

# PRIMARY SQUAMOUS-CELL CARCINOMA OF THE KIDNEY AS A SEQUEL OF RENAL CALCULI \*

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An unusual case of renal tumor that has recently come under my observation carries so much evidence as to the relation of trauma and tumor formation, as well as to other problems of pathology, that it seems worthy of publication. It concerns a case of primary squamous-cell carcinoma of the kidney, arising as a sequel of renal calculi.

## REPORT OF CASE

*History.*—A man, aged 57, a tailor, entered the Cook County Hospital, June 13, 1921, two weeks before his death, complaining of abdominal pains of six months' duration, associated with frequent burning micturition, and a loss of about 30 pounds (13.6 kg.) in weight. There was no history of pain characteristic of renal colic, although he said that he had suffered from pain over the bladder when he was 20 years old; beyond this there had been no previous illnesses. Venereal infection and alcoholism were denied. He had never noticed blood in the urine, although it was turbid.

*Examination.*—The only positive findings on examination were these. On the right side of the abdomen there was a tender mass about the size of a coconut, extending from the costal border to 5 cm. above the umbilicus. Roentgen-ray examination revealed the presence of multiple stones in an enlarged right kidney. The cystoscope showed the vesical mucosa congested without ulceration. Ureteral catheterization showed that the right kidney did not function. With 1 c.c. of phenolsulphonephthalein, injected intravenously, the dye showed in the urine from the left ureter in six minutes, but none appeared from the right side in thirty minutes. The phenolsulphonephthalein test, intravenously, yielded 30 per cent. in the first half hour and 20 per cent. more in the second half hour from the left side. The urine contained albumin, pus, and blood, but few casts. A 25 per cent. solution of sodium bromid was injected by the ureteral catheters, the right side taking 20 c.c., the left 10 c.c. Roentgenograms then revealed, on the left side, a somewhat enlarged left kidney with slightly enlarged multiple calices; the right kidney showed a pelvis of irregular shape, apparently with escape of the injected fluid into the substance of the diseased kidney. The stones seemed to be not only in the kidney but also in the surrounding soft tissues.

Blood analysis gave the following figures: total nonprotein nitrogen, 39.27 mg. per hundred c.c.; urea nitrogen, 18.4 mg.; uric acid nitrogen, 2.27; creatinin nitrogen, 1.47. The leukocyte count was 11,800.

Following the ureteral catheterization the patient had a chill, and he continued to grow progressively weaker, usually with a subnormal temperature. On June 28, under local anesthesia, the right kidney was opened and three large

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dendritic caculi, each about 3 cm. in diameter, were removed, together with large amounts of pus. The patient continued to sink, and died the next day, a postmortem examination being made about six hours after death.

*Necropsy Findings.*—The body was that of a medium sized man, with white skin showing no icterus. The superficial lymph glands were not enlarged. There was a recently sutured wound, about 14 cm. in length, in the back, below and parallel to the right twelfth rib. There were no other external abnormalities.

**Abdominal Cavity:** There was 1 cm. of subcutaneous fat in the midline. The mesenteric lymph glands were not enlarged. The lower pole of the left kidney extended slightly below the crest of the ilium. The peritoneal cavity was free from fluid and its surface was smooth and shiny. A tumor mass at the site of the right kidney extended to the anterior axillary line. The colon extended over and in front of the renal mass and was attached to the liver and mass by dense fibrous adhesions. A white nodule, 1 cm. in diameter, which resembled a neoplasm, was removed from the peritoneum in this region. When this was cut, it exuded a white, necrotic, softened material. There were no adhesions about the spleen or gallbladder.

**Chest Cavity:** There were no abnormalities. The mediastinal glands were not enlarged.

**Heart, Aorta and Vessels:** The heart was large in proportion to the weight of the body, weighing about 350 gm. The coronary vessels and their orifices were normal. There was no fibrosis of the myocardium. All valves were normal. The ascending aorta showed a few small yellow streaks which were more numerous in the arch than in the abdominal aorta. The lymph glands around the abdominal aorta were enlarged and continuous with the right kidney mass. The inferior vena cava was free from thrombi and compressed somewhat with lymph glands but it was not occluded. The left renal vein was compressed by lymph glands.

The trachea and esophagus were both normal.

**Lungs:** The lower portion of the right lower lobe was slightly boggy and contained little air; but there was no consolidation. There was an extensive calcification of one right peribronchial lymph gland. The weight of each lung was 400 gm. The lower lobe of the left lung contained small subpleural hemorrhages and a few small slightly consolidated areas over which the pleura was smooth and glossy. Yellow pus exuded from the bronchi in this region, together with a little fluid.

**Spleen:** There were no gross changes.

**Liver:** The liver weighed 2,120 gm. The organ as a whole was enlarged; the surfaces were rounded, moist, swollen and soft in consistency. There was no increase in connective tissue. The gallbladder was normal in size and contained no concretions.

**Stomach:** The stomach showed no gross abnormalities. Below the pyloric ring there were two pouches or diverticula, each about 1.5 cm. in size, in the duodenal mucosa, with no evidence of inflammation or ulceration.

**Pancreas:** This was normal.

**Kidneys:** The left kidney was larger than normal, weighing 300 gm. and measuring 14.5 cm. long, 7 cm. wide and 6 cm. thick. The organ was soft, mottled and irregular in outline with a nonadherent capsule which was attached to the perirenal tissue. The cut surfaces showed areas of marked disintegration, hemorrhage and softening with one abscess, 2 cm. in diameter, underneath the

capsule. The cortex was 10 mm. thick. The pelvis showed no ulceration. The ureters were of normal size and showed no ulceration but contained purulent material.

The right kidney weighed 800 gm. It measured 21 cm. long, 13 cm. wide and 7 cm. thick, and it was adherent to the perirenal tissue which was indurated and contained several abscesses up to 3 cm. in diameter. The kidney was firmly adherent to the perirenal tissue over the entire surface; and about the pelvis, extensions of tumor growth had produced nodules and strands of neoplasm in the perirenal tissue itself. The ureter was completely occluded at its junction with the pelvis, the lower portion of which was completely filled by masses of irregular cancer tissue, about 5 mm. thick, surrounding the entire



Fig. 1.—Squamous-cell carcinoma of the renal pelvis;  $\times 60$ ; showing the infiltration of the submucous tissues by carcinoma with formation of masses of keratin scales. The lining of the cavity is formed by stratified epithelium.

pelvis. The cut section of the kidney disclosed a complete loss of all recognizable kidney tissue. The organ consisted essentially of a mass of branching communicating cavities directly continuous with the pelvis, some of which extended to the capsule. The surfaces were bathed with thick pus in which a few small remains of the original calculus were found. Between the pus-filled cavities were masses of white cancer tissue with irregular necrotic surfaces, in places covered with blood clots. The cancer tissue infiltrated through the renal capsule into the perirenal fat in many places. The pelvic surfaces were

rough; but only occasionally was anything suggestive of a papillary character to be seen. In some places the shell of cancer tissue was only 1 or 2 mm. thick; in others, masses from 2 to 4 cm. thick remained. The kidney consisted practically of a pus-filled cavity formed by distention and ulceration of the renal pelvis, with walls composed entirely of cancer tissue. The portion of the stones obtained at the operation, together with the fragments found at necropsy, weighed 33 gm., air dried at room temperature. They constituted a typical dendritic calculus which had broken apparently spontaneously into three large fragments and four smaller ones. When fractured the surface was roughly crystalline. The external surface was lobulated, roughened, and showed some soft deposit on a harder central portion.

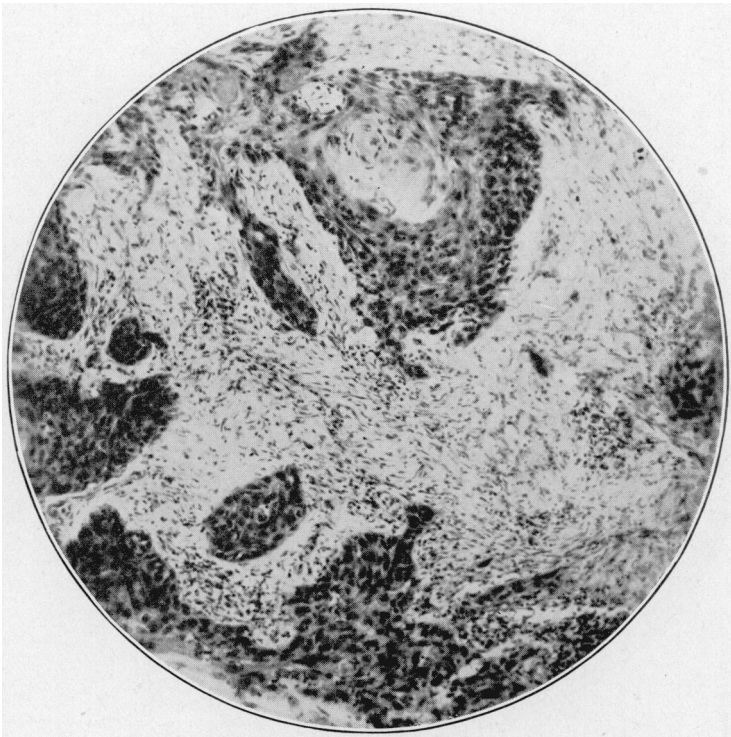


Fig. 2.—Squamous-cell carcinoma of the renal pelvis;  $\times 110$ . Higher magnification to show the resemblance to squamous-cell carcinoma of the skin.

The lymph glands around the kidney were enlarged, up to 5 cm. in diameter, by white neoplastic tissue, with most of them showing suppurative softening.

Suprarenals: The left suprarenal was normal; the right was infiltrated with a white tissue, without much enlargement or nodule formation, apparently by direct extension from the kidney.

Bladder: The bladder contained a purulent material. The mucosa was hyperemic and contained much granulation tissue about the trigon, together with many small hemorrhages but no ulceration or tumor growths. Both ureteral orifices and the urethral orifice were normal.

The prostate, seminal vesicles and testicles were normal.

**Skeleton:** No metastases could be found. The vertebral column showed marked exostosis with complete ankylosis of many of the vertebral articulations.

**Histologic Findings.**—The white neoplastic tissue which replaced the right kidney and many retroperitoneal lymph glands, as well as the tumor nodule found in the peritoneum, consisted everywhere alike of typical squamous-cell carcinoma characterized by extensive formation of whorls of stratified keratinized epithelium. It differed not at all from the keratinizing carcinomas that are found in the skin or mouth. Nowhere were there structures resembling the ordinary papillary carcinomas of the renal pelvis, or the medullary transi-

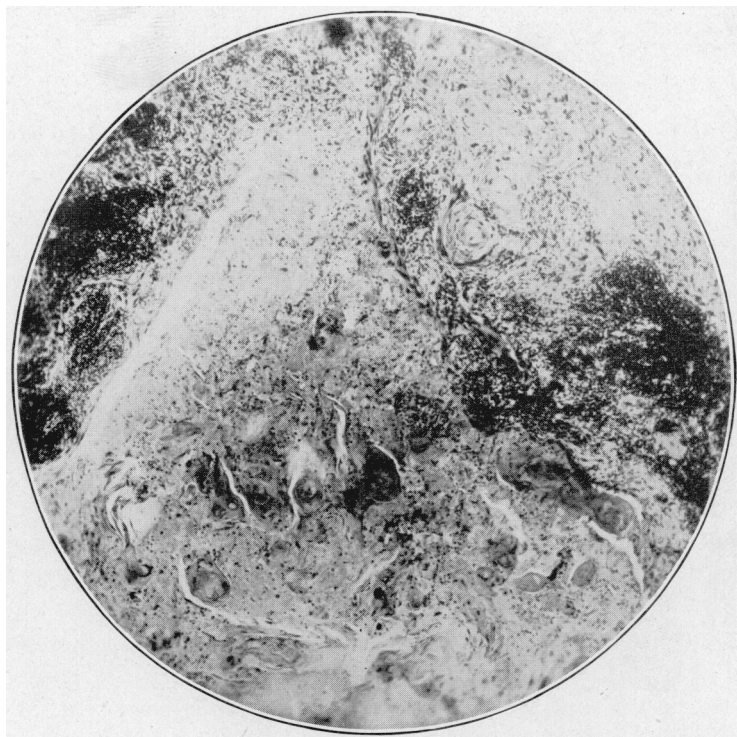


Fig. 3.—Metastatic squamous-cell carcinoma in a retroperitoneal lymph gland;  $\times 60$ . Most of this field is occupied by masses of hornified epithelium.

tional cell carcinomas. In all parts of the tumor growth, both primary and secondary, there was acute suppurative inflammation. In none of several sections examined were any remains of the kidney tissue to be seen. The right suprarenal was partly replaced by carcinoma of the same type as that in the kidney.

The left kidney showed only the usual changes of an acute ascending suppurative nephritis.

No microscopic changes of present interest were found in the other organs.

*Anatomic Diagnosis.*—This was: right nephrolithiasis; diffuse infiltration of the right kidney and perirenal tissues with squamous-cell carcinoma; acute suppurative pyelonephritis with complete destruction of the parenchyma of the right kidney; recent nephrostomy wound of right kidney with drainage; carcinomatous infiltration of right suprarenal; metastatic carcinoma nodule in peritoneum; secondary carcinoma and suppuration of retroperitoneal lymph glands; ascending suppurative nephritis of left kidney, acute cystitis and ureteritis; compression of inferior vena cava and left renal vein; hypertrophy of left cardiac ventricle; senile arterial sclerosis, moderate degree; atrophic pulmonary emphysema; calcified tubercle in a right peribronchial lymph gland; acute suppurative bronchitis and early hypostatic bronchopneumonia of left lower lobe; acute parenchymatous swelling of liver, and marked exostosis of the vertebral column.

Samples of the renal stones were mixed together and analyzed for me by Miss Mary E. Maver, who obtained figures indicating an average percentage composition as follows:

$\text{Ca}_3(\text{PO}_4)_2$ —70.70;  $\text{Mg}_3(\text{PO}_4)_2$ , 21.35;  $\text{CaCO}_3$ , 7.95.

No oxalic acid, uric acid, xanthin or silicic acid was present.

This is, then, a phosphate calculus, which is an unusual type of concretion to be found in the renal pelvis. There is a current statement in the literature to the effect that renal calculi are ordinarily composed chiefly of uric acid or urates; but more recent writers have reported that calcium oxalate is usually the chief component. Rowlands<sup>1</sup> found that twenty-two renal stones were composed almost entirely of calcium oxalate; phosphates were commonly present, and uric acid was absent or was found only in traces. Max Kahn<sup>2</sup> analyzed sixteen stones and found from 29.5 to 94.7 per cent. of calcium oxalate, from 0.2 to 40.6 per cent. of uric acid, from 2.1 to 56.2 per cent. of phosphorus pentoxid, and no carbonate. Only two of these stones consisted chiefly of phosphate, and only two had much uric acid (40.6 and 23.6 per cent), while all but three had more than 70 per cent. of calcium oxalate.

Such calculi as the one in this case, composed chiefly of a mixture of calcium and magnesium phosphate, ordinarily indicate the presence of long-continued ammoniacal decomposition of the urine. Under such cases these salts may precipitate on a previously existing urate concretion, and the urates in time may dissolve out and be replaced by phosphates, constituting the process of "metamorphosis" of calculi.<sup>3</sup>

1. Rowlands: *Biochem. J.* **3**:346, 1908.

2. Kahn, Max: *Study of the Chemistry of Renal Calculi*, *Arch. Int. Med.* **11**:91 (Jan.) 1913.

3. Wells, H. Gideon: *Chemical Pathology*, Ed. 4, 1920, p. 461.

## DISCUSSION OF LITERATURE

The infrequency of tumors of this sort is indicated by the following statement made by Ewing<sup>4</sup> in his work on neoplastic diseases:

Squamous-cell carcinoma of the pelvis was described by Kundrat in 1891 and later cases have been reported by Rundle, Graupner, Kischensky, Beisenbruch and Scheel. These remarkable tumors are usually of large size when discovered, but Battle observed squamous changes in a small villous tumor of the pelvis and Rundle found the upper ureter invaded by a squamous carcinoma of moderate dimensions. In other cases the pelvis has been distended and the wall infiltrated by a bulky growth. The kidney is either transformed into large cysts by hydronephrosis or infiltrated and destroyed. The squamous changes are very pronounced and much of the growth may be composed of epithelial pearls, many of which are hornified or calcified. In Schmorl's case, distant metastases showed the same structure. That the pelvic and ureteral epithelium is capable of extensive epidermization is well attested by the reports of Wendel of numerous cases of leukoplakia, usually associated with calculi. Rokitsky described a very advanced condition, with much scaly desquamation, as "cholesteatoma." Ziegler found marked epidermization in pyelitis calculosa, and Beselin reported an advanced case with tuberculous pyelitis. Yet all cases are not associated with calculi or leukoplakia, so that the excessive hornification must be regarded as a tendency inherent in the growth.

In a case studied by the writer in a woman of 58 years, the kidney and tumor measured 14 by 19 cm. The tumor involved chiefly the extrapelvic fat but had occluded the lower half of the pelvis, along which it invaded the kidney. The renal cortex was thinned out over several large smooth-walled cysts. The ureter was destroyed down to the bladder. There were metastases in aortic and mesenteric nodes and in the uterus. The main bulk of this large tumor was composed of hornified and slightly calcified epithelial pearls surrounded by a moderate number of spindle or cubical granular epithelium. The transition from one to the other type of cell was very sharp.

Kaufmann says: "Squamous epithelial cancers occur, which sometimes follow epidermoid transformation of the mucosa, e.g., as a result of concretions. In one such case in Basle the renal pelvis contained a large branching stone (oxalate nucleus with calcium salt mantle) weighing 93.1 gm."

The case reported by Kischensky<sup>6</sup> resembles my case in many respects, especially in the complete replacement of the entire kidney by squamous-cell carcinoma; it also extended into the liver and diaphragm and produced metastases in the regional lymph glands and in the right knee. There was not only squamous-cell cancer tissue, but also areas of transitional and cylindric epithelial growth, and papillomatous formations. In addition to the hornification there was considerable

4. Ewing, James: *Neoplastic Diseases, a Textbook on Tumors*, Ed. 1, Philadelphia, W. B. Saunders Company, 1919, pp. 743-744.

5. Kaufmann: *Spezielle path. Anat.*, Ed. 6, 2:877.

6. Kischensky: *Ziegler's Beitr.* 30:348, 1901.

calcification. However, in this case no concretion was present. He gives a full discussion of the literature on tumors and metaplasia of the renal pelvis to that date.

While squamous-cell cancers of the kidney are rare, as a matter of fact, any type of epithelial tumor seldom arises in the pelvis of the kidney, for in 1921 Miller and Herbst<sup>7</sup> in reporting a case of papillary tumor of the pelvis mentioned only fifty-three others as previously reported. Metastases were observed in fifteen of these cases. Kretschmer,<sup>8</sup> in 1917, reviewed the literature on "Primary Non-papillary Carcinoma of the Renal Pelvis," of which he found forty-three cases, including one of his own. In eleven cases there were found, associated with the tumor, renal stones. Necropsies were secured in but nineteen cases, with metastases found most frequently in the liver (eight cases), and in five cases there were osseous metastases. He makes no particular reference to the question of hornification, and from his abstracts of the case reports it is not possible to determine this matter exactly, since the terms pavement epithelioma and epidermoidal cancer are used vaguely. Apparently only about five cases were definitely keratinizing squamous carcinomas, and in three of these renal stones were found. The cases described by Kaufmann and Ewing were not included in Kretschmer's summary. In all, I have found eleven cases of squamous-cell carcinoma of the renal pelvis sufficiently thoroughly reported to be unquestionable. In these the presence of calculi is mentioned in six.

A case reported by Primrose<sup>9</sup> is particularly interesting since it arose in the pelvis of a horseshoe kidney with calculous pyonephrosis. Unfortunately, necropsy was not obtained and only the observations made at operation are recorded.

Recently Scholl<sup>10</sup> has reported six cases of squamous-cell carcinoma of the urinary bladder, in only one of which did stone occur. In reviewing the literature on the topic he discusses also cases of squamous-cell carcinoma of the renal pelvis. He states that in 195 tumors of the kidney observed at the Mayo Clinic there was only one squamous-cell carcinoma of the pelvis of the kidney; but he does not mention whether there was or was not a stone present. This is presumably the case recorded, but not fully described, by Wilson.<sup>11</sup>

7. Miller, E. M., and Herbst, R. H.: Papillary Epithelioma of the Kidney Pelvis, *J. A. M. A.* **76**:918 (April 2) 1921.

8. Kretschmer, H. L.: *J. Urology* **1**:405 (Aug.) 1917.

9. Primrose, Alexander: Squamous-Cell Carcinoma of the Kidney, *J. A. M. A.* **75**:12 (July 3) 1920.

10. Scholl, A. J., Jr.: Squamous-Cell Carcinoma of the Urinary Bladder, *Arch. Surg.* **3**:336 (Sept.) 1921.

11. Wilson, L. B.: *Collected Papers of the Mayo Clinic*, 1912, p. 303.



Scholl also makes the following statement:

Leber reports the case of an infant of 4 months in whom the epithelial lining of the pelvis of the kidney was composed of many layers of cells showing cornification; a similar condition was found in the infant's eye. This case suggests a congenital origin. Lecène holds that the process in these cases is due, not to chronic inflammation, but to developmental changes in the genito-urinary tract. Wilson suggests that epidermoid growths of the pelvis of the kidney may be due to inclusions of ectodermal cells carried from the rectum to the kidney by way of the cloacal wall.

The last suggestion is, of course, purely hypothetical. The frequent existence of metaplastic changes in the urinary tract from chronic irritation and the fact that chronic irritation usually precedes squamous carcinoma in the urinary tract provides adequate explanation for such cases as have been observed.

As to the frequency of squamous-cell carcinoma in the urinary bladder, Scholl quotes the statement of Geraghty that in 180 epithelial tumors of the bladder at Johns Hopkins Hospital there was but one of this type. At the Mayo Clinic, however, there were found in 333 neoplasms of the bladder the six cases of squamous-cell epithelioma which Scholl describes. Among 113 bladder tumors studied by Buerger<sup>12</sup> there were five squamous carcinomas.

In their review of the comparative pathology of renal tumors Slye, Holmes and Wells<sup>13</sup> mention only the following cases in which squamous epithelial growths have been observed in the kidneys of lower animals: "Baird<sup>14</sup> has reported a case of keratinizing epithelioma in the kidney of a fowl, and Borrel and Masson<sup>15</sup> have also described a renal tumor in a fowl which showed both cylindrical and squamous elements."

#### SIGNIFICANCE OF METAPLASIA

The occurrence of metaplasia in the urinary tract has been described especially often, presumably because the transitional epithelium has to undergo less alteration to produce squamous epithelium than does the columnar epithelium of the bronchi, uterus and the gallbladder, where metaplasia has been occasionally observed. Richey<sup>16</sup> has recently discussed the topic of metaplasia in the renal pelvis in some detail, and makes the following statement:

That leukoplakia may be the predecessor of carcinoma is indubitable. Osler states that 20 per cent. of leukoplakia of the tongue becomes carcinomatous,

12. Buerger, L.: *Surg., Gynec. & Obst.* **21**:179 (Aug.) 1915.

13. Slye, Holmes and Wells: *J. Cancer Res.*, to be published.

14. Baird, A. T.: *J. Cancer Res.* **2**:103 (Jan.) 1917.

15. Borrel and Masson: *Bull. de l'ass. franç. p. l'étude du cancer*, Paris, **4**:172, 1911.

16. Richey, DeW. G.: *J. Lab. & Clin. Med.* **5**:635 (July) 1920.

while Albarran, Barker, Ewing and others indicate that leukoplakia in any organ should be watched carefully for malignancy, often being, in the absence of early carcinoma, very suspicious of precancerous changes. Morris collected twenty-seven cases of tumors originating in the kidney pelvis, of which ten were malignant, while recently Kretschmer was able to gather forty-three instances of nonpapillary carcinoma of the renal pelvis, including twenty-one of apparent transitional or squamous type. The former author states that the most frequent form of carcinoma is transitional or squamous-cell, pointing out that long-standing irritation may lead to the transformation of the renal epithelium to an epidermic character, with a resultant leukoplakia which may be the starting point of squamous-cell cancer.

The formation of metaplastic squamous epithelium brings forward two puzzling topics, one chemical, the other embryologic. The chemical peculiarity is that squamous epithelium is characterized by the formation of keratin, which is a definite chemical compound, formed normally, as far as is known, only by cells of ectodermal origin, including the neurokeratin of the central nervous system. When cells of endodermal origin, such as those lining the gallbladder, or those of mesodermal origin, such as those lining the renal pelvis or the uterus, take on the function of forming this peculiar, insoluble, sulphur-rich, indigestible protective chemical, keratin, they have assumed a chemical function which seems to be far removed from their normal capacity. Hence we must conclude that metaplasia involves not only a morphologic but a chemical transformation in the cells.

For tumor pathology another problem arises. When cells assume the proliferative activity that is characteristic of malignancy, they usually lose their more recently acquired functions and retain chiefly the simple vegetative function of proliferation. But when a transitional or columnar epithelial surface becomes squamous through metaplasia, and the same protracted irritation that produced the metaplasia continues until cancer results, we find that the newly acquired property of forming keratin has become fixed and the cancer is a keratinizing, squamous-cell carcinoma. One would expect the epithelium to approach its original, simpler embryonal character, rather than exhibit and retain so profound and recently acquired an alteration as the production of keratin.

#### SUMMARY

The formation of keratinizing squamous-cell carcinoma in the renal pelvis is a rare occurrence. In the case reported, which is of this sort, the metaplasia of the transitional epithelium to the squamous form was apparently the result of chronic irritation from renal concretions.