PROPHYLAXIS OF VIRUS INFECTIONS, WITH SPECIAL REFERENCE TO THE USE OF VACCINES*

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When discussing the prevention of virus diseases we should consider both non-specific hygienic measures and specific prophylactic vaccination. I will not deal with the hygienic aspects, which for some viruses may be more important than inoculation. It may, however, be noted in passing that with regard to some of the more important viruses we are still ignorant of the relative importance of various modes of transmission and therefore do not know upon what hygienic measures to rely. There is still dispute about how the poliomyelitis virus most commonly spreads—by manual or fly-borne contamination or by inhalation. Even in the case of the big group of air-borne upper respiratory infections we know less than we thought we knew some years ago. Are the minute droplet nuclei most important? Or the coarser particles which fall quickly and dry up, and which are then re-dispersed as dust? Or the infected particles spread by the shaking of handkerchiefs and the shaking of hands? I must leave this matter now, except to plead for more fundamental work on modes of transmission as a necessary first step to putting effective hygiene into operation.

Immunity in Virus Diseases

In 1931 I gave a lecture on immunity in virus diseases (Andrewes, 1931). The matter has been discussed many times before and since then, but there seem to be no new principles to bring to your notice. With the old principles you are doubtless familiar enough. Many viruses are conveniently adaptable; patient search and chance have placed in our hands modified viruses attenuated enough to be capable of being used with safety in the living state yet sufficiently unchanged antigenically to give potent and sometimes enduring immunity. Yellow-fever vaccine, which is in this class, sets us a standard to which we would like all vaccines to attain—a single dose which causes no inconvenience, or at most a slight headache, and an immunity so long that we may almost say, "It may be for years, it may be for ever." The modified yellow-fever virus, 17D, now used for making such vaccines, turned up somewhat fortuitously; deliberate attempts to produce another, equally useful, variant virus failed. Lately, so many viruses have been grown and attenuated by growth in fertile eggs that we may hope for more conveniently modified variants to be discovered.

Some viruses can be inactivated, apparently irreversibly, by formaldehyde or other means and still immunize. Large doses must be given in order that enough antigen may be introduced, and these large doses may cause local reactions; a limit may thus be imposed on what can be conveniently

given. Immunity after the giving of killed vaccines is much less durable than after the best of the live attenuated vaccines; raised immunity for a year is the sort of result to expect. Formaldehyde is the most generally used inactivating agent, but others, particularly ultra-violet irradiation, are proving to have advantages in some instances. For reasons obscure to us, inactivated vaccines immunize fairly well against some virus diseases—for example, influenza—and very poorly against others—for example, smallpox.

I now turn to discuss two general aspects of virus-prophylaxis: the importance of serological strains of viruses, and the possible application in practice of the so-called interference phenomenon. Influenza affords the best illustration in both instances.

Serological Races of Viruses

We are increasingly forced to realize that many viruses, like many bacteria, have serological races differing enough to affect the results of attempted vaccination. This is true of influenza and poliomyelitis among human diseases. The variations among the influenza and poliomyelitis viruses are far from being understood. Fortunately, variola, yellow-fever, measles, mumps, and some other virus infections are, so far as we know, not apt to vary in antigenic make-up in such a troublesome way. There are two distinct influenza viruses, A and B, believed to be antigenically unrelated to each other: A seems to be the more important. It is within these two groups that minor variations occur to vex us. There are certain classical strains of influenza A studied in laboratories all over the world—the original WS, the PR8, and the Melbourne strains. Whenever in a fresh outbreak new A strains are isolated they are found to differ in serological and cross-immunity tests from these classical strains, and usually, so far as has been tested, from strains recovered from other epidemics. There are always significant cross-reactions, and any two strains may be fairly close together or rather wide apart. Unfortunately there has been no detailed comparison of strains collected from outbreaks in different years in any one country or from different countries in the same year. Therefore we do not know whether there exist limited numbers of types, as with pneumococci and other bacteria, or whether the influenza A virus is capable of an indefinite number of biochemical modifications of a basic structure.

The antigenic variations are important from the points of view of vaccine preparation and of epidemiology. Vaccines have been made in the United States from fluids of infected hens' eggs. In the autumn of 1943 against an A epidemic, and in 1945 against a B outbreak, these vaccines gave most encouraging results. In 1943 the vaccine—in five out of six centres at any rate—apparently reduced the

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incidence of A infection fourfold (Commission on Influenza, 1944). In 1945 a tenfold to twentyfold reduction of B influenza seemed to have been achieved (Francis *et al.*, 1946; Hirst *et al.*, 1947). The 1943 trial was favoured by two factors: first, the epidemic hit the communities under observation only a week or two after the vaccinations; and, secondly, there had been incorporated in the vaccine a very recently isolated strain obtained from a local outbreak in the previous spring. There was a rather rapid assumption that the problem was solved: over 5 million doses of vaccine were given to American troops in 1943-4, and still more in 1945-6. Doubtless the influenza virus chuckled to itself, and quietly mutated to a sufficiently distinct form. At any rate numerous American trials of vaccine in 1947 showed a total absence of protection against the 1947 brand of influenza (Francis *et al.*, 1947). Tests in this country were almost equally discouraging (Mellanby *et al.*, 1948). I have been told that vaccines now being made in the U.S.A. contain recently isolated strains, but I fear that the virus is still chuckling, and that until we know more about its possible range of variation it is useless to produce vaccine on a vast scale. Trials of aspects of vaccine making and testing, other than those concerned with antigenic variants, are of course needed all the time.

Influenza A in America and over here has a 2-3-year periodicity. Influenza B, which is probably a more effective antigen, has a longer, 4-6-year cycle (Commission on Acute Respiratory Diseases, 1946). The fact that the cycles have any regularity at all probably depends on a regular rate of waning of herd-immunity. The periodicity is unfortunately not so regular that we can prophesy with confidence that any particular year will or will not have an influenza epidemic. This lack of precision is perhaps due to this same faculty of the influenza viruses for antigenic variation. If a mutant happens to turn up unusually remote from previous strains it will be able to spread widely and initiate epidemics earlier than would otherwise be the case. In 1945-6 there was good evidence that influenza B was unusually active all over the world, beginning in the mid-Pacific, spreading south to Australia, east to the Caribbean, to North and South America, and later to Europe (*Bull. U.S. Army med. Dept.*, 1945). In 1947 at least one of the novel antigenic types of A which successfully defied the vaccine in America proved to be identical with strains current over here at the same time. All this suggests that the epidemiology of influenza needs to be studied on a world-wide basis.

The World Health Organization has accordingly obtained the consent of the Medical Research Council to set up at the National Institute for Medical Research at Hampstead a World Influenza Centre. This will gather information about the doings of influenza all over the world, and will collect from and distribute to interested laboratories strains of virus. It is hoped that regional influenza laboratories in other countries will collaborate, particularly in collecting local strains, and that we may in time obtain some picture of the behaviour of influenza on a canvas which is really world-wide. If it should appear that new strains are in fact globe-trotters, the possibility exists of anticipating their arrival from abroad and greeting them with really homologous and therefore effective vaccines.

The occurrence of poliomyelitis outbreaks seems related in part to the hygienic conditions of a country and to the opportunities for exposure to virus during infancy. But on top of this is the likelihood that serological variants of poliomyelitis may be spread about, distinct enough to be able to infect people with good resistance to a local strain. The epidemiology of both influenza and poliomyelitis is complex: common to both, as a major cause of the complexity, is the problem of antigenic variation. We have

not yet got a vaccine of real promise against poliomyelitis; even if we had one, we should still have to sort out the antigenic variants of the virus.

"Interference" as a Prophylactic Measure

Against a rapidly spreading influenza pandemic of a new type the most rapid vaccine production might well be much too slow. On this account Burnet and Foley (1940) have urged that we should seek attenuated viruses which can be given in the living state by the respiratory route; these could be given in relatively much smaller dose and thus be prepared for large populations much more rapidly. Unfortunately, trials with such attenuated influenza viruses in man have not yet given encouraging results. An approach similar to this involves the attempted practical application of the so-called "interference phenomenon." Virus-workers have known for over a decade that certain viruses will interfere with or suppress the activity of other viruses inoculated at the same time or shortly before. The two viruses may be variants of one species, as in the interference of neurotropic with viscerotropic yellow fever (Hoskins, 1935), or two antigenically related species or even two antigenically unrelated species. Possibly similar effects are dependent on different mechanisms in different instances.

The phenomenon can most easily be studied as it concerns the exclusion of a phage particle from attack upon a bacterium by another phage which has got there first. Apparently even one phage particle can so modify the bacterium, perhaps its surface, perhaps its enzyme equipment, that particles arriving later are unable to enter and have to stay outside and starve (Delbrück, 1945). The phage arriving first can still exclude the one arriving second though the former has been inactivated by ultra-violet irradiation. The phenomenon as regards animal pathogenic viruses is most easily studied in those which grow in the fluids of infected fertile eggs. Is it, one wonders, something of purely academic interest, invented to amuse virus-workers in their laboratories, or does it play a part in epidemiology in real life and can it be applied to the control of disease?

Interference by one influenza virus with another can be shown very readily in infected eggs, but in my experience is much less easily demonstrated in infected mice. Lately my colleague, A. W. Gledhill, and I have been carrying out experiments in ferrets with more success. We used a strain of influenza B which caused practically no fever or symptoms in ferrets. This was given to ferrets intranasally and followed one, two, or three days later with a dose of virus A which produced severe symptoms in control animals. In the B treated ferrets no fever or symptoms developed either from the B or subsequent A infection, and the ferrets were later immune to both viruses. The B by itself induced no true immunity to A, for if the interval between giving the B and the A viruses was extended to a week or more the A infection pursued its normal course or was even worse than usual. The interference is thus effective for a very limited period, presumably while an actual, though inapparent, B infection is in progress. As yet we have been unsuccessful in interfering with an A infection by means of an attenuated A strain. Our results are brought a step nearer to practical application by the finding that B infection also protected ferrets against A when they were exposed for two days to contact with other A-infected ferrets. Controls were readily infected by such contact. These experiments can be repeated regularly, but only within rather narrow experimental limits, and possible practical application depends on the results of much further work. It seems, however, worth while to

draw attention to the possibility of preventing virus disease in the future by means rather different from orthodox immunological methods.

Recent Progress in Prophylaxis of Other Virus Infections

I will conclude with some very brief items of news concerning other viruses not already mentioned.

Mumps.—Mumps virus has now been grown in fertile eggs and has been shown to resemble influenza A and B, fowl-plague, and Newcastle disease of fowls in its ability to agglutinate red blood cells of certain species. These five viruses seem to form a natural group. Like influenza, mumps can be modified by egg-passages, and there are hopes that an attenuated virus suitable for immunization of man may be developed (Enders *et al.*, 1946). Gamma-globulin prepared from mumps convalescent serum has been stated to be of value in preventing orchitis when given early in the disease (Gellis *et al.*, 1945).

Measles.—Measles virus has also been cultivated in eggs, but its presence can be recognized only by transfer back to rhesus monkeys or human volunteers. Egg-passage attenuates it for children, but one cannot yet advocate its practical use for immunization. Its attenuation is not quite enough to satisfy us; on the other hand, the immunity produced is far from complete (Stokes *et al.*, 1943). Prevention or attenuation of measles by immune serum is an old story. It may be noted, however, that for this purpose concentrated gamma-globulin is better than placental globulin (Greenberg *et al.*, 1945).

Rubella.—This has not yet been transmitted to laboratory animals, and the gaining of knowledge about it lags accordingly. Literature is piling up (Editorial, 1947) concerning the occurrence of congenital abnormalities such as cataract in babies born of mothers who suffered from rubella in the early months of pregnancy. Common sense will warn us to shield such mothers at all costs from unnecessary risk of exposure to the disease.

Rabies.—It has been claimed that animals may be experimentally protected against rabies more effectively by concentrated immune rabbit-serum than by traditional vaccines (Habel, 1945). Many people wonder whether, if Pasteurian vaccines do prevent rabies, the effect is not due to something like the interference phenomenon I discussed earlier rather than to immunization in the usual sense. I say advisedly "if" they are effective, for I note with surprise how little notice is officially taken of the late L. T. Webster's (1942) challenge in his book on rabies. He maintained that there was very slender scientific evidence that such vaccines prevented rabies at all when given after infection.

Smallpox.—Experience in the recent war confirms our belief that, because of varying susceptibility and immunizability, vaccination cannot be depended upon to protect an individual, but (and may no one quote the first half of this sentence away from its context) vaccination is still a reliable means of preventing and controlling smallpox outbreaks, since it will protect most subjects. It has been known for some years that vaccinia grown in tissue cultures or in fertile eggs can be obtained free from all bacteria, and that such a vaccine will immunize man (Buddingh, 1943); but this method of vaccine manufacture has not yet been taken up and seriously tested in comparison with calf or sheep lymph.

Encephalitis.—Viruses cause several forms of mosquito-borne encephalitis in America and the Far East. There is, also, in Russia a tick-borne encephalitis related to the louping-ill of sheep which occurs on the Scottish borders. Against all of these infections formalized vaccines seem to confer a considerable degree of protection. The cause of sporadic encephalitis in this country is unknown.

The Common Cold.—Work on the aetiological agent at the common cold research unit at Salisbury continues. We have not yet succeeded, as two groups of American workers claim to have done, in growing a virus in eggs. Nor, I need hardly say, have we yet produced a vaccine.

More virus vaccines in the future are likely to be made in fertile eggs. At present yellow-fever vaccine, so grown, is of proved value; so is influenza vaccine within the limits I have discussed. Nearly all the development in this field is going on overseas. I believe that far-sighted manufac-

turers of biological products in this country would do well to gain experience in this field and contribute their share to its development.

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STREPTOMYCIN RESISTANCE IN PULMONARY TUBERCULOSIS

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Strains of *Mycobacterium tuberculosis* isolated from patients before treatment are remarkably uniform in their sensitivity to streptomycin (Middlebrook and Yegian, 1946; Youmans and Feldman, 1946; Medical Research Council, 1948c). However, during the course of treatment strains often develop a variable degree of resistance to the antibiotic (Youmans *et al.*, 1946; Report to Council on Pharmacy and Chemistry, 1947; Canada, 1947; Hinshaw and Feldman, 1947; Fisher, 1948; Sadusk and Swift, 1948; Medical Research Council, 1948b). A controlled series of cases of pulmonary tuberculosis has been treated with streptomycin under the auspices of the Medical Research Council, and the result of these trials is reported elsewhere (Medical Research Council, 1948a). Among the group of patients receiving streptomycin, 13 were treated at the Brompton Hospital, and from these were obtained sufficiently detailed data on the development of streptomycin resistance to justify a further report.

Method of Investigation

Type of Case.—Patients were aged from 15 to 30 years and suffered from acute progressive bilateral pulmonary tuberculosis of recent origin. Cavitation was present in all. Before treatment 11 had numerous acid-fast bacilli in direct smears of the sputum; 2 had acid-fast bacilli present only in sputum concentrated or in small numbers in direct smears. There were 10 women and 3 men.

Dosage of Streptomycin.—Every six hours 0.5 g. was given intramuscularly. In the earlier part of the trial treatment was continued for six months, but this was later

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