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PERSPECTIVES IN THE CONTROL OF EPIDEMIC INFLUENZA

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PART I

PROGRESS IN RELATION TO AIRBORNE INFECTION

MODERN progress in the control of the infectious diseases of man and animals has been astonishing. The era of modern sanitation which has been so successful in diminishing the toll from the zymotic diseases has been succeeded so swiftly by the discoveries of chemotherapeutic and antibiotic agents that it is hard to adjust oneself to the pace of advance and to see clearly what can and cannot be done at the present time. A useful perspective may be obtained from the Table I below which gives for comparison the mortality from various infective diseases in Great Britain at the beginning and mid-point of the present century. It is clear from this table that though the death-rate has fallen in every instance, the degree of reduction varies greatly, being

TABLE I.—DEATHS FROM ZYMOTIC DISEASES IN 1898 AND 1948

Cause of death	*Number of deaths* 1898	1948	*Death-rates per million* 1898	1948
Measles and rubella	13,260	329	422	8
Influenza	10,405	1,240	331	29
Whooping-cough	10,175	748	324	17
Diphtheria	7,661	156	244	4
Enteric fever	5,708	48	182	1
Scarlet fever	3,548	36	113	1
Smallpox	253	0	8	0
Chicken-pox	116	10	4	0·2
Typhus	47	0	1	0
Cholera, diarrhœa and dysentery	30,096	3,131	959	72

(Modified from Percy Stocks, Table V, *Brit. med. J.*, 1950, **1**, 55.)

particularly impressive in the case of enteric fever and diphtheria. Yet, the mortality from diseases such as scarlet fever and measles has also declined even though specific measures of control have not been developed against them. The position in regard to influenza and whooping-cough is, however, much less satisfactory and if figures for morbidity as opposed to mortality rates were available, there would be still less cause for congratulation. The unsolved problem of influenza is not, however, best visualized by reference to a table of this sort because of its characteristically epidemic incidence. The wider view of a century of experience is necessitated and a consideration of influenza over such a long period yields some interesting facts (Martin, 1950).

The first of these is the virtual extinction of influenza in the years following the outbreak of 1847 with particularly low levels immediately prior to the great pandemic of 1890. Secondly, ever since 1890 influenza has maintained annual epidemics much greater in incidence than in the previous forty years, the peak being reached in the pandemic years of 1918–19. Thirdly, since 1930, the annual peaks have attained generally lower levels particularly in the last seven years (fig. 1). Martin (1950) points out that this recent subsidence in influenza is shown not only by the reduction in the height of the peaks but also

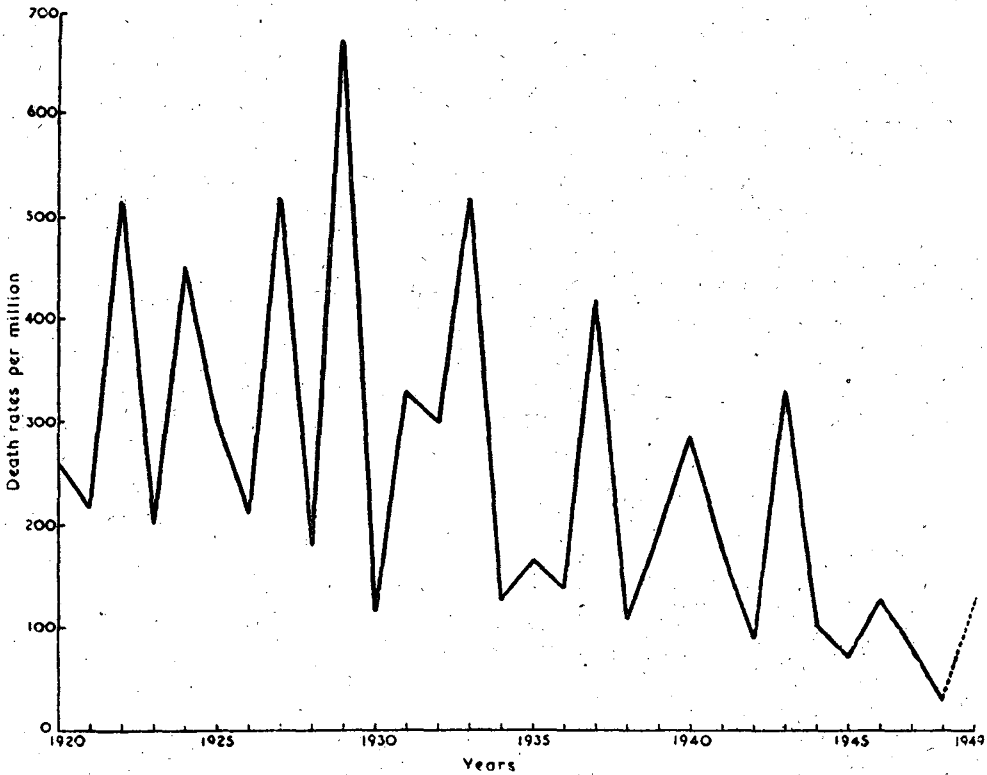

FIG. 1.

(After W. J. Martin, 1950, *Brit. med. J.*, **1**, 267.)

in a diminution in the base-line in between the epidemic prevalences, and hazards an opinion that if the present trend in influenza mortality continues, a further period of virtual extinction as in the years preceding 1890 may occur.

Since 1932 when the influenza virus was first identified in the laboratory by the pioneer work of Smith, Andrewes and Laidlaw (1933), it has been possible in this country to identify the viruses causative of the various British outbreaks. This information has been of great epidemiological significance, for it has shown that influenza virus infection does not occur annually. It thus appears that the peaks of influenza mortality as shown in fig. 1 are associated with infection by the influenza viruses chiefly of that serological type referred to as A but that the intervening troughs of mortality occurred in years when neither this nor the B group of the influenza viruses were recovered. In other words, the statistical approach to influenza mortality is obscured by the existence of other clinically similar respiratory tract diseases which are unrelated ætiologically to the known influenza viruses. Yet, both the influenza virus epidemics and the unknown conditions of the respiratory tract appear to have undergone cyclical changes which are hard to relate to known conditions of life. The essential perspective which must be attained is thus that of a changing pattern of disease related in all probability to the ecology of man and of the viruses which flourish in the human respiratory tract. Against this background all past attempts at prophylaxis have been puny experimental probings which have left unsolved almost as many problems as those for which they have suggested a solution.

Mechanism of Spread of Influenza

The history of those virus infections which thus far have yielded to human attempts at control indicates that success is likely when methods of spread have been clearly delineated. Thus, smallpox prophylaxis in this country at present depends as much upon the limitation of spread from known cases and contacts as upon immunization with vaccine lymph. Yellow-fever control is likewise dependent equally upon the destruction of mosquitoes and upon immunization. The factors which govern the spread of influenza and other airborne virus infections of the respiratory tract are, however, still obscure.

Airborne infection is possible in three main ways : via the minute droplets and droplet nuclei which float and remain suspended in the air for long periods, via the larger droplets with a short trajectory such as are expelled in sneezing, and via dust particles contaminated with dried secretion. Experimental studies with influenza virus (Bourdillon and Glover, 1948) have shown that ferrets can be infected by airborne particles either fine (3–6μ) or coarse (16μ) in size and the former-sized particles are capable of remaining suspended in air for considerable periods. Virus can also be recovered in an infective form after drying on a blanket, or in the form of dry dust exposed near a ferret infected with influenza (Edward, 1941). Thus all three methods of contagion of influenza by airborne routes are theoretically possible, yet it is still not known whether any one of the three methods is more important than the others from the standpoint of human epidemics. A consideration of the number of droplets, many of large size, which are expelled during a single sneeze, leads one to the conclusion, however, that direct contagion from one individual to another is a more likely mode of spread than indirect methods involving dust or contaminated air.

The source of infection seems obvious in the case of influenza because large amounts of virus can be demonstrated in the nasal and throat secretions during the early phases of the disease. However, virus has been clearly demonstrated in the throat of a healthy individual during an outbreak of influenza so that at such times apparently healthy persons may act as sources of dissemination of virus. Well-recognized instances indeed exist of outbreaks of influenza which appear to have followed the paths of travellers from an infected area to other areas previously unaffected, and such travellers may have remained clinically well in the intervening period (Hare and Mackenzie, 1946). There is thus good evidence that influenza may reach a community either by a direct chain of infection or by the medium of healthy carriers. But the question of the mode of persistence of virus within a community is still unsettled. There is little direct evidence to support the view that influenza virus remains latent in a particular community in between epidemics for proven sporadic cases of virus infection are relatively uncommon. Nevertheless some events strongly suggest that a community can in fact be carrying virus even though overt cases of influenza have not occurred amongst it for some considerable time. Thus in the Ocean Island outbreak described by Isaacs *et al.* (1950), a severe epidemic of influenza A occurred among immigrant Polynesian labourers and followed on the heels of the arrival of a ship from China conveying Chinese workers. The latter did not fall ill during the epidemic of influenza but serological evidence after the outbreak suggested recent influenza virus infection amongst them. The ship carrying the Chinese workers had been overcrowded and coughs were prevalent but there had been no outbreak of influenza; the journey had occupied three weeks and the Chinese labourers were placed in quarantine for twenty-four hours after landing. The outbreak began nine days after release of the Chinese from quarantine. It is difficult not to accept the view that the Chinese "herd" had come to terms with the virus which they brought with them and that from this source the infection spread to the virgin soil of the Polynesians in whom it evoked a high percentage of clinical attacks. A parallel may perhaps be drawn between such occurrences and the school outbreaks of influenza familiar in this country. Epidemics of influenza usually begin within the first week of assembly of scholars (School Epidemics Committee, 1938) and this circumstance suggests a build-up from the admixture of virus-infected individuals with susceptibles consequent upon the bringing together of the community once more.

The method of evolution of influenza epidemics in a military community is very difficult to analyse. The view that recruiting initiates an unstable situation from the standpoint of respiratory tract infection is certainly a sound one. Epidemics of respiratory illness are far more severe in establishments with a high rate of turnover than in stable human groups. But laboratory investigation of these recruit outbreaks indicates that influenza virus infection is heavily outnumbered by a condition termed febrile catarrh or acute respiratory disease (A.R.D.). The prolonged studies of the American Commission on Acute Respiratory Diseases during World War II established this fact on a firm foundation and British experience (Stuart-Harris, 1947) agrees with their findings. When the influenza virus becomes active in a community such as a Training Centre it may well be unappreciated clinically that any change has occurred because of the clinical resemblance of febrile catarrh to influenza. Indeed if a severe outbreak of influenza does result, it is usually appreciated on the basis of the numbers of those clinically ill rather than on the appearance of unusual clinical characters. Nevertheless, as the American workers at Fort Bragg have shown (Commission on Acute Respiratory Diseases, 1948) the conflagration of influenza may involve seasoned men and recruits to an equal extent, whereas febrile catarrh is almost exclusively confined to recruits with less than three months' Service experience. It is therefore impossible to dogmatize concerning the origin of outbreaks of influenza virus infection in Service communities although in this country, at any rate, the military are involved as an integral part of the community when the civilian herd becomes the battleground for the virus-host interaction.

Finally, the concept of global spread of influenza must be mentioned because consideration of recent experience in connexion with the Influenza B wave of 1945–46, and the influenza A epidemic of 1949 (Andrewes, 1949), indicates that a distant origin is at least as probable as a local resurgence of infection. The events of 1949 indeed indicate most clearly that whether the influenza epidemic of next winter is to materialize or not may depend on events in an area remote from these shores. This, no doubt, is the reason for the success for a time, of quarantine measures applied to whole islands, as was done in the case of Australia and of the Samoan islands in 1918. Quarantine, however, merely postponed the epidemic in Australia and it cannot be regarded as a practicable measure when applied to entire communities.

The Development of Methods of Control of Airborne Infection

A formidable spate of publications appeared during and after World War II which reported experimental and field observations on methods of combating airborne infection. Amongst these were the observations of British workers (van den Ende *et al.*, 1940; van den Ende *et al.*, 1941) on the value of dustlaying measures in the prevention of periodic pollution of the air such as occurs during sweeping a floor, bed-making and so on. Dust-laying alone is not, however, effective against infection by airborne droplets and for these, methods of aerial sanitation aimed at the direct destruction of bacteria suspended in the air, or of the trapping of infected droplets, have been developed. Nevertheless, although it has been abundantly demonstrated that it is certainly possible to reduce greatly the bacterial content of the air of a room, it is a far cry from this to the prevention of airborne infection owing to the universality of the atmosphere and the impossibility of application of the sterilizing procedure except on a restricted scale. The two main lines of work which have been followed have been air-sterilization by chemical aerosol droplets and vapours, and by ultraviolet irradiation. In addition to this, the effect of increasing the rate of ventilation of the air and of interposing a barrier such as a mask must be mentioned.

(*a*) *Chemical Disinfection.*—The work of Bourdillon and his associates at the Medical Research Council's laboratory is the most important British contribution to this subject (Bourdillon *et al.*, 1948). It is not possible to summarize the work adequately in an article such as this ; but chemical disinfectants are regarded as being of greatest assistance in special situations, such as rooms where clean air is particularly needed, or during epidemics of airborne disease. There is a wide choice of chemicals including hypochlorites, triethylene glycol, propylene glycol, resorcinol and alkyl resorcinols, lactic acid and other αhydroxy-acids. The compound α-hydroxy-αmethyl butyric acid possesses many theoretic advantages but is less easy to obtain than lactic acid. Resorcinol is particularly suitable for intermittent disinfection for short periods. All these chemical agents can be dispersed into the air by more than one method but vaporizers or hand sprayers appear to be the most important. Their efficacy in disinfecting the air is not to be doubted though with the exception of lactic and other hydroxy-acids, their activity is much greater against suspended droplets than against dry dust particles. It is not the purpose of this paper to outline the circumstances governing the efficacy of measures such as chemical disinfectants. These are fully detailed in the Medical Research Council's report, but their major limitation is clearly that they can do little more than to lessen the risk of contagion by airborne droplets possibly emanating from a distant source. They are clearly ineffective against direct contagion during coughing or sneezing which as already suggested may be important in relation to the spread of influenza.

(*b*) *Physical Methods of Disinfection.*—The simplest methods of sterilizing air, either by heat or filtration, are of course effective when the air of individual rooms or of buildings can be dealt with in this manner. Bourdillon and Colebrook (1946) have shown the efficacy of a ventilation plant installed in a dressing-room for burns whereby a positive air-flow over the vicinity of the patient of clean filtered air avoids a superadded wound infection during the manipulation of dressings. Nevertheless such methods are of restricted application whereas the irradiation of the air by ultraviolet light can be applied on a much larger scale. Ultraviolet radiation is of chief significance in relation to airborne droplets and is relatively ineffective against dust-borne organisms ; it is, however, most effective at low relative humidities of the air thus contrasting with chemical agents which are more active at high humidities. The application of ultraviolet radiation in field trials has been chiefly explored in the U.S.A. as will be mentioned later. Care must be taken to restrict radiation to the upper air of rooms or to act as a barrier or screen at an entrance to a room because of its harmful effect upon the eyes and skin.

(*c*) *Trapping of Droplets by Masks and Handkerchiefs.*—It has been repeatedly pointed out that the foundation of work on aerial sanitation is insecure because the relative importance of the variously-sized infective droplets in the transmission of infection is unknown. Granted that influenza can be transmitted by minute particles suspended in the air for long periods, it is still not certain that this is the usual method of spread compared with the direct contact between individuals during talking, coughing and sneezing. For such methods of transfer, it is necessary to adopt more direct methods such as the use of masks in order to encourage expelled droplets into a downward trajectory. The difficulty in persuading individuals to wear masks is, however, considerable. A more practicable measure is to encourage the use of handkerchiefs which will trap the droplets. Dumbell *et al.* (1948) have shown, however, that handkerchiefs alone are a possible source of contagion because of the number of bacteria liberated on shaking them, and the incorporation on the handkerchief of a disinfectant such as hexyl resorcinol (Dumbell and Lovelock, 1949) is therefore suggested as a measure of some practical importance.

Present Significance of Methods of Air Hygiene

Practical application of the various techniques developed to attack the problem of airborne infection has hardly progressed yet beyond the stage of experimental gropings. Trials in hospital wards, schools, canteens, mess decks, underground shelters and the like have been made by workers both in this country and in the U.S.A. But a critical evaluation of these techniques in terms of their effect on airborne contagion is not forthcoming in many instances. Clearly it is not enough to be able to say that the bacterial content of the air is reduced. What is wanted is an estimate of the decrease in respiratory tract infection, if any, which has been achieved. Furthermore, the value of the measures in terms of the particular bacterial or virus infections encountered is desired rather than a block estimate of undifferentiated sickness. This latter point raises the difficulty of diagnosis which has been a stumbling-block in many of the investigations. The hotch-potch of acute respiratory disease includes streptococcal infection of the throat, influenza and the ætiologically unknown febrile catarrhs, atypical pneumonias and the common cold. It is by no means to be expected that bacterial and virus infections will respond equally to the various measures employed.

The most promising experiments so far have centred around the limited problem of cross-infection in wards such as children's and infants' wards, dressing-rooms and so. The hæmolytic streptococcus is a most important cause of such cross-infection and there seems no doubt from the work of Wright and her co-workers (Wright, Cruickshank and Gunn, 1944) that a significant effect on cross-infection by streptococci in cases of measles may be obtained by dust-laying on floors and bedding by oil especially if conditions are favourable for a high rate of infection. Other workers (Rountree, 1947) have had less success, however. Ventilation and ultraviolet light radiation have also given helpful results. One of the most interesting studies is that from the Cradle clinic at Evanston (Rosenstern, 1948). A combination of air-conditioning, mechanical barriers and germicidal lights have been found to be effective in reducing cross-infection not only of the skin but also of the respiratory tract so that it has not been necessary, for instance, to exclude nurses with colds from the unit. But, it cannot be emphasized too much that the problem of cross-infection in such restricted surroundings is not really comparable with that of the prevention of respiratory infection in the field.

Field studies on any considerable scale have been largely carried out in the U.S.A. although valuable field data in relation to the reduction of bacterial contamination of the air have been obtained in this country by Bourdillon and his associates (Bourdillon *et al.*, 1948). American workers have largely concentrated on the use of ultraviolet radiation and dust-control so that there is a dearth of information regarding the value of chemical measures of disinfection. An instance of the apparent uselessness of such measures when applied to a limited portion of an individual's aerial environment is provided by McConnell (1949). Triethylene glycol was vaporized into the air-duct of a room housing 500 workers at an Insurance Company's offices, a similar room being kept as a control. No significant difference was obtained in the incidence of minor respiratory illness in those individuals supplied with treated air, but as the bacterial content of the air was also unaffected, it may be doubted whether the technique was really efficacious. The majority of field workers, however, have concentrated on measures to restrict airborne infection during sleep, and studies from the U.S. Army and Navy demand pride of place because of their careful and extensive nature.

The Commission on Acute Respiratory Diseases (1946*a*, *b*) carried out two experiments at Fort Bragg in an effort to evaluate the effect of double-bunking in barracks and also the effect of dust-laying procedures. Double-bunking in the barracks of two platoons of a training battalion was associated in 1943–44 with a significantly lower rate of acute respiratory disease (febrile catarrh) than the normal procedure of housing in single bunks in the barracks of two control platoons. Although an outbreak of influenza A occurred during the period of observation, the troops were then engaged on field manœuvres so that the relative incidence could not be compared. During the winter of 1944–45, oiling of bedding and of floors of barracks, mess halls and recreation halls was carried out in the quarters of certain platoons of four training battalions. The Commission found that there was some reduction in the admission to hospital of cases of respiratory disease in an endemic period but that no advantage was found in the " oiled " group during an epidemic period of acute respiratory disease. No influenza or streptococcal outbreak occurred during the winter. These studies were carried out amongst recruits in whom a high incidence of respiratory disease was to be expected. The dust-laying procedure was certainly effective in reducing the bacterial contamination of the air, and the apparent ineffectiveness of the measures as a whole may have been due to the type of respiratory disease prevalent during the period. This diagnostic differentiation is of great importance in all such field experiments in view of the possibility that streptococcal infections may be controlled by dust-laying measures more readily than those due to viruses. Thus the experiments reported by Anderson, Buchanan and MacPartland (1944) in which a striking difference in respiratory infections during a three-month period in a British Army unit was attributed to oiling of floors, can be criticized because of the absence of diagnostic procedures among those reported ill with respiratory infection and also because of the short period of observation.

Results similar to those obtained at Fort Bragg were obtained by Shechmeister and Greenspan (1947) at a U.S. Naval Training School. During a thirteen-month period the oiling of floors and blankets reduced air contamination and lowered the carrier rate for hæmolytic streptococci. However, no apparent effect was observed on the rate of respiratory disease including catarrhal fever, tonsillitis and pharyngitis and scarlet fever during a period of high incidence, although some slight reduction was seen during a period of low incidence. A more prolonged series of studies also carried out in the U.S. Navy was reported from two Naval Training Stations between 1943 and 1947 (Willmon, Hollaender and Langmuir, 1948; Langmuir, Jarrett and Hollaender, 1948). The major plan of this study was the installation of ultraviolet lamps in the barracks in order to provide an intense radiation of the upper air and of the floors under the bunks and in the aisles. Dust-laying procedures were combined with the radiation in some years. In each of the four years of this study the total admissions to hospitals from respiratory diseases were consistently lower from the radiated groups than from control groups. The degree of reduction was 20 to 25 per cent. However, during an explosive outbreak of influenza A in 1943, the difference in admissions from the radiated and control barracks was insignificant. Also during an outbreak of hæmolytic streptococcal infection, dust-laying measures alone and uncombined with ultraviolet radiation were ineffective in controlling the epidemic.

Although the results of these studies may at first sight seem disappointing and even at variance with each other, some general conclusions appear possible. The first point seems to be that single measures alone are less effective than a combination of measures. Secondly epidemic periods whether of bacterial (streptococcal) or of virus infection appear to resist those measures which have been tried, whereas endemic periods of respiratory illness can definitely be influenced. Thirdly, the methods which have been tried may have failed because they are inefficient in regard to the degree of aerial disinfection which they achieve or because they do not affect the mode of spread which is normally utilized by the acute infections of the respiratory tract. Clearly, the need for continued research in regard to both these possibilities is urgent if any advance is to be made.

Conclusions

The epidemiological background of influenza and other acute virus infections of the respiratory tract is one of great variability. Experience in the past twenty years in this country suggests that, at present, a gradual decline in intensity of outbreaks and of intervening endemic levels is in progress. This has occurred at other periods in the past and, in particular, immediately prior to the pandemic of 1890, and does not therefore indicate a permanently favourable situation.

The mechanism of spread of influenza, though following the general method of airborne infection, is not finally settled. The reservoir of infection may be that of an apparently healthy herd, or by constant chain of transmission by actual cases of the disease from one country to another. Conditions within a group of individuals which favour the development of a particularly intense outbreak of influenza have not yet been defined.

A review of the present status of methods of sterilizing the air, and of diminishing dust contamination suggests that though something can be achieved in regard to a lessening of the level of endemic respiratory tract infection, less success is attained during sharp outbreaks. The reasons for this lack of success are not apparent and further research into fundamental aspects of airborne infection is needed. There is no firm foundation at present for the adoption of particular methods aimed at the control of bacterial or virus contamination of the air or dust unless direct contact infection can also be minimized.

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