Respiratory and Enteric Viruses in Man and Animals

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IN CONTRAST with the usual studies of the zoonoses, which focus on transmission of the infectious agent from animals to man, this study focuses on the similarities of the animal virus to the human virus and compares the infections produced in each species by these viruses. Viruses of the respiratory and enteric tracts of man and animals are discussed here.

Respiratory Infections

Most of the current studies of respiratory diseases of man and animals are aimed at determining their virus etiology, and considerable progress has been made, particularly since the advent of tissue culture methods.

The relatively new hemadsorption technique (*1*) is used extensively in work with many of the respiratory disease viruses. Essentially, this is a system in which red blood cells of various species, depending on the virus, are added to the infected tissue culture tubes. The red blood cells will adhere to the surface of the infected cells. Hemadsorption has been used for establishing the identity of isolates as well as isolating the virus from clinical specimens.

Hemadsorption is a specific phenomenon which is dependent upon the hemagglutinating properties of the virus. It was first reported in 1957 by Vogel and Shelokov who worked first with the influenza viruses and later extended these studies to certain other members of the myxovirus group.

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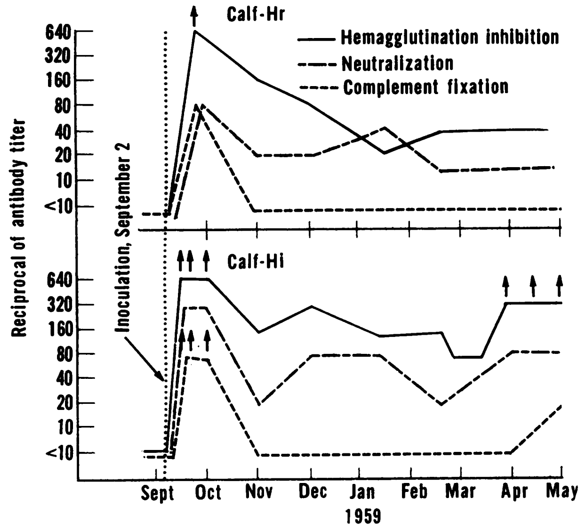
This technique has been used to good advantage in our laboratories. The recovery of parainfluenza 1, 3 (*2*), and possibly 4 (*3*) viruses, from children was largely due to the use of hemadsorption because many of the strains of parainfluenza 3, particularly, produced no cell degeneration on original isolation from children, and the virus was detected only by the use of hemadsorption. The first suggestion that a virus recovered from cattle with shipping fever might be a myxovirus resulted from the use of hemadsorption. It was then relatively simple, by using type-specific human parainfluenza 3 antiserum, to demonstrate the relationship of this virus to the human virus (*4*).

When this newly described hemadsorption technique was used in conjunction with monkey kidney tissue cultures, two new myxoviruses were recovered from children with respiratory illnesses (*2*). One of the viruses, the present parainfluenza 3, was significantly associated with febrile illness during an outbreak of respiratory disease in a nursery. About the same time the present parainfluenza 1 virus was also recovered from children. In a study of 1,738 children in three hospitals in the Washington, D.C., area, one or the other of these two hemadsorption viruses was recovered from 54 (6 percent) of 879 patients with respiratory disease. It appeared that the two viruses were capable of causing a wide variety of clinical manifestations including croup, pneumonia, bronchiolitis, pharyngitis, and mild febrile disease. Table 1 shows the recovery of parainfluenza 1 and 3 viruses from children with various respiratory disease syndromes.

Evidence of year-round occurrence of hemadsorption virus infections has been obtained (*5*). Other recent evidence relative to reinfection of children with these viruses indicated that the first infection would appear to be the most serious one and would result in a clinical illness, whereas subsequent infections were mild or inapparent (*5*). Thus, with these viruses it is probably quite possible to have repeated infections from childhood on through adult life, but clinical illness is observed most frequently in children experiencing their first infection. It is likely that a similar situation exists in cattle relative to infection and reinfection with parainfluenza 3 virus. Infections with these agents can occur the year round, but clinical illness is generally produced in the fall and winter months. There may be a similar occurrence in cattle; however, there is as yet no evidence to substantiate such a claim. Why such a seasonal relationship exists no one knows, but it could account for the occurrence in human and cattle communities of many infections which cause no illness, whereas in other communities where infection may occur during the fall and winter the same virus may account for a considerable amount of illness.

Progress in the study of respiratory diseases of animals has also gained new momentum since the use of tissue culture methods. Two viruses of importance in bovine respiratory disease have been studied in tissue cultures. The first was the virus of infectious bovine rhinotracheitis (IBR), and the second, the bovine strain (SF–4) (*6*) of myxovirus parainfluenza 3. I shall confine my remarks to studies of parainfluenza 3.

Development and persistence of hemagglutination and complement-fixing antibodies following infection



Parainfluenza 3 virus has been recovered repeatedly from cattle with respiratory disease (*6*, *7*). Definitely establishing this virus as a cause of respiratory disease, however, has been somewhat difficult, with one exception. According to Sinha and associates, this exception

Table 1. Recovery of parainfluenza 1 and 3 viruses from 879 hospitalized children with various respiratory disease syndromes [1]

Illness	Number tested	Virus isolation					
		Parainfluenza 3		Parainfluenza 1		Total	
		Number	Percent	Number	Percent	Number	Percent
Pneumonia	244	4	1. 6	0	0	4	1. 6
Croup	54	2	3. 7	9	16. 7	11	20. 4
Bronchiolitis	77	1	1. 3	0	0	1	1. 3
Pharyngitis [2]	57	2	3. 5	3	5. 3	5	8. 8
Mild respiratory tract disease:							
Febrile	311	7	2. 2	19	6. 1	26	8. 9
Afebrile	108	4	3. 7	2	2. 8	6	5. 6
Undetermined	28	0	0	1	3. 6	1	3. 6
Total	879	20	2. 3	34	3. 9	54	6. 1

[1] See reference 2.
[2] Including patients with pharyngitis and bronchitis combined or mild pharyngeal component with bronchitis predominating.

occurred during the study of an outbreak of shipping fever in a group of cattle recently transported from Texas to Kansas. Many of the cattle developed severe respiratory signs and several died or were killed. Parainfluenza 3 virus was recovered from the nasal secretions and from lung tissue of many of these animals. Affected cattle showed fourfold or greater antibody rises in their convalescent serums. However, the most important evidence in this outbreak was that the animals which did not become sick had preexisting parainfluenza 3 antibody.

In our studies (*7*, *8*) we were able to recover virus from sick cattle and demonstrate fourfold or greater antibody rises in the convalescent serums but were never fortunate enough to show that animals with preexisting antibody were refractory to the disease. We were able to infect experimentally a calf with the virus and produce a rise in temperature and mild respiratory symptoms. The chart shows the antibody response of this calf (Hi) following infection (*8*). Also, its penmate (Hr) became infected even though the virus was administered in separate quarters. This calf showed no clinical signs of infection. Of further interest is the evidence of reinfection shown by one of these calves (Hi). This would appear to be an analogous situation to that observed by Chanock and others (*5*) in which reinfection of children was common and produced a mild or inapparent infection.

Table 2. Distribution by month of parainfluenza 3 antibodies measured in cattle by complement fixation and hemagglutination inhibition tests

Month	Number tested	Complement fixation		Hemagglutination inhibition	
		Number positive [1]	Percent positive	Number positive [2]	Percent positive
1958					
June	71	4	5. 6	58	81. 6
July	148	9	6. 8	127	85. 8
August	82	9	10. 9	46	56. 1
September	30	3	10. 0	24	80. 0
November	129	29	22. 9	85	65. 9
December	76	18	23. 2	55	70. 5
1959					
January	[3] 112	5	4. 4	85	76. 0
February	[3] 31	3	9. 6	23	74. 1
March	[3] 107	3	2. 8	92	86. 0

[1] Complement fixation antibody of 1:8 or greater.
[2] Hemagglutination inhibition antibody of 1:20 or greater.
[3] These serums were tested approximately 1 year after the other serums were tested.

Table 3. Distribution by State of parainfluenza 3 antibodies measured in cattle by hemagglutination inhibition tests

State	Number tested	Number positive (1:20 or greater)	Percent positive
Maryland	339	245	72
Virginia	454	319	70
Pennsylvania	134	114	85
Indiana	163	138	84
Iowa (Sioux City)	32	17	53
Minnesota (St. Paul)	28	21	75
Michigan	21	20	95
Illinois (Chicago)	20	14	70
Missouri (East St. Louis)	17	15	88

A serologic survey of cattle being slaughtered was conducted in Baltimore, Md. (*8*). Table 2 shows the numbers of cattle positive by months as measured by the hemagglutination inhibition and complement fixation tests. While the numbers of positive cattle by the hemagglutination inhibition test were essentially similar each month, the complement fixation test (a test showing only recent bovine infections) showed a marked increase in positives in November and December—months when shipping fever or bovine respiratory disease is more prevalent.

As shown in table 3, cattle from all of the States tested had varying numbers of positives. Roughly 75 percent of all cattle tested had antibodies. Serologic evidence of infection of cattle has also been shown from as far off as Tahiti and Japan.

Preliminary studies with formalin-inactivated vaccines suggest that protection can be produced (*9*).

Parainfluenza 3 viruses recovered from man and animals (*4*), although sharing an antigenic similarity, as in table 4, show a species distinction (*10*). Guinea pigs exposed to a single aerosol infection with the human or bovine prototype viruses developed fourfold or greater antibody responses to the homologous than to the heterologous strain of the virus. However, when guinea pigs were exposed to multiple infections with the same viruses, the ability to differentiate serologically the strains of virus coming from humans and bovines was lost.

Gastrointestinal Tract Viruses

By use of the tissue culture method, a great number of viruses have been recovered from the gastrointestinal tract of man. Many of these belong to the enterovirus group (*11*). Certain of these enteroviruses (poliomyelitis, Coxsackie, and some of the ECHO viruses) are known to cause disease in man. However, the relationship of many of the enteroviruses to disease is circumstantial or unknown.

Many viruses have also been recovered from the gastrointestinal tract of animals. There has been a tendency, in most instances without adequate data, to include a number of these viruses in the enterovirus group. Several viruses, however, have been shown to possess the qualities of enteroviruses, such as mouse-poliomyelitis (Theiler's encephalomyelitis) virus and one recovered from normal swine by Betts (*12*) that produces central nervous system symptoms in colostrum-deprived pigs.

Table 4. Hemagglutination inhibition antibody titers of strain-specific guinea pig serum pools when tested with human and bovine strains of parainfluenza 3 virus from various parts of the United States, Canada, and other countries

Number of strains showing indicated pattern	Reciprocal of hemagglutination inhibition titer	
	HA–1 guinea pig serum pool	SF–4 guinea pig serum pool
Human:		
5	80	20
6	160	20
7	160	40
5	320	80
Bovine:		
1	40	320
4	20	160
1	<20	80
1	<20	40

Table 5. Virus isolation and serologic data on a 3-day-old Holstein calf inoculated intranasally with a human strain of type 2 reovirus

Days after inoculation specimen was obtained	Virus isolation results			Hemagglutination-inhibition antibody titers		
	Feces	Nose	Urine	T1	T2	T3
0	0	0	------	<10	20	40
1	0	0	0	------	------	------
2	0	0	------	------	------	------
3	0	0	------	<10	20	40
4	0	0	------	------	------	------
5	0	0	0	------	------	------
6	+	0	0	<10	40	20
7	+	0	0	------	------	------
8	+	+	------	------	------	------
9	+	0	------	<10	80	20
10	0	0	0	------	------	------
11	0	0	------	------	------	------
12	0	0	0	20	≥320	20
13	0	0	------	------	------	------
14	0	0	------	------	------	------
15	0	0	------	10	160	<10
22	------	------	------	10	160	<10
29	------	------	------	<10	160	<10

In our laboratory, we have been conducting a study for the past 1½ years on the biology of the viruses recovered from the gastrointestinal tract of cattle. Some objectives of this work are (*a*) to study the seasonal prevalence of these viruses, (*b*) to investigate the lateral spread of these infections, and (*c*) to explore possible relationships of such organisms to those of man.

So far, we have only published studies on the reoviruses. The term "reovirus" was recently proposed (*13*) as a group name for a number of viruses formerly designated as being identical with, or related to, ECHO type 10. The reoviruses were removed from the ECHO group and placed in this new classification because they share a number of important biological properties, such as size and type of cytopathogenic effect in tissue culture, which distinguishes them from the other ECHO viruses. Rosen (*14*) has shown that the human and animal viruses which fit into this group can be segregated into three distinct serologic types, referred to as types 1, 2, and 3.

This group of viruses would appear to have a wide host range, having been recovered from cattle (*15*), mice (*16*), man, chimpanzees, and monkeys (*13*). There is also serologic evidence of infection in rabbits, guinea pigs, different species of monkeys, horses, swine, cats, and dogs (*17*). No antibodies have been found in chickens or turkeys (*14*).

Reoviruses have been recovered from children with mild febrile illness (*18*), those with diarrhea, and a child with steatorrheic enteritis (*13*). In animals, one of the virus types was recovered from cases of rhinitis in chimpanzees and a similar type from the lung of a monkey dying of pneumonia (*13*). These viruses have been recovered in different parts of the world from uninoculated monkey kidney tissue cultures (*19, 20*).

Only the recovery of type 3 reovirus from cattle has been reported in the literature (*15*); however, we have recovered all three types (unpublished data). Calves have been infected with all three human types. No signs of illness were observed, but, as shown in table 5, relative to type 2 reovirus, the virus was excreted in the feces and specific antibody was produced. While these experiments were being conducted, a 9-month-old Hereford calf was housed in the same barn. The calves received aerosols of various reovirus types outdoors so the Hereford calf never came in contact with the virus from this source. Nevertheless this calf became infected with all three virus types (table 6).

Table 6. Serial hemagglutination inhibition antibody titers of a 9-month-old Hereford calf in contact with calves experimentally infected with human reoviruses

Date of serum (1958–59)	HI antibody titers		
	Type 1 [1]	Type 2 [2]	Type 3 [3]
10/31	<10	<10	<10
11/14	<10	<10	<10
11/21	<10	<10	<10
11/29	<10	<10	<10
12/5	40	<10	<10
12/11	40	<10	<10
1/19	80	<10	<10
2/6	80	<10	<10
2/13	80	<10	<10
2/20	160	10	<10
2/27	160	20	<10
3/6	160	10	<10
3/13	160	10	<10
3/22	160	20	20
4/27	40	10	10
5/17	40	20	10

[1] Contact inoculated 10/31.
[2] Contact inoculated 1/30.
[3] Contact inoculated 2/28.

The type 3 virus recovered from the naturally infected calves reacted in the hemagglutination inhibition test similarly to the human isolates.

No illness was observed in any of the calves from which we recovered these viruses, nor was any illness seen in experimentally infected calves. There is as yet no evidence whether cattle infect man or vice versa.

Conclusion

It has become increasingly evident that disease in man and animals represents only a small part of the total picture of infection. This would suggest that man and animals and many of their parasites have had a long history of "togetherness" in which an amiable relationship has been established. If this is so, then it would seem that infections by the parasites of man and animals would tend to stay within the same species rather than change long-established patterns of behavior. However, man may get into trouble when circumstances interject him into the midst of some of the animal infection cycles for which his past antibody experience would ill serve him or he would be exposed to groups of organisms which have no related counterparts in man; this latter possibility is illustrated by Q fever infections of man. Rickettsial infections, at least in this country, are not common. It would appear that infection of cattle and sheep with *Coxiella burnetii*, the causative agent of Q fever, is an innocuous event even though the organisms multiply in large numbers in the placenta and other organs. This infection of animals would have gone unnoticed had not man intruded into the environments of the animals and developed a very obvious, debilitating disease.

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Glaucoma Detection Program

In a new plan to speed up the detection of glaucoma in its early stages and thus to reduce the toll of blindness, the Public Health Service is distributing to all States and local health agencies conducting glaucoma detection programs questionnaires on the extent, methods, and results of the programs. The National Society for the Prevention of Blindness will make the questionnaires available to all its affiliates.

The Service will analyze the information and issue periodically summaries for the use of the health agencies.

In addition to indicating the actual prevalence of glaucoma in the United States, the plan is designed to provide the Service with complete and continuous information on glaucoma detection activities and will also give official and voluntary health agencies information on new methods of early detection of the disease.