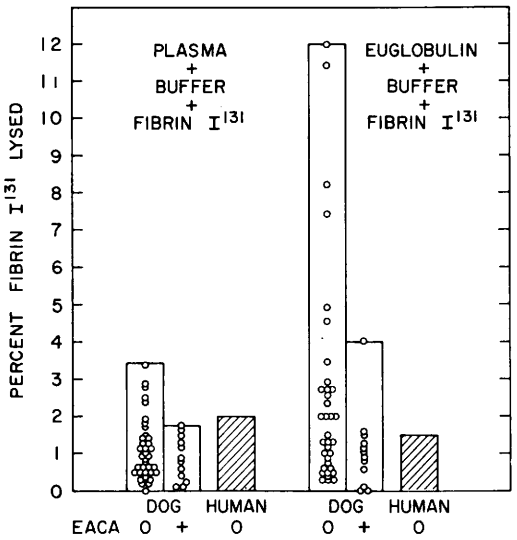

FIG. 1. Fibrinolytic activity of dog plasma and plasma euglobulin fraction before and after EACA treatment.

control samples and one of 12 samples from treated dogs. Neither profibrinolysin nor anti-fibrinolysin (progressive) concentrations were changed following EACA.

Fibrinogen I^{131} survival. Table I illustrates the half-life of fibrinogen I^{131} in control and experimental dogs. No increased survival was noted in the treated dogs. Half-life in the control dogs approximated our previous observation of 2.4 days(6).

Comment and summary. The average daily dose of EACA was 9.0 g, a very large amount as compared to the usual human dose of 10 to 20 g per day. *In vitro* tests (not illustrated) demonstrated that EACA inhibited dog fibrinolysin and SK-activation of profibrinolysin at concentrations of 0.02-0.06%. In the treated dogs the "spontaneous" fibrinolytic activity of the plasma and its euglobulin fraction were significantly lessened. No changes in coagulation factor levels or in survival of fibrinogen I^{131} were noted.

TABLE I. Fibrinogen I^{131} Half-Life (Days).

Dog No.	No EACA	Dog No.	EACA	
620	1.85	620	2.25	(2)*
547	2.05	547	3.3	(1)
545	2.2	545	2.1	(1)
696	2.45	696	2.05	(2)
538	2.65	538	2.0	(2)
525	3.3	525	1.7	(2)
542	1.75	622	1.75	
856	2.05	698	1.80	
611	2.25	619	1.90	
490	2.35	513	2.10	
700	2.55	576	2.05	
711	2.70	1770	3.05	
Mean	2.35		2.17	

* Order of test in parentheses.

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Serological Comparison with Rabbit Antisera of Hog Cholera Virus and Bovine Virus Diarrhea Virus.* (28795)

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Cross precipitin reactions by the diffusion technique(1,2) suggested an antigenic relationship between hog cholera(HC) virus and bovine virus diarrhea (BVD) virus. Comparison of these viruses, however, by cross neutralization, using convalescent BVD sera produced in cattle and convalescent HC sera produced in swine, indicated that the two viruses were different, although repeated inoculations of HC virus into swine allowed

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sera of some pigs to neutralize BVD but with a comparatively lower titer(3,4). The precise relationship between these viruses seemed further obscured after an inoculation of BVD virus was shown to protect pigs against an inoculation of HC virus that killed uninoculated littermate controls(5). This protection did not appear to be the result of complete immunity with demonstrable antibodies, but seemed to be an induction of primary response which accelerates antibody formation after exposure to HC virus(6). Because BVD virus and HC virus can be propagated in rabbits(7,8), comparison of both viruses in a single animal species not considered a natural host for either virus appeared desirable.

Methods. Six rabbits were divided in 2 groups of 3 each. In 1 group, each rabbit was given intravenously 10 ml of a 10% spleen suspension from a pig infected with virulent strain A HC virus. After 3 weeks, one of these rabbits again was inoculated with hog cholera virus, another was inoculated intravenously with 10 ml of tissue cultured Oregon strain BVD virus, while the remaining rabbit was not reinoculated. In the other group, each rabbit was inoculated with 10 ml of tissue cultured BVD virus and, after 3 weeks, one was given BVD virus, another was given HC virus, while the remaining rabbit was not reinoculated. This study was repeated.

All rabbits were bled at time of the initial inoculations, again 3 weeks later when second inoculations were made, and 4, 7, 10, 14, and 21 days afterwards. Antibody assays for BVD and HC antibodies were conducted by standardized neutralization tests(9,10).

Results. Each rabbit that had received a single inoculation of BVD virus developed BVD antibody titer of 2 after 21 days, and this titer increased slightly to 10 at the end of 6 weeks. Rabbits that had received a second inoculation of either BVD or HC virus produced BVD antibody titer of about 40 within 4 to 7 days. Sera from rabbits that had received either 1 or 2 injections of BVD virus did not neutralize HC virus. Rabbits that had received BVD virus followed by HC virus developed an antibody titer of 20 to each of the viruses within 4 to 7 days, and later this titer increased to 60 (Fig. 1).

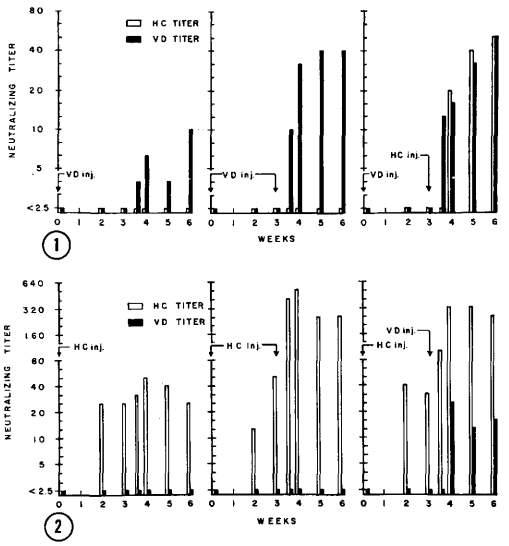

FIG. 1. Neutralizing antibody response of rabbits to a single inoculation of bovine virus diarrhea (BVD) virus, to 2 inoculations of BVD virus, and to an inoculation of BVD virus which was followed by an inoculation of hog cholera (HC) virus.

FIG. 2. Neutralizing antibody response of rabbits to a single inoculation of hog cholera (HC) virus, to 2 inoculations of HC virus, and to an inoculation of HC virus which was followed by an inoculation of bovine virus diarrhea (BVD) virus.

Within 21 days, after a single inoculation of HC virus, rabbits developed a titer of 25, which later increased slightly. A second inoculation of HC virus stimulated secondary response and an HC antibody titer of 640 was found; no BVD antibody was detected. When the second inoculation consisted of BVD virus, however, secondary response was observed to both HC virus and BVD virus, with a titer of approximately 320 for HC virus and 40 for BVD virus (Fig. 2).

Discussion. If the neutralization test can be interpreted as accurately differentiating between types, the evidence produced here has shown clearly that HC virus and BVD virus are distinct immunological types. Yet, undoubtedly these two viruses should be considered heterotypes because an antigenic relationship has been demonstrated by the gel-diffusion method(1,2) and by immunofluorescence(11). Also, both viruses have been shown to have the same density gradient, a

similar size, both were sensitive to ether and chloroform, the stability of each was similar at the same range of temperatures, and both were shown to be RNA viruses(3,4).

Of particular interest, reciprocal induction of primary response in rabbits between HC and BVD viruses should be considered another important criterion for demonstration of heterotypic relationship. In the natural host, secondary response was not observed in calves given BVD virus followed by HC virus nor in pigs given HC virus followed by BVD virus. Certain confusion in heterotypic relationships by this criterion, therefore, may follow use of sera from natural hosts for comparative purposes. Confusion also has resulted from repeated injections of HC virus in pigs that led to cross neutralization, although homotypic titers were comparatively greater, but whether this was the result of quantitative or qualitative effects was not determined. In fact, a significant problem suggested by these studies is a determination of whether heterotypically produced antibodies are a mixture or a single antibody.

Summary. Comparison between BVD virus and HC virus in rabbits showed no cross neutralization. Inoculation of either virus followed by the other produced antibody quickly (secondary response) to both. In addition to other shared characteristics, induction of primary response is considered additional proof of heterotypic relationship.

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Endotoxin Induced Resistance to Infections and Tolerance. (28796)

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Among the various biological effects elicited by bacterial endotoxins, the most important are the ability to produce fever, to cause leukopenia, to damage tumors, to elicit the Shwartzman phenomenon and to increase resistance to a variety of infectious agents. When endotoxin is administered repeatedly, tolerance to many of its actions develops. This diminution of action on repeated administration develops with respect to the lethal effect of endotoxin, its pyrogenicity, its leukopenic action and to the occurrence of the Shwartzman phenomenon. The purpose of this present study was to ascertain whether repeated administration of endotoxin might result in a diminution of its ability to increase resistance to infections. Knowledge regarding such relationships is of importance. If it could be shown that tolerance to the endotoxin-induced increased resistance does not develop, such a finding, apart from its therapeutic implications, would be an indication that increased resistance to infections is produced in a different manner than the other actions of endotoxin to which tolerance can be produced.

Materials and methods. All experiments were carried out with Swiss-Webster CF1 male mice weighing 18 to 22 g. Endotoxin prepared from *E. coli* 026:B6, Difco Batch #449944, was used in all experiments.

To measure lethality, endotoxin was in-