THE ETIOLOGICAL AND PATHOLOGICAL ASPECTS OF SQUAMOUS-CELL CARCINOMA OF THE PENIS AMONG THE CHINESE

AN ANALYTICAL STUDY OF 107 CASES

S. K. NGAI, M.D.

(Department of Pathology, Peiping Union Medical College, Peiping)

INTRODUCTION

Between 1921 and 1931, 87 cases of squamous-cell carcinoma of the penis from the Peiping Union Medical College Hospital and 20 cases from various other hospitals in China have been studied by the Surgical Pathological Laboratory of the Department of Pathology, Peiping Union Medical College.

Although the literature on the subject of penile carcinoma is voluminous in foreign countries, and although some investigators (7, 10, 26, 29, 66) have drawn attention to the fact that the frequency of penile cancer is much higher among the Chinese than among Westerners, no close analytical study of this condition has been made in China. The present series of 107 cases represents one of the largest single groups of cases yet reported.

INCIDENCE

Various statistics give the average frequency of penile cancer as 18.3 per cent in China (7, 10, 26, 66), 18.9 per cent in the other Far Eastern countries (57, 68, 81), and 4.9 per cent in Continental Europe (9, 52, 83, 94). Wolbarst (99), in America, reported penile cancer as representing 2 per cent of all cancers in males, and Andrews (2), in Great Britain, found it to constitute only 1.27 per cent of 7881 cases of primary cancer. It appears, therefore, that there exists a wide variation in the frequency of penile cancer in different localities, the highest figures noted being in the Far East.
and the lowest in Great Britain and America, with Continental Europe in between the two (Chart I).

**Etiology**

*Age:* The age distribution of our patients is shown in Chart II. The average age is 43.74 years, the two extremes being twenty-three and seventy-four years. Forty-four patients, or 41.12 per cent, were below forty years of age and 63, or 58.88 per cent, above forty. Bercovitz (7) in Hainan reported, among other tumors, 29 cases of penile cancer; 18 of his series, or 62.07 per cent, were above, and 11, or 37.93 per cent, were below forty years of age. Mendelson and Ellis (68) reported an average age of 38.1 years among their 13 cases in Siam.

An analysis has been made of the age distribution in the cases reported among Westerners, and a comparison with our present series is shown in Chart II. It will be observed that the greater number of our cases fall between the ages of thirty-five and fifty-four, while in the Western cases the peak is between forty-one and seventy. From these figures it appears that penile cancer develops about a decade earlier among Chinese than among Westerners.

Although Barringer and Dean (6) included one case and Dayal (24) another case occurring below twenty years of age, and although Küttner (52) reported two cases, Heimann (46) one case,
and the author two cases in patients less than twenty-five years of age, such findings are infrequent. The frequently quoted case of "cancer of the penis" reported by Creite (21) in a boy two years old was proved by Schultze (86), on re-examination of the original material, to have been hemangio-endothelioma.

Civil State: Of the 87 individuals in the series from this hospital 8, or 9.19 per cent, were single, 77, or 88.51 per cent, married and 2, or 2.30 per cent, widowers. No conclusion can be drawn from the high incidence of married men in this series, since most men in China over the age of thirty are married, although no statistical data on the percentage of married men in the general population are at present available.

It has been repeatedly stated that carcinoma of the penis is the result of contact with a cancerous cervix (12, 18, 19, 27, 34, 41, 68). That actual implantation of tumor by coitus, "cancer à deux," may take place is, however, hard to prove. In our present series, no inquiries were made as to this point.

Occupation: From Table I it appears that penile cancer is most prevalent among farmers and coolies; in other words, among the economically poor. Dormanns (29) also draws this conclusion from a study of data obtained from questionnaires sent to private practitioners in South China, who, as a rule, handle almost exclusively wealthy and intellectual patients and who report having seen no cases of penile cancer. This might be explained by the fact that ignorance and negligence of personal hygiene on the part of the poor would favor the growth of penile tumor, but it must be remembered in any case that the bulk of the hospital patients, as of the population in general, consists of the poorer class of people. In the absence of a comprehensive statistical study, any conclusion drawn in this light is apt to be misleading.

Table I: Distribution of Occupation in Cases of Penile Carcinoma

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer</td>
<td>41</td>
</tr>
<tr>
<td>Coolie</td>
<td>11</td>
</tr>
<tr>
<td>Merchant</td>
<td>11</td>
</tr>
<tr>
<td>Peddler</td>
<td>3</td>
</tr>
<tr>
<td>Teacher</td>
<td>3</td>
</tr>
<tr>
<td>Clerk</td>
<td>3</td>
</tr>
<tr>
<td>Servant</td>
<td>2</td>
</tr>
<tr>
<td>Soldier</td>
<td>2</td>
</tr>
<tr>
<td>Military officer</td>
<td>1</td>
</tr>
<tr>
<td>Student</td>
<td>1</td>
</tr>
<tr>
<td>Cook</td>
<td>1</td>
</tr>
<tr>
<td>Apprentice</td>
<td>1</td>
</tr>
<tr>
<td>Shoemaker</td>
<td>1</td>
</tr>
<tr>
<td>Official</td>
<td>1</td>
</tr>
<tr>
<td>Story teller</td>
<td>1</td>
</tr>
<tr>
<td>No occupation</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
</tr>
</tbody>
</table>


In certain occupations which give rise to repeated irritation to the genital organs, of long standing, carcinoma of the penis has been reported (26, 72, 100). Here, again, without a comprehensive statistical study, no definite conclusion is warranted.

**Heredity:** In the present series there is only one case with a history of cancer in the family, the father of one patient having also suffered from tumor of the penis. Barney (5) reported a similar occurrence among his 100 cases.

**Venereal Disease:** In 85 cases questions were asked regarding the history of venereal exposures. Forty patients, or 47.06 per cent, admitted such exposure, while 45, or 52.94 per cent, denied it. Eighty-five patients also mentioned gonorrheal infection, 32, or 37.33 per cent, admitting a history of gonorrhea and 53, or 62.67 per cent, denying it. A blood Wassermann test was done in 72 cases, 65 of which, or 90.27 per cent, were negative; 3, or 4.17 per cent, were doubtful; and 4, or 5.56 per cent, were strongly positive. In one case the tumor growth is said to have started from an unhealed chancre. Similar observations have been made by a number of investigators (5, 23, 27, 30, 35, 43, 65, 90).

These data seem to show that venereal diseases have no important bearing on the occurrence of tumor.

**Trauma:** Only 4 patients gave a history of injury to the penis. The first was a man of forty-seven, who had had phimosis since childhood and began at the age of thirty-seven to have urethral discharge, although he denied venereal exposure. For treatment, he had applied hot onion, and then a sharpened brick, heated red hot, to the meatus of the urethra. Ulceration followed this procedure and growth started. One patient had been hit on the penis and another kicked by a horse. In the fourth case the nature of the trauma was not stated.

A small number of cases in which previous injuries of various kinds were closely related to the onset of penile tumor have been recorded in the literature (31, 44, 51, 56, 61).

The relationship between trauma and tumor formation is, however, very difficult to determine, since it is often impossible to ascertain whether or not the injured part was already in a state of malignant change before the injury. One cannot exclude the possibility that trauma and tumor may occur together merely as a matter of coincidence. The scarcity of cases reported suggests, indeed, that trauma plays a very minor rôle, if any, in the etiology of penile carcinoma.

**Phimosis:** Under phimosis, we include both the genuine congenital tight prepuce and the long and redundant foreskin. Of the 88 patients giving definite statements regarding phimosis, 87, or 98.86 per cent, gave a positive history. This figure is significant
in that it is the highest percentage of incidence of phimosis reported, the percentages reported by others ranging from 17.72 to 85.

Many authors (6, 34, 62, 75, 99) have pointed out the apparent immunity of the Jews to penile carcinoma. Some (81, 102) believe that this immunity is racial, but the fact that one case has been reported in an uncircumcised Jew (99), while not a single case has been recorded among circumcised Jews, strongly suggests that the immunity is acquired through the ritual practice of early circumcision. On the other hand, it appears that circumcision during adult life does not always provide immunity. Our series includes the case of a fifty-three-year-old man in whom penile cancer developed fifteen years after circumcision done at thirty-five; also 7 cases in which cancer appeared from a few months to two or three years after the same operation on account of papillary or ulcerative lesions within the preputial sac (see below). Other authors (25, 45, 73, 89, 96) have also reported cases of penile cancer in circumcised individuals, but failed to specify whether the circumcision was done during infancy or adult life, a point of great importance since it has been emphasized (99) that no cancer of the penis has occurred in persons undergoing early circumcision.

Effect of Circumcision and Excision of Tumor on Growth: In our series, circumcision by "local doctors" had been done in 7 cases, in all of which there had been either papillary or ulcerated lesions inside the preputial sac. In addition, there were 14 cases in which surgical intervention in the form of circumcision or excision of tumor had been done on account of tumor or "ulcer." In all these cases tumor soon developed in the operative wound, and in some of the cases the recurrent tumors grew much more rapidly than the primary growths.

Pathology

Macroscopic Pathology

Of the 107 cases, gross specimens from only 87 were available for the present study. The data on the other 20 were obtained from the records, when available.

Size of Growth: For convenience of classification, the tumors are arbitrarily divided into three grades: small, medium-sized, and large, with diameters of less than 3 cm., 3 to 6 cm., and above 6 cm., respectively.

The size is known in 89 cases: 17 tumors, or 19.10 per cent, were small; 51, or 57.30 per cent, of medium size; and 21, or 23.60 per cent, large. Lewis (58) found among his 34 cases 7 tumors less than 1.5 cm. in diameter, 13 between 1.5 and 3.0 cm. in diameter
with the shaft free of tumor involvement, and 14 measuring 3.5 cm. or more in diameter with destruction of the shaft. Barringer and Dean (6) reported 10 cases with tumors of 5 sq. cm. or less, 3 with tumors of 15 sq. cm., 8 with tumors of 15 to 30 sq. cm., and 13 with tumors of 20 sq. cm. or more; the largest growth being the size of a base-ball, involving the distal three-fourths of the penis, and covering about 40 sq. cm.

It will be observed that the tumors of the present series are comparatively larger than in cases previously reported, which is probably explained by delay in seeking medical aid.

**FIG. 1**
TIGHT FORESKIN, THROUGH THE ORIFICE OF WHICH PAPILLARY GROWTHS ARE VISIBLE; MULTIPLE ULCERATIVE FISTULAE. GRADE II

**FIG. 2**
PHIMOSIS AND EDEMATOUS FORESKIN; LARGE ULCERATED AREA OVER THE DORSAL ASPECT OF THE PENILE SHAFT, IN WHICH NODULAR GROWTHS ARE PRESENT. GRADE III

**FIG. 3**
MULTIPLE ORIGIN OF PAPILLARY GROWTH FROM BOTH THE GLANS PENIS AND FORESKIN

**Appearance of Growth:** The appearance of the growth in 87 cases was of four different types. Nine cases, or 10.34 per cent, were leukoplakia-like; 44 cases, or 50.58 per cent, papillary; 25 cases, or 28.74 per cent, nodular; and 9 cases, or 10.34 per cent, infiltrative. Barney (5) reported that among 81 cases, 46 were papillary and 35 infiltrative. Of Barringer and Dean’s (6) cases, 56 per cent showed indurated ulcers and 36 per cent papillary growth; in the remaining 8 per cent the type of growth is not recorded. Lewis (58) had in his series 21 cases that were ulcerative with crater-like centers and cartilaginous rings, 11 fungating, papillary growths, ulcerated at one point or another, and 2 cases of proliferative growth without ulceration. Kaufmann (49) concluded that the papillary tumor was the more frequent form and the infiltrative carcinoma the rarer.
In the leukoplakia-like form, one or more areas of the glans penis or of the inner surface of the foreskin show a whitish, firm, rough, granular plaque, with or without suggestion of a papillary tendency. These plaques are usually secondarily infected and covered with a small amount of purulent exudate. The margin is slightly raised and sometimes overhanging. Occasionally the whole glans penis and the entire inner surface of the foreskin show this type of change (Fig. 8). As the name suggests, this type shows a marked resemblance to leukoplakia.\(^1\) The tumor, however, is well formed and has passed beyond the stage of ordinary leukoplakia. Differentiation between the two is often difficult macroscopically, so that microscopic examination should be done.

The papillary form (Figs. 5 and 6), usually known as a "cauliflower-like" growth, is by far the most frequent and constitutes 50.58 per cent of our cases. Although the growth may have a single site of origin, it usually arises from more than one focus;

\(^1\) Precancerous lesions of the penis, such as leukoplakia, leukokeratosis, kraurosis, or the older "psoriasis praepu tilti" have been mentioned by a number of authors (22, 28, 34, 39, 40, 48, 80, 85). Lesions similar to the so-called "Paget's disease" and "Bowen's disease" occurring on the glans penis have been described (3, 17, 87, 92, 93, 101), and the rare form of erythroplakia on the glans penis is reported by some investigators (60, 76, 79). Carcinomatous change following all the conditions mentioned above has been observed, and these lesions should be considered as precancerous.
but owing to the close proximity of the papillae the multiplicity of origin is obscured (Fig. 3). In cases of tight foreskin, the underlying tumor may protrude from the small preputial orifice (Fig. 1), or it may break through and appear in one or more places on the surface of the foreskin, with fistula formation (Figs. 1 and 2). Fistulae were observed in 23 cases in the present series. In such cases, a mere slit through the overlying foreskin will expose the tumor mass. Occasionally one sees cases, such as described by Küttnner, in which the tumor growth spreads between the skin of the penile shaft and the corpora cavernosa toward the root of the penis, so that the organ is uniformly thickened and cylindrical in shape, composed of a stiff skin shell which is ulcerated in its inner surface and encloses the corpora cavernosa like a piston. Often the glans penis is still visible, a condition which Küttnner (52) described as similar to "a turtle that sticks the head out of its shell." Secondary infection by pyogenic microorganisms, causing a layer of purulent exudate over the growth, is invariably present, so that the surface of the growth is soft and moist. In cases where infection is not so marked, however, and in areas that are not covered by the remaining foreskin, the tumor surface is rather hard and dry. In such cases, needle-shaped, brittle, spinous, hard, dry structures may be present. These may be so grouped as to appear like a hard brush, as in a case reported by Maresch and Chiari (64). The shape and size of the growths vary not only in different tumors, but also in different parts of the same tumor. The stroma may be thin and delicate, or it may be thick and abundant.

In addition to the secondary infection, retrogressive changes of the tumor itself set in sooner or later, leading to necrosis and eventual loss of tumor tissue. As these processes go on, simultaneously with tumor invasion of the penile shaft, gross mutilation and eventual loss of the organ may occur (Figs. 5 and 6). In late cases, tumor masses may extend directly and creep on to the pubic and scrotal skin (Figs. 5 and 6).

The nodular type of growth (Fig. 2) forms 28.74 per cent of our cases and is, therefore, not so uncommon as originally claimed by Küttnner (52), who considered it even rarer than the infiltrative type. This type of tumor is generally of medium size, rarely larger than a tennis ball, having a knobby appearance, with a broad base to each nodule, and arising usually from the glans penis but occasionally from the prepuce. It has a suggestion of papillary character, but, in general, the resemblance is slight. The growth is almost always covered by a layer of purulent exudate.

The infiltrative or ulcerative type is the least frequent of all,
forming about 10 per cent of our cases. It rarely attains a size larger than 3 or 4 cm. in diameter and consists of crater-like ulcers on the glans penis with granular, often superficially hemorrhagic surface and roughly nodular and firm overhanging borders. Atypical papillary or nodular protuberances may be present at the edge. Secondary infection is invariably present and, strangely enough, mutilation of the organ is not so conspicuous as in the other types, although it may be present in cases of long standing.

In both the nodular and infiltrative growths, tumor masses may be seen in the corpora cavernosa (Fig. 7) without appearing to have any direct connection with the primary tumor in gross.

When the blood spaces of the spongy bodies are invaded, tumor tissue may fill up the entire corpora cavernosa of the penis.

Although the above seemingly distinct types of growth have been distinguished, transitional forms occur, the exact classification of which may be difficult.

**Extent of Growth:** In more than 60 per cent of our cases the tumor was confined to the prepuce and glans, about 40 per cent had involvement of the shaft, and about 5 per cent involved also the pubic and scrotal skin. The latter group, however, are always cases of long standing.

**Initial State of Growth:** In Table II, it will be seen that the initial state of the growth has been variously described; the most common forms are "nodules" or "pimples" and "warty growths."

**Starting Place of Growth:** Positive information was obtained in only 89 out of our 107 cases regarding the starting place of the
growth (Table III). It will be observed that the glans penis was mentioned slightly more frequently as the starting place of the growth than the prepuce. The growth not infrequently arose from the coronary sulcus and occasionally from the meatus.

According to Demarquay (27), growth starts most frequently on the glans penis. Barney (5) and Leighton (56) agree to this, and Thomsen (95) further specifies that the locality is frequently on the dorsal aspect of the glans near the corona. Kaufmann, however, found that of 33 cases, 20 started on the prepuce and 13 on the glans.

**TABLE II: Initial State of Growth in Penile Carcinoma**

<table>
<thead>
<tr>
<th>State of Growth</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule or pimple</td>
<td>49</td>
<td>(51.58%)</td>
</tr>
<tr>
<td>Warty growth</td>
<td>28</td>
<td>(29.48%)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>8</td>
<td>(8.42%)</td>
</tr>
<tr>
<td>Sore</td>
<td>3</td>
<td>(3.16%)</td>
</tr>
<tr>
<td>Ulcer of meatus</td>
<td>8</td>
<td>(8.42%)</td>
</tr>
<tr>
<td>Small abrasion</td>
<td>1</td>
<td>(1.05%)</td>
</tr>
<tr>
<td>Fissure</td>
<td>1</td>
<td>(1.05%)</td>
</tr>
<tr>
<td>Traumatic wound</td>
<td>1</td>
<td>(1.05%)</td>
</tr>
<tr>
<td>Chancre</td>
<td>1</td>
<td>(1.05%)</td>
</tr>
<tr>
<td>Patches of granules on prepuce</td>
<td>1</td>
<td>(1.05%)</td>
</tr>
<tr>
<td>Swelling of mid-portion of shaft</td>
<td>1</td>
<td>(1.05%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>95</td>
<td>(100.00%)</td>
</tr>
</tbody>
</table>

*These data are compiled according to the patients' own statements, but in some cases modifications were made after a careful questioning so as to put the initial state of growth into the correct class.

**TABLE III: Starting Place of Growth in Penile Carcinoma**

<table>
<thead>
<tr>
<th>Place of Growth</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glans</td>
<td>39</td>
<td>(43.82%)</td>
</tr>
<tr>
<td>Prepuce</td>
<td>37</td>
<td>(41.58%)</td>
</tr>
<tr>
<td>Coronary sulcus</td>
<td>11</td>
<td>(12.36%)</td>
</tr>
<tr>
<td>Frenulum</td>
<td>1</td>
<td>(1.12%)</td>
</tr>
<tr>
<td>Meatus</td>
<td>1</td>
<td>(1.12%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>89</td>
<td>(100.00%)</td>
</tr>
</tbody>
</table>

Tumor arising from the urethra is rare; when it does occur, the site is usually the meatus. Leighton (56) reported one case in which the origin was claimed to be in the urethra at the penoscrotal junction. Such a case is undoubtedly rare.

Inguinal Lymph Nodes: Inguinal lymph nodes were received for examination in only 52 of our cases.

Although some of the other types of tumor give rise to very bulky secondary growth (33), carcinoma of the penis rarely produces bulky metastases, as shown by the cases in this series.

**Histopathology**

Microscopically, penile carcinoma is composed of squamous epithelial cells, or the prickle cells of the epidermis, in different
Fig. 9. Well differentiated prickle cells with intercellular bridges in tumor masses; numerous mitotic figures at the growing margins.

Fig. 10. Abundant formation of pearls in tumor mass.

Fig. 11. Eleidin pigment appearing in the form of small granules in the cytoplasm of tumor cells.
degrees of cell differentiation. The growth practically always takes its origin from the epidermis covering the glans penis and inner surface of the foreskin, although some authors have claimed an occasional origin from the urethral mucous membrane.

In well established cases of epithelioma, invasion of the underlying stroma is the important part of the histological picture. One sees many irregular masses penetrating into the subcutaneous tissue, the dartos, and the soft areolar tissue, but they cease to proceed further when they reach the deep fascia, which is a thick layer of tough and hyalinized fibrous tissue. In cases of long standing, however, this barrier is eventually broken through, so that tumor cell masses appear in the cavernous tissue.

![Fig. 12. Tumor Cells in Perineural Lymphatic Vessels](image)

In papillary growths, the formation of papillae is the outspoken feature. These papillae are generally covered with fairly well differentiated and hyperplastic squamous epithelial cells, with moderate or marked hyperkeratosis. The stroma stalk may be composed of very thin or thick strands of loose and vascular connective tissue infiltrated by small round cells and other types of wandering cells. In addition to these outgrowing papillae, downward projections of epithelial masses are invariably present—a point of distinction from the usual benign papilloma or warts which are sometimes present on the external genitalia. These masses vary greatly in size and shape and are irregularly arranged, but the individual cells that make up the mass are rather uniform in size, larger than the normal prickle cells, polygonal in shape, having small or large vesicular nuclei and distinct acidophilic nucleoli and finely granular acidophilic cytoplasm (Fig. 9). Intercellular spines are often remarkably evident. In some cells, lamellated epithelial or keratin pearls may be present (Fig. 10).
In some cases, eleidin pigment can be demonstrated in the layer of cells surrounding the pearls (Fig. 11). Mitotic figures are present in moderate numbers and are mostly typical and symmetrical.

As secondary infection and ulceration are invariably present in these cases, leukocytes in varying numbers are often met among the tumor masses. In the periphery of these cells, the epithelial cells, whose nuclei are dark and round or oval, are generally cuboidal in shape and are often arranged parallel to each other, resembling the cells of the malpighian layer of the normal epidermis, but without a definite basement membrane. In rare cases, the tumor cells may so arrange themselves as to suggest adenoid or cystic carcinoma. In such cases, small or large cyst-like spaces lined by a layer of squamous epithelial cells may contain necrotic cells and keratin material.

While tumor cells may be well differentiated, as above described, they may also become irregular in shape and size, have many atypical mitotic figures and hypochromatic nuclei and less acidophilic cytoplasm, with loss of intercellular spines. A few cells, however, may be sufficiently differentiated to form typical pearls. In very rapidly growing tumors, the epithelial cells may be totally undifferentiated and may even be represented by masses of densely packed spindle-shaped cells. In the rare infiltrative growth, the tumor cells may not form masses at all but be scattered about, infiltrating the underlying tissue. In all these rapidly growing tumors, multinucleated tumor giant cells are frequently seen.

Degeneration and necrosis of isolated tumor cells and cell

![Fig. 13. Tumor Mass in a Vein. V. Elastic Tissue Stain](image)
masses are frequently seen. In the cell masses, necrosis may involve either the central portion or the entire mass. Different grades of cell degeneration are also to be noticed.

The stroma is always infiltrated by a large number of small round cells, a few mononuclear wandering and plasma cells, and occasionally a moderate number of eosinophiles, which in some cases may be abundant. In cases with infection, polymorphonuclear neutrophiles may be present in varying numbers. Occasionally foreign-body giant cells may be seen surrounding necrotic tumor cells. The blood vessels are usually dilated and may, in rare cases, contain tumor cells in the lumen (Fig. 13). Tumor cells in the lumina of the lymphatics at the growing margin are not infrequently encountered. Perineural lymphatics are occasionally seen to contain tumor cells (Fig. 12), which may encroach upon and press against the nerve fibers.

Grading: According to the method of Broders, our cases are graded as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>55</td>
<td>55.60%</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>21.49%</td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>15.89%</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>11.22%</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

It will be observed that most of the cases fall into Grades I and II, a fact which is interesting in comparison with epitheliomas of the lip, the majority of which are of Grades II and III (11a) and with those of the cervix, which are usually of Grades III and IV (11b).

Table IV: Gross Appearance and Grade of Penile Carcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Leukoplakia-like</th>
<th>Papillary</th>
<th>Nodular</th>
<th>Infiltrative</th>
<th>Unknown</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>37</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>7</td>
<td>11</td>
<td>0</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>44</td>
<td>25</td>
<td>9</td>
<td>20</td>
<td>107</td>
</tr>
</tbody>
</table>

It is always advisable to examine a number of sections taken from various regions of a tumor, for sections taken from different regions of the same tumor often show different degrees of cell differentiation. The impression that we have obtained from our cases is not in agreement with Broders' conclusion (11c) that, as a rule, there is practically the same grade of malignancy throughout a carcinoma. The variation of the microscopic picture in
different parts of the same tumor necessitates a more guarded conclusion as to the degree of malignancy when only a single piece of biopsy material is examined.

The correlation of the gross appearance of the tumor with the grade of malignancy was analyzed, and the result is shown in Table IV. In the light of this study, there would seem to be some relationship between the gross character of the tumor and the grade of malignancy. Most of the papillary forms were of Grade I or II; the nodular forms of II or III; and the infiltrative forms of Grade III or IV. The recognition of this relationship is of help to the clinician in estimating the approximate degree of malignancy of the growth from the gross appearance alone.

A study of the age of the patient in relation to the grade of the tumor (Table V) demonstrated no important relationship be-

### Table V: Age of Patient and Grade of Penile Carcinoma

<table>
<thead>
<tr>
<th>Age</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>30-39</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>40-49</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>60-69</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>70</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>23</td>
<td>17</td>
<td>12</td>
<td>107</td>
</tr>
</tbody>
</table>

The number of cases is probably too small, however, to be of real value in a correlative study of this type.

**Mitosis**: Mitotic figures vary in number as well as in form. Quantitatively there is a direct relationship between the number of mitotic figures and the grade of tumor according to cell differentiation, as shown in Table VI.

### Table VI: Number of Mitoses and Grade of Penile Carcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitosis</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>I</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>42</td>
</tr>
</tbody>
</table>

Mitotic figures, as observed in these cases, vary considerably, but the majority of them are typical, either symmetrical or bipolar,
although atypical and abortive types are also seen in rapidly growing tumor masses. Gametoid mitosis is occasionally seen, for the most part at the growing margin of the tumor masses. Amitotic division of tumor cells is apparently present in tumors of Grade III and IV, as suggested by the multinucleated tumor giant cells.

**Cellular Infiltration in Stroma:** Infiltration of the stroma by small round cells, which are generally regarded as lymphocytes, is invariably present in carcinoma of the penis. Murphy and others (69) showed, in their experimental studies, that lymphocytic infiltration signifies a reaction of immunity, limiting the growth of cells and establishing local tissue immunity. A correlation of the degree of lymphocytic infiltration in the stroma and the grades of the tumor was made (Table VII). Although our result is not striking, it suggests that as the tumor becomes more malignant the degree of lymphocytic infiltration in the stroma is lessened. In the presence of chronic secondary infection and necrosis, however, the significance of this finding is considerably decreased.

**Table VII: Lymphocytic Infiltration in Stroma vs. Grade of Penile Carcinoma**

<table>
<thead>
<tr>
<th>Grade</th>
<th>+++</th>
<th>++++</th>
<th>++++++</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4 (7.27%)</td>
<td>11 (20.00%)</td>
<td>40 (72.73%)</td>
<td>55 (100.00%)</td>
</tr>
<tr>
<td>II</td>
<td>1 (4.34%)</td>
<td>2 (8.70%)</td>
<td>20 (86.96%)</td>
<td>23 (100.00%)</td>
</tr>
<tr>
<td>III</td>
<td>2 (11.76%)</td>
<td>8 (47.06%)</td>
<td>7 (41.18%)</td>
<td>17 (100.00%)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (25.00%)</td>
<td>5 (41.67%)</td>
<td>4 (33.33%)</td>
<td>12 (100.00%)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (9.34%)</td>
<td>26 (24.30%)</td>
<td>71 (68.36%)</td>
<td>107 (100.00%)</td>
</tr>
</tbody>
</table>

Plasma-cell infiltration in the stroma has also been regarded as a sign of immunity in the latter part of the tumor process. No relationship between the degree of plasma-cell infiltration and the duration of the tumor could be demonstrated in this series.

Eosinophil infiltration in the stroma was present in over half of our cases. From a correlative study it seems quite clear that there exists no definite relationship between the degree of eosinophil infiltration in the stroma and the malignancy of the tumor. The significance of eosinophil infiltration is not understood, and the results of the present study do not seem to throw any new light on the subject. Certainly they do not support the view that its presence is a sign of favorable prognosis (78), nor the popular theory that its presence is due to hemorrhage in the tumor. Such infiltration does often represent a late manifestation of the inflammatory reaction, but even here we do not know what are the factors in the body which determine the proliferation of the eosinophils.
Invasion of Corpora Cavernosa: Among 84 cases examined, invasion of the corpora cavernosa by the tumor tissue occurred in 45. Invasion takes place more readily in tumors of higher malignancy, even though the average duration is shorter than in the more benign growths.

Invasion of the corpora cavernosa is usually checked by the thick sheath surrounding the spongy tissue. After penetrating through the tunica, the tumor spreads either in the tissue (49) or in the blood spaces (53). In our cases, spreading in the tissue, with compression of the blood spaces, was the more common. Extension in the tissue takes a longer time to involve the whole penile shaft than does extension by way of the blood spaces, which results in a rapid involvement of the entire shaft. In such cases priapism is likely to occur, due either to the occlusion of the blood spaces by solid tumor masses (21) or to thrombosis (36). Priapism in one of our cases is explained on the former basis.

Modes of Extension

In addition to the usual method of direct spread, extension of carcinoma of the penis is accomplished by invasion of the lymphatics, or of the blood stream, or of both. Evidence of lymphatic invasion was present in 21 of our cases, of blood invasion in 4, and of both in 3. Of the 7 cases in which the blood stream was invaded, blood vessels were involved in 2 and the cavernous spaces in 5.

In the lymphatics the tumor may spread in two ways: by direct extension (so-called lymphatic permeation) and through embolus formation. In direct extension a hard cord of tumor tissue may be present on the dorsal surface of the penis along the median line, marking out the main dorsal lymphatic trunk (5, 37, 49, 74, 95). We agree with Küttnner (52) that such a finding is rare, not a single case of this type appearing in our series or in Küttnner's. On the other hand, tumor emboli in the lymphatics are frequently encountered and are, therefore, much more important. They give rise to isolated secondary tumor nodules a considerable distance from the primary growths.

According to the statements of different investigators (23, 42, 52, 71), it is clear that the lymphatics of the foreskin, the glans penis, and the skin of the penile shaft empty directly into the inguinal lymph nodes. But there is a lack of agreement as to whether or not the lymphatics of the deeper portion of the penis empty directly into the pelvic lymph nodes. That some of the lymphatics actually drain directly into the pelvic nodes seems to be proved beyond doubt by the finding in them of metastatic penile tumors while the inguinal nodes remain uninvolved (28, 32, 52).

Extension of penile carcinoma by way of the blood stream is
not a frequent occurrence. It usually follows invasion of the blood vessels or the blood spaces of the corpora cavernosa. Occasionally it follows the invasion of a large femoral vessel by a metastatic tumor in the femoral lymph nodes, in which case a widespread internal metastasis will occur (49, 50, 52, 54, 59, 77, 98). In one of our cases the metastatic tumor in a femoral lymph node almost eroded through the wall of the femoral vein.

METASTASES

Inguinal Lymph Nodes: The inguinal lymph nodes were examined in 52 cases, of which 35 showed no metastatic tumor and an enlargement due solely to inflammatory process. The other 17 cases, or 32.69 per cent, showed metastatic tumor growths. Küttnner (52), in a series of 56 cases, stated that the inguinal nodes were enlarged in 71 per cent, although only 32 per cent were proved to be cancerous. Barney (5) stated that of a series of 66 cases, 75 per cent showed metastases. Kaufmann (49), in a series of 48 cases, found that 40 had carcinomatous metastases in the inguinal nodes and that 30 out of these 40 were bilateral. Such wide variation in different reports regarding the frequency of inguinal node involvement is due probably to the difference in the clinical criteria by which the inguinal lymph nodes are removed.

The results of correlative studies as to the frequency of metastasis and the physical character of the primary tumor (size, and grade of malignancy) are presented in Tables VIII and IX. While

<table>
<thead>
<tr>
<th>Size</th>
<th>No Metastasis</th>
<th>Metastasis (+)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>1 case (100%)</td>
<td>0 cases (0.00%)</td>
<td>1 case (100%)</td>
</tr>
<tr>
<td>Medium</td>
<td>10 cases (67.86%)</td>
<td>9 cases (32.14%)</td>
<td>28 cases (100%)</td>
</tr>
<tr>
<td>Large</td>
<td>8 cases (80.00%)</td>
<td>2 cases (20.00%)</td>
<td>10 cases (100%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 cases</td>
<td>6 cases</td>
<td>13 cases</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>35 cases</strong></td>
<td><strong>17 cases</strong></td>
<td><strong>52 cases</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>No Metastasis</th>
<th>Metastasis (+)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>21 cases (95.46%)</td>
<td>1 case (4.54%)</td>
<td>22 cases (100%)</td>
</tr>
<tr>
<td>II</td>
<td>10 cases (71.43%)</td>
<td>4 cases (28.57%)</td>
<td>14 cases (100%)</td>
</tr>
<tr>
<td>III</td>
<td>2 cases (25.00%)</td>
<td>6 cases (75.00%)</td>
<td>8 cases (100%)</td>
</tr>
<tr>
<td>IV</td>
<td>2 cases (25.00%)</td>
<td>6 cases (75.00%)</td>
<td>8 cases (100%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>35 cases</strong></td>
<td><strong>17 cases</strong></td>
<td><strong>52 cases</strong></td>
</tr>
</tbody>
</table>

these studies permit no definite conclusion as to the relationship between the frequency of metastasis and the size or extent of the
primary growths, it is clearly shown that the frequency increases in the tumors of the more malignant grades, III and IV.

As to the metastatic growths, it seemed of interest to determine whether they showed any deviation in structure from the primary tumor. Our study (Table X) indicates that, as a whole, the structural type in the metastatic tumor is fairly well preserved, although there is a tendency for it to be slightly more anaplastic and to show more retrogressive changes, such as degeneration and necrosis.

**Internal Metastasis:** Among the fatal cases in our hospital, two were examined at autopsy, but neither showed any internal metastasis. Barney (5) stated that over 15 per cent of his cases had metastases in the vital organs, this conclusion being based on clinical manifestations, but not on autopsy. Winiwarter (98) saw a case with one pulmonary tumor nodule; Ricord and Ressel (77) saw a case with many nodules in the lungs; Lebert (54) reported 2 cases with metastasis to the lung and liver; Legallois (59) one case with metastases to the heart, lung, and liver; and Kaufmann (49) one case with tumor metastases in the heart, lung, pleura, spleen, liver, and kidneys. Keller (50) found metastases in liver and peritoneum, and Küttnner (52) found a rather generalized metastasis in 2 cases. It seems, then, that internal metastasis is not a common complication in carcinoma of the penis.

**Testis:** Testes were examined in 26 cases. In 25 cases they were normal; one case showed fibrosis and atrophy of the tubules. None showed metastatic tumor.
General Systemic Effects of Growth

Loss of Body Weight: In 79 cases mention of the general systemic effect was made. Loss of body weight to the extent of emaciation occurred in only 7 cases, or 8.86 per cent, in our series, while 62 patients, or 78.48 per cent, suffered no loss of weight, and 10, or 12.66 per cent, only slight loss. This is in contrast to carcinoma of the gastro-intestinal tract, in which loss of body weight is frequent.

Blood Picture: Routine blood counts were done in 80 hospital cases. From these studies, it may be said that moderate secondary anemia is present in only a small percentage of cases, but leukocytosis is more commonly seen. In practically all these cases both anemia and leukocytosis can be satisfactorily explained by the presence of varying degrees of infection.

Urine: Routine urinary examination was done in 79 hospital cases of our series. To summarize the findings, the urine in these cases is usually of light yellow or straw color, rarely bloody, slightly cloudy or turbid, having a normal specific gravity, mostly acid in reaction, with albumin varying from a faint trace to two plus in about two-fifths of the cases, no sugar unless diabetes mellitus is also present, frequent pus cells, and not infrequently red blood cells in the sediment. The fact that over 70 per cent of our cases showed an acid reaction is probably of no significance, since litmus was frequently used in earlier years and acid reaction to this indicator was regarded as normal.

The presence of pus cells and red blood cells in the sediment is not at all surprising, when an ulcerating tumor mass is present on the external genitalia.

Death

Of the patients who have been followed up, 11 have died: 6, or 54.5 per cent, died of postoperative complications, 4, or 36.4 per cent, of "recurrence" (†), and one of "ulcer of the neck."

As the follow-up study of these cases is exceedingly difficult, the result obtained is not at all instructive. However, from the reports received, postoperative complications seem to occupy an important place in the cause of death. Intercurrent diseases, such as pneumonia, sepsis, etc., are frequent causes of death, although some authors (52) rank these after metastasis and cachexia. Death due to the latter cause is, in our opinion, rare. Copious hemorrhage may occur in cases of penile cancer, probably due to the erosion of the larger blood vessels, such as the femoral, and generally leads to a fatal outcome. Few cases of such nature have been reported (50, 52, 74, 98).
In a consideration of the etiology of the present series of cases, one is struck by the fact that in practically every one there is a history of phimosis, while in the literature no case of penile carcinoma has been reported in a circumcised Jew. Thus there is reason to believe that certain conditions associated with or resultant from phimosis may have some bearing in the production of the tumor. These conditions are (a) the retention of the urinary products, (b) the accumulation of desquamated epithelium and secretion of Tyson's glands, and (c) lack of cleanliness of the preputial sac which favors (a) and (b).

The urinary products usually contain, among other things, indol, skatol, indigo, and some lipolytic and proteolytic ferments. Although it is not definitely known whether the above mentioned substances are present in all of our cases, the importance of their presence must be recognized. In view of the fact that marked epithelial hyperplasia with downward growth into the stroma has been produced experimentally by subcutaneous injection of 5 per cent indol and 5 per cent skatol in rabbit fat (91), and by similar injection of indigo suspended in water or gum arabic (16), one must seriously consider the relationship between the presence of these substances in the preputial sac and penile carcinoma, especially in view of the fact that these substances may be accumulated there for long periods of time.

The secretion of Tyson's glands may also have some direct influence on the production of tumor. This secretion, according to Lehmann (55), contains a high percentage of fatty material. It is unlikely that these fatty substances can themselves cause any important change in the epithelium, but under the action of the ferments and others, they may in time decompose, become rancid, saponify and produce other substances which may directly stimulate epithelial growth. That this may be so is suggested by the formation of tumors under somewhat similar, though by no means identical, conditions, such as the production of carcinoma of the breast in animals following the ligation of the main ducts of the mammary glands (4).

That the tumor is actually the direct result of the stimulating action of the accumulated or retained materials from the urine or Tyson's glands is proved by the fact that practically all of the tumors have their origin in the epithelium directly exposed to the

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2 In analyzing human smegma, he found that it contains 52.8 per cent of ether extract, 7.4 per cent alcohol extract, 6.1 per cent water extract, 9.7 per cent salt, 5.6 per cent albuminate, and 18.4 per cent residue. Of the fatty material, the acid number is 18.4, saponification number 142, and iodine number 41.2. The unsaponified part contains very little cholesterin.
smegma, arising from the glans penis, the inner surface of the prepuce, or the sulcus.

There seems to be reason to believe that the effect of the smegma may be latent for a considerable length of time, which probably explains the finding of penile carcinoma in cases where circumcision has been done several months or years previous to the appearance of the new growth.

The frequency of penile cancer in the Far East, as previously stated, is much higher than in Europe and America. Dormanns (29) explains this high frequency by the popular practice of applying highly irritating plasters for the treatment of gonorrhea, chancre, and chancroid lesions. There is no satisfactory proof of this contention. In our patients, about 63 per cent denied gonorrheal infection and none of those admitting gonorrhea or syphilis mentioned the previous use of any plaster. The only explanation that we can offer is that the lack of personal hygiene and the limited practice of circumcision among Asiatics favor the prolonged irritating action of the smegma on the susceptible epithelium.

It has been pointed out by various investigators, as well as by the present author, that cancer occurs earlier in Chinese than it does in Westerners. This may be a matter of racial difference, although the underlying cause is not clear to us.

It is a pleasure to acknowledge the author's indebtedness to Dr. J. R. Cash, formerly Professor of Pathology, Peiping Union Medical College, for suggestion of this work; to Drs. C. H. Hu, J. W. Spies, F. R. Dieuaide, and W. P. Ling for valuable suggestions and aid in the preparation of this paper, and last, but not least, to the Department of Surgery of Peiping Union Medical College for permission to use a part of their clinical material.

BIBLIOGRAPHY

2. ANDREWS: Cited from Barney.
CARCINOMA OF THE PENIS AMONG THE CHINESE

(b) Epithelioma of the genito-urinary organs, Ann. Surg. 75: 574, 1922.
31. DUPYTTREN: Cited from Kaufmann.
35. FORSTER: Cited from Maresch and Chiari, p. 367.
47. Hey: Cited from Maresch and Chiari, p. 367.
51. Krükenlein: Cited from Martin.
54. Lebert: Cited from Kaufmann.
CARCINOMA OF THE PENIS AMONG THE CHINESE 283


69. Murphy, J. B., and others: Studies on x-ray effects. VI. Effect of cellular reaction induced by x-rays on cancer grafts, J. Exper. Med. 33: 299, 1921.


76. Queyrat: Cited from Louste.


88. Sibley: Cited from Kaufmann.


96. TRAVERS: Case of cancer of the penis commencing with paraphimosis, Lancet 1: 182, 1827.