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Antigenicity and Infectivity of Extracts of Virus-Induced Rabbit Papillomas.

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The antigen which binds complement when mixed with sera neutralizing the Shope papilloma-virus bears an evident relation to the virus itself; for it is present in high titer in virus-containing extracts of papillomas, it is retained by filters which hold back the virus, and its effectiveness is destroyed by the same amount of heating which renders the virus non-pathogenic.[1] The experiments now to be reported throw further light on this relation.

Tests with Extracts of Non-Infectious Papillomas and of Normal Skin. On inoculation the Shope virus gives rise to papillomas in both domestic and cottontail rabbits; yet only infrequently can it be extracted in active state from the domestic-rabbit growths, and occasionally those of cottontails fail to yield it. Papillomas from 6 cottontail and 8 domestic rabbits, which were produced by the virus yet from which it could not be recovered, have been extracted as usual and tested repeatedly for capacity to bind complement under optimal conditions. Most of these non-infectious extracts failed to bind complement, but a few bound it in a very low titer. Extracts of the normal skin of 3 cottontail rabbits also failed to bind complement, whereas the highly-infectious extracts of their naturally occurring papillomas bound it completely on concurrent test.

Antigenicity of Extracts of Non-Infectious Papillomas. Shope has found that extracts of virus-induced papillomas, which yield no active virus on extraction, will elicit virus-neutralizing antibodies when injected intraperitoneally into rabbits of homologous species.[2] He has generously sent sera from 9 domestic rabbits immunized in this way for complement-fixation tests. They bind complement when tested with suitable antigens, and their capacity to do so varies directly with their ability to neutralize the virus. The sera of 3 normal domestic rabbits failed to bind complement in the same test, as have all other normal sera tested under like conditions.

In order to elicit antibodies with extracts of non-infectious papillomas, crude suspensions of their tissue must be used, Berkefeld V filtrates of these suspensions having proved devoid of antigenicity, in my experience, even when large amounts were injected.

1 Kidd, John G., PROC. SOC. EXP. BIOL. AND MED., 1937, **35**, 612.

2 Shope, R. E., *J. Exp. Med.*, 1937, **65**, 219.

Effect of Irradiation with Ultraviolet Light. The papilloma-virus is very resistant to ultraviolet light, perhaps because of adaptation consequent on its exposure to sunlight under natural conditions. Exposure of the fibroma-virus for less than 5 minutes under a mercury-vapor lamp* at a distance of 48 cm. renders it completely non-infectious;[3] while irradiation for 20 to 90 minutes under the same conditions has been found necessary to reduce or abolish the infectivity of the papilloma-virus in potent 10% extracts. Such exposures did not diminish the complement-binding capacity of these materials, however, nor did irradiation for 120 minutes.

Effect of Variations in pH. The infectivity of papilloma-extracts is known to be immediately destroyed at certain pH levels, slowly at others.[4] To learn the reaction of the complement-binding antigen to variations in pH, portions of two extracts were incubated at 37°C. for 14 hours at various pH levels, with adjustment of all to pH 6.8 thereafter. At pH 4.4 and 9.0, both materials remained highly infectious and capable of binding complement completely, as also at 6.8; whereas at pH 1.8, 2.8, and 10.5 both the pathogenicity and complement-binding capacity of the extracts were abolished. At pH 9.8, however, the extracts lost almost completely their infectious properties, but retained undiminished their capacity to bind complement.

The fixation of complement under the conditions described manifestly involves a specific antigen-antibody union—a reaction, that is to say, which is specific in the rigid immunological sense. The complement-binding antibodies are elicited under the same conditions as the virus-neutralizing, and in the same relative proportions; while the complement-binding antigen is very closely related to the virus, perhaps identical with it. Drastic procedures (heating, treatment with strong acid or strong alkali) abolish both the infectivity and complement-binding capacity of papilloma extracts; but less injurious measures (irradiation with ultraviolet light, treatment with weak alkali) can render extracts non-pathogenic without destroying their complement-binding capacity.

* Alpine Sun Lamp, Hanovia Chemical Co.

[3] Rous, P., McMaster, P. D., and Hudack, S. D., *J. Exp. Med.*, 1935, **61**, 657.

[4] Wyckoff, R. W. G., and Beard, J. W., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 562.