Section of Epidemiology and Preventive Medicine

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Prevention of Influenza

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The Prevention of Influenza by Influenza Vaccine

The first human experiments entailing subcutaneous inoculation with a preparation of influenza virus took place thirty years ago. Francis & Magill (1936) then found that an inoculation of living influenza A virus produced an antibody response, particularly in those with low levels of pre-existing antibody. Andrewes & Smith (1937) elicited a similar antibody response using formolized, inactivated virus, and thus opened the way for immunization. The first successful field trial of inactivated influenza A vaccine, with a reduction in attack-rate among inoculated persons of at least 66%, was organized by the US Commission on Influenza in 1943 (Commission on Influenza 1944). Since then many field trials have taken place, some as successful as that of 1943, some entirely unsuccessful and most with a lesser degree of protection, ranging from 30 to 40% among those inoculated with vaccine. Yet from the standpoint of public health influenza vaccine has made a negligible contribution. Some authorities such as Langmuir *et al.* (1964) have even expressed deep scepticism of the value of influenza vaccine and point out that influenza outbreaks of varying degrees of severity continue unchecked in spite of vaccine. There are many reasons for this lack of achievement by immunization and I shall attempt to detail some of them, beginning first with the lessons derived from field trials of inactivated vaccine.

Success or Failure in Field Trials of Inactivated Influenza Vaccine

The varied experiences of field trials conducted either by the Medical Research Council Clinical Trials Committee, the US Commission on Influenza or independent workers have revealed certain factors which lead to success or failure of vaccine protection. In spite of the different basis of assessment of the results of trials of vaccination, which in Britain has been purely clinical and in the USA largely serological, there is agreement that under particular circumstances vaccine has given either no protection at all or very good protection from influenza.

Thus complete absence of protection has occurred when the strain of virus used to prepare the vaccine was antigenically distinct from that causing the outbreak. In 1947, vaccine made from virus A strains gave no protection against A1 influenza in various American trials (Francis *et al.* 1947, Sigel *et al.* 1948, Loosli *et al.* 1948). In 1957 a polyvalent A and A1 vaccine was deliberately used by the MRC Clinical Trials Committee in a trial comparing its effects with those of A2 and B viruses prepared as monovalent vaccines. The attack-rate of A2 influenza was identical in the groups given B or polyvalent A vaccines (Swine, PR8 and A1 virus strains) but was sharply reduced one week after inoculation in those receiving A2 vaccine (Medical Research Council 1958). Nevertheless it should be pointed out that minor differences in antigenic structure between vaccine and challenge strains have proved to be of little significance in trials conducted between the occurrence of major antigenic changes in the prevailing strains of virus. This is probably because a single dose of monovalent vaccine has a boosting effect on pre-existing antibodies present before inoculation (Medical Research Council 1957).

Secondly, outbreaks occurring among immunized persons shortly after the administration of inactivated vaccine have usually revealed better protection than those occurring several months or a year after inoculation. At the end of two years the effect has largely disappeared so that reinoculation is then required to restore protection. Presumably such waning of effect is related to the falling-away of antibody titres induced by the original antigenic stimulus, as occurs after natural infection. Thirdly, most trials in which the control

unimmunized population has been heavily attacked by influenza have shown a better order of protection in the immunized group than those in which the expected attack-rate was 5% or less during a three-month period. This has been explained on the basis of a dilution of the specific illnesses caused by influenza viruses by other febrile illnesses due to non-influenzal respiratory viruses. Against a relatively pure background of influenza, whenever this has occurred, vaccine has then appeared to do relatively well. Some of the vaccine trials sponsored by the MRC Committee have taken place during outbreaks with relatively low attack-rates, as in the years 1953, 1956, 1962 and 1963 (Medical Research Council 1953, 1957, 1964). An observed rate of reduction of illness in inoculated persons by only 40% during these years might be related to this dilution of illness due to influenza viruses. It is nevertheless true to say that such moderate outbreaks of influenza are more nearly representative of the average outbreak in the general population than those causing a 10 to 20% incidence during a three-month period.

Possible Methods of Improving Inactivated Vaccine

Inactivated influenza virus vaccine produces protection by promoting an increase in antibodies in the serum and also in the nasal mucous secretion. The antibody titre thus induced depends in turn on the antigenic mass of virus protein present in the vaccine. Multiple doses of vaccine produce little better response than a single injection because of a peculiar inhibitory effect of antibody formed after the first dose, though this does not happen when the antigen is one not previously experienced by the inoculated person (Holland *et al.* 1958). Watery influenza virus antigen concentrated to produce an enhanced antigenic stimulus is pyrogenic after subcutaneous inoculation, particularly in children. An automatic limit is therefore set to the amount of antigen which can be incorporated in a single dose and the strength of commercial vaccine is almost arbitrarily determined by the clinical acceptability of the product.

In order to deepen and prolong the antigenic stimulus, oil-adjuvants have been added to inactivated virus vaccines. In this form less antigen is required to produce a more powerful antibody response and there is no febrile reaction. Such oil-adjuvant vaccines were used by the MRC Committee in clinical trials held in 1955, 1956, 1960, 1961 and other trials as yet unreported. Delayed local reactions including some with nodules undergoing liquefaction and extrusion of oil residues occurred in from 2 to 5 per 1,000 persons in the earlier trials but in only 3·3 per 10,000 in 1961 and 1962. Commercial emulsified vaccines which were used in over a million persons in Britain from 1963 to 1965 are known to have caused such delayed reactions in 40 persons. Though only a quarter of these had reactions of a cystic character requiring incision, the vaccine was withdrawn by the manufacturers except for persons at special risk during outbreaks of influenza. Further progress depends on the elaboration of new methods or the use of adjuvants which will not give rise even to such a low order of local reactions. It is certainly a pity that a vaccine with such an excellent immunizing potential should be considered to be unacceptable. One difficulty in work of this character is the lack of a suitable animal test to detect materials which may cause delayed reactions.

A second method of avoiding the unpleasant effects of inactivated vaccine is by eliminating the pyrogen and thus permitting the use of increased quantities of virus antigen in a single dose. Davenport *et al.* (1964) have described an ether-split hæmagglutinin vaccine which gives excellent serological responses without fever even in children. If a method of concentration of this vaccine can be developed commercially, such a vaccine would have many advantages over ordinary inactivated saline vaccine. Trials of the hæmagglutinin vaccine are in progress in the USA and the work on the concentration of split vaccine by the method of zonal ultra-centrifugation is already under way here. Recently, Webster & Laver (1966) have described the use of deoxycholate to split hæmagglutinin from whole influenza virus and a vaccine prepared by this method is being made in Australia. Perhaps it should be pointed out that concentrated and purified vaccine will hardly be less expensive than the ordinary variety and unless methods which are not costly are found the product will not be welcomed by health authorities.

Live Attenuated Influenza Vaccine

Much work has now been done with living virus attenuated in the laboratory and administered intranasally in drops or inhaled as atomized droplets. Large scale trials in the USSR have been carried out in the past few years and good levels of protection (i.e. 50%) have been claimed (Zhdanov *et al.* 1958, Smorodintsev *et al.* 1961). The Russian vaccine strain is selected from candidate viruses by preliminary trials in volunteers to establish that the virus is infective intranasally but of a low order of virulence. Such attenuated virus is not available for children because febrile

illnesses have been recorded with vaccines harmless to adults. Spread of virus from infected vaccinated adults has taken place but only to a minor extent. In Britain small-scale trials have been made to establish a basis for the production of infection by attenuated virus strains (Andrews *et al.* 1966, Beare *et al.* 1966). It is difficult to compare the results of inactivated and of live attenuated vaccines with such little British experience of the latter. The most attractive potential of live influenza vaccine is that such vaccine can be administered rapidly to large numbers of persons, even during an outbreak, with the prospect of a speedy effect at first by interference with epidemic virus and later by antibody production. It appears, however, that a relatively large proportion of the population at risk, at least 50% according to Professor A A Smorodintsev (1966, personal communication), must be given the vaccine in order to check the progress of an outbreak.

The need to change living virus vaccine strains in order to conform with the change in serological make-up of epidemic virus is as great as in the case of inactivated vaccines. Because the selection of suitably attenuated virus strains is difficult at present without using volunteers, work is in progress through the MRC Committee on possible laboratory markers which could be correlated with virulence for man.

The Philosophy of Influenza Control

The efforts which have been made in Britain to bring about influenza control have either been non-existent or have been confined to small groups of the population such as those with specified chronic disease who are at special risk during an epidemic or workers in industrial undertakings who are privately vaccinated by the management. In a disease so variable in its clinical effect as influenza, the consequence of this limited use of vaccine is dubious, and no proper attempt has in fact been made to determine the end-result. In the USA on the other hand, the armed forces have maintained a system of regular inoculation with inactivated vaccine which has been judged worth while. The effect on influenza in the American civilian population of the use of vaccine on a considerable scale during 1961 and 1962 including the sale of some 40 million doses in the latter year has, however, been criticized by Langmuir *et al.* (1964). As judged by excess mortality no statistical benefit was observed though there was evidence that the vaccine was not adequately utilized for the age-group of the population likely to die from influenza. Moreover, though it is widely assumed that influenza vaccine will prevent death from influenza in those over 65, this fact has yet to be demonstrated. The particular moment of death in the aged is often difficult to relate to particular episodes of infection and the MRC Committee's second trial in old persons from 1963 onwards has not given conclusive results either in favour of or against the value of vaccine.

The use of vaccine in industrial workers in any part of the world is hard to evaluate in the absence of a properly controlled trial. The morbidity from influenza varies widely from one group to the next in any one outbreak. Other respiratory virus infections cause clinical diagnostic confusion and too much cannot be expected from an attack upon only one of the components of the huge total of respiratory illnesses. Small wonder that the results observed in Britain and the USA have been extremely variable. Only in the USSR has a serious attempt been made to prevent influenza outbreaks in the general population by large scale use of live vaccine in the period shortly before the commencement of the expected season. Such a large use of vaccine did not prevent the outbreaks in Moscow and Leningrad in 1965, perhaps because an inadequate proportion of the population was immunized.

The two basic methods of control of an infectious disease by artificial immunization are first the use of vaccine in children to build and reinforce an enduring immunity and secondly, the attempt to block the spread of infection by the method of epidemic control. Immunization of children with influenza vaccine has been awaiting the development of a suitable vaccine preparation which can be used without fear of adverse febrile or local reaction. Split hæmagglutinin is the first such preparation which affords any prospect of success. Because of the importance of infection by parainfluenza viruses and RS virus in childhood, it is hardly likely that the new preparation will be used in children by itself. Epidemic control of an infection which has such a capacity as influenza to spread can hardly come about by a slow method of immunization such as is offered by inactivated vaccine. Nor would mass immunization be likely to attract the requisite degree of public support unless the epidemic was extremely virulent. Under such circumstances either inactivated or live vaccine would probably be acceptable but there might then be inadequate supplies.

It seems clear therefore that the faults in the various attempts to obtain control over influenza lie as much with the character of the disease itself as with the vaccines. Only when a more long-

lasting antibody response can be obtained by a preparation which is devoid either of pyrogenic or of local irritative effects, will it be worth while attempting to immunize other than special groups of the population. Even then it may well be more rewarding to attempt to reduce the susceptibility of the childhood and teenage sector of the population, than to attempt to bolster up the waning immunity of adult workers. It is perhaps in the latter that a combination of chemoprophylaxis and periodic inoculation may ultimately offer the best hope of success. Even so, chemoprophylaxis would be limited to the period of actual occurrence of an outbreak in order to avoid useless administration and possible harmful effects of the drug.

For the present, the surveillance of influenza outbreaks on a world-wide scale, the isolation and serological analysis of viruses recovered from all over the world and the matching of influenza vaccine for small-scale use by substitution of new strains when this is desirable, must continue. Influenza is a treacherous disease with a great capacity to surprise and to shock. Influenza vaccine has not so much been tried and failed but has never really been tried at all. The time is not ripe to exploit vaccine merely to reduce absenteeism in industry when influenza virus infection is not the chief enemy. Should better vaccines become available, the way will then open for the development of a proper plan for immunization against influenza and probably against other respiratory virus infections as well.

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Prevention of Influenza by Vaccination

Although the natural history of influenza is complex it has two main elements which exert a special influence on its control by vaccination. The first of these is the advent – at long intervals – of a new virus variant, against which the world's population has no immunity, and the consequent occurrence of pandemics. The second are the subsequent epidemics which, following the pandemic, occur every few years.

Three groups in the population are potentially at risk in such biennial or triennial epidemics. The first is the group infected by the new strain during the pandemic but whose immunity has waned to a point where they have again become susceptible. The second group consists of those who have been infected during the pandemic and made resistant to this strain but who are later re-exposed to an influenza virus of a different antigenic pattern. The third group are those not infected and who are thus still susceptible.

On the whole it appears that the third group is likely to be the largest; the epidemics which occur in the years following a pandemic probably result from the presence of large numbers of persons who have previously remained uninfected. It seems reasonable to assume, therefore, that one way to prevent epidemics would be to vaccinate such persons with a potent influenza vaccine containing the appropriate strain.

As regards pandemics, it seems that these could be curtailed only if large quantities of vaccine could be prepared quickly from the new strain and used on a very large scale.

Vaccines

The efficacy of influenza vaccines is not easy to assess by clinical trial because the immunity of the participants can only be known before the trial by antibody estimations, because the exposure to influenza which the participants will experience is bound to be uncertain, and because the symptoms of influenza are readily confused with those due to other viruses. However, taking all the evidence into account it appears that a potent influenza vaccine containing the correct antigenic strain will confer substantial protection (Davenport 1962).