of the analog compound and reported it seemed to diverge; the Johns Hopkins experiments with microwave techniques showed a steep rise in conductivity but no divergence. Cowan points out that the discrepancy between these two results cannot be due to barriers in the crystals.

Perhaps the most critical estimate of the reported evidence for superconducting effects comes from Bernd Matthias, at the University of California, La Jolla, who suspects that the results for the special crystals and for the analog compound are simply wrong. Matthias, who discovered the superconductor that functions at 20.8°K, suggests that the crystals being studied are ferroelectric, and that for such materials, conductivity maxima near certain critical temperatures are not unusual. Several researchers have objected to the fact that Heeger has so far been unwilling to lend any of the special crystals to other laboratories for testing.

(At Pennsylvania, Garito says that he and his co-workers have an open laboratory where anyone is welcome to collaborate, and that they have lent a batch of crystals to Paul Chaiken, at the University of California, Los Angeles, who was formerly a student with the Pennsylvania group. Follow-up experiments with the special crystals are probably not possible now, according to Heeger, because the crystals are quite fragile and partially coated with silver paint.)

Whether or not superconducting properties are ultimately confirmed, it is clear that (TTF)(TCNQ) and related (TCNQ) compounds have extraordinary conduction properties, and that only a few of the possible crystals have been studied. Because of the relative ease with which many variations of organic compounds can be synthesized, it is possible that the properties of organic superconductors could be tailored to fit many needs. The National Bureau of Standards, the Bell Telephone Laboratories, Monsanto Research and Development Laboratories, and the International Business Machines Watson Research Center are all beginning to study organic solids.

Concerning the three special crystals reported by Heeger and his associates, the consensus of other researchers seems to be "If he's right, he's got something fantastic."—WILLIAM D. METZ

References and Notes

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Influenza: The Last of the Great Plagues

Never, before influenza, has control of an infectious disease been contingent upon an understanding of the molecular biology of its agent. Control of cholera, for example, depends only upon a separation of sewage and drinking water; control of malaria depends primarily upon the eradication of mosquitos; and control of viral diseases such as yellow fever, smallpox, poliomyelitis, and measles depends upon isolation of the virus and production of vaccines. Yet 40 years after isolation of its causative virus and 30 years after development of a vaccine effective against it, influenza remains an embarrassing anachronism—the only infectious disease that appears periodically in life-threatening pandemics (global epidemics).

Influenza's persistence results from a unique genetic plasticity that enables the viral agent to undergo two types of antigenic shift: frequent (once every year or two), minor mutations that give the new variant a somewhat increased resistance to prevailing antibodies, and less frequent (once every 10 to 12 years), major antigenic shifts that circumvent nearly all preexisting immunity. The effects of these shifts can be devastating. During the winter of 1968–1969, there were more than 51 million reported cases of influenza in the United States attributed to a major new influenza variant first isolated in Hong Kong, and at least 20,000, and perhaps as many as 80,000, excess deaths attributed to influenza and its side effects. (Excess deaths are those beyond the number that would be expected in the absence of an epidemic.)

Even during the past winter, when only a minor variant—the so-called London flu—emerged, at least 2200 excess deaths in 122 U.S. cities were attributed to influenza and its side effects, especially pneumonia. In terms of the number of deaths each year, the combination of influenza and pneumonia is the fifth most serious public health problem in the United States, and in terms of days of work missed, it is the most serious.

Chills, Fever, and a Running Nose

Although the term "influenza" is used loosely by both physicians and patients, it should not be confused with the common cold, with other, less severe infections of the respiratory tract, or with gastrointestinal infections. Influenza is a brief, but severely incapacitating disease with an incubation period of 24 to 72 hours. Its abrupt onset is marked by chills, fever, headache, aching muscles, and extreme fatigue, followed by a running nose and a sore throat. A cough is nearly universal, and often severe. The disease usually runs its course in about 3 to 7 days, although fatigue may last longer. As with other viral infections, there is no specific treatment after the onset of symptoms.

Uncomplicated influenza is rarely fatal, except in patients with chronic diseases of the heart or lungs. Most influenza-mediated deaths arise from bacterial pneumonia or other severe infections that occur when the patient is weakened by influenza. These secondary infections can be largely controlled now, but were the cause of many deaths before the advent of antibiotics. An estimated 20 million people worldwide and more than 500,000 in the United States died of such complications during the influenza pandemic of 1917–1918.

Influenza vaccines have moderated the severity of epidemics in recent years, but the commonly used killed virus vaccines have several important deficiencies. One problem is that such vaccines, many scientists believe, are inherently less effective than those produced with attenuated viruses, and are thus only partially effective to begin with. A greater problem in the past has been the length of time required for adaptation of newly emerged human influenza viruses to growth in chick embryos for preparation of vaccines. Influenza spreads so rapidly that epidem-

ics or pandemics have been able to run their course before any preventive vaccines were available for their control. It has thus become essential to investigate the molecular biology of the influenza agent in order to cope more rapidly with newly discovered variants, and perhaps even to anticipate such variants before they emerge.

The agent of influenza is myxovirus influenzae, of which there are three antigenic types designated A, B, and C. Only influenzas A and B occur frequently, and apparently only influenza A is capable of causing pandemics. The varied abilities of the three types to provoke epidemics is presumed, but has not been proved, to result from the lessened ability of the B virus and the inability of the C virus to undergo the gross antigenic mutations responsible for the recurring pandemics of influenza A. Investigation on influenza (most of which has been sponsored by the National Institute of Arthritis and Infectious Diseases) has thus been centered on the A virus, so that much less is known about the B type, and almost nothing about the C type.

Influenza A is a medium-sized RNA virus, about 110 nanometers in diameter, which is delimited by a membrane composed of lipids and polysaccharides derived from the host cell and virus-specific protein. Work by several investigators, especially Purnell W. Choppin, Sondra G. Lazarowitz, and Richard W. Compans of Rockefeller University, New York City, and Irene T. Schulze of St. Louis University School of Medicine, St. Louis, Missouri, has shown that the virus contains at least five distinct proteins. At least three of these are inside the virion—that portion of the virus circumscribed by the lipid membrane. Preliminary evidence suggests that the internal virion proteins from all influenza A viruses of man and animals demonstrate similar responses to challenge with antibodies, and this antigenic similarity is the basis for classification of a virus as influenza A.

The smallest of the virion proteins, the membrane (M) protein with a mass of about 27,000 daltons, is present in the greatest abundance. Several lines of evidence suggest that the M protein is associated with the inside of the lipid envelope (Fig. 1), where it apparently forms a continuous shell that provides the major structural support of the viral membrane.

A somewhat larger protein, the nuclear protein (NP) with a mass of about 60,000 daltons, is the nucleocapsid subunit; the repeating NP subunits form helical structures that encapsulate the viral RNA. At least one, and perhaps two larger polypeptides with a mass of 81,000 to 94,000 daltons have also been isolated from the interior of the virion. Their function and precise location within the virion are not yet known, but many investigators believe that at least one of these may be the RNA transcriptase known to exist within the virus. RNA transcriptase is the enzyme that catalyzes synthesis of new viral RNA from the viral RNA template as the virus replicates in the host cell.

The remaining two polypeptides are glycoproteins that form projections or spikes on the surface of the virion. They are identified by their biological function as hemagglutinin and neuraminidase. Hemagglutinin (HA) binds the virus to neuraminic acid-containing receptors in the target cell; if the hemagglutinin function is inhibited, as by an antibody, the virus is no longer infective. Each hemagglutinin spike is composed of two identical subunits with masses of about 80,000 daltons apiece. Each of these subunits may, in some host cells, be cleaved into two smaller units—HA_1 with a mass of about 50,000 daltons and HA_2 with a mass of about 30,000 daltons—held together by disulfide bonds. HA_1 is about 20 percent carbohydrate and HA_2 about 5 percent.

The neuraminidase (NA), with a mass of about 70,000 daltons, functions by cleaving an alpha-glycosidic linkage between *N*-acetylneuraminic acid and a carbohydrate derivative in the host cell membrane. The effect of this cleavage is to free the virus from the host cell; removal of the NA spikes from the virion or inhibition of NA with antibodies has little effect on the infectivity of the virus, but either inhibits release of virus from the cell, and thus its spread to other cells. Some investigators, such as Doris L. Bucher of the Mount Sinai School of Medicine of the City University of New York, believe that the active enzyme is an NA tetramer.

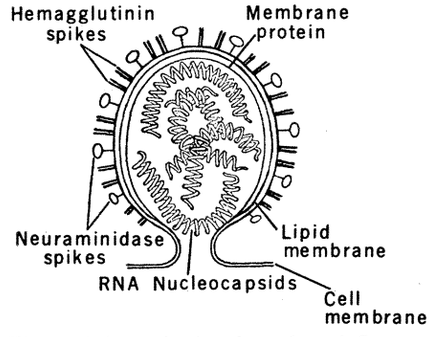

Fig. 1. Schematic drawing of an influenza virus emerging from a cell. [Source: Edwin D. Kilbourne, Mount Sinai School of Medicine]

It is through the hemagglutinin and neuraminidase moieties that the influenza virus interacts with its environment, and formation of antibodies specific for these glycoproteins is the primary response of an organism subjected to viral attack or to vaccination. Evolutionary pressure for selection of favorable mutants would thus be expected to be focused primarily on these proteins and, indeed, it is they that have been shown to undergo independent antigenic variation.

Point Mutations Give an Advantage

Peptide mapping of purified hemagglutinins (two-dimensional thin-layer chromatography to separate the component amino acids) from closely related influenza variants suggests that increased resistance to HA antibodies results from point mutations in the polypeptide chain—that is, from substitution of one amino acid for another at one or more sites on the polypeptide as a result of a change in the base sequence of the viral RNA. This substitution, when favorable, interferes with the antigen-antibody association necessary for inhibition of the hemagglutinin function and gives the mutant an increased chance of survival in a hostile environment. Similar point mutations have also been observed in the neuraminidase moiety. It appears, however, that only a finite number of such point mutations are possible before either the function of the protein is impaired or the virus gains no additional competitive edge from further substitutions. When that stage is reached, gross structural changes in the protein are required for further competitive advantage.

W. Graeme Laver of the John Curtin School of Medical Research, Canberra, Australia, and Robert G. Webster of St. Jude Hospital, Memphis, Tennessee, have demonstrated by peptide mapping that purified hemagglutinin from the Hong Kong or A_3 influenza virus subtype first isolated in 1968 has an amino acid composition grossly different from that of the antecedent A_2 subtype, although the amino acid composition of the neuraminidase from both strains is virtually identical. Since antibodies to

the hemagglutinin moiety are the primary determinant of influenza immunity, this major change in antigen composition largely circumvented existing immunities and initiated an influenza pandemic. Recent evidence from Jerome L. Schulman of Mount Sinai and from Arnold S. Monto and Alan P. Kendal of the University of Michigan, Ann Arbor, suggests, however, that residual antibodies to the neuraminidase antigen of the A_2 strain, present in many people, moderated the severity of the pandemic by providing at least partial immunity to the new variant. A much more severe pandemic occurred, for example, in 1957 when both surface antigens underwent such a gross shift.

The change in antigenic amino acid composition associated with the abrupt emergence of new influenza subtypes is far too large to be explained by conventional concepts of mutation or evolution. A different type of explanation must be found, and that explanation lies in the nature of the viral genome.

Influenza Has a Segmented Genome

The RNA of the influenza virus is found in five to seven discrete pieces, each in its own nucleocapsid, and its total mass is about 4 million daltons. Each of the pieces, suggests George K. Hirst of the New York University Medical School, New York City, is an intact gene that controls at least one characteristic of the virus. The unique genetic plasticity of the influenza virus arises from the ease with which these genes are interchanged among different viral strains.

If a host cell is simultaneously infected by two different subtypes of influenza virus, the genes from these subtypes undergo a random reassortment in the cell to produce not only the two original subtypes, but also one or more hybrid subtypes. Each of these hybrids has a different, but complete, set of genes, and inherits characteristics from each parent. This type of genetic recombination was first observed in influenza viruses, but has subsequently been recognized in reoviruses and certain plant viruses.

It is not absolutely necessary to invoke recombination to explain the minor antigenic mutations of influenza virus; these can be rationalized as merely point mutations in the conventional sense. But even this type of limited antigenic variation has never been recognized with other human viruses. Perhaps, speculates Edwin D. Kilbourne of Mount Sinai, the answer lies in both mutation and recombination.

Recombination within the infected patient could "rescue" noninfective mutations formed during infection because part of the altered RNA from noninfective virions could be incorporated into infective virions—thus creating an extended gene pool in which all mutations would be potentially salvageable, rather than only those that occur in infective virions. Such an explanation is reasonable if it is assumed that the influenza virus is exceedingly susceptible to the evolutionary pressures of homotypic antibodies, so that any mutant that is even slightly changed in either of its external proteins will have a tremendous survival advantage. It is also necessary to postulate that a certain density of infection is critical to survival of the virus, and that this critical density is not adequately maintained solely by the infection of newborn susceptible infants, as it is with measles and poliomyelitis.

Recombination within the infected patient, however, cannot explain the much greater mutations that occur once each decade, for all available evidence indicates that only one influenza subtype can exist in man at any given time. The emergence of a new subtype, such as the Hong Kong strain, is always accompanied by the abrupt disappearance of the antecedent subtype, so there is little chance for the appropriate recombination to occur in man. The most likely explanation, suggests Kilbourne, is that the recombination takes place in animal hosts.

First Isolated from Swine

The first recognized influenza virus was isolated from swine in 1931 by Richard E. Shope, then at the Rockefeller Institute, who postulated from circumstantial evidence that it was a human virus that had descended into swine. More recently, a virus that is antigenically indistinguishable from the Hong Kong subtype has been isolated in swine from Europe and Asia. Influenza viruses have, moreover, been isolated only from domestic animals and birds, further suggesting that the viral strains are human in origin. Most animal and human viruses exhibit almost no cross-infectivity, but Robert B. Couch of the Baylor College of Medicine, Houston, Texas, has overcome this objection by demonstrating both the infection of humans with equine influenza virus and the infection of horses with a human influenza virus.

In contrast to the situation in humans, however, the appearance of apparently new influenza virus strains in animals is not necessarily associated with the disappearance of previously recognized strains. According to Kilbourne, there are currently at least two discrete subtypes of equine influenza virus in circulation, at least eight avian strains of different HA subtype, and at least two subtypes in swine. The hemagglutinin and neuraminidase moieties of some of these subtypes are antigenically very similar to those of several human influenza viruses, both past and present.

Kilbourne thus theorizes that there are no true animal strains of influenza —only human strains that have become adapted to growth in animals. Because of the recombinational ability of the influenza virus, these varied strains serve as an extended pool upon which the human virus can draw in the face of increased evolutionary pressure from rising antibody levels in the population. In the course of their adaptation to animals, however, these strains have lost their ability to infect humans. They can thus return to their primary host only through a combination of events that includes the occurrence of an ecologic niche in man, as the contemporary strain is suppressed by rising antibody levels, and fortuitous genetic recombination to produce a new subtype that is infective in humans and that is not susceptible to existing antibodies. Such new subtypes have generally emerged, and will probably continue to emerge, in Asia, where men and animals continue to dwell in the same buildings.

The remarkable amount of knowledge gained about influenza within the past 10 years has produced some remarkable first steps toward control of man's last great plague. These steps will be considered next week in a succeeding article about the production of influenza vaccines.

—THOMAS H. MAUGH II

Erratum: Several errors occurred in the Research News story "ERTS: Surveying earth's resources from space" (6 Apr. 1973) by Thomas H. Maugh II. In column 3, page 50, the statement, "It thus maps an area of about 6.5 km^2 every day," should read "6.5×10^6 km^2." In Fig. 3, the land masses are identified as Manhattan and Staten Island; actually, the spit at the left of the figure is Sandy Hook, New Jersey, and the barrier beaches further north are Rockaway, Long Beach, and Jones Beach, from left to right. The negative for Fig. 4 was inadvertently flipped over so that the illustration is a mirror image of the actual picture. It has also since been brought to the author's attention that "the previously unsuspected difference in salinity" in the Great Salt Lake described in the caption of Fig. 2 was, in fact, well known before the ERTS picture was taken.