THE RÔLE OF THE NEURAL CRESTS IN THE EMBRYONAL ADENOSARCOMAS OF THE KIDNEY

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The malignant tumors of multiple tissues or adenosarcomas of the child's kidney form a group the appearance of which, in spite of an extreme polymorphism, is still characteristic enough so that their diagnosis is easily made by any experienced histologist.

CLASSICAL DATA ON THE STRUCTURE OF THE ADENOSARCOMAS

Renal Blastema: The diagnosis of renal adenosarcoma depends upon the existence of a special tissue complex, the varied aspects of which can easily be related one to another in the same fashion as are stages of histogenic development. In its primitive state this complex has a mesenchymatous foundation which is highly vascularized, with stellate cells forming a loose network through the interstices of which run collagen fibers. In this basic tissue are collections of cells, compressed one against the other, which are so poor in cytoplasm that their rounded or oblong nuclei are almost contiguous. These dense collections are not vascularized; they have the appearance of nodules or of irregularly ramifying cords beaded with swellings. Their peripheries are always vague and indefinite throughout their extent, formed by cells which are more and more widely separated, branching and in continuity with the surrounding mesenchymatous network. In places these borders appear distinct and the nodules or cords seem to push back the loose mesenchyme about them; but an examination with high magnification shows after all a symplastic continuity between the cell groups and the loose mesenchyme which surrounds them in such a fashion that the compact masses and the basic mesenchyme form a whole and seem to correspond to two states of a single tissue.

In the cell masses are epithelial elements in the form of vesicles or hollow tubes with narrow lumen and lined by an epithelial coat of cuboid or very tall

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cylindrical cells with their nuclei placed at different levels. These vesicles or tubes are sometimes sharply isolated from the surrounding compressed cells by a basement membrane and sometimes indistinctly limited externally and in continuity with the cells. Elsewhere the cells of the nodules outline denser spherical groups or cords which manifestly represent caricatures of the vesicles or tubes. One cannot escape the idea that the cells of the masses and the epithelial cells are derived from each other. Now, since one can make the same observation about the loose mesenchyme and the masses, it follows that not only the loose mesenchyme and the cell masses but also the epithelial structures seem to correspond to different forms of one and the same tissue.

The nice question is to determine which of these three forms, loose mesenchyme, cell masses or epithelial formations, precedes the others. If only the primitive complexes are considered, nothing is found which permits a decisive answer. Happily, however, some of these complexes carry their differentiation—and this varies with different tumors—to a greater or less degree. The epithelial formations increase in size at the same time that the cells of the masses decrease in number. The tubes become tortuous, are surrounded by a limiting collagenous membrane: their cells become cuboid and sometimes acidophile, one end bends like the handle of a crosier and produces a caricature of Bowman's capsule with a rudimentary glomerulus. The cells not employed in the formation of tubes become connective-tissue elements. In a word, the initial vague mass is transformed into a more or less typical nephron. In some tumors the glomeruli may be entirely typical and the tubes, which doubtless secrete, may become cystic.

Hence the three associated forms in the complexes succeed one another in the following order: loose mesenchyme, proliferation in foci and crowding together of the mesenchymatous cells (masses and cords), tubular differentiation of most of the latter and evolution of the rest into connective tissue. This series of forms recalls so precisely the different histogenic stages of the convoluted tubule in the middle of the renal blastema that their identification is forced upon the majority of observers. The complexes which we have just described have the characteristics of metanephrogenic blastema.

To these nephrogenic complexes are linked other less typical structures which denote the more or less selective proliferation of one or another of the three elements of the blastema. Thus a number of renal tumors contain foci of spindle-cell sarcoma which would indicate the proliferation of the primitive mesenchyme alone; or sarcomatous foci of small rounded and closely packed cells resembling the cells of the masses; or tubular carcinomatous foci, trabeculated or acinar. One even finds occasionally foci of tubular proliferations with epithelium, in some places endothelial-like, resembling that which lines the inner surface of Bowman's capsule, in other places cuboid with large dark nuclei, identical with that which covers the embryonal glomeruli.

The renal tumors of children are never made up entirely of one or another of these forms. When they are present, the forms are localized. Sometimes they make up enormous masses which, if they are examined by themselves, may give the illusion of a simple tumor. A searching investigation always succeeds in bringing to light some part of the blastema with its usual complexity.


Associated Elements: Other elements are frequently associated with the blastema and its more or less atypical derivatives. In the first place striated muscle fibers are often noted. While in some cases they form almost all of the tumor and lead to a diagnosis of renal rhabdomyoma, more often they are assembled in small masses or scattered hit or miss, at least apparently so, in the tumor mesenchyme between the compact masses. Less commonly these tumors contain smooth muscle fibers; still more rarely cartilaginous or even bony nodules. One may also find in them epidermoid cords isolated or in continuity with the gland-like tubes. Finally, there are encountered in certain blastematos masses clear spots without nuclei made up of fibrillary felt-like protoplasmic prolongations of the cells which surround them and recall at the same time the “rosettes” of the medulloblastomas (Bailey and Cushing) and the “sympathogonic capsules” (Poll) of embryonal sympathomas.

From this inventory one can draw the following provisional conclusion. The complex renal tumors of childhood always contain renal blastema and this manifests itself under various aspects, of which some, typical and complex, recall the appearance of normal blastema in various stages of its evolution, while others, atypical and simple, correspond to its proliferation in its primitive mesenchymatous form or its secondary epithelial form.

Very often immature striated muscle fibers are mingled with the renal blastema. Hence the names which have been applied to these tumors—adenosarcoma (Birch-Hirschfeld), nephroma (Albrecht and Trappe), adenosarcoma (Aschoff), mesodermic mixed tumor (Wilms, Borst)—seem perfectly justified. If ectodermic elements are associated with them, in an epidermoid or nervous guise, the name ectomesodermic mixed tumors (Borst) seems better to fit them.

Finally, and this is a fact of great importance, the endoderm and its derivatives do not seem to play any rôle in these tumors.

Whatever it may be, the constant presence of nephrogenic blastema and its habitual dominance confer upon these complex tumors a regional character all the more striking since no other embryoma situated elsewhere contains it with the same regularity and in the same marked fashion.

Origin of the Adenomyosarcomas: Most of the theories advanced to explain the renal embryonal adenosarcomas of the kidney have been inspired by the presence of the nephrogenous tissue described above. That of Birch-Hirschfeld and Cohnheim, abandoned by everyone, held that the nephrogenous tissue corresponds to the mesonephros and not to the metanephros. Those of Wilms, of Albrecht, of Busse and Muus, of R. Meyer, and others, and that originally favored by Ribbert, support the metanephrogenous nature of the tumor blastema but differ especially in their explanations of its presence and that of the tissues associated with it in renal tumors. All are agreed in ascribing these latter to a local developmental fault. They are dysembryoplastic tumors and not teratomas or embryomas resulting from the evolution of totipotential germs.²

² There have been described rare cases of true renal teratomas. These are tridermic tumors in which ectoderm, mesoderm, and endoderm are associated as they are in epignathi and ovarian and testicular teratomas. These renal teratomas form a separate group which is not discussed here.
Ribbert, however, who had first believed in the presence of nephrogenic tissue in the renal adenosarcomas, later reversed his opinion. In the 1914 edition of "Geschwulstlehre" (p. 680 et seq.) he enters upon a spirited discussion of the so-called nephrogenic blastema. He believes that what is considered such is derived from neuroepithelium and neurospongium. Hence the so-called "adenosarcomas of the kidney" are embryomas of the same type as those of the ovary. There is nothing renal about them except the site of origin. They do not any more come from renal constituents than ovarian embryomas come from ovarian tissues. The more or less reduced number of their tissues is only a case of "more or less unilateral development," the underlying cause of which remains unexplained.

It is strange that such a statement, supported by a clear description, a concise discussion, and numerous illustrations, and advanced by a histologist of Ribbert's importance, has not provoked any reaction. Even more, it has not even been cited in the classical treatises which have since appeared.

In a recent paper F. Harbitz (1932), who seems unaware of Ribbert's second opinion, expressed his own belief in the neuroepithelial nature of the structures which are classically ascribed to renal blastema. In eighteen adenosarcomas, of which he describes only three in detail, he finds no clear cut nephrogenic blastema. Everything which one might consider as such ought rather to be identified with various kinds of neuroblastomas: *i.e.* embryonal sympathomas, medulloblastomas, and medulloepitheliomas (according to Bailey and Cushing's terminology). According to him the adenosarcomas of the kidney should be called ecto (neuroepithelial)-mesodermic mixed tumors. Harbitz, moreover, formulates this hypothesis with discretion for, he says, his interpretation rests exclusively upon stained preparations in which cell form is not sufficiently well defined and he invites other pathologists to verify his observations.

Thus, two pathologists working independently come to the conclusion that there is no nephrogenic blastema in the renal adenosarcomas and interpret the structures which are usually attributed to mesodermal tissue as neuroepithelial products.

Between these two opposed conceptions apparently no reconciliation is possible.

**Personal Investigations**

I have always warmly admired Ribbert. One never loses time when one attempts to verify his original ideas. For many years I have compared his text and illustrations with the pictures furnished by a dozen adenosarcomas without succeeding in convincing myself of the absolute accuracy of his interpretation.

Let us see what are the arguments upon which Ribbert bases his nervous conception of the cellular masses and the tubes which they contain.

**First:** They are clearly limited on the side of the loose connective tissue. Thus, these are epithelial elements in contact with connective tissue and genetically different from it.

**Second:** The epithelial tubes with stratified nuclei do not have the structure of urinary tubules.
Third: The epithelial tubes are not always included in the cell masses and they can grow by themselves in connective tissue.

Fourth: The tubes are sometimes in relation with epidermoid formations, which should not be ascribed to a ureteral bud but to ectoderm.

For Ribbert all the structural peculiarities of these formations characterize them as elements of embryonal spinal cord neuroepithelium and spongiosblasts, and show their genetic relationship with ectoderm.

These four arguments have a debatable value:

First: In the primitive forms, as we have seen, the cell masses are never really distinct and separate from the loose mesenchyme which surrounds them, but are in symplastic continuity with it; and this is observed neither in normal embryonal spinal cord nor in the medulloepitheliomas, where the nervous elements are always clearly distinct from the surrounding connective tissue, whether they push it back or whether they infiltrate it.

Second: In the normal metanephros the new-formed urinary tubes in the beginning have an elevated epithelium with nuclei which are enmeshed and pseudo-stratified, without being neuroepithelial.

Third: The young urinary tubes always become isolated from the small-celled blastema, and the latter loses its special characteristics in giving birth to the urinary tubes. These then continue their growth and differentiation in the connective tissue.

Fourth: The epidermoid formations can just as well be regarded as ureteral as epidermoid.

Similar objections can be made to the arguments of F. Harbitz.

On the other hand, the more advanced evolution of the masses in many tumors, which even goes so far as to produce nephrons containing malpighian corpuscles, completes the proof. The nephrogenic blastema, therefore, really exists in the renal adenosarcomas.

In the course of my studies I have made two observations which seem to me important:

(a) In the adenosarcomas with a young blastema (cellular masses with poorly defined edges containing vesicles or few and short epithelial tubes) there are often, in the middle of the cell mass, spherical mats of vaguely radiating fibrils. These are surrounded by nuclei like those described by Ribbert. To me, however, these structures are neither neurospongial nor neuroglial but, as Harbitz said, sympathetic—the sympathogonic capsules of Poll.

(b) In many adenosarcomas, whether their blastema be young, differentiated, or atypical, I have found spherical ganglion cells. Some of these are small and bare while others are voluminous and surrounded by a capsule of satellite cells. These cells are scattered throughout the loose mesenchyme which separates the masses, very often in the vicinity of or in the interstices of the striated muscle fibers in all stages of their differentiation.

Now these encapsulated ganglion cells strewn throughout a mesenchymatous tissue are certainly not medullary. They can only be spinal ganglion cells or sympathetic cells. On the other hand, the presence of sympathogonic capsules included within the young blastematous masses would seem to imply the presence of primitive sympathetic elements. This gives new support to Ribbert’s theory of nervous origin, but the theory must be greatly modified.
First: Contrary to what Ribbert thought, it must be admitted that the nephrogenic blastema certainly takes part, probably invariably, in the formation of adenosarcomas of the kidney.

Second: We agree with him that it seems probable that nervous tissue is a frequent if not a regular constituent of these tumors. But this nervous tissue—save for those exceptions which are always possible—is not neuraxial tissue, but sympathetic tissue. It is necessary to verify this assertion, and if it is confirmed, to determine the genesis of the ganglion cells, their relations to the renal blastema and to the third regular constituent of adenosarcoma, striated muscle tissue.

These are the problems suggested to me by the examination of ten of these tumors undertaken for the purpose of verifying Ribbert’s theories. To solve these problems it was necessary to apply neurological technics to the adenosarcomas, and to compare the results of stains and silver impregnations. This is what I have been doing since 1930. Three adenosarcomas have been divided into slices, some of which have been fixed in Bouin’s fluid and the others in formol or chloral. The former have been stained by the usual methods, the others impregnated with silver according to the technics of Bielschowsky and Cajal. The Bielschowsky method has given the most useful results.

Observation No. I

Child of fourteen months. A white, soft, voluminous (500 grams) tumor has destroyed the upper pole of the kidney and has pushed the lower pole downward. Its limits toward the cortex are clearly outlined by a compressed parenchymatous layer. Toward the medulla, on the other hand, its limits are vague. The two lower calices, the only ones remaining, are enlarged. Their epithelium is elevated by little projecting nodules of an opaque white appearance.

The tumor tissue has broken the capsule at one point and by this route has infiltrated the fat of the kidney bed from top to bottom. The inferior pole of the kidney is engulfed in a soft, diffuent, yellowish-white mass, but is separated from it by its intact capsule.

We shall study first the intracapsular portion of the tumor, then its extracapsular extension.

I. Stained Preparations: (1) Intracapsular Portion: Throughout its extent the tumor has the aspect of an adenosarcoma composed of a very primitive type of renal blastema. Mesenchymatous ground substance, compact cords, and vesicles or epithelial tubes are everywhere associated, but their relative proportions differ with different areas. From this variation there result quite dissimilar local appearances which are united by intermediate forms. One gains the impression that each one of these observed pictures corresponds to the momentary status quo of the same tissue in a constant state of flux. I shall describe only three of these aspects.

(A) The mesenchymatous tissue predominates. It forms large strands of myxoid aspect, branching cells anastomosing in a network. In their meshes is a hair-like arrangement of very fine sinuous collagen fibrils, interlaced in all planes and bathed by a serous fluid which can scarcely be stained. Here and there one sees, larded throughout its substance, short irregularly ramified tubes and above all little epithelial vesicles with the tiniest of lumens. Sometimes a mass with tightly compacted nuclei is interposed between the vesicles and the myxoid tissue. Sometimes this mass is very small and laterally placed; sometimes it has the shape of a crescent and sometimes that of a more or less thick completed ring. In every instance the epithelial vesicle or the small complex consisting of vesicle and cell mass have an almost spherical shape and the loose mesenchyme surrounds them on every side. We shall study first the simple tubes and vesicles and later vesicles bordered by cell masses.
Figs. 1–4. Observation No. 1, Type A: Mesenchymatous Tissue Predominating

Fig. 1. Vesicle recently isolated in young mesenchymatous tissue, with nuclei still closely placed, resulting from the final evolution of a blastematous cord into elements which are either mesenchymatous (dark nuclei), myoblastic, or neuroblastic (clear swollen nuclei with large nucleoli). The vesicle is limited by a collagenous basal membrane. The epithelium is cylindrical with large basally placed nuclei, all of which are resting.

Fig. 2. Isolated vesicle in a loose, vascularized mesenchyme (two capillaries are cut, one transversely the other obliquely) in contact with the unbroken basal membrane. The nuclei are in active multiplication. One in mitosis (anaphase) is seen at one side. Elsewhere they are dividing by amitosis and are disposed at various levels.

Fig. 3. Vesicle isolated in loose textured mesenchyme and beginning of budding (silver impregnation of connective-tissue fibers). The basal membrane is in continuity with the collagen framework of the mesenchyme. It is broken at one point by a bud of vesicle cells which invade the mesenchyme.

Fig. 4. Vesicle budding around its entire periphery and giving birth below to a mass of undifferentiated cells.

Simple tubes and vesicles: Simple tubes and vesicles are narrow. Their lining epithelium rests externally upon a reticulated argyrophile basal membrane in continuity with the fibrillar web of the surrounding mesenchyme. This epithelium varies in its conformation. In some instances its cells are cuboid, very distinct, have a slightly convex apical membrane, a homogeneous weakly acidophile cytoplasm, and a spherical, centrally placed nucleus. Tubes of this type have the aspect of involuted convoluted tubules. They differ from the latter, however, in that they are short and often ramified.

Certain vesicles are distinguished from the preceding by their greater size, due espe-
Figs. 5 and 6. Observation No. 1, Type A: Mesenchymatous Tissue Predominating

Fig. 5. Vesicle budding on one side alone and surrounded on half of its periphery by small, closely crowded, undifferentiated cells, quite distinct from the loose mesenchyme which surrounds them. Observe the apparent stratification of the epithelial nuclei which are in amitotic division.

Fig. 6. Vesicle budding on one side only and flanked by a compact mass of cells which have invaded the loose mesenchyme alone, respecting its collagen network. These cells are still quite distinct from the surrounding mesenchyme. (Silver impregnation of the collagen.)

Vesicles with cell masses: It is around these vesicles with elevated epithelium that the cell masses are formed. From all the evidence, the small cells which compose these masses are derived from the lining of the vesicles. Here and there an epithelial nucleus surrounded especially to the thickness of their epithelium. This is of a more or less elevated cylindrical type. Depending upon the vesicle and the height and narrowness of its cells, the nuclei are basilar (Fig. 1) or layered in several planes (Fig. 2), i.e. enmeshed one with another. Some of them are situated in the apical pole of the cell. Mitoses are rare and are always near the apical pole. Amitoses are frequent.
Fig. 7. Observation No. 1: Transition between Types A and B

A budding vesicle is surrounded by a compact mass of small undifferentiated cells. At three different points the covering of the vesicle and the mass have fused. Apparently the entire vesicle is destined to be effaced in transforming itself into undifferentiated cells (see Fig. 8). The borders of the mass are indistinct. Mesenchymatous transformation has already commenced.

by a thin layer of cytoplasm pushes back the basement membrane, breaks it, and penetrates the mesenchyme. Following it through the same hole, other nuclei arranged in files and united in the same syncytium are found crowded together outside of the basal membrane and in contact with it. There, in an active state of multiplication by mitosis, they first stretch the collagenous meshwork, then break it, and isolate the vesicle from the mesenchyme (Figs. 3 to 6). If the vesicle buds on one side only, then the mass is lateral (Fig. 6) or in the form of a crescent (Fig. 5); if on all sides, then the mass is spherical.

This solid mass grows in the same way in which it is born: by proliferation and persistent budding of the epithelium of the vesicle and also by mitotic multiplication of the emigrated nuclei. In the beginning it is entirely distinct from the mesenchyme, which it first invades and then pushes back, and its external contour is clear. Little by little the latter shades off because the peripheral cells of the solid mass ceasing from multiplication become separated one from the other (Fig. 7). Remaining constantly anastomosed, they become branched and are transformed into mesenchyme. This transformation is progressive. The cellular layer is at first compressed, then becomes more and more loose-textured. Its meshes are narrow in contact with the solid mass but become larger, little by little, from within outward (Figs. 8 and 9). The interstices of the cells are occupied by a colorless fluid in which appear extremely fine collagen fibers.

The branched cells and fibrillar web of this new mesenchyme become so well adjusted to the cells of the old mesenchyme that the exact line of division between the two mesenchymes cannot be exactly determined. In certain cases, however, the areola of the new mesenchyme springing from the cell mass stands out from the old mesenchyme by its clear aspect, which is due to the wider separation of its cells and its poverty in collagen. Moreover, one can determine the approximate division between the two mesenchymes thanks to an important fact: the cell masses never contain capillaries and the mesenchyme which comes from them becomes vascularized only at a late period. Its periphery, which is at first avascular, is later outlined by the ideal plane which reunites the capillaries of the old mesenchyme (Fig. 8).

The above description leads us to an unexpected statement. The typical "blastematos" complex at which we have arrived, made up of a loose mesenchyme, a cellular
Fig. 8 (left) shows a large mass of small cells. In the center of the mass the cells are crowded together and strictly contiguous. In this crowded region there was doubtless formerly a vesicle which has disappeared. Outside of this compact mass, the cells gradually become more widely spaced. At the periphery they are still more widely separated and form a clear areola of young mesenchyme. This pushes the older mesenchyme toward the base and the sides. The latter is vascularized and darker below because it is rich in collagen and muscle fibers (see Fig. 9).

In the upper part of the mass is a newly formed vesicle with cylindrical cells having nuclei arranged in a single plane. This vesicle is without external limits and not yet freed from the mass of undifferentiated cells where it was formed.

Fig. 9 shows the lower border of the same mass, enlarged. Observe the progressive transformation of its peripheral cells into stellate elements forming a new mesenchyme, loose textured, clear and without vessels, which pushes back in front of it the old, dense, dark vascularized mesenchyme. This old mesenchyme contains a ganglion cell and numerous young striated fibers which cannot be recognized with this magnification.

Mass, and an epithelial vesicle, does not seem to result from a local condensation of the mesenchyme in which a vesicle appears. On the contrary, it is the vesicle which first appears; the cell mass is developed from the vesicle and the mesenchyme from the cellular mass. The observed facts prove that such is the sequence of the phenomena and that the reverse order is untenable.

(B) The mesenchyme and the cords are equal in amount (Figs. 8, 9 and 10). In this case the cords are moniliform, branched, and separated by myxoid bands. The former have more or less vague borders in continuity with the surrounding mesenchyme. Vesicles distinguish them. Most of these are in the center of the swellings and the rest are marginal.

These vesicles are of two distinct types. Some of them are surrounded by a discontinuous basal membrane. Their epithelium is thick, with stratified nuclei in active multiplication. Depending upon a central or marginal situation, it buds in all directions or on one side only; the cells emigrate into the mass and increase it. Secondly, a number of vesicles disappear as if their epithelial cells had been transformed into the cells of the mass. There are other vesicles which are without external boundary. Their cylindrical cell lining is everywhere in contact with the mass, with which it is blended. One gets the impression
FIG. 10. OBSERVATION NO. 1, TYPE B (MSENCHYME AND CORDS EQUAL IN AMOUNT

GENERAL ASPECT OF THE TUMOR

Moniliform masses and cords contain vesicles. The cords have indistinct peripheries. They are separated one from the other by a loose mesenchyme developed from their surfaces.

The vesicles themselves show great individual variation. Some are large with an epithelial lining having stratified nuclei; they are the budding vesicles, the product of undifferentiated cells (see Fig. 7). Others are small and have a low epithelium: these are vesicles in the process of formation. Some of these especially above and to the left have isolated themselves in a loose-textured mesenchyme resulting from the complete transformation of the small cells of a blastematous cord (return to Type A).

that these vesicles are born of the same cells of the mass which, locally, become epithelial and orient themselves about a cavity.

Hence one may think that if the primitive vesicles (aspect A) engender the isolated mass in which they disappear, these isolated masses may in their turn engender the vesicles and these latter may become in their turn the point of departure of new masses side by side with the former. This indefinitely repeated cycle explains the progressive transformation of an isolated cord-like mass, studded with swellings and branched, each branch being separated from its neighbor by loose mesenchyme to which its superficial region gives birth.

In places a segment of a cord seems to undergo the mesenchymatous transformation en bloc. Its cells separate themselves and become branched right up to the vesicles, which thereafter are isolated in the new mesenchyme. Thus the A type, which served us as a point of departure, becomes established.

In short, the very varied aspects of type A and type B tumor tissue can be arranged without difficulty according to a simple order which has some chance of being consistent with their chronology. At the same time a more extended study permits four statements which singularly complicate the problem.

First: Here and there, very rarely a lobe of one of the cords is replaced by a group of vesicles or by a sinuous tube, the intervals between which are occupied by small undifferentiated or branched cells. Still more rarely in this tubular mass there appears a crescent-shaped cavity which recalls the appearance of a very young Bowman's capsule without the glomerular tuft.

Second: Several cords, in addition to their budding or nascent vesicles, show clear spots.
FIGS. 11–13. OBSERVATION NO. 1, TYPE B: MESENCHYME AND CORDS EQUAL IN AMOUNT

Fig. 11. In the center a cord with indistinct outlines is in continuity with a more or less loose mesenchyme. In the upper part of the mass are two new-formed epithelial vesicles still fused with the undifferentiated cells. Below is a typical sympathogonic capsule; nuclei arranged coronally about a central fibrillary interlacing network (see Fig. 15).

Fig. 12. Above is a budding vesicle. The lining is composed of very narrow cylindrical cells. The nuclei are placed at varying levels. There are two buds (darker cells), one beginning (two nuclei), the other in full activity (three nuclei arranged in tandem, two of which have migrated outside of the vesicle). Below is a small vesicle in process of formation; to the right, mitosis in an undifferentiated cell.

Fig. 13. Margin of the sympathogonic capsule: developing striated myoblast in actual contact with nerve fibers.
Very dense cords are separated by strands which are paler but very rich in elongated cells. In the cords one observes a vesicle (left) and compact masses of small cells. To the right, close to one of these masses, is a sympathogonic capsule.

These spots correspond to regions where the nuclei are separated one from another by a fibrillary meshwork which is colored by cytoplasmic stains. Some of these meshworks are spherical, with a radiating orientation. These are typical sympathogonic capsules. The nuclei bordering them are identical with those of the compressed cells of the mass (Fig. 11).

Third: The vessels which nourish the neoplastic tissue are in the middle region of the myxoid strands, which corresponds to the most distant mesenchyme of the cords, and is therefore the oldest. This same region contains in addition sparse but very well differentiated ganglion cells, some voluminous and contained within capsules of satellite cells, others smaller and in direct contact with the collagenous framework.

Fourth: Finally, there are striated muscle fibers either embryonal or in later stages of their development. These fibers are sometimes isolated but more often collected into small fasciculated and plexiform groups scattered in the mesenchyme. Some of them are included among the small cells which bound the cords. One may even find them among the elements of a sympathogonic capsule (Fig. 13).

Most often ganglion cells and muscle cells are localized at the same points. Most of the muscle bundles in evolution contain ganglion cells in their interstices, either isolated or arranged in files.

(C) The cords predominate over the mesenchyme (Fig. 14). In regions of this type the very large cords anastomose in every direction and are formed principally of compressed cells. In their midst one finds occasional vesicles and here and there small spherical masses limited by a collagen membrane. These masses appear to have been born on the spot. They do not bud. They are made up of cells with spherical nuclei and slightly acidophilic cytoplasm. Their significance is doubtful. Perhaps they correspond to an abortive, very atypical nephroid evolution. At great intervals, the same cords contain typical sympathogonic capsules.

Outside of the places where they anastomose the cords are bordered by an indistinct myxoid zone or by a more condensed mesenchyme with elongated fasciculated cells in whose interstices there are collagen fibers. This oriented mesenchyme gives an impression of spindle-cell sarcoma. Here and there some elongated elements contain acidophile fibrils.
CHART 1. Recapitulation of the Primitive Histogenesis of the Adenosarcomas

1. V1 Vesicle in repose in a vascular mesenchymatous tissue.

2 and 2.1 The birth by budding of the masses of small undifferentiated cells. The masses push back the capillaries and mesenchyme.

3. Budding continues; undifferentiated cells have multiplied. At the border the more widely spaced cells form a new mesenchyme which pushes back the old mesenchyme and capillaries (Type B).

4. Vesicle V1 has disappeared. Another, V2, has formed at the border of the mass, which continues to form loose mesenchyme at its periphery (Type B).

5. A new vesicle, V3, appears, as well as a sympathogonic capsule (CS). The original mass is deformed and now appears branched and moniliform. At its periphery it forms a loose mesenchyme in which appear muscle fibers and neuroblasts. Capillaries coming from the older mesenchyme have invaded the new mesenchyme. The undifferentiated cells which surround the vesicle V2 (4) undergo a mesenchymatous transformation, become more widely spaced, and free this vesicle (return to Type A), which will become comparable to V1. This last may bud and give birth to a new generation of undifferentiated cells.
which are caricatures of muscle fibers. Of these last, only occasional ones show cross
striation. In this confused sarcomatoid tissue, stains do not permit the discovery of any
ganglion cells.

Considering all these facts together, one draws from them the conception that the B
and C types of cell cords in places have a nervous aspect due to the presence of sympatho-
gonic capsules, while at the same time they are forming nephroid elements. In other areas
they form a mesenchyme in which both muscle fibers and ganglion cells appear. It is
enough to confound one's imagination.

![Figure 15](image)

**FIG. 15. OBSERVATION No. 1, TYPE B: BIELSCHOWSKY PREPARATION SHOWING SYMPATHOCONIC
CAPSULE WITH ITS FIBRILLAR CENTER FORMED BY THE INTERLACING OF NEURITES DERIVED
FROM THE CORONALLY ARRANGED, RACQUET-SHAPED NEUROBLASTS. X 600**

This incomplete impregnation gives an excellent demonstration of nine of these neuroblasts,
two of which are bipolar. In complete impregnations one learns that all of the nuclei belong to
neuroblasts, but the neurites are so numerous that it is difficult to follow them and especially dif-
ficult to draw them. To the left and above groups of unipolar and bipolar neuroblasts are seen.
In the upper right corner is a mass of undifferentiated cells with a bipolar neuroblast; in the lower
left corner a strand of fasciculated structure through which pass several sinuous neurites.

In order to throw some light on this confusion, it is pertinent to investigate the origin
of the ganglion cells which are found in the mesenchyme by the aid of neurological methods
(see below).

*(2) Extrarenal Portion:* This part of the neoplasm differs completely from that which
has just been described. Here are no cords, no myxoid tissue nor tubes, but almost every-
where is a confused accumulation of small cells with minimal cytoplasmic bodies, sometimes
spherical, sometimes tapering, with spherical or oblong nuclei and, in places, capillaries.
At wide intervals, cutting through the serried nuclear ranks, are larger clearer strands com-
posed of larger cells with a clear vesicular nucleus and a large nucleolus. These cells, which
resemble young neurocytes, are both crowded about large capillaries and are also scattered
widely in a fibrillary substance with cytoplasmic reactions.
To sum up, this infiltrating portion does not possess any characteristic of renal blastema. This association of very small undifferentiated elements and neurocytic and fibrillary strands gives the impression of a pure sympathoma, especially a sympathogonic one evolving at rare intervals towards the sympathoblastoma and the ganglioneuroma.

II. **BIELSCHOWSKY IMPREGNATIONS**

**Type A Regions:** The silver shows several moniliform branched nerve fibers, sometimes flanked by schwannian nuclei, in the loose mesenchyme. Following the fibers in serial sections one eventually finds the ganglion cells from which they spring: rounded cells, sometimes encapsulated, provided with numerous prolongations which are themselves included in the mesenchyme. The isolated vesicles and tubes themselves never contain argentophile elements, nor, ordinarily, do the small compact masses which are formed from their budding. Exceptionally I have observed among the undifferentiated cells situated at some distance from the vesicle, nuclei surrounded by a thin black cytoplasmic areola prolonged at one side by a very delicate filament which was directed toward the neighboring mesenchyme and mingled with it. From all the evidence, these racquet-shaped cells are newly formed neuroblasts.

**Type B Regions:** If one examines the moniliform cords one finds in many of them, but not in all, young neuroblasts with a unipolar racquet form or, when more developed, provided with two prolongations at opposite poles, i.e. bipolar or pluripolar.

Certain lobes of the cords seem to undergo the neuroblastic transformation en bloc. This is especially the case with those which contain a sympathogonic capsule (Fig. 15). The silver outlines in black the central interlaced fibers and shows that each fiber is a single prolongation of one of the cells which are arranged coronally about it. After they become intertwined, these sinuous prolongations become reassembled in little bundles which escape from the capsule, cross the cell mass, and become engaged in the mesenchyme, where one can trace them for long distances. They follow the capillaries, for which they show a remarkable predilection. In their course these bundles receive numerous fibrils emanating from

![Figure 16](image-url)
racquet-shaped neuroblasts situated beside them and from bipolar neuroblasts included within their interstices.

Other cells situated outside the coronal capsule transform themselves in like manner into racquet-shaped structures. Either their prolongations are arranged in bundles, which themselves pass towards the mesenchyme, or they lose themselves among the undifferentiated cells of the mass and form there an inextricable plexus.

Other lobes without sympathogonic capsules are dotted with innumerable neuroblasts whose prolongations run in every direction. It is proper to note that these neuroblasts are never in contact with vesicles, but always separated from them by several layers of undifferentiated cells.

**Fig. 17. Observation No. 1, Type B: Bielschowsky Preparation Showing a Group of Neuroblasts of Various Sizes, Most of Which Are Pluripolar and Have Developed Within a Mass of Undifferentiated Cells. X 450**

Five of them form a little ganglionic group. One of them (left) is glued to a capillary; its axone surrounds the latter as it makes a spiral turn.

Side by side with these lobes where the majority of the cells undergo at the same time a beginning of neuroblastic transformation are other regions where the transformation affects only a small number of cells and in which these latter are in various stages of their evolution (Fig. 16). Their nucleus becomes turgid, then spherical; their cytoplasm, more abundant, grows richer in neurofibrils which, at first situated on the side of the single prolongation, surround the nucleus and then outline one or several varicose dendrites. The nucleus of these cells divides by amitosis; then the neuroblast splits and the two daughter cell bodies separate one from the other but remain united in tandem by tangled hair-like prolongations.

This progressive transformation and this proliferation of neuroblasts are accompanied by their migration in the mesenchyme developed from the cord. The further away the cells are from their original cord, the larger they are. The most highly developed are distinctly multipolar. Sometimes they are gathered together into small ganglion-like groups (Fig. 17). Sometimes they are separated and dispersed in the mesenchymatous strands while still continuing to multiply. This last fact is habitual in the regions where numerous muscle cells appear: the neuroblasts situated in the interstices of the myoblasts send out varicose prolongations parallel with the budding muscle fibers.
Here and there in the strands, one finds voluminous ganglionic cells with large spherical nucleus, with multiple varicose prolongations, of which one, thicker than the others and very long, seems to be an axone (Fig. 18). Between these cells and the adult cells described in Type A all gradations are to be observed.

Type C Regions: The cords present here and there groups of racquet-shaped neuroblasts coronally disposed about a meshwork formed by their filiform prolongations. Except

![Fig. 18. Observation No. 1, Type B: Bielschowsky Preparation Showing a Ganglion Cell of Apparently Bipolar Aspect Situated in a Mesenchymatous Strand (Type A). × 740](image)

The prolongation on the right is probably an axone and passes among the elongated, probably Schwannian nuclei, which adhere to it. The prolongation on the left is thick and fibrillar and is divided into dendrites outside of the plane of the section. Two other slender dendrites escape from the lower border of the cell, which is therefore in reality pluripolar.

![Fig. 19. Observation No. 1, Type C: Bielschowsky Preparation. × 600](image)

To the left is a mesenchymatous sarcomatoid strand; to the right a cord of undifferentiated cells. Between the two can be seen five racquet-shaped or bipolar immature neuroblasts. At the junction between the cord and the mesenchyme are numerous bipolar neuroblasts, one of which is binucleate and elongated in the same direction as the sarcomatoid cells.

For these sympathogenic capsules there are few young neuroblasts in the confused mass of small cells.

In contradistinction, along the edges of the cords (Fig. 19) and in the sarcomatoid tissue which surrounds them the silver puts in evidence a multitude of elongated cells, bipolar and pluripolar, sending out short and stubby or long and moniliform prolongations engaged between other colorless cells. These prolongations form a meshwork oriented according to the long axis of the bundles. In other words, the prolongations are formed by an association of cells consisting of both myoblasts and neuroblasts stretched out in the same direction, the latter occupying the interstices of the former.
Thus, the highly differentiated ganglion cells which one finds in areas of Type A are united by every possible morphological intermediary to the racquet-shaped neuroblasts which appear in small numbers in the compact masses developed from the vesicles and in the moniliform cords of Type B, and to the elongated neuroblasts of Type C. The neuroblasts have from the start evident nervous characteristics. They multiply, invade the mesenchyme with their neurites, then with their cell bodies, increase in volume, and pursue their differentiation. The sympathogonic capsules and the racquet-shaped cells on one side and, on the other, the multipolar cells, which are at first naked and later encapsulated, characterize the two extremes of an evident sympathetic neurogenesis.

Certain elongated nuclei which mark out the nervous fibers or bundles have without any doubt the significance of schwannian nuclei. The same statement applies to the capsular cells which envelop the adult ganglion cells.

It must then be admitted that the compact cords contain not only cells of sympathetic derivation but lemmoblasts.

The impregnations show that the cells of nervous potentialities are not evenly divided among the cords. At certain points they are excessively numerous (sympathogonic capsules), elsewhere they are scattered, and in still other places they seem to be lacking. However, except so far as the sympathogonic capsules are concerned, stains do not show any difference between these cords, whether they are entirely or partially or not at all neurogenic. Always and everywhere their small cells come from tubes or vesicles, construct vesicles or tubes, and build mesenchyme. Exceptionally they build nephroid tubes.

**Extrarenal Portion:** This region, badly fixed, was impervious to all impregnations.

*Observation No. II*

Female two years old; spherical tumor weighing one kilo. A sheath of compressed renal tissue is recognizable near the upper pole. The capsule which covers this renal vestige is continuous with the capsule of the tumor. The tumor tissue is white, soft, divided into rounded areas of a diameter of 1 or 2 cm. by firmer bands of a fibrous appearance. Here and there are necrotic or hemorrhagic areas.

I. **Stained Preparations.** The structure of the tumor is quite uniform (Fig. 20). In general the basic tissue is made up of a rather dense mesenchyme formed of elongated cells parallel one with the other. In their interstices collagen fibers are abundant. This mesenchyme of compressed cells outlines the strands which fill in the intervals between the cords of small cells. At certain points cords and strands are united in an indistinct myxoid region where the two tissues are continuous one with the other. Elsewhere they are quite distinct. Small cells of cord and strand are contiguous without transition types between the two, but no limiting membrane isolates one from the other.

The proportion of epithelial formations and small cells varies greatly in different areas. In some the lobes of the cords contain only a single vesicle or a short tube with elevated cylindrical epithelium. Elsewhere tubes and vesicles are numerous, and undifferentiated small cells occupy their interstices. In still other places tubes and vesicles are found alone or almost so. Spurs of connective tissue and vessels coming from the strands separate the tubes and vesicles by degrees. Their epithelium remains high cylindrical and nowhere has the acidophilia of a renal tubule. However, at wide intervals and rarely they form a rudimentary caricature of Bowman's capsule. Except in that instance alone their significance is undetermined. One can just as well consider them renal as neuroepithelial. Nowhere does one find any sympathogonic capsules.

Examining the mesenchymatous strands with high magnification, one is struck by the number of immature or highly differentiated striated fibers which they contain. In places the muscle cells with double striation form the largest part of the strand. They are slender, columnar, or tapering at their extremities. Between them stains have not allowed me to find any ganglion cells.

II. **Bielschowsky Impregnations:** This specimen, fixed a little late, has not given as complete impregnations as the former. In the cords, however, I have seen young neuroblasts, isolated or grouped in masses among the small cells. They are altogether primitive neuroblasts, unipolar and racquet-shaped or pluripolar. At the periphery of the cords the
The general aspect is comparable to that of Type B of Observation No. 1 (see Fig. 10). It differs from it, in the first place, by the greater number of vesicles and tubes in the cords. Most of these epithelial formations are lined by an elevated epithelium disposed in several planes. A second difference is the relatively narrow mesenchymatous strands. Most of the lightly stained nuclei which can be seen belong to immature striated fibers.

Neuroblasts are quite numerous and send one or more prolongations toward the mesenchymatous strands which they enter.

The strands themselves are traversed by numerous neurites insinuated between the elongated cells and with the same orientation. In some places following the neurites one encounters neuroblasts emigrated into the strands, neuroblasts whence these neurites emanate. These neuroblasts are elongated and multipolar, more voluminous than those in the masses.

In one of the impregnated blocks I found structures which were not present in any of my stained preparations. These are large strands of a sarcomatous aspect, with large cells among which appear vesicles and branched tubes with cylindrical lining cells resting upon a more or less continuous basal membrane. In places, the latter are surrounded by small cells resembling the cells of the cords above described. Between these small cells and the large elements of sarcomatous aspect are found all grades of transition. One gains the impression that the sarcomatoid tissue results from the transformation on the spot of small cells of the cords and that the vesicles and tubes are relics of epithelial formations among these latter.

In this rather confused complex occur numerous collections of younger or more developed neuroblasts, in places outlining groups of ganglions composed of multipolar cells. The prolongations of these cells insinuate themselves among the sarcomatoid elements, of which many form caricatures of differentiated muscle cells.

**Observation No. III**

Male, two years old. A spherical tumor weighing 800 grams occupies the site of the kidney and bears along its internal border two small neighboring protrusions which are the two renal poles. These two remnants of glandular parenchyma are both separated from the tumor by a layer of compressed renal tissue. They do not appear to have been invaded at any point. They are united by a deformed pelvis. In short, the tumor has developed in the mid section of the kidney and has divided it into two sections.
FIG. 21. OBSERVATION NO. 3: PARTIAL RENAL EVOLUTION OF A BLASTEMATOUS MASS

At the left are undifferentiated cells; at the right renal tubes (low acidophile epithelium and a Bowman’s capsule). Outside of the mass, at the right and below, are several renal tubes scattered in a tissue of mesenchymatous aspect with pale nuclei, comparable to those in the mesenchyme which surrounds the mass (see Fig. 23).

The tumor presents two very different aspects. Two-thirds of the mass is solid, firm and pale, and envelops the other third, which is honeycombed with areolar cavities like a polycystic kidney. There is no clear division between this and the solid portion; the dimensions of the cysts increase progressively from the margin of the cystic zone to its center. One gains the impression that it is the tumor tissue itself which locally becomes cystic.

I. STAINED PREPARATIONS: (1) Solid Part: The lower magnifications show that the tumor is divided into nodules strongly colored by the nuclear dyes. These nodules are incompletely isolated by more or less thick bands of a fibrous aspect, which indent the nodules and seem to be getting ready to divide them into fragments. The nodules themselves are made up of agglomerations of moniliform cords, the intervals between which are occupied by a dense, richly nuclear mesenchymatous tissue.

Primitive Blastema: Certain nodules and especially their borders are dominated by compact cellular cords with indistinct margins in continuity with a myxoid tissue and hollowed-out by vesicles and short tubes. Here the appearance of a very primitive nephroid blastema is clear.

More Differentiated Blastema: In continuity with the cords mentioned above, or forming nodules by themselves, are others with more definite contours pitted with more numerous vesicles and tubes which seem to be formed at the expense of the undifferentiated cells.

These epithelial formations are of two different types: Some are frankly renal, made up of tortuous tubules with narrow lumens and slightly acidophile cuboid epithelium. Here and there very distinct Bowman’s capsules appear at their ends with an endothelioid lining of the concavity and cuboid cells with large nuclei on the convexity. Often these capsules are multiple and intercommunicating. Tubules and capsules are surrounded by a collagen membrane. Between these elements one finds undifferentiated cells and capillaries but never any glomerular tufts (Fig. 21).

The other epithelial formations are of an uncertain type: they are composed of vesicles lined with taller cylindrical epithelia with a more basophilic cytoplasm and nuclei frequently interdigitated. Some vesicles sprout and make small undifferentiated cells. Others are united by massive cords. Elsewhere this same epithelium forms sinuous tubes. Often vesicles, cords, and tubes are associated. Always they are enclosed within a mass of small undifferentiated cells. Sometimes they are isolated from these by a collagenous limiting membrane.
At different points a single cord contains mixtures of the two epithelial types, renal and indeterminate, or a single one of the two. It is difficult to say whether the “indeterminate” type represents an early stage of the nephroid type or something else. It is evident that these vesicles and tubes with very tall and slender epithelial cells whose nuclei are interdigitated have a neuroepithelial as well as a renal aspect. Whatever they may be, these indeterminate epithelial formations result from the transformation in situ of small undifferentiated cells. But some of them with a cylindrical cell lining bud and give birth to new undifferentiated cells (See Observation No. I, Type B).

**Strands:** The tissue with a mesenchymatous aspect which fills in the intervals between the cords and forms between them more or less thick strands, itself comes from the cords. This fact is evident in those cords with indistinct boundaries which one encounters bordering some nodules; the myxoid evolution of the cortical cells of the cords is identical with that which I have described in observations Nos. 1 and 2. It is less evident in the depths of the nodules where the cords have sharply defined edges and the dense mesenchyme composed of elongated cells causes them to parallel one another and form more or less thick strands of a sarcomatous aspect. These cords have voluminous ovoid nuclei, frequently in mitosis, and contain abundant albuminous and fatty droplets.

On closer inspection one finds numerous places where it is apparent that the small cells of the cords are transformed into mesenchymatous cells. Instead of ceasing to multiply, however, these cells proliferate. Instead of separating, they remain in contact with one another. They become elongated and arranged in bundles.

These elements, which seem so much alike in the beginning, later become differentiated. Some take on the character of long, branched connective-tissue cells. Others become striated muscle cells, whose frequency varies from one area to another. All of these elements proliferate and grow, thus increasing the thickness of the strands which they form. At this stage the stains show that in the interstices of the muscle fibers, which are intercrossed or grouped in bundles, there are typical ganglion cells. These are isolated or arranged in short rows. The largest of these contain Nissl bodies in the periphery of their cytoplasms.

To sum up, the nephroid blastema is still recognizable at this stage. Its essential characteristics are maintained, but its cords of small undifferentiated cells contain more epithelial formations, among which there are numerous renal tubes. On their edges the cords produce a vascular mesenchyme which separates them, and in which nerve and muscle cells appear.

**The Final Evolution of the Cords:** In places those cords which are composed of several different tissues are thicker and contain in their interstices typical embryonal renal tubes. This new feature is easily explained. In some areas there are lobules composed of interwoven renal tubes whose convolutions are separated by a mixture of small undifferentiated cells and connective-tissue cells or by a mixture of connective-tissue cells, ganglion cells, and young muscle cells. One gets the impression that all of the elements of a cord which are not used in the formation of renal tubes either evolve in situ into connective tissue or become transformed pell-mell into muscle or nerve cells. These, moreover, are formed only on the edges of the cords in the strands which separate them. The end-result of this evolution of the cords is their disappearance. In their stead only renal tubes are seen, in a mixture of connective tissue, muscle, and nerve elements. These elements merge with the primitive strands and enlarge them accordingly.

The thick strands always fuse with the broad bands which surround the nodules, and which are similar in structure except that they have evolved farther. These broad bands are made up of loose connective tissue. In places they contain bundles of thick striated fibers, some of which are embryonal, with axial nuclei, while others are adult, with marginal nuclei. Between these are thinly scattered large ganglion cells, small ganglion cells, and here and there tubes, segments of renal tubules, and Bowman’s capsules without glomerular tufts (Fig. 22).

In brief, each nodule seems to represent a center of proliferation where the blastema grows and gives rise to epithelial elements, some of which are certainly renal while the nature of the others is doubtful. It also produces ganglion cells, connective tissue, and striated fibers.
(2) **Cystic Portion:** I have pointed out above the indefinite limits of the cystic region. Towards its center the cysts are large, lined by a single layer of definitely acidophile, cuboid cells, and separated by narrow connective-tissue strands. Toward the periphery of the cystic region the cysts become increasingly smaller, and are widely separated by compact tumor tissue. They can be seen to develop from nephroid tubes which are still surrounded by small undifferentiated cells (Fig. 21).

In the same region there are, moreover, cords and masses in all stages of nephroid evolution. There are no muscle fibers or ganglion cells in the myxoid tissue which surrounds these cords and masses, or in the denser tissue which is rich in collagen. Here the blastema gives rise only to connective tissue, and to renal tissue which is recognizable not only because of its structure but because of its secretory functions. My only regret is that I did not think of analyzing the contents of the cysts chemically.

**II. Bielschowsky Method:**

(1) **Solid Portion:** Bielschowsky's method brings out very little of the structure of the cords. Very infrequently in regions where there are vesicles with tall cylindrical epithelium it impregnates tiny neuroblasts, with two, three, or four processes, among the undifferentiated cells.

In the strands of sarcomatous cells without evident muscle fibers, the Bielschowsky method shows very sparsely scattered extremely small neuroblasts. These are angulated and elongated. Some are situated at the edges of the cords, while others are situated in the middle of the sarcomatoid tissue. Their processes are varicose. One or two of them weave in and out among the undifferentiated cells of the cords, while the others are entangled in the interstices of the mesenchyme.

In the thicker strands the Bielschowsky method brings out muscle cells which are much larger than those shown in the stained sections. The cells are very slender, but their double striation is perfectly outlined by the silver. There are more numerous neuroblasts, which are often arranged in rows and connected by the hair-like extensions of their processes.

In the still thicker strands, where there are large striated fibers which can be clearly seen in sections stained by ordinary methods, nerve cells abound (Fig. 21). These are of all sizes, some as small as the cells of the masses and the strands which do not contain...
muscle, others very large. Their number varies from one point to another, and is sometimes considerable. There are often from six to ten per field (3 mm. apochromatic Zeiss objective and compensating ocular No. 7). They are found chiefly in the interstices of the muscular bundles. Their form is variable. Some are rounded, others elongated in the direction of the muscle fibers which surround them. All are multipolar and send out multiple varicose, slightly sinuous processes, which extend along the muscle fibers. Some of the processes are short. One of them is extremely long. In certain fortunate preparations it can be followed for 50 or 60 microns, but not further. This is not because it ends at this point, but because it leaves the plane in which the section is cut, and it is very difficult to identify it and follow it in the next sections. Whether long or short, these processes extend along the muscle fibers in close contact with them. Some of the processes send out small collateral processes which encircle them and are then lost to view. At no point have I seen anything resembling a motor plate.

In these huge fibromuscular bands which separate the nodules, the ganglion cells are more widely scattered. Their absolute number is probably not decreased, but they are distributed in proportion to the increase in mass which results from the differentiation of the connective and muscle tissues in which they lie. These adult cells, which are often

FIG. 23. OBSERVATION No. 3: BIELSCHOWSKY PREPARATION SHOWING ULTIMATE AND COMPLEX EVOLUTION OF THE BLASTEMA. × 600

Two renal tubes are cut transversely and a rudimentary malpighian corpuscle is included in a crowded mixture of cells of a fibroblastic aspect, striated muscle fibers, and nerve cells in various stages of evolution. Below are three young neuroblasts; at the left, ganglion cells; here and there, neurites the cells of which cannot be seen. At the right is a muscle fiber and side by side with it are sinuous neurites.
encapsulated and are often grouped to form small ganglions, have multiple processes. One of these processes, which is very long and often of large caliber, can be followed for a considerable distance along the muscle fibers. Here and there elongated schwannian nuclei are attached to them.

To sum up, one gains the impression that the nerve cells originate in the cords and migrate in the mesenchymatous strands. There they increase in number and differentiate into multipolar ganglion cells. In contact with them numerous muscle cells appear, grow, and differentiate.

(2) Cystic Portion: My impregnations of the definitely cystic region have all failed. Since this failure may have been due to the thinness and the lack of homogeneity of the tissue, I have made other attempts with blocks of compact tissue taken from the very edges of this region. Some of these have shown structures comparable with those which have been described above: neuroblasts scattered in the cords, ganglion cells, and muscle fibers in the strands. One other contained only nephrogenic masses with immature tubes and typical glomeruli. I could not discover in it a single neuroblast, nerve fiber, or muscle fiber.

Comparison of the Three Tumors

The three adenosarcomas which I have just described have an indisputable appearance of family relationship. All three contain a complex of mesenchymatous elements, of cords of small cells and epithelial formations which correspond very exactly to the metanephrogenic blastema. This blastema proliferates and perpetuates itself in its primitive form in the three tumors but, contrary to what one might expect, the fertile portion of this blastema is not the loose and branching-celled mesenchyme but the cords of small cells and the epithelial formations. Between cords and epithelial formations the relations are most peculiar; the cords give birth to the epithelial vesicles, which may in their turn give birth to cords in an indefinitely renewed cycle.

The stellate mesenchyme, far from forming the cords, is on the contrary formed by them. It is the small external cells of these latter which progressively are transformed into mesenchyme. In the same fashion the fertile cords are separated one from the other by mesenchymatous strands developed from them, and the elements of which become progressively older the further they are separated from the cords and occupy the middle region of the strands.

In the first tumor, the blastema almost everywhere has the same primitive characteristics. Its nephrogenic potentiality becomes evident only at the rare places where it caricatures tubules provided with rudimentary Bowman capsules. Everywhere else it manifests a neurogenic potentiality not only by the presence of sympathogenic capsules but also by a production of neuroblasts, which, born in the cords, pursue their evolution in the mesenchyme, which itself comes from the cords and separates them. In the same fashion the cords behave themselves like a blastema where there are differentiating at the same time sympathetic neurones, mesenchyme, and in places rudimentary nephrons. Further, in this same mesenchyme born of the cords and inhabited by young neurones, striated muscle cells are constructed.

In the second tumor the blastema presents in places an aspect just as primitive as the first but everywhere, in addition, the epithelial formations with elevated cells occupy a larger space at the expense of the small crowded cells. The nephrons are rare but more highly developed. The neurogenesis
is abundant, but sympathogenic capsules are lacking. Young neuroblasts are rather rare; larger and more highly differentiated neuroblasts predominate and are found especially in the strands. One gets the impression that the neuronoformative aptitude of the small cells of the cords, so important in the first tumor, is here on the decrease, and that most of the neuroblasts are already formed and have nothing to do but pursue their differentiation without, however, ever attaining an adult aspect. The strands are more or less rich in muscle cells, developed in situ and in addition highly differentiated.

In the third tumor the primitive blastema exists only in very limited areas at the periphery of the nodules. In the depths it has differentiated, giving birth to epithelial formations some of which are indeterminate while the others are indisputably renal. Young neuroblasts are very rare. Differentiated neuroblasts, young and adult ganglion cells abound in the strands, especially in those which are rich in muscle fibers. In places, nephrons, ganglion cells and young muscle fibers are closely intermingled; in other places the blastema forms only renal tissue (cystic areas); elsewhere only muscles and adult or semi-adult nerve cells are found.

To sum up, the three tumors seem to form a series. In the first, a rudimentary and fertile blastema gives birth to countless sympathetic, muscular, and mesenchymatous elements as well as renal rudiments. In the second, the neurogenesis is less and the neuroblasts are more differentiated, as are the muscle fibers and the renal epithelium. In the third, the differentiation is still further advanced: the rudimentary or functioning (cystic) differentiated tubules form an important part of the tumor; the connective tissue, the neurones and the young and adult muscle fibers form the rest of it. The small cells of the cords grow fewer proportionately as differentiation progresses and disappear entirely in the areas where it has terminated (supporting strands of the cysts, nephro-musculo-ganglionic strands).

Everything takes place as if not only the nephrons but also the sympathetic cells, the muscles, and the mesenchyme had a common origin in the primitive blastematous cords, and as if the complex and pluripotent blastema formed first the sympathetic and mesenchymatous elements, themselves destined to become partially muscular, then the renal tubes and, while doing this, disappeared.

Without doubt these three tumors do not represent all the embryonal adenosarcomas of the kidney. The different aspects of their constituents, however, is so like those which one observes in the majority of adenosarcomas that one may be permitted to suppose that their significance, as it emerges from our study, has a general application.

**Discussion**

Among the facts which emerge from this study, there is one which I believe does not require any discussion: the existence of nephrogenous tissues in the embryonal "adenosarcomas" of the kidney. The presence of rudimentary nephrons (first case), more differentiated ones (second case), and altogether typical ones (third case), is decisive. And, since the nephrons are constructed in the blastematous cords at the expense of their cells, and these
cords disappear when the renal tubules are completely differentiated, it is necessary to recognize the reality of metanephrogenous blastema in these tumors. Ribbert and Harbitz were therefore both wrong, the former in denying it and the latter in doubting it.

One fact, however, proves that Ribbert and Harbitz were partly right: the enormous development of nervous tissue in these tumors. Only, the latter tissue does not have, either in the three cases studied here or in any case in my collection, the significance which is assigned to it by these authors. It is not neuraxial tissue developed from the medullary tube, which is itself developed from the neural plate. Such an origin would be acceptable for neuro-epithelial tubes surrounded by neurospongium separated from the mesenchyme by a limiting membrane; it would be all the more acceptable if this neurospongium was developed from fixed neuroblasts and little by little was transformed into neurones, neuroglial cells, and fibers. I have observed nothing like this in my tumors.

What I have seen is young neuroblasts in blastematous cords, morphologically identical with those of nephrogenous blastema, which emigrate—or seem to emigrate—and differentiate in a mesenchyme which is derived from the same cords as they are. These cords can contain (first case) sympathogonic capsules. In every case the ganglion cells born of these neuroblasts are pluripolar elements, encapsulated by satellite cells and contained within a tissue of the aspect of connective tissue.

The sympathetic nature of these neuroblasts and neurones could not be doubted. What then is the significance of the blastema from which they develop, which at the same time produces satellite cells (Schwann cells) and mesenchyme?

Embryology teaches us that the neural plate and the neural groove which follows it form the neuraxis, its fixed neurones and its neuroglia and probably (Raven) part of the sympathetic system. The rest—the most important part of the sympathetic—comes from two ectoblastic bands situated symmetrically at the borders of the groove, themselves also neuroectodermic but taking no part in the construction of the neural tube. From these ectoblastic bands are developed the deep cells which become isolated from the epithelium, force themselves into the mesoblast, multiply there, and form masses behind and on the sides of the medullary tube.

These masses or neural crests are formed of small and compressed cells. Their contours are ill-defined and vague. In these masses are individualized first the neuroblasts, not fixed ones like those of the neuraxis but migrants which will become spinal and sympathetic neurones; second, the supporting elements attached to the preceding, the lemmoblasts, from which are developed the cells of Schwann, and also, third, cells with mesenchymatous characteristics (Landacre). It is on their borders that the crests undergo this mesenchymatous evolution and this it is which assists in giving them an indistinct contour. To this mesenchyme developed from the neuroectoderm of the crests, Stone has given the name of mesectoderm.

What are the destiny and the degree of extension of this mesectoderm?

I do not, of course, deny the possibility of a participation of neuroepithelium from the neural plate in the construction of certain mixed tumors of the kidney.
We only begin to recognize it in the cranial crests of the Urodelae. Stone and Raven have shown that it furnishes a part of the connective tissue which surrounds the neuraxis, that of the fins and, what is still more surprising, a part at least of the cartilaginous skeleton of the branchial arches. Our information is less precise so far as the dorsal and lumbar crests are concerned. It is known only that they form the chorion of the region. In the higher vertebrates, and especially in man, we know only that the mesectoderm exists; its destiny is unknown.

The general characteristics of the neural crests and of the “neurogenous blastema” of our tumors are identical. In both cases, an epithelium composed of tall cells with interdigitated nuclei gives rise to a blastema composed of small undifferentiated cells, among which are differentiated migrant neuroblasts, schwannian elements, and mesenchyme.

Everything leads us to believe that the indistinctly margined neurogenous cords of the renal tumors represent neural crests. But while in the normal embryo the neuroectoderm which borders the neural plate, and later the crests which develop from it have only a very ephemeral existence and disappear because all their elements are precociously differentiated into neuroblasts, nerves and connective tissue, in our renal tumors this same neuroepithelium proliferates for a long time in its primitive aspects, forming neuroepithelial vesicles and tubes; these vesicles forming masses, themselves long fertile, the homologues of the crests. In these masses, on the one hand, vesicles, the parents of new masses, are constructed; and, on the other hand, neuroblasts and Schwann cells are differentiated while their peripheral elements form mesenchyme, which is the equivalent of mesectoderm.

It must be admitted that numerous “undifferentiated” cells in the cords are in reality sympathogonia. In places these sympathogonia accumulate, at the same time undergo a beginning sympathoblastic evolution, and construct “sympathogenic (which it would be more proper to call sympathoblastic) capsules” identical with those observed in immature ganglia of the sympathetic chain and in sympathomas. These capsules, moreover, have a very ephemeral existence and are broken up when the sympathoblasts enlarge and become differentiated. Locally the sympathogenic elements may proliferate alone and construct in the renal tumor, as well as out of it, pure sympathomas, as was the case in the extracapsular portion of our first tumor.

On the other hand, it is possible that certain bipolar ganglionic cells included in the mesenchymatous strands represent a spinal ganglionic element coming from the tumoral crests. On this point, I do not dare make any definite statement. What is certain is that the majority of tumoral neurones are multipolar and without any doubt sympathetic.

Up to this point everything is easily explicable: the renal adenosarcomas seem to contain two germinal cell groups, one the equivalent of a neural crest blastema, the other of a nephrogenous blastema. But, if in certain tumors the sympathetic nervous tissue (first case) or the nephrogenous tissue (third case) can proliferate in a pure state, this unilateral proliferation is local and secondary. As a rule, nervous and renal elements seem to be developed from a common blastema, having at the same time the characteristics of the neural crests and the renal blastema.
To this extraordinary statement must be added another: the muscle fibers appear in the new formed mesenchyme and even in the cords of small cells themselves, and everything goes to show that they come from a common neuro-nephrogenic blastema!

It cannot be a question here of different tissues growing side by side and secondarily penetrating one another. When one sees a striated myoblast formed right in the center of sympathoblasts grouped in a capsule (Fig. 13), or when one sees a hardly differentiated nephron whose twistings are included within a confused mass of undifferentiated cells, of neuroblasts, and of young muscle fibers (Fig. 23), it cannot be a question of secondary interpenetration but of differentiation in situ of elements having different potentialities, previously mixed. Now these elements with different potentialities without any doubt form part of a blastematous cord. It is this one, therefore, which is pluripotent.

If one attempts to reconcile classical embryological conceptions with these facts, one reaches the conception that each pluripotent cord contains, first, neuroectodermic germs equivalent to the neural crests; second, nephrogenous mesoblastic germs; third, myogenic germs representing myotomes. These elements are necessarily associated from their beginning, from the very earliest weeks of embryonic life. They continue to proliferate mingled together and in their most primitive form during the months of fetal life, to which must be added the years which precede surgical operation or death. The nervous, muscular, and renal differentiated elements to which this mixed blastema gives rise, appear only at a late period and locally exhaust its multiple potentialities; in the most highly differentiated tumors this primitive blastema persists locally with its fertility and pluripotency.

Now if one considers in the embryo the moment when the neural crests, the myotomes and the metanephrogenic blastema appear, it is established that if the crests and the myotomes are sufficiently contemporaneous and neighboring so that their "illegal mixture" (R. Meyer) may be possible, this is not true also of the nephrogenous blastema. The appearance of this latter occurs only long afterward, when the crests have disappeared after having formed differentiated elements and when the myotomes are already muscle fibers.

This chronological difficulty did not escape Wilms. To explain the tissue mixture of the "mesodermic mixed tumors" he carried their origin back to the inclusion of mesodermal germs before the separation of the mesoderm into sclerotome, myotome, and nephrotome. But if this early origin explains up to a certain point the association of renal, muscular, and connective tissues in the adenosarcomas, it less easily explains the permanence of the association of their undifferentiated germs in the blastematous cords; for one must not forget that it is from the cords and their fecund, undifferentiated cells, all alike, that there come, very probably, the generations of tumor nephrons, muscles and mesenchyme which appear during the months and years of tumor growth. Especially it does not explain why these same cords in their most primitive form before the production of nephrons give birth to neurons characteristic of the crests. Still less does it explain the indisputable fact of the formation of the blastema by the vesicles isolated in the tumor mesenchyme. I am referring here to those masses of undifferentiated cells which result from
the proliferation of the vesicle epithelium and its cellular budding outside of
the basement membrane (type A of tumor No. 1).

Thus everything occurs as if these vesicles were the sole and earliest tissue
of origin of the tumor, since the small cells of the cords which come from them
are the blastema in which neurones, mesenchyme, muscle, and nephrons are
differentiated.

Now the neurones in question for the most part have the characteristics
of sympathetic neurones. The vesicles from which indirectly they are derived
and which are never present either in the sympathetic system or its tumors,
can only be neuroepithelial vesicles derived, not from the neural plate, but
from the lateral neuroepithelium of the neural crests. The undifferentiated
cells from which they come directly are elements of the neural crests. The
mesenchymatous cells which are developed also from the undifferentiated cells
are mesectodermic.

Up to this point the reasoning is orthodox; the neuroepithelium, cords,
neurones, and mesectoderm of our tumors form a series of elements which can
be identified with the lateral neuroepithelium and its successive derivatives:
neural crests, neurones, and mesectoderm of the normal embryo. They do
not differ from it except by the persistent fertility of their initial forms: the
neuroepithelium (the vesicles) and the undifferentiated elements of the crests
(the cords).

The argument becomes heretical, however, if one pursues it in conformity
with the facts revealed by the adenosarcomas: these same elements of the
crests which are the cords formed of vesicle neuroepithelium give rise not only
to the derivatives of the crests (neuroblasts, lemmoblasts, mesectoderm) but
also to striated muscle and rudimentary nephrons. This leads to the concep-
tion that in the normal embryo, certain striated muscles and the nephrogenic
tissue have for their origin not the mesoderm (mesendoderm) but the mes-
ectoderm of the neural crests. That is enough to cause the rejection in toto
of all I have said so far.

Nevertheless, the facts are there. There is no use saying they are "patho-
logical;" one must reckon with them and try to explain them even if it is
necessary to have recourse to hypotheses which descriptive and experimental
embryology has not yet advanced.

The conception of the neuroepithelial origin of myogenic and nephrogenic
mesenchyme does not rest upon any experimental fact, I confess, and hence
appears to be of an absurd audacity. But would it not have been considered
absurd, only ten years ago, if some pathologist had presumed, on the basis
of observations made on a tumor of the neck, to suggest that the branchial
cartilages developed perhaps from the cranial crests?

The dysgenetic tumors are great empiricists, and the knowledge gained
from them must not be rejected on principle.

After all, the "renal adenosarcomas" do not contain those cellular mon-
strosities characteristic of cancers in the adult. Their cells are typical.
They form groupings identical with certain transitory tissues in the normal
embryo: neural crests and nephrogenous blastema. But instead of being
ephremeral and disappearing because their elements have become differen-
tiated, these tissues in blastomatous proliferation perpetuate themselves in
their primitive form for months and years, at the same time perpetually furnishing elements which themselves ripen, evolve, and differentiate. It is the variable proportion of the primitive blastema and the differentiated tissues derived from it, the stage of differentiation of these latter at the moment of histological fixation, and their capricious distribution which produce the polymorphism of the renal adenosarcomas. But looked at separately, all the constituents are typical, even more typical than those which form the greater part of the tissue grafts with which the embryologists are content.

In so far as the reality of the genetic relationships between muscle and nerve tissue is concerned, different facts argue in its favor in the same fashion as do the renal adenosarcomas. There is first of all Marinesco and Goldstein's myogenic "medulloepithelioma" of the cerebellum, which could very well be a complex nervous tumor—at the same time medulloepithelioma and neuroepithelioma of the cranial crest—included within the cerebellum. Next there are the observations made on rhabdomyomas of nerves (Gratia, Orlandi, P. Masson), whose striated cells come not from myotomes but from constituents of nerves originating from the neural crests.4

The nature of these relationships is disputable. One may suppose that the muscular evolution of certain constituents of the blastema is predetermined, epigenetic. One may also suppose that it is secondary and induced by the nervous tissue acting the rôle of organizer of the mesectodermic elements: nothing up to the present permits one to choose.

In so far as the connection between the lumbar crests and nephrogenic tissue is concerned, we have before us only the facts revealed by the adenosarcomas. However paradoxical they may be, they are sufficiently eloquent in themselves. How can one explain without this connection the development of neuroblasts, lemmoblasts, and mesectoderm first, and later of nephrons, from a common blastema morphologically identical with the neural crests?

If one permits the supposition that the neuroepithelium, father of the lumbar crests, has as derivatives not only the neuro-mesectodermic elements but certain muscles and the nephrogenic mesenchyme, one will easily conceive that the displacement and the precocious neoplasia of some elements of this neuroepithelium may be the sole source of mixed tumors of the kidney which are at the same time nervous, mesectodermic, muscular, and nephrogenic. This means having recourse to a hypothesis basically scarcely more audacious than that of Wilms, to explain the origin, site, and the complexity of the embryonal adenosarcomas of the kidney. These pluripotent germs of connective, muscular and renal, and for good measure neurogenic tissue, which appear in the guise of blastematous cords, I derive from the neuroepithelium (vesicles), from which I have seen them develop (Case No. 1).

Resumé and Conclusions

The three renal tumors studied in this work present the classical characteristics of the embryonal adenosarcomas. Their study by ordinary methods and by neurological impregnations shows that they are composed not only

4 This special point will be developed in another paper.
of the renal glandular elements, mesenchymatous elements, and striated muscle admitted by the majority of authors, but also of neuroepithelial and nervous elements which can be linked with the lateral lumbar neuroepithelium and the neural crests derived from it. Their "nephrogenous blastema" is composed of undifferentiated cellular cords formed by neuroepithelial vesicles. These cords have the structure of neural crests and give origin first to neuroblasts, especially of a sympathetic type, to lemmoblasts, to a mesectodermal mesenchyme, and to striated muscle fibers. These same cords later disappear in giving birth to rudimentary nephrons.

The tumor blastema is, therefore, neurogenic, sclerogenic, myogenic and nephrogenic. Its neurogenic properties show the certain participation of the lumbo-lateral neuroepithelium and its crests in the construction of mixed tumors of the kidney. Its myogenic and nephrogenic properties raise a question: Are the lumbar crests the possible source of certain striated muscles and of the metanephrogenic blastema? The reply belongs to experimental embryology.

If one reflects upon the frequent presence of spinal and sympathetic ganglia in a number of teratomas composed of adult tissue, it is permissible to believe that these elements themselves come from neural crests but that these neural crests have existed as such only in the very earliest stages of the development of the tumors and have rapidly disappeared as they do in the normal embryo because they have become differentiated. It is only in malignant teratomas with immature tissues that one can hope to encounter them.

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BIBLIOGRAPHY

LANDACRE: J. Comp Neurol. 33: 1, 1921.