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Immunity in Influenza: The Bearing of Recent Research Work

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ABSTRACT.—The duration of immunity to influenza in man is difficult to assess from clinical data because of the difficulty of diagnosing the disease with certainty; two influenza-like attacks suffered by a patient within a short period may not have the same ætiology.

Serological relationships amongst strains of influenza virus are complicated. It seems probable that strains cannot be rigidly classified into types but that several antigens are present, distributed amongst strains in varying proportions.

The relationship of pandemic (1918–19) influenza to that of recent lesser epidemics is obscure. The supposed origin of swine-influenza in the U.S.A. in 1918 and the presence of antibodies to swine-influenza in the sera of most adult human beings have led to a suggestion that swine-influenza is a survival in the pig of 1918–'flu. The serological evidence for this view is now seen to be capable of other interpretations.

Factors concerned in the immunity of experimental animals to influenza are discussed—degrees of immunity in the ferret; immunity of the nasal passages to big doses of virus; immunity of the lungs; immunity to contact infection. Active immunity runs parallel with titre of neutralizing antibodies so long as one is dealing with one strain of virus. Cross-tests amongst different strains complicate the picture.

In planning vaccination of human beings we wonder:—

(1) Whether, on general epidemiological grounds, an attempt to vaccinate against influenza virus is likely to be profitable.

(2) Whether the production of a rise in antibodies in man will be a good guide to the immunity induced by a vaccine.

(3) Whether we are right in using killed virus and in fearing a live vaccine.

(4) What strains we ought to use in making a vaccine.

(5) When and how often we should vaccinate.

RÉSUMÉ.—La durée de l'immunité contre la grippe est difficile à estimer d'après les données cliniques à cause de la difficulté d'un diagnostic certain. Deux maladies ressemblant à la grippe chez un même malade à un court intervalle peuvent ne pas avoir la même étiologie.

Les relations sérologiques entre les souches du virus de la grippe sont compliquées. Il semble probable que les souches ne peuvent être classifiées rigidement en types, mais que plusieurs antigènes sont présents, distribués en proportions variées parmi les différentes souches.

La parenté de la grippe pandémique (1918–19) avec les épidémies récentes moins importantes est obscure. L'origine supposée de la grippe porcine en Amérique en 1918 et la présence d'anticorps contre la grippe porcine dans la plupart des sérums humains adultes ont mené à la suggestion que la grippe des porcs représente la survie chez le porc de la grippe de 1918. On comprend aujourd'hui que les évidences sérologiques supportant cette idée peuvent être interprétées autrement.

Les facteurs intéressés dans l'immunité des animaux expérimentaux à la grippe sont discutés : degrés d'immunité chez le furet, l'immunité des voies nasales envers de hautes doses de virus, l'immunité des poumons, et l'immunité à l'infection par le contact. L'immunité est parallèle au titre d'anticorps neutralisants tant qu'on s'occupe d'une seule souche de virus. Les épreuves de l'immunité croisé parmi les différentes souches rendent les résultats plus compliqués.

En considérant la vaccination humaine nous nous demandons :

(1) s'il est probable, d'après les principes épidémiologiques généraux, qu'un essai de vaccination contre le virus grippal soit utile ;

(2) si la production d'une augmentation du taux d'anticorps chez l'homme sera une bonne indication du degré d'immunité produit par un vaccin ;

(3) si nous avons raison d'employer un virus tué et de craindre un vaccin vivant ;

(4) quelles souches nous devons employer en préparant un vaccin ;

(5) quand et à quels intervalles il faut vacciner.

ZUSAMMENFASSUNG.—Die Dauer der Immunität bei der Influenza des Menschen ist auf Grund klinischer Daten deshalb schwer festzustellen, weil eine sichere Diagnosestellung nur schwer möglich ist : zwei influenza-ähnliche Erkrankungen, die ein Patient innerhalb eines kurzen Zeitraumes durchmacht, können eine verschiedene Aetiologie haben.

Die serologischen Beziehungen zwischen den verschiedenen Stämmen des Influenzavirus sind verwickelt. Wahrscheinlich können die Stämme nicht streng in verschiedene Typen eingeteilt werden, vielmehr scheinen mehrere Antigene vorhanden zu sein, die unter den verschiedenen Stämmen in verschiedenen Mengen verteilt sind.

Die Beziehungen zwischen der pandemischen Influenza 1918–19 und der kürzlich beobachteten weniger ausgedehnten Epidemien sind unklar. Der vermutungsweise angenommene Ursprung der Schweineinfluenza in den Vereinigten Staaten im Jahre 1918 und das Vorhandensein von Antikörpern gegen Schweineinfluenza im Serum der überwiegenden Mehrzahl von erwachsenen Menschen haben zu der Vermutung geführt, dass die Schweineinfluenza die im Schwein überlebende Form der Influenza des Jahres 1918 darstellt. Indessen weiss man jetzt, dass die serologischen Befunde auch in anderer Weise gedeutet werden können.

Es werden einige Faktoren besprochen, die bei der Immunität der experimentellen Tierinfluenza von Bedeutung sind : Immunitätsgrade beim Frettchen, Immunität der Nasengänge gegenüber grossen Virusdosen, Immunität der Lungen, Immunität gegen Kontaktinfektion. Die aktive Immunität geht mit dem Titer der neutralisierenden Antikörper parallel, solange es sich um denselben Virusstamm handelt. Kreuzweise Versuche mit verschiedenen Stämmen komplizieren das Bild.

Bei der geplanten Impfung des Menschen tauchen folgende Fragen auf :

(1) ob auf Grund allgemein-epidemiologischer Erwägungen der Versuch einer Impfung gegen Influenzavirus Aussicht auf Erfolg hat ;

(2) ob die Vermehrung der Antikörper beim Menschen einen guten Massstab zur Beurteilung der durch die Vaccine hervorgerufenen Immunität darstellt ;

(3) ob es richtig ist abgetötetes Virus zu verwenden und einen aus lebendem Virus bestehenden Impfstoff für gefährlich zu erachten ;

(4) welche Stämme zur Herstellung der Vaccine verwendet werden sollen ;

(5) wann und wie oft geimpft werden soll.

WE are all interested in influenza from one point of view or another ; it may therefore be of some value if I recount something of what is known of immunity to influenza in experimental ferrets and mice, and consider how far this knowledge is applicable in our attempts to understand the natural history of influenza in man and to guard against human infection.

On previous occasions summaries have been presented of the evidence for considering epidemic influenza as a disease due to a virus or closely related group of viruses (Andrewes, 1937). I do not propose to consider that evidence now, but to assume that influenza is a virus disease and to start out from that point. There is, however, a matter which cannot be so lightly dismissed : exactly what disease are we talking about ? Few would, I think, dispute that the name " influenza " covers

a variety of conditions, and unfortunately no one clinical criterion is yet available to help us to differentiate certainly between the virus disease and others resembling it. We have attempted the formidable task of trying to relate recovery of virus with a particular clinical picture. With this end in view my colleague, Dr. Stuart-Harris, with Drs. Chalmers and Cowen, has studied epidemics diagnosed as influenza occurring at schools or in the Services, and has sent garglings from patients to Hampstead to be tested in ferrets and mice by Dr. Wilson Smith and myself (Stuart-Harris, Andrewes, and Smith, 1938). The correlation of clinical and laboratory findings has shown that in years in which there is no major epidemic the minor outbreaks labelled influenza usually fail to yield a ferret-pathogenic virus. On the other hand, at epidemic times, as in early 1933 and 1937, it has been easy to recover virus from the large majority of garglings tested. We have provisionally considered the latter group as epidemic influenza and labelled the others " febrile catarrhs ", a name intended to be merely descriptive and not to imply a uniform ætiology. In other words, from the scrap-heap " influenza " we have removed an entity, identified it as " epidemic influenza " and then renamed the residue of the scrap-heap " febrile catarrhs ". While it is not yet easy to decide on clinical grounds to what group an isolated patient belongs, yet there are broad differences between the groups of patients in the virus-positive and virus-negative outbreaks so far studied. For instance, in epidemic influenza the onset is commonly abrupt ; in febrile catarrhs there are often premonitory catarrhal symptoms for some days before the patient has fever and has to go to bed. In epidemic influenza, in contrast to the other group, constitutional symptoms such as headache, malaise, and aching, predominate over catarrhal manifestations such as sore throat, coryza, and cough, particularly in the early stages. But of single cases it cannot yet be certainly stated on clinical grounds that this patient has or has not got epidemic influenza. During the 1936–37 epidemic two features, believed to be characteristic of "real 'flu" were absent from many patients from whom virus was actually recovered ; there was no regular tendency to protracted convalescence and so-called post-influenzal depression ; there was usually no leucopenia, most blood-counts taken in the acute stage being within normal limits.

I have gone into this matter at some length because I wish to emphasize that in endeavouring to find out how long the immunity of human beings to influenza lasts, one cannot place reliance on clinical reports that a given person had two attacks of influenza within, let us say, two months, or even on statements that a given institution passed through two outbreaks within a fairly short period. One may even be led astray by the occurrence of widespread outbreaks of something which looks like 'flu, yet isn't 'flu. Francis (1937) has described an epidemic diagnosed as influenza occurring in California in February and March 1936. Clinically and epidemiologically it resembled epidemic influenza much more closely than it did the febrile catarrhs just described ; in three towns there was an incidence of 30–40%. Yet he wholly failed either to recover influenza virus from the cases or to detect any rise of antibodies against influenza virus during convalescence. Another virus altogether, designated as the virus of acute meningo-pneumonitis, was recovered from ferrets inoculated with garglings from these cases. I say advisedly " recovered from the ferrets inoculated with the garglings " because Francis and Magill (1938) are themselves uncertain whether the virus undoubtedly came from the human material. It is at any rate possible that there is another virus which causes epidemics of an influenza-like disease in man, apart from the virus we have been studying.

It is also possible that different epidemics may be caused by serologically distinct races of influenza virus. It was thought at first that all human 'flu viruses were serologically identical, but as with foot-and-mouth disease virus, horse encephalomyelitis, poliomyelitis, and many other viruses, it now appears that serological varieties exist. If the ferret were still the only experimental animal known to be susceptible to influenza virus these differences would probably be still unrecognized.

Ferrets immune to one strain of influenza are immune, as a rule, to another, though immunity to homologous virus probably persists longer. Sera of a ferret recovered from any strain usually neutralize filtrates of any other strain. Quantitative differences in neutralizing power would be hard to demonstrate, for the ferret is too expensive an animal to use readily for elaborate quantitative titrations of sera. Mice, however, can be so used, and when sera began to be titrated quantitatively in mice, it became apparent that all human 'flu viruses were not serologically alike. Magill and Francis (1936) first demonstrated that this was so, using two strains of American origin, the PR8 and Philadelphia strains. In the last three years they have continued to worry at this problem ; so has Burnet in Australia, and so have we at Hampstead. The various laboratories have used rather different techniques, and the results obtained have not always been wholly concordant. Burnet (1937 *a*), for instance, has been growing viruses on the chorio-allantoic membranes of chick eggs and mainly studying the neutralizing power of sera in that way. Francis and Magill and ourselves have used neutralization tests in mice, but while the American workers have used immune rabbit sera and failed to obtain good results with immune ferret sera, our experience has been just the opposite. We recently agreed with them to publish our results simultaneously, and these have lately appeared in the *British Journal of Experimental Pathology* (Magill and Francis, 1938 ; Smith and Andrewes, 1938). In spite of differences in detail certain broad truths seem to emerge from the work of all the investigators.

First, there are undoubtedly serological differences amongst different human influenza viruses. Secondly, the viruses cannot readily be divided into types like pneumococci ; the various strains show more complicated overlapping relationships. We have tried to disentangle the confusion by selecting four strains which were much more specific and overlapped very little, and testing all other strains against these. We thus obtained evidence suggesting that four major antigens were represented in the different viruses, occurring in very different proportions. A few strains, our specific strains, were made up almost all of one antigen, with very little of the rest ; others (" master-strains ") contained all four in fairly equal proportions ; others (" intermediate strains ") were neither very specific nor very polyvalent.

Burnet (1937) attempted to divide the viruses serologically into Old World and New World strains ; this classification was all right for the strains then available to him, but most of those which have turned up recently in Europe have been more of the New World than of the Old World type. None of the strains yet isolated from America has, however, proved to be as highly specific as any of our specific types. Magill and Francis (1938) have, however, described minor differences amongst them, such as will allow hardly any two to be considered as identical. They are inclined to think that the viruses recovered from the 1936–37 epidemics in Europe and America are more closely related to each other than to strains obtained in previous years. We are disinclined to admit that much as regards English viruses ; the most widely differing strains appeared near London early in 1937, a most interesting point epidemiologically.

These serological races of influenza clearly have importance from two points of view. First, one wants to know about them in planning any experiments on active immunization against the natural disease. Our attempts to reduce the apparent chaos of different strains to order were directed largely to that end. Secondly, it will be of interest in the future, particularly in epidemics more limited than that of 1936–37, to see how far one serological race of virus is responsible for a given outbreak, to learn the epidemiological importance both of the major differences in strains which we have studied, and also of the more subtle distinctions amongst influenza viruses which Magill and Francis have been concerned with.

In particular we wonder what relation the virus of the 1918 influenza bears to the virus recovered from recent outbreaks. There is a natural tendency to think that

the disease was essentially the same as that caused by the virus we are discussing. Clinically they were alike except that severe pulmonary complications were far commoner in 1918.

Francis (1938) quotes American data which indicate that the first wave of the epidemic of 1918 afforded some protection against the second wave but not against the third, and neither of them against the 1920 epidemic. He thinks it possible that the third wave and the 1920 epidemic were due to an agent quite different from that of the first two 1918 waves; possibly one of the agents concerned was more closely related to that of the disease he studied in California in 1936.

It has been suggested in several quarters that swine influenza represents a survival in the pig of the 1918 type of epidemic 'flu. Apparently swine 'flu first appeared in the Middle West of America in August 1918 and has recurred annually ever since. Pigs are susceptible experimentally to human influenza, and Shope (1938) has obtained serological evidence that they may become spontaneously infected under field conditions; pigs fed on garbage at two institutions where influenza was prevalent were found a little later to have in their sera antibodies to the human but not the porcine strain of virus. It has been found that most adult human sera in England, America, and Australia, contain antibodies against swine influenza virus, while those of children born since about 1925 do not; the suggestion is obvious that the virus which stimulated their formation may have ceased to be prevalent since that year. However, this serological evidence has since been shown to be capable of other interpretations. Repeated inoculation of an animal with one strain of human virus broadens the zone of reactivity of its serum so that serum which at first is active particularly against the homologous virus, comes to react with other human viruses and even with the less closely related swine virus. A remarkable opportunity occurred for showing that the same was true of man. Search of the records revealed that St. Helena was the only place which certainly escaped the 1918 pandemic. Dr. Wilkinson, the Medical Officer, kindly sent us in 1935 sera from some of the inhabitants and these, to our great interest, mostly failed to neutralize swine 'flu virus as well as English sera did; for that matter they had but little antibody to human 'flu either. In the following year an outbreak of influenza occurred in St. Helena, and subsequent bleedings showed that most of the persons bled had sera with antibodies effective against both human *and* swine viruses. While we did not recover virus from this epidemic it seems likely that it was one of human influenza, and if so it appears that the porcine type of antibody can appear in man, as in experimental animals, as a result of infection with another type of virus (Stuart-Harris *et al.*, 1938). Burnet and Lush (1938) have adduced other serological evidence to favour this view. What we may call the "1918 'flu = swine 'flu" theory is thus deprived of any support from the serological studies of human sera. It is, however, not thereby disproved, only rendered more highly speculative.

In any event it seems a reasonable supposition, from what we know of biological instability of viruses in general and influenza virus in particular, that the 1918 'flu was due to a mutant or mutants of influenza virus. Such mutation may very well have affected first its antigenic structure—a change showing itself in the succession of waves of the disease—and secondly its affinity for the lungs. Two strains of the WS virus have been evolved in the laboratory, one capable of producing in ferrets a pneumonia which is often fatal, the other causing lesions only in the upper respiratory tract. A variant which especially attacked the lungs of man might associate itself with particular readiness with one or other of the pathogenic bacteria which caused such havoc in the epidemic twenty years ago.

I will now turn to some observations which concern closely attempts at active immunization of human beings.

In experimental animals immunity to influenza lasts for some months. It is a rough-and-ready rule that the smaller the animal the shorter tends to be the immunity,

so that we might expect on this basis that immunity to influenza in man would last for at least a year, perhaps more. There are, in ferrets, grades of immunity. For the first three months after infection there is what we may call Grade A immunity—proof against massive doses of virus given up the nose ; in Grade B, from three months onwards, the ferret is immune to the milder test of infection by contact, and, moreover, though he may take a nasal infection his lungs are still protected, so that even a highly lung-adapted strain of virus will not give him pneumonia. After a year or more he may sink to Grade C with no demonstrable immunity at all.

Influenza virus will only infect ferrets with certainty when given up the nose ; by subcutaneous and other routes the virus will commonly not infect. One can thus vaccinate with living virus given subcutaneously. Normal ferrets so vaccinated can be given a Grade B but only exceptionally a Grade A immunity ; that is, they can be protected against contact infection and against lung lesions, but not against massive intranasal doses of virus. Also, if one takes a ferret whose immunity after infection has waned from the A to the B level, subcutaneous vaccination will readily push it up to the A level again. Unfortunately we have failed, having given normal ferrets a Grade B immunity by vaccination, to push it up by further vaccination to the stage of complete resistance to the virus. Nevertheless, the ferret experiments are encouraging from several points of view to the would-be vaccinator of human beings.

(i) Man is not likely to be asked to withstand massive doses of virus up the nose. A Grade B immunity, effective against contact infection, may be good enough.

(ii) Even if we fail to protect wholly against infection, we may give so much immunity that, if another 1918-type of influenza occurs, we can protect the lungs by vaccination and so save many lives.

(iii) Most adult human beings have had influenza at one time or another and thus, like recovered ferrets, have some basic immunity. Vaccination may avail to push up this immunity from the B to the A level.

Before discussing further the possibilities of prophylactic vaccination in men I must make it clear that we are open to conviction as to whether active immunization is the right way to tackle the control of influenza. Are we convinced that a fall in the immunity level of the community is such an important factor in the causation of epidemics that an increase in that immunity level, supposing we can produce it, will prevent or modify an epidemic ? We have, of course, no grounds for such conviction. Nevertheless, the possibility of effective vaccination opens up an obvious and hopeful line of attack.

Epidemics come so infrequently, and strike so irregularly, that it is a most difficult task to test the value of human vaccination ; we have to vaccinate a community and then wait and see whether within a few months an epidemic strikes that community —a most exasperating and disappointing method of research. In hopes of getting some sort of guide as to the effect of vaccines in man, we have tested the rise in antibodies produced in them by vaccination. Thirty soldiers thus tested developed a most encouraging rise in antibody titre, averaging twenty-five-fold. We used formolized filtrates of infected mouse lungs and found that one dose of 2 c.c. produced as good a rise as did two doses spaced a fortnight apart. We tested the sera by examining their neutralizing activity for the same strain of virus (WS) as was used for the vaccination ; the increase against a serologically distinct strain was less, averaging only five-fold. Does this rise in antibodies mean increased active immunity ? Hoyle and Fairbrother (1937) have suggested that the titre of complement fixing antibodies may be a guide to susceptibility. The level of antibodies to the WS virus in the sera of man is, however, certainly not proven to be a guide to his susceptibility to attack during an epidemic. Smorodintseff *et al.* (1937) have reported that the success of an attempt at experimental infection of human volunteers with a passage strain of virus was closely related to the presence or absence in the sera of the volunteers of antibodies active against the same strain.

Here once more ferret experiments yield interesting information. In ferrets infected with the WS strain of virus there is good correlation between active immunity and the content of neutralizing antibodies in the serum. We have compared all sera with a standard immune horse-serum ; ferret sera five times as good as that standard usually accompany complete (Grade A) active immunity ; ferret sera better than one twenty-fifth of the standard usually imply at least a Grade B immunity. So far, so good ; but when we stop dealing with our WS strain and study swine influenza and other human influenza viruses it is a different story. Ferrets may be infected with swine influenza and with some of the serologically distinct strains of human influenza viruses ; on recovery they are usually immune to the WS strain although they may have few or no antibodies against it. Shope (1937) has found the same thing to be true of pigs recovered from swine influenza, and we have seen it also in mice. We therefore use antibody titrations as a guide in our human tests only because we have nothing else available.

The vaccines we have so far used on human beings have been treated with 1 : 5,000 formaldehyde, a procedure which can be relied upon to inactivate the virus. Such formolized vaccines will immunize ferrets and mice. We have thus played for safety in preferring to use a killed vaccine, although we know that killed vaccine is less effective than living, and that American workers have used living virus without ill-effects to vaccinate some hundreds of people. It must be remembered that virus used for vaccination will be introduced by the relatively safe subcutaneous route, and will also have been modified by animal passage ; much experience shows that repeated passage of influenza virus in the mouse renders it less virulent for the ferret and vice versa. Burnet (1937 *b*) has described a strain propagated on hen's eggs which readily kills the embryos of the inoculated eggs but is of very low pathogenicity for the ferret and mouse. He has inoculated this strain intranasally into man without producing disease ; no epidemic has yet occurred to prove whether persons so treated develop active immunity. In theory, this method of giving attenuated live virus intranasally might be expected to give a better immunity than would virus, alive or dead, introduced parenterally, for the virus in the respiratory tract would presumably multiply. It should therefore be possible to immunize more rapidly and with tiny doses of vaccine. But any reliance on the modification or attenuation of influenza virus by animal passage must at present be insecure ; a change taking place in one direction may, under appropriate conditions, be reversed. On the whole, since killed virus has been shown experimentally to produce immunity in animals, it seems worth giving it a trial in man before embarking on the more hazardous venture of using living viruses. At the same time it will be well to gain knowledge of how an attenuated virus might be employed, particularly to give rapid immunity in face of a dangerous killing epidemic.

The next in a succession of conundrums concerning vaccination are these : What source of virus should be used, and what strains of virus can best be included in a vaccine. The evidence available suggests that more virus can be obtained from mouse lungs than from ferret tissues or chicken tissue-cultures, though the last source would be far more convenient for large-scale manufacture of vaccine. So far, however, no evidence is to hand that inactivated tissue-culture vaccine is of any value for immunization. On theory, a polyvalent master-strain containing all the important antigens would be the one to choose for immunizing. Unfortunately our master-strains are all of low titre. In fact no strain except perhaps PR8 approaches the highly specific WS strain in titre, and so far as we can tell, this higher titre really reflects a greater quantity of virus in the lung emulsions of the mice infected with this strain. In a test now in progress we are using a vaccine made of a mixture of the high-titre monovalent WS and the rather lower-titre but relatively polyvalent PR8 ; this seems the best compromise to adopt for the time being.

Finally, when should one vaccinate ? Obviously a month or two before the next

epidemic is the time to choose. Since 1929 widespread epidemics in Britain have come at four-year intervals, but we hardly dare to hope that this regularity will be permanent, especially as other European countries have not experienced the same periodicity. At any rate, recent outbreaks have mostly begun in December or January ; so October and November are probably good months in which to vaccinate. One dose of vaccine brings up the antibody titre against the homologous virus very well, but it may prove that repeated doses are necessary to produce in man a broad immunological response with antibodies active against several strains.

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