CLINICAL CONFERENCE

Infections Due to Adenoviruses

By Heinz F. Eichenwald, M.D.
Department of Pediatrics, New York Hospital-Cornell Medical Center

DR. MOORE (Resident): E.P., a male born of Greek parentage, was 6 weeks of age at the time of his first admission to the New York Hospital. He had been well until 8 days prior to admission when he began to sneeze frequently, and his eyes began to water and his cry became hoarse. On the following day the family physician made a diagnosis of croup and prescribed tetracycline, 50 mg every 6 hours, nose drops, cough syrup and syrup of ipecac. Six days before admission an intermittent cough was noted. The patient's condition remained essentially unchanged until 2 days prior to admission when he became febrile, anorectic and developed a paroxysmal type of cough which occasionally terminated in vomiting. At this time penicillin, intramuscularly, was added to the regimen. He was admitted to the New York Hospital with the diagnosis of pneumonia.

The past history, family history and review of systems were noncontributory.

Physical examination revealed a well-nourished, white male with no evidence of respiratory distress. Rectal temperature was 39.3°C, apical pulse rate was 150/mm, respirations were 30/mm. There was no retraction or cyanosis. Examination of the ears was normal. There was a grayish-white, plaque-like, exudative lesion over the left lateral aspect of the soft palate. The pharynx was injected. Shotty lymphadenopathy was present in the cervical chains bilaterally. There was a sinus tachycardia with no cardiac murmurs audible. The lungs were clear to percussion and auscultation. The liver was palpable 1 to 2 cm below the costal margin. The spleen and kidneys were not palpable. The remainder of the examination was not remarkable.

Laboratory studies revealed the following: Urinalysis, normal; hemoglobin, 13.5 gm/100 ml; leukocyte count, 20,000/mm³, with 62% lymphocytes, 1% monocytes, 1% eosinophils and 36% polymorphonuclear leukocytes. Culture of the throat grew out N. sicca and an achromobacterium. Roentgenogram of the chest revealed increased bronchovascular markings bilaterally. Tuberculin test (O.T. 1:1000) was negative. Adenovirus, type 3, was cultured from the throat and appropriate serologic studies performed on acute and convalescent sera revealed a significant rise in titer against this virus.

Attempted oral feeding of a clear-liquid diet resulted in paroxysms of coughing. Therefore a nasogastric tube was inserted and the patient fed in this manner for a period of 5 days. Procaine penicillin, 150,000 units intramuscularly every 12 hours, was given. During this time the patient's cry continued to be hoarse and exudative lesions developed over the tip of the tongue. He became afebrile the day following admission and was able to take oral feedings without incident on the sixth hospital day. The remainder of the hospital course was uneventful and he was discharged after 12 days.

Of considerable interest to us was the development of a similar illness in three nurses who cared for this patient during the first 3 days of hospitalization. Adenovirus, type 3, was isolated from their throats, and significant rises in specific antibodies in their sera were also observed.

DR. EICHENWALD: This patient has been presented in part for historical interest: this was the first proven case of adenovirus infection in the New York Hospital. There have been many others since that time.

The patient's course was also instructive to us. We were surprised at the high degree of contagion which was demonstrated by the subsequent illness of three out of five nurses who had handled the baby during the initial days of hospitalization. Adenovirus, type 3, was isolated from their throats, and significant rises in specific antibodies in their sera were also observed.

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plained of a low-grade fever, a severe, mildly productive cough, and was diagnosed as having "acute bronchitis." Virus was isolated from all three nurses.

Throat swabs were also obtained from all other nurses working on the ward at the time; in one adenovirus, type 3, was demonstrated in the throat and antibodies developed in the serum, but despite close follow-up she never developed any recognizable clinical illness.

We learned from this small outbreak that the same type adenovirus, and even the same strain, can apparently produce a variety of different clinical manifestations. The agent in this instance was associated with laryngitis and bronchitis in an adult, a grippe-like illness in an infant, a grippe-like illness in an adult, bronchitis with fever in another, pharyngitis, conjunctivitis and fever in a third, and no disease in the fourth.

A discussion of the newly isolated viral agents inhabiting the respiratory tract, including the adenoviruses and others not yet appropriately named, seems pertinent at this juncture. Most of you are familiar with the basic work on the adenoviruses of Drs. Huebner, Hilleman and others. Certain points, however, are worthy of emphasis.

The adenoviruses, also termed APC, ARD and RI agents, comprise a rather well-defined, biologically quite closely related group. At present, 13 human types have been described which differ chiefly in their antigenic components. All possess a common complement-fixing antigen; thus the complement-fixation test cannot be used to differentiate them. They can, however, be separated into their respective types by means of neutralization tests carried out in tissue culture—a technique which is not easy.

Although these agents show close biologic relationships, one must avoid generalizations about the clinical effects of the entire group. Each serologic type has pathogenic potential of its own.

The problem of incriminating any newly discovered, commonly occurring agent in the pathogenesis of certain defined clinical syndromes is much more difficult than might appear at first. One or more viruses is present almost constantly in the nasopharynx of normal, well children. It is obvious, therefore, that the simple association of a virus with an illness does not necessarily establish an etiologic role for that virus, or for a bacterium similarly isolated. For example, we would not incriminate a coliform bacillus as the cause of viral hepatitis simply because the organism is present in the stool of practically every patient having this disease. That one must be similarly cautious with viruses cannot be emphasized too strongly.

One fact is gradually becoming increasingly apparent: Just as there is a normal bacterial flora, there may be a normal viral flora, not only in the nasopharynx but even within cells of the deeper structures of the body. Perhaps some of these agents can undergo change from a resting or inactive phase to a destructive phase, if some alteration in the host cell occurs. Herpes simplex, for example, follows this pattern. The infection is apparently acquired in childhood, and the host may continue to harbor the virus for the rest of his life. A variety of different stimuli affecting the host will set off multiplication of the agent, resulting in classical "fever blisters." As the virus becomes inactive again, the blisters heal, only to recur weeks, months or even years later.

Perhaps more pertinent to our discussion of the complex interrelationship of host and parasite is an observation made by us as well as other investigators. We studied a group of preschool children who had close and daily contact with each other. An accurate health record for each child was kept, and this was correlated with the results of weekly throat-swab examinations, using bacteriologic and virologic techniques. The expected outbreaks of respiratory infection could usually be correlated with the appearance of one or another respiratory virus in the members of the study group. Occasionally, however, all members of the group were exceptionally healthy—without rhinitis, cough, or otitis—despite the appearance of one or another virus type in the throat of every child. Here then is an agent which Dr. Huebner has facetiously called "the virus of good health." If we were to produce a vaccine against it, we would theoretically be protecting the children against good health, and they would be ill all the time. An understanding of these theoretical considerations is necessary for a proper interpretation of virologic data.

Now to return to the adenoviruses. You will recall that types 1 and 2 usually produce respiratory infections in children under 5 years old.

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of age. Most commonly, they cause a rather mild, febrile infection of the upper respiratory tract associated with pharyngitis and rhinitis. However, in the past year we have accumulated evidence showing that under certain conditions these two types, along with type 3, may descend below the level of the larynx and cause the clinical syndrome commonly called bronchiolitis, and on occasion laryngotracheobronchitis. This latter syndrome is apparently more often caused by an entirely different respiratory infectious agent, not related to the adenoviruses.

A virus commonly associated with laryngotracheobronchitis was isolated independently in Cincinnati, in Toronto and in the New York Hospital, and thus far only one distinct type has been identified, although more may exist. This virus, too, follows a rather common pattern. It can cause a whole spectrum of disease, from a barely noticeable catarrh to a severe and fulminant illness.

It has been generally believed that laryngotracheobronchitis and the related diseases have a bacterial etiology, chiefly H. influenzae, type B, but also, on occasion, other bacteria. Some investigators have never accepted this idea and have expressed the view that the cause was viral in nature. These two opinions are not as contradictory as might be supposed. The classic example of swine influenza may be cited as an illustration; in this condition a virus and a bacterium combine their activities to produce a disease.

Another familiar example, although undoubtedly not a very good one, may be taken from the highly fatal influenza pandemics of 1918. Here an influenza virus and the bacterium H. influenza coexisted with sufficient frequency in severe cases that data obtained by available microbiologic tools were often interpreted to indicate that the bacterium rather than the virus was the cause of influenza. Similarly, in laryngotracheobronchitis and associated diseases, only the bacterial agents could be isolated until the sensitive technique of tissue culture became available.

It seems likely that in some diseases of the respiratory tract the action of both viral and bacterial agents is necessary for the typical disease picture to appear. The virus initiates the inflammation of the respiratory passages, preparing a fertile field for bacterial invasion. Any one of a number of different bacterial species can act as secondary invaders.

A good example of bacterial-viral interrelationship exists in an interesting and irritating condition which might be termed the "stuffy-nose syndrome" of premature infants. All of us have probably seen these small infants with stuffed up and runny noses which persist for a week or more. Some of our recent work indicates that this condition may be caused by a virus and a hemolytic staphylococcus aureus working together. We have seen healthy infants with either the virus or the bacterium in the nasopharynx, but when both are present simultaneously in the same infant, a "stuffy" nose is noted.

Finally, the importance to the practitioner of the demonstration of the existence of the new respiratory viruses might be considered. At the present time, all this information is probably chiefly of academic interest. It does not really influence the practitioner's approach to respiratory illness. There is now proof that a majority of respiratory infections are primarily viral in nature, which many people have long suspected.

The diagnostic techniques of respiratory virology are too cumbersome and slow to permit ready application to every-day practice. The patient presented today was treated with tetracycline and with penicillin. The discovery of a viral etiology of the patient's infection required almost 3 weeks—to late to be of any assistance in the management of the acute illness. Eventually detailed studies of viruses will permit us to delineate more clearly the role these agents play in disease, with the hope that once this problem has been adequately defined, specific vaccines can be prepared and used intelligently.

Apart from these long-range practical and public health goals, the study of these respiratory agents gives us a fascinating example of the relationship of man to microbes, and of the microbes to each other.

**Dr. Levine:** This is the first time that I have heard of the "stuffy-nose syndrome" in premature and young infants being due to a symbiosis between a virus and hemolytic staphylococcus. Are there any questions?

**Question:** Is the leukocyte count low in adenoviral infections?

**Dr. Eichenwald:** The leukocyte count is often normal, but in approximately 30% of the cases, the leukocytes may range from 15,000 to 25,000/mm³ manifesting even a shift to the
left despite the presence of an adenoviral infection. Perhaps this is due to secondary bacterial invasion.

**Question:** Other than specific vaccines, do you have any suggestions as to therapy?

**Dr. Eichenwald:** These agents are extremely small. They are biochemically, perhaps, similar to the polioviruses. No antibiotic agents at the present time have any effect on them, and only potent enzyme poisons will inhibit their multiplication inside of cells. If secondary bacterial invasion is not present, all one can do is to provide relief from symptoms with fluids, acetylsalicylic acid, and other time-honored remedies.

**Question:** Is it possible to make a differential diagnosis at the time of the initial examination, before treatment is started?

**Dr. Levine:** In other words, have you studied enough patients so that you can suspect a viral disease, as opposed to a bacterial disease?

**Dr. Eichenwald:** Usually I cannot differentiate them.

**Question:** Is there a permanent immunity to an individual strain of a specific species of these viruses?

**Dr. Eichenwald:** The immunity is long-lasting. How long is not known. It is probably in the range of 5 years or more. It may be permanent, but the information is not available to give a complete answer on that point.

**Dr. Levine:** Recurrent upper respiratory infections are therefore due to different strains of viruses.

**Question:** Does a viremia occur, and have these virus groups ever been implicated in viral infections of the central nervous system?

**Dr. Eichenwald:** Virus was isolated directly from the blood of one of the nurses mentioned earlier in the discussion, on one occasion. There have been informal reports suggesting that some of the adenoviral agents have caused clinical manifestations of encephalitis. However, strict criteria for implicating these agents have not been applied and I think we shall have to wait before a definite statement can be made.
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