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EPIDEMIC AND ENDEMIC INFLUENZA

THE influenza pandemic that followed the war of 1914-18 was the source of a large volume of information, restricted to the clinical and epidemiologic fields, regarding virus diseases in general and influenza in particular. In the interval between that pandemic and the present time, however, the new science of modern virology has emerged. This was to be expected, partly because of continued improvement in virologic and immunologic techniques, and partly because of a decline in importance of general bacteriology, resulting from the development of potent chemical and biological antimicrobial agents. Basically, therefore, the major difference between the post World War I influenza pandemic and that of 1957-58 (Asian influenza) is that modern virologic methods could be used to study the latter, but not the former. The reports of two recent studies[1, 2] are now available to provide us with valuable information about the first influenza pandemic within the era of modern virology. These studies have taken advantage of the unprecedented opportunity that has existed to study the manner in which the new pandemic virus came into balance with its human host. Other extremely pertinent questions also arose and have been answered, namely, "What happens to the virus between epidemics?" and "Is the seeming cyclical disappearance and reappearance of the influenza virus explainable on the basis of extrahuman reservoirs?"

In order to answer these questions, serologic, virologic and clinical studies were carried out as reported by Hayslett *et al.*[1] and Kaye *et al.*[2] The serologic investigations were conducted in two disparate populations in the post-pandemic period, namely a group of Navajo school children in Northeastern Arizona, and a group of medical students in New York City. They included complement-fixation and hemagglutination-inhibition tests, which were used to detect influenza antibody responses; and these were correlated with the occurrence of clinical influenza in the respective groups. From these investigations of two quite separate populations of differing age, environment and geographic location, there has been demonstrated the *continuing occurrence* of serologically proved influenza during the post-pandemic period.

One of two mechanisms must be operative in modifying the situation in such a way that pandemicity gives way to endemicity. These are (a) loss of virulence of the organism and (b) progressive elevation of specific antibody titres in the population by repeated infections. Since loss of virulence would be an unusual state of affairs in virus passage, and since there is evidence that the severity of clinical influenza may be modified by prior specific experience with the virus, it is to be expected that progressive elevation of the titre of specific antibody in the population by repeated infection should result in increasingly less apparent infection or disease. It therefore seems probable that a point will be reached after any influenza pandemic, and apparently has been reached after the 1957-58 pandemic, at which specific immunity is so high that even inapparent multiplication of the virus is virtually curtailed. It now seems that a situation exists with respect to the influenza A2 virus similar to that observed following the post World War I epidemic. This situation is that influenza has become a scattered sporadic disease, or, for that matter, an epidemic one in isolated situations in which a larger dose of virus has been provided as a challenge. From these studies it appears that, between epidemics, the influenza virus "continues to circulate among the human population in endemic fashion producing *infection* which is clinically unrecognizable because it is seldom associated with *disease*". This happy state of affairs has resulted from an increasingly widespread elevation in antibody titre in progressively larger segments of the population, which, in turn, has been the result of endemic infection. This is another way of stating that, as population immunity rises, an increasing proportion of infections become clinically inapparent. It appears unnecessary, therefore, to suggest an extrahuman reservoir of influenza virus in the post-pandemic period. In other words, *the inter-epidemic reservoir of influenza virus is man.*

As distinct from the purely serologic aspect, clinical and virologic studies were carried out in 20 patients with proved influenza who were admitted to a large metropolitan hospital early in 1960, at a time when there was no apparent epidemic of influenza in that city. The cases were carefully studied, and all patients were proved to have influenza caused by the A2 (Asian) virus on the basis of virus isolation or antibody studies or both. Certain interesting items of information soon

became apparent. For example, it was early evident that most patients with influenza but without pulmonary infiltrates were less than 40 years of age and had no underlying disease. In contrast, those with pulmonary complications were older and usually had underlying disease, most commonly cardiopulmonary disease. The disease in these patients showed a wide variation in severity, ranging from mild tracheobronchitis to fatal pneumonia. In some cases, the pneumonia was concomitantly viral and bacterial. It is of great interest that three patients aged 46, 29 and 41 had severe and fatal influenza virus pneumonia, a fact which calls to mind the observation that, during the post World War I pandemic, it was the patient in this age group who suffered the most severely. It was emphasized that six of seven patients with underlying cardiopulmonary disease developed pulmonary infiltrates and that three of these patients became critically ill. This observation throws some doubt on statements concerning the "virulence" or "avirulence" of influenza virus, and it would seem that this feature must be evaluated in relation to the presence or absence of underlying cardiopulmonary disease in the individual patient.

It is now probable that large-scale epidemics caused by influenza A2 virus will probably no longer occur. However, this happy result has nothing to do with the virulence or potential of influenza A2 virus to cause disease. Rather, it is dependent on the development of increasing immunity in the general population. S.J.S.

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THE RUBELLA SYNDROME OF CONGENITAL MALFORMATION

IN RECENT years, as solutions have been found for many of the infections and nutritional problems that affect man in postnatal life, medical interest has been directed increasingly toward the exploration of pathogenic factors acting in prenatal life.

In general, the causes of congenital malformations may be classified as genetic, chromosomal, and environmental.[1] Of the environmental causes, rubella infection is probably the best known means by which a syndrome of congenital malformations may be induced in children. The "rubella syndrome" resulting from maternal infection with rubella consists of malformations of the heart and of the eye (cataracts, retinal disease, congenital glaucoma and microphthalmos), as well as hearing defects, mental retardation and dental defects. Other congenital malformations which have been found to occur following maternal rubella have not as yet been encountered in association with this infection sufficiently frequently to establish a causal relation.

The incidence of congenital malformations following maternal rubella shows wide variation in various reports in the literature. In the original retrospective studies in this field, the reported incidence of defects was about 75% when the maternal rubella occurred during the first four months of pregnancy and about 23% when this infection developed during the last five months. More recent prospective studies have estimated that congenital malformations or defects occurred in 16.9% of liveborn infants of mothers who contracted rubella during the first trimester or in the first 12 weeks of pregnancy, and that fetal death occurred in 16% of such pregnancies. It is likely that the true incidence of defects resulting from pregnancies complicated by rubella lies somewhere between the extremes reported by retrospective studies on the one hand, and prospective studies on the other.

When a mother develops rubella, there is a generalized viremia, and the virus crosses the placental barrier and damages the most actively proliferating embryonic cells, which may lead to arrest of their development or to their death.[2] Thus the nature of the resultant malformation(s) depends on the stage of fetal development at the time of infection.

The most common eye defects attributed to maternal rubella, in descending order of frequency, are congenital cataract, chorioretinitis, microphthalmos, and glaucoma.[3] Rubellar cataracts are bilateral in 75% of cases and these do not differ from other congenital cataracts. The type of cataract produced depends upon the time at which the interference with development occurs, the critical period in development of the lens being from the fourth to the eighth week of gestation. Chorioretinitis is the next most frequent ocular defect due to maternal rubella. This lesion has a peak incidence following infection during the second month, and occurs most commonly in the absence of cataract, or in the opposite eye in cases of uniocular cataract. Congenital glaucoma occurs most frequently following rubella during the fourth and fifth month of gestation, and is due to interference during the development of the iridocorneal (filtration) angle.

In a series of 17 patients admitted to the Children's Hospital in Winnipeg for treatment of congenital malformations, there were 14 in whom a definite diagnosis of maternal rubella during pregnancy was made, two instances in which the mother suffered from fever without rash, and one in which maternal varicella had occurred during pregnancy.[3] The most common defect was cataract, which occurred in 13 of the 17 patients. Retinopathy was noted in four cases, microphthalmos in two, and glaucoma in two. Cataract was bilateral in five cases. Three of the cases of retinitis occurred in the opposite eye in patients with uniocular