

Implications of Recent Viral Studies

By ROBERT J. HUEBNER, M.D.

SOON AFTER the bacterial causes of respiratory illnesses were delineated, it was noted that certain filterable viruses also caused such diseases. When the viruses of influenza, psittacosis, and Q fever finally became known a few years ago, it seemed that the rest of the respiratory disease problem would be solved without difficulty. Only three more agents, the viral causes of the "common cold," of acute respiratory disease (febrile catarrh), and of primary atypical pneumonia remained to be found.

However, the number of viruses that might be involved was not realized. Indeed, quite recently, River's textbook, *Viral and Rickettsial Infections of Man*, listed only about 60 viral agents. Today, only a few years later, with the widespread application of new techniques now available in virology, more than 65 additional, newly recognized viruses have been demonstrated in man. One would be justified, therefore, in thinking that we now know much more about the viral causes of respiratory disease. True, we do know a little more. But while isolating viruses is no longer so difficult, the eventual solution of the problem of respiratory disease is more complex.

The "new" viruses are found with great frequency in the upper part of the respiratory tract and in the enteric tract. They have been

called "viruses in search of disease." Most of them are lumped under arbitrarily selected family designations such as Coxsackie, ECHO, and adenoviruses (APC-RI viruses); in addition, there are viruses such as the Sendai virus from Japan, various exanthema viruses including those reported by Neva and Rake, the virus of cytomegalic inclusion disease, and many other completely unclassified agents.

The discovery of these new agents has led to considerable progress in the etiological delineation of a number of common illnesses. It is well established that 6 to 8 of the group A Coxsackie viruses cause herpangina, a specific and very common upper respiratory disease of children with fever and other systemic involvement. Group B Coxsackie viruses have been shown to cause not only epidemic pleurodynia, but also nonbacterial meningitis, which until recently was probably most often diagnosed as nonparalytic poliomyelitis. Some of the viruses in the ECHO group, particularly type 6, have also been incriminated in the etiology of nonbacterial meningitis. The recently discovered adenoviruses cause febrile respiratory and ocular illnesses. Acute respiratory disease (ARD) of military recruits is known to be caused by at least three adenovirus serotypes. Other serotypes cause a newly described illness, pharyngoconjunctival fever (Greeley's disease), and still other types have been incriminated in the etiology of simple febrile pharyngitis and simple conjunctivitis. One type has been shown to be regularly associated with epidemic keratoconjunctivitis.

Polyvalent Vaccines

One of the more obvious opportunities provided by the easy demonstration and cultiva-

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tion of so many new viruses is the preparation of effective prophylactic vaccines for the prevention of some of the very common nonfatal illnesses. Last year, our group at the National Institute of Allergy and Infectious Diseases, Public Health Service, reported a successful test of an adenovirus vaccine in which we were able to show good protection of vaccinated volunteers against experimentally induced attacks of pharyngoconjunctival fever.

At the present time Dr. Joseph Bell and I, in cooperation with U. S. Navy Medical Research Unit No. 4, are engaged in field trials of a commercially produced polyvalent vaccine containing adenoviruses types 3, 4, and 7. These studies are being carried out at the Great Lakes Naval Training Station, Great Lakes, Ill., and will eventually embrace observations on some 16,000 military recruits. Preliminary analysis of data now available show that in the vaccinated recruits there is at least a 50 percent reduction from expected rates of acute respiratory disease. These results are encouraging, not only because it may now be possible to prevent some of the more severe respiratory viral diseases, but also because they suggest that similar vaccines can be made, if it proves desirable, against representatives of the other new groups of agents, such as Coxsackie, ECHO, and exanthema viruses.

What bearing do these new developments have on the total problem of acute respiratory disease? Unfortunately, despite the notable progress in finding the etiological agents of respiratory diseases, the cause of most of them must apparently still be found, particularly the causes of those generally termed "common cold."

Of course, a good deal depends on what is meant by "common cold." To begin with, it is not the only term in popular use. "Virus X" has some obscure yet special meaning to some lay groups. Physicians in many areas use the terms "virus infection" or "virus" to characterize essentially unexplainable illnesses. It seems only a matter of time before a new virus, known as "virus X²" will emerge.

In my opinion, the term "common cold" requires considerable analysis. Recent work with volunteers has convinced some of us that a large number of so-called common colds are

not due to viruses but to other factors, not the least of which are of psychosomatic origin. The nasopharyngeal symptoms of the common cold have occurred in a high proportion of volunteers, whether or not they received virus-containing or virus-free materials. Evaluation of some of these volunteers showed in psychological tests a rather significant association of high gullibility scores with complaints of upper respiratory illness. Although more work will be necessary to put these observations on a solid basis, our findings in numerous volunteer studies indicate that susceptibility to suggestion represents a more powerful inciter of "runny" noses than any virus which we have as yet discovered.

Well-controlled evaluations of the prophylactic value of common cold vaccines and the therapeutic effects of antihistamines have shown that innocuous control materials have remarkable effects in the apparent prevention and cure of colds. More significant perhaps than the fact that these control materials seemed to perform quite as well as the presumably active materials being tested was the fact that 50 percent or more of persons receiving simple saline vaccines and sugar pills in double-blind studies regularly reported prevention, modification, or cure of colds by these innocuous substances.

Loosli's recent studies of the occurrence of common colds in industry showed that a comparatively small number of industrial workers contributed most of the absenteeism attributable to common colds. It is difficult for a virologist to conceive of viruses behaving in so illogical a manner. I might add, as the father of 8 children, 6 of whom are in school, that I cannot escape the feeling that there is very definite association of "colds" with Monday mornings. It is difficult to think of even "virus X" as causing these Monday morning episodes. Perhaps there is a "Monday morning" virus. However, I think the Victorians had a better word for it. The expression "she is indisposed" occurs time and time again in Victorian literature. It is possible, of course, that occasionally this truly represented a "viral indisposition," but I wonder whether such a virus could be grown even with modern tissue cultures or that present or future miracle drugs could cure it.

Bacterial Allergies

Of course, in addition to these rather unsubstantial ailments, there is a definite problem of specific microbial disease of nasal and pharyngeal areas, much of which is the consequence of acute infection. Here, again, it is pertinent to ask how much of recurrent respiratory illness might be due to bacterial allergies. Another hypothesis which possibly should be given more consideration is that some of the latent viruses, such as adenoviruses, persisting in the tissues of most respiratory tracts may become activated by undetermined factors and cause recurrent inflammation of the mucous membranes in those areas.

As in the case of recurrent herpes infection, such hypothetical occurrences might be expected to result in less severe illnesses than those produced by the primary infection. We have hesitated to suggest that reactivation of the adenovirus agents, demonstrably present in the nasopharyngeal passages of most persons, might represent a possible cause of common colds, since in most of those from whom such agents are recovered during afebrile illness there is generally no increase in adenovirus antibodies.

However, recurrent herpes virus infections also are not followed by any measurable antibody response. In view of the fact that adenoviruses have been isolated on several occasions from the respiratory secretions of persons with afebrile respiratory illnesses or typical common colds, the hypothesis that colds may be due to reactivation of these agents may possibly have been discarded too readily. After all, the activation of latent agents is not a rare or unknown phenomenon. The psittacosis virus in its natural host may be regarded as an agent essentially latent with the capacity of being activated at intervals. It is precisely during these exacerbations of infection and illness that birds become an important source of infection to other birds and to man.

"Unmasking" Viruses

The notable progress in the definition of acute viral diseases through application of new virological techniques is sure to be followed by more intensive application of these techniques. The development of even better ones offers

promise of further progress in the study of the varied causes of acute and chronic human disease. It seems inevitable, as new and different tissues are introduced and utilized in tissue culture, that many more viral agents will be encountered. The long-term culture of normal or abnormal tissues, which is essentially a simple, if newly applied, technique for isolating viruses, may possibly turn out to be of even greater importance.

Several years ago, Dr. Wallace P. Rowe and I described viruses emerging from the epithelial cell outgrowths of human adenoids. These agents, which had a special tropism for human epithelial cells, were the first representatives of the adenovirus family of viruses to be recognized; they were found in the epithelial cells of most adenoids and tonsils, generally after 18 to 30 days of continuous culture of the original cells. They could not be demonstrated in such tissues by conventional methods of virus isolation. Serotypes 1, 2, and 5, the most commonly encountered, were subsequently shown to be acquired most often in early childhood, yet they are unmasked from the adenoids of older children and adults quite as readily as from those of infants. There is little question that following primary infection these viruses become latent or chronically infecting particles. More recently, we also succeeded in unmasking the salivary gland virus, the cause of cytomegalic inclusion disease, from the fibroblastic outgrowth of adenoids.

This agent, which was only recently first isolated in tissue culture by Dr. Margaret Smith, has long been a collector's item among pathologists who specialize in recognizing its existence in fixed tissue taken at autopsy. Subsequently, our research group and Dr. Thomas Weller at Harvard also demonstrated the agent in adenoid tissues, in biopsy of liver tissue, and from the urine of living persons, some with evidence of cytomegalic inclusion disease.

With the development of serologic techniques for studying this agent, it now appears that the salivary gland virus is a widespread infectious agent in man, approaching almost total infection in older age groups. We have also occasionally picked up herpes virus in tissue cultures of adenoid cells, and it is noteworthy that we succeeded in isolating three separate viruses,

an adenovirus, the salivary gland virus, and the herpes virus from the epithelial and fibroblastic outgrowth of the adenoid of one person.

The recent report that many different viruses have been isolated from monkey renal tissues which had been used in the production of poliomyelitis vaccine represents another interesting example of the "unmasking" of viruses from cells. The many ideas implicit in new information of this sort cannot be developed here. Perhaps the most important point is that whole areas of acute and chronic human disease, unexplained except that they are assumed to be noninfectious in origin, must be reexamined in the light of the new concepts concerning the nature and consequences of viral infections.

The simple fact that from two tissues, the human adenoid of man and the kidney of the monkey, 25 or more immunologically distinct viruses have been unmasked, supports the con-

cept that the human cell itself must be regarded as having a considerable viral flora. Should this concept, which of course is not new to those working with bacterial and plant viruses, prove to be true, it cannot fail to have tremendous influence upon future investigations into the cause of human disease, regardless of its apparent lack of connection with microbial infection. For instance, a virologist can hardly conceive how human cells could remain uninfluenced by the viruses growing within them, and, furthermore, how such experiences could fail to be an important factor in the malfunction and erosion of cells which the clinician calls "degenerative or chronic disease."

It seems to me only a matter of time until the clinician and virologist find themselves collaborating not only in an effort to cure sick cells but also in attempting to prevent such occurrence.

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