

with parasites long affecting one species.<sup>5</sup> 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,<sup>5</sup> 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.<sup>6</sup>

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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.<sup>1</sup> 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.<sup>2</sup> 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*.<sup>3</sup> To ascertain whether the course of the growth is influenced by the cir-

<sup>5</sup> Smith, Theobald, *Parasitism and Disease*, Princeton, 1934, Princeton University Press.

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

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

<sup>2</sup> Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607.

<sup>3</sup> Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607.

culating antibodies we have tattooed or intradermally inoculated the virus at many points on the sides of 2 comparable groups of domestic rabbits, in addition rubbing it into broad scarified areas on the abdomen of one of the groups, producing in this way confluent papillomatous masses which appeared sooner and enlarged much faster than did the growths on the sides. The latter were all charted at short intervals, and the virus-neutralizing power of the hosts' sera was determined from time to time. Such power was absent prior to inoculation and its rate of development, though differing somewhat from individual to individual, on the whole varied *pari passu* with the increase in bulk of the papillomatous tissue. The power appeared sooner and became much greater in the animals developing large abdominal masses, yet the growths on their sides differed no whit in magnitude and course from those of the control animals. A negative outcome of reinoculation with the virus, on the other hand, proved directly referable to the possession of neutralizing power by the blood.

With the chicken tumors no such categorical test has been feasible. But resistance directed against the virus and ineffective against the cells has long been recognized, as has also the presence of a virus-neutralizing principle in the blood of fowls with growing sarcomas.<sup>4</sup>

*Host Conditions Affecting the Papilloma Cells.* Many such conditions, local and general, have been reported.<sup>5</sup> The papilloma cells are easily stimulated or depressed. To local tissue conditions and tissue reactions, to dyes and bacterial infection, they respond as do other neoplasms, including the chicken tumors.

*Influence of the Cells on the Virus.* The virus affects the host organism only secondarily; its first and enduring relation is with the cells. It is pathogenic for epidermis only, and "epidermicity" is of more consequence to it than the rabbit species.<sup>6</sup> Many facts indicate that cells impelled to proliferation by the virus may yet provide a milieu in which this cannot enduringly thrive, the result being a retrogression of papillomas which were vigorous in the beginning. The skins of some rabbits of susceptible breed have certain gross characters which mark them as relatively unsuited to the virus, which produces in them infrequent growths that eventually retrogress as a rule. The tumors resulting from the broadcast inoculation

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<sup>4</sup> Andrewes, C. H., *Lancet*, 1934, **2**, 63.

<sup>5</sup> Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1934, **60**, 701, 723, 741.

<sup>6</sup> Shope, R. E., *J. Exp. Med.*, 1933, **58**, 607; Rous, Peyton, and Beard, J. W., *J. Exp. Med.*, 1934, **60**, 701, 723, 741; Beard, J. W., and Rous, Peyton, *Proc. Soc. Exp. Biol. and Med.*, 1935, **33**, 191.

of several large skin patches of a susceptible animal generally behave in the same way, all developing or disappearing together; but when the virus is brought in contact with relatively few cells at each site, by puncture inoculation, the variation in incidence and course of the papillomas is not inconsiderable. The individual cells would seem to offer differing conditions to the virus. Yet still these conditions do not range so wide that some papillomas go on while others of the same host are retrogressing. To see whether the range could be widened experimentally, the scattered papillomas on one side of a number of rabbits were repeatedly injected with Scharlach R., those of the other side serving as controls. The stimulated growths enlarged with extraordinary rapidity, forming great fungoid masses which continued to enlarge after the injections had been discontinued, and they have proved fatal in one instance. The control papillomas remained small and dry, but they progressed also save in 2 instances in which all dwindled and disappeared while the stimulated papillomas continued to proliferate. Weeks later, however, these retrogressed as well, despite a continuance of the dye injections. Some adverse condition of the host or of its cells had eventually become dominant. Host resistance to proliferating neoplastic cells as such, and a persistingly unfavorable virus-cell relationship are both attested causes for the generalized retrogression of chicken tumors.