THE ORIGIN AND DEVELOPMENT OF RENAL ADENOMAS AND THEIR RELATION TO CARCINOMA OF THE RENAL CORTEX (HYPERNEPHROMA)

ALBERT J. TRINKLE, M.D.
(From the Department of Pathology, University of Minnesota)

Renal adenomas were first clearly described by Sturm in 1875. The purpose of this investigation is to study in detail the origin and development of these tumors and their relationship to hypernephromas.

MATERIAL AND METHOD OF STUDY

The material available for study consisted chiefly of microscopic sections from the Department of Pathology at the University of Minnesota. In addition some specimens were obtained from fresh autopsy material. The tissues were all fixed in 10 per cent formalin, imbedded in paraffin, and stained with hematoxylin and eosin. A number of cysts and adenomas were available in serial sections. The specimens studied were as follows:

(a) Numerous examples of persistence and dilatation of tubules in subcapsular wedge-shaped areas of atrophy. These are believed to represent the starting point of cysts and adenomas.

(b) Six simple cortical cysts, one in serial sections.

(c) Five small papillary cysts, four of which were studied in serial sections.

(d) Thirty-seven cystadenomas, of which 13 were single and 6 multiple simple papillary cystadenomas. Fourteen were solid cystadenomas. One papillary and two solid cystadenomas were studied in serial section.

(e) Three alveolar adenomas, a single paraffin section of each.

(f) Four tubular adenomas, one of which was studied in serial section.

(g) Four small but typical hypernephromas which had not metastasized.

This material was studied microscopically in an effort to work out the origin and development of the adenomas and to determine whether there is any evidence that adenomas may develop into hypernephromas.

RENAL LESIONS ASSOCIATED WITH ADENOMAS

It is well known that arteriosclerotic kidneys presenting large coarse pits on the surface are frequently the seat of multiple adenomas. Ewing considers the common papillary cystadenomas seen so frequently in arteriosclerotic kidneys as secondary to vascular occlusion. Metzner, Kaufmann, Sabourin and others have also stressed the frequent association of adenomas and arteriosclerosis. Bell states that adenomas are rather frequently seen in hypertensive kidneys but are rare in the contracted kidneys of chronic glomerulonephritis. This is due probably to the fact that there is rarely a primary
obliteration of arteries in the latter disease, the atrophy being due primarily to obliteration of glomeruli from intracapillary obstruction. There is general agreement that papillary cystadenomas and related tumors are found chiefly in arteriosclerotic kidneys.

**Frequency and Macroscopic Features**

Keyes states that adenomas of the kidney are comparatively common in adult life. They are usually no larger than a pea and may be even smaller; rarely they are as large as a walnut. They occur singly in 75 per cent of the cases, but some are multiple and others bilateral. They are usually situated in the cortex and occur with equal frequency in the two kidneys. Judd and Grier reported a case of multiple adenomas in which the tumors ranged from 3 mm. to 12 cm. in diameter. They considered the large tumors malignant. Dschu-Yü-Bi reported a similar case. The tumors in his patient were distributed for the most part over the cortex, but a few were confined to the medulla. Numerous reports of large papillary cystadenomas are found in the literature, and in some instances clinical signs of a renal tumor are recorded (Judd and Simon, Kretschmer and Doehring, Cunningham and Swan).

In the series we have studied the adenomas ranged from microscopic examples to tumors 4 cm. in diameter. Frequently the lesions were multiple and in one instance the kidney was studded with tumors situated for the most part in the cortex, though a few were deeply placed and one was confined to the medulla. The very small tumors closely resemble miliary tubercles, while the larger ones are slightly yellowish in color. The small tumors are rarely hemorrhagic but the larger adenomas frequently appear mottled on section, this being due to the fact that they frequently contain large blood spaces. We have found that small adenomas cannot be distinguished grossly from small fibromas, leiomyomas and adrenal rests.

Adenomas are frequently seen in routine post-mortem examinations. Nuernberg found 66 examples in 2,250 autopsies.

Weichselbaum and Greenisch found renal adenomas limited to subjects over thirty years of age, steadily increasing in number with age, and present in 10 per cent of all subjects over eighty. In Nuernberg’s series of 66 cases, the average age was sixty-one years. In our series the average age was sixty-two. In general it may be said that adenomas are most prevalent past middle life and seem to increase in frequency with advancing age, which is significant in view of the fact that there is also an increase in the incidence and severity of vascular disease of the kidneys with age. None of the adenomas in this series was associated with hypertension.

**General Features of Cysts and Adenomas**

(a) **Small Subcapsular Cysts:** Small subcapsular cysts, like adenomas, occur chiefly in arteriosclerotic kidneys. In all but 2 of a series of 66 cases in which adenomas were present Nuernberg found either gross or microscopic cysts in the kidneys. Kaufmann has pointed out that cysts and papillary adenomas are frequently associated. It is generally agreed that all cysts of
the kidney are congenital in origin, except the small subcapsular cysts found in arteriosclerotic kidneys, and it is only these subcapsular cysts that are usually thought to be related to adenomas. They are situated, as a rule, in or adjacent to areas of scarring. On section they appear as thin-walled sacs lying in the cortex or projecting above the surface of the kidney. The cyst wall is lined with flattened cuboidal epithelium.

(b) Papillary Cysts: Simple papillary cysts are frequently associated with papillary adenomas and undoubtedly stand in close relationship to them. McFarland reported a case of multiple adenomas of the kidney in an elderly male in which the tumors were associated with numerous small cysts. Many of these showed papillary ingrowths projecting into the cyst cavity. Nuernberg noted that structures appearing grossly as cysts frequently contained small papillary invaginations. This he considered evidence in favor of the theory that adenomas had their origin in cysts. Similar observations have been made by Sabourin, Phillipson, Ricker, Nauwerck and Hufschmid, and others. Phillipson noted that some tubules, instead of undergoing atrophy, dilated and occasionally exhibited proliferative growth in the lining epithelium. Nauwerck and Hufschmid have accurately described and illustrated small papillary cysts and think that they bear a definite relationship to the papillary adenomas of the kidney. They described the lining cells as hyperplastic with deep-staining nuclei and finely granular eosinophilic cytoplasm.

(c) Papillary Cystadenomas: Metzner, in 1888, described a tumor the size of a walnut occurring in the kidney of a seventy-five-year-old woman. This tumor was made up of cystic spaces, projecting into the lumen of which were papillary ingrowths covered with epithelium of the clear-cell type. He called this tumor a cystoma papilliform and considered it to be of adrenal origin. Albarran and Imbert described similar tumors but believed that the origin was definitely from renal tissue. Zehbe described small papillary cystadenomas accurately and pointed out the similarity in structure between many of the very small tumors and the larger ones. His tumors ranged in size from a millet seed to a walnut. He described a large tumor similar in structure to the very smallest, composed of numerous chambers formed by connective tissue covered with epithelium, each chamber forming a typical papillary cystadenoma.

The simple papillary cystadenomas that we have studied were all small, ranging in size from microscopic lesions to small tumors several millimeters in diameter. Adenomas larger than these were almost without exception solid tumors. Microscopically, these papillary cystadenomas consist of small cystically dilated tubules and cysts lined with deep-staining epithelium which at different places is thrown into papillary processes supported by a stroma of young connective-tissue cells, which contains small capillaries. The epithelial cells are of the cuboidal type and the nuclei have a tendency to lie in the basal portions of the cells. Both nuclei and cytoplasm stain more deeply than cells in the adjacent normal renal tubules. This process may be limited to one small cyst or may involve numerous adjacent cysts or cystically dilated tubules. Some early adenomas show hydropic degeneration of the epithelial cells, while others consist wholly of dark cells. In either event the cytoplasm remains finely granular, although the granules are less distinctly made out in
the clear cells. All of the small papillary adenomas follow this general structural pattern with a few variations.

**Solid Tumors: Papillary Type:** We have considered a papillary cystadenoma to be of the solid type when the papillary processes so fill the cyst cavity that there remains no appreciable space. The larger tumors are really papillary adenomas rather than papillary cystadenomas. The typical papillary cystadenomas are usually small structures and are frequently overlooked by the pathologist, whereas the tumors of the solid group are usually larger and more conspicuous, and for that reason are more likely to be preserved.

Zehbe described the transformation of a cystic tumor into a solid structure. He pictured the cyst as being filled with proliferating epithelial processes, each lying on a connective-tissue trabecula. These processes branch and rebranch until the cyst cavity is obliterated. Zehbe has also described larger adenomas, chiefly of the papillary type, but showing in some areas tubule formation. Keyes, Bieck, Kaufmann, Stoerk and others have described similar papillary tumors showing areas of tubule formation. Stoerk and Zehbe have both pointed out the fact that frequently in the solid type of papillary adenoma there are patchy areas of large clear cells. Dschu-Yü-Bi recently described similar patchy areas in compact tumors of the papillary variety. He suggested from their location in the central parts of the tumor that deficient oxidation was the causative factor in the production of hydropic degeneration. We have in our series numerous similar examples of adenomas of the solid type showing early hydropic degeneration. The larger adenomas are usually invested with a fibrous capsule, occasionally containing atrophic glomeruli and tubules in its substance. From the capsule trabeculae of variable thickness penetrate the tumor, branching to follow the course of the adenomatous processes.

**Tubular and Alveolar Adenomas:** Tubular adenomas have been described by Norman, Ricker, Metzner and others. Unfortunately examples of this interesting type of tumor are uncommon and we have only four examples available for study.

Alveolar adenomas are also a poorly understood group and many tumors described in the literature as such really belong to the other groups. We have four such tumors in our collection. Microscopically these tumors are characterized by polyhedral cells arranged in alveolar fashion (Fig. 12). Many of the alveolar spaces are about the size of convoluted tubules and are completely filled with these large cells, each closely adjoining its neighbor to give a pavement-like appearance. One is impressed with the resemblance of these adenomas to certain types of hypernephroma. A close relationship between alveolar adenomas and hypernephromas of the dark cell type has been suggested by several investigators but never established.

**Origin and Development**

(a) **Cysts:** The frequent occurrence of small subcapsular cysts in contracted kidneys has led to a general agreement that they are derived from obstructed tubules. All other cysts of the kidney are believed to be congenital (Bell). The recent work of Oliver, Lund, and Luey on the abnormal
renal architecture in diseased kidneys has led to several important findings. They were able to show that a tubule belonging to a hyaline glomerulus does not always undergo atrophy, but may hypertrophy, dilate, and even become hyperplastic. Hyperplasia is dependent upon a renewed blood supply. Oliver was able to demonstrate in many instances Ludwig's vessel, dilated to the size of the afferent arteriole, arising from the sclerosed vessel. This acts as a shunt around the occluded glomerulus, thus supplying the affected tubules with blood. The hyperplastic tubules increase in length as well as in diameter, often kinking upon themselves to cause obstruction. They emphasize the observation that tubules may continue to live and grow after their glomeruli are completely occluded. Staemmler has also noted numerous capillaries in an area of scarring in which the glomerulus was hyaline and the tubules dilated. We believe that tubules of obstructed glomeruli may also obtain a new blood supply from the capsule and probably from the adjacent renal tissue as well.

Fig. 1 shows a small subcapsular cyst situated in a wedge-shaped area of atrophy. The patient was a man of seventy-two. The scar was caused by gradual occlusion of a small artery. These cysts are believed to originate from persistent portions of a tubule whose glomerulus has been destroyed.

(b) Papillary Cysts: Papillary cysts develop from either local or generalized proliferation of the lining epithelium of the small simple cysts. Proliferation may be limited to a small area of the cyst wall, or it may develop...
throughout a considerable portion of a tortuous tubular cyst. Proliferation of the lining epithelium results in the formation of papillary invaginations which protrude into the lumen to form the early papillary cyst (Fig. 2).

(c) Papillary Cystadenomas: Papillary cystadenomas develop both from papillary cysts and directly from simple cysts (Figs. 3 and 4). Connective tissue from the surrounding stroma grows into the epithelial projections to lend them support. These are then capable of branching and rebranching to form a complicated intracystic network, typical of the papillary cystadenomas (Figs. 5 and 6). Cross-section of the invaginated process shows it to consist of epithelial cells arranged in rosette fashion about a central core of young connective tissue. Capillaries invade the connective tissue to provide nourishment. The growth of an adenoma is central and expansive in character. As it grows, it compresses the adjacent renal tissue, causing pressure atrophy of the tubules and glomeruli. Many of the adjacent tubules disappear, but the connective-tissue stroma persists to form a well defined capsule. The thickness of the capsule is usually proportional to the size of the adenoma.

(d) Solid Tumors: Solid papillary adenomas develop directly from cystadenomas. As the proliferative reaction within the cyst continues, the cavity becomes completely filled with a network of branching papillary processes (Fig. 7). The larger solid adenomas may retain the purely papillary type of growth, or, as has been pointed out by Ricker and Zehbe, the connective tissue of the processes may become thinned out toward the center. This leads to variations in structure. The cells continue to proliferate and come to lie in long cords (Fig. 8). In places capillaries and thin strands of connective tissue separate them. Another variation in structure may occur. The pro-
Connective tissue can be seen growing into the papillary processes. It is but a short step from a papillary cystic tubule to a small papillary cystadenoma. Same case as Fig. 2.

The patient was a man of sixty-six. Serial sections show these cysts to be continuous. Numerous small papillary ingrowths are to be seen. The epithelium of the cysts stains more deeply with hematoxylin than the normal tubules.

Liberating epithelium may bud off from the mother stalk and thus form small masses of epithelium free from connective tissue. These epithelial buds may then differentiate into tubules. Apparently this is the manner in which papillary adenomas develop tubular elements, and the larger adenomas described in the literature as being of the tubular variety frequently show areas of papillary structure suggesting that they arose in this manner.
Hydropic degeneration is seen occasionally in small adenomas in the cystadenoma stage. This change is more frequent, however, in the larger solid tumors. The centrally located cells in the budded-off epithelium which lacks supporting connective tissue are the first to show this change. The peripheral cells surrounding them often retain their dark-staining characteristics (Fig. 9). This fact lends support to the theory that deficient oxygen
The patient was a man of sixty-one. The tumor measured 3 cm. in diameter. There are both dark and clear cells present. Note arrangement of the clear cells in long cords. In other areas, the structure of simple papillary adenoma is present.

may be a factor in hydropic degeneration, but probably does not explain it in full. In addition, one must assume that proliferating tubular epithelium is predisposed to this type of change since it does not occur in normal tubules affected by vascular disease.

(c) Transitions to Carcinoma of the Cortex (Hypernephroma): We have studied one case in which the kidneys were the site of multiple adenomas
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FIG. 9. SOLID PAPILLARY ADENOMA

Note the patchy distribution of the hydropic cells. These tend to develop first in the central portions of the tumor. The patient was a woman of forty-eight.

FIG. 10. HIGH-POWER VIEW OF A SOLITARY TUMOR OF THE KIDNEY MEASURING 0.5 CM. IN DIAMETER

The patient was a woman of seventy-two. The structure is that of a typical hypernephroma. This represents an excellent example of the transition form of adenoma. The cells are of the clear type. A similar structure may be found in some of the advanced papillary adenomas.

varying in size from those scarcely visible to the naked eye to large tumors, one of which was 4 cm. in diameter. The smaller tumors proved to be early papillary adenomas. The structure of the large 4 cm. tumor was also that of a papillary adenoma save in parts where a structure indistinguishable from hypernephroma obtained. Areas of tumor showing the structure of a benign
adenoma merge with tumor tissue which histologically is that of a malignant hypernephroma. The adenomatous epithelium stands out in sharp contrast with the epithelium of the hypernephroma-like portion of the tumor. The former consists of small cuboidal dark-staining epithelial cells, while the latter shows larger cells, with more abundant cytoplasm, larger nuclei, and more prominent nucleoli. There are areas in which the cells are in cord-like formation, some being hydropic; in other places a tubular arrangement is seen. A study of this tumor clearly suggests a transition of an adenoma to hypernephroma (Fig. 8).

We have four other examples of small tumors which appear to be transition forms of adenomas. Each is a small tumor, the sizes varying from 0.5 to 2 cm. in diameter. The characteristics are those of both benign adenomas of the papillary type and early hypernephromas. In areas, the small cuboidal cells, some of the dark cell type, others clear, are in papillary arrangement. Here the adenomatous character of the tumor is suggested. In other areas the cells, which are predominately hydropic, are arranged in cords, and present the picture of definite hypernephroma (Figs. 10 and 11).

For purposes of comparison, four early but typical hypernephromas were studied. These tumors measured, roughly, between 3 and 4 cm. in diameter. All were encapsulated and had not metastasized. In each, areas were readily found which were strikingly similar to the transition forms of adenoma described. Both clear and dark cells were usually present. The nuclei varied more in size and in affinity for the basic dyes. In some the nucleoli were more prominent and occasional mitoses were seen. In some areas the cord-like arrangement and papillary structure were lost and the tumor consisted of masses of less differentiated cells.
Evidence That Hypernephroma Originates from Adenoma

Grawitz in 1883 presented the theory that hypernephromas develop from adrenal rests. This gained wide acceptance for a time, but was soon disputed by Sudeck, Stoerk and others. Stoerk suggested the following sequence: contracted kidneys—cyst formation—papillary cystadenoma—hypernephroma. Zehbe held similar views and thought that hypernephromas were derived from adenomas. Nobiling noted that malignant tumors of the kidney were frequently associated with benign tumors and cited a case in which one kidney was the seat of miliary adenomas, while the other contained a hypernephroma. Both Gray and Creevy have described adenomas of the kidney presenting a structure similar to hypernephroma. Judd and Grier think that adenomas of the kidney belong to the hypernephroma group and that they tend to become malignant.

The age incidence of adenomas closely parallels that of hypernephromas. The average age incidence in our series of adenomas was sixty-two years. In Nuernberg's series of 66 cases, it was sixty-one years. The average age incidence of 108 cases of hypernephroma collected from the autopsy records of the University of Minnesota was sixty-one years. Paschen collected 268 cases and found the greatest incidence in the fifth decade, while Gasparian in his series found the highest incidence in the sixth decade.

Presumptive evidence for the origin of hypernephromas from adenomas lies in the fact that very early hypernephromas are seldom found. We have no examples measuring less than 1.5 cm. in diameter. Tumors smaller than this, while occasionally having the gross appearance of hypernephroma, in-
variably belong to the adenoma group. It must be admitted, however, that the border line between the two groups of tumors is arbitrary.

**Discussion**

It has been pointed out that adenomas of the kidney occur most frequently in kidneys which are the seat of vascular disease. They also occur with the greatest frequency in the advanced years of life. These facts suggest that adenomas are the result of a proliferative reaction on the part of the tubules, which have been cut off from their primary blood supply. Papillary cystadenomas arise in the following manner. After occlusion of the afferent arteriole, the glomerular tuft becomes avascular. In the majority of instances the corresponding tubule undergoes atrophy, but occasionally it continues to grow and becomes hyperplastic. This change is dependent upon a renewed blood supply. As a result of hyperplasia, epithelial folds are produced which project into the lumen, converting the cystic tubule into a papillary cyst. Connective tissue of the renal stroma grows into the epithelial invaginations, forming a supportive stalk. These processes branch and rebranch to give the characteristic papillary cystadenoma. Growth, which is of the central expansive type, converts the tumor into a solid structure. As the tumor compresses the adjacent renal tissue, a fibrous capsule develops. The connective tissue of the papillary processes may fail to be carried along with the proliferating epithelium, leaving the cells lying in long cords. Occasionally masses of budded-off epithelium differentiate into tubules. These processes account for the variations in structure observed in the larger adenomas. Hydropic degeneration is prone to occur in the larger adenomas. The scattered distribution of the hydropic cells in the central portions of some adenomas suggests that deficient oxygen may be a factor. This does not appear to be the only factor. Large adenomas of the papillary type may show areas in which the structure is indistinguishable from that of hypernephroma. This type of adenoma represents a true transition stage. The similarity in structure between certain early hypernephromas and large papillary adenomas supports the theory that hypernephromas develop from adenomas.

**Summary**

Adenomas of the kidney occur most frequently in adults over fifty years of age. They are found most commonly in kidneys which are the seat of vascular disease.

Papillary adenomas arise from the epithelium of hyperplastic tubules and cysts. The hyperplastic tubules and cysts are found in areas of vascular occlusion and their development appears to be dependent on the reestablishment of a blood supply.

Growth of papillary adenomas may result in the formation of structural variations which are similar to the structure of certain hypernephromas. Transition forms of papillary adenomas have been described in which a structure indistinguishable from hypernephroma is present. A similarity in structure has been pointed out between some of the early hypernephromas and large
adenomas. The available evidence seems sufficient to justify the conclusion that some hypernephromas develop from papillary adenomas.

Bibliography

C. A. Kaemmerer & Co.
WEICHELBAUM AND GREENISCH. Cited by Ewing, p. 782.