nervated vascular tissues, which are devoid of norepinephrine, retain their tone and are highly reactive to intravenous catecholamines.

Preservation of the endotoxin-detoxifying power in the denervated half of the spleen, and its loss in the innervated half, indicate that the injury to function is the direct result of poor blood flow to the tissues owing to excessive activity of the locally released norepinephrine.

Summary. In dogs with part of the spleen denervated, the morphologic and functional injury that shock inflicts is restricted to the non-denervated part of the spleen. The denervated part escapes injury because denervation prevents release of norepinephrine from its stores. It is the norepinephrine released in the innervated tissue that accounts for the injury to this tissue, including its vascular muscle, and hence for the progressive failure of the circulation of the non-denervated animal. The circulating catecholamines do not play a significant role in production of this injury or in the vascular collapse and death.

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Infection of Suckling Cottontail Rabbits with Shope's Fibroma Virus.* (29585)

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Myxoma virus and the virus of Shope's fibroma are closely related(1). Both viruses produce localized, self-limiting tumors in their adult natural hosts(2,3), wild *Sylvilagus* rabbits. In domesticated and wild European rabbits *(Oryctolagus cuniculus)* each virus produces a very different disease. Myxoma virus produces a generalized, rapidly fatal disease(4). Low passage fibroma virus produces only localized proliferation in domestic rabbits(5). In neonatal domestic rabbits, however, fibroma virus can cause fatal disease of a rapidly acute or slower neoplastic type(6,7,8). The response of the neonatal natural host to fibroma virus has not been reported. In this paper are described some effects of fibroma virus on suckling eastern cottontail rabbits *(Sylvilagus floridanus)* and this response is compared to that reported for the young European rabbit.

Materials and methods. The virus used in this study was isolated from grossly typical

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fibromas occurring on the feet of a wild-trapped eastern cottontail rabbit. This rabbit was captured in the Madison, Wisconsin area in November, 1959. This fibroma virus isolate is designated the M1 strain. To avoid alteration of the virus by repeated passage in domestic rabbits, the virus was alternately passaged through domestic and cottontail rabbits. The virus used in this study had undergone 2 domestic and 1 cottontail rabbit passages. Stock virus was prepared by inoculation of 0.2 ml of inoculum containing about 10^3 domestic rabbit intradermal infectious doses ($DRID_{50}$) into each testicle of a sexually mature domestic rabbit. These rabbits were given 10 mg of cortisone acetate intramuscularly for 10 days, beginning 2 days prior to inoculation of virus. The testicles were aseptically removed 7-8 days after inoculation and minced with scissors. The tissue was homogenized in a Waring Blendor as a 10% testicle suspension in tissue culture medium 199 with 10% calf serum. Larger pieces of tissue were centrifuged out of suspension at 3000 r.p.m. for 15 minutes. Ampoules of the virus were stored at —65°C. The $DRID_{50}$ of the virus stocks was periodically determined by inoculation of replicated 2-fold serial dilutions into young adult domestic rabbits.

New Zealand white domestic rabbits came from the Veterinary Science Department colony. Cottontail rabbits were live-trapped in the Madison and Manitowoc, Wisconsin areas. Pairs of cottontail rabbits were confined in large, semi-natural outdoor pens. Pregnant cottontails were confined in small nesting cages not more than a week before parturition. Owing to the difficulty in inducing female cottontails successfully to raise litters in close confinement, the number of known-age young cottontails available for experiment was small.

Cottontail and domestic rabbits were inoculated intradermally in the gluteal region with 320 $DRID_{50}$ of fibroma virus in 0.05 ml of inoculum. Resulting tumors were measured weekly at the widest point in each dimension with calipers. Tissues of cottontails which died from the infection were taken for virus isolation and histopathological examination. Isolation was attempted by intradermal inoculation of tissue suspensions into young adult domestic rabbits. Appearance of fibromas grossly resembling those resulting from virus titrations were taken as *de facto* evidence of the presence of infectious fibroma virus in the tissue suspensions.

Results. Differences in the reactions of cottontail rabbits and domestic rabbits are summarized in Table I. Domestic rabbits of less than 6 days of age had a mean death time of 11.2 days. Cottontails of the same age group receiving the same dose of virus by the same route as was given to the domestic rabbits had a mean death time of 27.8 days. The mean tumor size index in this same age group, however, was 13.1 for domestic rabbits and 84.1 for cottontails. Even in older animals which uniformly survived the infection, tumor indexes were consistently higher among cottontails. In the 9-42 day age group the mean time to regression was 28.1 days for domestic rabbits and 62.0 days for cottontails. The presence of maternal antibodies may have influenced the outcome of the disease in 3 cottontails.

Very large tumors resulted at the site of inoculation in cottontails infected at less than a week of age. These tumors were larger and of a different aspect than natural tumors occurring in older cottontails in the field (Fig. 1, 2). In 6 of 7 cases mortality resulted in cottontails of this age group. One young cottontail weighed 210 g at death. Of this, the primary tumor at the site of inoculation weighed 101 g.

At post mortem, the large primary tumors readily separated into 2 concentric hemispheres (Fig. 3). The inner hemisphere appeared to have its origin in subcutaneous connective tissue. The smaller satellite tumors surrounding the primary tumor also appeared to have sprung from subcutaneous connective tissue. Small foci of tumor cells were grossly visible in the kidneys and occasionally in the liver and in the spleen. These foci appeared as bundles of fibroblasts, with numerous mitotic figures. The foci were microscopically similar to the primary and satel-

TABLE I. Comparison of Primary Tumor Size, Death Time or Time to Complete Tumor Regression and Influence of Maternal Antibody in Young Cottontail and Domestic Rabbits Inoculated with Fibroma Virus.

	Cottontail rabbits				Domestic rabbits			
Age (days) at inoc‡	Tumor size index	Days to regression	Death time (days)	Maternal antibody	Tumor size index	Days to regression	Death time (days)	Maternal antibody
1	27.9*	—	18	0	8.6*	—	10	0
1					10.6	—	10	0
2	67.6	—	22	0	29.8	—	11	0
3	29.6	90	—	1,600†	12.6	—	12	0
4	131.4	—	24	0				
4	139.3	—	22	0				
4	129.6	—	45	0				
6	63.1	—	36	0	3.7	—	13	0
6					1.8	39	—	0
9	14.8	75	—	800				
9	3.8	75	—	800				
14	58.2	69	—	Unk	12.5	—	25	0
14	37.8	69	—	Unk	11.9	35	—	0
14					13.1	30	—	0
14					12.3	30	—	0
21					9.0	27	—	0
21					8.5	25	—	0
21					12.5	25	—	0
21					5.7	21	—	0
21					2.6	30	—	0
28	15.3	42	—	Unk	2.7	32	—	0
28					1.7	32	—	0
28					.9	32	—	0
28					.9	26	—	0
28					.3	26	—	0
42	7.5	42	—	Unk				
49					5.1	28	—	0
49					4.6	28	—	0
49					3.7	30	—	0
49					3.7	28	—	0
49					.9	28	—	0
56					2.9	21	—	0
56					2.4	28	—	0
56					1.5	30	—	0

* The tumor index was computed by multiplying measurements (cm) of the tumor at widest point in each dimension.

† Domestic rabbit ID_{50} of fibroma virus neutralized per 1.0 ml serum.

‡ Inoculated with 320 domestic rabbit ID_{50} of Shope's rabbit fibroma virus.

lite tumors. In the kidneys, slight inflammatory infiltration was observed in the glomeruli and in the tubules of the medulla and cortex. Signs of central nervous disorder (opisthotonos, nystagmus and torticolis) occurred 3-5 hours prior to death. No gross or microscopic brain lesions were found which would account for this behavior.

Virus was successfully isolated from dead cottontails from kidney, spleen, liver, lung, brain, primary tumor and satellite tumor tissues. The virus could not be isolated from blood or from grossly normal skeletal or cardiac muscle.

Discussion. The suckling natural host, the eastern cottontail rabbit, and the suckling domestic rabbit do not respond similarly to the same dose and route of fibroma virus. The proliferative response was much more marked in cottontails. The tumors at the site of inoculation were larger and persisted longer. Suckling domestic rabbits suffered a more acute disease, succumbing to fibroma virus in nearly half the time that it took

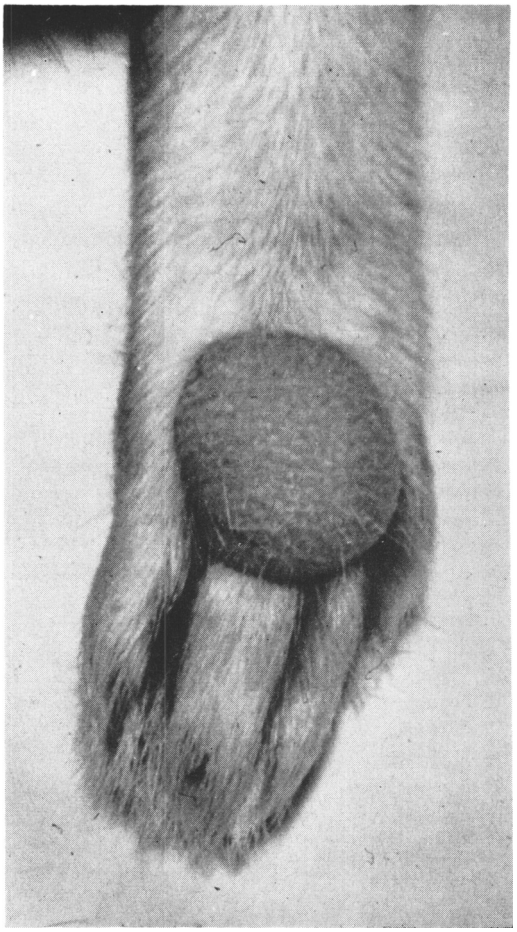

FIG. 1. Naturally occurring tumor on right front foot of cottontail rabbit.

cottontails of the same age to die. In no case was the acute inflammatory response associated with rapid mortality of suckling domestic rabbits(6,7,8) observed in cottontails. Harel and Constantin(8), using an unspecified quantity of the Shope OA strain of fibroma virus, infected 15-16 day old domestic rabbits causing nearly 100% mortality. Harel's and Constantin's observations coupled with the data from Table I suggest that fibroma virus may be more lethal for neonatal domestic rabbits than for cottontail rabbits of the same age. Lower mortality among cottontails was probably due to their proliferative rather than acute inflammatory response.

Selection for a proliferative rather than the acute inflammatory response on the part of the natural host is geared to mutual survival of host and virus in nature. Fibroma virus has been reported from New Jersey (3), Maryland(10), New York(10), Michigan(10,11) and now Wisconsin. All of these areas experience winters cold enough to cause prolonged periods of inactivity of the supposed vector, the mosquito(11). The ability of the virus to cause a proliferative response sustained enough to last through the winter without interfering seriously with the well being of the host would be an obvious advantage. This appears to be the case in nature. Fibromas are capable of persisting in infectious form for at least 10 months(11). Gross fibromas have been observed in the field throughout the coldest months(9,10,11).

In spite of the close relationship between myxoma and fibroma viruses, myxoma virus has a propensity to produce a more acute, less proliferative disease than fibroma virus in domestic rabbits at least. The mechanism of this difference in effect may also be a result of climate-arthropod selection. Myxoma virus occurs naturally in warmer climates, where mosquitoes are less subject to seasonal

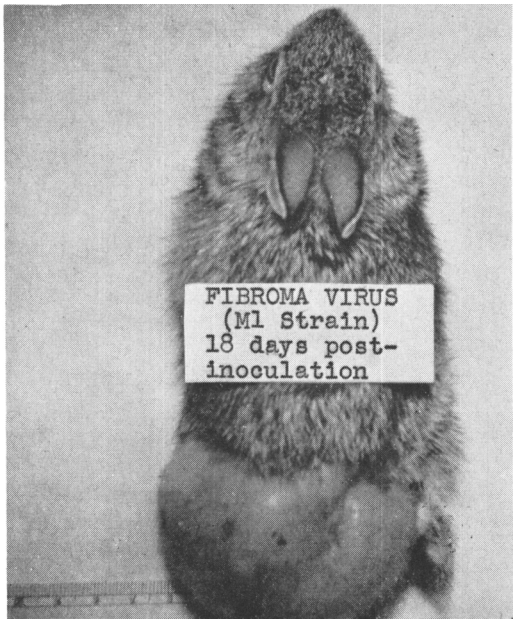

FIG. 2. Tumor resulting 18 days following intradermal inoculation of 320 domestic rabbit intradermal ID_{50} of fibroma virus into a 3-day-old cottontail rabbit.

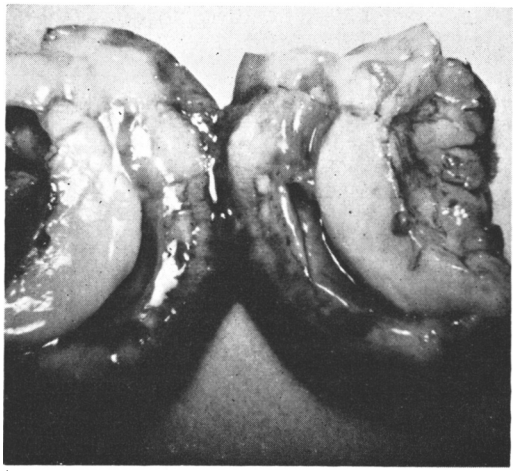

FIG. 3. Cross section of a tumor from site of intradermal fibroma virus inoculation of a suckling cottontail rabbit, showing arrangement as 2 concentric hemispheres.

inactivity. Under these circumstances it would seem likely that there would be less selection for a virus producing as sustained a proliferative response as does fibroma virus. Tumors resulting from mosquito transmitted myxoma virus persist for 10-40 days in the natural host, *Sylvilagus brasiliensis*(2). This period is far shorter than the persistence of fibroma-induced tumors in the eastern cottontail rabbit(11).

Summary. Intradermal injection of 320 domestic rabbit infectious doses of Shope's fibroma virus caused mortality in cottontail rabbits *(Sylvilagus floridanus)* infected at 6 days of age or younger. Cottontails infected at 14 days of age or younger developed immense primary tumors at the site of inoculation. Fatal cases were observed to have foci of tumor cells in the kidneys and occasionally in the liver and spleen. The virus could be isolated from fatally infected animals from kidney, spleen, liver, lung, brain, and tumor tissues. The same dose of virus given by the same route to domestic rabbits *(Oryctolagus cuniculus)* of the same ages produced a more acute, more rapidly fatal and much less proliferative disease. The possible ecological significance of these observations is discussed and contrasted with effects of the closely related myxoma virus.

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Oxidative Rates and Phosphorylation in Sarcosomes from Experimentally-Induced Failing Rat Heart.* (29586)

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Recent studies on the respiratory rates and phosphorylating efficiency of heart mitochondria (sarcosomes) in experimentally induced congestive cardiac failure indicate contradictory results. Schwartz and Lee(1) report that heart sarcosomes, isolated from guinea

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