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This is to certify that we the undersigned, as a committee of the Graduate School, have given Frederick Roman Sanderson final oral examination for the degree of Master of Science in ^{Surgery} We recommend that the degree of Master of Science in ^{Surgery} be conferred upon the candidate.

Minneapolis, Minnesota

May 23 1911

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Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Frederick Roman Sanderson for the degree of Master of Science in Surgery. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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T H E S I S

EPITHELIOMA OF THE PENIS
(A Study of Fifty-Four Cases)

Frederick Roman Sanderson

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fulfillment of the requirements for the
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Epithelioma of the penis occurs infrequently. In two thousand cases of general epithelioma observed in the Mayo Clinic from November 1, 1904, to July 22, 1915, and studied by Broders, there were thirty cases of epithelioma of the penis. Barney studied ninety-three cases treated at the Massachusetts General Hospital for the thirty-three years from 1872 to 1905. According to the annual report of the United States Marine Hospital Service for the five years ending June 30, 1891, Sawtelle states there were 70,826 patients treated, of which number seventy-three had epitheliom involving different regions of the body. In seven the penis was the site of the lesion. Paget says that cancer of the penis forms 1 per cent of all cancers. Other authors give figures varying from 1 to 3-per cent.

From 1906 to 1915, inclusive, there were 7,367 operations at St. Mary's Hospital for primary carcinoma in all regions of the body. Only thirty-three (.45 per cent) were for epithelioma of the penis. During the same period 22,984 males of all ages were operated on for various surgical conditions. Thirty-three of this number were operated on for epithelioma of the penis. The ratio of operations for epithelioma of the penis to all other operations on male patients is as one to 696.

Etiology

Epithelioma of the penis, as Dabney states, occurs when men are "in the sunset of life, rather than in the warm morning of youth". According to Kuttner, Kaufman, Barney, and others, 75 per cent occur in men in the fifth, sixth, and seventh decades of life. Jahn, quoted by Kretschmer, found in a study of 1161 cases collected from the literature, that approximately 75 per cent occur

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red in the same decades. Like carcinoma in general, cases occur occasionally in the young individual, and there have been cases reported in the second decade of life. Barney's youngest patient was 25 and his oldest 82. Reviewing by decades the ages of the fifty-four patients with epithelioma of the penis studied in this paper forty-four (81.3 per cent) occurred in the fifth, sixth, and seventh decades; nineteen (35.1 per cent) in the sixth decade alone. The youngest patient was 29 and the oldest 80.

Age by decades of the fifty-four patients with epithelioma of the penis.

Third	Fourth	Fifth	Sixth	Seventh	Eighth
1	5	18	19	7	4
1.8%	9.2%	33.3%	12.1%	12.9%	7.4%

The average age was 52.8 years.

Occurrence by years.

1906	1907	1908	1909	1910	1911	1912	1913	1914	1915	1916	1917	1918	1919
1	3	7	2	3	0	3	3	4	6	3	4	11	4

Significant in the occupation of these patients, 44.4 per cent were farmers. The high percentage of epithelioma of the penis in the farmer in this series may be accounted for by the fact that a large proportion of the patient coming to the Clinic for treatment are from the rural districts. It is interesting to note that of 256 cases of squamous-cell epithelioma of the skin studied by Broders 53.96 per cent were farmers. Morton observed that cancer of the penis occurred almost always in men in the lower walks of life, of neglectful and uncleanly habits.

Heredity apparently is not a factor in the etiology of epithelioma of the penis. Forty-three patients made a definite statement concerning malignancy in the family, and in seven instances (16.2 per cent) a history of cancer was obtained. A negative cancer history was obtained from 83.7 per cent of the patients. Barney obtained a cancer history from only one patient, and, strange to note, the father had died of cancer of the penis.

The civil state of patients with epithelioma of the penis is interesting if we are to consider contact infection from cancer of the cervix and vagina as a possible etiologic factor. Most authors discredit such a view, but, nevertheless, cases have been reported in the literature. Mesirow reports the case of a husband who developed cancer of the penis after the death of his wife from cancer of the cervix, and quotes McFarland, who found eight cases in the literature where cancer of the penis was thought to be due to contact with a cancerous cervix. Mesirow believes that from the knowledge of the infectious nature of epithelioma in animals, rats and chickens especially, there is a possibility of transmission of epithelioma in man by infection. Bruce, Outland, and Clendenning, and others have reported similar cases. There was no such case in this series. Fifty of these patients were married and four were single.

Probably no civilized race is immune to epithelioma of the penis, but it is an established fact that in Jews the disease rarely occurs, and some writers say never. Kretschmer quotes Professor Djeniel Pacha, who in four years at a military school at Constantinople, which only admits Mussulmen, operated on five patients with epithelioma of the penis. Kuttner quotes statistics of Kambouroglou, chief physician of the German Hospital in Constantinople, which show that cancer occurs as often in persons with a prepuce as in those without it, and that circumcision and early operation for phimosis do not prevent the occurrence of cancer. Nevertheless it must be admitted that the prepuce is no longer necessary to man's requirements, as acknowledged in the Mosaic law, with the direct result that epithelioma of the penis is a rarity in Jews, and that until we know more definitely the cause of cancer, circumcision should be practiced more frequently than it is.

Epithelioma of the penis does not occur as often in negroes as in whites. This is the opinion of Dabney, who lives in the South. In Barney's

series of one hundred cases there was not a negro, and he was able to find only one such case in the literature. Broeman, Thomas, and McCoy have since reported cancer of the penis occurring in the negro.

The exact cause of epithelioma of the penis, as of cancer elsewhere, is unknown, but the writings of all authors state that chronic irritation is a most important factor in the production of this type of cancer. Wilkins goes so far as to state that cutaneous cancers are always located where there have been tumors, scars, moles, warts, keratoses, or some form of irritation. Broders, in his article on squamous-cell epithelioma of the skin, found that in over one-half of the patients the site of the cancer was preceded by a mole, wart, pimple, scab, or ulcer.

The primary contributory etiologic factor in epithelioma of the penis is phimosis. This observation is established by most writers. Barney states that 85 per cent of the patients had phimosis. Kuttner found it in 54.5 per cent. Demarquay reports phimosis in forty-two of fifty-nine cases. Jahn, quoted by Kretschner, found it in 45 per cent of 664 cases. Travers states that cancer of the penis begins with either phimosis or paraphimosis, and reports a case of the latter. In thirty-four cases in this series a definite statement or a record of the prepuce was made, and in all phimosis was present. The duration of the phimosis was stated in twenty, and is as follows:

Congenital phimosis	18
Many years' duration	1
12 years' duration	1

These figures suggest that early circumcision may have some influence upon the prevention of cancer of the penis.

There are other conditions of the penis favoring chronic irritation and resulting scar formation which some authors call pre-cancerous; namely, venereal warts, pimples, ulcers, moles, balanitis, leukoplakia, chancer, chancroid, and pre-putial calculus.

The development of cancer in the scar of a chancre has been reported in many cases. Barney reports two of this type. Demarquay saw ten in a series of fifty-nine. Similar cases have been reported by Cunningham, Broeman, and others. There were five cases in this series in which a history of chancre was given. A blood serum Wassermann was done on nineteen of the fifty-four patients, and the reaction in the blood was positive in one and negative in eighteen. The history of the patient with the positive Wassermann is interesting in that the penis had been entirely destroyed, and was missing. Case 298278, a negro, 47 years of age; occupation, hod carrier, gave a history of Neisserian infection at the age of fifteen; and during the past year received three intravenous injections for lues. Nineteen months before presenting himself at the Clinic he had noticed a yellowish, irritating and painful discharge from beneath the prepuce. Shortly afterward a small, hard nodule appeared on the glans; this gradually grew and encircled the penis, and finally caused the glans to drop off. The glands in the inguinal region, which became enlarged and broken down, bled freely at times. Examination showed the penis to be missing at the level of the abdominal wall. There was a raw, ulcerating area in the inguinal region, with indurated, irregular edges. The scrotum was oedematous and hard. Several perineal fistulas draining a bloody discharge were present. The Wassermann reaction gave a total inhibition; the hemoglobin was forty-four, and there were 3,450,000 erythrocytes. The urine contained some blood and many pus cells. A specimen excised for diagnosis showed squamous-cell epithelioma. The case was inoperable, and the patient died in less than a year.

Genito-urinary conditions other than phimosis prior to the development of epithelioma of the penis.

	<u>Patients.</u>
Gonorrhoea	7
Chronic balanitis	5
Chancer	5
Chancroid	2
Small growth on prepuce	2
Sore	1
Ulcer	1
Abscess	1
Scaling area on glans	1
Venereal wart	1

The concomitant association of lues and cancer has been observed on numerous occasions, and is especially striking in cancer of the tongue. New states that over 50 per cent of patients with cancer of the tongue have an associated lues. Demarquay places lues second in prominence as the predisposing cause of epithelioma of the penis, and reports ten cases in a series of fifty-nine.

Three of Barney's patients had a definite history of trauma, which must be recognized as a possible precursor of epithelioma of the penis. He also reported six patients whose wounds failed to heal following a previous circumcision, with the subsequent development of cancer in the unhealed scar. He classified these under the heading of trauma. In this series there was one patient who gave a definite history of trauma, and four in whom epithelioma developed in the wound of the circumcision.

One patient developed epithelioma one year following circumcision.
 One patient developed epithelioma six months following circumcision.
 Two patients developed epithelioma in the unhealed wound of the circumcision.

McGavin thinks that the repeated fissuring of the phimotic preputial orifice, as a result of forcible stretching by the wedge-like action of the glans during sexual intercourse, results in scar formation and thickening, thus creating fertile soil for the development of cancer.

Duration of fifty-four cases of epithelioma of the penis:

One year or under	31
One to two years	14
Two to three years	4
Three to four years	2
Four to five years	1
Not stated	2
Longest duration	4.5 years
Shortest duration	5 weeks
Average duration	1.33 years

I have been rather conservative in estimating the duration of the lesions, and that some degree of error exists must be admitted, because the duration was estimated either from the time the patient first noticed the lesion or from the time the home physician was called upon for relief and stated definitely that a lesion was present. This may account for the rather short average duration. It is very difficult in some cases, especially in those where the lesion is obscured by an overlying adherent prepuce, to say definitely when the growth started; the only symptom for weeks or months preceding the discovery of the lesion may have been pain or a sub-preputial discharge. There were only two patients in whom the duration was over four years. Forty-five of fifty-two gave a history that the lesion was present for two years or less. The average duration for all the cases was 1.33 years.

Pathology.

Epithelioma arises from either normal or chronically inflamed epithelium. The initial lesion generally appears as a simple warty growth, an eroded papule, a small hard lump, or, finally, as an ulcer. In every patient in this series except three the initial lesion was a proliferating growth, either a small mass, wart, bunch, scaly spot, lump, nodule, pimple or papule. In the exceptional three an ulcer was noted as the initial lesion.

The established lesions are of two distinct types, the carcinomatous ulcer and the cauliflower proliferating growth. The latter has a tendency

at times to ulcerate, and for that reason some authors mention it as a third type. Kuttner, Ewing, and others have observed that the papillary growth is of a lesser degree of malignancy and of longer duration than the ulcerated destructive lesion with a more rapid and malignant course.

An attempt has been made to classify these cases in groups according to the degree of cellular activity, after the method of Broders in his study of squamous-cell epithelioma of the skin. The degree of cellular activity is graded on a basis of 1 to 4; that is, if the epithelioma has a marked tendency to differentiate it is of low-grade malignancy such as group 1; if there is no tendency for the cells to differentiate, the epithelioma is regarded as most malignant, and is graded 4. The intermediate grades are determined by the proportion of differentiated and undifferentiated cells in the epithelioma. The number of cells showing mitotic figures also influence the grading.

In this series of fifty-four epitheliomas fifty-three were of the squamous-cell type, and one was of the melanotic type. Following is a table giving the grades of epithelioma on a basis of 1 to 4, according to cellular activity:

	<u>Cases</u>	<u>Percentage</u>
Grade 1	7	12.9
Grade 2	33	61.1
Grade 3	13	24.07
Grade 4	1	1.85

Duration and size of epithelioma

	<u>Grade 1</u> <u>(years)</u>	<u>Grade 2</u> <u>(years)</u>	<u>Grade 3</u> <u>(years)</u>	<u>Grade 4</u> <u>(years)</u>
Longest duration	2.	3.5	4.5	4.
Shortest duration	.50	.096	.17	
Average duration	1.51	1.26	1.33	

	<u>Centimeters</u>	<u>Centimeters</u>	<u>Centimeters</u>	<u>Centimeters</u>
Largest size	7	9	4.5	Not stated
Smallest size	1	1.2	1.5	
Average size	3.78	3.5	1.12	

	<u>Grade 1</u>	<u>Grade 2</u>	<u>Grade 3</u>	<u>Grade 4</u>
Operable epithelioma	7	27	11	1
Operable (palliative)	0	1	1	0
Inoperable epithelioma	0	3	1	0
Operation refused	0	2	0	0
Greatest diameter	9 centimeters			
Average greatest diameter	3.48 centimeters			

It is observed that the average duration of the epithelioma was longest in grade 1 (1.51 years); next longest in grade 3 (1.33 years), and shortest in grade 2 (1.26 years). The average size of the epithelioma seems to bear direct relation to the degree of malignancy; the less malignant the growth, the larger its size, and the more malignant the growth, the smaller its size. The average size in grade 1 was 3.78 centimeters, in grade 2, 3.5 centimeters, and in grade 3, 1.12 centimeters. All in grade 1 were operable; twenty-seven of thirty-one in grade 2 were operable, and eleven of thirteen in grade 3 were operable. There were four inoperable cases, three of which were in grade 2, and one in grade 3.

With some difficulty, on account of the early ulceration of some of the papillary growths, the types of the established lesion in this series were grouped as follows:

	<u>Total cases</u>	<u>Group 1</u>	<u>Group 2</u>	<u>Group 3</u>
Carcinomatous ulcer	25	0	18	7
Proliferating cauliflower growth	13	6	5	2
Ulcerated cauliflower growth	4	1	2	1

It is seen that twenty-nine of forty-two lesions were ulcerated. Only one case of grade 1 epithelioma was ulcerated, while seven were of the cauliflower type. Eighty per cent of both grade 2 and grade 3 cases were ulcerated, which establishes the interesting observation that epitheliomas of low malignancy rarely ulcerate, and that 80 per cent of the more malignant epitheli-

omas do. There was one lesion which presented two distinct types, an ulcer at the corona, and two small paillary growths along the glans.

The glans has been named by nearly all authors as the most frequent site of the original lesion. Barney, Demarquay, and Kuttner found this to be so. Kaufman places the prepuce first and the glans second. In thirty-eight cases in this series twelve had their origin on the prepuce and twenty-six on the glans. The usual areas on the glans at which epithelioma develops are the ventral surface close to the frenum, and the dorsal surface at or near the corona. Wilkins states that squamous-cell epithelioma is especially prone to appear at the junction of the skin and mucous membrane, as is so strikingly seen at the corona.

In order that the pathology and behavior of epithelioma of the penis, especially as regards recurrence and metastasis, may be more clearly understood, it will probably be well to review briefly its surgical anatomy. The isolated position of the penis confers upon it the advantage of constant supervision, thus affording early treatment and removal of the diseased part to a distance from the body. The earliest stage of the lesion can be observed in a manner which is impossible in an organ placed within the body, as the stomach or uterus.

The penis is a very vascular organ composed of a mass of erectile tissue enclosed in three cylindrical compartments, the corpora, cavernosa, and the corpus cavernosum urethrae. It is covered with skin and superficial fascia which is continuous with that of the scrotum and pubis. The glans is formed by an enlargement anteriorly of the corpus cavernosum urethrae. At the neck of the glans the skin overlying it becomes infolded upon itself to form the prepuce. The inner layer of the prepuce is covered by mucous membrane which is reflected over the glans to become continuous with that of the urethra.

A knowledge of the lymphatics of the penis is very important, as extension of the epithelioma takes place usually through these channels. From the anatomical investigations of Kuttner the following important surgical facts

were concluded:

1. The lymph vessel reticulum of one-half of the penis passes continuously into that of the other.
2. The large efferent lymph branches, especially the medianly placed, frequently give branches to the glands of each side; in rare instances a crossing of vessels not placed medially is said to occur.
3. The lymph vessels of the prepuce, especially of the inner surface, the glans, and the urethral mucosa communicate with each other.
4. The majority of the superficial and deep lymph tracts lead to the inguinal glands. The penis is connected by direct lymph vessel connections to the medial and lateral upper groups of inguinal glands.
5. The small glands on the anterior surface of the symphysis are usually imbedded in a plexus arising from the deep lymphatics of the penis.
6. There are numerous lymph tracts of the penis which, without passing to the inguinal glands, pass directly to the glands in the interior of the pelvis; that is, the iliac lymph glands, the hypogastric glands, and the anterior and lateral vesical glands. The connection with the pelvic glands is through the deep vessels of the penis as well as those of the urethral mucosa.

In no other organ of the body are the relations more favorable for early widespread metastasis of carcinoma than in the penis, yet metastasis to distant organs is rarely seen. Kaufman collected nineteen cases from the literature, and Kuttner reported one of his own. Where remote metastasis occurs, the liver and lungs are most frequently involved. In 1916 Menetrier and Martinez reported a case where the patient died of epithelioma of the penis, and at autopsy the only remote metastasis was found in the pericardium. Barney states that metastasis to vital organs occurs in over 15 per cent of all patients. There was no operative mortality in our group, and as all of the deceased patients died at home there was no instance where an autopsy was done. In three

cases the home physician reported remote metastasis; two in the liver, and one in the lung.

The size of the epithelioma does not usually govern the degree of metastasis or the time at which metastasis occurs. Lesions of small dimension will metastasize to the regional lymphatics early in the process, while large growths, especially the cauliflower type can be present for a long time without regional lymphatic involvement.

The work of Kuttner and others has shown that local extension takes place in the spongy tissue of the penis by direct infiltration of the cancer cells, metastatic extension almost exclusively through the lymph vessel system, and rarely through the blood stream.

The regional lymph glands, especially the inguinal, are most regularly involved, yet it has been shown that the pelvic glands have been involved without any demonstrable involvement of the inguinal glands. This direct lymphatic connection between the penis and the glands of the pelvis at once compels early diagnosis and early radical treatment to insure a complete cure.

The involvement of the regional lymph glands influences the prognosis of this disease. Of fifty-six cases reported by Kuttner there were forty which showed enlargement of the lymph glands, but of these there were only eighteen where the glands were carcinomatous. In seven of the eight cases reported by Cunningham metastasis to inguinal glands had already taken place, and in every instance it was bilateral. Barney found enlargement of the lymph glands in over 75 per cent of the patients, 60 per cent of which were carcinomatous. The pathologic findings in thirty-nine cases where the regional lymph glands were removed are shown in the following table.

	<u>Cases</u>	<u>Percentage</u>
1. Inflammatory glands	24	61.5
2. Glands showing epithelioma ...	15	38.4
1. Bilateral	6	
2. Right	4	
3. Left	2	
4. Not stated	3	

In twenty-five cases where the glands were removed 30 per cent of the grade 2 epithelioma showed metastasis, 71 per cent of grade 3, and not one case of grade 1.

In this series recurrence was seen in fourteen (29.1 per cent) of forty-eight patients operated on. Every patient heard from in whom recurrence was reported has subsequently died of epithelioma.

<u>Location</u>	<u>Grade of epithelioma</u>	<u>Time of recurrence following operation (years)</u>	<u>Pathology of glands</u>
1. Left inguinal region	2	Not stated	Left - epithelioma
2. Left inguinal region	2	Not stated	Glands - epithelioma
3. Stump and inguinal region	2	1.	Inflammatory
4. Stump and right inguinal region	2	.58	Glds.removed elsewhere
5. Stump and right inguinal region	2	.25	Glands - epithelioma
6. Stump	3	.16	Left - epithelioma
7. Right inguinal region	3	.125	Right - epithelioma
8. Right inguinal region	3	.2	Right - epithelioma
9. Right thigh	3	1.33	Glands - epithelioma
10. Right inguinal region	3	.083	Right - epithelioma
11. Above pubis and abdominal extension	2	.33	Glands - epithelioma
12. Perineum and inguinal region	3	5.	Glands not removed
13. Inguinal region, stump, and rectum	2	.75	Inflammatory
14. "Different places"	2	.5	Bilateral epithelioma

The average time of recurrence was ten months following operation.

Most recurrences in this group took place within one year. Metastasis to the inguinal glands was present at the time of the primary operation in ten of the fourteen patients in whom there was a recurrence. Barney reported four cases in which recurrence took place after a period of five years.

Case 131456 is especially interesting because it demonstrates the occasional tendency of epithelioma to remain dormant, with practically no extension, over a period of years. The patient was a farmer fifty-five years old, who gave a history of lues twenty years before, for which he had received

several intravenous injections and had taken iodids by mouth for years. A circumcision was performed fifteen years before for phimosis and a little warty growth on the prepuce. A wart-like growth reappeared on the penis one and one-half years before the patient came to the Clinic, and this gradually extended and invaded the whole organ. Bleeding from the growth was frequent. Examination revealed a large, cauliflower-like growth, 10 cm. in diameter, involving the whole penis, with beginning extension to the scrotum, which was markedly oedematous. The glands in both inguinal regions were enlarged and very hard. The hemoglobin was thirty-seven, and the urine contained many pus and blood cells. The penis was amputated at the pubic arch, with excision of the scrotum and testicles. The regional glands were not removed, as it was thought that the extension of the epithelioma had progressed too far to be totally removed by an inguinal dissection and removal of the glands. A section showed squamous-cell epitheliom, grade 3. The patient returned after five years, on account of severe pain in the right thigh and inguinal regions, and a local recurrence. Examination showed an elephantiasis of the right leg, which measured 70 cm. around the thigh. There was a mass of hard glands in the right inguinal region and smaller glands on the leg. In the left perineal area there was a recurrence with ragged, bleeding edges. Hemoglobin was sixty-four, and an x-ray of the chest was negative. Three x-ray treatments and two radium treatments were given, with a marked diminution in the size of the recurrence. The patient died of epithelioma several months after leaving the Clinic.

Symptoms.

Pain and discharge from the prepuce are early symptoms. The pain is variable, rarely severe, and may be acute, but is as a rule of the dull type. If the lesion is located in such a position that urine passes over it during micturition, a burning sensation is complained of. Pain may be confined to the penis, or referred to the scrotum, inguinal region or pelvis.

In recurring epithelioma with marked glandular extension, the pain becomes extreme and unbearable, requiring morphia constantly for relief. One patient dying of extensive glandular epithelioma described the pain as equivalent to the sensation which would follow the application of a red hot poker to the skin. Fifty per cent of the patients complained of pain.

The type of discharge varies. When the growth is completely covered over by the prepuce the discharge is usually foul and purulent, and sometimes bloody. The papillomatous growths have a tendency to bleed, and at times severe hemorrhage occurs. Three patients in this series gave a history of hemorrhage. Kuttner described a case in which the patient was so weak from loss of blood that he was unable to walk without assistance.

Some patients seek relief for the "sore" which has resisted the usual forms of treatment for venereal lesions of the penis and has continued to spread. The growth ulcerates and extends from the prepuce on to the glans, destroying the tissues of the penis as it progresses. It is surprising at times to find that such a very destructive lesion can produce so few disagreeable symptoms.

Some patients seek relief for urinary disturbances, either painful urination, frequency, or difficulty in voiding. The urethra is rarely encroached upon by the epithelioma sufficiently to cause difficulty in voiding, and seldom sufficiently to cause complete retention, except in those cases of epithelioma arising from the urethra itself. When the urethra is invaded and is a part of the ulcerating process a purulent anterior urethritis is usually present, with resultant painful, burning urination. LePileur and Dibet report a case of almost complete urethral obstruction with constant bladder distention. The patient, in an effort to relieve his suffering, had cut into the penis, endeavoring to make an opening for the passage of the urine.

Occasionally the symptoms are so mild and the discomfort produced

by the growth so trivial, that the penial lesion is discovered on examination when the patient presents himself for relief of some other condition. There were two such patients in this group; one came to the Clinic for gall-stone attacks, and the other for a painful right knee. Both were entirely ignorant of any trouble with the penis. The phimotic prepuce obscured the lesion from view, and the symptoms produced by the lesion, if any, were so mild in comparison with their other ailment that they were entirely overlooked by the patient, and the epitheliom was discovered on routine examination. Many of these unfortunate patients are seen at such a late period of the malignant process that the penis is partially or completely destroyed and metastasis has already taken place in the regional lymphatics. A large metastatic carcinomatous ulcer, with irregular hard edges and a huge crater in the center was observed in two patients.

Treatment.

The prophylaxis necessary for the prevention of epithelioma of the penis is equally as important as in any other disease. Unfortunately, however, such measures are not always employed in these cases. McGavin sums up the preventive treatment as follows: (1) Avoidance of venereal contamination, (2) personal cleanliness, (3) removal of all warts, (4) early treatment of any cause of irritation, and (5) circumcision.

Some authors advise circumcision in all males. This is a somewhat radical view and should be compromised by circumcision in all persons with a phimotic prepuce, or in whom a long prepuce has a tendency to produce chronic irritation with resultant inflammatory changes in it or the glans. According to McGavin, the prepuce has long since outlasted its original function "of conserving a high degree of sensitiveness in the glans in that period of man's history when it was essential that the sexual activity of man should be maintained at a high pitch, which would insure the speedy increase of the race".

The operative treatment of epithelioma of the penis should be just as radical as in cancer of other organs. Any temporizing method usually fails. Cautery amputation of the penis at the pubic bone, together with a thorough excision of the inguinal glands, is the operation of choice. Some authors advocate complete excision of the penis, with removal of the scrotum and testicles, and transplantation of the urethra into the perineum. This type of operation is somewhat radical as a routine procedure, but has its place in certain extensive epitheliomas involving the scrotum. Partial amputation is still being performed in an effort to save a portion of the penis, but this procedure, although occasionally successful, will be a failure in most instances. Kuttner showed by his work that cancer elements could be found in the corpora cavernosa at a distance of 7 cm. beyond the visible border of the carcinomatous lesion. Any attempts of cure by partial amputation carries with it the danger of local recurrence.

Undoubtedly radium has an important place in the treatment of epithelioma of the penis, but not as a substitute for surgery in the operable lesions. It is indicated in those cases in which the malignant process has become inoperable or when inoperable recurrences appear. One patient in this series who was treated with radium writes (after three years) that, as far as he is able to judge, there has been no return of the disease. Radium may be used in conjunction with surgery; that is, applied over the growth and inguinal regions before and after operation. If at the time of operation the inguinal glands are found to be involved, combined radium and x-ray therapy is indicated at intervals postoperatively until it is reasonably certain that there is no return of the disease.

Complications.

The operative mortality in this series is nil. Reports of Kuttner, Barney, and others show that operative deaths are few; the former reported fifty-three operations and three deaths; the latter gives an operative mortality of 1 per cent. Death is usually from infection, pneumonia, or secondary hemorrhage.

Contraction of the urethral meatus, with resultant urinary difficulty, is a distressing complication which occurred in twelve patients in this series. In five it was necessary to dilate the contracted urethral orifice, and two were compelled to use a catheter at times for relief.

A frequent complication in cases where the inguinal glands were removed was the breaking down and sloughing of the inguinal wound, necessitating rather prolonged hospitalization. The frequency of infection in the inguinal wound has been noted by other writers. In thirty-five patients in whom amputation of the penis and excision of the inguinal glands were done the average number of days spent in the hospital was nineteen; the average total number of days these patients were under treatment was thirty-nine.

Murphy noted this frequent wound complication and explained that it was due to infection of the wound through its contamination from the regional glands harboring pyogenic organisms secondary to the mixed infection in the ulcerated carcinomatous growth of the penis. He recommended a two-stage operation and advised removal of the inguinal glands subsequent to amputation of the penis.

Conclusions.

1. The incidence of epithelioma of the penis is small. It represented .45 per cent of all cancer, and 1.5 per cent of all epithelioma. It occurred once in every 696 males of all ages.
2. Farmers were more often affected than any other class of man - 44.4 per cent.
3. The greatest number of cases (35.1 per cent) occurred in the sixth decade. Eighty-one and three-tenths per cent occurred in the fifth, sixth and seventh decade. The average age was 52.8 years.
4. There was a history of cancer in the family in sixteen and two-tenths per cent.

5. There was no case in which contact infection from a cancerous cervix or vagina could be suspected.
6. Phimosis was seen in over 50 per cent of the patients.
7. Negroes are not as frequently affected as white men.
8. Lues was rarely associated with epithelioma of the penis.
9. A previous penial lesion existed in the majority of cases.
10. Trauma played a minor part in the etiology.
11. The longest duration of the lesion was 4.5 years; the shortest five weeks; the average 1.37 years, and the average greatest diameter 3.88 cm.
12. The cauliflower type of epithelioma is less malignant than the carcinomatous ulcer and runs a longer course.
13. The glans was the original site of the lesion in twenty-six cases, and the prepuce in twelve.
14. Remote metastasis was rare.
15. The inguinal glands were involved with epithelioma in 38.4 per cent, and were inflammatory in 61.5 per cent.
16. Recurrence was noted in 29.1 per cent. Every patient with recurrence died of epithelioma.
17. Circumcision in itself is not a sure preventive measure, but should be performed in all cases in which phimosis is present and in which a long prepuce causes inflammatory changes in it or the glans.
18. The operation of choice is a cautory amputation of the penis at the pubis, and subsequent second stage removal of the inguinal glands.
19. Eighty-two and six tenths per cent of twenty-three deceased patients who had been operated on died from epithelioma.
20. Of eight patients with metastasis, in whom at the time of operation the inguinal glands were removed, 87.5 per cent died later of epithelioma, and 12.5 per cent are alive, without recurrence.

21. Of eighteen patients without metastasis, in whom at the time of operation the inguinal glands were removed, 82.2 per cent are living, without recurrence, and 17.6 per cent died of epithelioma.

22. Of two patients operated on without removal of the inguinal lymph glands 100 per cent died of epithelioma.

23. In patients with metastasis the duration of life after operation was: One patient alive after 12.88 years; for the patients dead, 1.38 years.

24. In patients without metastasis the average duration of life after operation was, for the patients alive, 4.33 years; for those who died of epithelioma, 3.99 years.

25. The average duration of life of the two patients who were operated on without removal of the inguinal glands, and who subsequently died of epithelioma, was 2.87 years.

26. The average duration of life of all patients operated on who are alive, without recurrence, or died from other causes, was 5.69 years, and those who died of epithelioma, 1.96 years.

27. The total good results following operation, according to the grade of epithelioma, are 100 per cent for grade 1; 57.1 per cent for grade 2; and 40 per cent for grade 3.

28. The total poor results (patients dead of epithelioma) following operation, according to the grade of epithelioma, are: Grade 1 - 0; grade 2 - 42.8 per cent, and grade 3, 60 per cent.

TABLE NUMBER 1

<u>Treatment elsewhere of epithelioma of the penis</u>	<u>Cases</u>	<u>Percentage</u>
1. Non-surgical,		
One or more treatments with salve, paste, caustics, acid, Roentgen-ray, antiluetic treatment with salvarsan, neosalvarsan or allied preparations intravenously, or intramuscularly, iodids and mercury...	5	9.2
2. Surgical,		
One or more operations	21	38.8
3. Combined surgical and non-surgical,		
One or more operations with one or more treatments with salve, paste, caustics, acid, Roentgen-ray, et cetera	13	24.08
4. Total number of cases treated elsewhere (secondary cases).....	39	72.08
Cases without previous surgical or non-surgical treatment..	15	27.82

Surgical procedures elsewhere in 31 cases of epithelioma of the penis:

Circumcision alone	15
Circumcision with excision of growth	3
Circumcision and incision of inguinal "bubo"	1
Excision of growth	4
Incision of abscess	5
Cautery to recurrence	1
Dorsal slit	4
Dorsal slit and excision of growth	1
Excision of specimen	4
Unknown operations	2

TABLE NUMBER 2

Operations at Mayo Clinic for epithelioma of the penis:

Number of cases operated on	48
Inoperable	4
Refused operation after diagnosis was made	2
1. Radical amputation of the penis, including the scrotum and testicles, with removal of the inguinal glands	3
2. Radical amputation of the penis and double castration, without removal of the inguinal glands	1
3. Amputation of penis (at pubis) with knife or cautery, and removal of inguinal glands alone or inguinal and femoral glands	26
4. Amputation of the penis (at pubis) with knife or cautery, without removal of the inguinal or femoral glands	3
5. Partial amputation of the penis with knife or cautery, and removal of the inguinal glands alone, or inguinal and femoral glands	8
6. Partial amputation of the penis with knife or cautery, without removal of the inguinal or femoral glands	2
7. Excision of growth with cautery and removal of inguinal glands	2
8. Excision of growth with cautery without removal of the inguinal glands .	1
9. Re-amputation of the penis. Glands removed elsewhere	1
10. Excision of mass of degenerating right inguinal glands	1

TABLE NUMBER 3

GENERAL ULTIMATE RESULTS

Patients traced (operable, 29; operation palliative 2; inoperable, 4; operation refused, 1)	36 (66.6 per cent of 54)
Patients operated on	31
Patients living	12 (38.7 per cent of 31)
1. Living over 5 years without recurrence	6 (50 per cent of 12)
2. Living less than 5 years without recurrence .	6 (50 per cent of 12)

DURATION OF LIFE SINCE LAST OR ONLY OPERATION

	<u>Over 5 years</u>	<u>Less than 5 years</u>
Longest	12.88 yrs.	3.12 yrs.
Shortest	5.08 yrs.	2.1 yrs.
Average	8.98 yrs.	2.15 yrs.

DEATHS

Patients	24 (61.3 per cent of 36)
1. Patients with operable epithelioma	18 (75 per cent of 24)
2. Patients with inoperable epithelioma	4 (16.6 per cent of 24)
3. Patients on whom palliative operations were done	2 (8.3 per cent of 24)

CAUSE OF DEATH OF PATIENTS OPERATED ON. DATA FROM RELATIVES, HOME PHYSICIANS AND CLINICAL RECORDS.

Known cause	23
Epithelioma	19 (82.6 per cent)
Paralysis	1
Pneumonia	1
Old age	1
Primary epithelioma of left jaw and cheek	1
Unknown	1
Operative mortality	0

TABLE NUMBER 4

Patients with metastasis operated on and inguinal lymph nodes removed.

Total		13
Information received from		8 (61.5 per cent of 13)
	Grade 2	Grade 3
Patients living		1 (12.5 per cent of 8)
Good result	0	1 (100% of 1)
Patients dead.....		7 (87.5 per cent of 8)
Poor result	3 (42.8% of 7)	4 (57.1% of 7)

TOTAL RESULTS

Good (patient recovered from epithelioma)	1 (12.5 per cent of 8)
Poor (patients dead of epithelioma)	7 (87.5 per cent of 8)

CAUSE OF DEATH

Epithelioma	7 (100 per cent of 7)
No information received	5 (38.5 per cent of 13)

- NOTE: 1. One patient on whom a removal of the left metastatic inguinal nodes was done four months after amputation of the penis died of epithelioma eight months after second operation.
2. One patient on whom amputation of the penis and removal of bilateral metastatic inguinal lymph nodes were done reported six months after operation, with recurrence in "several places", marked weight loss and "skeleton" appearance.

TABLE NUMBER 5

Patients without metastasis operated on, with removal of inguinal lymph nodes:

Total 26
 Information received from 18 (69.2 per cent of 26)

	Grade 1	Grade 2	Grade 3	
<u>Patients living</u>				10 (55.5 per cent of 18)
Good result	1 (20% of 5)	4 (80% of 5)		
Fair result	1 (20% of 5)	2 (40% of 5)	2 (40% of 5)	
<u>Patients dead</u>				8 (44.4 per cent of 18)
Good result		2 (100% of 2)		
Fair result	1 (50% of 2)		1 (50% of 2)	
Poor result		2 (66.6% of 3)	1 (33.3% of 3)	
Cause unknown	1			

TOTAL RESULTS

Good (patients recovered from epithelioma and living over 5 years or recovered from epithelioma and died from other cause 7 (41.1 per cent of 17)

Fair (patients recovered from epithelioma and living less than five years, or recovered from epithelioma and died from other cause 7 (41.1 per cent of 17)

Poor (patients died of epithelioma) 3 (17.6 per cent of 17)

CAUSE OF DEATH

Epithelioma 3 (42.8 per cent of 7)

Primary epithelioma of left jaw and cheek 1

Pneumonia 1

Paralysis 1

Old age 1

No information received 8 (30.7 per cent of 26)

TABLE NUMBER 6

Patients operated on without removal of inguinal lymph nodes:

Information received 2 (40 per cent of 5)
 Patients living 0

Grade 2 Grade 3

Patients dead
 Poor result 1(50% of 2) 1(50% of 2)

TOTAL RESULTS

Good (patients recovered from epithelioma, living or
 recovered from epithelioma and died of other cause . 0

Poor (patients died of epithelioma) 2 (100 per cent of 2)

CAUSE OF DEATH

Epithelioma 2 (100 per cent of 2)

No information received 3 (60 per cent of 5)

Duration of life of five patients operated on without removal of inguinal lymph
 nodes:

Information received 2

Patients living 0

Grade 2 Grade 3

Patients dead
 Poor result 1 1
 Duration .076 years 5.67 years Average 2.87 years
 No information received 3

TABLE NUMBER 7

Duration of life after operation of thirteen patients with metastasis:

Information received 8 (61.5% of 13)

	<u>Grade 2</u>	<u>Grade 3</u>	
Patients living			
Good result		1	12.88 years
Patients dead			7
Poor result	3	4	
			Average of all grades
	<u>Years</u>	<u>Years</u>	<u>Years</u>
Longest	1.02	3.96	2.49
Shortest	.87	.82	.84
Average	.94	1.82	1.38
No information received			5 (38.5% of 13)

Duration of life after operation of twenty-six patients without metastasis:

Information received 18 (69.2% of 26)

Patients living 10

	<u>Grade 1</u>	<u>Grade 2</u>	<u>Grade 3</u>	
Good result	1	4		
Fair result	1	2	2	
				Average of all grades
	<u>Years</u>	<u>Years</u>	<u>Years</u>	<u>Years</u>
Longest	5.08	11.51	2.09	8.33
Shortest	3.12	2.16	2.34	2.54
Average	4.10	6.8	2.21	4.33
Patients dead				8
Good result		2		
Fair result	1		1	
Poor result		2	1	
				Average of all grades
	<u>Years</u>	<u>Years</u>	<u>Years</u>	<u>Years</u>
Longest	1.23	10.04	2.35	4.54
Shortest		.87	1.91	1.39
Average		5.86	2.13	3.99
Cause unknown	1			
No information received				8 (30.7% of 26)

TABLE NUMBER 8

Duration of life of patients operated on - all grades.

Patients living 12

	<u>Good result</u>	<u>Fair result</u>	<u>Poor result</u>
Longest	12.88 years	3.12 years	
Shortest	5.08 years	2.09 years	0
Average	9.02 years	2.49 years	0

Patients dead 16

Longest	10.04 years	1.91 years	5.67 years
Shortest	8.87 years	1.23 years	.82 years
Duration	9.45 years	1.57 years	1.96 years

*NOTE: One patient treated with radium only has lived two years and eight months since first seen, without recurrence.

Duration of life of patients operated on, who are still living, without recurrence or dead from other cause; and of patients who died of epithelioma of all grades:

	<u>Alive and well, or dead of other cause</u>	<u>Died of epithelioma</u>	<u>Average of all cases</u>
Longest	12.88 years	5.67 years	11.77 years
Shortest	1.23 years	.82 years	1.02 years
Duration	5.69 years	1.96 years	3.82 years

RESULTS FOLLOWING OPERATION

	<u>Grade 1</u>	<u>Grade 2</u>	<u>Grade 3</u>	<u>Grade 4</u>
Information received	3(50% of 6)	14(50% of 28)	10 (83.3% of 12)	0
Patients living	2(66.6% of 3)	6(42.8% of 14)	3 (30% of 10)	
Good result	1(50% of 2)	4(66.6% of 6)	1 (33.3% of 3)	
Fair result	1(50% of 2)	2(33.3% of 6)	2 (66.6% of 3)	
Patients dead	1(33.3% of 3)	8(57.1% of 14)	7 (70% of 10)	
Good result		2(25% of 8)		
Fair result	1(100% of 1)		1 (14.2% of 7)	
Poor result	0	6(75% of 8)	6 (85.7% of 7)	
Not stated	1			

Total good and fair results (patients recovered from epithelioma and are living, or recovered and died from other causes):

3(100% of 3) 8(57.1% of 14) 4 (40% of 10)

Total poor results (patients died from epithelioma):

0 6(42.8% of 14) 6 (60% of 10)

Total result not stated: 1

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Fig. 1. Grade 1 epithelioma showing high degree of differentiation.



Fig. 2. Grade 2 epithelioma:
(a) completely keratinized areas or pearly bodies, (b) undifferentiated cells.

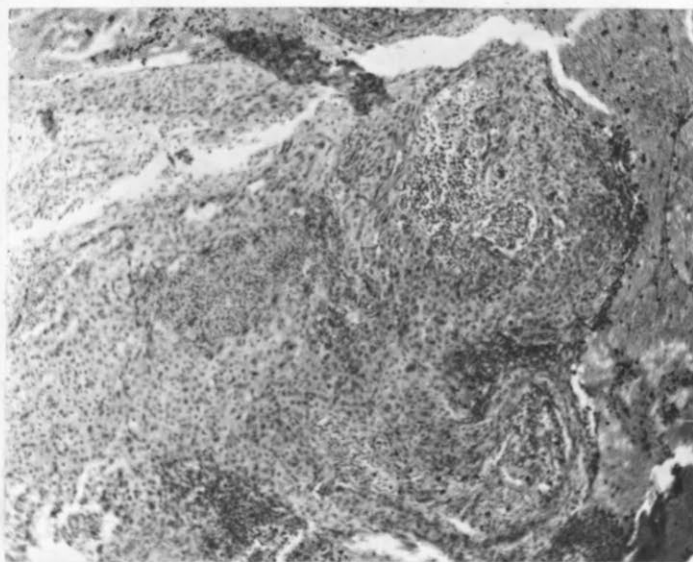


Fig. 3. Grade 3 epithelioma showing very little differentiation.

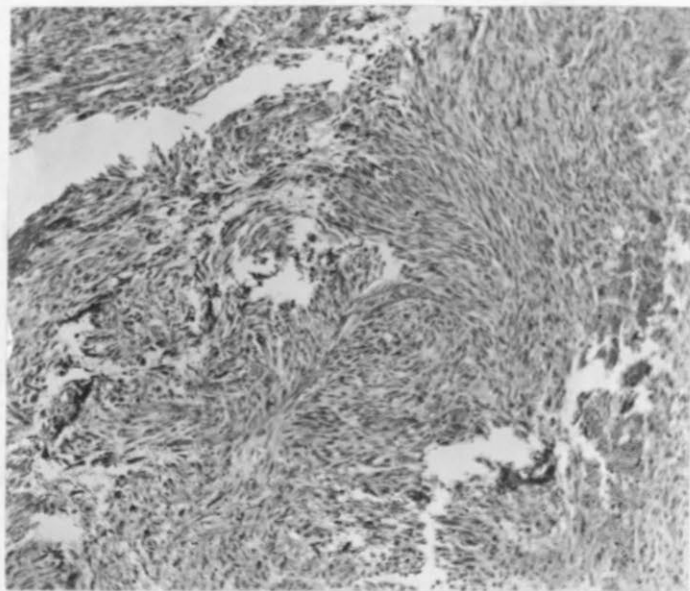


Fig. 4. Grade 4 epithelioma showing no differentiation.