Panel Urges Wide Use of Antiviral Drug

NIH group says amantadine should be used for both prevention and therapy of influenza A in the next epidemic

A minor victory was achieved last month by advocates of antiviral chemotherapy when a consensus development conference sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) recommended that the drug amantadine hydrochloride be used for both prevention and therapy of all types of influenza A. This recommendation marked the first time that widespread use of an antiviral agent has been advocated by any quasigovernmental body and, as such, may mark significant progress toward more general acceptance of the concept of antiviral chemotherapy. The decision may also have finally put to rest nearly 20 years of dispute about the efficacy of this drug.

The antiviral properties of amantadine (which is marketed under the trade name Symmetrel by E. I. du Pont de Nemours & Company) were first reported in 1963 by George Gee Jackson and his colleagues at the University of Illinois Hospital in Chicago. They found that daily ingestion of the drug inhibited the infection of volunteers inoculated with the then prevalent Asian (H2N2) strain of influenza A. Subsequent clinical trials demonstrated that the drug produced as much as a 70 percent reduction in clinical illness from influenza A and, in 1966, the Food and Drug Administration (FDA) approved the use of amantadine for prevention of respiratory infections caused by Asian (H2N2) influenza A. By that time, though, the so-called Asian flu was only a laboratory artifact.

Influenza A is unique among the major disease-producing viruses in the ease with which it can undergo changes in the two major glycoproteins, hemaglutinin and neuraminidase, that reside on the viral surface and permit recognition by the immunological system of the host. A change in either or both of the antigens permits the virus to infect an organism that has developed immunity to influenza A by producing antibodies against the original antigens. It is this capacity of influenza A to undergo antigenic shifts that leads to periodic pandemics and that necessitates production of a new vaccine each time a new variant is observed. Influenza B, a related virus, does not undergo such shifts and thus does not cause pandemics. Amantadine apparently inhibits uncoating of the influenza A virus (and thus replication), and its activity is completely independent of the nature of the two glycoproteins that provide viral identity. It has little effect on influenza B.

When the Hong Kong (H3N2) strain of influenza A was first detected in Europe in 1968, Du Pont obtained samples of the new variant and demonstrated in tissue culture systems that it was at least as susceptible as the Asian strain to amantadine. The company then issued a press release suggesting that Symmetrel could be used for prophylaxis of Hong Kong flu. FDA objected to this conclusion because there had been no clinical trials in humans against the new variant. The agency required Du Pont to send a "Dear Doctor" letter to every physician in the country stating that the claims for efficacy of Symmetrel against Hong Kong (H3N2) influenza A could not be validated until clinical trials were completed. These trials had, in fact, been begun as soon as possible, and they confirmed the tissue culture results, but they were not completed until the epidemic was practically over.

Meanwhile, Albert B. Sabin, now at the Medical College of South Carolina, published a "Special Communication" in the June 1967 issue of the *Journal of the American Medical Association* in which he argued against the use of amantadine. Sabin and others contend that the biochemistry of viruses is so similar to that of human cells that antiviral agents cannot exert a selective activity. In that article, he summarized all the negative aspects of the first clinical trials of the drug and concluded not only that amantadine is ineffective but also that it is not safe. He also vigorously castigated FDA for issuing even limited approval for Symmetrel. The combined effect of this article and the subsequent "Dear Doctor" letter apparently produced such a negative effect on physicians that the drug was virtually unused in the Hong Kong flu epidemic.

Symmetrel would probably have been withdrawn from production in the United States shortly thereafter had not the late Robert Schwab of Massachusetts General Hospital in Boston discovered that amantadine alleviates some symptoms of Parkinson's disease through a mechanism completely different from its antiviral activity. FDA approved this use of Symmetrel in April 1973. Meanwhile, large-scale studies in Great Britain, Czechoslovakia, the Netherlands, Sweden, and, especially, the Soviet Union continued to demonstrate that amantadine provides a significant reduction in clinical illness caused by influenza A.

Bolstered by the European findings and the fact that Symmetrel remained on the market as a therapeutic agent for Parkinson's disease, Du Pont submitted a revised application to FDA which showed that laboratory studies of amantadine in tissue cultures and in eggs are valid predictors of its efficacy against new strains of influenza in humans. The company thus argued that clinical trials were not necessary every time a new variant of influenza A appeared, a concession that had already been granted to manufacturers of influenza vaccines. At about the same time, the World Health Organization adopted the current nomenclature for influenza viruses, which recognizes that the variants of influenza A differ only in their antigenic determinants and not in their fundamental biochemistry. In 1976, therefore, FDA finally ruled that Symmetrel could be marketed for use against all strains of influenza A. Despite the wide concern about the possibility of an epidemic of "swine" influenza A in 1977, there has been no major outbreak of influenza since that approval. There have been minor outbreaks of Russian (H1N1) influenza A among people under the age of 25 during the past two winters, and some scientists view this as a harbinger of a new pandemic.

In March of this year, Joseph Califano, then the Secretary of Health, Education, and Welfare, held a conference on influenza. One outcome of that con-

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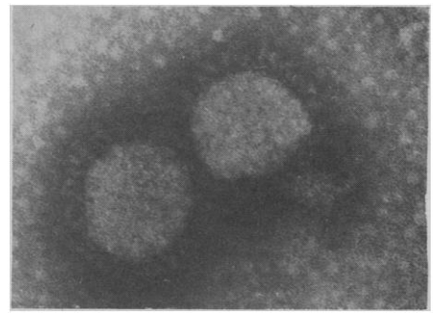
ference was the recommendation that "experts meet before the next influenza season to reach a consensus on technical issues relating to amantadine and to provide specific guidelines for the medical community." The consensus development panel was thus convened under the chairmanship of Jay Sanford, dean of the Uniformed Services University of the Health Sciences. The panel* met on 15 October at the National Institutes of Health to hear reports from various scientists who have been engaged in amantadine research.

Prophylactic use of amantadine was reviewed for the panel by Jackson, Arnold S. Monto of the University of Michigan, and Viacheslav F. Krylov of the Ivanovsky Institute of Virology in Moscow. Their presentations summarized the clinical studies that have now been conducted on more than 110,000 subjects. These studies, taken together, indicate that amantadine can reduce influenza A infections by 35 to 50 percent and can reduce clinical illness from influenza A by 50 to 70 percent. That means that a significant percentage of individuals who are infected by influenza A despite having taken amantadine never develop clinical illness.

R. Gordon Douglas of the University of Rochester Medical Center summarized recent clinical studies of therapy of influenza A with amantadine. These studies generally demonstrated that such therapy is effective if it is begun within 48 hours of the onset of symptoms. For example, 15 of 16 clinical studies showed that amantadine reduced the height of fever significantly and reduced its duration by about 50 percent. Nine of the 16 studies showed a similar effect on other symptoms. And two of the three studies in which shedding of the virus was measured showed a significant reduction of both frequency and quantity of virus shedding; this suggests that an influenza A victim treated with amantadine is less likely to infect others. Taken together, Douglas says, these studies suggest that the duration of disabling illness could be shortened by amantadine therapy from the normal 4 days to as little as 1.5 days, so that patients can return to school or work 1 to 2 days earlier.

Krylov and Thomas Cate of the Baylor College of Medicine reviewed the potential side effects of amantadine use. Results from the many clinical trials indicate that minor nervous system symptoms, including insomnia, light-headedness, nervousness, difficulty in concentration, and drowsiness, may occur in as many as 7 percent of individuals receiving the recommended 200 milligrams of amantadine daily. These effects typically begin within a few hours of the receipt of the first dose and are transient. Mild impairment of intellectual acuteness may also occur in a small percentage of individuals but disappears upon cessation of therapy. The drug does not appear to provide analgesia or euphoria, however, so that there seems little potential for abuse.



The influenza A virus.

One significant concern, according to Gary Noble of the Center for Disease Control, is the potential for selection of amantadine-resistant strains of the influenza A virus. Such strains have been observed to develop at a relatively high frequency in tissue cultures. Fortunately, though, he says, no resistant strain has yet been isolated from humans.

The major dissenting voice at the conference, once again, was that of Sabin. Putting aside his argument against the efficacy of amantadine, he now contends that the role of the influenza A virus in upper respiratory diseases is not as important as was once thought. Influenza-like upper respiratory tract illnesses, he says, are caused by hundreds of viruses. His own analysis of data from the National Center for Health Statistics, he argues, indicates that, even during epidemics, influenza A infections constitute only a small part of the total problem of clinical influenza.

During the 7 years from 1 July 1970 to 30 June 1977, according to health interview data from the center, about 30 percent of the entire U.S. population suffered "bed-disabling" clinical influenza during each of the three nonepidemic years compared with 36 percent during each of the four epidemic years. In addition, 28 percent of the population had "bed-disabling" upper respiratory tract infections during influenza A nonepidemic years compared to 26 percent during epidemic years. Furthermore, Sabin adds, "While mortality from influenza itself continues to be higher by several thousand deaths during epidemic years, the higher annual mortality rates from pneumonia, heart disease, and bronchopulmonary diseases that regularly occurred during influenza epidemics prior to 1971 have not occurred since then." Mortality from these conditions has been declining at about the same rate during epidemic and nonepidemic years.

Sabin thus concludes that even extensive use of a hypothetical drug that is 100 percent effective against both influenza A and influenza B—which amantadine certainly is not—"could not be expected to have a significant impact on the massive problem of total bed-disabling influenza disease." Sabin does not say so, but presumably the same argument could be made opposing vaccination against influenza. But other investigators, such as Sir Charles Stuart-Harris of the University of Sheffield Medical School in England, argue just the opposite: that the impact of influenza A has been underestimated and that the influenza-associated deaths from pneumonia and cardiovascular disease have actually increased.

The panel agreed with the latter viewpoint and concluded that amantadine has significant potential in reducing the morbidity and mortality associated with influenza A, particularly among the elderly in institutions and those who care for them. They recommended that the drug be used for prophylaxis for periods of 4 to 6 weeks (the normal length of an influenza epidemic in a community), when there is epidemiological and virological evidence of influenza A infection, in: children and adults at high risk of morbidity or mortality because of other diseases; adults whose activities are essential to community function and who have not been vaccinated for influenza A; and individuals in "semi-enclosed environments," especially older persons, who have not been vaccinated. The panel stressed that vaccination should remain the primary form of prophylaxis against influenza A, but concluded that amantadine should be used as an adjunct to the vaccine in the recommended groups when vaccination is not possible and to provide supplementary protection during the 10 days between vaccination and the development of protective antibodies.

The panel also recommended that amantadine be used therapeutically in the same groups recommended for prophylaxis. In addition, they urged that it be used in patients diagnosed as having life-threatening influenzal pneumonia, in

*Other members of the panel were Robert H. Moser, executive vice president of the American College of Physicians; John D. Nelson of the University of Texas Southwestern Medical School; Manuel Rodstein of the Jewish Home and Hospital for the Aged in New York City; Karl Rolls of the Doctors Hospital Medical Complex in Sarasota, Florida; Morton N. Swartz of Harvard Medical School; and Laryl Lee Delker, a public member of the Panel on Bacterial Vaccines with Standards of Potency.

infants with influenza-associated croup, and in individuals whose community function requires that they be returned to work as soon as possible. Other groups may also be suggested for both therapy and prophylaxis once there is a better understanding of the pharmacokinetics of the drug and its efficacy in infants and children.

Although not strictly within the scope of their charge, the panel also made some other recommendations. They argued especially that there is a need for new procedures and facilities to enable rapid diagnosis of influenza A infection. This would ensure that the drug is used only to treat viral infections against which it is effective. The panel also encouraged the study of analogs of amantadine, especially rimantadine, that appear to have greater efficacy and fewer side effects.

Apparently anticipating the panel's recommendation, Du Pont increased its stockpile of Symmetrel to nearly four times its normal size. The company now has enough amantadine on hand to treat 5 million individuals for 10 days, a stockpile with a retail value of about $25 million. That is enough to handle regional outbreaks of influenza A, but not enough to handle an epidemic or a pandemic. Production of the drug takes about 6 months, and therefore it would be in short supply if stockpiles are depleted by an epidemic. Because of the poor reception of the drug by physicians in the past, however, the company probably does not feel justified in increasing the stockpile. Only time will tell, therefore, whether the drug will make a significant contribution the next time the influenza virus undergoes an antigenic shift and once more starts its travels around the world.—THOMAS H. MAUGH II

The 1979 Nobel Prize in Physiology or Medicine

The 1979 Nobel Prize in Physiology or Medicine has been awarded to Allan MacLeod Cormack, 55, of the Physics Department, Tufts University, Medford, Massachusetts, and Godfrey Newbold Hounsfield, 60, of the Central Research Laboratories of EMI, Ltd., Hayes, England, for the invention of the x-ray diagnostic technique computer-assisted tomography (CAT), also known as computed tomography (CT).

At a recent international meeting, a distinguished British radiologist opened the proceedings with a paper dedicated to the history of CAT. After his presentation, a member of the audience commented on the pioneering work of Cormack. The speaker, quite candidly, stated that he was not aware of Cormack's contribution. This widespread lack of awareness, even among the cognoscenti, of the work of one of the 1979 Nobel laureates, is one of several unusual, indeed unprecedented, features of this year's award. Other unusual features are the fact that the two honored investigators have no background in biology or medicine and that their discovery is not in the "basic" life sciences but rather in "applied" research. The history of the development of CAT—an extraordinary technique which in little more than 7 years after its introduction has had an unmatched impact on the radiological sciences (*1*)—is fascinating and in many respects instructive.

Cormack, born in South Africa and educated at Cambridge University in nuclear physics, was a member of the physics faculty at the University of Capetown when, in 1956, the affiliated Groote Shuur Hospital lost their regular physicist and called the Physics Department for help. Because Cormack was the only nuclear physicist available, he was assigned to the hospital for $1\frac{1}{2}$ days per week, during which time he supervised isotope administration and film badge calibration and performed other duties of a radiological physicist. His involvement with radiotherapy treatment planning demonstrated to him the need for accurate values of attenuation—that is, the amount the x-ray beam weakens as it passes through the patient's anatomy—and led him to wonder if these could be obtained from x-ray measurements made outside the body. It occurred to Cormack that if enough x-ray projections or views were taken at a variety of different angles, there would be enough information to determine uniquely and quantitatively the internal structure and, further, that images reconstructed in this manner could be diagnostically useful. That fall he went on sabbatical to the Cambridge Electron Accelerator at Harvard University, where he took enough time from his regular research to derive a mathematical theory for image reconstruction. Upon his return to South Africa in 1957, he proceeded to test the theory with a laboratory simulation. The test object was a circularly symmetrical assembly of aluminum and wood; because it was symmetrical, only one projection was needed. Projection data were taken using a collimated beam from a 7-mCi ^{60}Co source, which emits gamma rays with energies of 1.2 and 1.3 MeV, and using a Geiger counter as the radiation detector, while the object was translated through the beam in 5-mm steps. The data were then mathematically processed to obtain the attenuation coefficient as a function of radius; the results agreed nicely with the known construction of the phantom.

Late in 1957, Cormack moved to the United States to join the Physics Department of Tufts University. While doing other research, he continued to putter with his pet project until he derived an alternative mathematical approach that was better suited for calculation. In 1963 he repeated the experiment with similar equipment, but with a nonsymmetrical phantom of plastic and aluminum. This time the data processing was too extensive for hand calculation and computers were used. Cormack showed his results to several radiological physicists, but was unable to uncover any interest in his idea. The two experiments were published in the *Journal of Applied Physics* (*2*, *3*), with the hope that they would be noticed. They were not.

Hounsfield's early and totally independent work began 10 years after Cormack's. His inspiration came not from a medical environment, but from pattern recognition studies at the Central Research Laboratories of EMI. In 1967 he

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