it has recently been suggested that the primary magma forms large chambers at the base of the crust, where crystal fractionation removes large quantities of olivine, clinopyroxene, and plagioclase, while the magma is renewed by more primary liquid from below. Such a chamber would serve both to buffer the variation in the magnesium/iron ratios and concentrations of nickel and chromium and to reduce them substantially (*20*).

That many problems remain concerning the origin of the Columbia River basalts is certain. But the wealth of chemical and mineral data now available on these rocks has provided a clear picture of the development of this immense volcanic outburst. The tectonic events associated with the eruptions are well understood and must now be reconciled with the larger concepts of plate movement and the causes of magma generation at depth. We have learned that the variation in composition between flows resulted from processes at depth rather than processes at or just below the surface, and current evidence suggests that the larger chemical differences between oceanic and continental basalts may be more closely related to the thickness of the overlying crust than to crustal contamination. Studies may now focus on the relative merits of models that emphasize the partial melting at depth of a heterogeneous, iron-rich mantle source, and more complex models in which magma reservoirs at the base of the crust fractionate early refractory minerals but are periodically tapped by a volcanic eruption and refilled by more partial melt from below.

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21. The systematic survey of the Columbia River basalts in the last 10 years has involved the close cooperation of many geoscientists. I am particularly indebted to the work of D. A. Swanson, T. L. Wright, V. E. Camp, S. P. Reidel, and to the research team at Rockwell International, Richland, Washington. I am also grateful for the many helpful suggestions for the improvement of the manuscript by T. L. Wright, G. G. Goles, and R. D. Bentley.

Variation of Influenza A, B, and C Viruses

Peter Palese and James F. Young

Although in this era we have witnessed the eradication of smallpox and can view the eradication of poliomyelitis and measles as a distinct possibility, the prevention of epidemic and pandemic influenza remains beyond our current capabilities. A number of factors may contribute to the problem of influenza control, but the major factor that has limited our ability to control the disease is the capacity of influenza viruses (*1*, *2*) in nature to vary rapidly and undergo changes in antigenic structure that circumvent the protective effects of a patient's immune response. This variability of influenza viruses is in marked contrast to the antigenic properties of other viral agents, such as polio virus or measles virus, which appear to remain essentially unchanged. The situation with influenza viruses also differs from that of herpes or rhinoviruses which coexist as a number of variants in the population but do not undergo the rapid changes that are observed in influenza viruses.

The number of people contracting influenza can vary considerably from year to year. Although a pandemic of the severity observed in 1918 has not occurred in the last six decades, serologic evidence suggests that a new influenza virus strain may infect more than 50 percent of a population within a period of 2 years (*3*) and cause death in many compromised patients. For example, from 1968 to 1981 an estimated 150,000 people died of the effects of influenza virus infections in the United States alone (*4*). In addition to influenza, Reye's syndrome, a disease with a high mortality rate in children, has been associated with influenza viruses (*5*). Typically, this disease involves an inflammation of the brain and fatty degeneration of the liver.

Influenza viruses have long been known to cause disease in other animals besides humans. For example, fowl plague virus causes high mortality in chickens and is of great commercial sig-

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nificance. Also of interest are influenza virus strains that can affect the health of turkeys, pigs, or race horses. These agents are important not only to veterinarians and others concerned with animal husbandry, but also to virologists and epidemiologists who must attempt to understand the interaction of these viruses in different species and their potential for causing disease in humans.

Summary. Influenza is caused by highly variable RNA viruses belonging to the orthomyxovirus group. These viruses are capable of constantly changing the genes coding for their surface proteins as well as for their nonsurface proteins. The mechanisms responsible for these changes in type A influenza viruses include recombination (reassortment) of genes among strains, deletions and insertions in genes, and, frequently, point mutations. In addition, old strains may reappear in the population. Influenza viruses of types B and C appear to vary to a lesser degree. The mechanisms responsible for changes in these viruses are not well characterized.

General Features of the Influenza Virus Group

Influenza viruses are RNA-containing viruses that can be easily differentiated from other agents and represent a unique viral group, the orthomyxoviruses (*1, 2*). They differ significantly from other RNA or DNA viruses infecting eukaryotic cells, both in virion structure and mode of replication. All members of the orthomyxoviruses appear to have a common architecture, with glycoprotein molecules on the surface of the particles, a lipid bilayer membrane, and a core consisting of the matrix (M) protein layer and a ribonucleoprotein complex (Fig. 1). The ribonucleoprotein complex is made up of the segmented RNA genome, nucleoprotein (NP) molecules, and three different polymerase (P) proteins.

There are also major differences among influenza viruses permitting their classification into three types—A, B, and C. The type A viruses share serologically cross-reactive M and NP proteins, both of which differ from the internal proteins of type B and C strains. Furthermore, although the lengths of the eight RNA segments of different type A strains are largely conserved, they are different in size from the eight genomic RNA segments of influenza B viruses and from the seven RNA segments of influenza C strains. Comparative complementary DNA-RNA (cDNA-RNA) hybridization analysis has also demonstrated that extensive sequence homologies on the RNA level among members of the same type are absent among strains belonging to different types.

In contrast, nucleotide sequencing of the 5′ and 3′ ends of the genomic RNA's of strains of types A, B, and C revealed a high degree of conservation of the terminal 10 to 20 nucleotides, suggesting a common evolutionary progenitor (*6*). Similarly, protein sequence data on the hemagglutinins of types A and B show conserved stretches of amino acids in some areas of functional importance. For example, cleavage of the hemagglutinin (HA) precursor of influenza A and B viruses into HA1 and HA2 subunits results in HA2 molecules with common amino terminal sequences (*7*). It has been suggested that this conserved sequence is dictated by the functional requirement of a cleaved hemagglutinin for virus infectivity (*7*).

It also appears that the three influenza virus types may differ in their degree of variation. Although types B and C vary in their surface antigens, the B as well as the C strains are generally believed to undergo less antigenic variation than the A strains (*8*). Furthermore, comparison of the RNA's of recent A, B, and C virus isolates by means of cDNA-RNA hybridization analysis suggests that with respect to the overall genome structure influenza C viruses change less than do members of the B type, which, in turn, change less than strains of the A type (*8*). However, these conclusions may have to be qualified once comparative nucleotide sequence data on the genes of types B and C become available.

Epidemiology

As surveillance and biochemical techniques have improved, much has been learned about the epidemiology of influenza and the agents causing it. The type C influenza viruses, although widespread, are of minor concern to man since infection with these viruses is infrequently associated with disease. Influenza B viruses are more often associated with disease in man than type C, but the type A viruses are the most important because of their association with pandemic influenza. In addition, type A strains appear to be the only influenza viruses with a natural host range that includes, besides man, other animals such as pigs, horses, and birds.

A type A influenza virus was first isolated from man almost 50 years ago, and since that time tens of thousands of virus isolates have been identified on all continents of the world. From the characterization of these strains and the analysis of the immunological status of the population the following picture emerges with respect to the epidemiology and variability of the virus (Fig. 2).

1) From 1934 (and probably as early as 1918) until 1957 influenza A viruses belonging to the H1N1 subtype (*9*) circulated throughout the world. Strains of the H2N2 subtype were prevalent between 1957 and 1968, but in 1968 these strains were replaced by H3N2 strains which are still circulating now. Each time a new subtype appears, immunization against or infection with the previous subtype strains is inadequate to protect against infection and disease with the new viruses.

2) In 1977, strains of the H1N1 subtype were reintroduced into the population, and for the first time a period began in which strains of two subtypes, H1N1 and H3N2, cocirculated. Some of the H1N1 isolates have been shown to contain genes derived from H3N2 strains, providing evidence that reassortment of genes between human influenza viruses can occur in nature (*10*).

3) In addition to the dramatic changes that occur in the surface antigens of strains belonging to different subtypes (antigenic shift), small antigenic differences have been observed in the surface proteins of strains belonging to the same subtype (antigenic drift). These minor changes are sufficient to permit reinfection of and disease in humans previously infected with influenza virus strains of the same subtype.

4) Although antigenic drift in the surface proteins and variation in the genes coding for the nonsurface proteins have been observed among influenza B and C viruses (*11*), different subtypes of influenza B and C viruses have not been identified, and, unlike influenza A viruses, types B and C do not appear to undergo rapid major genetic or antigenic changes.

Mechanisms for Variation

The genetic variability of influenza viruses involves many mechanisms, as outlined in Table 1. Many data suggest that new strains of A subtypes emerge

Table 1. Some of the mechanisms responsible for the genetic variability of human influenza A viruses.

Events leading to different subtypes
1. Reassortment of surface protein genes occurs between different strains (possibly involving animal strains)
2. Reemergence of strains which had previously been in circulation is observed
Events leading to variation within subtypes
1. Point mutations occur in genes coding for surface as well as nonsurface proteins
2. Short deletions and insertions are observed in genes coding for hemagglutinins and neuraminidases
3. Reassortment may lead to the exchange of genes coding for nonsurface proteins

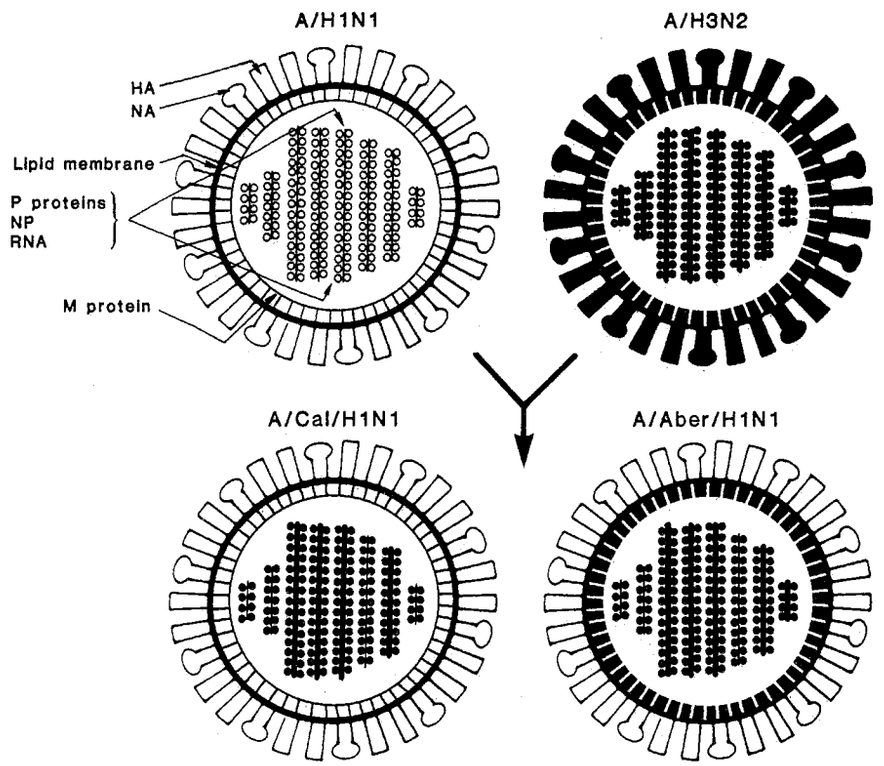

Fig. 1. Schematic diagram of influenza A virus and gene derivation of the H1N1 recombinants A/Cal/10/78 and A/Aberdeen/v1340/78. Influenza A virus particles are characterized by spikes on the surface consisting of hemagglutinin (rectangles) and neuraminidase (mushrooms), by a host-derived lipid membrane, an underlying matrix (*M*) protein layer, and by the ribonucleoprotein (RNP) complexes which are composed of eight RNA segments associated with the nucleoprotein (*NP*) (circles) and the three polymerase (*P*) proteins (circles). The structure of influenza B and C viruses is similar except that influenza C viruses appear to lack a neuraminidase gene. The diagram also shows the genotype of A/Cal/10/78 virus which derives the NP and the three P genes (heavy bars in RNP) and the corresponding proteins (filled circles) from an H3N2 subtype parent through recombination (reassortment). The remaining four genes (light bars in RNP) and the corresponding proteins are derived from an H1N1 subtype parent. The A/Aberdeen/v1340/78 H1N1 recombinant derives a fifth gene from an H3N2 parent (heavy bar for the RNA segment and filled rectangle for the M protein). The appearance of A/Cal- and A/Aberdeen-like strains in the population proves that recombination (reassortment) of genes among human influenza viruses occurs in nature (*10*).

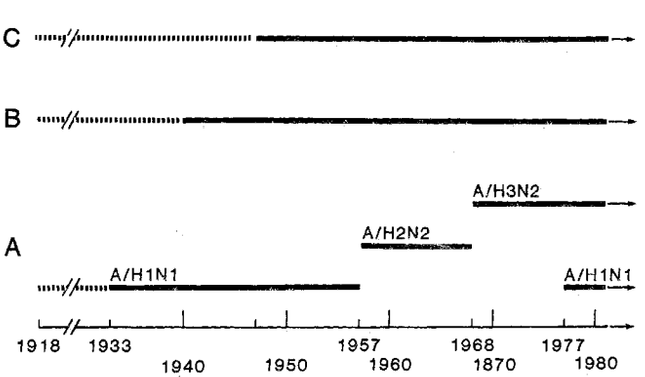

Fig. 2. Prevalence of influenza A, B, and C viruses in man over the last decades. Broken lines indicate that virus isolates are not available from these periods (only indirect evidence is available). Influenza A viruses of the H1N1, H2N2, and H3N2 subtypes were identified during certain time periods as indicated.

through recombination (reassortment) of genes among different strains (*12*). In the case of H3N2 strains, the most convincing evidence for this hypothesis comes from biochemical results based on peptide mapping and RNA-RNA hybridization (*12*). In these strains, transfer of the H3 hemagglutinin gene from an animal virus to the prevalent H2N2 human strains, via recombination, may have generated the new human subtype strain (H2N2 × H3N? → H3N2). Although only three different hemagglutinin subtypes have been identified among human isolates, animal strains belonging to at least nine additional HA subtypes (*9*) may be potential donors for new human strains. However, recombination was probably not the mechanism which led to the emergence of the H1N1 strains in 1977. Rather, evidence obtained by oligonucleotide mapping of the RNA's of the 1977 H1N1 strains suggested the reappearance of H1N1 strains virtually identical with those that had been in circulation some 27 years earlier. Sequencing of cloned genes, nucleic acid hybridization, and serologic analysis confirmed this unusual finding of reappearing strains (*13, 14*). Clearly, the precise mechanism for this reappearance of H1N1 strains remains obscure and future studies must determine whether human strains can remain dormant and be recycled at different times.

Evidence for possible antigenic recycling has been obtained by analysis of serum from infected humans. Davenport *et al.* and Masurel (*15*) reported that serum samples collected from aged persons before the H3N2 pandemic in 1968 contained antibodies to H3-like agents and that stored serum samples from people born before 1887 cross-reacted with H2N2 strains which appeared in 1957. These results led to the speculation that H3N2-like viruses may have been responsible for epidemics in 1900 and that H2N2-like viruses may have been the pandemic agents of 1889. This indirect and limited evidence on earlier strains could be interpreted as indicating that there are only a limited number of viral antigens that have the potential to cause epidemics and pandemic and that these antigens may be recycled.

In contrast to the major shifts in the surface proteins of strains of different subtypes, drift in the proteins of strains belonging to the same subtype is mediated through point mutations. Furthermore, it appears that hemagglutinin and neuraminidase genes of strains belonging to one subtype may vary by short deletions or insertions of triplets in the coding region (*16*). However, it is not known

whether these changes contribute significantly to altered antigenic or biological properties of strains. Finally, cocirculating strains may exchange genes coding for the nonsurface proteins. For example, the H1N1 prototype strains A/Cal/10/78 and A/Aberdeen/v1340/78 derive four and five genes, respectively, from cocirculating H3N2 strains (Fig. 1) (*10*). This mechanism of "shuffling" genes possibly may enable the virus to change rapidly, generating more successful variants. This may be reflected in the many recombinants of the H1N1 subtype that have been isolated during recent winter seasons.

One additional mechanism, which has not yet been shown to operate in nature, is true intramolecular recombination. Further sequencing studies will be required to examine this possibility.

Variation in the Hemagglutinin Gene

Much of the recent knowledge on the variation of hemagglutinin is based on the evaluation of sequence data, antigenic studies with monoclonal antibodies, and the elucidation of the three-dimensional structure by means of x-ray diffraction patterns of the crystallized protein. Hemagglutinin genes of the three human subtypes H1, H2, and H3 have been sequenced (*17*), as well as two hemagglutinin genes from avian strains (*18*). The data show that there are significant differences among the subtype hemagglutinins both on the nucleotide as well as on the amino acid level, and in all comparisons the HA2 subunits appear to be more conserved than the HA1 portions (Tables 2 and 3). It therefore appears that the discrimination of subtypes is primarily due to extensive sequence changes in the HA1 subunit.

Sequence analysis of hemagglutinin genes of viruses belonging to the same subtype provided data to evaluate the molecular basis of antigenic drift. The most extensive collection of data is available for H3 hemagglutinins (*17–19*). In comparing the hemagglutinin gene of a 1968 H3 strain with that of the A/Bangkok/1/79 H3 strain isolated 11 years later, a total nucleotide difference of only 4.7 percent was observed, with most of the changes again being localized in the HA1 subunit. This translated to a total change of approximately 10 percent of the amino acids and suggested the presence of several variable regions within the HA1. These data, in conjunction with analysis of the three-dimensional structure of the A/Aichi/2/68 hemagglutinin (*20*) and nucleic acid and protein data of other H3 hemagglutinins delineated four major antigenic sites on hemagglutinin molecules (Fig. 3). These last studies were particularly helped by the analysis of hemagglutinin variants generated in the laboratory and by the characterization of epidemic strains by means of monoclonal antibodies (*21*). Future studies will show whether the mapping of these four antigenic sites adequately explains the antigenic diversity of hemagglutinin molecules. It is conceivable that mutations in other areas of the molecule also contribute to the complex nature of the antigenicity of different hemagglutinins.

Table 2. Comparison of H1, H2, and H3 hemagglutinin genes. The sequence data for the H1 (A/PR/8/34), H2 (A/JAP/305/57), and H3 (A/Aichi/2/68) hemagglutinins are from (*17*).

Subtype	Total length (nucleotides)	HA1 (amino acids)	HA2 (amino acids)
H1	1778	326	222
H2	1773	324	222
H3	1765	328	221

The possible role of glycosylation in antigenic variation is unknown. Extensive differences in the oligosaccharides linked to the hemagglutinin have been observed in several studies (*22*); however, the significance of oligosaccharides in influencing antigenic determinants both by steric effects or direct involvement remains to be defined.

Although type A hemagglutinins may show a great degree of variability, three basic features appear to be conserved: the amino acids at the amino terminal of HA2, a carboxyl terminal hydrophobic tail of HA2 that is believed to anchor the molecule in the viral membrane, and many cysteine residues along the entire sequence. Thus, all the hemagglutinins appear to retain a basic structure which permits them to mediate a series of important biological functions such as adsorption and penetration of the virus into cells.

Variation in the Neuraminidase Gene

The second surface glycoprotein antigen, the neuraminidase spike, consists of a single uncleaved polypeptide in a tetrameric form embedded in the viral envelope. The neuraminidase, like the hemagglutinin, undergoes antigenic shift. In human strains only two subtypes, N1 and N2, have been identified, and these show little or no serologic cross-reactivity. Seven additional neuraminidase subtype strains exist in the animal virus population (*9*). Shift of the neuraminidase genes of human isolates does not appear to be linked with specific hemagglutinin subtypes, since the N2 neuraminidase has been found in association with both H2 and H3 hemagglutinin subtypes.

Minor antigenic change or drift has also been observed in strains belonging to one neuraminidase subtype (*23*). Little is known about the quantitative aspect of these changes in different strains although RNA gels and oligonucleotide and peptide maps amply demonstrate the variability of this gene and its gene product (*24*). Partial sequence data from several N1 neuraminidase genes have revealed the presence of deletions near the amino terminus of the protein (*16*). Since only one neuraminidase gene sequence has been published to date (*25*), a more detailed characterization of variation must await the availability of additional sequence data and the three-dimensional structure analysis of the crystallized protein.

Genes for Nonsurface Proteins

Variation in nonsurface proteins has not been studied in detail. Peptide differences (which may not necessarily reflect detectable antigenic changes) have been observed in all the nonsurface proteins including the NS2 and M2 polypeptides which are derived from spliced messenger RNA molecules (*8*, *26*). Some results, however, do suggest that minor antigenic variability occurs in the NP as

Table 3. Conservation of nucleotides and amino acids among H1, H2, and H3 hemagglutinin genes. The data for the H1 (A/PR/8/34), H2 (A/JAP/305/57), and H3 (A/Aichi/2/68) hemagglutinins are from (*17*).

Comparison	Nucleotide conservation (%)		Amino acid conservation (%)	
	HA1 subunits	HA2 subunits	HA1 subunits	HA2 subunits
H1 and H2	61	72	58	79
H1 and H3	45	58	35	53
H2 and H3	45	57	36	50

well as the M protein of influenza A viruses (*27*). Furthermore, on the nucleotide level it has been found by oligonucleotide mapping and RNA-RNA hybridization analysis that changes occur in all six genes coding for nonsurface proteins of various strains (*28, 29*). Complete nucleotide sequences are available for the NP, M, and NS genes of A/PR/8/34 virus and the M and NS genes of additional strains (*30, 31*). A comparative analysis of the sequenced NS genes of strains A/PR/8/34 and A/Udorn/72, isolated 38 years apart, revealed a nucleotide difference of 8.8 percent. This difference corresponds to an average change of two nucleotides per year. If one accepts the notion that these nucleotide changes are sequential and cumulative, one may draw an evolutionary tree that highlights the relationships among different NS genes. As indicated in Fig. 4, the result places the origin of the NS gene of the H1N1 strain (which reappeared in 1977) around 1950, a date that was also suggested by previous analyses with different techniques (*13, 14*). Clearly, the placing of genes on evolutionary trees is made difficult by the problem of sampling; that is, to what extent is a particular isolate representative of other isolates obtained in the same epidemic year. However, the finding of nucleotide substitutions that are conserved in virus isolates obtained later argues that to some extent at least these substitutions are linear and cumulative. Indeed, where nucleotide substitutions were more closely studied by sequence data, those in the hemagglutinin genes of different H3 subtypes were found to be roughly linear and cumulative (*32*).

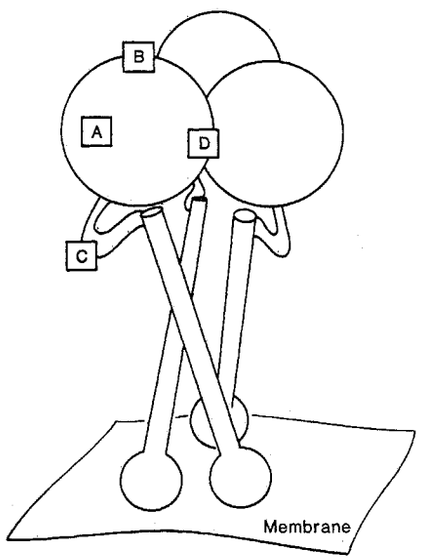

Fig. 3. Schematic diagram of the hemagglutinin trimer of A/Aichi/2/68 virus. The structure was obtained by Wilson *et al.* and Wiley *et al.* (*20*) through x-ray diffraction pattern analysis of the crystallized protein. Each trimer contains a stem and a globular domain which contains the variable antigenic determinants A, B, C, and D (as indicated on the left trimer). Diagram is slightly modified from (*20*).

Like the genes coding for the surface proteins, those coding for nonsurface proteins may also undergo reassortment, as was mentioned before. This adds another dimension of genetic variability and further complicates the genetic analysis of epidemiologically important influenza virus strains.

Another interesting aspect of variation in influenza virus genes (*30, 31*) was observed when the sequences of the M genes of A/PR/8/34 and A/Udorn/72 were compared. It was found that the M1 and M2 proteins, both coded for by the M gene, varied to a different degree (2.8 and 11.3 percent). A similar observation was also made for the NS1 and NS2 polypeptides coded for by the NS gene. This suggests that different selective pressures are operating to alter the evolution in different parts of the same gene.

Is the Mutability Uniquely High?

As outlined above, variation in influenza viruses is a multifaceted phenomenon involving many different mechanisms. But do influenza viruses have a uniquely high mutation frequency? Several experimental techniques have been used to address this question, including monoclonal antibody analysis of changes in proteins and oligonucleotide map analysis of RNA's.

Data measuring the frequency of variants selected with monoclonal antibodies are difficult to interpret since they do not accurately reflect mutation rates (*33*). Similarly, oligonucleotide analysis of variants isolated after passage in vitro under nonselective conditions has not allowed us to calculate a precise error rate for the replication of influenza viruses (*33*). Attempts to solubilize the influenza virus polymerase and measure the fidelity of the reaction in vitro have also been unsuccessful. Thus it has not been possible to compare the error rate in influenza virus replication with that of other animal viruses. Until such data are available, it is difficult to determine mutation frequencies of influenza viruses and to assess the possible contribution of the error rate of the polymerase to the epidemiology of influenza.

It is clear, however, that influenza viruses appear in nature in a greater abundance of variants than other viruses. Factors other than mutation rates may influence the selection of influenza virus variants in nature and thereby result in what appears to be a higher mutation rate. For example, in the case of influenza the immune response in some patients may lead to subneutralizing conditions that favor the selection of variants through several cycles of virus replication. Furthermore, the sheer number of people infected with influenza viruses during an epidemic may result in the formation of large numbers of variants. Alternatively, the change of one or more amino acids in the influenza virus hemagglutinin may change the antigenic character of the virus sufficiently to permit its escape from neutralization, whereas a similar number of amino acid changes may not provide such a selective advantage for other kinds of viruses. Finally, the proteins of influenza viruses may simply tolerate amino acid substitu-

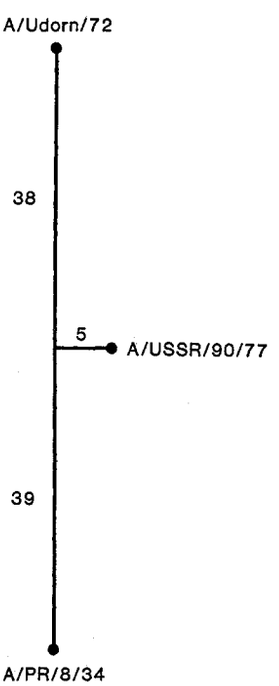

Fig. 4. Possible evolutionary relationships among NS genes of different influenza A viruses. The NS gene of A/PR/8/34 virus differs from that of the 1972 isolate A/Udorn/72 by 77 nucleotides (the total length of the NS gene is 890 nucleotides). The 1977 isolate A/USSR/90/77 shares 39 differences with the Udorn/72 strain; only five changes lie on a separate evolutionary pathway. (The one nucleotide position which is changed in all three strains is omitted from the analysis.) [Data from (*14*) and (*31*)] If one assumes a constant increase in changes over time, the evolutionary tree places the A/USSR/90/77 virus NS gene in a period between 1950 and 1955. This finding would agree with earlier results indicating that the 1977 H1N1 strains are indeed 1950-like strains (*13, 14*).

tions more readily than do those of other viruses, which could result in the survival of a great number of influenza virus variants.

Other animal viruses with DNA or RNA as their genome may lack one or several of the features possessed by influenza viruses that enable them to emerge as successful epidemic variants. To define these characteristics it will be necessary to obtain comparative data on the antigenic potential and the mutational frequencies of different viruses as well as on the ability of these viruses to undergo extensive changes. In addition, factors influencing transmissibility and virulence will have to be further defined in molecular terms.

Outlook for the Future

With the advent of improved biochemical and biophysical techniques much has been learned about the variation of influenza viruses and their epidemiology. However, we are still far from being able to predict the course of variation in nature or mimic the process in the laboratory. Experiments aimed in this direction have ended in failure. However, this should not deter investigators from attempting to design strategies to overcome the disease caused by this ever-changing virus. Such strategies might be based on the use of interferon or synthetic compounds that interfere with processes of the virus that remain largely conserved from strain to strain. For example, agents that could selectively inhibit the influenza virus–specific polymerase are obvious candidates.

More useful at this time appear efforts at immunoprophylaxis with vaccines prepared from live and killed influenza viruses. Although such vaccines have been in use for some time, they do not provide complete protection nor have they been designed to overcome the variability of the causative agent. Recombinant DNA techniques now lend themselves to the development of more effective vaccines. Transcription of the viral RNA into DNA and cloning into plasmid vectors permit genetic manipulation of influenza virus genomes. If influenza viral RNA is produced from cloned DNA and can be rescued into infectious virus it may be possible to construct stable attenuated virus that can be used as live virus vaccine. This approach may soon be feasible since the full-length DNA transcript of poliovirus, another RNA virus, has been shown to be infectious in mammalian cells (*34*). In addition, laboratory strains of influenza virus may be constructed which contain altered antigenic determinants.

Theoretically, such live virus vaccine strains could provide a wider range of protection than is presently possible. Alternatively, genetic engineering methods may be used to produce, at low cost, viral antigens or portions of viral antigens in bacterial or yeast cells for use as killed virus vaccines. Synthesis of modified antigens that exhibit determinants cross-reactive among strains may lead to preparations that represent a significant improvement over conventional vaccines.

Another recent development that may help to overcome the inherent problem of producing a broadly effective influenza virus vaccine takes advantage of the chemical synthesis of specific peptides (*35*). These peptides have been shown to be immunogenic, and synthesis of the right amino acid stretch deduced from known viral sequences or construction of a suitable cross-reactive immunogen containing multiple determinants may lead to the ultimate influenza virus vaccine. Obviously, there are many questions that remain to be answered before any of these developments can be translated into an effective vaccine. At the same time it is also clear that these recent developments have great potential and provide us with intellectually stimulating ideas to address and overcome old problems.

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American Medicine's Golden Age: What Happened to It?

John C. Burnham

Summary. In the first half of the 20th century, American physicians enjoyed relative freedom from adverse comment in mass and highbrow media. In unexpected ways the physicians' high ideals and the campaigns against socialized medicine brought criticism not only of the priestly but also of the technical functions of the medical profession. In the late 1950's this led to a campaign to modify the elevated position of physicians in American society.

During the first half of the 20th century, up until the late 1950's, American physicians enjoyed social esteem and prestige along with an admiration for their work that was unprecedented in any age. Medicine was the model profession, and public opinion polls from the 1930's to the 1950's consistently confirmed that physicians were among the most highly admired individuals, comparable to or better than Supreme Court justices (*1*). Highbrow and mass media commentators alike associated medical practice with the "miracles" of science and made few adverse comments on the profession (*2*). By the 1970's, however, statesmen of medicine were writing unhappily about being "deprofessionalized" in the wake of attacks by articulate and knowledgeable critics, attacks that by 1981 were reflected specifically in substantial mistrust of the profession among the public at large (*3, 4*). One can conduct a historical postmortem of this unexpected turn of events by examining changes in direct public depreciations of the medical profession, using the different kinds and levels of criticism of M.D.'s as indicators of what happened.

The attitudes of leaders and shapers of opinion and of the public toward physicians did not translate directly into the behavior of patients. For economic and social reasons, amounts of money spent by Americans on medicine continued to increase dramatically even when attitudes changed. But, as was revealed both by polls and by a resurgence of alternatives to conventional medical practice, over time the critics not only affected doctors' sensibilities but also demonstrably damaged the social credibility of the profession as a whole (*4, 5*). Since public acceptance is necessary for a profession to function, the criticism had tangible effects.

A long and honorable tradition of denigrating doctors was known to Aristophanes and Molière and continued to flourish in 19th-century America (*6*). As late as 1908 a set of satirical "Medical maxims" in this tradition included, for example (*7*):

> Diagnose for the rich neurasthenia, brainstorm, gout and appendicitis; for the poor insanity, delirium tremens, rheumatism and gall-stones . . . fatten the thin, thin the fat; stimulate the depressed, depress the stimulated; cure the sick, sicken the cured; but above all, keep them alive or you won't get your money.

But in those same early years of the 20th century, the tradition of doctor baiting tended to die out as the golden age of medicine dawned. Whereas the post-1950's resurgence of criticism that culminated in Ivan Illich's *Medical Nemesis* (*8*) recalled traditional themes such as physician greed, pretension, and imposition, the later critics were also responding to new and untraditional characteristics of both medical practice and American society (*9*). Moreover, the few particular criticisms that survived in the golden age helped shape and define the new deluge.

Evolution of the Medical Image

During the 19th century, physicians seeking to professionalize their calling were fair game for hostile comment, with quacks and sectarians on one side and the practitioners' actual therapeutic impotence on the other. Some aristocrats of medicine and the medical ideal they represented did enjoy high prestige, but most (often deservedly) did not. Occasionally, antimedical diatribes based on these earlier struggles persisted after the 1890's, along with other anachronisms like attacks on the germ theory of disease. But by and large, in the wake of medical, and particularly surgical, successes, publicity about the profession was favorable, and leaders of the American medical profession succeeded by the early 20th century in their campaign to persuade the public to want and expect uniformly well-trained, well-paid physicians who themselves set standards of practice (*10–12*).

So effective was favorable publicity about both science and doctors that Americans in general began to view extensive medical care as a life necessity. Expansion of hospital care at the beginning of the century was an important indication of the change.

After some years, publications of the Committee on the Costs of Medical Care (1928–1933) and other surveys generated

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