Experimental Feline Herpesvirus Infection in the Pregnant Cat

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Intravenous inoculation of pregnant cats with feline herpesvirus produced minimal illness but resulted in abortion, intrauterine fetal death and congenital fetal infection. Placental lesions included multiple infarcts in the placental labyrinth, thrombosis of maternal vessels in the endometrium and placenta, and multifocal necrosis of the giant-cell trophoblast and endometrial epithelium in the junctional zone of the placenta associated with eosinophilic intranuclear inclusion bodies. The virus was isolated from all the placentas and uteri but from none of the fetuses aborted 6–9 days after maternal intravenous inoculation. Viral antigen was demonstrated in the uterine vessels and in the junctional zone of the placenta at this time. On postinoculation day 26, viral antigen was demonstrated in the chorioallantoic membrane on the fetal side of the placenta and in the liver of a congenitally infected fetus. Although all 4 pregnant cats inoculated intranasally with feline herpesvirus aborted, neither virus, viral antigen nor significant lesions were detected in the uteri, placentas or fetuses. Abortion after intranasal inoculation was interpreted as a nonspecific reaction secondary to the severe, debilitating upper respiratory disease that occurred. (Amer J Path 65:173–188, 1971)

HERPESVIRUS INFECTIONS of man and animals usually involve the upper digestive or respiratory tracts. Infection during pregnancy, however, may result in abortion or congenital fetal infection.[1–9] Generalized infection of newborn infants by herpes simplex and varicella viruses has been recognized for over 30 years [10,11] and there is evidence that these viruses can be transmitted transplacentally.[1–4] The association of the equine,[6] bovine[7,8] and canine[9] herpesviruses with abortion and congenital infection suggests that there are common pathogenetic mechanisms by which indigenous herpesviruses affect the gravid uterus. Yet, relatively little information is available regarding the pathogenesis of abortion, fetal death or fetal infection caused by herpesviruses. Descriptions of lesions in the placenta are limited.[12–15] The distribution of lesions and herpesviral antigen in the uterus, placenta, and fetus has not been studied in a natural host system. Transplacental infection by herpes simplex virus has been demonstrated in the rabbit [15,16] and

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mouse.[17] Localization of herpes simplex antigen in the uterus and placenta has been attempted only in the mouse.[17]

Feline herpesvirus (feline rhinotracheitis virus) is usually associated with acute upper respiratory disease in the cat.[19,20] We have observed that pregnant cats spontaneously infected with feline herpesvirus (FHV) frequently abort.[21] The effects of FHV infection during pregnancy have not been studied. We undertook this study to evaluate experimental FHV infection in the pregnant cat as a model to study the interactions of herpesviruses with the gravid uterus. The specific objectives of this investigation were (1) to determine whether FHV produces abortion, fetal death or fetal infection after intranasal or intravenous inoculation of pregnant cats, (2) to characterize the lesions produced in the uterus, placenta and fetus and (3) to correlate the lesions with the presence of virus and viral antigen.

Materials and Methods

Virus

The C-27 prototype isolate of FHV* was used. A viral stock (representing the twenty-first subpassage *in vitro*) was prepared in a continuous line of feline embryonic kidney (CrFK).† The cell-culture medium was harvested at 72 hours postinoculation, frozen and thawed twice and clarified by centrifugation at 1000 *g* for 15 minutes.

Animals, Inoculation, Necropsy

Ten pregnant, specific-pathogen-free (SPF) cats between day 42 and 50 of gestation were used. The cats were selected from a breeding colony of cesarian-derived cats maintained in strict isolation. Preinoculation serum samples were collected from all the cats. Four cats were inoculated intranasally and 5 intravenously with 10^8 $TCID_{50}$ of feline herpesvirus (FHV) in 1.5 ml of cell-culture medium. One control cat was inoculated intravenously with 4.0 ml of medium from uninfected CrFk cell cultures.

After inoculation, clinical signs of illness and the rectal temperature were recorded daily. The cats were necropsied the day of abortion except for 2 that were killed when signs of impending abortion were evident on postinoculation day (PID) 6 and 26 (Table 1). Representative sections of all organ systems from the dams and fetuses were fixed in either Zenker's or Bouin's fixative. Paraffin-embedded histologic sections were prepared and stained with hematoxylin and eosin.

Virus Isolation and Serum Neutralizing Antibody

Ten percent weight/volume suspensions of placenta, uterus, liver and spleen from each cat and of liver, spleen and adrenal from each fetus were prepared in

* Obtained from Dr. J. H. Gillespie, New York State Veterinary College, Ithaca, NY, as the twentieth cell-culture passage. The virus had been plaque-purified 3 times.

† Originated by Dr. R. A. Crandell and obtained from Dr. F. W. Scott, New York State Veterinary College, Ithaca, New York.

Table 1—Experimental Feline Herpesvirus Infection in Pregnant Cats

	Route of inoculation	
	Intravenous	Intranasal
Abortion and necropsy, days postinoculation (PID)	6–26	7–14
Number of cats	5	4
Lesions		
Uterus and placentas	5/5	0/4
Fetuses	1/5*	0/4
Viral antigen		
Uterus and placentas	5/5	0/4
Fetuses	1/5*	0/4
Virus isolation		
Uterus and placentas	5/5	0/4
Fetuses	1/5*	0/4
Vagina	4/5	2/4†
Blood	2/2‡	0/2
Spleen and liver	0/5	0/4

* Postinoculation day (PID) 26 only.
† PID 6 only.
‡ PID 2 and 3 only.

Hanks' balanced salt solution. Plasma and blood for virus isolation were collected from PID 1 through 6 from 2 cats inoculated intranasally and 2 inoculated intravenously. Premoistened Dacron vaginal swabs were collected between PID 2 and 7 from 4 cats and from each cat at the time of abortion. The swabs were expressed in 2 ml of balanced salt solution plus 5% fetal bovine serum. Amniotic fluid was collected from fetuses of 2 cats inoculated intravenously (PID 6 and 26). Technics previously employed for virus isolation [20] were used except that CrFK cells were substituted for primary feline kidney cells. Parallel titrations in our laboratory have indicated that CrFK and primary feline kidney cells are equally sensitive to FHV. Four cell-culture monolayers were inoculated with 0.2 ml of the following: tissue suspension, fluid in which vaginal swabs had been expressed, amniotic fluid or plasma. The monolayers were incubated for 1 hour at 37 C and washed once before medium was added. The cultures were examined for 5 days. The presence of FHV was identified by the characteristic cytopathic effect associated with eosinophilic intranuclear inclusion bodies.

Serum for neutralizing-antibody assay was collected from each cat on the day of necropsy. Neutralizing antibody was assayed using twofold serial dilutions of heat-inactivated serum. One thousand 50% tissue culture infective doses ($TCID_{50}$) of virus contained in 1.0 ml were added to 1.0-ml aliquots of serum. The mixture was incubated for 1 hour at room temperature before inoculation of 0.2 ml onto each of five CrFK cultures. After 5 days, the 50% neutralizing titer was computed by the method of Reed and Muench.[22]

Immunofluorescence

Sections of placenta, uterus, liver, spleen, maxillary turbinate and costochondral junction from each cat, along with liver, spleen, adrenal and turbinate from at least 2 fetuses of each litter were frozen in liquid nitrogen. The tissues were sectioned on a cryostat at −20 C and fixed in cold acetone before staining by the direct

method. Globulin from a cat hyperimmunized with FHV (neutralizing titer 1:256) and from a control SPF cat (titer< 1:2) was separated as outlined by Cherry *et al.*[23] The globulin was conjugated with 12.5 μg of fluorescein isothiocyanate (FITC)/mg of protein. Unconjugated FITC was removed by gel filtration using Sephadex G-25. The conjugates were absorbed with feline liver homogenate and rabbit liver powder. Rhodamine-conjugated bovine serum albumin was used as a counterstain. The following controls were used to establish the specificity of the anti-FHV conjugate: fluorescence in infected but not in uninfected cell cultures, absence of fluorescence in tissue sections from the control cat, absence of fluorescence in FHV-infected tissues and cell cultures after incubation with conjugated globulin from the control cat, blocking of fluorescence by preincubation with unconjugated anti-FHV globulin but not with control globulin.

Results

Cats Inoculated Intravenously

Clinical Signs

Two of the 5 cats inoculated intravenously aborted on PID 6 and 1 aborted on PID 9. Sanguinous vaginal discharge occurred within 24 hours prior to abortion. The remaining 2 cats were killed on PID 6 and 26, when a sanguinous vaginal discharge was present suggesting impending abortion. Other signs of illness were minimal. There was transient fever on PID 2 or 3 and mild serous nasal discharge.

The control cat inoculated with media from uninoculated CrFK cultures remained free of illness and delivered normal, term kittens.

Gross Lesions

Macroscopic lesions were present in the placentas of 2 of the 5 cats inoculated intravenously (PID 6 and 26). Multiple, well-delineated, 0.5–1.5 cm, gray to white foci were present on PID 6. The lesions contrasted sharply wth interspersed regions of grossly normal, red placental tissue (Fig 1). On cross section, the lesions usually involved the entire thickness of the placenta. Similar but more extensive lesions were present in the placentas of the cat killed on PID 26.

Three of 5 fetuses examined *in utero* on PID 6 were dead and autolyzed while the remaining 2 were viable. All 4 fetuses examined by hysterotomy on PID 26 were dead and 2 were partially macerated (Fig 2). The autolyzed fetuses were red-brown, friable and surrounded by brown, odorless, clear to slightly turbid fetal fluids. Severe placental lesions were always associated with dead fetuses. The most severely affected fetuses were nearest the body of the uterus. Six of the 12 fetuses aborted by the remaining 3 cats were alive when aborted. Viability of the remaining fetuses at the time of abortion could not be determined since the fetal membranes were not removed by the dams

and the fetuses were not discovered immediately. No pulmonary aeration was present.

Gross lesions were detected in 1 fetus from the cat killed on PID 26. Several 0.5-mm gray foci were present beneath the capsule of the liver. No other gross lesion was detected in this fetus or the other fetuses.

Microscopic Lesions

The following changes occurred in varying proportion in the placentas and uteri of all the cats inoculated intravenously: (1) regions of coagulative necrosis in the placental labyrinth, (2) thrombosis of maternal vessels in the placenta and uterus, (3) degeneration, necrosis and eosinophilic intranuclear inclusion bodies in the giant-cell trophoblast and endomentrial epithelium in the junctional zone of the placenta, and (4) separation of the placenta from the endometrium at the junctional zone.

Multiple regions of coagulative necrosis were grossly visible in the placentas of 2 of the 5 cats (Fig 1 and 2). Usually, the lesions involved the entire thickness of the placenta but not the endometrium (Fig 3). The sharply delineated, segmental, coagulative necrosis of all placental components, with no associated inflammatory reaction, was interpreted as infarction. The portion of the placental labyrinth nearest the endometrial junction appeared to be the first affected. Thrombosis of maternal arteries entering the junctional zone of the placenta was associated with overlying infarction. In addition, endothelial and medial cells in some endometrial arteries were pyknotic and karyorrhectic (Fig 4).

Degeneration and necrosis of the multinucleated syncytial trophoblast in the junctional zone occurred in all the placentas. Eosinophilic intranuclear inclusion bodies (Fig 5) were detected in the giant-cell trophoblast and the subjacent endometrial epithelium in the placentas of the 3 cats examined on PID 6. The degenerative changes in the endometrial junctional zone were often associated with thrombosis of maternal arteries entering the placenta and infarction of the overlying labyrinth. Inclusion bodies were restricted on the multinucleated syncytial trophoblast and endometrial epithelium in the junctional zone and were not detected in the cytotrophoblast, syncytial trophoblast, decidual cells or endothelial cells in the placental labyrinth. The endometrium of the 3 cats that aborted was moderately infiltrated by neutrophils.

On PID 26, in addition to the lesions described above, there was

diffuse necrosis of the chorioallantois covering the fetal side of all the placentas. The chorioallantoic membrane was necrotic regardless of whether the underlying placental labyrinth was viable or infarcted. No inclusion bodies were present on PID 26.

No significant microscopic lesions were present in 16 fetuses examined between 6 and 9 days after maternal inoculation. Scattered foci of hepatic necrosis were present in 1 of the 2 fetuses that was not severely autolyzed *in utero* on PID 26 (Fig 6). A few hepatocytes contained eosinophilic intranuclear inclusion bodies. Lesions were not detected in other organs of this fetus.

A few 0.2- to 0.5-mm foci of necrosis associated with intranuclear inclusion bodies were present in the vaginal epithelium of the cats killed on PID 6. Similar lesions were present in the adrenal cortex and nasal epithelium of the cats. No other lesions were detected in the cats inoculated intravenously.

Immunofluorescence

Viral antigen was demonstrated in the walls of uterine blood vessels of 2 of the 3 cats necropsied on PID 6 (Fig 7). Fluorescence occurred in endothelial, intramural and perithelial cells. Focal fluorescence was also detected in the multinucleated trophoblast and the endometrial epithelium in the junctional zone of the placentas of 2 cats killed on PID 6. Neither infarcted nor viable regions of the placental labyrinth contained viral antigen. On PID 26, viral antigen was localized in the chorioallantois covering the fetal margin of the placenta (Fig 8). No fluorescence occurred elsewhere in the placentas or endometrium on PID 26. No fluorescence occurred in the liver, spleen, maxillary turbinate bone or costochondral junction of any of the 5 cats.

Viral antigen was detected in the liver of 1 fetus on PID 26. Multiple, discrete foci of fluorescence were present (Fig 9) which represented foci of necrosis histologically (Fig 6). No specific fluorescence was present in other organs from this fetus or in the liver, spleen, adrenal or turbinate of 8 other fetuses from the cats aborting between PID 6 and 9.

Virus Isolation

FHV was isolated from the placentas of each of the 5 cats inoculated intravenously (Table 1). The virus was recovered from the uteri of the cats killed on PID 6 and 9 but not from the uterus of the cat killed on PID 26. The virus was also recovered from the amnionic fluid on PID 26 and from the vaginal swabs collected between PID 4 and 9.

Viremia was detected only on PID 2 and 3 in the 2 cats from which blood was collected daily. The virus was not isolated from the blood, plasma, spleen, or liver of any of the cats on the day of necropsy (Table 1).

Suspensions of lung, liver and spleen of 8 fetuses examined between PID 6 and 9 did not yield virus. The only viral isolation from fetal tissues was made from the liver of the fetus examined on PID 26, in which lesions and viral antigen were also demonstrated.

Serum Neutralizing Antibody

None of the preinoculation sera had neutralizing activity at a 1:2 dilution. Neutralizing activity was detected only in the serum of the cat killed on PID 26 at a titer of 1:20/100 $TCID_{50}$ of virus.

Cats Inoculated Intranasally

Clinical Signs

Severe upper respiratory disease characterized by fever, anorexia copious nasal and conjunctival exudate, paroxysmal sneezing, dyspnea and weight loss occurred in all 4 cats. All of the cats aborted between PID 7 and 14. No vaginal discharge was detected prior to abortion.

Lesions

No significant lesions were detected in the 11 placentas and fetuses from the 4 cats inoculated intranasally. The only changes present in the uteri were edema, congestion and hemorrhage at the site of placentation. No necrosis was present in the placental labyrinth, giant-cell trophoblast or endometrial vessels. No inclusion bodies were detected in the uteri or placentas.

Healing foci of necrosis in the vaginal epithelium were present in the cats killed on PID 9 and 13. Extensive necrosis of nasal epithelium similar to that previously described after intranasal inoculation of FHV [19,20] was evident in all the cats inoculated intranasally.

Immunofluorescene

No specific fluorescence was observed in sections of placenta, uterus, liver, or spleen of the cats. Neither was viral antigen detected in liver, spleen, adrenal or turbinate from any of 8 fetuses examined.

Virus Isolation

FHV was isolated from vaginal swabs of 2 cats on PID 6. The virus was not detected in the blood, uterus, placenta, liver, spleen or fetuses of the cats inoculated intransally (Table 1).

Discussion

The results of this study indicate that feline herpesvirus can produce placental lesions, fetal death and fetal infection when introduced into blood of pregnant cats. Abortion after intravenous inoculation appeared to be the result of virus-induced lesions in the uterus and placenta. Abortion after intranasal inoculation appeared to be a nonspecific reaction secondary to severe, debilitating upper respiratory disease rather than a direct viral effect on the gravid uterus since no viral infectivity, viral antigen or significant lesions were detected in the uteri, placentas or fetuses.

The absence of significant viremia in the cats inoculated intranasally probably accounts for the lack of viral localization in the uterus and placenta. Although extensive viral replication and necrosis occurred in the nasal mucosa after intranasal inoculation, the virus was apparently confined to the upper respiratory tract and was not detected in the blood or plasma. This is compatible with previous studies [20] in which FHV was isolated from only 1 of 21 blood samples collected between 2 and 13 days after intranasal inoculation. The presence of virus and lesions in the vaginas of 2 of 4 cats inoculated intranasally suggests that either undetected viremia resulted in vaginal but not placental infection or that external spread of virus occurred from the mouth or nares to the vagina. In contrast to our findings with FHV, intranasal inoculation or spontaneous infection with infectious bovine rhinotracheitis (IBR) virus and equine rhinopneumonitis virus results in abortion associated with fetal infection.[24,25] In equine rhinopneumonitis, there is leukocyte-associated viremia which persists as long as 33 days after intranasal inoculation.[25] However, IBR virus, like FHV, is not usually detectable in the blood during upper respiratory infection.[24] It should be emphasized that maternal FHV infection was evaluated only in the sixth week of gestation. Placental and fetal infection may be more readily induced at other stages of gestation by transient viremia of low magnitude which likely follows intranasal inoculation.

FHV antigen was demonstrated in endometrial vessels 6 days after the virus was inoculated intravenously, when 2 cats aborted and a third had signs of impending abortion. Viral localization in endometrial vessels has not been previously described in spontaneous or experimental infections with herpesviruses. Virus-induced vascular lesions which activate the intrinsic coagulation mechanism [26] could explain the pathogenesis of the placental thrombosis and infarction that occurred after FHV was inoculated intravenously. The areas of coagu-

lative necrosis in the placental labyrinth were not due to cytolytic viral replication since they did not contain inclusion bodies or viral antigen. Viral inclusion bodies and viral antigen were restricted to the endometrial epithelium and giant-cell trophoblast in the junctional zone of the placenta. McKay [27] found that, in experimental pregnancy toxemia in the rat, necrosis of the giant-cell trophoblast in the junctional zone of the placenta was followed by fibrin thrombi in the maternal vascular spaces, suggesting that procoagulant factors were liberated by the degenerating trophoblast. FHV infection of the giant-cell trophoblast and endometrial epithelium, therefore, may also serve to alter the coagulative homeostasis of the placenta, resulting in thrombosis, infarction and placental separation. When placental lesions are not severe enough to cause early abortion and/or fetal death, congenital fetal infection may subsequently occur.

Coagulative necrosis in the placental labyrinth has also been reported in association with congenital infection by herpes simplex virus [13] and IBR virus.[12] Molello *et al* [12] suggested that the placental lesions associated with inoculation of IBR virus were not due to a direct viral effect on the placenta but rather were the result of circulatory alterations occurring after fetal death. Similar lesions, however, have been reported in the placentas of viable, premature infants congenitally infected with herpes simplex and varicella viruses.[13,14] Our observations indicate that the placental lesions in cats inoculated intravenously with FHV are induced by the virus and precede fetal infection and fetal death. Six days after FHV was inoculated intravenously, virus, viral antigen and lesions were present in all the placentas but in none of the fetuses examined, and lesions were present in the placentas of some viable fetuses. Placental infection independent of fetal infection has also been observed in herpes simplex and mumps infection in hamsters,[18,28] in murine cytomegalovirus infection [29] and in human rubella infection.[30,31]

Vaginal infection by FHV is significant in light of the association of the canine [32] and bovine [33] and human [34] herpesviruses with vaginal or cervical infection. Experimental vaginal infection by FHV has recently been reported.[35] Respiratory and genital subtypes of FHV differing in neutralization kinetics, cytopathic effect or DNA density as do the subtypes 1 and 2 of herpes simplex virus [34,36] have not been recognized thus far. Bowling *et al* [37] did not find significant differences in cytopathic effect, neutralization slope or DNA density between respiratory and genital isolates of IBR virus.

The persistence of FHV on the fetal side of the placenta on PID

26 despite the presence of neutralizing antibody in the maternal blood is consistent with evident indicating that transfer of antibody through the feline placenta is minimal.[38] Focal hepatic necrosis was present in the fetus congenitally infected with FHV. Similar lesions are associated with congenital fetal infection by the equine,[39] bovine [8,40] and human [10] herpesviruses.

Although a direct viral effect on the gravid uterus could not be demonstrated after intranasal inoculation, the tropism that the FHV exhibited for the uterus and placenta after intravenous inoculation warrants further study of its role in spontaneous feline abortion and fetal disease. Experimental feline herpesvirus infection in the pregnant cat constitutes a promising model for study of the interaction of indigenous herpesviruses with the uterus, placenta and fetus.

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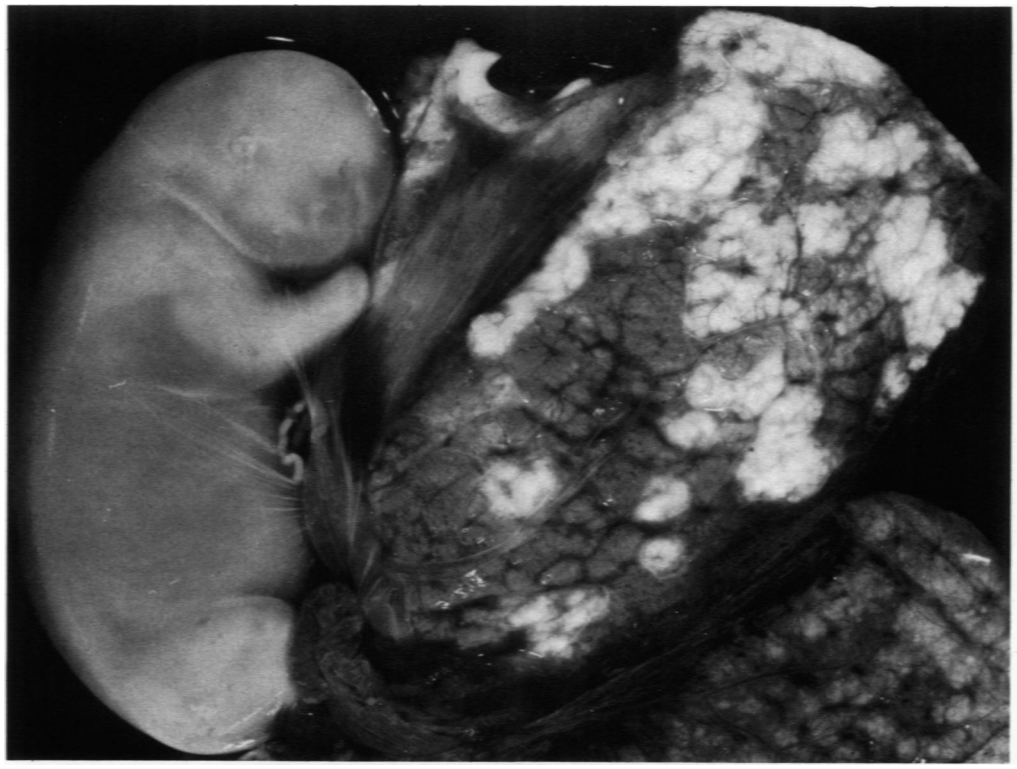
[Illustrations follow]



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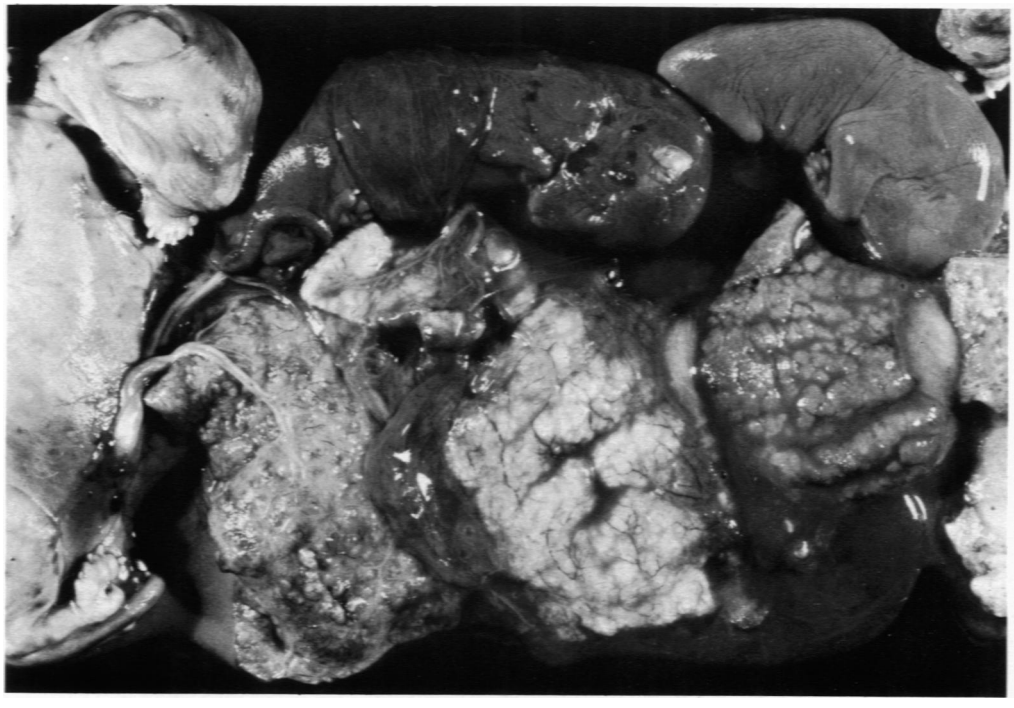

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Fig 1—Placenta and fetus 6 days after the mother was inoculated intravenously with feline herpesvirus. Multiple, well-delineated, white to yellow areas of necrosis are present in the placenta. The fetus was dead *in utero*. **Fig 2**—Placentas and 3 fetuses 26 days after the mother was inoculated intravenously with feline herpesvirus. The fetuses were dead *in utero* and 2 are macerated. There is extensive placental necrosis.

Fig 3—Microscopic appearance of one of the placental lesions shown in Fig 1. The uniform, coagulative necrosis of all components of the entire placental labyrinth, with no associated inflammatory reaction, was interpreted as infarction. The endometrial epithelium (*E*) is not involved (H&E, × 125).

Fig 4—Pyknosis and karyorrhexsis (*arrows*) in the wall of an endometrial vessel of a cat 9 days after feline herpesvirus was inoculated intravenously (H&E, × 535).

Fig 5—Eosinophilic intranuclear inclusion body (*arrow*) in a giant-cell trophoblast in the junctional zone of the placenta of a cat 6 days after feline herpesvirus was inoculated intravenously (H&E, × 535).

Fig 6—Focus of necrosis (*arrows*) in the liver of the fetus shown at the extreme left in Fig 2. The fetus was dead *in utero* 26 days after the mother was inoculated with feline herpesvirus (H&E, × 416).

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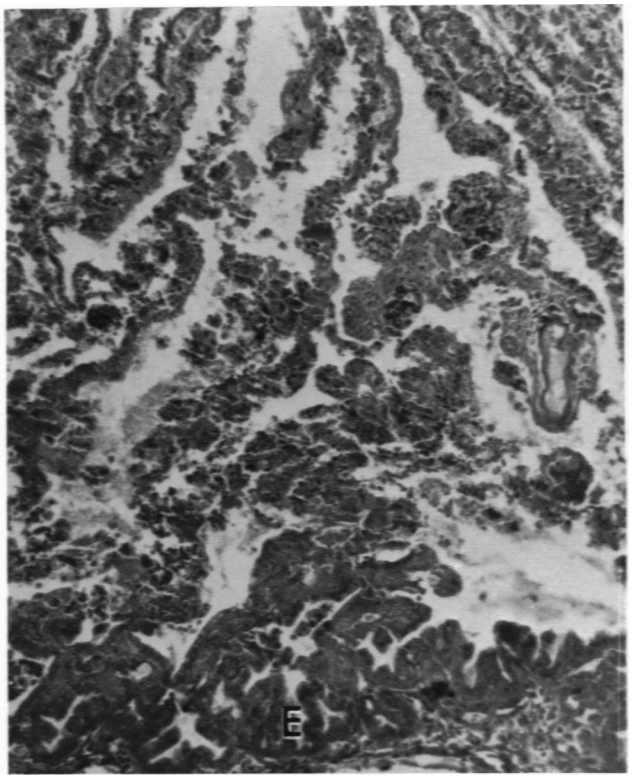

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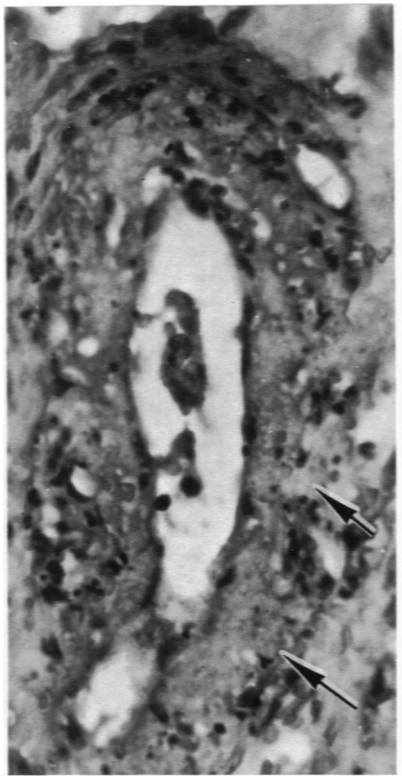

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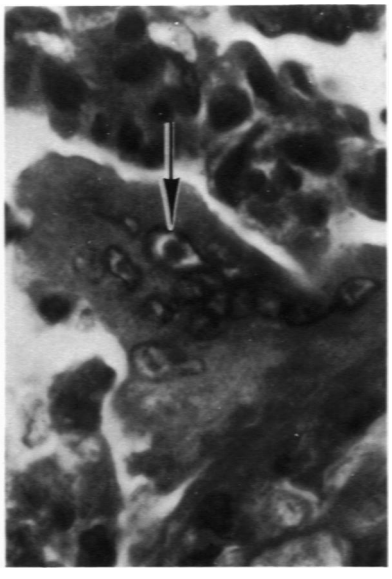

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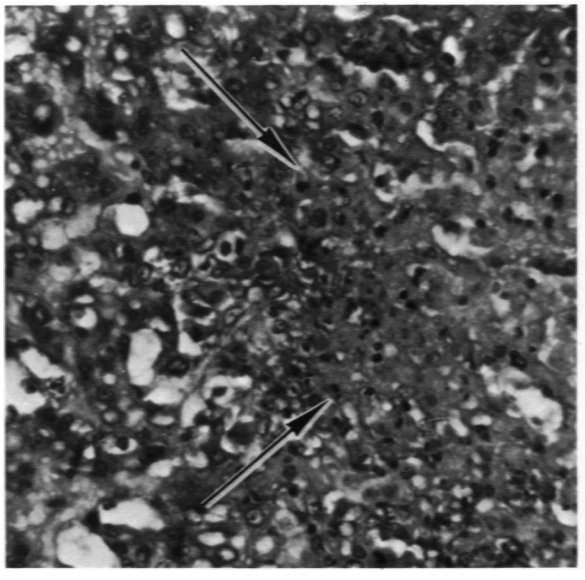

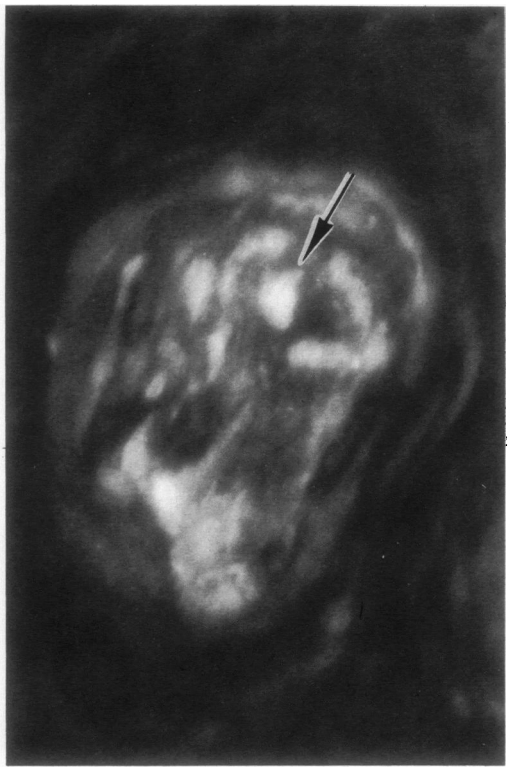

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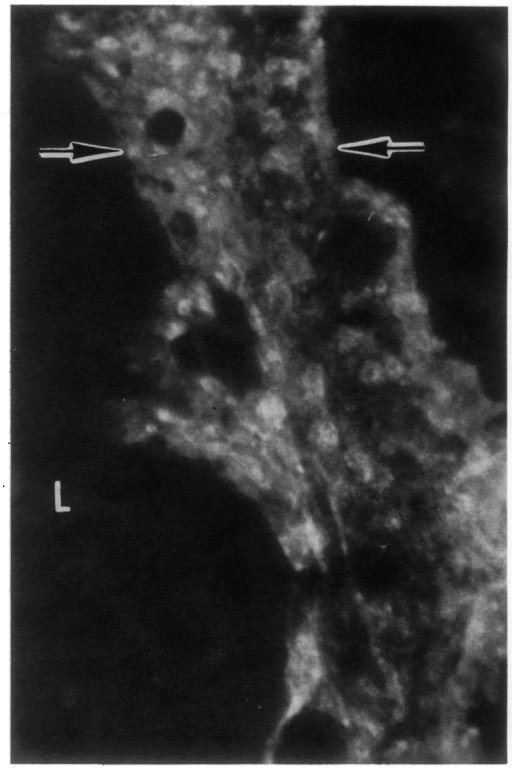

8

Fig 7—Viral-specific fluorescence in a thrombosed endometrial vessel of a cat that aborted 6 days after with feline herpesvirus was inoculated intravenously (immunofluorescence, × 535). **Fig 8**—Viral-specific fluorescence in the chorioallantoic membrane (*arrows*) comprising the fetal border of the placenta; 26 days after the mother was inoculated intravenously with feline herpesvirus. No viral antigen is demonstrable in the placental labyrinth (*L*) (immunofluorescence, × 125).

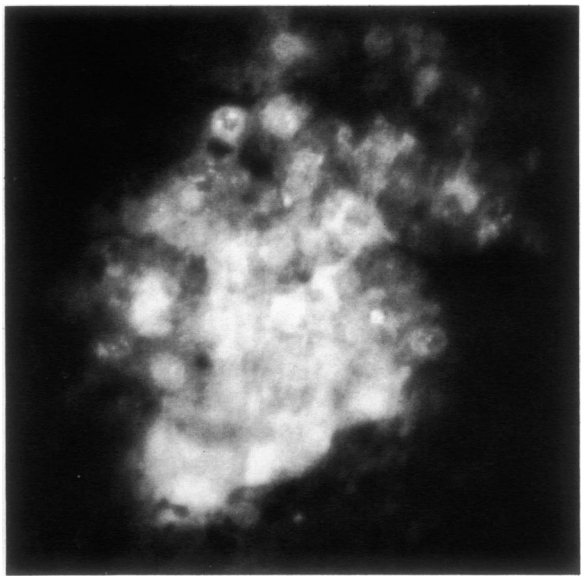

Fig 9—Focus of viral-specific fluorescence in the liver of a fetus 26 days after the mother was inoculated intravenously with feline herpesvirus. Compare with histologic appearance of a similar lesion in the same fetal liver in Fig 6 (immunofluorescence, × 315).