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PROBLEMS OF ACUTE RESPIRATORY DISEASE†

FOREWORD

In the period of John Paul's lifetime in medicine, great changes have occurred in the face and philosophy of infectious disease. His work has contributed greatly to those changes. Being of sound and inquisitive mind, itchy foot, and unlimited resources, he has moved through many intellectual and geographic areas in unending pursuit of pathogenic facts and inferences. When he went to Yale in 1928 he joined the stimulating company of Blake and Trask in an association which I, too, had enjoyed. This team of Paul and Trask produced a remarkable combination of bold and meticulous research, bringing clinical, pathological, and microbiological competence to epidemiological studies of poliomyelitis. As Director of the Commission on Neurotropic Virus Diseases for fifteen years, he brought together a splendid group of investigators whose contributions have been legendary. And, of course, studies of hepatitis grew under his art and persuasion.

It has been a rare privilege to have had close and continued association with John Paul over these many years; to watch the determined approach to difficult problems with courageous and imaginative skill. But there have also been many periods to enjoy in a relaxed manner, social, and cultural interests he so expertly developed. It has been a great life whose lively facets will continue to glisten and to gain luster long after the official academic curtain has fallen.

Many forget that John Paul was earlier a student of respiratory disease and its familial distribution. When I first knew him he was, like so many of the modern virologists, a pneumococcus expert. It seems quite fitting, then, to present as a token of respect for his versatile achievements and of personal affection, some remarks on the Problems of Acute Respiratory Disease.

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The oft-repeated statement that the infectious diseases are conquered seems ridiculous when one considers the number of cases and com-

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plexity of acute respiratory disease. The U.S. National Health Survey reports that in the year July 1957-June 1958[1] among the noninstitutionalized population, 36.5 percent of work-loss days, 45 percent of bed-disability days, and 67 percent of school-loss days were caused by acute respiratory disease. It constituted 60 to 66 percent of all acute conditions in every age group. In comparison with 764 million days of bed-disability for all chronic conditions, were 593 million days caused by acute respiratory disease. Although 1957-58 was an epidemic influenza year, data for 1958-59[2] and 1959-60[3] still emphasize the great segment of illness and disability created by acute respiratory disease as measured in total incidence, incidence rates, or bed days.

The burden is especially heavy during the developmental period of life. Since we have a "younging" population, with an estimated 40 percent under 20 years of age by 1970, it is clear that the bulk of respiratory disease looms progressively larger. The vigorous, productive years are also repeatedly disrupted. The work-loss from acute respiratory disease in 1957-58 was 219 million days; in 1958-59, 190 million, in comparison with 226 million work days lost from circulatory, digestive, and arthritic diseases and impairments from injury or other origin. These urchins of frequent, repetitive respiratory illnesses clearly take a formidable toll. On the basis of general experience and comparison of mortality rates from respiratory disease, it seems evident that the situation is no less prominent in other nations and regions where other infections and nutritional inadequacies present additional serious loads.

The size of the problem is compounded by the multiplicity and heterogeneity of the etiological agents: bacterial, viral, fungal, and others. This complexity was early postulated on epidemiologic and immunological grounds, but the actual identification of numerous serologic types among pneumococci and other bacteria prepared investigators for a similar pattern among the respiratory viruses. It developed rapidly with recognition of the influenza viruses, the adenoviruses, the hemadsorption viruses, some enteroviruses, some not yet clearly classified, reoviruses, or a group which the British Salisbury team suggests may be sufficiently different and characteristic to classify separately.

The response to infection varies widely from the inapparent, the afebrile with respiratory symptoms, and the mild febrile illness to severe and pneumonic disease. Variation occurs also with age, season, experience, strain, or special conditions such as institutional or military life. Therefore, a great bulk of the illness is more an epidemiologic syndrome than distinct clinical syndromes readily associated with specific etiological agents. The

popular diagnosis of "a virus" is thus fairly precise. Nevertheless, some of the agents tend to incite a certain set of clinical signs with greater regularity than others so that within these limits of clarity an etiological relationship may be suspected.

INFLUENZA VIRUS STRAINS

Generally, clinical influenza is recognized in epidemics occurring at relatively short intervals. They are most frequently associated with type A virus. For a decade or so strains of a closely related antigenic character spread about the world in large and small prevalences so as to give a high level of immunity. A popular thesis held that these recurrences were the result of a directional alteration by which the successive strains were progressively discarding the characteristic antigen of the previous year and picking up entirely new constitutive antigens. The evidence does not appear in keeping with that idea.

Rather, the strains of a period appear to comprise a group or family with close similarities, but varying quantitatively in a random fashion about a central pattern. This hypothesis, which seems in accord with the cumulative information, is that the virus comprises a large number of demonstrable antigenic components which may, by rearrangement, develop phenotypic alterations about the prototype. They do not represent progressive recessions from the initial strain becoming increasingly remote with the passage of time.[4]

Nevertheless, at intervals of 10 years or so, we have witnessed the appearance of major variants whose dominant antigen is relatively new to most of the human population. They are the Asian variant of type A (1957), the A′ (1947), the initial A (PR8-WS 1933-34), and the swine influenza virus. That they are not entirely novel is indicated by the reduced incidence of the disease in the older segments of the population, by the demonstration of antibody in serum of the adult population before the recognized appearance of the strain, as in 1947 and 1957; and by the appearance of antibody to swine virus, in convalescent children for example, at a time when the virus as such is not demonstratably prevalent. Each of these features tends to emphasize the expression of common antigens existent in various strains.[5]

The pattern of antibody response appears in infancy and childhood to be largely directed against the dominant antigen of the prevalent virus family. With successive exposure that antibody is steadily reinforced by the stimulus of similar, though secondary, antigens of infecting strains so that it persists at high levels and constitutes the antibody characteristic of that

cohort throughout life. In the meantime, antibody to other constituent antigens is also acquired and a broad resistance, less influenced by strain characteristics, is thus developed.[6]

What are the mechanisms by which these major sports come into general circulation? It has been suggested that they arise in many parts of the world simultaneously rather than spreading from area to area by transfer. It seems quite unlikely that, with the numerous arrangements possible, one combination would erupt spontaneously in such a diffuse manner. The evidence of spread from place to place has been so clearly charted repeatedly, especially in 1957, that little doubt remains of this fact. Moreover, the antibody pattern of the population in widely separate regions is much the same in a given period of time, indicating that most strains do become disseminated throughout the world whether associated with recognized large pandemics or not.

What are the other possibilities? Dr. Richard E. Shope has long been interested in the possibility that a masked form of virus persists and can be activated by varied, provoking stresses.[7,8] Our knowledge would require that there be a malleable viral nucleus which can be activiated to yield various antigenic patterns rather than a relighting of the same old virus. I do not think this too difficult to visualize as a biological phenomenon, and it could occur in man or in other species.

But there is an alternative proposal: The virus maintains an essentially fixed character in another host and will reenter the human population when conditions are favorable. The swine virus of the United States is an example. The same idea has been expressed by Mulder[9] about the 1957 Asian strain—that it has been resident among swine in Asia, maintaining its antigenic composition over many years, before reappearing in the human population. We agree that a virus with a similar dominant antigen was prevalent in the 1889-90 period and that the antibodies to this antigen found in older people before 1957 refer to their childhood experience with a similar strain. But if animal sources of fixed strains are the common basis for human epidemic or pandemic recurrences, then certainly this reservoir has yet to be demonstrated. The recent identification of strains from horses and ducks has not led to serological recognition of their dissemination in man; nor have the animal surveys since 1957 led to any significant evidence of distribution of the 1957 virus in various animal species. Zhdanov[10] has suggested that the animal strains are old human strains which have become so established in those hosts as to represent errant dead end kids. In the gospel of St. Matthew it tells of the casting of devils into swine; that was probably influenza. But we are dealing in these respects

with only secular revelations, and the entire subject must be kept under critical scrutiny.

On the other hand animal diseases, even respiratory infections, are not frequently transmitted from man to man. (Perhaps pneumonic plague is an exception.) The rapid variation in influenza stains suggests *rapid* transfer. The widespread rapid distribution of the numerous influenza mutants emphasizes the active role of human agencies. But even sharp antigenic variation is not necessarily associated with increased virulence or epidemic dispersibility. In fact, these two characteristics are to a large extent independent variables. We have recorded the shift with years in the age distribution of antibody in the human population to the various type A families and believe that this altering base of immunity is an important factor in selection and dissemination of the major influenza variants. Since the breadth of antibody is dependent upon experience with strains of varied composition, inexperienced children exhibit the highest incidence of infection by any or all strains, and also most limited reflection of viral antigens. With the passage of time antibody to succeeding dominants is acquired, but large gaps develop in the immunity of the community to viral antigens which prevailed when the older segments of the population were young. These gaps invite a rearrangement of viral antigens to enter the population and provide the opportunity for rapid passage and development of epidemic potency. Thus, a resurgence of older or suppressed antigens occurs to complete a cycle of antigenic repression and renewal.

Such a variant may arise in any region, and if transfer to other susceptibles is furthered by crowded conditions, it may increase its epidemic potential, possibly its virulence, and proceed on its adventurous path. I believe that the 1957 strains are notable support for this hypothesis and that a swinelike strain can be expected one of these days. That the antigens for this remodeling are still available in current strains has been already indicated in data from the virus laboratory at the University of Michigan.[11] Maassab obtained indications that fresh glacial acetic extracts of Asian strain induced antibody in mice which cross reacted with PR8 and swine strains, while whole virus did not. Berlin and Minuse both showed that hyperimmunization with the Asian strain gave cross protection against the PR301 strain of 1954. Davenport and Hennessy have recently shown that immunization of rabbits with ether-purified HA fractions of the PR8 strain induced cross titers to FM-1 and swine strains while the intact virus did not. Mulder[9], and Lief and Henle[12] have brought additional evidence of the common antigens in Asian virus and earlier A strains. It is on this basis

that our concepts of control and prevention by vaccination have been developed.

OTHER RESPIRATORY AGENTS

While influenza represents the most consistent and prominent cause of general epidemics it is also apparent that the large body of day-by-day respiratory infections is of other etiology. The institutional studies of Huebner, Bell, Chanock, and co-workers[18] have sharply emphasized the steady smog of respiratory infection which constitutes the child's garden of viruses. Again, they are commonly clinical nondescripts, epidemiologically obscure, and even identification of a viral or bacterial agent is at times of doubtful etiological significance. Nevertheless, certain patterns have emerged in distinct form.

One of the most interesting variations is the behavior of the adenoviruses. Originally recognized as unsuspected residents of tonsillar tissue, they have become increasingly notable as agents of sustained epidemics in military recruits, especially types 4 and 7.[14] They may account for as much as 80 percent of the febrile respiratory illness in those populations but, surprisingly, are ordinarily of small moment among college populations of similar age. It is possible that in recruit populations a minor infection is accentuated by the concentration and constant renewal of susceptibles under unusual physiological stress to a position of exaggerated clinical severity. Theoretically, one would like to postulate the provocation of a latent virus under these conditions. Serologic evidence indicates, however, that recruits do not arrive with a latent infection but acquire it during the period of intensive basic training.

Seasoned troops remain essentially immune. It appears, then, that the viruses remain in the camp, reaching steadily for the new arrivals, and are therefore a place infection. Among children Bell and co-workers[18] have noted the apparent reactivation or reappearance of virus in the same individuals at sporadic intervaals for months after the initial infection. Moreover, there are indications that the reappearance is more common in the winter than in the summer months. This type of intermittent excretion may well be the source for continued infection among recruits.

Certain aspects of the human situation are appearing also among adenovirus infections being recognized in calves, pigs, and chickens. There are many intriguing possibilities in this finding. But the hopeful fact is that inactive adenovirus vaccines containing the commonly involved types have been repeatedly shown to be highly effective. Certain studies have demon-

strated that combined influenza and adenovirus vaccine is highly effective against both sets of viral respiratory disease.

The types prevalent among children and civilian adolescents are ordinarily different from the military, and often illness or antibodies develop without clear evidence of onset. It seems likely, as with pneumococci or streptococci, that different types form groups of different significance.

I shall not pursue further the etiogolical analysis of acute viral respiratory disease except to emphasize again the complexity and multiplicity of the agents. It is important to recall however, that bacterial agents continue to play an important role in acute respiratory disease, especially with respect to mortality. Influenza and pneumonia, mostly bacterial, are still the great killers of infants and a progressive threat to those over 45 years old. More than 350,000 cases of "streptococcal sore throat" were reported in the United States in 1960. In Michigan 9,300 cases of scarlet fever and 1,700 cases of rheumatic fever were reported in 1960. The roles of hemophilus influenza and pneumococcus are still of major consequence.

PREVENTIVE MEASURES

With this array of participating agents, what control or preventive measures can be visualized?

1. I believe that there still remains a hope for hygienic barriers compatible with normal social activity. Our inadequacy cannot seem much greater than that of the fecal hygienist of a century or so ago. If essential extrahuman reserviors exist, as with tuberculosis or brucellosis, efforts can be directed toward their suppression.

2. The progressive knowledge of antigens, antibodies, and immunity continues to direct attention to specific preventive immunization. Vaccination against epidemic influenza can be effective if properly used, with preparations combining the proper types and strains. The evidence exists as well for certain adenoviruses. Is it, then, necessary to assume that each and every one of the agents must be used in vaccines to give the total effect required? I do not know. It may be, as I think has been the case in enterovirus outbreaks, that the suppression of certain agents paves the way for a buildup of others.

On the other hand, rapidly increasing knowledge points to the sameness in structure and basic pathogenesis among many of these agents. It has been easy to visualize and demonstrate the feasibility of compounding vaccines with numerous components and various agents. This practice is enhanced by the use of adjuvants so that small amounts of purified antigens can be immunologically effective and multiple antigens can be employed. They can

be more potent as primary immunizers and boosters, and their effects can be sustained at higher levels for longer periods. At the moment this is the best outlook for specific immunization. But advances in the knowledge of virus transformation, recombination, and genetic determinants may provide simpler methods for compiling a basic immunizing unit of many potentials from essential chemical components.

3. Some form of enhanced general resistance of high efficiency has been considered for a long time. There is little doubt in my mind that much of the decline in mortality from certain diseases, such as scarlet fever, before antibiotics was the result of increased protection in childhood with consequent effects on the vigor of physiological resistance. One day the many splinters may be molded into a functional system which can be modified intelligently. Complement, opsonins, phagocytosis, clonal selection of cells or their stimulation, and properdin, all indicate the possibilities. New agents and new adaptation might well break through these basic mechanisms. A broad refractoriness such as occurs in cellular repair, or the recently discovered interferon, point in other directions. Interference with infection or epidemics (Sydenham) may be developed with attenuated viruses. But I believe that, of itself, this approach provides only a first line of defense.

4. Finally, in my opinion, the most likely resources at present are related to chemoprophylaxis and therapy. The data from our laboratory alone have shown the feasibility of protecting against experimental disease, such as paralytic poliomyelitis in monkeys. The rapidly advancing knowledge at the molecular, cellular, and organic levels of the mechanisms of viral development and infection can be expected to reveal common factors or reactions susceptible to chemical alteration. Consequently, the hope is to override the restrictions of multiple immunological types just as is true in chemoprophylactic control of pneumococci, streptococci, and others, in which the prophylactic effects have been clearly demonstrated by reduction of mortality and disease incidence. Our studies[15–17] are clearly pointing out the way in which drugs may differentiate the significance of RNA and DNA in viral development and exert specific influences on the RNA and DNA viruses.

The problem is still great; the need for new ideas, persistent optimism, and bold undertakings is even greater.

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