A case of secondary hypernephroma of the iris and ciliary body / Burton Chance.

A CASE OF SECONDARY HYPERNEPHROMA OF THE IRIS AND CILIARY BODY.*

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PHILADELPHIA.

The man whose history is here detailed came under my observation first in the wards of the Germantown Hospital on Oct. 11, 1905. He had had hemorrhoids, and Dr. C. A. Whiting had operated recently for the removal of them. The house surgeon, Dr. Markle, called my attention to the man because of there being, as he supposed, a growth in the left eye.

At the time I made my examination the patient was in what he deemed his usual good health and suffered only from his rectal disease. In the month past he had been annoyed by obscuration of his sight, especially of the left eye, though that eye was neither painful nor tender. I discovered on his body, beneath the skin, over the region of the costo-cartilaginous junctions on the thorax, several nodular enlargements. These masses were movable and reminded me of the enlargements of the cervical glands common in constitutional syphilis. In the left groin there was a large bubo.

Arising from the middle pillar of the iris of the left eye, and on the horizontal meridian, was a spherical tumor, mottled gray in color and approximately 4 mm. in diameter. No signs of inflammation were present. On the nasal side of the globe were several leashes of dilated blood vessels which were arranged triangularly with the base at the limbus. The tumor was flattened against the posterior membrane of the clear cornea.

The iris presented no other abnormality. The pupil was round, about 4 mm. in diameter and changed freely to various stimuli. By oblique illumination no defects in the lens were noticed. The anterior chamber was of the depth of that of the fellow eye; the tension being only slightly raised above that of the right. No tenderness was elicited.

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The right eye presented no anomaly. Vision of the right equaled 6/6, of the left 6/30, Snellen. The iris contracted when a solution of atropin was instilled, and the pupil was broken by the projection of the mass into the pupillary space.

The tumor appeared to rise from the radiating muscular fibers. There was but slight protrusion backward, the base therefore was buried in the pigment layers of the iris; the anterior surface was flattened against the endothelial membrane of the cornea. It was globular in outline though somewhat nodular in conformation and was attached to the iris by

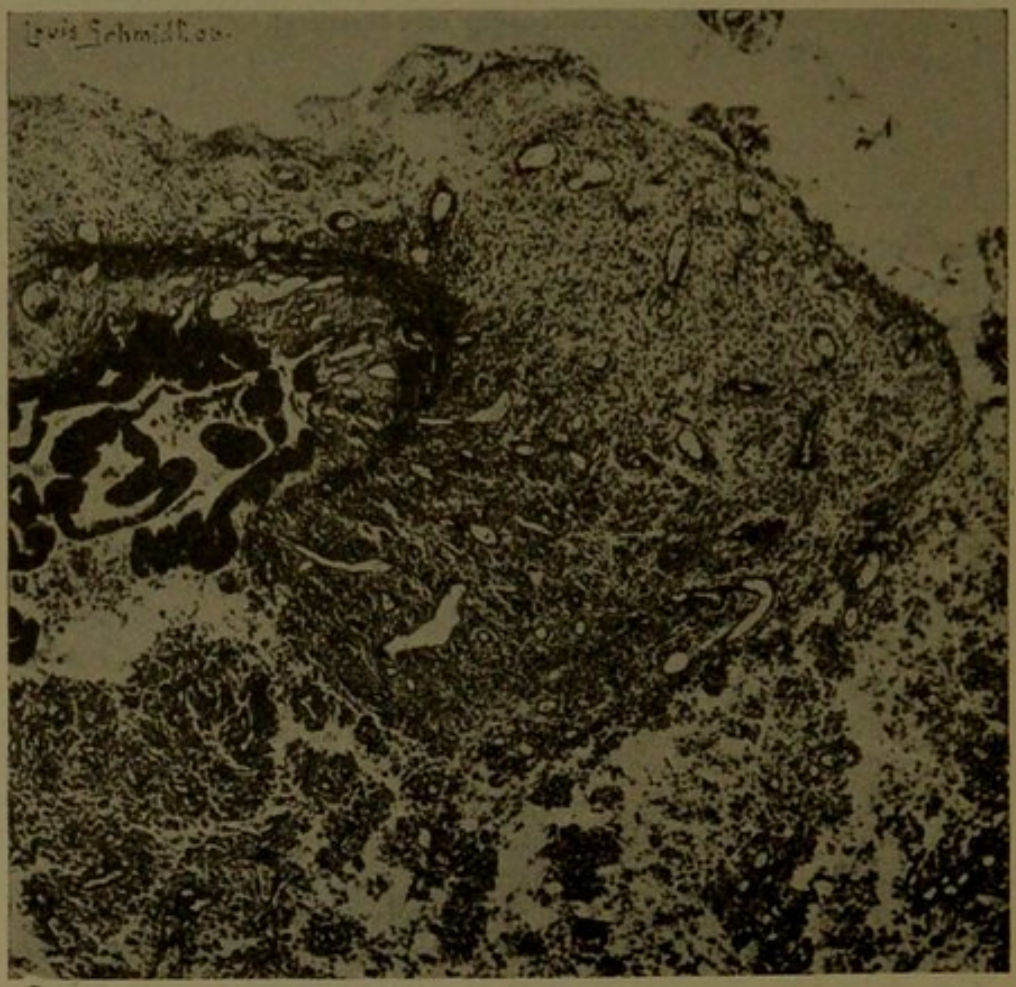

Fig. 1.—Section of iris tumor. Secondary hypernephroma.

a short broad pedicle. It resembled the small granulomata frequently seen in the conjunctiva at the apex of the socket remaining after an enucleation. The tumor was highly vascular, the fine loops giving a pink stippling to the grayish-yellow color of the denser portions. The lens was clear; the vitreous had begun to disorganize, for there were large floating masses in it, while more deeply situated was the semblance of "brick dust" deposit. The optic disk was round; its upper border whole, while about the lower was a wide, sharply-cut conus.

This conus I conceived to have been formed by an axial distension rather than to have been a part of a general inflammation of the choroid that was present in other parts of the fundus, and because the refraction of the eye was measured by a minus 4 D lens. The choroiditis was of comparatively recent origin. The macular region was not affected. The retinal epithelium was markedly absorbed; the outlines of the tortuous vessels were blurred, but no hemorrhages were noted.

The patient, aged 40, stated that shortly before admission to the hospital his attention had been called to the presence of a small lump in his eye. This lump, he was certain, had increased in size rapidly though it never had been painful, neither had the eye been inflamed. In the spring of 1903, this eye had been struck with a small stone. The man said that he applied for treatment at the Wills Hospital. The injury must have been slight and the symptoms transitory, because only a simple lotion was prescribed and he was advised to report again to be fitted for glasses. His recollection of the examinations made of his eye at that time, were not strong, yet he remembered that his condition was such as to occasion comments from the surgeon in charge and his staff to several visitors present in the clinic. It may be presumed, however, that no unusual growth was perceptible then, for the man would have had the recollection of an allusion having been made to it had such a thing been noticed. I have not been able to find any record of such a case as this at the Wills Hospital; therefore the antecedent history is uncertain.

The man was a carpenter; married and had three children. His childhood had been healthy; in adolescence he had a simple attack of typhoid fever. In 1902 he became infected with syphilis. He was not treated for this disease, for, shortly after noticing the initial lesion of it, he was arrested for drunkenness and loafing and was committed to one of the penitentiaries. He declared to me that he was refused treatment by the resident medical officer of that institution. After serving his term he returned to his work, but even then he had had only the most irregular kind of treatment. No member of his rather large family had a history of consumption or of tumors.

I suspected this to be a case of sarcoma of the iris, yet in view of the general history, I did not forget to consider the probability of there being a specific element in the genesis of the tumor. Accordingly, for 5 days, the ointment of mercury was vigorously applied thrice daily. At the end of this course there was a perceptible softening of the subcutaneous tumors, but that of the iris remained unaffected.

A few days later, when the eyes were examined again, there were evidences of cyclitis in the left. The sclera was

faintly injected and numerous precipitates were lodged on Descemet's membrane. In the right eye were signs of active chorioretinitis, though the blue iris was healthy. By October 20, the ciliary injection had increased considerably, while the tumor appeared to have spread out slightly, and to be less closely applied to the cornea. Also, it had become distinctly lobulated and irregular in outline. I believed that I had to deal with a very active and malignant process. The patient refused to have the eyeball removed, but on October 23, after inventing many pleas by which to escape from the hos-

Fig. 2.—Section of iris tumor.

pital, he at last consented to an operation for the removal of the tumor. I removed the tumor by a wide iridectomy. The incision was made with a broad keratome in the nasal limbus. As the space between the limbus and the tumor was small, and as I feared to lacerate the tumor, I withdrew this knife and lengthened the incision by lateral strokes with a narrow angular blade. This part of the operation was prolonged by a very annoying hemorrhage. With a many-toothed capsule forceps, I caught up as much of the surrounding iris as could

be grasped, and withdrew the entire mass with the tumor and excised it with spring scissors. Great and prolonged hemorrhage followed. Much of the effused blood escaped from the anterior chamber after the wound was flushed with boracic acid solution. The toilet of the wound, however, was performed satisfactorily, after which I applied a light compress over each eye and then bandaged both.

Seven hours later the patient was resting comfortably, and when the dressings were removed early the next morning only slight operative reaction was present. The wound had closed and the chamber had reformed. Atropin was instilled and the bandages were reapplied. The eye soon healed. The edges of the coloboma were adherent to the lens capsule. This synechial attachment in all probability had existed prior to the operation, for it was with difficulty that the iris could be caught into the jaws of the forceps, and doubtless this lack of resiliency occasioned the profuse hemorrhage that followed the excision of the iris. The lens was clear, though there were several clumps of pigment on the capsule. In about two weeks the patient was discharged from the hospital.

In order to study the histology of the tumor the specimen was intrusted to Dr. C. M. Hosmer, of the Medical Laboratories of the University of Pennsylvania, who prepared for me many beautiful sections from almost the entire tumor, which he has stained by a variety of methods.

The tumor springs from the anterior surface of the iris, and the site of it occupies the middle portion of the section which was excised. The normal tissues about the base of the tumor are destroyed by the infiltration of the tumor cells. The outer portion of the iris is apparently uninvolved and the sphincter remains intact.

The tumor is without a capsule or other limiting membrane. The substance of it is composed of numerous thin-walled blood vessels and spaces which branch in many directions in the midst of cellular elements. In the iris stroma are a few vessels having normal coats, yet elsewhere, the vessels or spaces are formed by channels, with thin coats of fibrous connective tissue, lined with endothelial cells which are in the process of proliferation. (Fig. 1).

The cells are arranged in layers. They are large and present a variety of shapes, passing from the columnar, when next the blood vessels, to the polyhedral, oval or round, according to the pressure made on them as the periphery of the tumor is approached. In the iris stroma the cells are not clustered about the vessels but are more generally distributed. (Fig. 2).

The individual cell is composed of fine granular protoplasm and a large nucleus with a distinct nucleolus. The cells are evidently multiplying rapidly, for, in many of those lying nearest to the vessels there is more than one nucleus, each with its own nucleolus, though no karyokinetic figures are

discerned. At a distance away from the vessels, too, the nucleolation is seen, yet here the protoplasm has become vacuolated as though degenerative processes had set in. At that time, judging from the character of the cells and of their arrangement about the vessels, the growth was regarded as a perithelial sarcoma by Prof. Allen J. Smith, of the University of Pennsylvania, to whom I showed the slides.

I saw the patient at various times subsequent to his leaving the hospital. Within the week of his discharge he was committed to the House of Correction on the charge of vagrancy. This was early in November. He was released on

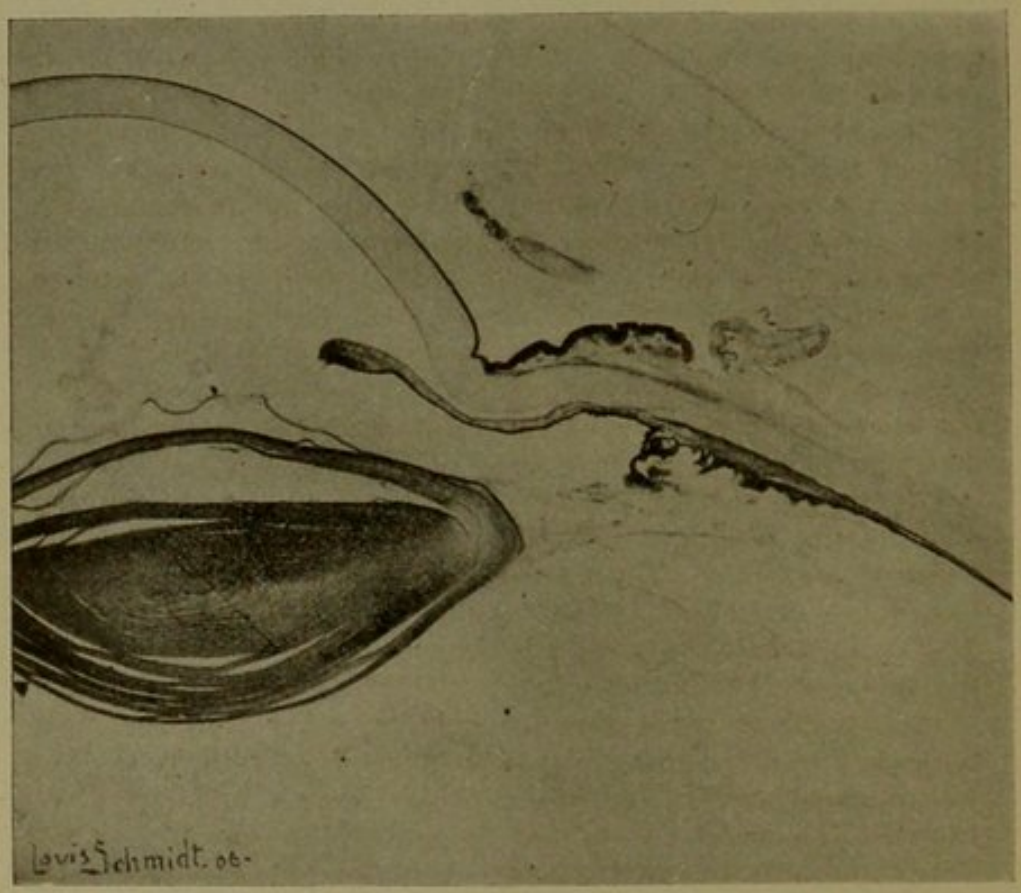

Fig. 3.—Involvement of ciliary processes.

December 22. I visited him there. During his confinement specific remedies were administered to him and he soon gained in weight. In the week following his release from the hospital, my records show that the cornea continued clear; the sclera was without injection; the cicatrix was absorbing; the anterior chamber deep and the aqueous free from precipitates. The iris coloboma had become quadrate rather than triangular because of the adhesion of the pillars to the lens capsule. The remaining portion of the iris was healthy and responded to the action of atropin. The lens was unclouded and the state of the vitreous unaltered. The nerve head had become swollen and it was impossible to study its features in detail. The

choroidal inflammation was extending in all directions. The condition of the right eye remained unchanged.

Early in January, 1906, the man's testicles had become somewhat enlarged and he complained of pain and heaviness. I referred him to Dr. Hilary M. Christian. Later, he turned up in Dr. Christian's ward at the Philadelphia General Hospital, where he was treated with anti-syphilitic remedies. While there, a number of small nodes were noticed lying beneath the skin on his thorax, like those I had discovered while he was under my care. These softened and became smaller when mercury was pushed, in the same manner as those which I have already described. Several of them were excised, and pronounced sarcomata by Dr. Rosenberger, pathologist of the hospital.

On January 26, the man was anxious for me to see his eyes, and he asked to be allowed to come to me. To all appearances the ocular conditions had not changed; but on February 1, he came again, complaining of intense pain in the left eye. There was a small foreign body on the cornea, but, in addition, the cornea was steamy and surrounded by a ring of ciliary injection, while the iris was obscured by the turbid aqueous. The tension was not elevated. I removed the foreign body and bandaged the eye after instilling solutions of cocain, dionin and atropin. Four hours later the symptoms had not abated.

A day or two later, I was informed that he had returned to Blockley, but this time he entered the Eye Wards. On February 7, I was invited to visit the patient through the courtesy of Dr. John Welsh Croskey, the alternate of Dr. Charles A. Oliver who was unable to serve at the hospital because of an illness.

The patient's ocular symptoms had become more profound. There was greater injection, greater cyclitis, haziness of the lens, a more clouded vitreous and an indistinct fundus. The intraocular tension was elevated, and yet the tension of the right eyeball was equal to that of the left. The man lay curled up in his bed; he had lost weight, and presented signs of cachexia. In the days following, the pain increased so greatly that he begged for the removal of the eye, fearing the right eye might become similarly diseased.

On Saturday, February 17, Dr. John Welsh Croskey removed the eye, and the large inguinal gland also; he most kindly gave the specimens to me. The globe measured 25 mm. in the anteroposterior diameter, 23.5 mm. in the vertical, and 23 mm. in the transverse. It had been most cleanly dissected from the socket; the sclera being smooth, and the attached nerve, which measured 6 mm. in length, appeared healthy. No tumor was detected in the globe by transillumination, and on section of the globe no evidences of a neoplasm were apparent. The vitreous chamber contained a shrunken

mass of vitreous, the retina had been detached pathologically, and the nerve was swollen. The cornea had become clouded; the anterior layers of the iris were covered with a grayish exudate and the lens had become cataractous and was dislocated toward the nasal side. Dr. Harold Goldberg, pathologist of the Wills Hospital, prepared the globe and stained several sections in the usual double stains. The globe had been divided horizontally, in order that the region of the coloboma might be included in each of the sections which were taken from the upper half of the globe. Study of these sections

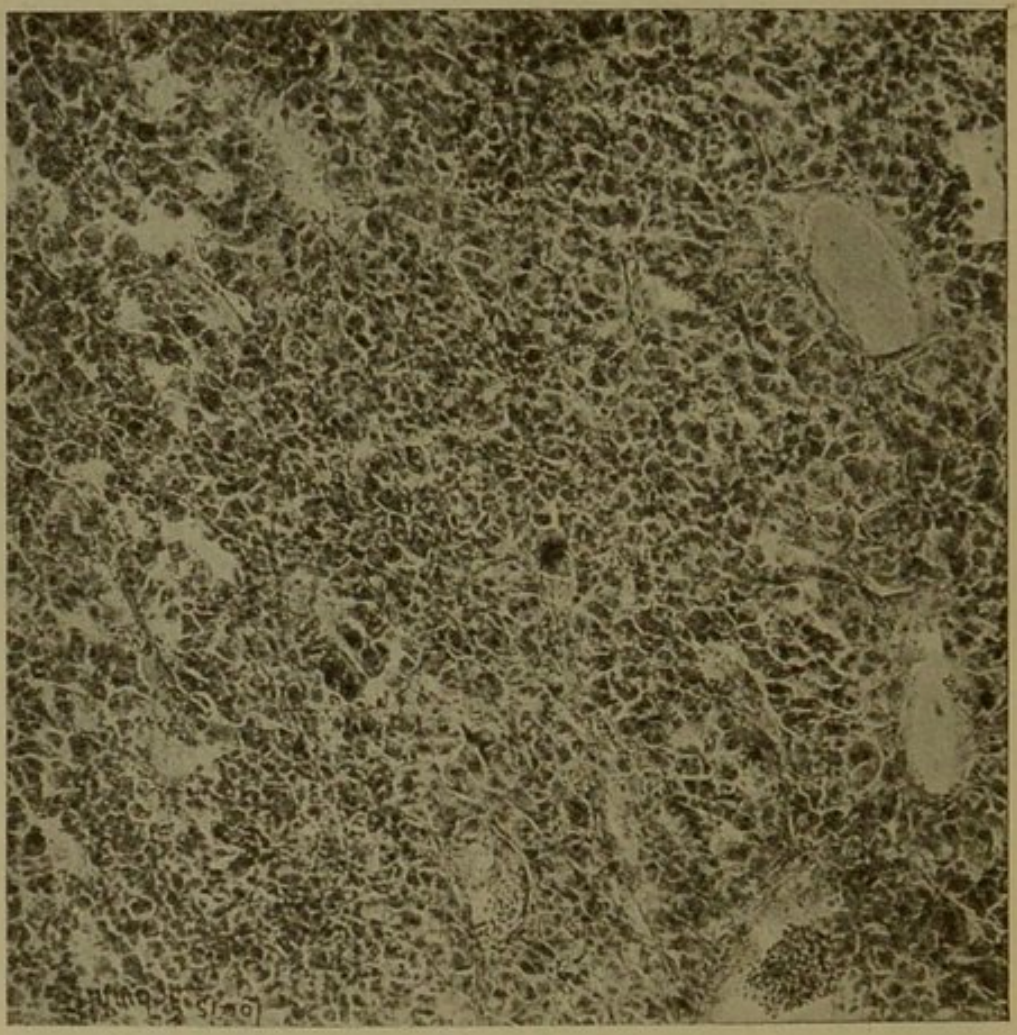

Fig. 4.—Original tumor—from kidney.

elicited the following details: Except at the sclerocorneal junction, where there is a moderate leucocytic infiltration, the cornea is not affected; and polymorphonuclear leucocytes occupy the angles of the anterior chamber and extend over the surface of the iris. Newly proliferated connective tissue cells have invaded the stroma of the iris. The lens is dislocated, its capsule is separated, its fibers shrunken and opaque. The ciliary body is atrophic; the inner surface is covered by

a leucocytic exudation; the pigmentation is excessive and the endothelial cells have proliferated greatly.

In addition to the changes described, the processes have been destroyed by a papillary new growth, composed of small round cells with deeply stained nuclei. The growth extends into the vitreous chamber; some of the cells have escaped and have been caught in the shrunken and degenerated vitreous. There are no signs of the new cells having invaded the choroid which has become atrophic while the pigmentary elements are prolific. The fiber layer of the retina is thick. The retinal vessels are greatly enlarged and engorged with blood and leucocytes. The nerve head is swollen; the fibers atrophying from the leucocytic infiltration, and the endothelial cells are increasing. In Dr. Goldberg's opinion this ciliary neoplasm is a small round celled sarcoma in which there are signs of melanotic changes. (Fig. 3).

In the latter part of March the patient returned to the Germantown Hospital. He was emaciated and weak. The orbital socket had remained healthy. The right eye showed evidences of advancing choroiditis. On April 17, he showed violent symptoms of acute intestinal obstruction. Dr. Francis Stewart opened the abdomen and discovered a long intussusception in the ileum, which he reduced. The abdominal viscera were studded with neoplastic formations. The position of one of these tumors was such as to effect an invagination of the intestinal tube. The patient rallied from this shock. About May 10, the abdominal wound burst; a day or two after, the intestinal wall ruptured and a fecal fistula became established.

In the second week in May I took all of my preparations to Professor Smith; he had not seen the sections of the subcutaneous nodules. These nodules have a distinct and fatty capsule. The growth is made up of large flat cells in which are large nuclei, though many contain nucleoli and some are multinucleated. The cells are divided into masses by dilated alveolar walls. These walls are almost completely made up of capillary blood vessels. Dr. Smith thought this tumor resembled the tumor found in the iris and he believed it to be an endothelioma. A day or two later, however, while studying the three different specimens, and comparing them in detail, a diagnosis of hypernephroma was made, and Dr. Smith urged that in the event of an autopsy, special care should be given to the examination of the kidneys and neighboring structures, with the expectation of finding such a primary growth. On Monday, May 21, the patient died.

Thus ends the clinical history. I believed that I had been dealing with a case of primary tumor of the eye. The diagnosis has been reversed completely by the findings just indicated, and in the examination of the tissues after death.

Death was caused by an intussusception of the ileum.

This intussusceptum is a couble one, one portion being directed upward and the other downward. The apices of the two intussuscepta meet in the lower part of the mass. Each apex is formed by a tumor, the larger being 3.5 cm. by 3 cm. in size, sufficient to have caused a partial obstruction in the intestine, and thus to have facilitated the invagination of the gut. On the inner surface of the intestine are many tumors, in size varying from 1 mm. to 2 cm. In the mesentery are a number of enlarged glands and tumor nodules, ranging up to within 1 cm. in diameter. None of the abdominal organs contained these nodules except the left kidney. In the envelop of this kidney are 8 or 10 small tumors, the largest about 1 cm. in diameter. Most of these masses are nodular, reddish-gray in color, and very much resemble the appearance of the tumor found in the iris.

At the lower pole of the kidney, and protruding from it, is a rounded tumor, from 3 to 4 cm. in diameter. This tumor involves the kidney though it is surrounded by a distinct capsule; the gross appearance is like that of the other tumors already noted. At the upper end of the pelvis, in the substance of the kidney, is a smaller mass resembling the larger one, though it has not so definite a capsule. The right kidney is not involved, except in the perirenal fatty envelop where are a few small secondary nodules. The suprarenal bodies are not affected. The portions of the lungs removed from the thorax do not contain any neoplastic formations; neither were any found in the heart.

The sections from the kidney show that organ to have been changed but little. The tumor is divided into long narrow alveoli by delicate fibers and branching blood vessels. In some fields the blood vessels or spaces seem to be the only marks of division. This alveolar arrangement strongly suggests the fascicular zone of the suprarenal gland. The cells, which are epithelioid in type, vary much in size and shape; being polyhedral, oval or rounded according to the pressure made on them, and they seem to spring from the septa, forming distinct mantles about the blood vessels. The cells have much homogeneous protoplasm and a large nucleolated nucleus. Neither here, nor in any of the sections examined subsequently, were any of the coarse granules commonly met with in functionating adrenal tissues seen. The size of the nuclei is irregular; in several instances the nuclei occupy nearly the entire cell, and in others, the cells are polynucleated. In Professor Smith's opinion, the general appearance of the specimen corresponds with that of a hypernephroma. (Fig. 4.).

The intestinal growth involves the submucosa. Its histologic appearance is exactly like that of the renal tumor. The basal cells are more densely packed than those at the periphery, where also the mantles about the vessels are pronounced. A

section from the mesentery displays features common to the other nodules.

The sections of the subcutaneous nodules and of the inguinal gland have been prepared with less care than the others, and they present artefacts, yet, except for minor distinctions, their characteristics correspond to those of the structures already described.

The tumor of the ciliary body is regarded by Professor Smith as identical with the others. The cells spring directly from the surface of the processes. They are not supported by an intercellular stroma, but in several places are seen delicate outgrowths of fibrous tissue in which are blood vessels about whose thin walls are grouped the tumor cells. The retina is involved near the equator, the cells being confined to the inner layers. They are closely packed about the narrow blood spaces and they are smaller and apparently younger than the cells found in the iris and the ciliary processes. In this specimen the polynucleation is marked. The iris tumor bears a strong likeness to the gross structures of the other tumors. The central, basal part is dense, while the peripheral portions are loosely arranged in indefinite and coarse branches. Under higher powers the central portion is alveolated, while the peripheral is composed of thin-walled vessels surrounded by the layers of cells.

Having these sections before us one after another, we may safely declare that we are dealing with a case of hypernephroma. The primary tumor developed from an adrenal rest in the left kidney. The secondary metastasis has been conveyed by the blood, although the deposits in the mesentery might have been carried there by the lymph stream as well as by the blood.

The term hypernephroma is applied to tumors arising from suprarenal glandular tissue. It is of recent origin and was used for the first time in 1896 by Birch-Hirschfeld.[1] The genesis of these tumors was not understood before 1883, and they were called by many different names, as lipoma, sarcoma, adenoma, angioma, endothelioma, etc. In that year Grawitz,[2] in his paper, "The So-called Lipoma of the Kidney," described their real character as arising from the suprarenal tissue, whether in the normal position in the gland or from aberrant fragments found in other organs and known as "adrenal rests." The term is not applied to growths in the suprarenal itself, but to those arising from the "rests" located elsewhere.

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1. Lehr. d. Path. Anat., V. Aufl. I. p .262. 1896.
2. Virchow's Archiv. f. Path. Anat., 1883, xciii, p. 39.

Notwithstanding the statement to the contrary, these tumors can not be rare; general surgeons are reporting hypernephromata with increasing frequency; indeed, since the death of my patient, I have learned of several recent cases, and in the literature of malignant tumors of the kidney they have been found to be very common. The embryologic development of the suprarenals is in close relation to that of the primitive kidney and of the sexual organs; it is not to be wondered at, therefore, that particles of this glandular tissue should be found misplaced in the kidney, or elsewhere, having been located as "rests" in new situations.

The degree of their malignancy, from the onset of the symptoms to a fatal termination, is very great and varies from 6 weeks to 3 years, although in some instances there has been no malignancy at all, and the tumors have been found only by accident in postmortem examination. The malignancy is shown by an invasion of the kidney and contiguous organs, or by more distant metastasis. The mode of metastasis is conceded to be by the venous circulation through the medium of the renal vein and the vena cava. Although the period between the death of the man and the presentation of this communication has been very brief, I have done all that I could to search through the literature on this subject. I have not been rewarded by finding the report of an instance in which the metastasis has extended to the eye. It is doubtful whether an accurate diagnosis of hypernephroma can be made before an exploratory operation. The most important symptoms are hematuria, renal colic and the detection of a tumor. All these may occur together, any one may occur alone, or, as in the case we are studying, they all may be absent. The general symptoms, consisting of asthenia, depression and emaciation, were distinctly marked, however, in this case. I could not describe the rapid change in this man's health in other terms than by the comprehensive one of "cachectic."

It is quite impossible to guess how long the process had existed in this man. It is not unlikely that it was a hyphema that the surgeons noticed when he went to the Wills Hospital in 1903, and it is conceivable that such an effusion might have been caused by the lodgment of an embolus in an iridic vessel. Hypernephromata, in the sense of their being adrenal rests, may arise in early

life, then lie dormant for years and develop rapidly with fatal effects after 40 years of age.

The microscopic characters of the tumor and of the metastatic deposits described in this paper are fairly representative of the histology of hypernephromata, and I may not here enter into any discussion of the histogenesis of this class of tumors. For those who wish to investigate the subject I will refer them to the singularly comprehensive studies of Aloysius Kelly[3] and to the more recent contributions of Hoche,[4] Albarran and Imbert.[5] In a report of two cases by Keen, Pfahler and Ellis,[6] a summary of the present status of the subject is given and a complete bibliography is appended to their paper.

It must be admitted that the opportunity to study this case is an unusual bit of good fortune. To all who have been associated with me in it I can only express my most sincere thanks for their courtesy to me and for the pains they have taken in the preparation of the data. I must express my indebtedness to Professor Smith for his kindly interest and helpfulness, without which it would have been impossible to have completed this paper.

There has now been presented a complete history of a case which at the beginning appeared to be one of a primary tumor of the eye, with a probable convection to the internal organs. Examination after the death of the subject shows that the process was the reverse, and the further study showed that it was of unusual pathogeny, with manifestations in an organ not hitherto mentioned as having been the seat of a secondary invasion by such a tumor.[7]

The result of this study leads me to wonder what a thorough examination of the internal organs in cases of ocular tumors with fatal metastasis might lead to if it were possible to follow the cases to necropsy. In analyzing the histories of primary tumors of the eye, the records show that it has not always been possible to do this. The relations, therefore, as to cause and effect, between

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3. Phila. Med. Jour., 1898, July 30.
4. "Les Lesions Du Rein," Paris, 1904.
5. "Les Tumeurs Du Rein," Paris, 1903.
6. Trans. Coll. of Phys., Phila., 1904, p. 251.
7. Dr. Verhoeff has called my attention to the report of a case of epithelial tumor of ciliary body published by R. Schlipp of Wiesbaden, in v. Graefe's Archives, 1899, xlviii, p. 353. Schlipp presumed that he was dealing with an unusual form of endothelioma; but, studying his paper in the light of my own case, I am convinced that the tumor he described was an hypernephroma. The patient was a young girl.

the ocular tumors and the internal growths have not in all cases been defined. May it not be true, then, that many instances of so-called primary tumors of the eye which come under the observation of the ophthalmic surgeon, and in which the opportunity for a confirmation by autopsy has been lost, are, in reality, secondary to some concealed primary growth?

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