A GANGLIONEUROMA IN THE NECK OF A CHILD *

JOSEPH MCFARLAND, M.D., Sc.D., AND SAMUEL W. SAPPINGTON, M.D.

(From the McManes' Laboratory of Pathology, University of Pennsylvania, and the Hahnemann Medical College, Philadelphia, Pa.)

Neoplasms of nervous origin are always interesting because of their comparative rarity, their doubtful origin, their variable structure, the difficulty of properly naming and classifying them, and the uncertainty of their clinical behavior. The particular tumor whose description follows was therefore welcomed and the result of its study made the starting point of a thorough literary and critical survey of the group of tumors to which it was finally assigned.

REPORT OF CASE

Clinical History: A. C., a white female, 7 years of age, whose parents are living and well, was delivered by a normal labor, weighing at birth 9½ pounds. She was breast fed for 1 month only.

The first teeth erupted at 3 months but the teeth of the first dentition were all poor in quality. Infancy and early childhood were uneventful, but at 5½ years of age, a swelling made its appearance in the region of the cervical lymph nodes and continued to enlarge until, her parents becoming apprehensive, she was brought to the hospital. She was thought to have tuberculous adenitis and was given a course of five X-ray treatments, 3 weeks after the last of which she was admitted to the Hahnemann Hospital on Feb, 16th, 1931.

On admission the patient was rather pale, though apparently well nourished. Examination showed the breathing to be slightly obstructed and the tonsils enlarged. A large, smooth, nodular mass was present in the right side of the neck which was not tender, and did not fluctuate. Blood examination on admission showed hemoglobin 70 per cent, erythrocytes 3,500,000, leukocytes 5900. A second blood examination made March 4th showed the hemoglobin to be 72 per cent, erythrocytes 4,290,000 and leukocytes 6200, of which 58 per cent were polymorphonuclears, 35 per cent lymphocytes, and 7 per cent transitionals. The temperature varied between 97 and 99.8° F., and the pulse between 76 and 118.

On Feb. 23rd, 1931, a tonsillectomy was performed and a pharyngeal abscess opened. The general condition then improved, though no change occurred in the swelling in the neck and the temperature continued to rise occasionally.

An examination of the chest made March 5, 1931, showed bronchial breathing, more tubular than usual, in the midportion posteriorly, with broncophony

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and well transmitted tactile fremitus and râles. Heart normal. A Mantoux test was performed on the right forearm and reported positive.

An X-ray examination of the chest made March 10, 1931, showed distinct thickening of the roots of the lungs with extension to both bases and to the right upper lobe. There were a few calcified areas at the roots of the lungs and some mottling of both upper lobes. The disturbance at the roots of the lungs was thought to be in the bronchial lymph nodes.

On March 12, 1931, another Mantoux and a von Pirquet test were performed on the left forearm, and on March 18th both were reported negative.

On April 4th the patient was released on the mother's request, and the diagnosis recorded as tuberculous adenitis.

She was readmitted to the hospital on April 23, 1932. Blood examination gave 7400 leukocytes, of which 61 per cent were polymorphonuclears, 38 per cent lymphocytes and 1 per cent basophiles. Two days later the hemoglobin was 91 per cent, leukocytes 6200, of which 82 per cent were polymorphonuclears, 13 per cent lymphocytes, 2 per cent transitionals and 3 per cent eosinophils. After two more days there were 65.5 per cent polymorphonuclears (55.5 per cent mature, 7 per cent immature and 3 per cent metaleukocytes), 28 per cent lymphocytes, 4.5 per cent transitionals, and 2 per cent eosinophils, with abundant platelets, many broken, poorly stained and degenerated white cells. The red cells were normal. The temperature, 100° F. on admission, descended to 99° F. that night, and remained at that point.

On April 27, 1932, an X-ray examination of the chest showed the conditions previously reported, except for pulsation in the right infraclavicular region thought to be characteristic of tuberculous infection.

On May 4, 1932, the patient was operated upon and a firm encapsulated tumor about the size of a lemon was removed from a position deep down in the neck. At the upper pole it appeared to be attached to some bony structure; elsewhere it was free.

Specimen from the operation consisted of two masses of tissue, one 6 by 5 by 4 cm., the other 5 by 3 by 2.5 cm., weighing 90 gm. They were white, fairly firm and easy to section, but the gross appearance was not characteristic of any recognized condition. There were no areas of caseation and no suggestion of tuberculosis.

After the operation the temperature of the patient varied about 100° F. for a week or so, then gradually descended to reach normal by May 20th. Additional X-ray treatments were given for prophylaxis against recurrence, on May 24th and May 27th, and the wound having healed the patient was discharged June 18th, 1932.

She reported at the hospital for follow-up examination June 24th, when she looked well and said that she felt well.

She was again seen on May 5th, 1934 (2 years later), and seemed to be quite well. Her mother, however, said that she coughed during the day and was nervous during the night. She also turned her head to one side when swallowing, probably because of the effect of the operation scar.

Careful examination of the scar and its neighborhood showed no evidence of any recurrence of the tumor. She has, however, a curious soft swelling, sharply limited to the left side of the tongue, thought by the mother to have developed after leaving the hospital. An X-ray examination of the chest showed no sign of metastatic tumors in the lungs.

Microscopic Examination

The tumor consists of a fibrillar background or stroma in which are scattered cells and cells in groups.

The fibers that make up the greater part of the tumor present considerable diversity of appearance. Some are extremely fine and wavy, others coarse and collagenous. The indistinct bundles of fibers intertwine so that they are always cut both longitudinally and transversely. Some have their respective fibrils widely separated, as in edema, others are compact. There is an occasional tendency to hyalinization, and at many points a granular breaking down followed by colliquation necrosis leading to the formation of minute indefinite spaces.

The nuclei of the fibrillar tissue are elongate, oval and vesicular where the fibers are coarse; elongate, slender and more uniform where they are fine and wavy. In many places distinct palisades of nuclei show indubitably that the fibers belong to nervous tissue. A few definite nerve fasciculi are seen, but may belong to antecedent nerves about which the tumor has grown. Except in them, no medullary sheaths were found.

The cells distributed through this background of fibers seem to form an ascending series that begins with small cells not unlike lymphocytes and ends in typical ganglionic nerve cells. The various forms — neurocytes, neuroblasts, sympathoblasts and ganglion cells — occur together. Individual cells in all or any of these stages of development are scattered singly or in groups throughout the whole tumor.

Small cell groups of spindle shape, and composed of a few large unmistakable nerve cells, with abundant cytoplasm, beautiful vesicular nuclei and large distinct nucleoli, flanked by smaller cells tapering off to very small ones at the ends of the spindle, not infrequently occur in the intervals between the fibers.

Larger collections of cells constitute a striking picture. A good many correspond with the ganglionic nerve cell groups characteristic of ganglioneuroma, and adjacent to them palisade arrangement of the nuclei shows the fibrillar tissue to consist of Schwann cells. There is no doubt but that the tumor is a ganglioneuroma. But it is not without its eccentricities. Many of the cells are immature forms closely or loosely massed together in a very delicate or loose stroma,

or in indefinite spaces in the stroma. These cell aggregations, so numerous, so large, and so indefinite, misled some of those who first examined the tissue into the error of believing that they were looking at some form of malignant epithelial tumor.

The cells represent all of the stages of development, but instead of each progressing regularly to the ganglion cell stage, those of all stages seem to multiply at random, then degenerate or liquify.

Scarcely a nerve cell, primitive or advanced in development, appears to be in a state of good health. Large ganglionic cells with beautiful vesicular nuclei commonly have finely or coarsely vacuolated cytoplasm, or they possess two, three or four nuclei, uniformly developed and healthy; or, one or several nuclei may appear normal while others may be mitotic, pyknotic or vacuolated. Mitoses, not frequent, may be found in the cells of the same group. In adjacent groups there may be none. Judging by this criterion the growth of the tumor should have been slow and should have progressed by multiplication of cells, now here, now there.

The retrogression and colliquation of the ganglion cells was attended by finer, then coarser vacuolation, then fraying at the edges. In some cases there was cytopyknosis and karyopyknosis in which the nuclei became small, dark colored bodies eccentrically situated toward the surface of the cell whose cytoplasm was solid, uniform and eosinophilic.

The general impression resulting from the study of sections stained by hematoxylin and eosin, iron hematoxylin, Weil's and Bielschowsky's methods may be summed up as follows. The neoplasm is a ganglioneuroma whose development began with the multiplication of embryonal neurocytes, and continued through the continued multiplication of those primitive cells and their evolving descendants up to the stage of ganglion cells. Whether perfected ganglion cells can multiply is uncertain, but many which seem to have reached perfection contain two, three and four nuclei and show an occasional mitotic figure. These ganglion cells probably give off neuraxons, which account for the nerve fibrils brought out by the Bielschowsky stain, and seem to excite the proliferation of the Schwann cells which show the palisades of nuclei. Then the ganglion cells, and many of the sympathoblasts not yet that far developed, lose their vitality, retrogress and dissolve into the jelly-like accumulations by which the collections of dying cells are surrounded. In a few

instances the dead cells calcify so that occasional, small, irregularly rounded aggregations of lime salts occur in the tissue. The generations of cells that have matured, produced fibrils and disappeared, account for the neurofibromatous stroma or matrix of the tumor.

Comment

Wahl [137] in speaking about ganglioneuroma in his excellent and complete paper credits its name "ganglioneuroma" to Odier [97] in 1803, its origin from sympathetic ganglia to Günsburg [59] in 1845, and its position with respect to other nervous tumors to Virchow in 1863. With the subsequent publications of Loretz,[84] Key,[8] and Weichselbaum [140] the tumor became a well established and generally recognized entity that has attracted more and more attention and led to the reporting of more and more cases with the passage of time, as shown in the papers of Wahl,[137] Hook,[66] Rapp,[110] Pick and Bielschowsky,[106] Dunn,[42] von Fischer,[46] Riggs and Good,[112] Smirnoff,[128] and Bigler and Hoyne.[20]

It is interesting to see that the number of reported cases increased from 33 in 1911, 36 in 1913, and 68 in 1932, to the present total of 143 that can be drawn from our bibliography. Accuracy regarding the number of published cases is impossible because of the difference of opinion as to just what tumors shall be included under the name ganglioneuroma. Ever since the tumor was first described by Odier the criterion for its identification seems to have been the presence of an abnormal number of ganglion nerve cells, but Gibberd [53] has described as ganglioneuromas two tumors in which no ganglion cells were found in the sections examined by Mr. R. Davies-Colley, his pathologist.

Pick and Bielschowsky [106] in 1911 expressed the opinion that the tumors of the group to which the ganglioneuromas belong, originate through embryonal malformations or the displacement of multipotential embryonal neurocytes, and consist of "ripe" or "unripe" neuroblasts. This idea agreed with that of Brossok [25] in 1911 and Dunn [42] in 1915, and was elaborately discussed, especially with reference to the benignancy and malignancy of the tumors by von Fischer [46] in 1922.

According to von Fischer the primitive nerve cells, or sympathogonia, as they multiply to form tumors may maintain their primi-

tive or original shape and indicate their nature solely by the formation of the finest fibrils which lie between the cells without any kind of definite arrangement. A tumor of this structure is called "sympathogonioma" by Kohler, and constitutes the most primitive variety of neuroblastoma. With a slightly more advanced stage of differentiation these fine fibrils are gathered into coils or skeins about which there is a more or less distinct arrangement of the sympathogonia to form rosettes, while elsewhere numbers of the cells are advancing in size and differentiation to sympathoblasts or the antecedents of the ganglion cells. A tumor of this slightly higher structure is called "sympathoblastoma." When the number of sympathoblasts begins to exceed the number of sympathogonia, and more definite ganglion cells appear, singly or in groups, amid bundles of fibers and cells of Schwann, the tumor becomes "ganglioneuroma simplex."

It thus appears that two entirely different appearing tumors, the sympathoblastoma (neurocytoma of Marchand [89] and Wright [142]) and the ganglioneuroma, simply represent the beginning and terminal stages in the neoplastic development of the embryonal nerve cells of which they are made up.

But the vegetation and differentiation of the cells do not regularly parallel one another. The cells may remain in the stage of sympathogonia or neuroblasts, when the tumors, purely cellular, highly malignant and metastatic, are easily mistaken for small round cell sarcomas; or some of them may persist in that primitive state while others differentiate into ganglion cells with nerve fiber and Schwann cell additions, giving rise to tumors, parts of which seem to be of one kind, other parts of another kind. Such a tumor was described by Robertson [116] as a ganglioneuroblastoma.

As the respective malignancy or benignancy of the nerve cell tumors is the result of the failure of the cells to mature on the one hand, and the perfection of their maturation on the other, any tumor containing sympathoblasts (or neurocytes) may be considered as malignant, or potentially malignant, in proportion to the number and vegetative activity of the primitive cells it contains. It is the small size of the primitive cells, their independence, and the ease with which they can be transported that are responsible for the metastases. It may therefore be assumed that every metastasis consists primarily of such primitive elements. But just as at the

primary seat of occurrence many of the cells progress in differentiation and some reach the final stage of ganglion cells, so in the metastases some or many of the cells may advance to complete differentiation and some or many ganglion cells be found in them. It may even be possible for all of the cells to complete the differentiation to ganglion cells incapable of multiplication so that an originally malignant tumor may become benign. Such a case was studied by Cushing and Wolbach.[38]

The tumors are further divided into *ganglioneuroma immaturum* and *ganglioneuroma imperfectum*. These names explain themselves.

It is interesting that the ganglion cells sometimes seem to retain the power of multiplication until complete specialization is attained. Many of the cells, whose appearance suggests maturity, may be found in mitosis, or to have two or many nuclei.

Ganglioneuromas of the central nervous system have their histological structure increased in complexity through the presence of neuroglia elements of all kinds and in all stages of development. These constitute a special group of tumors to which the name ganglioglioneuroma has been applied.

But most peripheral ganglioneuromas also contain neuroglia-like cells, Schwann cells and nerve fibers.

Age Incidence

Ganglioneuroma may occur at any age. Von Fischer [46] found one in a stillborn infant. The tumor studied by Clegg and Moore [33] was present when the child was born. It is frequently said to be a tumor of childhood, but of 98 cases with age data we find 33 to have been less than 10, and 64 more than 10 years of age. Five of the cases in our bibliography were beyond 60 years of age, *viz.* Guizetti [58] 57 years, Brüchanow [26] 65 years, Bianchi [18] 68 years, Uyeyama [134] 69 years, Friedrich [48] 73 years, and Weichselbaum [140] 79 years.

Sex Incidence

It is also said to occur more frequently in female than male patients, and for this there seems to be some reason, as in 99 cases with sex data 56 occurred in females and 43 in males.

Anatomical Distribution

The left side of the body was affected in 22 and the right side in 16 cases. Many of the tumors, especially the mediastinal and retroperitoneal, are without information as to the side of the body in which the tumor originated.

The anatomical distribution is so general that ganglioneuromas may be encountered almost anywhere. The cases referred to in our bibliography were distributed as follows:

I. ABDOMINAL

(1) Intestinal
- Poate and Inglis [107]

(2) Mesenteric
- Bland-Sutton [21]
- Goodhart [56]
- Jones [71]
- MacNaughton-Jones [87]
- Paterson [101]

(3) Pancreatic
- Bianchi [18]

(4) Pelvic
- Beneke [14]
- Chiari [32]
- Newmann [95]
- Pick [105]
- Schorr [125]
- Stoeckel [130]

(5) Renal
- Bigler and Hoyne [20]

(6) Retroperitoneal
- Babcock [9]
- Berner [17]
- Busse [29]
- Cappell [31]
- Chiari [32]
- Cripps and Williamson [37]
- Fabris [43]
- Falk [44]
- Fischera [47]
- Glockner [55]
- Heinrici [65]
- Hortolomei, *et al* [67]
- Jergesen [70]
- Kopřiwa [77]
- Krecke [79]
- McFarland [86]
- Miller [93]
- Oelsner [98]
- Ohse [99]
- Rapp [110]
- Rosenbach [118]
- Sato [120]
- Schleifstein [121]
- Soyka [131]
- Strada [133]
- Wegelin [139]

(7) Sacral
- Chiari [32]
- Günsburg [59]

(8) Suprarenal
- Bigler and Hoyne [20]
- Brüchanow [26]
- Buzni [30]
- Dalton [39]
- Dunn [42]
- Gamna [50]
- Geller [51]
- Hook [66]
- Jaffé [69]
- Oberndorfer [96]
- Peters [104]
- Ribbert [111]
- Schmidt [122]
- Wahl [137]
- Wassmund [138]
- Weichselbaum [140]

(9) Exact Site Not Known
- Arpino [6]
- Bartlett [11]
- Behan [12]
- Beneke (coeliac) [14]
- Roman and Arnold [117]
- Smirnoff [128]

II. CEPHALIC

(1) CEREBRAL AND CEREBELLAR

Achúcarro [1]
Arpino [6]
Berblinger [15]
Bielschowsky [19]
Cushing and Wolbach [38]
DeJong [72]
Dumas [40]
Katzenstein [74]
Lhermitte and Duclos [83]
Marinesco [91]
Olivecrona [100]
Pick and Bielschowsky [106]
Robertson [116]
Schmincke [124]
Uyeyama [134]

(2) CRANIAL NERVES AND GANGLIA

(a) Trigeminal

Benda [13]
Cooper [35]
Fabris [43]

(b) Gasserian

Günsburg [59]
Hackel [60]
Haenel [61]
Marchand [90]
Risel-Zwickau [114]

(c) Ocular

Krauss [78]
Perls [103]

III. CERVICAL

Benda [13]
DeQuervain [106]
Freund [49]
Friedrich [48]
Geymüller [52]
Glinski [54]
Harbitz [63]
Haven and Weil [64]
Loretz [84]
MacAuley [85]
Martius [92]
Riggs and Good [112]
Shirai [127]
Sommerfelt [129]
Stout [122]
Von Fischer [46]
Woods [143]

IV. FACIAL

Clegg and Moore [33]
Dunn [42]
Key [8]

V. PERIPHERAL

(1) FLANK

Wilmoth, Bertrand and Patel [141]

(2) KNEE

Hagenbach [62]

(3) SKIN

Kredel and Beneke [80]
Montgomery and O'Leary [94]

VI. MEDIASTINAL

Babcock [9]
Bergonzi [16]
Bigler and Hoyne [20]
Brunner [27]
Ranzi [109]
Rosenson [119]
Riggs and Good [112]
Scott and Palmer [126]
Von Rindfleisch [113]

VII. THORACIC

Borst [22]
Guizetti [58]

VIII. VASCULAR

Anschütz [7]
Jacobsthal [68]

From this summary of 127 cases it will be found that seventeen of the reported tumors were, like ours, situated in the neck. The case reports, accompanied by the necessary data, show eleven of the patients to have been children and four adults. The cervical tumor of earliest occurrence was in von Fischer's [46] case of a stillborn in-

fant; that of latest occurrence, Friedrich's [48] case in a woman aged 73 years. The average age of the affected children was 5 years, of the adults 40 years. Five of the tumors were said to have been on the left side, five on the right.

Our case, therefore, adds one more to the seventeen reported cervical ganglioneuromas, one more to the eleven tumors reported as occurring in children and one more to those occurring in the right side of the neck.

Single and Multiple Tumors

Ganglioneuromas usually occur singly, but may be multiple, and when so the tumors may be either in close relationship with one another, widely separated or generally distributed. In the case reported by Knobelauch [76] there was one tumor in the facial-auditory region at the anterior end of the body, and another in the sacral region at the posterior end. Other multiple tumors have been reported by Haven and Weil,[64] Henrici,[65] Kredel and Beneke,[80] Knauss,[75] Montgomery and O'Leary,[94] Roman and Arnold,[117] Risel-Zwickau,[114] and Soyka.[131] When there are many widely distributed tumors the condition is frequently spoken of as ganglioneuromatosis, and the distributed lesions may be systematic or symmetrical.

Systematic multiple ganglioneuromas to the number of eleven, all in connection with the cranial nerves were observed by Risel-Zwickau.[114]

Symmetrical multiple cases have been reported by Günsberg,[59] Clegg and Moore,[33] and by Kredel and Beneke,[80] whose patient had about 160 separate tumors, and Montgomery and O'Leary,[94] in whose case the skin of the patient was studded with cutaneous ganglioneuromas on the trunk and extremities, while the vermiform appendix removed at operation showed increase of ganglion cells. The patient studied by Knauss [75] had about sixty subcutaneous ganglioneuromatous nodules scattered over the trunk and thigh. Lhermitte and Duclos [83] observed a case with multiple larger tumors whose occurrence, preceded by pigmentation of the skin, seemed more like von Recklinghausen's disease than ganglioneuromatosis and raises interesting questions as to the relation between neurofibromatosis and ganglioneuromatosis, a matter beyond the scope of this paper.

Ganglioneuromas also sometimes occur in association with tumors of other kinds. Thus Hackel [60] observed one associated with meningioma, and Bianchi [18] one intimately associated with carcinoma of the pancreas.

Gross Appearances

The physical qualities and gross appearances of ganglioneuromas are not sufficiently characteristic to enable the diagnosis to be made without the aid of the microscope. They are of all sizes up to that of a human head. They are usually rounded, nodular, more or less definitely encapsulated, sometimes firmer, sometimes softer. Cystic ganglioneuromas have been reported by Kopřiwa [77] and Poate and Inglis.[107]

The primitive types are softer and more uniform because of the greater proportion of cells, the mature forms more fibrillar because of fiber formation by both nerve cells and Schwann cells, and the associated formation of reticulum and collagen bundles. The cut surface usually presents a distinct fasciculation. There may also be porosity which results from the degeneration of whole groups of the ganglion cells, sometimes before, sometimes after their maturation.

Prognosis

The prognosis can be made only through microscopic examination, and even with its aid it is difficult to foretell what will happen. Judgment must be based upon the developmental stages attained by the majority of the cells found. The more primitive and embryonal the cells, the more malignant the tumor; the more differentiated they are, the more benign. Unfortunately, as has already been pointed out, the same tumor may show both primitive and perfected types of structure, as in Case 2 of Beneke,[14] the cases of Dunn [42] and Martius.[92] Such cases must be looked upon with suspicion.

Malignancy, or what has been described as malignancy, is usually shown by metastasis. Cases with metastases have been reported by Beneke,[14] Berner,[17] Bianchi,[18] Brossok,[25] Busse,[29] Chiari,[32] Jacobsthal,[68] Miller,[93] Pick,[105] and Wahl.[137] The case reported by Key [8] is included by some critics, excluded by others.

In the case reported by Beneke [14] the tumor was made up chiefly of embryonal cells and the metastases, also composed of very small cells, were in the lymph nodes and vena cava. Metastases to the liver were found by Jacobsthal [68] and Wahl [137]; to the kidneys by Wahl [137] and Pick,[105] who also observed one on the surface of the diaphragm. There seem to be no cases of metastases to the lungs.

As the tumors seem frequently to be of multicentric origin and systematic distribution, a certain amount of caution must be exerted in judging whether multiple tumors result from metastasis. For example, the multiple tumors of the skin reported by Montgomery and O'Leary [94] can no more be thought of as metastatic than those of von Recklinghausen's disease.

Treatment

The literature seems to make no mention of recurrent ganglioneuromas. Most of the patients whose tumors were accessible and surgically removed seem to have been cured. Failures resulted when unexpected complications arose. There is no evidence that treatment by X-ray or radium is of value.

Summary and Conclusions

The tumor described is a well characterized ganglioneuroma. In it, however, nerve cells of all stages of development from neuroblasts to ganglion cells occur, and among them is a stroma made up of Schwann cells and nerve fibers.

It occurred in the neck of a little girl, and seems to be the twelfth case of its kind to be placed on record.

Three years after operative removal the patient is living, with no return of the tumor and no metastases.

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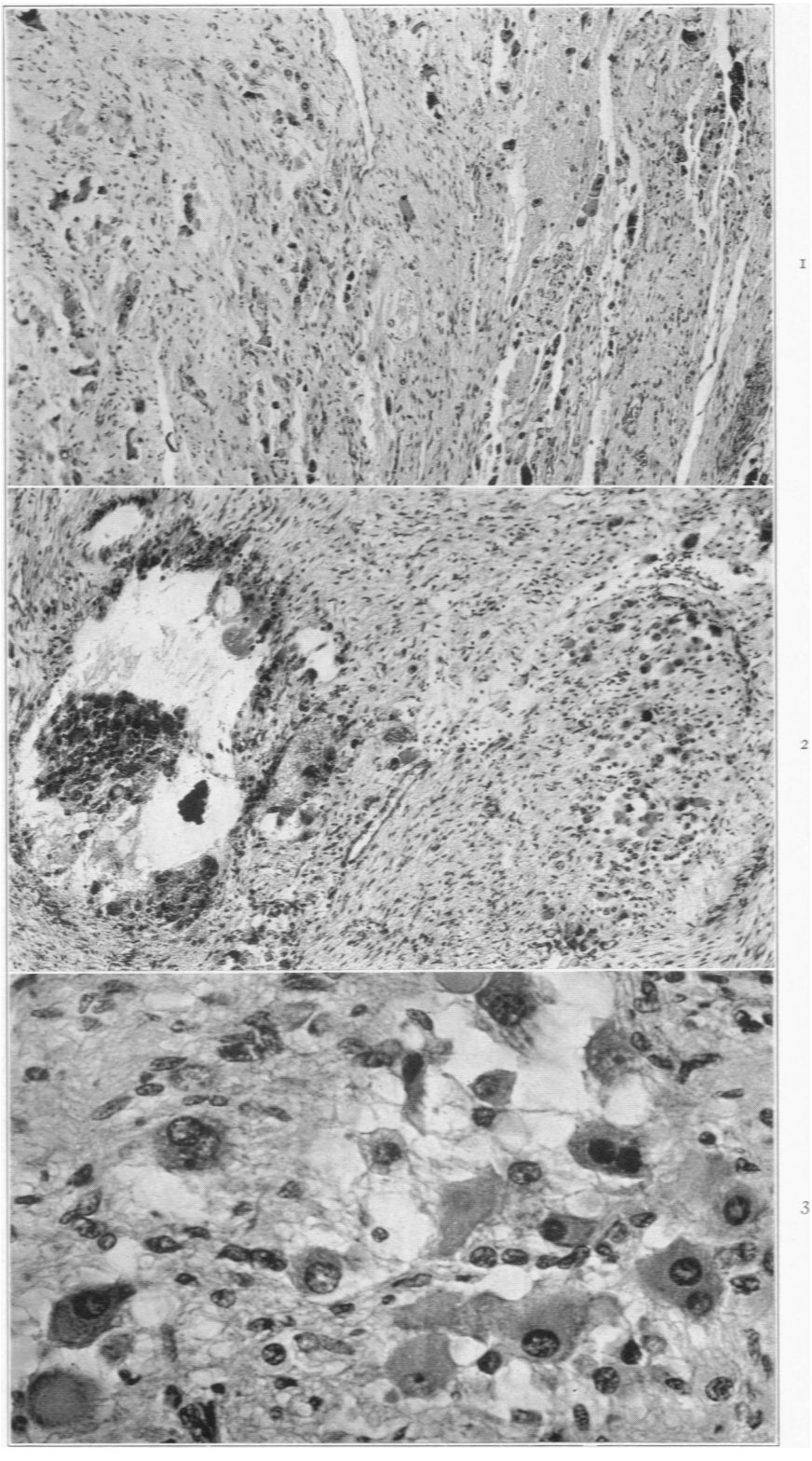
DESCRIPTION OF PLATE

Plate 62

Fig. 1. Low power view of the general structure of the tumor with the neurofibromatous background and scattered, small collections of nerve cells.

Fig. 2. A field showing a ganglion of normal appearance with adjacent nerve and Schwann fibers and cells at one side, with an overgrown, degenerating and calcifying mass of cells opposite.

Fig. 3. Nerve cells in various stages of development up to that of ganglion cells.



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