The Effects of in utero Viral Infection on Embryonic, Fetal, and Neonatal Survival: A Comparison of SMEDI (Porcine Picorna) Viruses with Hog Cholera Vaccinal Virus

H. W. Dunne, J. T. Wang, C. D. Clark, J. F. Hokanson, T. Morimoto and G. R. Bubash*

SUMMARY

SMEDI and hog cholera viruses were shown to have marked effects upon the survival of the embryo (from conception to 30 days of gestation), the fetus (from 30 days of gestation until birth), and the neonatal pig (from birth until five days after birth). Embryonic infection was characterized by death and absorption of the embryo and in some instances the return to estrus after an irregular estrous cycle. Embryonic infection also may have been responsible for the development of some abnormal pigs. Fetal infection caused death with mummification of one or more fetuses and occasionally all fetuses in the uterus. Infection established in early gestation produced effects on the fetus which apparently persisted until after birth and varied from a persistent viremia (as in hog cholera infection) to an undefined lack of resistance in the newborn (as in SMEDI virus infection). Hog cholera vaccinal virus was the more virulent of the two virus types and reacted somewhat like rubella virus, in that infection apparently could be established in the fetus even in middle trimester of pregnancy, and possibly later. SMEDI viruses, in contrast, were less virulent and were most pathogenic when the dam was infected during the first 30 days of pregnancy. Immunity against either virus could be established in the nonpregnant gilt and was most effective in preventing intrauterine infections with that virus. However, with as many as 10 enteroviruses (five are known to cause intrauterine infection) it was believed that maintaining a closed breeding herd and introducing new stock into contact with the breeding herd at least 30 days before breeding time might be a safer means of control.

RÉSUMÉ

On a démontré que le virus SMEDI (stillbirth, mummification, embryonic death, infertility) et celui de la peste porcine ont un effet prononcé sur la survie de l'embryon, du foetus et du porcelet nouveau-né. A l'état embryonnaire, l'infection entraine la mort et la résorption de l'embryon et, dans certains cas, provoque le retour à l'oestrus après un cycle irrégulier. A ce stade également, l'infection pourrait avoir été la cause d'anomalies. Durant la vie foetale, la maladie entraîne la mort et la mommification d'un ou de plusieurs foetus et, occasionnellement, de tous les foetus présents. Lorsque l'infection apparaît au début de la gestation, elle entraîne des conséquences qui, selon toute apparence, persistent jusqu'après la naissance, allant d'une virémie persistante jusqu'à un manque de résistance mal déterminé du nouveau-né. Le virus de la peste porcine s'avéra le plus virulent des deux, pouvant infecter le foetus jusqu'à la fin du deuxième mois de gestation et peut-être même plus tard. En revanche, les virus SMEDI se révélèrent moins virulents et leur action pathogène fut plus marquée lorsque les truies étaient infectées dans les 30 premiers jours de leur gestation. Il fut possible d'immuniser les truies non-gestantes contre l'un ou l'autre des virus. Dans le cas de 13 entérovirus, cependant, il semble que le meilleur moyen de contrôle etait de garder les animaux reproducteurs en quarantaine et d'introduire tout nouveau sujet dans le groupe, au moins 30 jours avant les accouplements.

*Department of Veterinary Science, The Pennsylvania State University, University Park and the Pennsylvania Agricultural Experiment Station.
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Present address of C. D. Clark: BAI Laboratory, Department of Agriculture, Harrisburg, Pa.
Present address of T. Morimoto: National Institute of Animal Health, Kodaira City, Tokyo, Japan.

INTRODUCTION

The association of SMEDI, porcine picorna (entero) viruses with reproductive failure in swine was reported previously (12). These viruses were isolated from fetuses and stillborn pigs originating on farms where serious intrauterine and newborn losses occurred. Early evidence suggested that the SMEDI viruses which apparently had no acute clinical effects upon the dam, were associated with intrauterine infections resulting in stillbirth, mummification, embryonic death, and infertility. The name SMEDI was derived from the first letters of those conditions for the purpose of identification of the then unidentified viruses. It was further shown that the conditions observed on farms could be reproduced in pregnant, virus-susceptible, properly fed gilts, by the inoculation of SMEDI viruses during the first month of pregnancy (12). Subsequently, characterization studies proved these viruses to be enteroviruses and classification studies showed them to be related to enteroviruses isolated in Canada, Japan, England and other areas of the United States (12, 14, 36, 42). Currently, there appear to be at least 10 serogroups of porcine picorna (entero) viruses (14, 42). SMEDI viruses A, B, C, D and E are included in four of these groups. SMEDI A and D though serologically related are not identical and D is considered a subgroup of A.

The purpose of this study was to confirm the association of SMEDI viruses with reproductive problems and to compare the relative effects of these viruses with the effects of hog cholera virus on the embryo, fetus, and neonatal pig in relation to time of exposure and immunity in the dam. Recently obtained data, and that reported previously (10, 11, 42) were combined in this paper to provide more concrete evidence of the relative importance of SMEDI and hog cholera virus infections *in utero*. Where data were repeated, it was so noted.

MATERIALS AND METHODS

Viruses

The viruses used included three SMEDI viruses, A, B, and C (11) grown on primary porcine kidney cells, and two commercially produced vaccinal strains of hog cholera virus, one lapinized and the other modified by growth in pig leukocytes and then produced as whole blood virus by the inoculation of a pig (10).

Inoculations

The inoculum for SMEDI viruses contained from 1×10^6 to 1×10^7 TCID. Recommended vaccination doses of hog cholera virus (5.0 ml of the commercial vaccine) were used. Viruses were inoculated subcutaneously, orally, and by aerosol. Gilts were exposed to the virus during all seasons and at gestation periods from four to 78 days. Both immune and susceptible gilts were inoculated.

Experimental Animals

There were 145 gilts used in the experiment including 80 principals and 65 controls. With few exceptions, all gilts were of Yorkshire or Yorkshire cross breeds, and were raised as colostrum-deprived pigs derived by hysterectomy. They were maintained in a closed herd except for the occasional addition of a new boar or in one case the addition of new gilts. New animals were maintained in isolation for at least 30 days and had their feces cultured for the isolation of viruses before introduction into the breeding herd.

Susceptibility of Hosts

The immune status of gilts was determined prior to breeding. Only gilts with no detectable neutralizing antibodies were exposed to viruses except in those tests where gilts were intentionally immunized.

Feed

Gilts were handfed with feed commercially prepared according to a formula recommended by swine nutritionists,[1] and containing levels of vitamins A, B_{12} and E well above minimum requirements.

Housing

The facilities varied from sophisticated indoor isolation units under well controlled conditions to outdoor open air isolation pens with cement block floors and walls and 30-foot isolation "corridors" on all sides. All pigs were taken by hysterectomy, and each litter maintained in a separate

[1]Supplied by Dr. J. L. Gobble, Dept. of Animal Science, The Pennsylvania State University.

isolation room. Control gilts were bred so that some farrowed at both the beginning and at the end of the experiment. The outdoor units were used to provide conditions comparable to those "on the farm." Later these units were partially replaced by totally roofed and screened units for all infected animals to eliminate the possibilities of bird and rodent transmission of viruses.

Control Techniques

To demonstrate that the adverse effects observed during the experiment with SMEDI viruses were due to the infecting agent and not other viruses, anti-body titers against the known SMEDI agents were determined on serum samples from all gilts before they were inoculated, and on serum samples taken at the time of hysterectomy. The absence of a rise in titer to viruses other than the inoculated virus indicated a satisfactory test. SMEDI viruses to be inoculated into gilts were previously inoculated subcutaneously into rabbits and into hog cholera susceptible pigs with neither the development of severe itching reactions associated with pseudorabies nor the development of hog cholera or immunity to hog cholera.

In later experiments, tissues from all pigs dying during the experiment were submitted to both frozen section and fluorescent antibody-cell culture test (FACCT) for all SMEDI viruses, hog cholera, and pseudorabies following methods used by others (5, 26, 27, 32, 33). Periodic serological tests of the breeding herd were made for leptospirosis and brucellosis.

All bred gilts on experiments were subjected to hysterectomy at the termination of the gestation period. Blood and serum samples were collected from the dam at that time and the number of live pigs, stillborn pigs, and mummified fetuses was recorded.

The number of corpora lutea (CL) and the number of pigs living five days after birth were recorded only in the last series of experiments. The number of embryonic deaths was calculated to be the difference between the average number of ova which failed to develop in the controls and the average number which failed to develop in the virus infected gilts. The total number of ovulations was calculated to be the number of CL present in both ovaries at the time of hysterectomy. "Normal" loss of ova was considered the average difference between the number of live, stillborn, and mummified fetuses and the number of CL in the control gilts. Abnormal loss of ova, referred to as embryonic deaths was the difference between "normal" loss of ova in the controls and the loss of ova at some stage of development before 30 days of gestation in the infected gilts.

Sections of placenta and dead pigs (and

TABLE I Gross Data on Exposure of Susceptible and Immune Gilts to Viruses During Pregnancy

Immune Status	Day Infected after Breed.	Gilts			No. Pigs			Total Pigs Living 5 Days/Born Alive		C.L./ Fetuses		Pigs Born Abnormal
		Total No.	Non-gravid	Gravid	Live	Still-born	Mummified					
Exposure to SMEDI Viruses												
Suscep.	21–27[a]	32	3	29	193	6	69	35/86	(12)	154/110	12)	4[b]
Suscep.	31–78	7	0	7	62	0	3			55/47	(5)	0
Immune	4–7	2	0	2	22	0	0	19/22	(2)	12/10	(1)	0
Immune	21–27	7	0	7	67	0	1	21/25	(2)	35/31	(3)	0
Exposure of Susceptible Gilts to Both SMEDI and Hog Cholera Virus[d]												
Suscep.	7–8	7	2	5	18	0	23	9/18		40/31	(4)	3[b]
Exposure to Attenuated Hog Cholera Virus												
Suscep.	24[c]	6	4	2	10	2	1	7/10	(2)	22/13	(2)	0
Suscep.	35–42	3	0	3	28	0	2	12/26	(3)	34/30	(3)	0
Suscep.	60[c]	9	2	7	44	7	35	2/44	(7)	100/86	(7)	0
Immune	60–78	7	0	7	65	0	2	53/55	(7)	43/38	(3)	0
Suscep.	all controls[a]	65	6	59	512	5	18	211/269	(29)	163/139	(18)	2

[a] Includes date reported previously (8)
[b] Atresia ani, cleft palate, cerebellar hypoplasia, congenital tremors alone or in combinations.
[c] Reported previously (7)
[d] Aerosol infected with SMEDI virus; contact infected with hog cholera.
CL Corpora lutea
( ) Number of gilts from which data was available.

TABLE II Exposure of Susceptible and Immune Gilts to Viruses. Averages of Data from Table I

Virus Used	Immune Status	Day Infected after Breed.	Ave. No. Pigs per Litter				Excess C.L. (Ave.) Per Litter	Per cent of Pigs Abnormal
			Live	Still-born	Mummi-fied	5-Day[a] Living		
SMEDI	Suscep.	21–27	6.7	0.16	2.4	2.9	3.7	2.1
SMEDI	Suscep.	31–78	8.9	0	0.4	—	1.6	0
SMEDI	Immune	4–7	11.0	0	0	9.5	2.0	0
SMEDI	Immune	21–27	9.6	0	0.14	10.5[b]	1.3	0
SMEDI A and Hog Cholera	Suscep.	7–8	3.6	0	4.6	1.8	2.2	16.6
Hog Cholera	Suscep.	24	5.0	1.0	0.5	3.5	4.5	0
Hog Cholera	Suscep.	35–42	9.3	0	0.67	4.0	1.3	0
Hog Cholera	Suscep.	60	6.4	1.0	3.9	0.29	2.0	0
Hog Cholera	Immune	60-78	9.3	0	0.31	7.6	2.0	0
Control	Suscept.	—	9.7	0.08	0.31	7.3	1.3	0.4

[a] Hysterectomy derived, colostrum-deprived pigs.
[b] Data available from only 2 gilts-see Table I.
CL Corpora lutea

fetuses dying close to the time of hysterectomy) were taken for virus isolation and fluorescent antibody (FA) examination for SMEDI viruses A, B, C, D, and E, hog cholera virus, and pseudo-rabies virus.

RESULTS

The gross data are presented in Table I. It should be noted that these data as presented do not represent total figures for all animals in the experiments. Some of these data were not complete, particularly in earlier experiments, but all data which were available (Table I) were used and provided the basis from which data in Tables II, III, and IV were projected.

Groups are arranged according to the viruses used, i.e. SMEDI virus, hog cholera virus, the two viruses used together, and controls. Within these groups are subgroups based upon the immune status and upon the period of gestation in which they were infected. In column 3, the total number of gilts used in each group is given. Column 4 gives the number of gilts, which at the time of farrowing, were barren. Many of these clearly had returned to estrus but not within the estrous period and were not subsequently detected to be in estrus. The number of gravid gilts in column 5 indicates the number of gilts which subsequently farrowed. There were no abortions. The next three columns contain the total numbers of live, stillborn, and mummified fetuses composing the litters farrowed. These data are complete for all groups. In column 9, the total number of pigs living at five days is compared with the number born alive. The number of litters from which these data were taken is given in parenthesis. These data were fragmentary because survival was not considered in the early experiments and the newborn pigs were used for other purposes when the litters appeared normal. Column 10 also contains some fragmentary data on the number of corpora lutea compared with the total number of fetuses (mummified plus those born alive). The number of gilts involved in some groups was not adequate to be significant. Again, these data were accumulated after it became apparent that much could be learned from the number of corpora lutea present.

Table II presents data in terms of averages per litter, plus the per cent of pigs abnormal at birth. Table III projects the total survival of ova from conception to 30 days of gestation (embryonic stage), to birth (fetal stage), and to five days after birth (neonatal stage). These survival data are calculated on the basis of numbers of CL present at the time of hysterectomy. Table IV projects these data in terms of loss due to embryonic, fetal, and neonatal death during three periods of development.

Embryonic death appeared to be the principle cause of small average litter size (Tables II and IV). This was most pronounced when pregnant gilts were exposed to viruses prior to 30 days of gestation. The highest embryonic death loss (40.9%) occurred in gilts infected with hog cholera virus at 24 days of gestation, but these data were based on only two gilts (four were barren) of which one gilt had only two pigs. The other had eight pigs and was ap-

TABLE III Projected Survival of Ova and Newborn

Virus Used	Immune Status	Day Infected after Breed.	Per cent[a] Gilts Nongravid	Per cent Survival of Ova 30 days Gestation	Per cent Survival of Ova Until Birth	Per cent Survival of Ova 5 Days after Birth	Per cent 5-day Survival/Born Alive
SMEDI	Suscep.	21–27	9.4	71.4	56.5	22.9	40.7
SMEDI	Suscep.	31–78	0	85.5	80.4	nd	nd
SMEDI	Immune	4–7	0	83.3	83.3	75.0	86.4
SMEDI	Immune	21–27	0	88.6	88.6	76.0	84.0
SMEDI A and Hog Cholera	Suscep.	7–8	28.5	77.5	45.0	22.5	50.0
Hog Cholera	Suscep.	24	66.7	59.1	45.4	31.8	70.0
Hog Cholera	Suscep.	35–42	0	88.2	82.3	38.0	46.2
Hog Cholera	Suscep.	60	22.2[b]	86.0	29.1	2.0	4.5
Hog Cholera	Immune	60–78	0	88.4	86.0	82.2	96.4
Control	Suscep.	—	9.4	85.3	80.3	62.9	78.4

[a] Number of ova lost with return to estrus cannot be calculated. Total absorption would alter percentages markedly.
[b] Abortion — unobserved, must be considered here.
nd No data

parently unaffected by the virus. Infection with SMEDI viruses at 21-27 days of gestation caused the second highest embryonic loss (28.6%), and the group with combined hog cholera and SMEDI virus infection had the third highest loss (22.5%). Control gilts experienced a 14.7% loss. Gilts immune to the inoculated viruses and gilts exposed to the viruses after 30 days had embryonic death losses (and survival percentages for ova) comparable to that of the control gilts. Litter sizes for these last groups were also comparable to the control gilts except that the group exposed to hog cholera at 60 days had small litters (ave. 6.4) reflecting marked fetal death losses.

Several gilts were barren in those experiments in which hog cholera, and combined hog cholera and SMEDI viruses, were infected during the embryonic development period. Such gilts generally were not observed to return to estrus although many evidently did, as determined by follicular activity in the ovary at the time of hysterectomy.

Fetal death was reflected almost entirely by the presence of mummified fetuses which died throughout the period from approximately 30 days of gestation until shortly before birth. Sunken eyes and darkened skin (in white pigs) were the first observable indications that death had occurred before the time of birth and that the mummification process had begun. Judging from the gross appearance of fully developed pigs which had died before birth, the condition must be detectable at the most within 48 hours after death of the fetus. The earliest period in gestation that fetal death was detectable was approximately 30 days. These fetuses were recognized by the presence of a delicate rib pattern in small mummified masses which were approximately 2.5 cm in length. It was necessary not only to locate the small mass but also to remove all traces of the dehydrated placenta from the fetus to make such observations.

Fetal death with mummification also contributed to small litter size and was most pronounced (56.0%) in the group infected with both hog cholera and SMEDI viruses (Table IV). The group infected with hog cholera alone was next high with 48.1% fetal death. Hog cholera virus infection alone at 24 days resulted in a 23.2%

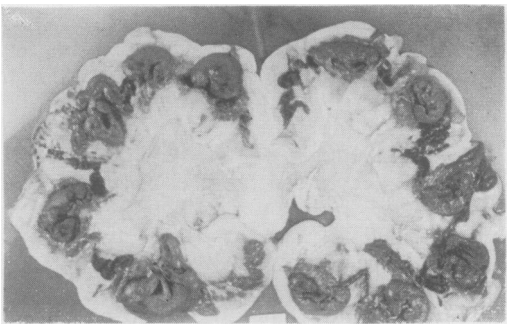

Fig. 1. Eleven mummified fetuses at 112 days of gestation in the opened uterus of a gilt experimentally infected with SMEDI A virus 25 days after conception.

fetal death rate, which was comparable to that associated with infections with SMEDI virus at 21-27 days (21.0%). All of these rates were considerably higher than that for the control gilts (4.3%). Fetal deaths in the immune groups compared favorably with the control group. There were no fetal deaths in the one SMEDI-immune group (only 22 pigs) and only 1/68 (1.5%) in another. There were 2/67 (3.0%) fetal deaths in the hog cholera immune group. In the group where the SMEDI viruses were inoculated at 31 to 78 days of gestation, the fetal death rate was 3/65 (4.6%). In one experiment, infection with vaccinal hog cholera virus at 35 to 42 days of pregnancy resulted in fetal deaths of only 2/30 (6.7%).

Neonatal loss (Table IV) was greatest (95.5%) in the group infected with hog cholera virus at 60 days of gestation. Survival was negligible in this group. Actually, all pigs in this group died before reaching two weeks of age. Neonatal loss in the group infected with SMEDI viruses at 21-27 days was 59.3% which was next high and almost three times the loss experienced in pigs from control gilts (21.6%). The group exposed to the hog cholera virus at 35 to 42 days was next with 53.8% and the combined infection group had a 50.0% loss. Complete data on neonatal survival were available from only 11 of the gilts in the groups immune to the viruses used in the experiment.

The survival of ova (Table III) from the day of ovulation until five days after birth appeared to be more successful in the immune group than in either the infected susceptible groups or in the controls. Survival in the immune groups were 75%, 76%, and 82.2%; the control group was 62.9%; the SMEDI infected susceptible group was 22.9%; and the hog cholera infected susceptible groups were 2.0%, 31.8%, and 38.0%.

Fluorescent antibody technique and FACCT detection and recovery of hog cholera virus from experimentally infected stillborn and newborn pigs was successful in 28 of 45 trials. Nineteen controls were negative. Of 48 stillborn and newborn pigs in SMEDI virus experiments, FAT tests were positive in four pigs and virus isolated in cell culture from only one. Most of the fetal deaths in the SMEDI infected group were in those litters infected between 21 and 27 days of gestation. No FAT tests were conducted on pigs from litters infected at 31 to 78 days. These experiments were done before the FA capability was established. All positive tests for the virus of hog cholera were made on pigs infected at 60 days of gestation and were either alive at birth or died shortly before birth.

Two colostrum-deprived hysterectomy-derived specific pathogen free (SPF) pigs four weeks of age were inoculated with hog cholera virus isolated from an *in utero* infected, newborn pig. They died in 16 and 24 days. The FAT test for hog cholera virus was positive in nasopharynx tissues particularly the tonsils. A chronic course (63 days) was observed in one of two eight-

TABLE IV Projected[a] Per Cent Death Rates for Embryos, Fetuses and Newborn Pigs from Virus Infected Gilts

Virus Used	Immune Status	Day Infected after Breed.	Embryonic Death (Conception to 30 Gestation	Fetal Death (30 days Gestation to Birth)	Neonatal Death (Birth to 5 Days After Birth
SMEDI	Suscep.	21–27	28.6	21.0	59.3
SMEDI	Suscep.	31–78	16.1	4.6	—
SMEDI	Immune	4–8	16.7	0	13.6
SMEDI	Immune	21–27	16.3	1.5	16.0
SMEDI A and Hog Cholera	Suscep.	7–8	22.5	56.0	50.0
Hog Cholera	Suscep.	24	40.9	23.2	30.0
Hog Cholera	Suscep.	35–42	17.7	6.7	53.8
Hog Cholera	Suscep.	60	9.1	48.1	95.5
Hog Cholera	Immune	60–78	11.6	3.0	3.6
Control	Suscep.	—	14.7	4.3	21.6

[a] Discrepancies of percentages are due to the use of the available data which do not represent complete data on all animals for the duration of all experiments. Complete data were not available for many of the earlier experiments (see Table I).

week-old primary SPF pigs inoculated with the same virus as above. Both died of hog cholera. Three eight-week-old and two 14-week-old, SPF pigs placed in contact with the chronically infected pig, contracted hog cholera and died after illnesses of 29, 30 and 75 days. All five of the pigs gave positive FAT and FACCT tests.

DISCUSSION

A definite difference between SMEDI and hog cholera viruses with respect to intrauterine infection was apparently associated with their relative virulence. SMEDI viruses appeared to cause major intrauterine losses only when the gilt was infected before 30 days of gestation. In contrast, hog cholera vaccinal virus was pathogenic through at least 60 days of gestation. It caused marked fetal losses in some groups of gilts but appeared less effective in others. Not all gilts appeared to be susceptible to virus infection particularly to the SMEDI viruses even though they had no detectable antibody titer to the virus prior to experimental infection.

The *in utero* effects of the virus of hog cholera in pregnant, susceptible gilts could be compared best with the *in utero* effects of rubella in pregnant susceptible women (16, 37). Hog cholera virus could infect the fetus at any period up to 60 days of gestation and was reported to be capable of infection at later periods during pregnancy (7). The virus localized in the nasopharynx, particularly the tonsils both in the newborn pig infected *in utero* and the pig acutely infected any time after birth. It could readily be isolated or demonstrated by FAT. It tended to persist in the newborn after birth, following intrauterine (45) infection and provided a source of spread of the infective agent to susceptible pigs.

The duration of such infections was not known, but infections with hog cholera virus in young pigs have been known to persist as long as 95 days (2, 13). Infection with rubella in the newborn infant was shown to persist for more than one year (38). Fetal abnormalities in hog cholera infection have been reported (45) but fetal death was more common. In human rubella infections, the number of abnormalities approached 50% (37). Hog cholera virus appeared to be much more virulent to the fetus than rubella virus. However, abortion was not common.

Infections with SMEDI viruses appeared to react differently from infections with hog cholera in that they appeared to be nonpathogenic to the gilt and often of low pathogenicity for the newborn. However, like hog cholera virus, they had a definite affinity for the fetus. These viruses occasionally could produce polioencephalomyelitis in the fetal and newborn pig but unlike human poliomyelitis virus, abortion was considered rare for the SMEDI virus infection and infrequent for the hog cholera virus infection.

Complete data for all areas of ova survival were not available from many experiments. In the early research reported here, neither the CL nor the five-day survival data were obtained. Also, many newborn pigs of the earlier experiments were utilized for other purposes, particularly if litters appeared normal. It was only after several experiments that many normal appearing litters from SMEDI-infected gilts were recognized as having had poor survival rates. Therefore, survival rates for ova through five days after birth were derived from somewhat fragmentary data as is shown in Table I. An example of the confusion created by the partial data is shown in Table II where survival litter size at birth was given as 9.5 pigs based on seven litters but survival at five days was 10.5 pigs, based on data from two litters only. For this reason, listing the gross data in Table I was pertinent.

The calculation of embryonic death is not without fault, but probably is as close as it is possible with current knowledge. First it assumes that in the controls, the lack of fetuses is most likely to be due to lack of fertilization of the ova rather than death of the embryo. In the infected group, it assumes that the decreased number of fetuses is due to infection and death of the developing embryo before 30 days of gestation with complete absorption. If the cause of the small number of ova developed can be attributed to the virus, it must have affected developing embryos and not the ova or sperm because of the period of gestation at the time of infection. The number of CL proved to be a useful measure in calculating embryonic deaths. However, certain exceptions were made. One gilt had 27 CL. None of the other 144 gilts on experiment had more than 19 CL. Normal ovulation for the pig is between 12 and 18 according to Polge *et al* (31). Twenty-seven CL was considered a case of superovulation,

and was not included in the data. The number of CL was shown by Longenecker *et al* (24) to be relatively constant in 30 gilts in which the CL were marked on day four of gestation. Four of 339 corpora lutea were not detected on the 40th day of gestation and eight were unmarked. The number of CL ranged from eight to 17. Embryos were needed in both horns between days 10 and 12 to maintain pregnancy, while embryos need be present in one horn only after the 12th day of gestation (8). Regression of CL may occur if all of the embryos in one horn are destroyed after the critical period of 10 to 12 days (9). It is also known that failure of one ovary to ovulate does not mean that there will be no fetuses on that side. It has been shown that migration of embryos to the empty side takes place on about day 9 of gestation (15). This prevents termination of pregnancy because of absence of embryos in one born on days 10 through 12. Therefore, the absence of CL on the side of the uterus where all fetuses are dead or where there are no fetuses, introduces a variable outside the limits of reliability. Such data are not valid.

Another factor influencing the data for determination of total survival of ova but which could not be measured was the loss of ova in those gilts which were barren at hysterectomy. Since approximately 10% of all gilts bred returned to estrus, a valid figure could not be assigned to those returning to estrus when infected before 21 days of gestation. Also, if a gilt infected between 21 and 30 days returned to estrus or was found to be barren at hysterectomy it could not be determined if any early return to estrus was missed or simply did not occur. The isolation of these animals made detection of estrus more difficult than under normal breeding conditions. Evidence of recent ovulation was sometimes observed in ovaries from such animals indicating that at least in the period near the time of hysterectomy the ovaries were functioning in an apparently normal manner.

A major problem in the experiments reported here was the inability to retrieve the SMEDI virus from fetuses or neonatal pigs which died shortly after birth. A possibility here is that the period at which the best fetal infection was achieved was very early in gestation, i.e. 20 to 27 days after breeding. No FA tests were conducted on pigs from sows infected with SMEDI viruses later in pregnancy. Even hog cholera vaccinal virus was not recovered from stillborn pigs and neonatal pigs from sows infected at 24 days. Recovery of the virus of hog cholera was quite successful, however, from pigs farrowed by gilts vaccinated at 60 days of gestation. It may be that unless the virus is passed from fetus to fetus within the uterus, subsequently causing some fetal death near the end of gestation or unless infection is in the middle or last part of gestation, the virus may not survive, at least in an infectious form, until the time of farrowing. All original SMEDI isolates were from stillborn pigs or fetuses not dead sufficiently long to show signs of mummification. This means they were probably dead not more than 48 hours. The first easily recognized sign of mummification, which is largely a dehydration process, is depression of the eye.

In addition to the SMEDI, hog cholera and pseudorabies viruses, viruses of an exotic nature have been shown to cause intrauterine infection in swine including the Japanese encephalitis virus (4, 18, 21, 38), Japanese hemagglutinating virus (35), and foot and mouth disease virus (40), none of which are found in North America at the time of this publication.

Recently, a new unclassified virus was reported in England (6) associated with porcine reproductive disorders, and IBR-IPV (infectious bovine rhinitis infectious pustular vaginitis) virus was isolated from the vaginal tracts of gilts with reproductive problems in Denmark (36). The roles of other viruses such as transmissible gastroenteritis, influenza and even swine pox with respect to *in utero* infection have yet to be explored.

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