THE RESULTS OF THE APPLICATION OF SPECIAL HISTOLOGICAL METHODS TO THE STUDY OF TUMORS.\textsuperscript{1}

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Plates XXXIV–XLVII.

The report which I have the honor of presenting to-night before this society on "The Results of the Application of Special Histological Methods to the Study of Tumors"\textsuperscript{2} is a continuation of work reported in 1905 under the title of "A Contribution to the Classification of Tumors."\textsuperscript{3} The results thus far obtained are of unequal value. Some groups of tumors have yielded much of interest, other groups little or nothing. I shall, therefore, limit what I have to say to those tumors which have proved of special histological interest. I shall first state briefly what has been found and then by means of lantern slides made from photomicrographs and drawings demonstrate visually as far as possible the same results.

The histological methods most used have been two, staining with phosphotungstic acid hematoxylin and with the anilin blue connective tissue stain after fixation in Zenker's fluid. In certain cases other fixatives and other stains have been employed. The value of these two staining methods is that they demonstrate clearly and sharply the fibrils which characterize certain cells and thereby render them easily recognizable. In the course of this work it has been found imperative to employ perfectly fresh tissue whenever possible, that is, tissue obtained at the operating table, cut into slices one to three millimeters thick, and placed immediately in the fixing solution. Zenker's fluid was found to be the best fixative for nearly all purposes. Formaldehyde proved

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The Study of Tumors by Histological Methods.

of little value. Most of the tumors on which this report is based were placed in fixatives within two seconds to ten minutes after removal from the body.

The aim of this study of tumors has been to render simpler and more exact if possible than is at present the case, the histological classification of tumors. The histological classification is the one used in distinguishing and grouping the cells of normal tissues. It depends on the differentiation of cells and of the secretions and intercellular substances produced by them, and is the only practical method available for tumors unless the cause or causes of them should be discovered; then an etiological classification might be possible.

A histological classification of tumors demands a careful study of normal tissue elements in order to discover as far as possible how one kind of cell differs from another so that the same points of distinction can be applied to tumors. The obvious reason for this study of the normal tissue elements is the well known fact that tumor cells tend to differentiate more or less perfectly like the normal cells to which they are related. This differentiation of cells in their cytoplasm and intercellular substances is seen especially in the slower growing and older parts of a tumor where, perhaps, the supply of nutrition is not so abundant as to favor rapid proliferation. The method of study indicated here is not new. The only credit that can be claimed in this work, is, perhaps, a more rigid application of well-known principles and the use of some newer histological methods.

Much still remains to be done even in this narrow field of the histological classification of tumors, but it is a subject which is fundamental and useful in many other lines of tumor work. It calls for intelligent cooperation on the part of clinicians and pathologists. The latter are helpless without material with which to work, and that material must be obtained perfectly fresh, not brought to the laboratory in dry gauze or cotton twenty-four hours after removal, or placed whole in a minimum of weak alcohol, or of formaldehyde, or even of carbolized water or common salt solution. The clinician with his control of material and his knowledge of the histories of cases has in his power the
opportunity to prove of great aid to the advancement of this branch of medical research. The pathologist for his part must realize the possibilities of more exact diagnosis and replace as far as he can such indefinite terms as spindle cell sarcoma, round cell sarcoma, and perithelial angiosarcoma, for example, with more exact terms, for each of the tumors thus characterized may originate from several different kinds of cells.

The ordinary connective tissue cell or fibroblast is a flat cell with a flat oval nucleus and delicate cytoplasm spreading out in one plane. It is definitely characterized by the production of two kinds of fibrils; fibroglia fibrils which run along the surface of the cytoplasm in the direction of the long axis of the cell, are straight or gently curved in their course, and pass on apparently from one cell to the next; and collagen fibrils which lie alongside of the cell but not attached to it and are fine and wavy in appearance. These two kinds of fibrils can be readily differentiated from each other by several different staining methods. The source of elastic fibrils is not yet determined, but it is certain that they are not regularly produced by every fibroblast and, therefore, they do not concern us here.

The cells of tumors arising from cells of this type tend to differentiate like the normal cells. They are flat cells with oval nuclei and produce both kinds of fibrils. The collagen fibrils are always the more abundant and the more easily stained and recognized. They surround in equal amount all cells growing at the same rate of speed. In fibromata the fibroglia fibrils like the cells themselves are few in number. The tumors are composed chiefly of a mass of collagen fibrils. In the more slowly growing fibrosarcomata (Plate XXXIV, Figs. 1, 2 and 3) the fibroglia fibrils are more prominent, but in those in which the cell proliferation is rapid the fibrils are very delicate and are seen with difficulty except when viewed on end. In fibrosarcomata containing large multinucleated cells (Plate XXXV, Figs. 1, 2, 3 and 4) these large cells often produce coarse fibroglia fibrils, but in giant cell sarcomata, while the spindle-shaped cells produce both kinds of fibrils, the giant cells produce neither. No difference was found in the tissue ele-
ments of those fibrosarcomata in which the cells grow in broad bands and of those in which narrow bands of cells twist and twine in every direction.

In keloids the cells produce both kinds of fibrils and the fibroglia fibrils were particularly prominent in one case of rapid recurrence.

There seems to be little reason for putting the myxoma and myxosarcoma in a class by themselves. The cells produce both kinds of fibrils in abundance as can be readily demonstrated by staining a section of a well-preserved umbilical cord at term. The only essential difference between a fibroblast and a myxoma cell is that in the latter the collagen fibrils are more or less separated from each other in places by a varying amount of fluid containing mucin. These tumors should be regarded at the most as a variety of the fibroma and the fibrosarcoma.

The smooth muscle cell is a long spindle-shaped cell with a more or less rod-shaped nucleus and dense cytoplasm which stains deeply with acid dyes, especially eosin. Sometimes the cytoplasm of the cell is abundant and it tapers very gradually beyond the ends of the nucleus; at other times it is less in amount and contracts abruptly, and then continues for three or four times the length of the nucleus in each direction as a small round rod tapering to a point at the end. The outer surface or cuticle of the smooth muscle cell is striated longitudinally. These striations, termed myoglia fibrils by Heidenhain, run close together at the ends of the cells so as to form in those cells in which the cytoplasm is slight in amount and rod-like, what seem to be coarse fibrils.

The myoglia fibrils are not so regular and well defined as either the neuroglia or the fibroglia fibrils, and they undergo post-mortem changes much more quickly. As far as can be determined from stained sections and from teased preparations they are limited to the cell to which they belong. This point is not easy to determine absolutely because smooth muscle cells overlap each other with great regularity and are closely cemented together as well as being surrounded with a varying number of collagen fibrils.

In leiomyomata (Plate XXXVI, Figs. 1 and 2) the cells tend to

*Ergebnisse der Anatomie und Entwickelungsgeschichte, 1898, viii, 3.*
undergo the same differentiation as the normal smooth muscle cells, and the development of myoglia fibrils is usually equally marked. As a consequence these tumors are sharply characterized and easily recognized even with the ordinary stains because of the shape of the cells and the density of the cytoplasm with its property of staining deeply with acid dyes. The cells vary much in diameter and in length in different tumors, but that causes no difficulty in the diagnosis. In the rapidly growing leiomyomata, however, the differentiation of the cells may be slight or even in the most rapidly growing parts of the tumors entirely wanting; then a tumor may be easily called a spindle cell sarcoma and regarded as a fibrosarcoma, or sometimes on account of the shape of the cells be classified as a round cell sarcoma. Three cases of rapidly growing and clinically malignant leiomyomata of the uterus will illustrate the points I wish to emphasize.

In the first a large tumor, dense in places but soft and friable elsewhere, involved the fundus of the uterus, and smaller nodules were present in the broad ligament. Complete removal was not possible and death followed in less than three years, apparently as the result of continued growth of the tumor. In this case the new growth was composed of well-differentiated smooth muscle cells with few collagen fibrils binding them together. Mitotic figures were numerous, showing that proliferation was active. The diagnosis of a rapidly growing, probably clinically malignant, leiomyoma was easy to make.

In the second case a tumor the size of a cocoanut in the posterior wall of the uterus was connected at its base with a mass the size of an orange projecting into the lumen of the uterus. The tissue of both masses was for the most part grey, soft, and friable like a sarcoma. Microscopically the tumor showed extensive invasion of the wall of the uterus. It was composed in large part of rather large spindle-shaped cells (Plate XXXVII, Fig. 2) showing the fibrils characteristic of smooth muscle cells. Mitoses were numerous. The rest of the tissue was made up of large round and multinucleated cells (Plate XXXVII, Fig. 3) without fibrils and showing even more mitotic figures. The two kinds of cells, spindle-shaped and round, were often in close apposition in the same microscopic field, and transitions between the spindle and the round cells with slight development of fibrils were plentiful.

In a third, rapidly growing, and very vascular tumor (Plate XXXVI, Fig. 3; Plate XXXVII, Fig. 1) of the uterus the cells in places, especially where they were invading the wall of the uterus, showed well the fibrils characteristic of smooth muscle cells, but elsewhere, especially where the blood spaces were large, the cells were undifferentiated spindle-shaped cells with relatively little cytoplasm. Such a tumor could easily be mistaken for a very cellular fibrosarcoma, for it sometimes does occur in this situation.
It is well to bear in mind that slow and rapidly growing smooth muscle tumors can occur in other parts of the body than in the uterus, such as the skin and the kidney, for example, and that the rapidly growing ones can readily pass through the hands of a pathologist, on routine hurried examination, as a spindle cell sarcoma without a suspicion of its true nature. This I know from personal experience.

The cells of the neuroglia tissue occur in two forms as ependymal cells lining the neural canal and the ventricles and as glia cells which are derived from the ependymal cells and lie between and support the elements of the central nervous system. The glia cells have spherical nuclei and produce characteristically staining fibrils which run along the surface of the cytoplasm of the cell to which they belong and extend out from the cell in all directions. Weigert was unable to determine definitely whether or not the ependymal cells produce fibrils, but it is probable that, with the exception of those covering the choroid plexus, they do.

In gliomata the cells show great variations in size and shape, but they always tend to differentiate like their normal prototypes, the ependymal and glia cells. The cells may be large or small, spherical or spindle-shaped, with few or many, fine or coarse fibrils. Gland-like cavities lined with ependymal-like cells occur in many of these tumors. All these facts in regard to gliomata are so well known that I shall limit my remarks to two very unusual cases which illustrate the value of the differential stains for fibrils.

The first case has already been referred to in print, but merits mention again in this connection. It was a tumor the size of a baseball occurring over the coccyx in a woman forty-four years old. For a year it had been growing rapidly. Before that time it had existed for twenty-five years to the patient's knowledge as a nodule the size of a hickory nut. Nearly a year and a half after the first operation the patient was operated on for metastases in the right groin. A year later a third operation was performed for recurrences over the coccyx and in the right groin and for metastases in the left groin. The patient died less than a year afterwards with recurrences in all three situations and with gradually increasing solidification of one lung suggesting metastases in it but no post mortem examination was obtained.

The original tumor and the recurrences all presented the same gross appearances: large and small distinctly encapsulated nodules usually closely bound together. The nodules for the most part
were fairly firm and elastic, but a few were somewhat soft. On section the surface was grey, translucent, and for the most part homogeneous. In some of the larger nodules, however, there were irregular areas of hemorrhage and of necrosis.

While the tumor in gross suggested the appearance of a sarcoma, the structure histologically is that of a carcinoma (Plate XXXVIII, Fig. 1). It consists of large and small alveoli of cells of an epithelial type embedded in a fairly abundant connective tissue stroma. In the most rapidly growing parts of the tumor the cells in the alveoli are often round, but as a rule they are more or less oval or spindle-shaped. The outlines of the cells are usually not very sharply defined. The nuclei are round to oval in shape, vesicular in type, and stain rather lightly. They contain numerous fine and a few coarse chromatin granules, but no distinct nucleolus. Mitotic figures (Plate XXXVIII, Fig. 3) are numerous.

The remarkable feature about this case is that fibrils are present in varying number between the cells which fill the alveoli. In some places they are very abundant, but in others they are few in number. They vary in thickness, but for the most part are rather coarse. Some of the fibrils are straight, but many of them are wavy.

Sometimes the cells in the peripheries of the alveoli immediately adjoin the connective tissue stroma, but often they are separated more or less from it by a layer of their own fibrils. Sometimes these fibrils run parallel with the stroma, at other times they lie perpendicular to it and terminate in swollen ends which unite laterally to form a sort of limiting membrane, just as the neuroglia fibrils do in the spinal cord of the embryo. The fibrils in the alveoli always run parallel with the long axis of the cells to which they belong.

In some of the tumor nodules the tumor shows another type of growth, namely, it becomes distinctly papillary. The cells in such cases are arranged in one or more layers around delicate papillary stalks containing blood vessels and a little connective tissue. The nuclei are in the ends of the cells farthest away from the vessels. Between the cells are a few fibrils radiating out from the central stalk.
In the smallest inguinal lymph nodes (Plates XXXVIII, Fig. 2) which were invaded the tumor cells extend along the peripheral sinuses in exactly the same way that metastases of carcinoma do, but everywhere they produce their own kind of fibrils.

This tumor probably originated from remains of the neural canal over the coccyx. These remains, in the form of gland-like cavities, can be demonstrated to be present in most, if not all, embryos as late as the fourth or fifth month, and probably persist in many to a much later period.

This case illustrates the close analogy existing between gliomata and epithelial tumors, in manner of growth, of metastases, and of malignancy. In another glioma, situated in the fourth ventricle, there was found a somewhat similar alveolar arrangement of the cells with reference to the stroma, and combination of ependymal and glia cells.

The second case came to post mortem examination under Dr. H. C. Low at the Children's Hospital and has not yet been reported in detail. The cause of death was a glioma originating in the lumbar region of the spinal cord. It had infiltrated and destroyed the lower part of the cord and then spread to the pia and along it, forming a thick layer surrounding the cord (Plate XXXIX, Fig. 1) throughout its entire length. It had also extended in the meshes of the pia all over the cerebellum (Plate XXXIX, Fig. 2) and cerebrum. Macroscopically the lesion resembled a thick inflammatory exudation with more or less organization, or possibly a diffuse tuberculous process, and was so diagnosed.

Microscopically the tumor is composed of rather large cells (Plate XXXIX, Fig. 3), for the most part of spindle shape. In places, however, the cells are more spherical and among them occur large multinucleated cells. Mitotic figures are numerous. The cells are surrounded by fibrils of but one kind and these stain in the same manner as neuroglia fibrils.

In places the tumor has invaded the upper part of the cord and the pons, but it is especially over the cerebellum that the invasion of the underlying tissue is most evident. Here the cells have spread everywhere between the leaflets of the cerebellar tissue and have infiltrated the molecular layer, and in places have destroyed the Purkinje cells and invaded the granular layer. Over the cerebrum both the growth of the tumor in the pia and the invasion of the underlying tissue are less marked.
This case, like the preceding one, illustrates the possibility of gliomata extending and invading tissues like other malignant new growths.

In regard to the epithelial tumors I am unable at present to make any special contributions. This group of tumors is large and it requires a long time in which to obtain type specimens of each variety, preserved under the best conditions. Unquestionably these tumors should be classified so far as possible, like their normal prototypes, according to the differentiation of their cells and secretions.

The phosphotungstic acid hematoxylin stain is useful in studying them not only because it brings out with great distinctness the nuclei and centrosomes as in other cells, but also because it stains the fibrils which occur in the normal epidermis and in those tumors of which the cells tend to differentiate like the epidermal cells. It also stains the fibrils (Plate XL, Fig. 1) which sometimes occur, for example, among the epithelial cells in cancers of the breast. In addition to these fibrils it brings out sharply the cuticular membrane of epithelial cells on the side adjoining a lumen and on that account may prove an aid sometimes in distinguishing the cells of certain epithelial tumors from endothelial cells which never exhibit such a membrane.

A few of the epithelial tumors already studied deserve, perhaps, brief mention, as they suggest what more careful histological study of this class of tumors may yield.

The epithelium lining the ducts and glands of the breast and the coil glands of the skin are surrounded by a layer of spindle-shaped cells which run parallel with the long axis of these structures. These cells are better developed and more numerous in some situations than in others and show definite fibrils of the myoglia type; that is, the fibrils tend to fuse at the spindle-shaped terminations of the cells so as to form what appear to be coarse fibrils.

In all types of benign adenomata of the breast these same cells with fibrils are present behind the lining epithelium and usually can be readily demonstrated but sometimes are poorly developed. As soon, however, as the epithelium of the breast takes on malig-
nant properties and begins to invade the surrounding tissue this row of smooth muscle cells disappears although the type of tumor may be typically glandular, and the epithelial cells then abut directly on the connective tissue of the stroma.

In epidermoid carcinomata the development of epidermal fibrils is often more extensive than in the normal skin and resembles closely the abundant formation of these fibrils often found under conditions of inflammation. In the type of carcinoma of the skin called non-cornifying by Ribbert and popularly known at present as carcinoma basocellulare, epidermal fibrils are usually present in small numbers as well as small, poorly developed epithelial pearls. The cells of this type of carcinoma resemble in their more or less elongated shape, small amount of cytoplasm and slight production of fibrils, the epithelial cells of hair follicles more than those of the surface epidermis and may represent differentiation like them.

In carcinomata of the breast straight and wavy fibrils (Plate XL, Fig. 1) are not infrequently found singly and in small clumps running between the epithelial cells. They are in no wise connected with the fibrils in the surrounding stroma. In the alveoli of some of the carcinomata of the breast numerous small cavities form between the cells and the edges of these cells develop a distinct cuticular membrane.

The stroma of carcinomata shows more of interest with the two staining methods employed than the epithelial cells themselves. As is well known the stroma is sometimes proliferating very actively and contains numerous fibroblasts in which mitoses can occasionally be found. In other cases the cells of the stroma show little or no activity and consist of a few fibroblasts surrounded by many collagen fibrils. Often these two conditions are found closely associated in the same tumor. When the fibroblasts of the stroma are active, fibroglia fibrils (Plate XL, Figs. 2 and 3) are found in great abundance; in the dense often hyaline parts they are few in number.

Occasionally great masses of fine and coarse elastic fibrils surround the ducts and the blood vessels in cancer of the breast. In the midst of these masses occur a few irregular cells surrounded by fibroglia fibrils. It would scarcely be justifiable, however, to conclude from this relation that these cells have developed the mass of elastic fibrils around them.
In a case of chorionepithelioma (Plate XLI, Figs. 2 and 3) of the uterus, where a diagnosis had been made and an assistant was able to be present at the operation and preserve the tissue immediately after removal, nothing in the way of fibril formation could be found in the tumor cells, but in the smooth muscle cells, especially those nearest the tumor, the myoglia fibrils were unusually numerous and coarse.

In one instance of cancer of the breast in which proliferation was very active the tumor cells seemed to have gone wild. Many of them were very large and often multinucleated. Single and multiple mitoses were present in great numbers. The centers of some of the large alveoli were hollowed out and filled with fluid in which cells in mitosis floated free. In places the stroma between the alveolar masses was invaded and overwhelmed by the tumor cells which were unusually large and showed many mitotic figures. Such places might suggest to some the transformation of a carcinoma into a sarcoma.

Another tumor, very recently received, bears more directly on the question recently raised in connection with the inoculable tumors of rats and mice, of the possibility of the transformation of a carcinoma into a sarcoma. The case is one of solid tumors of both ovaries with metastases in the omentum. Sections show in places a typical epithelial type of growth; definite alveoli filled with cells and in places glands lined with cuboidal epithelium. In other places the cells are of spindle type and are arranged in bundles which run in all directions. These cells give rise to fibroglia and collagen fibrils. Among these cells are other large, pale cells with eccentrically situated nuclei and with the cytoplasm transformed into a pale homogeneous material. The tumor probably represents an embryoma with slight differentiation of its cells, possibly the mesoblastic layer alone with the cells differentiating in part like the mesothelium, in part like the mesenchyma.

The study of certain epidermoid carcinomata, especially of the tongue and lip, are of interest in connection with the question of the possibility of the disappearance and cure of these tumors. Two cases in particular show marked invasion of many parts of the tumor by endothelial cells (Plate XLI, Fig. 1), many of which
have become transformed into foreign body giant cells. They are attracted by the cornified epithelial cells which they incorporate and gradually dissolve. The tumor cells in these areas often disappear and there then remain large masses of endothelial and giant cells. They, together with more or less reaction on the part of the surrounding connective tissue, often present a picture which resembles more or less closely tuberculous tissue or even a giant cell sarcoma.

The tumors arising from endothelial cells have proved interesting from the fact that these cells possess negative rather than positive characteristics, and yet they have some distinguishing features of their own. By endothelial cells I understand those cells of mesenchymatous origin which line the blood and lymph vessels, the inner surface of the dura and outer surface of the pia. They are flat cells with oval nuclei, a moderate amount of cytoplasm, and no intercellular substance; in other words they are not highly differentiated structurally and have little to characterize them. For this very reason, however, the cells stand out in marked contrast to strongly characterized cells, such as the fibroblasts and the smooth muscle cells.

Three groups of tumors arising from endothelial cells are recognized, (1) blood vessel, (2) lymph vessel, and (3) dural endotheliomata. Under these terms I include the angiomata because the endothelial cell is the only essential cell in all these tumors, and there is no reason for making an artificial division and considering separately the slow-growing ones in which definite vessels are formed (the angiomata), and those in which the cells grow rapidly and sometimes in solid masses (the endotheliomata). Such a separation tends only to complicate and confuse the subject.

Tumors arising from blood-vessel endothelium, the hemangioendotheliomata, are of fairly common occurrence, especially the capillary type, and some of them show active growth and extension. Their characteristic manner of invading fat tissue, their frequent extension into muscle tissue, and the way in which they surround the sweat glands are well known. It is to certain other interesting features that I wish to call attention here.

In the capillary angiomata the endothelial cells often line the vessels two to four layers thick and mitosis may occur in the cells
even in the outer layers. This proliferation causes narrowing of
the lumen of the vessel and sometimes complete occlusion. In this
way concentrically arranged masses or whirls of endothelial cells
are formed. These clumps of cells are then slowly invaded by
collagen fibrils from the surrounding connective tissue and gradu-
ally transformed by compression into flattened elongated cells which
resemble fibroblasts, but they produce no fibroglia or other kind
of fibrils. A somewhat analogous condition is seen in acute des-
quamative glomerulonephritis where the crescents of epithelial cells
are invaded by connective tissue cells and fibrils and gradually re-
placed by them. This proliferation of endothelial cells and occlu-
sion of the lumen was particularly well shown by a hemangioma
of the eyelid which extended to the orbit and invaded the eyeball.
For an opportunity to study this case I am indebted to Dr. F. H.
Verhoeff, of the Massachusetts Charitable Eye and Ear Infirmary.
In this tumor the vessels are of larger size than usual, though
distinctly of the capillary type. They have invaded many of the
nerves, destroying some of them partially, others completely.
Numerous mitotic figures (Plate XLIII, Fig. 3) prove that the en-
dothelial cells are proliferating rapidly. In many places the en-
dothelial cells are two to four layers thick around the lumen, which
may be much narrowed or even occluded. In other vessels masses
of endothelial cells project into the lumen (Plate XLIII, Fig. 2).
Collagen fibrils may be seen gradually extending in from outside
the vessel and forming a backing or support for the endothelial cells.
In this way a concentric perithelial arrangement of cells is pre-
sented, but the growth is entirely from the endothelium within, not
from a theoretical perithelium outside.
In a second hemangioma forming several discrete nodules in the
lower half of a leg and clinically so painful that it was supposed to
involve the nerves, the growth slowly returned in the same nodular
form and was removed a second time four years after the first
operation. The nodules consist of masses of blood vessels (Plate
XLIV, Fig. 1) with walls composed of endothelial cells four to eight
layers thick. The lumina are all small. In places the vessels are
packed so closely together that the separate vessels are made out
with difficulty. There is very slight reaction on the part of the
surrounding connective tissue and little or no extension of collagen fibrils in between the endothelial cells. This tumor is interesting for three reasons, the thick walls composed of endothelial cells already mentioned, the fact that in a few places the cells on the outer surface of the vessels are extending into the surrounding fat and connective tissue, and finally because in places the new formed vessels are growing and extending inside of arteries (Plate XLIV, Fig. 2) and veins. In the latter it causes marked dilatation of the vessel wall.

Apparently closely related to this tumor is a group of three small new-growths, two of which occurred in the bend of the elbow and were exceedingly painful on pressure. So far as can be made out they are slow-growing hemangiomas in which the endothelial cells have extended outside of the walls of the vessels and have invaded the surrounding tissue to a greater extent than in the case just mentioned.

Another case studied consisted of the original nodular growth on the back of a youth of sixteen and of three recurrent nodular masses. Each time on routine examination a diagnosis of spindle cell sarcoma was made. Most of the tumor tissue (Plate XLII, Fig. 1) presents that type of growth. In places, however, all of the nodules show on careful microscopic examination appearances which arouse attention. These consist of large and small concentrically arranged clumps of cells (Plate XLII, Fig. 3) and also in a few places of irregular branching masses of cells (Plate XLII, Fig. 2). The solution, in regard to the nature of the nodular masses and in regard to the source of the recurrences, lies in the fat tissue surrounding the nodules. This is being invaded in many places by capillary blood vessels (Plate XLIII, Fig. 1) with prominent endothelial cells in which mitosis is frequent. In all the larger tumor masses, from outside pressure or from internal proliferation the lumina of many of the vessels have become occluded: as a consequence the circulation of the blood was interfered with, and vessels were no longer formed. Instead, the proliferating endothelial cells have formed clumps or whirls and irregularly branching and connecting masses of cells. These collections of cells have been for the most part gradually invaded by collagen fibrils and
transformed into flattened, elongated cells. There is no reason to assume that the endothelial cells take on new properties and produce the fibrils. The endothelial cell is a definite entity with characteristics of its own and it retains them under a great variety of conditions. In this class of tumors the collagen fibrils are always most abundant around the blood vessels where connective tissue cells are present, and from there spread out in diminishing numbers among the surrounding endothelial cells.

Two cavernous angiomata, both congenital and both increasing in size and spreading since birth, throw light on some points connected with the difficult subject of endotheliomata. In both cases the tissue was dropped instantly at the time of operation into Zenker's fluid and was not sectioned until the blood in the vessels was coagulated. The first tumor occurred in the form of ten separate projecting nodules on the shoulder of an eight-year-old girl. The nodules varied from one to four centimeters in diameter. Microscopically they consist of thin membranes of connective tissue covered with flat endothelial cells (Plate XLIV, Fig. 2). In places the membranes are packed closely together: in other places they are widely separated so that cavities of considerable size are formed. In several places the arteries in and around the tumor are filled with these same membranous folds of connective tissue covered with endothelium. The veins (Plate XLV, Fig. 1) are much more extensively invaded and often greatly dilated. Indeed the presence of narrow bands of smooth muscle cells at the edge of many of the larger masses of tumor suggest strongly that they too were originally within vessels but have broken through the walls in places.

This tumor shows three other points of interest: (1) A few small collections of endothelial cells concentrically arranged, apparently where a vessel lumen has been obliterated by a growth of endothelial cells. (2) An occasional starting point of one of the membranous folds: an outgrowth from a vessel wall of a collection of endothelial cells of cuboidal form with a little connective tissue to support them. (3) Numerous oval and spherical, more or less completely organized thrombi, with a single small pedicle to connect them with the wall. The thrombi consist almost entirely of fibroblasts (Plate XLV, Figs. 2 and 3); in a few of them an occasional small blood vessel can be seen.
The second case was much more extensive and involved the right hand, arm, and shoulder of a girl (Plate XLVI, Fig. 1) of sixteen. Only three small nodules were removed, but in them the same growth within arteries and veins (Plate XLVI, Fig. 2), although to a less degree, was found.

This growth of endotheliomata within arteries and veins, with dilatation of the latter, throws light on the method of extension of these tumors and should prove of value clinically. It has been observed before, as far as I am aware, only in a case of rapidly growing endothelioma.

Lymphangioendotheliomata are rare and their diagnosis is usually not so positive and convincing as in the case of the blood vessel tumors where the contents of the vessels aid a great deal. I, therefore, report two cases with some hesitancy. The first, a rounded mass three centimeters in diameter was found subserous in a cornu of a uterus removed for a submucous leiomyoma. It consists microscopically of spaces lined with flat cells of the endothelial type and also of irregular collections and rows of cells of more cuboidal form, which often contain one to three large vacuoles (Plate XLVI, Fig. 3). These vacuoles seem to combine to form lumina around which the cells arrange themselves and flatten out as the vessels dilate. All stages between the solid masses of cells and the thin-walled vessel are present. This tumor has extensively invaded the muscle wall of the uterus.

The second case occurred in the left lumbar region beneath the muscles, but not connected with the kidney. It shows a similar condition, large dilated spaces lined with very low endothelial-like cells, and more cellular areas in which the cells are more or less spherical and often vacuolated. No mitoses were found in either case, indicating slow growth. The cavities contain a thin, serum-like fluid in which are a few lymphocytes.

Although the dural endotheliomata do not form vessels they have certain characteristics in common with the other endotheliomata. The cells grow in masses and form irregular whirls (Plate XLVII, Fig. 1) composed of flat cells closely packed together. In those tumors which are growing rapidly no intercellular fibrils are found between the endothelial cells. They occur only in connec-
tion with the connective tissue cells around the blood vessels which run irregularly through the tumor-mass and form a stroma which nourishes and supports it. In the more slowly growing tumors (Plate XLVII, Figs. 2 and 3) a small amount of connective tissue, usually in the form of a reticulum of collagen fibrils, extends in between the layers of endothelial cells and forms a support for them. It is unquestionably derived from the connective tissue cells around the blood vessels.

I have not touched on all classes of tumors in this brief report, but I have made evident, I think, what I am striving at.

1. To determine more exactly than has been done heretofore how each kind of normal cell is characterized so that it can be definitely distinguished from all other cells, and then apply this knowledge to the study of tumors.

2. To determine the essential cell in each kind of simple tumor and name the tumor accordingly.

3. To do away, as far as possible, with all names of tumors in which accidental and secondary features are put first and the true nature of the tumor is lost sight of, such as the names round, spindle, and mixed cell sarcoma, perithelial angiosarcoma, psammoma, fibroendothelioma, etc.

In the lantern slide exhibit which follows, I am indebted to Dr. S. B. Wolbach for the photomicrographs of sections and to Miss Etta R. Piotti for the drawings.

The following illustrations represent a selection of forty-three out of the one hundred shown at the lecture:

EXPLANATION OF PLATES.

PLATE XXXIV.

Figs. 1, 2 and 3 are from a fibrosarcoma and show fibroglia and collagen fibrils. The cells are seen flatwise in Fig. 1, sidewise in Fig. 2, and crosswise in Fig. 3.

PLATE XXXV.

Figs. 1, 2, 3 and 4 are from a fibrosarcoma containing many multinucleated cells.

Fig. 2 shows multiple mitosis.

Fig. 3. A multinucleated cell with numerous centrosomes.

Fig. 4. A coarse fibroglia fibril running over the surface of a multinucleated cell.
The Study of Tumors by Histological Methods.

PLATE XXXVI.

Fig. 1. An edematous leiomyoma showing what seem to be coarse myoglia fibrils.

Fig. 2 is a cross section from the same case and shows that the coarse fibrils are due to fusion of fine fibrils.

Fig. 3 shows a mitotic figure and coarse myoglia fibrils in a malignant leiomyoma.

PLATE XXXVII.

Fig. 1. Cross section of a malignant leiomyoma.

Fig. 2 shows spindle-shaped cells in another malignant leiomyoma.

Fig. 3 shows the spherical shape of cells in other portions of the same malignant leiomyoma.

PLATE XXXVIII.

Figs. 1, 2 and 3 are from the case of glioma over the coccyx.

Fig. 1 shows the alveolar arrangement.

Fig. 2. Early invasion of an inguinal lymph node.

Fig. 3. A mitotic figure of a neuroglia cell within an alveolus. The bending of the neuroglia fibrils is an artefact due to the action of the knife in cutting the paraffin sections.

PLATE XXXIX.

Figs. 1, 2 and 3 are from the case of glioma of the lumbar cord with extension in the pia along the cord and over the brain.

Fig. 1 shows the tumor surrounding the upper dorsal cord.

Fig. 2 shows the extension over the surface of the cerebellum.

Fig. 3 shows the histological structure of the tumor.

PLATE XL.

Fig. 1 shows the epithelial fibrils within an alveolus of epithelial cells in a cancer of the breast.

Figs. 2 and 3 show the fibroglia fibrils of the stroma of the same case in longitudinal and cross section.

PLATE XLI.

Fig. 1 shows a large group of endothelial cells ingesting the cornified cells of an epidermoid carcinoma. Many of the endothelial cells are multinucleated (foreign body giant cells).

Figs. 2 and 3. Low and high power views of a chorionepithelioma of the uterus.

PLATE XLII.

Figs. 1, 2 and 3 are from a hemangiendothelioma of the back of a youth of sixteen.

In Fig. 1 the cells have the appearance and arrangement of a spindle cell sarcoma.

Fig. 2 shows irregular clumps of endothelial cells, and Fig. 3 a large whirl of endothelial cells.

PLATE XLIII.

Fig. 1. From the hemangioma of the back of a youth of sixteen. The figure shows the type of capillary vessels invading the fat tissue outside of the tumor nodules.
FIGS. 2 and 3 are from the hemangioma of the eyelid invading the orbit. Fig. 2 shows masses of endothelial cells extending into the lumen. Fig. 3 shows mitosis of an endothelial cell and almost complete occlusion of a vessel by proliferation of the endothelial cells lining it.

PLATE XLIV.

Fig. 1. Hemangiioendothelioma of the leg and ankle; the figure shows the thick-walled vessels running in every direction. The endothelial cells of the walls are several layers thick and the lumina are exceedingly small.

Fig. 2 is from the same case and shows the growth extending within a small artery.

Fig. 3 is from the cavernous hemangioma of the shoulder and shows the characteristic type of growth.

PLATE XLV.

Fig. 1 is from the cavernous hemangioma of the shoulder and shows the tumor growing within and dilating a vein.

Fig. 2 and 3 are from the same case and show low and high power views of an organized thrombus consisting entirely of fibroblasts.

PLATE XLVI.

Fig. 1. Photograph of a clinical case of cavernous hemangioma of the hand and arm.

Fig. 2. Cross section of a small vein from the same case showing the tumor growing within the lumen of the vessel.

Fig. 3. A lymphangioendothelioma of the uterus showing the hollowed-out cytoplasm of some of the cells and the flattened cells lining the larger spaces.

PLATE XLVII.

Fig. 1. A cellular, rapidly growing dural endothelioma. The only collagen fibrils are in the small amount of connective tissue accompanying the blood vessels which run between the masses or whirls of endothelial cells.

Fig. 2 and 3 are from a slow growing dural endothelioma and show the reticulum of collagen fibrils which has extended in between the endothelial cells. In Fig. 2 the cells are seen flatwise and in Fig. 3 sidewise.