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Effectiveness of the Shope Papilloma Virus in Various American Rabbits.

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The virus causing cutaneous horns and papillomas in western cottontail rabbits (*Sylvilagus floridanus*, Allen) gives rise to vigorous growths of the same sort in domestic rabbits¹ (Genus, *Oryctolagus*). In animals of both kinds these growths have the immediate character of neoplasms,² and in domestic rabbits they frequently progress to cancer.³ For this reason, the biological range of effectiveness of the virus has a special interest.

Thus far rabbits only have proved susceptible to the virus. A Kansas dealer supplying cottontails with "natural" papillomas states that he has never seen them in any of thousands of jack-rabbits (*Lepus californicus*, Gray); yet in one of 24 he sent us a small but typical growth existed, hidden by the fur. Three mixtures were made of the host's blood serum with various proportions of glycerinated cottontail papilloma extract, and after incubation all were rubbed into the scarified skin of each of 3 domestic rabbits, which received also similar mixtures made with the sera of 4 other jack rabbits of the same lot. Growths developed at every site except where the mixtures with serum from the papillomatous animal had been inoculated.

The "natural" jack rabbit papilloma enlarged slowly for some weeks, when the animal died and it was removed to 50% glycerine. An extract made 36 days later and inoculated into scarified domestic, cottontail, jack and snowshoe rabbits (*Lepus americanus*, Erxleben), 3 of each, produced growths in all. They were indistinguishable from such as are caused by cottontail virus. In 2 further experiments 2 jack rabbits were inoculated with cottontail virus extracts of differing derivations. Growths appeared in 3 of the 4 animals, the fourth dying too soon to be deemed resistant. An extract of the glycerinated papillomatous tissue from 1 of the others gave rise to growths in 2 of 3 domestic rabbits and in 2 jack rabbits.

The findings justify the conclusion that the "natural" jack rabbit papilloma was due to the virus causing the disease in cottontails.

¹ Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607.

² Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1934, **60**, 701, 723, and 741.

³ Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1935, **62**, 523.

Two groups of 3 snowshoe rabbits each, obtained from Maine, were inoculated with cottontail virus. All developed growths. An extract of glycerinated papilloma from one was inoculated into 3 snowshoe and 3 domestic rabbits. Again growths developed in all.

The papillomas in snowshoe rabbits were a dirty yellow-gray during the first weeks, and softer and less elastic than those of domestic and cottontail rabbits, appearing somewhat greasy prior to drying into similar jagged masses. The growths in jack rabbits were rubbery and negro-black, with a living base that was notably shallow because the connective tissue cores supporting the papillae were so narrow that drying took place early, to masses which often became high and resembled lava. In their main histological features the growths of all of the various rabbits were alike, however. Sometimes creamy, basal pearls were present amidst the black of the jack rabbit papillomas; and one such growth, the most rapidly enlarging produced with virus from the "natural" jack rabbit papilloma, changed to a "papilloma of the second order" during the 4 months prior to death of the animal from intercurrent causes. This change in domestic rabbits precedes malignancy.

As a rule the papillomas appeared later and grew more slowly in snowshoe and jack rabbits than in domestic rabbits receiving the same inoculum. They regularly yielded active virus, however.

While the Shope virus is pathogenic for jack rabbits, it is far less effective in producing disease among them under natural conditions than in cottontail rabbits occupying the same territory. Possibly, indeed, it is not effective at all; for the papilloma reaching us on a jack rabbit may have resulted from accidental inoculation during the period between trapping and shipping, when cottontails with the growth were also handled. However this may be, the habits of jack rabbits will suffice to explain their general freedom from infection with a virus to which they are susceptible. They are surface creatures of regions without timber, and are solitary as a rule. Whether habits and environmental conditions are together responsible in the case of snowshoe rabbits and eastern cottontails, or whether the disease has not yet reached them is uncertain. New Jersey cottontails (*Sylvilagus floridanus mallurus*, Thomas) are readily infected experimentally, and the induced papillomas yield the virus again.⁴ In western cottontails the papillomatosis has been endemic for more than 50 years, and an equilibrium between parasite and host is in process of development, as so often

⁴ Shope, R. E., personal communication.

with parasites long affecting one species.⁵ Not a few cottontails prove resistant on inoculation with virus, and the spontaneous and induced growths, though often persisting for months or years, are well tolerated and nearly always retrogress in the end. Domestic rabbits, on the other hand, are so highly susceptible that the induced growths frequently progress and kill. But, as frequently happens in the case of parasites reaching new hosts, the disease produced is severe yet the parasitism itself is aberrant,⁵ as shown by the fact that from even the most vigorous papillomas of domestic rabbits only an attenuated virus can be recovered, and this infrequently.⁶

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Certain Factors Determining the Course of Virus-Induced Tumors.

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When retrogressing or enlarging, the chicken tumors due to filtrable causes and the Shope rabbit papilloma conduct themselves like other neoplasms.¹ Their course is determined by a variety of influences. The papilloma is especially suited to the study of these because of its accessibility and discrete character.

Influence of the Initial Virus State. Shope virus from some sources gives rise to progressively enlarging papillomas, and that from others to growths which tend to disappear. Virus artificially attenuated (by heating) causes infrequent, inactive growths which eventually retrogress.² In the literature on chicken tumors similar facts find larger illustration.

Host Conditions Affecting the Virus. The blood serum of rabbits carrying the papilloma neutralizes the Shope virus *in vitro*.³ To ascertain whether the course of the growth is influenced by the cir-

⁵ Smith, Theobald, *Parasitism and Disease*, Princeton, 1934, Princeton University Press.

⁶ Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607; *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 830.

¹ Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1934, **60**, 701, 723, 741.

² Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607.

³ Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607.