VETERINARY PATHOLOGY

HILTON ATMORE SMITH, D.V.M., M.S., Ph.D.

Late Research Associate, Baylor University College of Medicine; Consultant to the Armed Forces Institute of Pathology; Lecturer (Pathology) University of Texas Medical Branch, Formerly Professor of Veterinary Pathology at (successively) Washington State University, Colorado State University, Iowa State University, Texas A & M University; Consultant to Stanford Research Institute

THOMAS CARLYLE JONES, B.S., D.V.M.

Director of Pathology, Angell Memorial Animal Hospital; Associate Clinical Professor of Pathology, Harvard Medical School; Research Associate in Pathology, Cancer Research Institute of New England Deaconess Hospital; Consultant Staff, Peter Bent Brigham Hospital. Formerly Lt. Col., U. S. Army Veterinary Corps; Chief, Veterinary Pathology Section, Armed Forces Institute of Pathology

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intracerebral inoculation of mice and subsequent neutralization tests to determine the antigenic type. Differentiation from equine viral arteritis (p. 412) should be considered because both diseases are characterized by edema and hemorrhage in the subcutis, heart and lungs. The specific lesions in the musculature of arterioles in arteritis would be useful but isolation and identification of the virus should also be undertaken.

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TUMOR-FORMING VIRAL DISEASES

Papillomatosis in Animals

(Common Warts, Verrucae Vulgaris)

The common wart that adorns the finger of the small boy has its counterpart in nearly every animal species. In some animals, these warts are precise lesions that fastidiously refuse to grow anywhere but in a selected type of epithelium—in the mouth, for example. In others, massively huge and roughly keratinized warts indiscriminately involve large areas of the skin. Most warts are known from observation to be infectious by contact, and many have been shown by experiment to be transmissible with bacteria-free suspensions of macerated wart tissue. In cutaneous papillomas of the rabbit and goat, transformation of simple hyperplastic squamous epithelium to frankly malignant squamous cell carcinoma has been demonstrated. Thus it appears that papillomatoses represent infectious diseases caused by viruses and characterized by benign hyperplasia of stroma and epithelium, which may, under certain circumstances, undergo malignant change. These viruses may therefore be considered among those which induce tumor formation.

Bovine Cutaneous Papillomatosis.—In the bovine species, cutaneous papillomatosis is more frequent than in any other domestic animal. Its viral etiology seems to be well established. The disease is more common and severe in young animals; only partial immunity to reinfection develops, and neutralizing antibodies are not demonstrable in bovine serum. The disease is generally self-limiting and recovery without treatment is the usual course; but when lesions occur on the genitalia (see Fibropapillomas), they may interfere with reproduction.

An outbreak of papillomatosis described by Bagdonas and Olson[1] involved 82 (74.5 per cent) of a herd of 110 Hereford cattle in the course of two and one-half years. The incubation period following intimate natural contact was three and one-half to four months and the duration of disease was one to five and one-half months, all animals recovering spontaneously. Papillomas were observed by these workers to be most frequent on the neck, chin, shoulder and dewlap; less common on the ears, eyelids, throat, lips and elsewhere. The site of the lesions depends to a great extent upon points of skin contact between affected and susceptible animals.

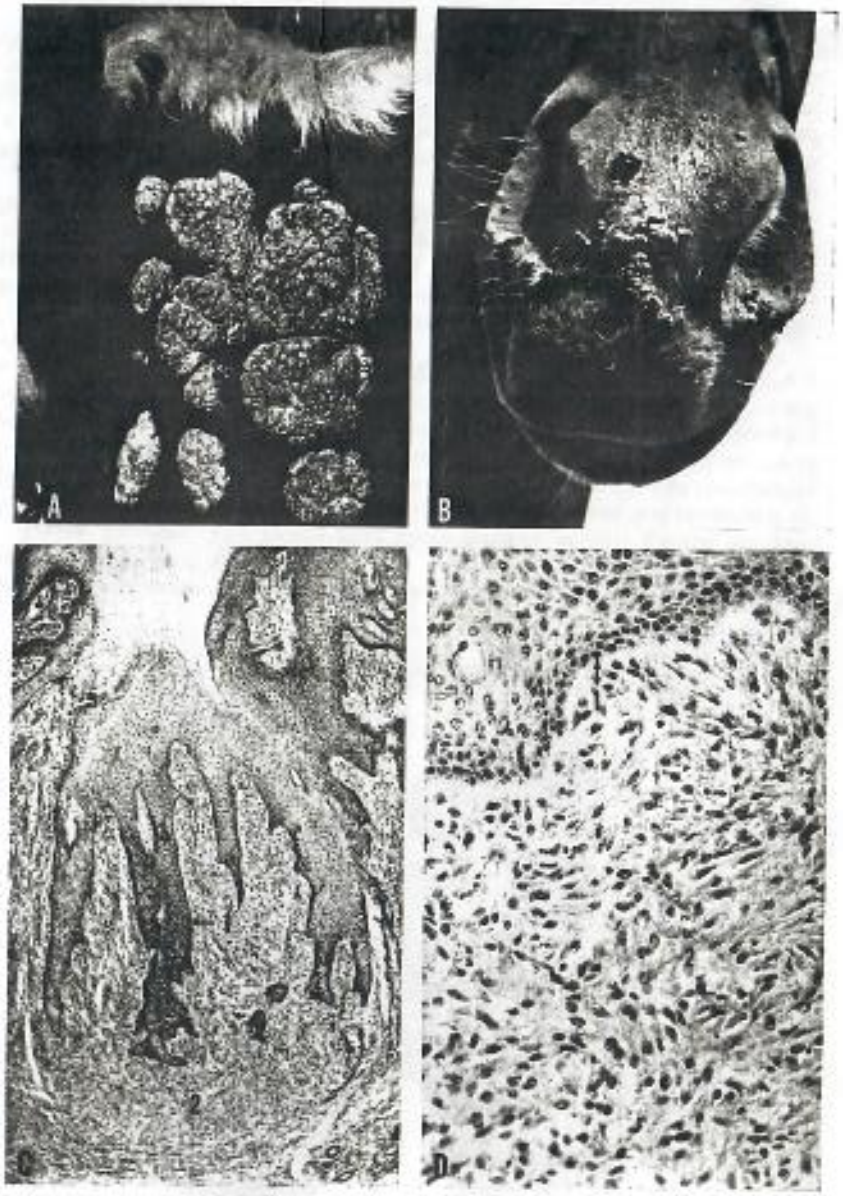

Fig. 145.—*A*, Bovine papillomatosis (warts) neck of a Hereford steer. *B*, Equine papillomatosis, nose of a horse. Photographs courtesy of Dr. Carl Olson, Jr. *C*, Experimentally transmitted bovine papillomatosis (× 33) 41 days after inoculation. Note elongated growth of epidermis (*1*) and cellular dermis (*2*). *D*, Higher magnification (× 210) with hyperplastic but sharply demarcated epidermis (*1*) and richly cellular dermis (*2*). AFIP 740316. Contributor: Dr. Carl Olson, Jr.

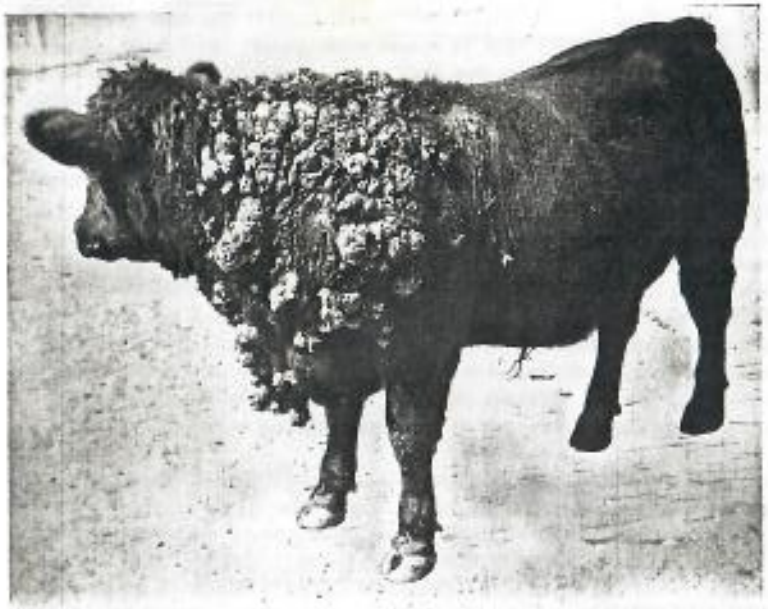

FIG. 146.—Bovine cutaneous papillomatosis (warts). Aberdeen-Angus steer.

Lesions.—The typical bovine wart appears grossly as a rough, cauliflower-like mass of varying size and irregular shape, elevated above the skin surface and attached by either a narrow stalk or a broad base. The lesions are first seen as numerous, closely spaced elevations of the skin, which are round and smooth but soon become rough and horny (Fig. 145).

Microscopically, the lesions are made up of greatly thickened epidermis, which is both acanthotic and hyperkeratotic, supported in elongated fronds by a core of hyperplastic dermis. In some lesions, particularly those induced experimentally by intradermal injection of the virus, overgrowth of the connective tissue elements of the dermis is a dominant feature. Thus the virus can induce proliferative growth in both epidermis and dermis.

Fibropapillomas of Bovine Genitalia.—Certain papillary lesions of the penis of young bulls and vagina of cows have been shown by numerous workers to be transmissible, and McEntee[9] has demonstrated that they are caused by the virus of cutaneous bovine papillomatosis. These fibropapillomas differ from ordinary warts not only in their location, but also in their structure, which is characterized by intense proliferation of connective tissue elements with only slight overgrowth of the overlying epithelium (Fig. 147). Interlacing bundles of large, spindle-shaped cells suggest fibroma or fibrosarcoma. Loss of epithelium and secondary infection may result in leukocytic infiltration and edema which increase the cellularity of the lesion and add to the difficulties of interpretation by the uninitiated pathologist. This specific entity is readily recognized, however, by one familiar with its characteristics. The lesions in the genitalia often present

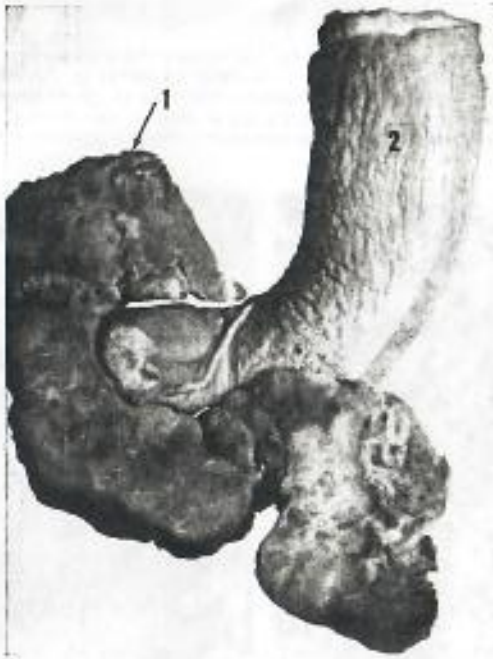

FIG. 147.—Bovine fibropapillomatosis. Large roughly irregular mass (*1*) on the glans penis (*2*) of a bull.

surgical problems and may recur after excision, but they do not metastasize and are usually self-limiting.

Equine Sarcoid.—The pathological characteristics of this growth are presented in the chapter on Neoplasms (p. 178). The entity was first recognized by Jackson[7] in South Africa, who found evidence suggesting that it was transferable from one part of the horse's body to another. He also thought that the abnormal proliferation was primarily epidermal, the underlying dermis later becoming affected and assuming a preponderant role. In these two respects he perceived a resemblance to the common warts (papillomas), which are known to have a viral origin.

Olson[13] has experimentally demonstrated what Jackson suspected, that the lesion can be transplanted from one cutaneous site to another in the same horse (autotransplantation). Later Olson and Cook[11] were able to produce a lesion resembling equine sarcoid by inoculating the horse's skin with material from bovine papillomas (warts), a unique crossing of species boundaries.

Equine Cutaneous Papillomatosis.—Common warts are most frequent on the nose, muzzle and lips of horses during their first and second years of life. These lesions are experimentally transmissible to horses by exposure of scarified skin to triturated suspensions of warts, before or after filtration through bacteria-retaining filters; calves, lambs, dogs, rabbits and guinea pigs are not susceptible. Natural transmission between horses appears to occur through simple contact.

The incubation period is two to three months; the duration of the lesions is about two months, spontaneous regression having occurred in all reported cases. Reinfection is rarely observed in animals which have recovered from the disease.

The papillomas of this equine disease are usually small, discrete, and attached by a narrow stalk, but in some cases they are very numerous and may be confluent. Small papillomas may appear as elongated, elevated nodules with a smooth surface, but larger ones have the rough surface characteristic of warts in other species.

Microscopically, hyperplastic, folded layers of squamous epithelium are supported by a thin core of connective tissue continuous with the dermis. Acanthosis and hyperkeratosis are prominent features in the affected epidermis. The outer layers of the acanthotic prickle cell layer exhibit so-called balloon degeneration, and aggregations of keratohyaline granules may be present in the cells. The lesions in general do not differ basically from those of papillomatosis in other species.

Canine Oral Papillomatosis.—Infectious papillomas have been known for many years[11] to occur in the oral cavity of young dogs. These lesions are transmissible by contact or through injection of bacteria-free suspensions of wart material, but will grow only on the oral mucosa, skin and other epithelial surfaces being refractory to infection. Only dogs are susceptible; attempts to infect

FIG. 148.—Canine oral papillomatosis. *A*, A verrucous mass (*1*) arising from the junction of oral mucosa and skin (*2*) (× 7). *B*, Higher magnification (× 160). Note extensive layer of keratin (*1*), long fronds of hyperplastic epidermis (*2*) containing some vacuoles (*3*) and eleidin granules (*4*). AFIP 197645. Contributor: Dr. S. Pollock.

guinea pigs, rabbits, rats, mice, monkeys and kittens have been unsuccessful.[8] Although cutaneous warts do occur in dogs, apparently they are not caused by the same virus that induces the oral lesions. The duration of oral papillomas is usually from three to five months.

The lesions may be single but more often are multiple, and in some dogs are so numerous as to interfere with mastication and deglutition. They occur anywhere on the oral mucosa, in the cheeks, tongue, palate or pharynx, but do not extend below the epiglottis or into the esophagus. The papillomas are sharply delimited, single or confluent cauliflower-shaped masses with a roughened surface, elevated from the oral mucosa.

Microscopically, the earliest lesion is seen as a sharply circumscribed segment of hyperplastic epithelium in which mitotic figures are frequent. The prickle cell layer becomes progressively thicker as the lesion grows; some cells lose their intercellular bridges and there is beginning papillary formation. Hyperkeratosis becomes a prominent feature, and although cells of the malpighian layer remain normal in size, the squamous cells become larger, their cytoplasm vacuolated or filled with albuminous material. The nuclei of the squamous cells either become greatly enlarged, or, in the outer layers, shrunken and distorted. The superficial cells apparently drop out, leaving a meshwork in the thick keratin layer. In old lesions, a few cytoplasmic inclusions, 1 to 5 microns in diameter, may be seen just under the keratin layer. These are interpreted as keratohyaline masses. In some sections basophilic inclusions, believed to be viral in nature, fill nuclei of epithelial cells. The underlying corium is relatively unchanged, but it sends out long vascular fronds to support the finger-like projections of hyperplastic epithelium. A few plasma cells and lymphocytes may be seen in the stroma underlying old lesions.

Cutaneous Papillomatosis of Rabbits.—An infectious papillomatosis of wild cottontail rabbits was originally investigated by Shope,[18] hence is often referred to as the Shope papilloma. The warts in this disease are usually found in cases of natural infection involving the skin of the inner surface of the thighs, abdomen, or about the neck and shoulders. The lesions are black or gray, 0.5 to 1.0 cm. in diameter and 1.0 to 1.5 cm. in height, and are covered with a thick layer of keratin. They can be transmitted without difficulty from one cottontail rabbit to another by injecting or applying filtered or unfiltered wart suspensions to scarified skin. Recently, evidence has been obtained to indicate that certain arthropods may transmit the virus of this disease.[4] Although domestic rabbits can be infected, the disease cannot be perpetuated in series in such breeds. However, once established in a domestic rabbit, the papillomas can persist for long periods, undergo malignant transformation and kill the animal by metastasis.[12] When these tumors become carcinomatous, they lose their pigment and differentiated characteristics, assume the features of squamous cell carcinoma, and can be transplanted to other domestic rabbits.

Oral Papillomatosis of Rabbits.—Spontaneous papillomatosis of the oral cavity of rabbits has been described by Parsons and Kidd[15] and demonstrated to be the result of a virus infection. The viral agent is distinct from the Shope papilloma virus (p. 425) which affects the epithelium of the skin but not of the mouth. These spontaneous papillomas are small, discrete, gray-white nodules, either sessile or pedunculated. Usually multiple and sometimes numerous, they are almost always situated on the under surface of the tongue, occasionally on

the gums, and rarely on the floor of the mouth. The lesions are predominantly small, with a smooth dome-shaped surface, but occasionally are larger, sometimes attaining a diameter of 5 mm., with a rugose, cauliflower-like surface.

Microscopically, the lesions appear as discrete nodules of thickened, folded, hyperplastic epithelium, supported by sharply demarcated stroma which may form delicate papillæ. In lesions of long standing, the prominent changes are seen in epithelial cells; those of the malpighian layer become large, coarsely vacuolated and irregularly polyhedral in shape. The nuclei of all layers, particularly of the prickle cells, become enlarged, vesicular and may contain eosinophilic inclusions. There is little tendency toward excessive keratinization of the affected epithelium; the outer layers merely appear denser and more eosinophilic in stained sections.

Caprine Papillomatosis.—Papillomatosis of goats may occur in either of two forms. Davis and Kemper[5] described cutaneous warts on the head, face, shoulder, neck and upper part of the forelimb, but not on the teats and udder, in one herd of Saanen goats. Moulton[12] reported papillomatosis limited to the teats and udder in another herd of goats of the same breed. The outbreak described by Moulton was initiated by the introduction of an infected goat into the herd, with the strange result that 50 to 150 black goats were affected, while not one of the 50 white goats exhibited lesions. The disease in this herd was of long duration, papillomas persisting more than five months with little sign of regression. Some of them looked like cutaneous horns, reaching a length of 3 cm., and usually having a rod-like or conical, rather than a papillary, shape. Massive discoid tumors develop in some instances, with frank squamous cell carcinomas arising by dissociation and downgrowth of epithelium. Although there was no generalized metastasis, one of these squamous cell carcinomas metastasized to the supramammary lymph node. Of 7 advanced lesions examined microscopically, 4 showed evidence of malignant transformation. Moulton was unable to cultivate the agent in chick embryos, and transmission to other goats was not attempted.

Papillomatosis of Monkeys.—A papillomatous lesion of the skin of a brown Cebus monkey, described by Lucké, Ratcliffe and Breedis,[8] was experimentally transmitted to another skin site on the same monkey and later to 11 of 13 other monkeys. Both Old and New World monkeys were included in the susceptible group. The incubation period was about two weeks; regression of the lesions occurred between the fourth and eighth months, and no evidence of malignancy was seen during a subsequent eight-month period of observation. This record adds another to the species of animals in which papillomatosis has been observed.

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Shope Fibroma

Fibromas occurring naturally in the skin of wild cottontail rabbits (*Sylvilagus*) were described by Shope in 1932[2] and shown to be caused by a filtrable virus. These lesions are also transmitted experimentally to domestic rabbits (*Oryctolagus* and the agent was demonstrated to be related to that of infectious myxomatosis (p. 428). The fibroma virus produces an effective immunity to subsequent infection by myxomatosis, although in other respects there is no resemblance between the two diseases.

The lesions in the Shope fibroma are often multiple and are described as elevations of the skin by a fibrous mass; the overlying epidermis is thickened and sends bulbous proliferating epithelium deep into the tumor. Large eosinophilic inclusions occur in the cytoplasm of the affected epidermal cells.

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Avian Leukosis Complex

The term avian leukosis has largely replaced "leukemia" as the designation for a group of avian diseases which are characterized by autonomous proliferation of leukocytes and their precursors. The subject is of such general interest to pathologists that it will be discussed briefly even though poultry pathology is outside the scope of this book. Ellerman and Bung[3] in 1908, transmitted avian