where fewer electrons are involved, values lower than −8 have been reported (*10*). For gallium at the *K* edge −10 has been observed (*11*). In the latter case the maximum negative value of f' occurs close to the inflection point of the rising wave of f''. Our extreme value of f' occurred at the inflection point of the rising absorption curve of cesium.

Our results are compared in Fig. 2 with values for some wavelengths available from conventional x-ray sources, to show how much the scattered wave amplitude is reduced at this *L* absorption edge.

The resolution of the monochromator (*9*) is approximately $\Delta\lambda/\lambda = 10^{-3}$, where λ is the x-ray wavelength. Thus we are measuring f' averaged over this wavelength range. It is possible that with a more monochromatic beam an even larger negative value of f' could be observed. This method is general, and similar experiments can be carried out with other elements at either the *K* or the *L* edge.

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Enzyme-Linked Immunosorbent Assay for Identification of Rotaviruses from Different Animal Species

Abstract. *Rotaviruses cause gastroenteritis in man and a wide variety of animal species. They cross-react in many immunologic tests and have a similar appearance by electron microscopy, making differentiation among them difficult. Rotaviruses derived from different host species were distinguished by postinfection serum blocking virus activity in an enzyme-linked immunosorbent assay (ELISA). Thirty-three rotavirus isolates from children living in three different parts of the world could not be differentiated by this technique, but they were distinct from four strains recovered from calves, and a series of strains isolated from piglets, foals, monkeys, and infant mice. The four bovine strains were similar, but they could be differentiated from the other animal strains, each of which exhibited a distinct pattern when tested by the ELISA blocking technique.*

Rotavirus is an important cause of gastroenteritis in infants and young children (*1*, *2*). Rotavirus infections have been documented in newborn calves, piglets, lambs, nonhuman primates, and other animals (*3*). Different members of the rotavirus group are similar in appearance by standard electron microscopic techniques, and they cross-react in a variety of immunological tests (*4*, *5*).

Several species of newborn animals are susceptible to infection with human rotavirus; however, the role of animal rotaviruses in human disease and the exchange of rotaviruses among species is not known (*6*, *7*). Elucidation of this area has been hampered by the lack of a simple method for distinguishing the different rotaviruses. This report describes the use of an enzyme-linked immunosorbent assay (ELISA) to distinguish members of the rotavirus group.

Human rotavirus was obtained from children with symptomatic diarrheal illness living in Washington, D.C. (strains USA 1 to 17), Santa Maria Cauque, Guatemala (Guat 1 to 10), and Dacca, Bangladesh (Bang 1 to 6). The specimens were tested either as a 2 percent stool suspension or a 2 percent stool filtrate. The animal viruses were obtained as described in Table 1.

Serums that contained antibodies to human rotavirus were obtained from children convalescing from rotavirus infection. Six serums were available from children living in the United States (infected with strains USA 1 to 6) and three were from children living in Bangladesh (infected with strains Bang 1 to 3). Antiserums to human rotavirus were also obtained from gnotobiotic calves and piglets (experimental infection serums) following infection of these animals with strains of human rotavirus (*6*, *7*). Antiserums to the UK and NCDV bovine viruses and to horse rotavirus were obtained from animals infected with the

Table 1. Viruses for ELISA blocking study.

Virus	Host	Country	Year (original isolate)	Source	Passage
USA 1 to 17	Human	United States	1974–1977	Human d.s.*	Original
Bang 1 to 6	Human	Bangladesh	1976	Human d.s.	Original
Guat 1 to 10	Human	Guatemala	1964–1967	Human d.s.	Original
NCDV 1	Calf	United States	1967	Bovine d.s.	Three times in gnotobiotic calves
NCDV 2 to 3	Calf	United States	1972	Bovine d.s.	Original
UK-1	Calf	United Kingdom	1973	Bovine d.s.	Original
P-1	Pig	United States	1974	Piglet d.s.	Five to six times in piglets
H-1	Horse	United Kingdom	1975	Foal d.s.	Original
EDIM	Mouse	United States	1957	Pooled mouse d.s.	Multiple times in mice
SA-11	Nonhuman primate	South Africa	1958	Simian rectal swab	Multiple times in African Green monkey kidney cells (AGMK)
"O"	Unknown	South Africa	1965	Intestinal wash cattle and sheep (offal)	Multiple times in AGMK

*Abbreviation: d.s., diarrhea stool.

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respective agents (Table 2). Antiserums to piglet and mouse rotaviruses were obtained from animals first infected orally with virus and then inoculated parenterally with virus emulsified in Freund's complete or incomplete adjuvant (*8*). Hyperimmune serums to human virus (USA-7), bovine virus (NCDV-1 and UK-1), simian virus (SA-11), and "O" agent (virus of unknown natural host) were produced in goats and guinea pigs by parenteral administration of purified virus mixed with Freund's incomplete adjuvant (*9*).

Viruses and antiserums (Tables 1 and 2) were assayed by means of an ELISA blocking test (*10*). Serums were serially diluted fourfold starting with a 1:10 dilution, and then were incubated for 2 hours at 37°C with an equal volume of solution containing rotavirus antigen. The unbound antigen was assayed by basic ELISA with hyperimmune goat antiserum to human rotavirus as the precoat; hyperimmune guinea pig antiserum to human rotavirus and alkaline phosphatase labeled goat antiserum to guinea pig globulin served as the indicator system (*11*). Serum from animals prior to infection or from normal newborns was the control serum. To ensure equivalent potency of reagents, each virus was first titered by ELISA to determine its limit of detectability, and ten times that concentration was used for the blocking test (10 units of antigen or virus). Similarly, each serum was titered for its ability to block 10 units of the homologous virus; if necessary, the serum was diluted to achieve approximately 50 percent blocking of 10 units of homologous virus at a working dilution of 1:1000.

The percentage blocking at each dilution was determined by the equation $(1 - A_2/A_1) \times 100$, where A_1 and A_2 are the absorbencies at 400 nm of the ELISA reaction after incubation with serums obtained before (A_1) and after (A_2) infection. The dilution that gave 50 percent blocking (BL_{50}) was determined (Fig. 1). Each virus strain was tested in duplicate against each antiserum. Statistical significance was determined by Student's *t*-test.

The antiserums used in the basic ELISA assay showed equal reactivity with different strains of rotavirus, regardless of the host species from which the virus was isolated. When tested in a blocking assay, these hyperimmune serums also blocked all types of rotavirus equally (Table 3).

However, serum obtained after gastrointestinal infection blocked the infecting rotavirus (homologous virus) more than it blocked rotaviruses derived from other host species (heterologous viruses); the

Table 2. Antiserums for ELISA blocking study.

Viral antigen		Host immunized	Mode of immunization*
Species	Strain		
Human	USA 1 to 6	Human	Natural
Human	Bang 1 to 3	Human	Natural
Human	USA 7 to 14	Calf	Experimental
Human	USA-8	Piglet	Experimental
Human	USA-7	Goat	Hyperimmunization
Human	USA-7	Guinea pig	Hyperimmunization
Calf	NCDV-1	Calf	Experimental
Calf	NCDV-1	Guinea pig	Hyperimmunization
Calf	UK-1	Calf	Experimental
Calf	UK-1	Guinea pig	Hyperimmunization
Piglet	P-1	Piglet	Experimental/hyperimmunization
Horse	H-1	Horse	Natural
Mouse	EDIM	Mouse	Experimental/hyperimmunization
Simian	SA-11	Guinea pig	Hyperimmunization

*Natural signifies that the serum was collected following naturally occurring rotavirus gastroenteritis. Experimental signifies that the serum was obtained following experimental introduction of the rotavirus into the gastrointestinal tract of the animal. Hyperimmunization signifies that the serum was obtained following parenteral immunization of the animal using incomplete Freund's adjuvant. Experimental hyperimmunization signifies that the animal was first infected orally and then boosted parenterally.

Table 3. Reciprocal serum dilution (log_{10}) producing 50 percent blocking (BL_{50}) of 10 units of antigen in ELISA assay. The maximum standard deviation noted for any determination was 0.3. The differences in BL_{50} of rotaviruses from different host species were statistically significant ($P < .001$) when infection serums were blocking agents. Differences in BL_{50} of different strains from the same host species were not statistically significant. Italicized values represent detected interaction between the virus strain and its homologous antibody.

Virus		Postinfection serums									Hyperimmune serums				
Host species	Strain	Human anti-USA 1 to 6	Human anti-Bang 1 to 3†	Bovine anti-NCDV-1	Bovine anti-UK-1	Porcine anti-P-1‡	Equine anti-H-1	Murine anti-EDIM‡	Bovine anti-USA 7 to 14§	Porcine anti-USA-8	G.P.‖ anti-USA-7	Caprine anti-USA-7	G.P. anti-NCDV-1	G.P. anti-UK-1	G.P. anti-SA-11
Human	USA 1 to 17¶	*3.4*	*3.0*	1.3	1.5	1.4	1.0	1.5	*3.1*	*3.0*	3.3	3.6	3.1	2.9	2.8
	Bang 1 to 6**	*3.1*	*3.2*	0.9	1.1	1.3	0.9	1.4	*2.9*	*2.8*	3.1	3.4	3.4	3.1	2.6
	Guat 1 to 10††	*2.9*	*3.0*	1.1	1.0	1.4	0.8	1.5	*2.8*	*2.9*	3.4	3.5	3.1	3.1	2.8
Calf	NCDV 1 to 3‡‡	1.1	1.3	*3.1*	*2.7*	1.2	1.0	1.3	1.2	1.4	3.2	3.9	3.8	3.6	2.9
	UK-1	1.3	1.4	*2.9*	*3.1*	1.1	1.0	1.1	1.4	1.3	3.4	3.9	3.7	3.6	2.6
Piglet	P-1	1.3	1.6	1.1	1.4	*3.5*	0.9	1.2	1.2	1.1	3.6	3.5	3.4	3.1	3.0
Horse	H-1	1.5	1.1	1.4	1.2	1.3	*2.7*	1.4	1.3	1.2	3.0	3.7	3.2	2.7	2.9
Mouse	EDIM	1.4	1.3	0.9	1.1	1.6	1.2	*3.6*	1.1	1.3	2.9	3.5	3.3	3.4	3.0
Simian	SA-11	1.5	1.4	1.1	1.5	1.3	0.8	1.3	1.4	1.1	3.1	3.4	3.0	3.3	3.2
Unknown	"O"	1.3	1.4	1.1	1.1	1.6	1.0	1.4	1.1	1.0	2.9	3.4	3.1	2.9	2.6

*Mean of six separate human convalescent serums obtained from human convalescents after infection with human rotavirus strains USA 1 to 6. †Mean of three separate serums obtained from human convalescents after infection with human rotavirus strains Bang 1 to 3. ‡Produced by gastrointestinal infection followed by parenteral hyperimmunization. §Mean of eight separate serums obtained from convalescent cattle after infection with human rotavirus strains USA 7 to 14. ‖Abbreviation: G.P., guinea pig. ¶Mean of 17 separate human rotavirus strains tested; USA 1 to 17. **Mean of six separate human rotavirus strains tested; Bang 1 to 6. ††Mean of ten separate rotavirus strains tested; Guat 1 to 10. ‡‡Mean of three separate bovine strains tested; NCDV 1 to 3.

BL_{50} of homologous serum was 50 to 100 times higher than the BL_{50} of heterologous serums, even when gastrointestinal infection was followed by hyperimmunization. The mean BL_{50} was 3.0 ± 0.1 for homologous serums and 1.2 ± 0.1 for heterologous serums ($P < .001$); in no case was overlapping reactivity observed between the two types of serums. Differentiation was not possible within the human strains or the bovine strains. However, the human and bovine strains were distinct from each other and from the rotaviruses of porcine, equine, simian, and murine origin, as well as from the "O" agent. Viruses of porcine, equine, and murine origin also exhibited specific reactivity patterns. Homologous infection serums were not available for the simian SA-11 virus or the "O" agent, but these viruses did not give similar reaction patterns to any of the other agents tested.

When calves or piglets were experimentally infected with human virus, the resulting antiserums blocked human rotavirus more effectively than bovine or porcine rotaviruses (Table 3). Similarly, virus recovered from feces of animals infected with human rotaviruses was blocked by antiserum to human rotavirus more efficiently than antiserum to calf or piglet rotaviruses. These results indicate that blocking activity is related to the virus strain rather than to the species of animal in which it is propagated.

We have shown that rotaviruses from different species can be distinguished by means of an ELISA blocking test utilizing serum obtained following infection. A rotavirus isolate diluted to 10 units of antigen can be tested against a panel of antiserums to determine whether one blocks with a BL_{50} at least ten times higher than the others. Similarly, a serum with antibody to an unknown rotavirus can be tested against a panel of agents with known specificity to determine which virus gave rise to the antibody. The assay is applicable regardless of the animal from which a particular virus strain or antiserum is derived.

Specificity was noted only with serums containing antibody induced initially or solely by infection. Serums obtained from animals only immunized parenterally with antigen prepared by the described techniques (*9*) reacted equally well with all of the rotaviruses. This suggests that such serums contain large amounts of antibody directed against common viral determinants, while serums collected after gastrointestinal infection contain antibody directed primarily against specific determinants.

Our findings confirm those of Thouless *et al.*, who were able to distinguish between different groups of animal rotaviruses by an immunofluorescence method (*12*). Woode *et al.* were able to partially distinguish animal and human rotaviruses by immune electron microscopy (*13*). However, neither of these methods is practical for large-scale epidemiologic studies.

Currently, the most specific method for distinguishing members of the rotavirus group is analysis of polyacrylamide gel migration patterns of different RNA segments of the rotavirus genome (*14–16*). Such analyses have demonstrated differences in the rate of migration of a varying number of RNA segments of rotaviruses derived from different species. Different rotavirus strains which infect the same species can vary by as many as three segments. The fact that the ELISA blocking test was able to distinguish viruses from different species but not viruses from the same species suggests that the RNA segments which differ among viruses from the same species code for proteins that are not involved in species specificity as measured by this method. Further studies on the proteins encoded by these RNA segments are necessary to elucidate this point. However, since study of the human virus requires a large quantity of rotavirus-rich human feces or fecal material from an experimentally infected gnotobiotic newborn animal, the method of RNA segment analysis is impractical for large-scale investigations.

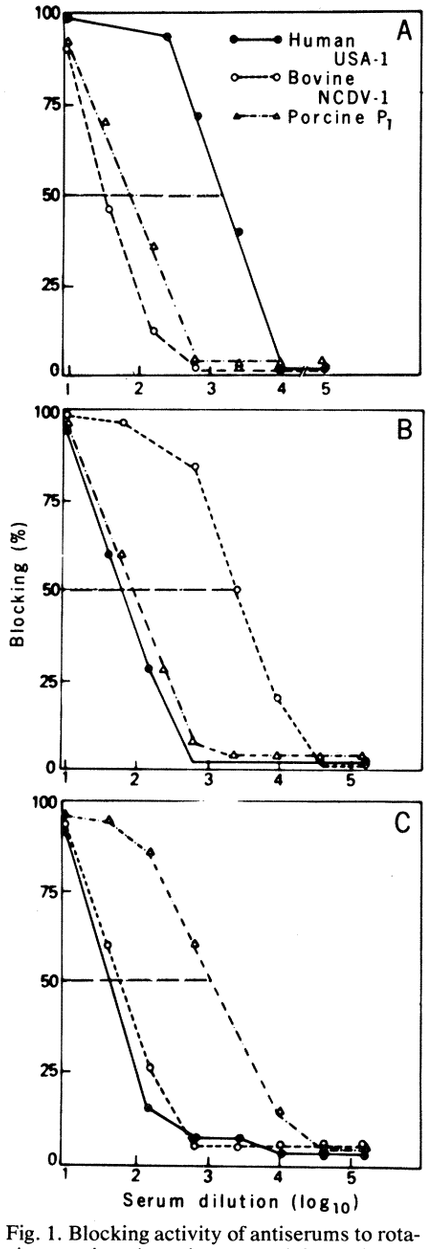

Fig. 1. Blocking activity of antiserums to rotavirus against homologous and heterologous rotaviruses. Antiserums for these titrations were (A) human antiserum to USA-1; (B) bovine antiserum to NCDV-1; and (C) porcine antiserum to P-1.

The observation that rotavirus infections occur in a variety of animal species as well as man has raised the possibility of human to animal or animal to human transmission. The role that animal reservoirs play in harboring rotaviruses for the human population and in the striking seasonal variation of human rotavirus infection (*3*) is also unknown. In the past, technical difficulties have prevented large-scale epidemiological studies to answer these questions. These questions can now be approached in a systematic manner using the ELISA blocking technique (*17*).

Note added in proof: Recently, Zissis and Lambert have described two serotypes of human rotavirus detectable by complement fixation and immune electron microscopic techniques, and Thouless, Bryden, and Flewett have described two, and possibly three different human rotavirus serotypes detectable by the immunofluorescence-neutralization method (*18*). Our further testing of a large number of human rotavirus isolates and infection serums by the ELISA blocking system has revealed the existence of a group which has a different blocking pattern than the other human and the animal rotaviruses. This group presumably represents another serotype of human rotavirus.

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Neuroleptic-Induced "Anhedonia" in Rats: Pimozide Blocks Reward Quality of Food

Abstract. *The dopamine receptor blocker pimozide attenuated lever-pressing and running for food reward in hungry rats. In each case the characteristic behavior of pimozide-treated rats was the same as that of undrugged rats when reward was simply withheld. Drug-induced performance difficulties were ruled out by the presence of periods of normal responding in drug-treated animals. Pimozide appears to selectively blunt the rewarding impact of food and other hedonic stimuli.*

Neuroleptics both alleviate the symptoms of schizophrenia and cause symptoms resembling those of parkinsonism (*1*). Animal studies have not yet suggested important hypotheses for understanding these effects in man, in part because there can be no very adequate model for schizophrenia in lower animals. However, the finding that neuroleptics alter the rewarding quality of intravenous amphetamine injections and intracranial electrical stimulation in rats (*2*) may have implications for understanding complex human behavior. If neuroleptics also block the reward value of natural rewards, this fact may be important for understanding aspects of schizophrenia and parkinsonism. The dysphoria of parkinsonism may reflect a loss of sensitivity to normally rewarding stimuli which parallels the similar loss induced by neuroleptics. The affective abnormalities of schizophrenia may reflect an oversensitivity to such stimuli, which is reversed by neuroleptics. We now report that the neuroleptic pimozide blocks the rewarding (*3*) quality of food for hungry rats, at doses that do not cause incapacitating sedation or motor side effects (*4*).

In the first experiment, four groups of six to eight rats each were tested daily in 45-minute lever-pressing sessions; each lever-press caused delivery of one 45-mg food pellet. Testing occurred 16 to 20 hours after the animals' daily 2-hour period of free food access. When stable lever-pressing for food was established (2 to 3 weeks), the groups were tested in various treatment conditions as follows:

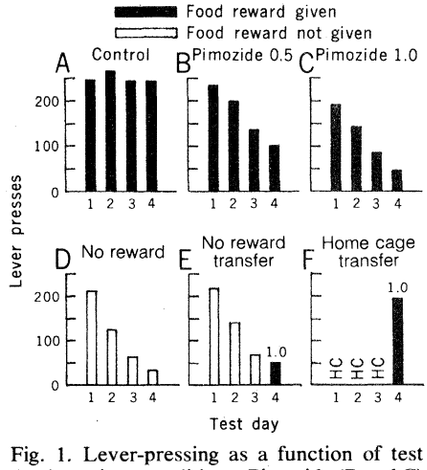

Fig. 1. Lever-pressing as a function of test day in various conditions. Pimozide (B and C) caused animals that received food pellets for lever-pressing to behave like undrugged animals that received no food for responding (D). The control conditions in (E) and (F) are explained in the text. Drug dosage is given as milligrams per kilogram.

one group was tested without reward (the pellet dispenser was not loaded); two groups were tested with normal reward 4 hours after pimozide treatment (0.5 or 1.0 mg per kilogram of body weight); and a control group received normal reward 4 hours after injection with the drug vehicle (*5*).

All groups responded vigorously at the start of the test sessions and slowed to only token responding after 45 minutes of testing. There were no significant differences in the total number of responses or in rates of responding at various times in the sessions (*6*). The fact that pimozide-treated animals responded as often as did the normally rewarded control group shows that there was no significant impairment of normal lever-pressing capacity by these doses of pimozide. However, these initial data do not make clear whether pimozide had any effect on reward function. The pimozide-treated animals, like the nonrewarded animals, might have responded out of habit and not because of food's normal rewarding or response-sustaining quality. It was not possible to say from this experiment whether pimozide-treated animals more closely resembled nonrewarded or normally rewarded animals.

In order to more clearly differentiate the behavior of nonrewarded, normally rewarded, and pimozide-treated rats, additional groups were tested in a second experiment with a repeated-test paradigm; these new groups were tested four times in treatment conditions, with two normally rewarded retraining days between tests.

Performance of nonrewarded animals became progressively less vigorous in this experiment; on the fourth test a mean of less than 30 responses was made whereas more than 200 were made on the first day and in the normally rewarded control condition (Fig. 1, D and A). Animals tested repeatedly with pimozide showed a similar decrease in number of responses per session (Fig. 1, B and C). Thus animals treated with pimozide, like nonrewarded animals, became discriminable from normally rewarded control animals by the fourth test day even though they were not so initially (*7*). The difference between pimozide-treated and control animals was greatest in the high dose condition.

The progressively reduced responding seen in successive pimozide tests cannot be attributed to cumulative drug effects, but must reflect some learning experience in the pimozide tests. This is clear from the performance of two additional groups. One group was given the first three pimozide injections (1.0 mg/kg) in

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