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SOME NEW OR LITTLE-KNOWN RESPIRATORY VIRUSES

C. H. ANDREWES
GRIZELDA WORTHINGTON
National Institute for Medical Research, Mill Hill, London, England

SYNOPSIS

The characters and relationships of a number of viruses of potential importance in human respiratory diseases are reviewed. Among the myxoviruses discussed are viruses related to influenza A (swine and horse influenza, British and Czechoslovak duck influenza, fowl plague), influenza B and C, mumps and Newcastle disease, and the para-influenzas. The ECHO viruses, 2060 and JH viruses, chimpanzee coryza agent and the common cold are also considered. In the final section of the paper the attempted transmission to laboratory animals of four myxoviruses is reported on.

There have recently come to light several viruses having a potential importance in human respiratory infections. These will be briefly reviewed below; the adenoviruses are not discussed, however.

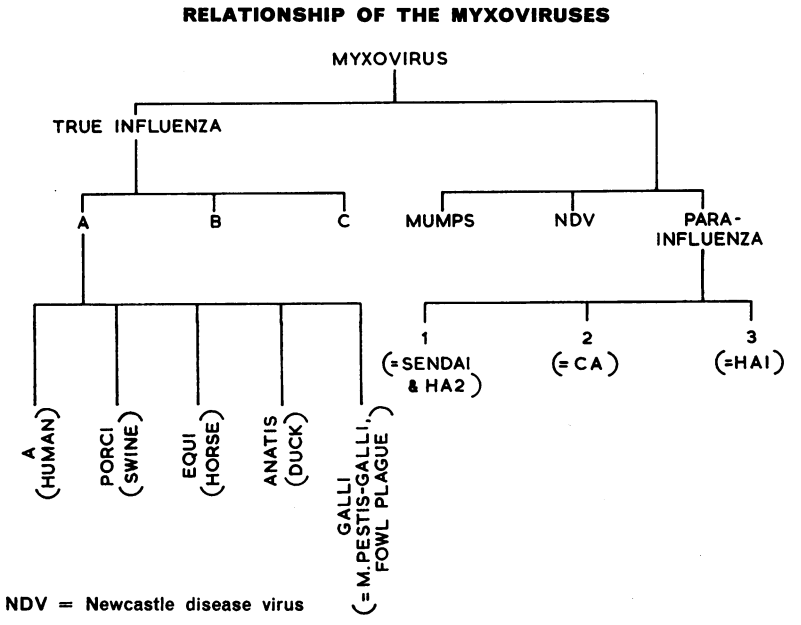
Myxoviruses

Most of these viruses belong to the *Myxovirus* group (Andrewes, Bang & Burnet, 1955). This group can conveniently be subdivided according to the scheme shown in the accompanying chart. The position of simian myxoviruses is still uncertain.

The basis for this subdivision can be seen in the table. The true influenza viruses differ from other myxoviruses by their smaller, more uniform size, ability to form filaments and absence of haemolysin production.

Viruses related to influenza A

A possible origin of Asian influenza in a domestic or wild animal in China has been suggested; this virus differs from earlier strains of influenza A not only antigenically but also in its insusceptibility to α-inhibitor and in other biological properties, so that an origin from immediately preceding human strains can be considered doubtful. It is therefore pertinent to record that there exist viruses related to influenza A, sharing a common complement-fixing antigen but pathogenic for very different hosts.



Swine influenza (Myxovirus influenzae-A porci). This was originally described by Shope (1931). North American strains isolated in years since 1931 have all been serologically related to the original strain; but British strains are antigenically different (Glover & Andrewes, 1943; Gompels, 1953). It is doubtful whether swine influenza has been prevalent outside the USA during the last decade. Reported isolations have in general been from laboratories where Shope's strain was already under study ; the hazards of laboratory " pick-ups " are now very familiar.

Horse influenza (M. influenzae-A equi). The term horse influenza includes diseases due to several viruses including that of equine virus abortion. There has, however, been isolated in Central Europe a true myxovirus affecting horses (Sovinová et al., 1957); this was prevalent in Czechoslovakia between May and October 1955. Serological studies suggest that it may be present in other countries.

Czechoslovak duck influenza (M. influenzae-A anatis). This was isolated in East Slovakia in the spring of 1956 (Koppel et al., 1956) from the nasal secretion, brain, lungs and liver of an affected duckling. Some 1250 out of 3000 ducks on one farm were attacked with an acute respiratory infection, usually fatal in 3-4 days; acute inflammation of the infra-orbital sinuses was the chief feature. The virus was infectious at a high dilution ($ID_{50} = 10^{-5}$) and was serologically unrelated (presumably by haemagglutinin-inhibition) to fowl plague or Newcastle disease.

CHARACTERS OF CERTAIN RESPIRATORY VIRUSES

	Influenza A	Swine influenza	Horse influenza	Fowl plague	Duck virus (British)	Duck virus (Czech.)	Influenza B	Influenza C	Newcastle disease	Mumps	Para-influenza
Influenza A CF antigen	+	+	+	+	+	+	0	0	0	0	0
Size (not > 110 mμ)	+	+	+	+	+	+	+	+	0	0	0
Filaments	+	+	+	+	+	+	+	+	0	0	0
Haemolysin	0	0	0	0	0	0	0	0	+	+	+
Growth in eggs :											
amnion	+	+	+	+	+	+	+	+	+	+	+±
allantois	+	+	+	+	+	+	+	+	+	+	+±
Pathogenesis (animals) :											
ferrets (intranasal) .	+	+	±	+	±	0	+	±	+	0	+
mice (intranasal). .	+	+	+	+	0	+	+	0	±	0	+0
new-born mice (intracerebral) . .	+0	0	+	+	0	+	+	.	+	+	+0
man	+	0	.	.	.	.	+	+	+	+	+
horse	.	.	+	.	.	.	.	.	.	.	.
swine	±	+	.	.	.	.	±	.	.	.	+0
fowl	0	0	0	+	0	0	.	.	.	.	.
duck	0	0	0	+	?+	+	0	.	+	0	.
Pathogenesis (tissue culture) :											
primate	+	+	0	+	+	+	+	+	+	+	+
bovine.	+	+	+	+	+	+	.	.	.	.	.
chick	+	+	+	+	+	+	+	.	+	.	.
duck	.	.	0	+	+	+	.	.	.	.	.

+ = positive character ; pathogenicity + at least after adaptation
± = character less definite
+0 = some strains positive, some negative
+± = positive but difficult or doubtful with some strains
0 = character negative
. = no test

British duck influenza. This virus was isolated by Mr G. B. Simmins of the Ministry of Agriculture Veterinary laboratories at Weybridge, England, from a pool of respiratory tissues from five ducklings with sinusitis. These came from a large duck farm in East Anglia where sinusitis

was troublesome. After a few allantoic passages this virus was not pathogenic for ducklings, so its relation to the duck sinusitis is still obscure. It showed no relationship in anti-haemagglutinin tests to other myxoviruses.

Fowl plague (M. influenzae-A galli or *M. pestis-galli).* The virus of classical fowl plague was shown by Schäfer (1955) to share the complement-fixing antigen of influenza A. Since it also resembles human influenza A in morphology and other properties, it seems to have little if any more right to be considered a " species " distinct from influenza A than have the swine and horse viruses.

Influenza viruses B and C

No comment upon these is necessary. They differ from the A strains in their different complement-fixing antigens but resemble them in other respects, so that we may consider a group of true influenza viruses to stand together, forming a group apart from the other myxoviruses now to be considered.

Mumps and Newcastle disease

These two viruses are to be seen from the table to share many properties with the next three viruses—Para-influenza 1, 2 and 3—which are grouped together in the table.

Para-influenza viruses

Three viruses have now to be considered, all resembling mumps and Newcastle disease as shown at the top of the table. A working group under the International Nomenclature Committee has been discussing the names of these viruses and is putting forward the proposals now to be mentioned.

Para-influenza 1 = Sendai, Haemagglutinating virus of Japan, or Influenza D (Kuroya & Ishida, 1953). Chanock's haemadsorption virus 2 (HA2 of Chanock et al., 1958) is closely related to it serologically and may be included with it. Sendai virus is endemic in stocks of laboratory mice in Japan and China, probably affects pigs also, and has been claimed as a cause of pneumonitis in new-born children in Japan and of an influenza-like disease in the USSR. On account of the affinities of the virus, the term " Influenza D " should not be encouraged. A virus, probably identical with HA2, has been recovered in the USA and Denmark from children with laryngo-tracheitis and other mild respiratory infections; it grows poorly in eggs.

Para-influenza 2 = Croup-associated (CA) virus (Chanock, 1956) = Acute laryngo-tracheitis virus (Beale et al., 1958). This virus has also been

isolated from children with laryngo-tracheitis by the use of tissue cultures. Antibodies to it have been found in 90% of adult human sera.

Para-influenza 3 = Haemadsorption virus 1 (HA1) (Chanock et al., 1958). This also has been recovered from children with minor respiratory infections. It grows well in tissue cultures but poorly in eggs.

The properties of these three viruses have not been recorded separately in the table since they have been insufficiently studied. All three of them seem likely to be causes of minor infections in children but to be infrequently concerned in producing disease in adults.

Simian viruses

At least one (SV5; Hull et al., 1956) of the numerous viruses which have been isolated in tissue cultures of normal monkey kidneys causes haemagglutination and appears to belong in the myxovirus group.

Other Viruses

ECHO viruses

The ECHO (enteric cytopathogenic human orphan) viruses are now included under the term enteroviruses: their separation from Coxsackie viruses is by no means easy. Several of them may be concerned in causing minor respiratory infections.

ECHO 10. This is believed to have caused common-cold-like symptoms in chimpanzees (Sabin, personal communication), and has also been isolated from children. It is larger than other ECHOs and may not belong naturally in the group.

ECHO 11. The U-virus from Uppsala (Philipson & Wesslen, 1958) appears to be an ECHO 11. It was believed by the authors to be a cause of cold-like illness in adults, but its status is obscure.

ECHO 20. ECHO 20 or JV1 virus (Cramblett et al., 1958) is in much the same category as ECHO 11.

2060 and JH

2060 (Mogabgab & Pelon, 1958) and JH (Price, 1956) viruses have been isolated in monkey kidney tissue cultures from minor respiratory disease in recruits or children. They seem to be closely related but distinguishable serologically. Attempts to produce common colds in adult volunteers with the JH virus gave equivocal results (Andrewes, 1958).

These viruses resemble ECHO viruses in some respects and may come to be classified with them. They have usually been propagated in cultures of monkey kidney cells from which simian viruses are all too easily picked up, replacing the original virus. The viruses labelled JH and 2060 in various laboratories may represent a number of different agents.

Chimpanzee coryza agent (CCA) or respiratory syncytial virus

This virus seems to stand apart from the others in various properties. It has been recovered from a chimpanzee with a " cold " and from children with respiratory infections, some mildly infected but others having bronchopneumonia.

Common cold

Though many of these cultivable viruses have been thought to produce cold-like symptoms, there is no evidence that any of them cause a substantial proportion of the commonest type of common cold. A virus from a typical cold was apparently cultivated in 1953 (Andrewes et al.), and colds were produced by cultures up to the tenth in series. Subsequent subcultures failed to do so and the authors have been unable to duplicate their original results. Since some of the viruses earlier described are grown, though with difficulty, one may hope that with further technical knowledge the true common cold virus or viruses will be cultivable also.

Pathogenicity of Some Myxoviruses for Laboratory Animals

Since the attempted transmission of some of the myxoviruses (particularly *M. influenzae-A equi* and *anatis*) has not been previously reported, a brief account follows.

Methods

Mice were inoculated intranasally under ether with 0.05-ml quantities of allantoic fluids or with 5% suspensions of lungs of infected mice when serial passage was carried out. Intracerebral inoculations into mice were of 0.03 ml allantoic fluid or brain suspensions for weaned mice and 0.01 ml for 1- to 2-day-old mice. Lung or brain suspensions were made in saline containing 9% Hartley's broth and 1% horse serum.

Ferrets were inoculated intranasally with 1-ml quantities under ether anaesthesia. Temperatures were taken and the animals examined daily. Blood was taken by heart puncture 14 days after infection.

Results

Horse influenza virus (M. influenzae-A-equi)

Mice. After two intranasal passages carried out at 3- to 4-day intervals small lung lesions 1-2 mm in diameter were seen; these appeared only in mice allowed to survive for 7 days. The lesions seen became progressively greater on passage and occasional mice died from the 4th passage on. At the 8th passage a homologous ferret antiserum was shown to neutralize the lung lesions completely. On intracerebral inoculation of 1- to 2-day-old mice, one or two inoculated animals showed hyperexcitability at the first passage; from the second passage onwards, in one of two series, mice died with convulsions, usually after 6, 7 or 8 days. Passages were made from mice which were ill 4-11 days after inoculation. After four passages, a test revealed neutralization of the virus activity by homologous ferret antiserum: 3 controls receiving virus and normal rabbit serum died after 5, 7 and 8 days; 2 of 3 receiving virus and antiserum survived, the third dying after 12 days. Weaned mice were apparently unaffected either by the original allantoic fluid or after three passages of virus through day-old mice.

Ferrets. An inoculated ferret had no fever or symptoms but showed good antibody production.

British duck virus

Mice. Intranasal inoculation of mice produced no symptoms; no virus was recovered by inoculation of eggs after three mouse-passages, carried out at 3-5-day intervals. Intracerebral inoculation of day-old and weaned mice produced no symptoms even after two serial passages.

Ferrets. A ferret showed no symptoms but had one spike of fever (104.2°F; 40.1°C) 24 hours after intranasal inoculation; anti-haemagglutinins of low titre were produced.

Czechoslovak duck virus

Mice. Those inoculated intranasally first showed trivial lung lesions at the fifth passage; these lesions were no more definite after a total of 17 serial passages. The interval used was 3-4 days as this had been found convenient in work with influenza. After the 17th passage, other intervals were tried and it was at once found that when the interval was reduced to 48 hours, extensive, often fatal, lung lesions were produced. At the 23rd passage, a neutralization test was carried out with hyperimmune rabbit serum: this completely inactivated a lung suspension which produced extensive lesions in 6 out of 6 control mice.

Ferret. No symptoms or fever were produced, nor did anti-haemagglutinins develop in the serum even after a " booster " dose subcutaneously.

Simian virus

This virus (SV5 of Hull et al.) did not survive four intranasal passages through mice; it survived three but not seven intracerebral passages in day-old mice.

The effects of these and some other viruses on cultures of tissues of several animal species are recorded in the table and will be described in detail by one of us (G.W.) separately.

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RÉSUMÉ

Les auteurs passent en revue un certain nombre de virus respiratoires nouveaux ou peu connus, la plupart appartenant au groupe des myxovirus. Au virus grippal A se rattachent certains virus grippaux d'animaux sauvages et domestiques: ils ont le même antigène de déviation du complément mais sont pathogènes pour des hôtes très différents. Font partie de ce groupe: le virus grippal du porc, du cheval, du canard de Tchécoslovaquie, du canard d'Angleterre, de la peste des poules.

Les virus grippaux B et C diffèrent du virus A par leur antigène de déviation du complément mais lui ressemblent à bien des égards. On peut donc grouper ensemble les virus grippaux vrais qui diffèrent des autres myxovirus par leur taille plus petite et plus uniforme, leur capacité à former des filaments, et l'absence d'hémolyse.

Les virus para-grippaux 1, 2 et 3 ont ainsi été dénommés par le Comité International de Nomenclature. Ils ressemblent aux virus des oreillons et de la maladie de Newcastle. Parmi les virus para-grippaux 1, il faut citer le virus de Sendai, le virus HA2 de Chanock; parmi les para-grippaux 3, le virus HA1 de Chanock.

D'autres virus peuvent provoquer des affections respiratoires mineures: les entérovirus (ECHO), difficiles à distinguer du virus Coxsackie, les virus 2060 et JH, le virus du coryza du chimpanzé, celui du coryza.

L'auteur a enfin étudié le pouvoir pathogène de certains de ces virus sur la souris et le furet.

REFERENCES

Andrewes, C. H. (1958) *Bull. Johns Hopk. Hosp.*, **103**, 1

Andrewes, C. H., Bang, F. B., & Burnet, F. M. (1955) *Virology*, **1**, 176

Andrewes, C. H., Chaproniere, D. M., Gompels, A. E. H., Pereira, H. G. & Roden, A. T. (1953) *Lancet*, **2**, 546

Beale, A. J., McLeod, D. L., Stackiw, W. & Rhodes, A. J. (1958) *Brit. med. J.*, **1**, 302

Chanock, R. M. (1956) *J. exp. Med.*, **104**, 555

Chanock, R. M., Parrott, R. H., Cook, K., Andrews, B. E., Bell, J. A., Reichelderfer, T., Kapikian, A. Z., Mastrota, F. M. & Huebner, R. J. (1958) *New Engl. J. Med.*, **258**, 207

Cramblett, H. G., Rosen, L., Parrott, R. H., Bell, J. A., Huebner, R. J. & McCullough, N. B. (1958) *Pediatrics*, **21**, 168

Glover, R. E. & Andrewes, C. H. (1943) *J. comp. Path.*, **53**, 329

Gompels, A. E. H. (1953) *J. gen. Microbiol.*, **9**, 140
Hull, R. N., Minner, J. R. & Smith, J. W. (1956) *Amer. J. Hyg.*, **63**, 209
Koppel, Z., Vrtíak, J., Vasil, M., Špiesz, Š. (1956) *Veterinářství*, **6**, 267
Kuroya, M., Ishida, N., & Shiratori, T. (1953) *Yokohama med. Bull.*, **4**, 217
Mogabgab, W. J. & Pelon, W. (1956) *Ann. N. Y. Acad. Sci.*, **67**, 403
Philipson, L. & Wessłen, T. (1958) *Arch. VirusForsch.*, **8**, 77
Price, W. H. (1956) *Proc. nat. Acad. Sci. (Wash.)*, **42**, 892
Schäfer, W. (1955) *Z. Naturforsch.*, **10**b, 81
Shope, R. E. (1931) *J. exp. Med.*, **54**, 373
Sovinová, O., Tůmová, B., Poutska, F. & Němec, J. (1957) *Čsl. Epidem.*, **6**, 213 (Also in *Acta virol. (Praha)*, 1958, **2**, 52—English edition)