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EPIDEMIOLOGY

The role of the World Health Organization in the study of influenza

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The World Health Organization (W.H.O.), since its inception in 1947, has given close attention to influenza. In its early years W.H.O. laid the foundations of its present network of over 100 national influenza centres and collaborating laboratories which today constitute the backbone of its influenza activities. The activities of the network include the isolation and characterization of influenza strains and the early notification of any changes in surface antigens, the preparation of reference reagents, standardization of diagnostic procedures, formulation of requirements for vaccines, training, and collaboration in research. The efficacy of the network has been proved in the 1957, 1968 and 1977 epidemics. Collaborative research organized by W.H.O. has made important contributions to our understanding of the epidemiology of influenza, including the possible role of lower animals as the origin of some pandemic strains. The latter subject is briefly discussed.

Rather than present the bare structural bones of the work of the World Health Organization (W.H.O.) in influenza since the inception of the Organization in 1947, I believe that it will be of more interest to sketch a somewhat personalized account derived from my having been a staff member for over 25 years, until 1976.

A number of the key people involved in W.H.O.'s work are at this symposium, and I hope I shall be forgiven if I do not mention some of them by name, as there are too many to acknowledge their individual contributions.

The early years

In the late 1940s and early 1950s, W.H.O. began to pay close attention to influenza, aware of the devastating experience of the 1918 pandemic and the helplessness felt should such another episode materialize – as unpredictable today as it was then. Scientific knowledge of influenza was then centred in a relatively few individuals and their coworkers, notably Andrewes, Stuart-Harris, Smith and Hoyle in the United Kingdom, Burnet and his group in Australia, the von Magnuses in Denmark, and Hirst, Francis, the Henles and a few others, including the 'loner' Richard Shope, in the U.S.A. When the late Tony Payne joined W.H.O. in the early 1950s to head the virus unit it was these people that he called upon to assist the Organization in developing a systematic and collaborative effort to deal with the influenza problem.

Let us recall that in the early 1950s we were well into the A prime era of the influenza strains. The mouse, ferret, egg, and the haemagglutination and complement-fixation techniques were the basic laboratory tools; only Richard Shope stubbornly persisted in his swine investigations, the one non-laboratory animal known to be susceptible to influenza infection.

Without doubt the greatest impetus to W.H.O.'s efforts at that time was given by Chris

(now Sir Christopher) Andrewes who guided what was grandly designated as the World Influenza Centre – a couple of laboratory rooms and some animal quarters at Mill Hill. From this very modest start Tony Payne, with the help of Chris Andrewes and Alick Isaacs, began to mobilize the leading influenza workers in different countries into a collective effort. This quickly evolved into the preparation and use of reference reagents for laboratory tests, uniform techniques for the isolation and identification of influenza strains, procedures for the production and testing of vaccines, and the creation of an information network of national influenza centres which would work in collaboration with the World Influenza Centre, a basic structure that operates today. In addition to the already well established groups mentioned previously, strong collaborating units were progressively enlisted, including those of Bela Tumova and Karel Raska in Czechoslovakia, Mulder and Hers in Holland, Smorodintsev and Zhdanov in the U.S.S.R., and workers in other countries.

My own role as chief of the veterinary section at W.H.O. during this period was a minor one, mainly confined to laboratory aspects of influenza and to keeping in view interesting developments in the veterinary field, notably the findings in 1955 and 1956 that influenza infections occurred in horses and certain avian species. For many years I had been fascinated by Shope's work on swine influenza and the relation of human and swine infections. The identification of influenza A infections in the equine and avian species stoked my interest in the epidemiology of animal influenza and its possible importance in human infections.

The 1957 Asian pandemic

The emergence early in 1957 of the Asian influenza pandemic strain, which was quickly recognized as totally different from preceding epidemic and pandemic strains, tested and proved the efficacy of the network mechanisms that had been developed in a few years. It also found W.H.O. ready to extend its animal studies in the following way.

In July 1957, soon after the onset of the new Asian (H2N2) virus pandemic and with a vague report from China that concurrent epizootics in pigs had occurred, W.H.O. convened a meeting of leading workers in influenza. Among other matters, and as a minor subject, we discussed the intriguing possibility that the strain might have emerged from an animal reservoir. Some of the group, with the strong backing of Andrewes and Burnet, and in the face of considerable scepticism, supported my proposal to investigate this possibility. I might add, parenthetically, that in the following year Chu Chi-Ming of the National Vaccine and Serum Institute in Ch'angch'un and who had previously worked at the World Influenza Centre, described the epidemiological characteristics of the 1957 epidemic in China. He pinpointed its origin in early February 1957 in the area of western Kweichow and eastern Yunnan (Chu Chi-Ming 1958). He also considered that since the new 1957 strain was radically different from the previously prevalent strain, it might have had its origin in an unexpected animal reservoir.

The first action taken by W.H.O. was to organize a worldwide survey of pigs and horses in 20 countries during and after the 1957–8 pandemic. The object was to determine whether infection with the H2N2 strain had occurred in these animals, and whether infection was related to the pandemic in man. The results showed that equine influenza caused by the A/equi subtype had occurred in horses in many countries in which it had not previously been reported and that swine influenza, caused by the A/swine subtype and long known in the U.S.A. had also recently occurred in pigs in Czechoslovakia and Germany. Suggestive evidence was obtained

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

that the new Asian pandemic strain had infected horses and pigs in some countries (Kaplan & Payne 1959).

The Asian pandemic spurred a rapid expansion of influenza research in the laboratory and field in all parts of the world. The expert groups convened frequently in Geneva by W.H.O. performed an invaluable function in promoting collaborative studies and agreeing on criteria for laboratory procedures, and in rapidly disseminating the results derived from these efforts. Much credit for this is due to Helio Pereira who headed the World Influenza Centre in the 1960s, and later to Geoffrey Schild, always with the vigorous and continuing support of Chris Andrewes. At W.H.O. in the early 1960s, Charles Cockburn took over the human influenza activities from Tony Payne who became an assistant director-general. Cockburn, a highly experienced epidemiologist, ably developed the activities of the W.H.O. network started by Payne.

Animal studies

Since 1957 W.H.O. has been trying to stimulate and coordinate studies on animal influenza in different parts of the world to shed light on the role of animals in the epidemiology of human influenza. The principal aims of these studies have been to determine (1) whether lower animals are of any importance as a prime source of the major antigenic shifts in the influenza A viruses that cause the recurring epidemics and pandemics in man, and (2) if they are important, whether it is because of the emergence of an animal strain with a slight change that is able to spread in man, or whether recombinations occur in nature between animal and human strains with the subsequent emergence of a new strain (or whether both kinds of events occur.)

Studies on animal influenza, however, proceeded for many years on a Cinderella-like basis, but they gradually increased in tempo, and by the early 1960s necessitated almost annual meetings in Geneva of the major collaborators to assess results and to plan investigations for the succeeding year. This work has continued, and in fact the next meeting of the group took place immediately after this symposium.

The locales where field studies have been carried out would satisfy the fantasies of any laboratory worker interested in the natural history of a disease. They have included investigations in shearwaters off the Great Barrier Reef of Australia, chickens in the Kamchatka peninsula and cattle and migratory birds and even whales in several other parts of the U.S.S.R., wildfowl off the rocky coasts of Alaska, gulls and other birds in islands off the coast of Norway, penguins in the Antarctic, migratory geese and ducks in Canada and along the Mississippi river, migratory fowl in India, sea birds off the coast of Peru, horses in Mongolia, and of course domestic turkeys, chickens, ducks, horses and pigs in numerous barnyards and abattoirs in many countries. (W.H.O. does not and cannot fund such undertakings; they are underwritten by funding sources available to the various investigators. The stimulation and coordination provided by W.H.O. is aided by very small sums extracted with some pain from the limited research funds available from W.H.O.'s regular budget.)

The results of these studies have been summarized elsewhere (Kaplan & Webster 1977), and recent findings are reviewed at this symposium by other speakers. We have not as yet arrived at definitive answers to the problems posed above, but we are rapidly advancing to a position where this will be possible. I shall now briefly state why, though I shall have to oversimplify since virus characteristics such as infectivity, transmissibility, and pathogenicity are probably polygenic functions that interact with other factors such as the status of the hosts affected.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

As I have just noted, the animal investigations have produced strong suggestive evidence that lower animals play an important role in the epidemiology of human influenza (Kaplan & Webster 1977). These animals, particularly the avian species, provide an immense and ineradicable reservoir for new H and N genes which, through recombination under natural conditions, could well provide the influenza genomes for new pandemics. Compelling evidence to support this hypothesis can now be sought more readily and accurately than before owing to recent rapid advances in various techniques, particularly nucleic and amino acid sequencing and monoclonal antibody studies. By means of these techniques, and other less discriminating methods such as degree of homology binding and oligonucleotide and peptide mapping, the influenza RNA gene segments (and their products) from related human and animal strains can be compared. As other papers in this volume point out, considerable information has already been accumulated in this way.

As definitive evidence we would need to find identical or nearly identical nucleic acid sequences in both the H gene segment of an animal strain that had been isolated before a major human pandemic and in the H gene of a related antigenically shifted strain which caused the pandemic. Nucleic acid sequencing and other evidence would be sought also for other genes. We shall have to await the next major human pandemic caused by an antigenically shifted strain and compare the virus with an animal strain already 'banked' in the expanding store of the latter being collected throughout the world.

The present W.H.O. programme

The present W.H.O. influenza programme, which centres on human infections, has two functions: first, to serve as an early warning system for new or altered antigenic subtypes, and second, to provide information on the epidemiological behaviour and antigenic character of prevalent virus strains. Emphasis is placed on the rapid isolation of strains in national laboratories and their characterization in the international influenza centres.

Global surveillance is carried out through the 101 national centres in 71 countries and two international laboratories: the W.H.O. Collaborating Centre for Reference and Research on Influenza in the Centre for Disease Control in Atlanta, Georgia, U.S.A., and at Mill Hill and Colindale in London (replacing by name the former World Influenza Centre). Of the national influenza centres, 46 are located in 39 developing countries, and the rest in developed countries.

The two W.H.O. influenza collaborating centres in Atlanta and London characterize and preserve representative strains from outbreaks in different parts of the world, and distribute these strains to research and vaccine production laboratories, advising on strains that should be included in vaccines. The centres, in collaboration with the Virus Diseases and Epidemiological Surveillance Units of W.H.O. in Geneva, collect and disseminate epidemiological information on influenza prevalence throughout the world. They also train research workers in specialized techniques.

The national influenza centres arrange for the isolation and serological diagnosis of influenza in patients, and send freshly isolated strains from each influenza outbreak to the international centres. They also provide virological and epidemiological information to W.H.O. in Geneva and to the international centres.

Virus strains are received by the international centres within one or two days of dispatch from national centres. These in turn are rapidly characterized, and when new or slightly altered

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

antigenic characteristics are recognized, quick action is taken to transmit this information worldwide and to provide the strains to vaccine producers.

The events surrounding the reappearance of the H1N1 strain in 1977 illustrate the efficacy of the W.H.O. influenza programme. In May 1977, several H1N1 strains were isolated from children during outbreaks in China, but information on these outbreaks was not known to W.H.O. at the time. On 7 December 1977, W.H.O. was informed by the U.S.S.R. Regional Influenza Centre in Moscow of a new variant of influenza A virus characterized as H1N1 causing several outbreaks in the U.S.S.R. On 8 December, the W.H.O. Collaborating Centres in Atlanta and London were informed of the isolation of H1N1 strains by the national influenza centre in Hong Kong. Strains from the U.S.S.R. and Hong Kong were confirmed by the two Collaborating Centres by 14 December. Information on the outbreaks and the identification of the new variant was given to all national influenza centres and vaccine producers and was published in the W.H.O. *Weekly Epidemiological Record* on 16 December. Inactivated antigen and antisera of the closely related reference strain A/FM/1/47 (H1N1) were sent to all the national influenza centres on 21 December. During the same week, strains were made available to vaccine producers. All this action was completed within 3 weeks of the report to W.H.O.

It should be source of great satisfaction to all collaborators in this work to know how effective, in practical terms, are their combined efforts. The absence of such a network is in fact inconceivable today. I do not doubt that such continued collaboration will in the relatively near future result in striking advances in our efforts to prevent and control this major remaining plague.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES