

## POSSIBLE INTERRELATIONSHIP OF ACANTHOMA ADENOIDES CYSTICUM (MULTIPLE BENIGN CYSTIC EPITHELIOMA) AND SYRINGOCYSTADENOMA (LYMPHANGIOMA TUBEROSUM MULTIPLEX)

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Unna<sup>1</sup> prefers, on anatomic grounds, to group all tumors derived from the prickle-cell layer under the precise and at the same time comprehensive heading of acanthomata. This term, first suggested by Auspitz,<sup>2</sup> serves admirably when it is desired to draw a sharp line of demarcation between these growths and those originating from other cutaneous structures. Unfortunately, in some instances the point of origin is a matter of doubt, and particularly is this true in many of the lesions that have been reported as examples of multiple benign cystic epithelioma. Typical instances of this affection, which was first described almost simultaneously by Brooke<sup>3</sup> and by Fordyce,<sup>4</sup> in 1892, are easily identified histologically, but some of the variant and mixed forms are extremely difficult to classify.

The tumor of this type which has given rise to the greatest amount of controversy is one first reported by Biesiadecki<sup>5</sup> and Kaposi,<sup>6</sup> and named by them "lymphangioma tuberosum multiplex." While it is generally conceded that these authors were mistaken regarding the origin of the growths, the designation bestowed by them has been allowed to stand, partly on account of priority, but principally because of the indefiniteness of our knowledge concerning the origin of the epithelial processes of which the tumors are largely composed. The sources from which the epithelium can be derived are limited—it must come directly from the prickle layer of the skin or hair follicle, from the coil or duct of the sweat apparatus, or from the endothelium of the blood-vessels, or, theoretically, it may develop from misplaced embryonic rudiments of one or more of these structures (a so-called Cohnheim's rest, or, according to Ribbert's theory of mechanic isolation, from cells that accident has removed from the influence of normal cell association).

An idea of the lack of unanimity of opinion among the various investigators may be gained by a very casual survey of the literature. Almost every observer has seen fit to rename the affection, giving it a title that corresponded with his conception of the origin of the epithelial accumulations. The resulting cognomens vary from the "cellulome épithélial éruptif" of Quinquaud,<sup>7</sup> and

the "navi épithéliaux kystiques" of Besnier<sup>8</sup> to the "hamangendothelioma cutis papulosum" of Waldheim<sup>9</sup> and the "navi cyst-epitheliomatosi disseminati" of Gassmann.<sup>10</sup> Recently we have had an opportunity to make a comparative study of multiple benign cystic epithelioma and lymphangioma tuberosum multiplex, and the findings are of interest as serving to emphasize the necessity of separately classifying these two varieties of non-malignant, cystic, cutaneous neoplasms.

## CASE REPORTS

**CASE 1.**—*Patient.*—A. M., male, married, laborer, aged 70 years, was first admitted to Dr. Walter Sutton's service (surgical) at the University Dispensary in April, 1911. His case was there diagnosed as one of multiple benign cystic epithelioma by Prof. W. K. Trimble, to whom some of the biopsied material had been sent for microscopic examination. When the clinic for skin diseases was opened in October, Dr. Sutton kindly referred the patient to us for further observation and treatment.

*Family History.*—The cutaneous history of the family is negative. The patient has been twice married, and has seven children, aged from 12 to 40 years, all of whom are living and in good health. So far as the father knows, none of them has ever been troubled with a skin disease of any kind.

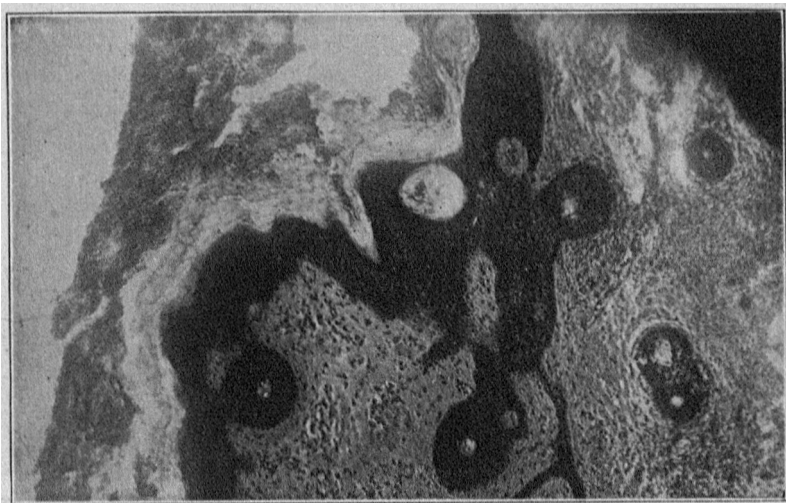


FIG. 1.—Acanthoma adenoides cysticum, showing epithelial strands extending inward from prickle-cell layer with numerous cysts. (Spencer  $\frac{1}{4}$  obj. No ocular.) Case 1.

*Personal History.*—The patient is a native of Ohio, and a resident of Missouri. His general health has always been fairly good. At various times, however, he has suffered from rheumatism, eczema, seborrheic dermatitis, and urticaria.

*Present Illness.*—The small tumors on the patient's forehead, neck, and back have been present ever since he can recollect. One of the larger growths, on the left side of the neck, became hard and indurated in June, 1911, and ulcerated a few weeks later. Clinically, a typical rodent ulcer resulted, and the entire lesion was excised by Dr. Walter Sutton in August, 1911.

*Examination.*—The patient was a well-nourished man, and appeared to be much younger than his age would indicate. The Wassermann sero-reaction was negative, and there was no response to tuberculin. There was some senile atrophy of the skin, particularly on the backs of the hands. The hair was thin, and there was considerable branny scalliness (seborrheic) on the scalp and face. There were a few pigmented nevi on the chest and back. The skin of the trunk was reddened, and there was a decided tendency to dermatographism. Irregularly scattered over the scalp, temples, neck, and chest were a num-

1. Unna: Histopathology of the Diseases of the Skin, Transl. by Walker, Macmillan Company, New York, 1896, p. 784.

2. Auspitz: Lehrbuch der Hautkrankheiten, Vienna, 1881.

3. Brooke: Brit. Jour. Dermat., 1892, p. 260.

4. Fordyce: Jour. Cutan. Dis., 1892, p. 459.

5. Biesiadecki: Untersuchungen aus dem pathol.-anat. Institute im Krakau, 1872, p. 2.

6. Kaposi: Hebra's Lehrbuch der Hautkrankheiten, Ferd. Enke, Stuttgart, 1876, II, 282.

7. Quinquaud: Tr. Internat. Cong. Dermat., Paris, 1889, p. 412.

8. Besnier and Doyon's translation of Kaposi's Pathologie und Therapie der Hautkrankheiten, II, 367.

9. Waldheim: Arch. f. Dermat. u. Syph., 1902, p. 225.

10. Gassmann: Arch. f. Dermat. u. Syph., 1901, p. 177.

ber, seven in all, of the small, pink, nodular tumors characteristic of multiple benign cystic epithelioma. The growths varied in size from a grain of wheat to a split pea, and did not disappear on pressure.

**Histopathology.**—Two of the lesions were excised for laboratory purposes, one from the left scapular region, the other from the right temple. The first piece of tissue was frozen and cut, the sections being stained by the usual methods. The second was fixed in formaldehyd solution, and mounted in paraffin. The findings were practically identical in the two tumors. The corium was somewhat disorganized, considerable quantities of blood, and large numbers of infiltrating round cells being present. No hair follicles, or sebaceous or coil glands were found in either of the specimens. Extending downward into the cutis from the basal layer of the epidermis were numerous long, slender chains of epithelium, two or three cells in width, which terminated in bulb-like cysts, filled with colloid substance and corneous material. Several snared-off sebaceous masses, such as have been described by Csillag,<sup>11</sup> were also to be seen. The chains were composed of cylindrical epithelium which reacted to the various stains in a manner exactly similar to the apparently normal cells in the overlying epidermis. No free tracts were to be found. The outermost covering of the club-shaped projections consisted always of a layer of cylindrical epithelium—in no instance could the presence of a double row of flattened, regularly arranged cells be demonstrated—and an inner zone of

**Examination.**—The patient is a brunette, with brown eyes and hair. Her skin is soft, smooth and flexible. There are a few acne lesions on the left side of the chin, and a slight tendency to rosacea over the nasolabial folds. The Wassermann test is negative, but there is a slight reaction to tuberculin. Irregularly arranged on the left side of the forehead are about twenty small, soft, flattened, pinkish-white, smooth-topped papules, somewhat larger than the head of an ordinary pin, and oval or circular in outline. The group forms a rectangular patch, 4 cm. wide and 6 cm. long. In some instances the lesions have apparently coalesced, the resulting tumor being irregularly fusiform in shape. There is a similar but smaller collection of lesions over the right temple.

On the right side of the chest, near the anterior border of the axilla, is a third group of the tumors, their arrangement appearing to bear some relation to Heitzmann's lines of cleavage. The individual lesions in this collection are more sharply outlined, and the tops are more pointed than those on the forehead. Following the administration of pilocarpin hydrochlorid, 0.01 gm. hypodermatically, drops of moisture appeared on the tops of some but not all of the lesions. At this time, while the patient was perspiring quite freely, the tumors were perceptibly increased in size, and distinctly more prominent than before the drug was given.

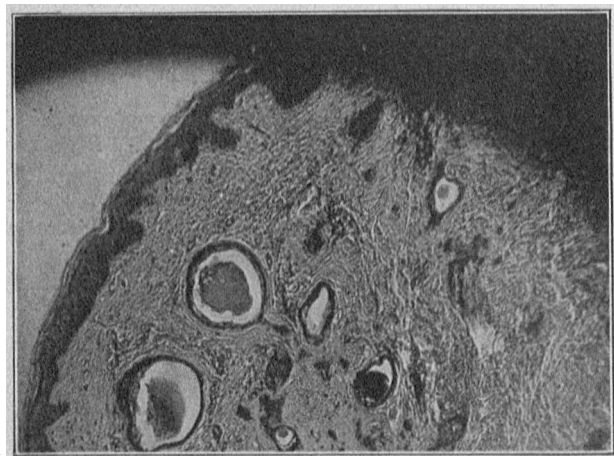


Fig. 2.—Syringocystadenoma. Section from apparently normal area on left side of body. Macroscopically, no tumors were visible. (Spencer  $\frac{1}{4}$  obj. No ocular.) (Case 2.)

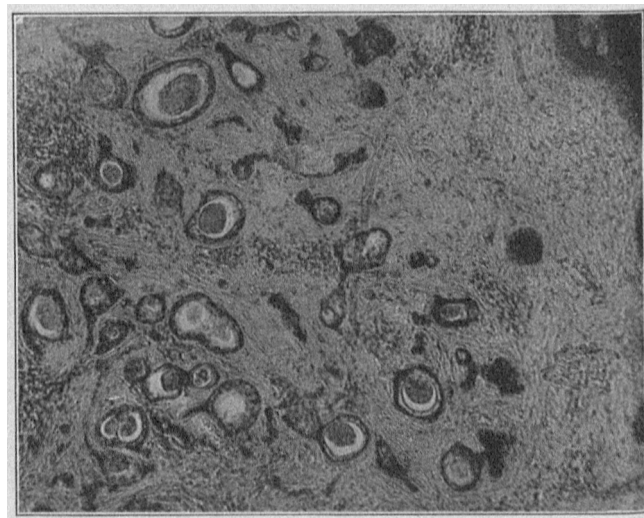


Fig. 3.—Syringocystadenoma, showing epithelial strands and cysts in the corium. (Spencer  $\frac{1}{4}$  obj. No ocular.) (Case 2.)

imperfectly stained, rounded epithelial cells, encircling a central mass of debris.

**CASE 2.—Patient.**—M. D., female, married, housewife, aged 39, was a patient of Drs. J. Phillip Kanoky and Richard L. Sutton, and we are indebted to Dr. Kanoky for permission to record the history and the microscopic findings.

**Family History.**—So far as the patient is able to discover, no other member of the family has ever had a similar disorder. She is the mother of three children, aged 16, 9 and 3 years respectively, all of whom are living and well.

**Personal History.**—The patient is a native of Missouri, and a resident of Kansas City. Her general health has never been good, although she has experienced no severe illnesses. She never feels well during the excessively hot weather, and ascribes her weakness and discomfort to her inability to perspire freely, a peculiarity to which she has been subject ever since she can remember.

**Present Illness.**—For many years there have been present numerous small, whitish or pinkish papules, varying in size from a hemp-seed to the half of a soup-bean, on both sides of the patient's forehead, and on the right side of her chest, near the anterior axillary border. The little tumors have never given rise to subjective symptoms, and slight attention has been paid to them.

**Histopathology.**—At various times, eleven of the growths, two from the forehead and nine from the axilla, together with two pieces of macroscopically normal skin from the sides of the trunk, were excised for microscopic study. The material was fixed in alcohol, formalin, or Zenker's solution. Two of the nodules were sectioned in a freezing microtome, and stained with scarlet R and Sudan III, alum-hematoxylin being used as a nuclear stain. The remainder of the material was mounted in celloidin or in paraffin, and cut at various angles (perpendicularly to, diagonally to, and parallel with, the surface), and the sections afterward stained with the usual dyes. In all, about eleven hundred sections were examined.

The pathologic changes in the epidermis were almost identical with those seen in Charles J. White's<sup>12</sup> case—an unchanged stratum corneum, a thinned granular layer almost devoid of granules, and a rete having a regularly arranged basal layer but composed of swollen, edematous cells, the nuclei of which were large and vesicular, and separated from the encompassing cytoplasm by a considerable space. In the majority of the specimens, the papillae were flattened or entirely absent. There was some cellular infiltration in the upper corium, but the blood-vessels, which were considerably lessened in number, exhibited no inflammatory changes, and the capillary endothelium appeared normal in every way.

11. Csillag: Arch. f. Dermat. u. Syph., 1906, p. 163.

12. White: Jour. Cutan. Dis., 1907, p. 49.

The elastic tissue was somewhat reduced in amount, although the distribution of the fibers was but little altered and the elastic network completely encircled the cysts, as in the cases reported by Dohi,<sup>13</sup> Gassmann and Stockmann.<sup>14</sup> Hair follicles and sebaceous glands were found in all of the nodules. Both the follicles and the appended glandular elements appeared to be normal. In those instances in which a complete longitudinal section of a hair follicle was secured, no budding or other abnormal condition was to be found. Occasionally, one of the long, wavy strands of epithelial cells, to be described later, was found in very close proximity to a pilo-sebaceous appendage, but careful search through the serial sections always showed the extremities to be free, and not connected with the follicle in any way. In addition, the reaction of the component parts of the two structures to the various aniline dyes was entirely different, and invariably served as a trustworthy method of identification.

The coil-glands were well developed, and exhibited no pathologic changes. In several instances the ducts could be traced entirely to the surface of the skin. There was no evidence of dilatation, or of cystic degeneration in either coil or duct, and no indication of budding or of other abnormal cell proliferation.

There was some collagenous degeneration of the connective tissue stroma, but the change was not marked.

Scattered through the cutis, from just below the basal layer of the epidermis down to the stratum of subcutaneous fat, were large numbers of round or oval masses of epithelium, and epithelial-lined tubules. Many of these cell collections possessed a stem-like appendage of epithelial cells, two cells in width, which frequently connected two or more of the glandular masses. In many instances these epithelial tracts were found extending in various directions through the corium. The nuclei of the cells were large, and stained much more deeply than those in the epidermis.

In several of the macroscopically normal sections from both sides of the trunk similar strands of epithelial cells were found, and in one specimen several budding processes and a few cysts were present. It would have been interesting to study sections of skin from parts of the body that are not so rich in coil glands as the axillae, but further material was refused.

Case 1 is a classic example of multiple benign cystic epithelioma as originally described by Brooke and by Fordyce.

C. J. White,<sup>15</sup> Jarisch<sup>16</sup> and Stelwagon<sup>17</sup> have reported similar cases in which the tumors underwent degenerative changes and exhibited evidence of malignancy. In this instance, the somewhat unusual sequel might be partially explained by the concomitant seborrheic dermatitis, which had been present for many years.

In Case 2, we have a typical representative of the Jacquet-Darier group. In general there has been such a remarkable uniformity in the reported cases referred to this group that it is exceedingly improbable that, as claimed by Möller,<sup>18</sup> some are of endothelial and others of epithelial origin. While it is true that actual connection of the epithelial strands and cysts with pre-existing sweat-glands has been missed by the majority of investigators, there are now several well authenticated instances in which such connection has been recognized.<sup>19</sup>

Hartzell<sup>20</sup> has reported a unique neoplasm which

resembled in some respects both benign cystic epithelioma and lymphangioma tuberosum multiplex. Frequently long, slender, epithelial branches were found extending from the sides of the follicles (as in the "trichopithelioma papillosum multiplex" of Jarisch<sup>16</sup>), while, occasionally, tracts of cylindrical epithelium were found running in all directions through the fibrous stroma. These chains were quite long, sometimes branched, and usually not more than two or three cells in width, presenting somewhat the appearance of coil gland ducts. Only a few of them terminated in cysts, and no connection could be traced between them and either the sweat apparatus or the blood-vessels.

It is very probable that this growth, which clinically did not resemble any hitherto reported, was simply a mixed tumor, and that the two types of epithelial structures composing it were in no wise related. The most important evidence in support of the sweat-gland theory of histogenesis of these tumors is the resemblance between the epithelial strands, nests and cysts, and the

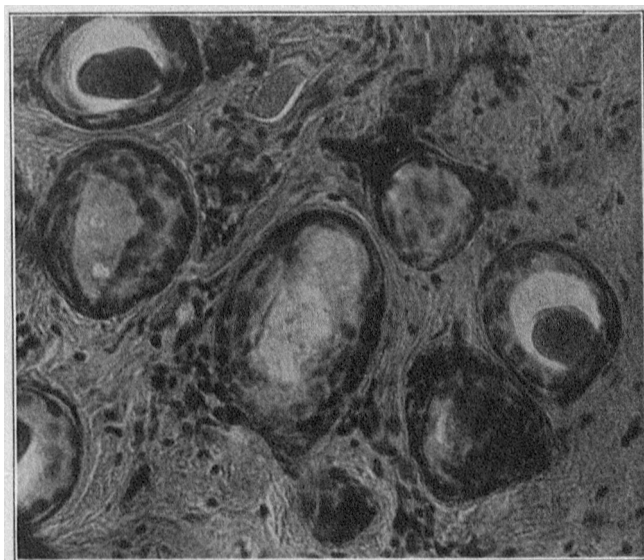


Fig. 4.—Syringocystadenoma, showing flattened epithelial lining of cysts, some of which contain hyaline bodies. (Spencer  $\frac{1}{4}$  obj. No ocular.) Case 2.

tubules of normal coil-glands. There is a manifest similarity between the narrow, often wavy or twisting strands of epithelium connected with the cysts and the normal tubules of coil-glands, but most significant and convincing is the presence in many of the cysts and tubular strands of the double row of epithelial cells, the outer row flat and the inner row cubical, precisely the arrangement so characteristic of the cellular lining of the sudoriparous tubules. While this arrangement is not in all places apparent in consequence of pressure of the contents of the cyst, proliferation of cells, and other obvious causes, it can be recognized in so many places that it cannot be doubted that it is a characteristic histologic feature of this class of tumors.

The decision of the question as to whether the tumor springs from previously normal sweat-ducts or from congenital or acquired defects of the sweat-glands is more problematic. Considerable weight is to be given Török's<sup>21</sup> argument, who made the first thorough study of the histogenesis of lymphangioma tuberosum multiplex, that the absence or rare occurrence of sweat-glands in the area of the tumor, in contrast to the presence of

21. Török: Monatsschr. f. prakt. Dermat., 1892, p. 182.

13. Dohi: Arch. f. Dermat. u. Syph., 1907, p. 63.
14. Stockmann: Arch. f. Dermat. u. Syph., 1908, p. 145.
15. White, C. J.: Jour. Cutan. Dis., 1894, p. 477.
16. Jarisch: Arch. f. Dermat. u. Syph., 1894, p. 164.
17. Stelwagon: Diseases of the Skin, W. B. Saunders Co., Phila., 1910, p. 634.
18. Möller: Arch. f. Dermat. u. Syph., 1902, p. 55.
19. Blaschko: Verhandl. d. Berl. dermat. Gesellsch., July 5, 1908.
20. Neumann: Arch. f. Dermat. u. Syph., 1900, p. 3.
21. Joseph and van Deventer: Dermato-histologischer Atlas der Hautkrankheiten, Berlin, 1906.
22. Flocci: Glor. Ital. d. mal. ven., 1904, p. 3.
23. Winkler: Arch. f. Dermat. u. Syph., 1907, p. 129.
24. Dohi: Arch. f. Dermat. u. Syph., 1907, p. 63.
25. Stockmann: Arch. f. Dermat. u. Syph., 1908, p. 145.
26. Hartzell: Brit. Jour. Dermat., 1904, p. 361.

these appendages in the normal skin, is indicative of the transformation of preexisting sweat tubules into tumor elements. The findings in the case here reported tend to confirm this theory, and the fact that epithelial strands, similar to those found in the tumor areas, may and do occur in apparently normal regions is additional evidence in support of this hypothesis.

In favor of the congenital theory is the occurrence in so many instances of the affection in early life, and especially its occurrence in several members of the same family. Schidachi<sup>22</sup> has produced similar cysts, even with epithelial strands, by occluding the sweat-ducts, and Unna<sup>23</sup> describes a budding epithelial process in spiroadenomata occurring in the neighborhood of varices of the leg apparently similar to the proliferative changes seen in some cases of lymphangioma tuberosum multiplex. Pick<sup>24</sup> objects to regarding these growths as true

designation "syringocystadenoma," suggested by Török, appears to us to be very appropriate, being expressive and at the same time concise.

The extremely interesting and very extraordinary example of sweat-gland tumor recently reported by Ormsby,<sup>25</sup> is exceedingly difficult to classify properly. So far as we can find, no similar case has ever before been described. Engman's<sup>26</sup> suggestion that the sudden and widespread multiplication of certain types of cells might be due to a specific chemical agent acting as a stimulant, as claimed by Starling in formulating his now generally accepted hormone theory, is of great interest, even though Webster's<sup>27</sup> careful and exhaustive analyses proved fruitless in this instance.

#### CONCLUSIONS

**Lymphangioma tuberosum multiplex** or, better, **syringocystadenoma**, is a non-malignant, cystic neoplasm derived from misplaced embryonal coil-gland elements. The cells still retain their sweat-secreting function, hence the tumors are true adenomata.

Although these growths are, in reality, benign cystic epitheliomata, they distinctly differ, both clinically and microscopically, from the *acanthoma adenoides cysticum* originally described by Brooke and by Fordyce. If the term "multiple benign cystic epithelioma" is to be retained, its use should be confined strictly to tumors of the Brooke-Fordyce group, and a more fitting and proper designation, as **syringocystadenoma**, adopted for the neoplasms which have so long been indexed under the euphonious but misleading appellation of "lymphangioma tuberosum multiplex."

We desire to express our very great indebtedness to Professor William H. Welch, of Johns Hopkins University, for his opinion regarding the syringocystadenoma sections. Much of the included summary is quoted almost directly from his personal communication to us, and we feel that his knowledge and discussion have gone far toward clearing up the puzzling subject in question.

#### TREATMENT OF NON-UNION OF FRACTURES \*

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A fracture which has been apparently properly reduced and treated according to the orthodox manner is supposed to go on to successful healing. Fortunately, this is usually the case. Occasionally, however, without any apparent cause, union fails to occur, and such an outcome is both distressing to the patient and embarrassing to the surgeon. Theoretically, bone should repair perfectly, as it belongs to the connective tissue group of tissues that are simple in construction and consequently easy of repair. We know that simple tissues repair readily, whereas the more complicated tissues, such as brain and epithelial and glandular structures, either do not repair at all, or else very imperfectly after a prolonged time. This is a simple, common-sense, biologic law that we would naturally expect. The exception in the case of bone is more apparent than real. The general connective tissue frame-work of the bone is built up even where no union occurs. The fault lies in the failure of the tissues to deposit lime salts, as the mineral

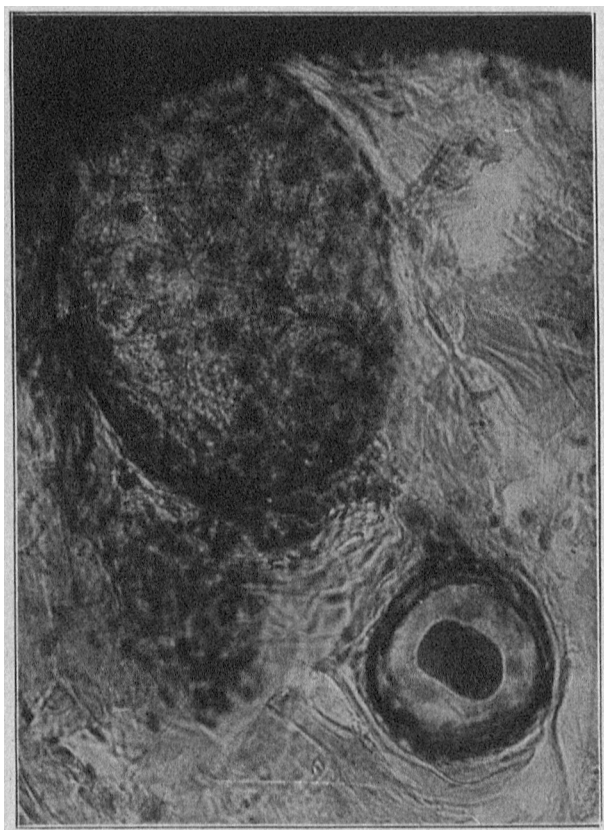


Fig. 5.—Syringocystadenoma, showing epithelial strand apparently developing from the covering of a sebaceous gland. Serial sections showed that there was no connection between the two substances. (Spencer 1/6 obj. No ocular.) Case 2.

adenomata, the question being whether there is anything in the nature of a true secretion. If the hyaline or colloid material in the cysts is merely the result of cellular degeneration the propriety of such names as *cystoma* and *cystadenoma* would be questionable, but Stockmann<sup>14</sup> has apparently shown that, in some instances, the cysts and tubules contain genuine secretion, and the fact that some of the tumors in our case increased in size following the administration of pilocarpin would tend to confirm Stockmann's findings. Strictly speaking, these growths are benign cystic epitheliomata, although that name had best be reserved for the Brooke-Fordyce type of neoplasm, and a more appropriate and descriptive one adopted for tumors of this group. The

22. Schidachi: Arch. f. Dermat. u. Syph., 1907, p. 3.

23. Unna: Histopathology of the Diseases of the Skin, p. 807.

24. Pick: Virchow's Arch. f. path. Anat., 1904, p. 312.

25. Ormsby: Jour. Cutan. Dis., 1910, p. 433.

26. Engman: Jour. Cutan. Dis., 1910, p. 444.

27. Webster: Jour. Cutan. Dis., 1910, p. 441.

\* Read before Richmond Academy of Medicine and Surgery, Nov. 14, 1911.