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Influenza Vaccines [and Discussion]

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VACCINATION

Influenza vaccines

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Inactivated influenza vaccines can now be made from purified haemagglutinin and neuraminidase. Although they have not been fully tested in the field they probably produce as good an immunity as whole virus vaccines and fewer reactions. They could be used against a new serotype in the face of a pandemic. Revaccination with killed vaccine may be effective, but one careful study in a school during the drifting of the H3N2 showed that it was not effective there overall. Live influenza vaccines have been made that were safe and effective and agreed methods are available for their evaluation. When the new generation of live vaccine strains are available, that have been more fully characterized genetically and functionally, they should be evaluated in substantial long-term field trials.

Previous reviews have summarized the fundamental scientific facts on which the present practice of influenza vaccination is based (Stuart-Harris & Schild 1976; Smith 1976; Beare 1975; Smith *et al.* 1976; Tyrrell & Smith 1979). The practice has been to grow influenza virus in embryonated eggs, harvest the allantoic fluids, purify and inactivate the virus particles and then give a standard amount of virus, based on haemagglutination titre, by intramuscular or subcutaneous injection. The newer scientific data reported at this symposium will no doubt have their effect on future methods of vaccination. One day we may use antigens prepared by 'genetic engineering'. However, before that day comes we have practical problems enough. We need to know how the new highly purified subunit vaccines behave, especially in subjects without previous experience of the antigen – as might occur in the case of a pandemic or in childhood. We need also to consider the relative merits of live and inactivated vaccines and how to develop policies for their use. The rest of this paper deals with selected topics in these subjects and reports recent studies, many of them undertaken under the aegis of the Trials Subcommittee of the Medical Research Council Committee on Influenza and other Respiratory Virus Vaccines.

The effectiveness of inactivated vaccines

Although it is quite easy to measure the antibody response to vaccine components, the crucial fact that we need to know is whether vaccines protect, and unfortunately we have relatively little information on the effectiveness of vaccines. This is largely due to the fact that field trials require large numbers of subjects, that they may fail because influenza epidemics do not occur when expected and that it is not easy to recognize influenza virus infections in the mixture of other acute respiratory diseases. It is not possible by clinical examination to recognize with certainty the difference between individual cases of diseases caused by influenza and other respiratory viruses so that the clinical effectiveness of a vaccine can only be assessed if laboratory tests for infection are done on each case or if by chance an intense epidemic occurs

in which most cases are due to influenza. Trials in military establishments and schools have been particularly useful in the past and probably give estimates of efficacy that apply in the general population.

Since attenuated influenza viruses have become available, these methods have been supplemented by deliberate intranasal challenge with such a virus; the results can be readily evaluated by clinical and laboratory examination of a relatively small number of subjects, and although it must be admitted that the virus and challenge method are not the same as in natural exposure, at least this is an experiment that measures resistance to an influenza virus infection. This can be important when trying to compare radically different types of vaccine, such as killed vaccine given parenterally and live vaccine given intranasally.

We have learned a great deal in recent years about the importance to immunity of various other antibodies besides the serum antihaemagglutinin (AH) antibody which has been measured in the past (see Potter & Oxford 1979). Undoubtedly antineuraminidase (AN) and secretory antibodies, either AH or AN, are important, whereas serum anti-M and anti-RNP antibodies are not. But this does not tell the whole story. The avidity of antibody is probably important as well as its amount and the antigen against which it is directed, but methods for measuring these have been little used. Cross-reacting antibody does not neutralize virus infectivity as well as specific antibody does, but techniques for separating antibodies of different avidity from human sera have not been applied to this problem. There are hints that cellular immune responses are also important: some of these may be more active locally than in the general circulation. Cytotoxic responses that occur only with histocompatible cells have recently been described (McMichael *et al.* 1977). Their effect on immunity is unknown. Even if we were sure that we knew all the components and could measure them, we do not know how to integrate the results to tell us the resistance of an individual to a virus. It was thought at one time that measuring secretory and circulating antibody would be sufficient, but this has not been borne out by experience. We can make a reasonable estimate from the serum AH antibody but to get much further in assessing the effect of administering a vaccine we need to have the results of the challenge experiments mentioned above. On the other hand, serum AH antibody measurements are very helpful when comparing the effect of vaccines of similar types, for instance those with and without adjuvants, and they can be readily carried out by haemagglutination inhibition (HI) or other tests on large numbers of subjects of various ages and in various situations.

To decide on the comparative value of different vaccines we need to know not only their relative effectiveness but also the relative frequency of undesirable or painful effects. Minor effects such as local soreness or redness, headache or respiratory tract irritation after a live vaccine can all be assessed on the small numbers, say 25–50 volunteers per group, that are required to assess the serological response to vaccine. However, much rarer responses may also have a profound effect on the acceptability or usefulness of a vaccine. It is thought that local pain and occasional fever and general malaise are part of the reason that vaccine acceptance rates decline steadily when vaccine is offered regularly to employees at work. Even trials with thousands of subjects do not exclude rare unpleasant side effects. For example, oil adjuvant vaccines were introduced in the U.K. after thorough clinical trials, yet in practice the vaccines were abandoned because they caused severe local reactions such as long-lasting brawny oedema of the arm or sterile abscesses. This was undetected in the trials, probably because the frequency was so low that cases did not occur until hundreds of thousands or more were injected,

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and also because injections performed by a research team are not the same as routine vaccination which is sometimes performed in less than ideal conditions in the hurly-burly of everyday life. For this reason, even after satisfactory clinical trials it is important to have a scheme whereby the use of vaccines, particularly newer modified products, can continue under surveillance or monitoring. A striking example of the value of this process is the detection of the occurrence of Guillain-Barré syndrome in a tiny proportion of Americans given the swine influenza vaccine (see Tyrrell & Smith 1979). Not only was this detected by the monitoring system but it was detected in time to stop vaccination, which was particularly important as the vaccine was being administered to guard against a threat of disease and not against an actual epidemic, so there was little benefit to set in the balance against even a tiny risk of illness and more rarely of death.

The current situation

Inactivated vaccine

I shall not dwell on the development and use of earlier vaccines (Davenport 1967), but mention that the technology of the research laboratory has been repeatedly applied to improve the quality of vaccines. For instance, a new epidemic virus is now hybridized with a laboratory adapted strain and in a few days a strain is produced that has the new surface haemagglutinin and neuraminidase and also the ability to grow to high titre in eggs, thus making vaccine available earlier and also more plentiful and cheaper. Vaccines have for several years been made from virus purified and concentrated by continuous-flow sucrose gradient centrifugation. Now, however, one or two manufacturers are supplying detergent-split vaccine which contains only haemagglutinin and neuraminidase subunits (Brady *et al.* 1976; Bachmayer 1975). These are clearly products that reach the ultimate in purification. However, they also produce problems. For instance, virus processed in this way does not behave like whole virus in the haemagglutination test which was previously used to standardize vaccines; however, it has been shown that the amount of antigen that can combine with a specific antiserum can be accurately estimated by means of a standardized single radial immunodiffusion (ID) test (Schild *et al.* 1975), and so one can check that the amount of antigen originally present in the virus particle is still present in the final product.

Earlier preparations of purified haemagglutinin were less active in evoking antibody responses than were intact virus particles. Thus it is not enough to show that a vaccine contains antigen that combines with antibody. It is also important to establish that these new preparations are potent immunogens and to develop control methods that will reliably distinguish between preparations that will be immunogenic and non-immunogenic for man. Preliminary evidence has shown that vaccines that contain no antigen by ID tests are non-immunogenic and that those that on electron microscopy contain well marked 'star' figures of reassociated subunits are likely to evoke antibodies (G. C. Schild, personal communication).

In view of the changed state of the antigen, a recent trial included groups given a wide range of different amounts of subunit vaccine. Some of the results are summarized in table 1, which shows that although a low dose of vaccine is non-antigenic the dose–response curve above the threshold is relatively flat. Table 2 shows that previous experience of the H1N1 serotype, which must have dated back 25 years or more, had a dramatic effect on the antibody response, which was higher, and evoked by a single small dose of antigen. From other sections of the study it was clear that two doses were needed to vaccinate unprimed subjects. These results are

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reminiscent of those found in earlier studies with swine influenza virus vaccines (Pandemic Working Group 1977). Figure 1 shows that the effect of priming could be seen in the response of all the older age groups. It was virtually the same whatever vaccine was used – three types of subunit vaccine or whole virus vaccine. It also turned out that the antibody titres evoked by killed H1N1 vaccine in young subjects declined rapidly, so that the proportion likely to be protected, those with HI titres not less than 40, was negligible 7 months after vaccination (table 3).

The local and general symptoms produced by vaccine were also recorded, and figure 2 shows that there was a dose-related increase in reactions to whole vaccine, that the reaction rates

TABLE 1. EFFECT OF AQUEOUS CTAB SUBUNIT H1N1 VACCINE ADMINISTERED SUBCUTANEOUSLY TO SCHOOLCHILDREN AGED 12–15 YEARS

		percentage with HI titres ⩾ 40			g.m.t.		
HA/μg	number of vaccinees	pre-vacc.	after 1st dose	after 2nd dose	pre-vacc.	after 1st dose	after 2nd dose
7	19	0	5	0	< 10	< 10	< 10
10	21	0	24	94	< 10	16	98
21	13	0	39	33	< 10	20	31
60	19	0	63	82	< 10	45	84

Adapted from Nicholson *et al.* (1979).

TABLE 2. EFFECT OF PREVIOUS EXPOSURE ON RESPONSE TO INACTIVATED VACCINE

(Response of subjects given 21 μg of aqueous CTAB subunit H1N1 vaccine.)

		percentage with HI titres ⩾ 40			g.m.t.		
age	number	pre-vacc.	after 1st dose	after 2nd dose	pre-vacc.	after 1st dose	after 2nd dose
12–15	13	0	39	33	< 10	20	31
⩾ 26	12	33	100	—	< 10	622	—

Adapted from Nicholson *et al.* (1979).

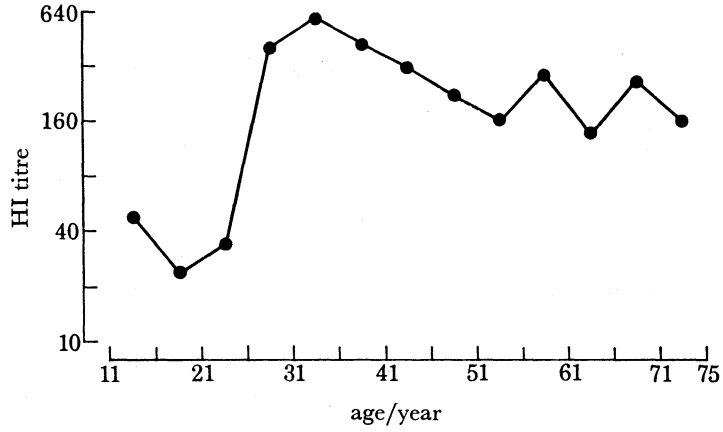

FIGURE 1. The 'priming' effect of previous antigenic experience: the antibody responses against H1N1 of volunteers given inactivated H1N1 vaccine. From Nicholson *et al.* (1979).

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were low with both aqueous subunit vaccines, but that there was some increase in local reactions in subjects given vaccine adsorbed to aluminium hydroxide. Local reactions were slightly more frequent in the younger subjects.

In view of the gaps in our knowledge of the exact means of immunity against influenza, we felt that it was important to demonstrate that subunit vaccines evoke not merely antibody responses but also immunity against infection, particularly in subjects that had no previous experience of the virus subtype. Therefore Professor Potter and his colleagues have undertaken on behalf of the Medical Research Council a trial in which student volunteers were given subunit vaccine and then challenged with a live attenuated influenza virus vaccine, administered as nasal drops. Some of the results are summarized in table 4 and show that subunit and whole vaccine induce resistance to infection by an intranasally administered live attenuated virus.

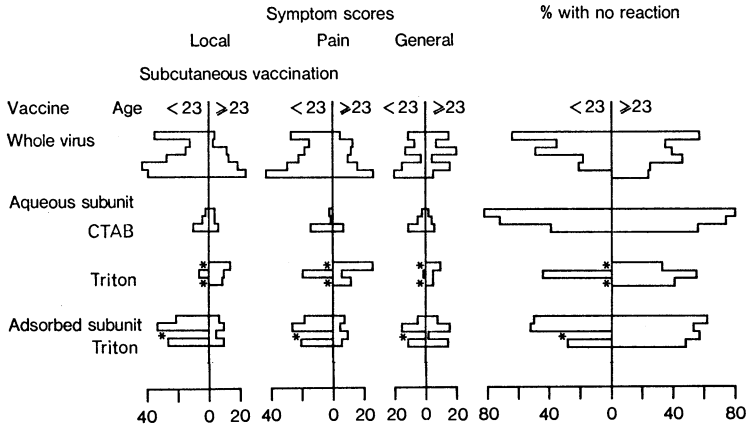

FIGURE 2. The frequency of reactions to vaccination with various H1N1 vaccines. The lengths of the bars indicate the frequencies of those with no reaction, or the mean symptom score, and the upper bars refer to those given lower doses of antigen and the lower bars given higher doses. The star shows where no data are available. CTAB and Triton refer to the detergent used in splitting the virus particle. From Nicholson *et al.* (1979).

TABLE 3. PERSISTENCE OF ANTIBODY AFTER WHOLE VIRUS H1N1 VACCINE TO SUBJECTS UNDER 23 YEARS

months after vaccine	cumulative percentage of 17 subjects with indicated HI titres				
	<10	≥10	≥40	≥160	g.m.t.
2	29	71	41	12	35
7	65	35	6	0	10

(G. C. Schild, personal communication)

TABLE 4. CHALLENGE OF UNPRIMED VACCINATED STUDENT VOLUNTEERS WITH *ts* ATTENUATED INFLUENZA A (H1N1)

vaccine	number tested	g.m.t. HI antibody before	g.m.t. HI antibody after	percentage infected on challenge
whole virus × 2	18	<10	29.8	11
aqueous subunit × 2	16	<10	17.9	13
absorbed subunit × 2	13	<10	16.1	8
live virus × 1	10	<10	72.5	10
none	33	<10	10	30

How often to vaccinate

The frequency of vaccination logically depends on the interplay of three factors, first the previous antigenic experience of the subject, secondly the duration and specificity of the antibody and immunity evoked by vaccines, and thirdly the frequency and extent of immune response against the 'drifted' antigens of subsequent epidemics, and the frequency and extent of this drift.

TABLE 5. VOLUNTEERS VACCINATED WITH 'OLD' VACCINES AND CHALLENGED WITH WRL105 ATTENUATED VIRUS INTRANASALLY

vaccine given	number of volunteers	percentage infected
A/Scot/74	27	4
A/PC/73	25	4
A/Eng/72	26	8
A/HK/68	25	29
B/HK/73	31	48

Adapted from Larson *et al.* (1978).

TABLE 6. RESULTS OF AN EPIDEMIC OF A/VICT IN SCHOOLBOYS AT CHRIST'S HOSPITAL, 1976

previous vaccination or infection	number vaccinated	attack rate (%)
infected A/Eng/72	62	2
infected A/PC/74	48	0
A/PC/74 vaccine	64	12
A/PC/74 vaccine + previous vaccine	134	22
no vaccine	67	21

Adapted from Hoskins *et al.* (1979).

We have already mentioned that the HI response to a 'new' antigen may be short-lived. It is important to consider the breadth of the anti-HA antibody response, particularly in experienced subjects, as 'drift' is occurring. Under these circumstances, antibody and immunity to infection has been observed in volunteers who were vaccinated with the original Hong Kong serotype of H3N2 virus or its successors and then challenged experimentally with a live strain which had undergone drift (table 5 (Potter *et al.* 1977)). As might be expected on general grounds, the experiment shows that better immunity was produced by using virus of the current serotype, as is the practice recommended by W.H.O. The size of the HI responses corresponded quite well to the immunity detected by challenge. Such results seem to support the use of killed vaccine in a 'drift' situation but also prompt one to ask whether it is necessary to change vaccine serotypes quite so often.

The cross-reactions detected by the HI test, however, deserve further consideration. First, the injection of a single antigen must induce the formation of an array of antibodies, varying in the exact antigenic configuration against which they are directed, and also in their affinity for these sites. These differences are in addition to the well known differences between the various classes of immunoglobulin, IgG, IgA and IgM for example. On general grounds I

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would suggest that an antibody with a high affinity for some part of a haemagglutinin will neutralize the virus that carries it and protect the individual who has such antibody. A full analysis is not possible at the moment, but it is possible to separate high and low affinity antibodies on an immunoabsorbent column or by elution from pelleted virus. The cross-reacting antibodies elute more readily and are less efficient in virus neutralization than specific antibodies.

In vaccinated subjects, it has been found that the presence of this cross-reacting antibody reduces the antibody response to a vaccine virus; that is, it can act as an immunosuppressant, even though in all probability it protects rather inefficiently. Thus the immune response tends to remain fixed – a subject who makes strain specific antibody against a virus makes more of the same when exposed to a 'drifted' strain.

With these thoughts in mind we can review the recent report of a study at Christ's Hospital School where children have been vaccinated annually before successive outbreaks of H3N2 viruses and the occurrence of influenza is carefully monitored by clinical and laboratory examination. The results show first that vaccination with homologous virus did prevent illness and infection in the initial outbreak, and that those that were not vaccinated and became infected were protected against reinfection by later viruses of the H3N2 group (table 6). However, repeatedly vaccinated subjects were not necessarily protected against later variants, and ultimately suffered from influenza. In fact, previous vaccination impaired the response to a current vaccine, as shown in rows 3 and 4. This was confirmed by examination of the records of two large groups of vaccinated children: the attack rate was 10% in those vaccinated once with current vaccine and 20% in those who had a previous dose as well as the current vaccine. The authors therefore doubt the value of a programme of regular vaccination against influenza A virus: they were able to show that over the total period of the study the incidence of influenza was not diminished, only deferred.

It has been stated before that regular vaccination is a desirable policy. These results may not apply to most of the population, but further studies are certainly needed to find out whether they do.

In summary, it seems that the subunit vaccines now available evoke antibody responses (and protection) in previously inexperienced subjects and could be used in the face of a pandemic as well as for routine vaccination. They are apparently well tolerated by young children and could be used to protect young children at special risk from influenza infections.

Live vaccine

The work on producing and selecting recombinant viruses for attenuated vaccines has been summarized by Murphy and colleagues, and their results will not be repeated here. It is therefore only necessary for me to discuss the ways in which such strains might be evaluated and used for vaccination. In recent years, methods of evaluating a potential virus as a vaccine strain have been to some extent standardized (Huygelen 1977). The process passes through several stages. First, the virus is administered in several doses to volunteers in isolation to show that it regularly produces an infection that evokes an antibody response but does not produce symptoms, at least nothing worse than a mild common cold in a minority of patients. It is also important to show that the virus is unlikely to be transmitted. This is likely to be true if the dose required to infect volunteers is large, while the amount shed in the secretions is small, and this can be established by determining the number of egg infectious doses required to infect

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volunteers and the amount of virus shed in their secretions. Direct experiments may also be done, and in these, inoculated and uninoculated volunteers live together (Beare *et al.* 1973), and one tests the uninoculated volunteers for virus infection; however, such experiments are difficult, the numbers used can only be small and so the results obtained are of limited value, particularly as the amount of virus shed varies from subject to subject and by chance the test group may not contain a subject who sheds a large amount of virus and can act as an efficient donor. At this stage it is also valuable to test if possible whether the virus shed is virulent. This may be done either by examining it for laboratory markers, if these are available, or by inoculation of further volunteers to see whether they develop influenzal symptoms. If these tests are satisfactory it is also desirable to perform some tests of respiratory function to show that there is no detectable effect on the lower respiratory tract of the infected subject (see, for example, Nicholson *et al.* 1977). Only at this stage are larger numbers of subjects tested for whether rarer unacceptable symptoms occur.

Much research has been done on a variety of strains, yet many investigators are unconvinced that live vaccination is practicable, and although one manufacturer produces live vaccine for use in the U.K., even in the U.S.S.R., where the work began, vaccine is not in general use although it has been shown to be effective there in the field by controlled trials (Slepushkin *et al.* 1967). Yet a number of important facts have been established. First, wild strains can be attenuated by passage, in the presence of horse serum or by the transfer of genetic material either from laboratory strains, such as PR8 or Okuda, or from 'master' strains with one or more *ts* lesions. The degree of attenuation can be such that no untoward symptoms are found at least by small or medium-sized studies. These viruses do infect, and induce antibody production, although the amount of circulating antibody is less than that induced by potent inactivated vaccines (Freestone *et al.* 1972). Nevertheless they induce resistance to infection with experimental challenge virus – in the U.S. studies, large doses of virulent viruses were used. So far, however, little work has been done to show that they prevent disease in epidemics. The largest controlled studies were done some years ago in the U.S.S.R. We detected some protection against disease more than 1 year after vaccination of an industrial group with virus attenuated by passage.

There have been worries that the virus may return to virulence, and this can happen when virus is transmitted artificially from one volunteer to another or shed for a long period; this must be the result of selection working on the inherent genetic instability of the virus. The same phenomenon is seen, for instance in live poliovirus, particularly with type 3 strains. Although it is obviously important to use as vaccines strains in which the reversion to virulence is minimized, the important question, which has not yet been answered, is whether given the reduced transmissibility of attenuated viruses there is any significant risk of a patient or his contact being made ill or injured by the vaccine, or that an epidemic might be started. In early studies H2N2 vaccine spread very little (McDonald *et al.* 1962) and the Fort Dix swine influenza viruses also failed to spread. Early Russian workers stated that it was necessary to use extra well attenuated viruses for vaccination of children and it now appears that this is because of the effect of anti-neuraminidase antibody, which partly protects against infection, so that a virus that will cause a mild or inapparent infection in a subject with AN antibody causes symptoms in an adult or child without it. This factor would probably also need to be taken into account in preparing vaccines for use in a pandemic situation in which the new virus might or might not carry a new serotype of neuraminidase. The Russian strain IKSHA was a satisfactory immunogen in

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the period immediately after 1957 when the H2N2 serotype first appeared (McDonald *et al.* 1962) but proved too attenuated later; as table 4 shows, a single dose of live attenuated vaccine can protect individuals with no previous experience of an H1N1 virus.

It has been suggested that we should vaccinate with neuraminidase using a recombinant with an irrelevant haemagglutinin, so that a wild virus infection will produce a mild illness rather than typical influenza (Kilbourne *et al.* 1970); this, however, has not yet been proved to be practical or acceptable, though if it could be shown to work it might give rise to the durable and broad immunity conferred by natural infections.

The evidence is strong that natural exposure to live virus confers a long-term immunity. This is shown by the trials at Christ's Hospital (table 6) and by the way in which H1N1 viruses have infected only those children that were born after the viruses disappeared from circulation in 1957. It may be that the immunity induced by live virus vaccines has some of the same qualities, namely broad specificity and durability, of natural infections and it would be desirable to investigate this.

Vaccination policy

The objective of current official vaccination policy is to prevent disease in particularly susceptible groups, such as those with chronic chest or heart disease (see Smith 1976). It is recommended that these subjects are revaccinated each year, though there is little formal proof that this protects them against disease or death. Vaccine may also be given to normal subjects at special risk, for example in hospitals or schools. Smith studied the effects of a programme of offering vaccine to employees of the Post Office (Smith 1974; Smith & Pollard 1979). This showed that, as expected, the offer was taken up by fewer and fewer employees as the years passed, and that the effect on the total number of days lost from work was small. However, there was some effect and it was calculated that allowing for the costs of administering the vaccine and the economic value of the days of absence saved, the programme as a whole was cost-effective. It would be valuable to know whether this would be true in other organizations and with other types of vaccination. It is important that the accounting is properly done – for example, the real costs of vaccination must include professional and administrative salaries and not just the cost of the vaccine and equipment for administering it.

This is not the time or place to go into all the factors that influence the uptake of vaccine when it is offered, but this is an important matter which could make all the difference between the success and failure of a vaccination campaign (Kavat 1976). The response of the individual depends partly on what he knows or believes to be the risk to him of suffering from influenza, and so will depend on general attitudes and how information about the disease is presented. Then it depends on what he thinks are the advantages of vaccination, and in this case he may well be influenced by his own experience or that of his friends, since influenza-like diseases due to other viruses are so common that it is often believed that vaccine is ineffective because the subject catches one of these just after a dose of effective vaccine. Furthermore, acceptance depends on the real or perceived disadvantages of vaccination, such as a sore arm, malaise, respiratory symptoms or even Guillain-Barré syndrome. It is worth remembering, however, that even if a fully effective, trouble-free vaccine were developed it would not be possible to prevent the disease in the population at large unless the public were persuaded to accept repeated vaccination.

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Discussion

B. A. Askonas (*Division of Immunology, National Institute for Medical Research, Mill Hill, London NW7 1AA, U.K.*). At this meeting we have heard much about the humoral antibody response to influenza infection or following vaccination and the fine specificity of the resulting circulating antibodies. However, there are other immune responses that have not been mentioned so far. I should like to draw attention to one particular type of cell mediated response which may have considerable importance in the body's defence against influenza, i.e. the killing of histocompatible virus infected cells by thymus-derived cytotoxic lymphoid cells (T_C cells) in the periphery (Doherty *et al.* 1976). Several groups have been defining the activity of cytotoxic T-cells in influenza infection of mice (Effros *et al.* 1977; Zweerink *et al.* 1977; Braciale *et al.* 1978). Intranasal infection of mice, and a second challenge with influenza virus *in vivo* or *in vitro* generates cytotoxic T-cells that kill influenza-infected target cells (either tumour cells or lymphoblasts can be used) provided these are histocompatible. The surprising findings were that a major proportion of the cytotoxic T-cells do not distinguish between the different subtypes of A influenza virus. This cross-reactivity occurs both at the level of secondary induction of T_C and of target cell killing, and contrasts the high specificity of circulating antibodies for each subtype of A virus. This is not a laboratory mouse artefact. McMichael & Askonas (1978) have been to define T_C in man. Since most people have been exposed to influenza infection and since T_C are cross-reactive for all type A influenza viruses, peripheral blood cells could be cultured with autologous cells infected with any type A influenza virus; after several days cytotoxic T-cells could be demonstrated (assayed with autologous WBC infected with type A virus and a panel of other people's WBC with known HLA specificities). The T-cells were specific for cells infected with type A influenza viruses and killing was HLA restricted, but the cells did not distinguish between the different subtypes of A virus. This poses important questions regarding the role of these cells in defence against infection, which virus protein is being recognized and the induction of cross-reactive T_C by different vaccination programmes. All of these aspects are being investigated and will undoubtedly influence future work on protection against influenza.

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E. D. Kilbourne (*Mount Sinai School of Medicine, New York, U.S.A.*). I know that time has not permitted Dr Tyrrell to dwell on all aspects of vaccination for influenza and therefore neuraminidase-specific vaccines have not been discussed. The choice may not be limited to live versus inactivated virus vaccines; rather the answer may be both Immunization with neuraminidase alone provides partial immunity that does not preclude subsequent infection with wild or vaccine viruses which provides the definitive immunizing step without exacting the price of disease. Others, including Dr Murphy and Dr Chanock, have shown that febrile

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reactions to insufficiently attenuated live virus vaccines in seronegative young children do not occur in the presence of pre-existing antineuraminidase antibody. Currently, we have studies in progress in six states of a neuraminidase-specific antigenically hybrid vaccine virus (Heq1N1 U.S.S.R.) in which the Heq1 haemagglutinin is an irrelevant 'carrier' of the contemporaneously relevant neuraminidase.

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