inoculations, rejected data from the Greek Army comparing the attack rates upon inoculated and uninoculated soldiers in the combatant units for the same reason.

The objection to such comparisons is that those who were inoculated may have been a selected group and may have differed in other relevant respects besides inoculation from those who received no injections. It is possible that an explanation of the fall in the average numbers of colds per year in the study of Diehl and his co-workers, quoted above, is that the volunteers who came forward were those with a particularly unfavourable experience in the previous year. Short-term immunity may therefore have contributed to the lower rates subsequently in students taking both vaccine and dummy capsules. In such a situation it would be unfair to compare the volunteers with students who did not take part, but it was entirely valid to compare the two groups of volunteers treated differently.

The argument that protected persons might be a selected group is not purely theoretical. In an ancillary study undertaken as part of the assessment of Salk vaccine against poliomyelitis in 1954 (Poliomyelitis Vaccine Evaluation Center, 1955) it was shown that the parents of children taking part in the investigation were on average a more prosperous group and had a longer period of high-school education; this might well be relevant in view of the demonstration in some American communities of an association between economic level and poliomyelitis morbidity. Similarly in a British trial of pertussis vaccine (Medical Research Council, 1951) it was found that the children whose mothers agreed to their participation were 88 per cent. immunised against diphtheria and 63 per cent. vaccinated against smallpox;
such levels, far higher than in the general child population of the same age in the same areas, probably indicated again that those who came forward were a selected group in which contact with infectious disease of all kinds might well differ from that among their fellows outside the trial.

In each method of comparison, by time trends before and after prophylaxis, by geographical comparisons between areas using and those not using prophylaxis, by comparison between those in a population given prophylaxis with their unprotected fellows, the results may not be a valid basis for assessing protection. Pearson (1904) laid down specifically the scientific principles for a proper assessment of any prophylactic procedure, and in subsequent correspondence hotly debated with Almroth Wright the claims made for the effectiveness of typhoid vaccine, but it is only in comparatively recent years that the controlled trial has been demonstrated practically as a fine tool for measuring prophylaxis.

Most of the prophylactic trials have concerned inoculation against infectious diseases so that many of the illustrations will be drawn from this field. There is no reason, however, why the method should not be more widely applied and provide, for example, the solution to current controversies over the value and place of tonsillectomy.

THE CONTROLLED PROPHYLACTIC TRIAL

The basic principles for a prophylactic trial are similar to those for therapeutic trials. Two groups are established, alike as far as possible, except that one is given the prophylactic and the other, the control, is not. These groups are then observed over the same period to see if the protected group has a lower incidence of the particular disease than the unprotected.

ETHICS

As in therapeutic trials ethical problems have to be resolved. Since the essence of a trial is the denial of a prophylactic to the control group, the first question is to decide whether a trial is justified at all. Unfortunately, so many prophylactics have been established on inadequate evidence that it is not hard to find justification for a field trial on even the most widely accepted of
preventive measures. Despite half a century of use, doubts concerning typhoid vaccine led to the recent trials in Yugoslavia (Cvjetanović, 1957) which showed that although a heat-killed, phenol-preserved vaccine gave substantial protection, an alcohol-killed and preserved vaccine gave very little.

In deciding whether a trial is justified all the possible indirect measures of a prophylactic's effect have to be considered, such as serological or biochemical changes which are known to be associated with susceptibility or immunity to the disease. Currently, the potency of diphtheria-immunising agents can be readily assessed by their ability to stimulate antitoxin formation, and a field trial of morbidity in immunised and control groups is no longer necessary. On the other hand, the relative failure of alcoholised typhoid vaccine in the Yugoslav trial suggests that indirect measures of potency, such as Vi-antigenicity, which this vaccine is designed to preserve, may not always be valid.

Leaving aside the question of whether the control group is to be given a placebo or not, there will always be some risk of untoward reactions to the prophylactic itself. The organisers of the trial must, therefore, ensure that these risks are minimised and that special attention is paid to their occurrence so that the trial can be stopped if necessary. It follows that the participants should be informed that they are being asked to take part in a trial, even if they agree to being kept in the dark regarding the actual treatment given. The opportunities for carrying out a trial without the necessity for taking the participants into one's confidence must be rare. Bell (1948) in the United States did succeed in running an excellent controlled trial of whooping-cough vaccine by giving alum precipitated combined pertussis vaccine and diphtheria toxoid to half of a group who thought they were being immunised against diphtheria alone. Whether such a procedure is ethical must remain a matter for personal judgement in each circumstance.

Ethical considerations influenced the form of the Medical Research Council's series of whooping-cough vaccine trials. In the initial series (Medical Research Council, 1951) groups given pertussis vaccines were compared with control groups given anticitarrhal vaccine, i.e., receiving no specific prophylactic against whooping cough. At this time there was real doubt about the efficacy of the vaccine and the published reports were
conflicting. These early trials showed convincingly the value of the vaccine, so that from then on it would not have been ethical to deny vaccine to a control group. Subsequent trials (Medical Research Council, 1956b) were planned, therefore, so that in each trial area the volunteers were randomly divided into two or more groups which received distinct whooping-cough vac-
cines whose performance could be compared one with another. Some continuity was maintained by using the same batch of vaccine for one group in each trial, one from the Michigan laboratory which had provided an outstandingly good vaccine in the earliest series of M.R.C. trials.

SIZE OF TRIAL

One of the big differences between prophylactic and thera-
peutic trials is the scale of the procedure. The proportion of the population likely to be attacked by a specific disease is usually small. Hence, unless the two groups in the trial are large there will not be sufficient cases in the unprotected to provide a stand-
dard against which the incidence in the protected group can be measured. In the American trial of gamma globulin in the short-
term prevention of poliomyelitis (Hammon et al., 1953), 55,000 volunteer children were required even though the areas specially chosen for the experiment were those suffering severe epidemics. In the placebo-control trials of Salk vaccine (Poliomyelitis Vac-
cine Evaluation Center, 1955) no such selection could be made and the treated and control groups each included 200,000 children observed for about eight months.

The approximate scale of a trial can be determined beforehand from estimates of the likely degree of protection afforded and of the incidence of the condition in unprotected persons. For a trial using equal numbers in protected and control groups, it can be calculated that 50 cases of the illness should occur in the controls to be reasonably confident of demonstrating significant benefit when the prophylactic on trial halves the risk. If the prophylactic is more effective less than 50 cases are needed among controls and vice versa. The size of the trial can then be any appropriate combination of numbers admitted and duration of observation likely to yield this number of cases in the un-
protected group.
The most important operation in a prophylactic trial is the allocation to the protected or control groups. Anything which allows conscious or unconscious selection of individuals to one or other group has to be avoided; it was on these grounds that comparisons between volunteers and non-volunteers have already been rejected. As in therapeutic trials the method of choice is random allocation. This can be achieved in several ways, and can be combined as required with stratification, e.g., into age and sex groups before allocation.

In the American trial of gamma globulin in poliomyelitis numbered boxes were prepared and arranged in random order, containing either the prophylactic or gelatin, which was indistinguishable on sight. This method had the advantage that no one without the key, which was held in New York, could have any idea how the groups were made up, but it required individually packed doses. This was avoided in one of the British series of whooping-cough trials where four series of bottles were made up labelled A, B, C, and D, two containing pertussis vaccine and two anticatarrhal vaccine for the controls. Lists were prepared for use in the clinics in which these letters were arranged in random order down the page. As each child attended for the first time his name was entered opposite one of these letters which indicated the bottle from which he would get his injections. Although which letters corresponded to whooping cough and which to anticatarrhal vaccine was kept secret, this method did allow comparisons to be made between the different lettered groups, and those close to the children were able to distinguish the severer degree of local reactions experienced by two of the groups. As it was still necessary to keep the allocation secret, the letters had to be covered over on the record cards until the follow-up was complete.

Sometimes it is unnecessary to keep the allocation blind and the procedure can be simpler. In the American Air Force studies in the prevention of rheumatic fever among patients with streptococcal infections (U.S. Armed Forces Medical Journal, 1951) the protected group were given penicillin intramuscularly while the controls were not, and there could be no mistaking which was which. It was sufficient, therefore, to allocate them according to the last digit of their Air Force serial number, even to penicillin
and odd to control groups. Similarly in the British B.C.G. vaccine trials (Medical Research Council, 1956a) the school leavers who volunteered were given a serial number on entry before any examination, clinical or radiological, had been made. After certain exclusions, those who were Mantoux negative were allocated to B.C.G. vaccine or control groups according to the last digit of this number. In another Medical Research Council whooping-cough vaccine trial, where the allocation could not be kept blind because of the different number of injections given to the two groups for comparison, the allocation was according to whether the child’s birthday fell on odd or even days of the month.

In Bell’s trial comparing mixed pertussis vaccine and diphtheria toxoid against diphtheria toxoid alone, the allocation was according to the month of birth of the child, odd months to one group, even months to the other. Subsequent checking showed, as would be expected, that this method had provided essentially similar groups. In the British assessment of poliomyelitis vaccine the allocation was also according to the month of birth but here the problem was more complex (Medical Research Council, 1957). Just under two million children had been registered for vaccine early in 1956 but supplies were sufficient for only about 200,000. The allocation was made by offering vaccine to all registered children born in November and to younger children born in March as well. The assessment was to be made by comparing the incidence of poliomyelitis in registered children born in the selected months with that in registered unvaccinated children born in other months. In the event, not all the eligible March and November born children presented themselves for vaccination and the question arose whether the defaulters were a selected group with a different liability to attack. As a first step in the analysis a check had to be made, therefore, that these defaulters suffered similar poliomyelitis incidence to the registered children who were never eligible at all. Only when this was assured was it possible to accept that the vaccinated children were not a biassed group of those eligible, and to compare the vaccinated group with the unvaccinated controls.

By such devices random allocation can usually be achieved. The method chosen often has to be carried out by workers in many centres and needs to be straightforward. To avoid the
additional complexity of randomisation, which however is seldom great, many workers have adopted simple alternation, first to prophylactic, second to control, third to prophylactic, etc. This system can give perfectly satisfactory results but its dangers need to be understood. In the first place it is an open method in which the operator knows what is coming next, and might withhold or accept a person in the trial depending on this knowledge. If the controls are getting indistinguishable treatment suitably coded this objection is no greater than in open randomised lists. A more cogent argument against simple alternation may be that the volunteers present themselves in some fashion which is selected by this method. For example, if a trial of some immunisation procedure is conducted during an epidemic, and the 1st, 3rd, 5th, etc. are given vaccine with the 2nd, 4th, 6th, etc. acting as controls, then the vaccinated persons as a group are exposed to risk earlier in the epidemic and therefore possibly subject to a different risk.

CHECKING THE SIMILARITY OF TREATED AND CONTROL GROUPS

When the groups have been allocated it is wise to check their similarity in respects other than the condition under study. This precaution was neglected in a study of the effect of early rising in preventing complications in the puerperium. Mothers were admitted alternately to two wards, in one of which early rising was practised and in the other a normal routine. The authors concluded that early rising led to no increase in complications and had certain advantages. They ignored the fact that in one ward there were 18 Caesarean sections and in the other only three in the same number of patients. This would suggest that the allocation had failed so that the groups were not alike at the start, and no proper comparison of complications could be made. By comparison the conclusion by Diehl and his colleagues (1938) that the common-cold vaccine was ineffective was strengthened by the demonstration that the vaccinated and control groups had had a similar experience of colds in the year before their experiment started. The reports of the Medical Research Council series of whooping-cough vaccine trials have routinely given evidence of the similarity of the groups under comparison, measured by a number of characteristics such as age, sex ratio,
number of children in the family, immunisation history and experience of infectious diseases other than whooping cough. When allocation can be shown to have produced groups which are essentially similar in such respects, greater confidence can be placed in the data directly concerned with measuring prophylaxis.

TREATMENT OF CONTROL GROUP

In some prophylactic trials both protected and unprotected groups have been given apparently similar treatment. The control group was given gelatin in the American gamma-globulin trial, the culture medium without any virus in the Salk vaccine trial, an anticitarrhal vaccine in the British whooping-cough vaccine trials. The advantage of such dummy treatments is twofold. It makes each volunteer feel equally part of the trial, whereas if some are given prophylactic and the rest nothing this might influence the degree of co-operation obtained from the two groups. The other gain, possibly of greater importance, is in the ability to keep the allocation blind when all receive apparently identical treatment. Where everyone is in the dark subjective measures can be used with confidence as there can be no bias introduced by patient or observer. If an observer had to diagnose a slight paroxysmal cough in a child known to have been vaccinated against whooping cough he might, because of a bias in favour of vaccine, decide it could not be pertussis. What is probably more likely than such ‘cheating’ is that the clinician would attempt to compensate for his known bias and label the case one of whooping cough against his better judgement. Either way, the knowledge of allocation might influence his opinion. If, on the other hand, the clinician is unaware of the allocation his diagnosis may sometimes be mistaken but will not, in the long run, favour either protected or unprotected groups.

Despite the advantages in giving a dummy prophylactic to the control group this ideal has often to be abandoned. In the first place there are prophylactics like B.C.G. vaccine whose local effects cannot be imitated. Where, on the other hand, there is so little reaction to the prophylactic that imitation is possible, there may be ethical objections to administering placebos to controls, and this group has to be left untreated. It would seem essential that whenever dummy injections are being given the participants
should be told that this is part of the plan before inviting them to volunteer.

FOLLOW-UP

Sometimes the period of observation after establishing the protected and unprotected groups is relatively short, as in the trial which showed a reduction in paralytic poliomyelitis two to eight weeks after giving gamma globulin, or it may extend for years, as in B.C.G. and pertussis-vaccine trials. Whatever the duration, it is vital that the same degree of observation is paid to both groups, and this is best achieved by regular visits or follow-up examinations. This was particularly important in the Medical Research Council's B.C.G. vaccine trial in school leavers where the control group among the negative reactors received no specific treatment. If subsequently a higher proportion of these had been lost sight of than of the vaccinated, it might have been difficult to say whether the defaulters were on average similar to the remaining controls who were observed; defaulting might have been the result of becoming infected or dying from tuberculosis, or on the other hand, because, being perfectly fit, there seemed no point in returning for examination. One of the strongest features of the B.C.G. vaccine trial was that by a combination of postal inquiries, visits by health visitors and re-examinations at mobile radiographic units 94 per cent. of the 56,000 participants had been brought into contact with the teams within the first 18 months, and this proportion was virtually the same in vaccinated and unvaccinated children.

OBSERVATIONS AND RECORDS

As in therapeutic trials observations have to be standardised and attention paid to the records. As far as possible objective measures of assessment should be used rather than subjective. Even if it is not a blind trial it is usually possible for bacteriological, radiological, and other laboratory examinations to be reported without knowledge of the individual's prophylactic status, and suitable measures to reduce observer error can be adopted where necessary.

To be certain that the illnesses observed in the protected and control groups are diagnosed accurately, laboratory confirmation will naturally be sought where possible. In some circumstances
such aids cannot be employed. The diagnosis of influenza, for example, can be confirmed in ordinary practice by observing a rise in antibody titre in the patient's convalescent serum. However, in a trial of influenza vaccine the vaccinated group will have higher initial titres than the controls as a result of their injections, if the antigen is potent; the same rise in titre observed subsequently in vaccinated and unvaccinated groups may not have equal significance for both.

Where the trial is a large one it will probably be useful to separate two series of records, those providing data on the characteristics of the population taking part, and those providing information on the illnesses occurring in this population. The former are likely to be numerous while the latter will be relatively few. In the planning of the trial the population characteristics which are important and obtainable, such as age and sex, are fixed so that the tabulation of the data on protected and control groups should flow naturally. Sometimes punched card methods will be necessary. If complicated cross-tabulations are not required it may, however, be easier to work through summary sheets prepared locally. This method was chosen in the British poliomyelitis vaccine assessment where tabulations on about 200,000 vaccinated and 1,700,000 unvaccinated children were assembled in three days by a staff of less than a dozen from specially prepared summary sheets sent by the 200 Local Health Authorities. Punching alone of individual cards for this total, without verification or sorting, would have taken far longer.

The records of illnesses affecting participants in the trial are clinical documents. As with therapeutic trials they must be drawn up beforehand, with agreed definitions, but should give scope for additional material. Each document needs to be checked for completeness and interpreted by a medical member of the team before it is passed on for analysis. It is at this stage that items like laboratory reports and radiological examinations are added. The number of records is often small enough to enable hand sorting to be done, and this method has the advantage of continuous scrutiny by the operator with further opportunity for checking and for learning the nature of the information recorded.

The analysis of the trial will usually take the form of a comparison of attack rates in the protected and control groups. If all the participants are observed for the same length of time, these
rates can be simply the proportion attacked in each group. If the volunteers come into the trial over a period of time and the trial stops at the same moment for everyone, then the period under observation will vary from individual to individual; in any case a number of volunteers are likely to drop out of the trial before its completion and will be seen for a short time only. In such circumstances the denominators for the calculation of incidence rates have to be person-months or person-years of observation obtained by summing the length in the trial of all the participants.

In the M.R.C. whooping-cough vaccine trials another measure proved invaluable. Whenever a child in the trial was known to be exposed to infection the source was noted and the outcome observed. It was found that the type of exposure could conveniently be divided into one of two kinds, close and continuous in the child's own family, usually from a brother or sister (*home exposure*), and casual and occasional outside the home, at school, in the street, while travelling, etc. (*other exposure*). Despite local variations in the incidence of whooping cough the proportion of control children who went sick after home exposures was high and constant at around 80 per cent. This high stable rate provided an invaluable yardstick against which to measure the protection afforded by vaccines. For example, the corresponding home-exposure attack rate among children receiving the best vaccines was only 10 per cent. (Medical Research Council, 1951).

A large-scale field trial of a prophylactic is a laborious and expensive undertaking. Such trials have been carried out particularly in infectious disease because immunisation procedures are highly developed and as a rule simple. Any prophylactic which required constant use in the diet would provide special problems of allocation and administration and would be even more difficult to assess by this method.

It is important to increase the efficiency of the method whenever possible. One direct way, rarely possible except in Service conditions and with mild or easily controlled illnesses, is to challenge both protected and unprotected groups. Hamilton Fairley's studies in Australia on the prophylactic effect of drugs like mepacrine in malaria are excellent examples (Fairley, 1945); after taking one or other of the drugs on trial the volunteers were exposed to infected mosquitoes. An early trial of influenza
vaccine (Henle et al., 1943) and recent American studies on adeno-virus (Huebner et al., 1955) and Asian influenza vaccines (Bell et al., 1957) followed the same general pattern. If the remaining steps are planned as carefully as in an ordinary prophylactic trial, such direct challenge, as in bioassay in animals, provides a highly efficient trial.

Such opportunities are rare. It therefore becomes vital that information from prophylactic trials is not wasted. One of the greatest contributions of the British series of pertussis-vaccine trials was the collaboration between laboratory and field studies (Medical Research Council, 1956b). Without the laboratory collaboration the field trials would merely have shown that certain vaccines, prepared some time before, had protected to a certain degree. They would not have guaranteed anything about the performance of later, untried vaccines, nor would they have given any hint how good or bad vaccines might be recognised in the future. However, by performing a series of different laboratory tests, serological and bioassay, on the same series of vaccines as were used in the field, it was possible to correlate the degree of protection in children with laboratory performance, and to recommend suitable standards of laboratory achievement for vaccines used in future (Armitage and Perry, 1957). The prophylactic trial is not an end in itself, but merely a stage in calibrating simpler methods of determining the potency of the prophylactic.

One further development probably needs study in future trials. It has been customary to give the prophylactic in one chosen dose only, and this has perhaps been encouraged by the difficulty of organizing a trial large enough to measure the effect of two or more different doses. Unless more than one dose is tried no direct information can be obtained on the dose-response curve. Since the fixing of a dose is necessarily arbitrary when a prophylactic is so little understood as to be on trial, the lack of information is a serious omission and may lead to unsuitable dosages being perpetuated.
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