IN SITU NEUROBLASTOMAS: A CONTRIBUTION TO THE NATURAL HISTORY OF NEURAL CREST TUMORS

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The subject of this study is a group of minute, incidentally encountered adrenal tumors which appear to represent an early stage in the histogenesis of neuroblastomas. These tumors are cytologically identical with typical malignant neuroblastoma, but are rendered distinctive by their microscopic size, and by the absence of demonstrable metastases. For such lesions, the term "*in situ* neuroblastoma" will be used in this paper.[1] Investigation of this group of lesions was prompted by the hope that they would serve as a basis for a more precise analysis of the histogenesis of neuroblastoma and related neural crest tumors. In a search for instances of the lesion, however, it became apparent that their incidence among young infants in our necropsy experience was higher than would be predicted from the known clinical incidence of neuroblastoma. This observation has important implications from the standpoint of the natural history of neuroblastomas, particularly in regard to the question of their spontaneous disappearance. For this reason, it seemed desirable to establish more precisely the nature and significance of *in situ* neuroblastoma. Toward this end, a complete review of our material and of the scant literature pertaining to such lesions was undertaken.

Material and Methods

From the incidentally encountered, clinically unsuspected neuroblastomas observed in our institutions, 13 were selected which conformed, by the following arbitrary criteria, to our proposed concept of *in situ* neuroblastoma: (1) The lesions were distinct tumor nodules, composed of immature neural crest elements indistinguishable from those of typical malignant neuroblastoma. (2) Adequate sections demonstrating the lesion were available. (3) There was neither gross nor microscopic evidence of tumor elsewhere in the body. (4) The lesion was not described in the original gross protocol, and hence was presumably detected only with the microscope. The last criterion was not a precise one, since review of the wet tissue from several cases demonstrated that the lesion was visible to the unaided eye if specifically sought. A definition in terms of maximum diameter of the lesion seems neither reasonable in our present state of knowledge nor justified in the absence of serial sectioning and uniform processing techniques.

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Of the 13 cases, cases 1 to 5 were found in the files of the Los Angeles Childrens Hospital (LACH), cases 6 to 9 at Cincinnati Children's Hospital (CCH), and cases 10 to 13 were made available from the files of the Cincinnati General Hospital (CGH). In Table I the distribution of cases at LACH and CCH is given in terms of the total number of necropsies, the necropsies in recent years, and the recent necropsies upon infants under 3 months of age. Separate consideration of more recent experience is given, since there has been a tendency toward more adequate sampling of grossly normal tissues in recent years. The material from CGH does not represent an exhaustive search of the files, so that statistical considerations are not valid.

TABLE I

INCIDENCE OF IN SITU NEUROBLASTOMAS

Los Angeles Childrens Hosp.	1928–1961	1952–1961	1952–1961 (under 3 mo.)
Necropsies	6,203	2,452	1,035
Cases	5	4	4
Incidence			1/259
Cincinnati Children's Hosp.	**1928–1961**	**1954–1961**	**1954–1961 (under 3 mo.)**
Necropsies	2,848	1,117	536
Cases	4	3	3
Incidence			1/179

In cases 2 to 5, semiserial sections were made of all remaining wet and embedded adrenal tissue. In these cases, sections containing the lesions were stained by a variety of techniques in addition to hematoxylin and eosin. These included Feulgen, periodic acid-Schiff, reticulum, and trichrome stains. Attempts at impregnation of neurofibrils were unsuccessful. In the remaining cases, 1 to 3 sections containing the lesion, all stained with hematoxylin and eosin, were available. All the original sections from each necropsy were reviewed to confirm the absence of metastasis or tumor emboli.

OBSERVATIONS

The salient features among the 13 cases under consideration are summarized in Table II. Representative specimens are depicted in Figures 1 to 3. The sizes of the lesions given in the table represent measurements made with an ocular micrometer on the histologic preparations. The fact that *in situ* neuroblastomas were encountered only in the adrenals almost undoubtedly reflects the fact that autonomic ganglia, dorsal root ganglia, and extra-adrenal paraganglia are not routinely examined microscopically. *In situ* neuroblastoma characteristically appears to be a lesion of early infancy, since no example was encountered over the age of 3 months. There was no apparent association with prematurity, as only 2 infants were born weighing under 6 pounds. The incidence of associated severe malformations was conspicuous; 9 infants (69 per cent) had severe malformations, including 7 with malformations of the heart or great vessels. In no case were multiple *in situ* neuroblastomas

TABLE II

CASES WITH IN SITU NEUROBLASTOMA

Case	Age (days)	Race	Sex	Associated conditions	Size of lesion (mm.)	Mitotic figures *	Pseudo-rosettes	Infiltration	Comments
1	30	Mexican Indian	M	Mitral atresia	2.4 by 1.6	1 in 1 to 2	No	Fetal cortex; vein wall	
2	9	Caucasian	M	Mitral atresia; anomalous pulmonary venous drainage	3.4 by 2.5	0	No	Fetal cortex	Mostly cystic
3	68	Caucasian	F	Right aortic arch with vascular ring	1.5 by 1.3	1 in 3 to 4	No	Fetal cortex	Extensive hemorrhage
4	32	Caucasian	F	Hydrocephalus; microphthalmia; cataracts; cleft palate	3.6 by 2.4	1 in 6 to 8	Rare	Adult cortex; vein wall	
5	35	Caucasian	M	Bilateral ureteropelvic stenosis with hydronephrosis	2.0 by 0.9	1 in 2 to 3	Many	Fetal cortex	
6	1	Caucasian	M	Transposition of great vessels	3.2 by 3.1	0	Many	Fetal cortex; vein wall	
7	2	Caucasian	M	Hypoplastic right ventricle; endocardial sclerosis; medial coronary fibrosis	App. 3 by 3 †	1 in 2 to 3	Rare	Adult cortex	Moderate hemorrhage
8	60	Caucasian	M	Acute interstitial pneumonitis (sudden death)	9.5 by 3.2	0	Rare	Fetal cortex; vein wall	Extensive necrosis; few ganglion cells near center
9	13	Caucasian	M	Arnold-Chiari malformation; imperforate anus; partial transposition of great vessels with ventricular septal defect; anomaly of right hand	0.7 by 0.4	1 in 2	No	Fetal cortex	
10	1	Negro	M	Erythroblastosis fetalis	5.0 by 2.2	0	Many	Fetal cortex	Severe edema with cellular necrosis
11	1	Negro	M	Hyaline membrane disease; prematurity (wt., 1,285 gm.)	3.1 by 1.4	0	Rare	Adult cortex; vein wall	
12	1	Negro	M	Prematurity (wt., 1,450 gm.)	App. 4 by 3 †	0	No	Fetal cortex; vein wall	Cystic; focal calcification
13	90	Caucasian	M	Tetralogy of Fallot	4.0 by 3.8	1 in 4 to 5	Many	Adult cortex; vein wall	

* The number of mitotic figures observed per high-power field.

† Figures approximate; sections incomplete.

encountered, although we have seen several patients apparently having multiple primary neuroblastomas, in which one or more of the tumors were histologically identical with those under consideration. These cases were excluded from the present study because of the impossibility of ruling out the metastatic nature of such lesions.

Particular attention was given to the possibility that some morphologic feature might be found to differentiate this group of tumors from neuroblastomas in general. However, in no way did their appearance differ from that of typical malignant neuroblastoma, except, of course, for their diminutive size. Mitotic activity was observed in 7 of the lesions, and in most of those without mitotic figures, only 1 section was available for study. In 4 cases, the adult cortex was infiltrated by the lesion, but in none was there involvement of the adrenal capsule. In the remaining cases, the lesion was confined to the medulla and fetal cortex. In every lesion, there was interdigitation of tumor cells at the periphery with adjacent adrenal tissue, an appearance suggesting invasiveness. There was no evidence of encapsulation, but partial pseudo-encapsulation was observed in case 2, apparently the result of pressure from the large cyst which comprised most of the tumor (Fig. 5). In 7 cases, there was definite infiltration of the wall of a medullary vein. In case 4, neoplastic cells had extended to the subendothelial layer (Fig. 4), but in no case were tumor cells seen within the lumens of vessels.

Degenerative changes were conspicuous, as is true for neuroblastomas in general. Cyst formation was prominent in cases 2, 8, and 12. Minute flecks of calcification were seen in case 12. In case 10, the entire lesion appeared edematous and seemed to be undergoing degeneration (Fig. 7). The edema involved only the lesion, sparing the adjacent normal adrenal tissue. In cases 3 and 7 the lesions were markedly hemorrhagic, without frank necrosis.

There was no evidence of differentiation into ganglion cells, with the possible exception of the lesion in case 8. Near the center of this tumor, in an area of partial necrosis, there was a small cluster of mature ganglion cells (Fig. 6). However, we could not be certain that this did not represent the inclusion of normal medullary ganglion cells. As these tumors were found in the course of histologic examination, there was no opportunity to utilize techniques demonstrating differentiation of chromaffin elements.

There was no consistent abnormality in the adrenals harboring these lesions, to give a clue to their pathogenesis. In cases 1 and 5, there was slightly delayed involution of the fetal cortex, and in case 5, minimal cytomegaly was observed in the fetal cortex. In every instance, there was normally mature medullary tissue adjacent to the lesion.

Review of the Literature

In view of the relatively large number of *in situ* neuroblastomas in our files, it was surprising to find that such lesions have been mentioned but rarely in the literature. We have found only one such specimen described in any detail. This was a tumor measuring approximately 2 mm., reported by Wells [2] (his case 2), which was encountered during the histologic study of the adrenals in an infant dying at the age of 1 day with multiple congenital anomalies. The tumor had an appearance typical of that observed in neuroblastoma, and was included by Wells in his series of congenital malignant neoplasms. However, in his discussion he expressed considerable doubt as to its actual nature and proposed that this was not in fact a true tumor, but "merely an abnormally large accumulation of undifferentiated sympatheticoblasts." Wells postulated further that such lesions might be present rather commonly in fetuses, usually undergoing either regression or maturation into normal medullary elements. Wells expressed the intention to publish this case subsequently in more detail, but we could find no evidence that he did so.

Morison [3] observed 3 neuroblastomas of microscopic size in the course of some 1,500 neonatal necropsies. In his brief mention of these lesions, he expressed a doubt as to their actual malignant nature and favored the concept that they may have been cell rests, not destined inevitably for malignant behavior.

Russell and Rubinstein [4] mentioned that in their series of personally observed neuroblastomas, one was of microscopic size. Dr. Russell [5] has kindly provided the additional information that this tumor was found in the adrenal of a premature female infant dying at the age of 6 hours. The infant also had a diaphragmatic hernia and a ventricular septal defect. Other authors [1,6] have mentioned that minute neuroblastomas may be encountered incidentally during necropsies upon infants, without further discussion of the subject.

Several references were to be found, mostly in the older literature, which possibly pertain to the lesions under consideration. Nicholson [7] stated that the only specimen possibly representing a "cell rest" that he had personally studied was "a small collection of basophile cells in the medulla of a suprarenal of a young woman." However, he felt unable to completely exclude the possibility of their being lymphocytes, and no illustration or further description was provided. This is particularly unfortunate, since this is the only reference we have found which possibly pertains to an *in situ* neuroblastoma occurring beyond the period of infancy.

Lubarsch [8] observed the persistence of aggregates of undifferentiated

cells, *"undifferenzierte Zellhaufen,"* in the adrenals of infants, particularly those dying of congenital lues. He noted that this phenomenon was relatively common during the first year of life, but occurred rarely thereafter. While he may have been referring to *in situ* neuroblastomas, it is more likely he was observing the normal persistence of undifferentiated medullary elements. This latter phenomenon, which may persist until puberty,[9] and has been observed in adults,[10] takes the form of isolated cells, or non-nodular aggregates, and is readily distinguished in most cases from the distinctly proliferative lesions under consideration. Lubarsch conceivably also may have mistaken extramedullary hematopoiesis or lymphocytic infiltration for undifferentiated medullary components.

Küster,[11] in 1905, published a case report concerning an infant with a large neuroblastoma in the right adrenal with liver metastases. In the left adrenal was a small neuroblastomatous focus, possibly metastatic but, judging from the illustration, very similar in appearance to an *in situ* neuroblastoma. Wiesel,[12] in a subsequent brief discussion of this case, mentioned that lesions such as that in the left adrenal were not uncommon in the adrenals of fetuses and young infants. Unfortunately, Wiesel did not elaborate, and a review of his monograph on the adrenal, published 3 years earlier,[9] disclosed no mention of the subject. However, since an illustration is available as a standard of reference, it must be assumed that Wiesel had observed *in situ* neuroblastomas and was of the opinion that they were not rare.

We may have overlooked other examples of *in situ* neuroblastoma in the voluminous literature on neuroblastoma, but it is apparent they have not previously been the subject of particular attention.

Discussion

In evaluating the significance of *in situ* neuroblastomas, the first hypothesis to be tested is that they are early neuroblastomas which would have gone on to become clinically apparent, had their "host" not succumbed to another condition. Our morphologic observations support this concept, as their appearance differed in no way from typical malignant neuroblastomas, and there was evidence both of proliferative and invasive activity. However, the frequency with which we have encountered *in situ* neuroblastomas is very much against this concept. If we assume for the moment that every potential neuroblastoma is present at the time of birth as a recognizable tumor, then the incidence of early neuroblastomas in the adrenals of a random population of young infants should not exceed the proportion of liveborn infants who will eventually be found to have primary adrenal neuroblastomas. (It is probable that

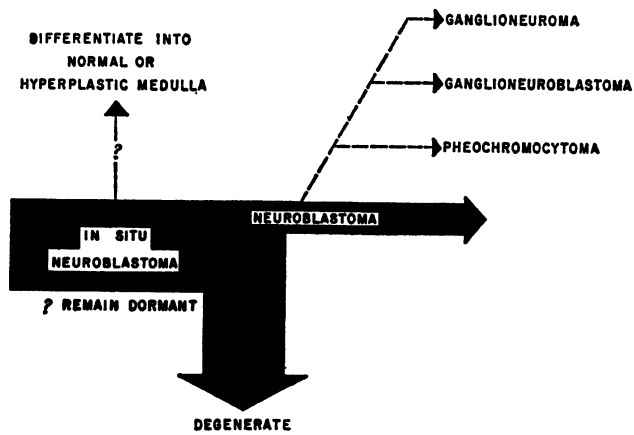
neuroblastomas may take origin beyond the period of infancy, since immature neural crest tissue persists at least until puberty.[9] In this case, the expected incidence of early tumors in infants would be even lower.) Information as to the proportion of liveborn infants who will eventually develop adrenal neuroblastoma is not directly available, but a calculation based upon published data (appendix), indicates a figure of the order of 1 per 10,000. This is in marked contrast to the observed frequency of *in situ* neuroblastomas in our institutions, as shown in Table I. It must be emphasized that our figures probably represent a minimum incidence, since in this retrospective study lesions were found only because they happened to be included in a random section of adrenal, and others must have been overlooked. In our institutions, an increased incidence during the periods covered in the right hand column of Table I can be correlated with the establishment of routine sampling of one and often both adrenals for microscopic study. It is apparent that the observed frequency of *in situ* neuroblastomas during this time period, in infants under the age of 3 months has been some 40 to 50 times the expected incidence based upon the above calculation. This apparent discrepancy might be explained in several ways:

1. *In situ* neuroblastomas are not necessarily small malignant neuroblastomas, but are benign histogenetic anomalies, or "cell rests." This hypothesis is contradicted by the appearance of these lesions. Apparent invasion of adjacent cortex was seen in every case, invasion of blood vessel walls in 6 of 13 specimens, and mitotic activity in 7 of 13.

2. The population examined is not representative. Since the minute lesions under consideration could in no way have contributed to the demise of the infants in which they were found, this hypothesis implies some selection factor predisposing infants with *in situ* neuroblastomas to an early death. The only repetitively associated factor in our cases was the presence of significant congenital malformations, particularly of the cardiovascular system. Willis [13] was unable to find evidence from the literature of a significant association between malformations and neuroblastomas. It is interesting that among the 5 cases with this association he was able to find, one was Wells' [2] case 2, which we would consider an *in situ* neuroblastoma. As was mentioned above, Russell's [4,5] case also had severe malformations. Perhaps a significant association of malformations with neuroblastomas does indeed exist, but has not heretofore been evident, since in most cases the infant succumbs to his malformation before the tumor becomes evident. If such is true, then a selection bias toward *in situ* neuroblastomas might be expected in a pediatric hospital. However, since 48 per cent of infants under the age of 3 months coming to necropsy in our institutions have been found to

have significant malformations, this apparent association may well be spurious. Final evaluation of this point must await the accumulation of further material. It is our hope that the present report will stimulate others to search carefully for *in situ* neuroblastomas. We recommend fixation of intact adrenals by a colorless fixative with good penetration, such as formalin, followed by careful sectioning at intervals of 1 to 2 mm., with embedding of any suspicious appearing areas. Only in this manner can the questions of their actual incidence, age distribution, and association with other conditions be resolved.

3. Only a small proportion of *in situ* neuroblastomas ever become clinically apparent. This seems, on the basis of information presently available, to be the most tenable hypothesis. That the majority of such lesions actually disappear is suggested by several observations. Of the 13 lesions in this study and the 2 from the literature for which specific data are available, none occurred in infants over 3 months of age. Also, degenerative phenomena were prominent in 6 of our specimens. Apparently spontaneous involution has been observed even in the case of larger, clinically overt neuroblastomas,[14] so that there is no reason to assume that a similar phenomenon could not occur in the case of much smaller tumors. We have rather frequently encountered small, ovoid or



TEXT-FIG. 1. The possible fates of *in situ* neuroblastomas. The leading theoretical possibilities are shown. Dotted lines are used to indicate the maturation of neuroblastomas into more highly differentiated neoplasms. This theory is supported by a considerable body of evidence, but has not yet been conclusively proved.

spherical calcified foci in the adrenals of infants and children (Fig. 8). It is possible that some such foci represent involuted neuroblastomas.

Other fates than degeneration or progressive neoplastic behavior might be proposed for *in situ* neuroblastomas. These are summarized in Text-figure 1. Maturation into normal or hyperplastic medullary ele-

ments was first proposed by Wells [2] and seems at least theoretically possible. A prolonged stage of relative dormancy, followed by accentuated growth, could explain the occasional appearance of neuroblastomas in adults, as proposed by Willis.[13] However, since isolated undifferentiated cells may persist in adults,[10] it is not necessary to assume that such neuroblastomas arose from pre-existing tumors. More controversial is the possibility that *in situ* neuroblastomas might mature into relatively differentiated neural crest tumors. This theory, championed by Willis,[13] is rather difficult to prove or to refute absolutely, unless it can be established that the ganglion cell is irrevocably post-mitotic. As Willis is aware, this is contradicted by tissue culture observations.[15] Whatever other fates these lesions may share, it seems probable that the majority disappear, either through involution or maturation, and that only a small proportion go on to become clinically apparent neuroblastomas.

Since the major purpose of this paper is to evaluate *in situ* neuroblastomas, we have not mentioned the somewhat larger neuroblastomas which also have been encountered unexpectedly at necropsy. At LACH, 3 such tumors have been encountered since 1952, all in infants under 3 months of age. One of these had extensive liver metastasis, but this went undetected since the child also had cardiac failure due to congenital heart disease. The other two, measuring 2.0 and 3.5 cm. in greatest diameter, respectively, were without demonstrable metastases. The larger of these tumors was largely necrotic, and conceivably was in the process of involution.

Our experience thus seems to indicate that of every 100 to 300 young infants coming to necropsy, 1 will be found to harbor a small, clinically unsuspected neuroblastoma. Hence it is somewhat surprising that such lesions have been given little attention in the literature. The only definite statement as to their incidence is that of Morison,[3] who found 3 examples in about 1,500 necropsies upon newborn infants. This figure is roughly comparable to ours, and is also about 20 times the expected incidence of early neuroblastomas. The apparent paucity of reported cases probably reflects, at least in part, the fact that in most general hospitals, the infant population coming to necropsy consists largely of stillborn and newborn infants. The large size of the adrenals of such infants due to the persistent fetal cortex reduces the random chance of encountering a lesion the size of an *in situ* neuroblastoma. Also, depending upon the interest of the prosector and of the department in the diseases of infancy and childhood, the grossly normal organs of such infants may not be subjected to complete histologic examination.

If only a small proportion of potential neuroblastomas pursue a progressive neoplastic course, it becomes of considerable practical as well

as theoretical importance to elucidate the factors determining the fate of a given lesion. If this is a reflection of intrinsic biologic differences present from the moment of their inception, then little hope for a successful attack upon the early lesion exists. However, if it is influenced by extrinsic factors, be they stimulatory or inhibitive, then hope for a preventive approach to neuroblastomas does exist. It has been established that the cure rate of neuroblastomas decreases with increasing age of the patient,[1,14,16] We do not know whether a given tumor increases in malignant qualities with the passage of time, whether those tumors appearing later are intrinsically more malignant, or whether some change in the "host" occurs with age, resulting in the stimulation (or loss of inhibition) of malignant characteristics. Certainly from the standpoint of their clinical behavior, tumors grouped under the term "neuroblastoma" because of histologic similarities are biologically a very heterogeneous group. Elucidation of the nature and causes of this heterogeneity should constitute a major advance in our effort to control neuroblastomas. We feel that clarification of the nature and significance of *in situ* neuroblastomas would constitute a major step in our understanding of the natural history of neural crest tumors. It is our hope that the present report will stimulate the accumulation and study of that additional material which is necessary before they can be fully understood.

Summary and Conclusions

Neuroblastomas of microscopic size have been encountered incidentally in the adrenals of young infants in our necropsy material with over 40 times the expected rate of occurrence. In 69 per cent of the cases severe anomalies were observed in other organs, the majority in the cardiovascular system. These tumors were identical to typical malignant neuroblastomas, showing evidence of invasive and proliferative activity. The 13 specimens observed all occurred in infants under the age of 3 months, and many showed degenerative changes. These observations suggested that the vast majority of potential neuroblastomas disappeared before becoming clinically apparent. Elucidation of the factors determining the fate of a given lesion would seem to offer clues toward more successful treatment of malignant neuroblastomas.

Appendix

Estimation of the Proportion of Liveborn Infants Who Will Develop Clinically Overt Adrenal Neuroblastomas

1. The mean annual incidence of solid tumors in children under age 16 years is approximately 7.5 per 100,000. This figure, provided by Pinkel, Dowd and Bross,[17] is based upon carefully documented studies

of the incidence of solid tumors in children residing in the Buffalo, New York, area between 1943 and 1956. A calculation based upon mortality figures for the entire United States for the period 1950–1957 [18] results in an almost identical figure, and requires extrapolation and correction factors for varying cure rates at different ages, etc., which are too unwieldy for the present purpose.

2. Liveborn infants will run this average annual risk 15 times before attaining the age of 16 years. Therefore $7.5 \times 15 = 113$ per 100,000 infants will develop solid tumors before the age of 16 years. Allowance for diminution in the size of the population at risk due to death from other causes would give a somewhat lower figure, but it is our intention only to arrive at an approximate estimate, so for purposes of simplicity the necessary correction is not made here.

3. About 15 per cent [14] of solid tumors in this age group are neuroblastomas. Therefore $0.15 \times 113 = 17$ per 100,000 children will develop neuroblastomas before age 16.

4. An average of the large and well-documented series of Gross, Farber and Martin [16] and Bodian [14] indicates that approximately 55 per cent of neuroblastomas in which the primary site is known arise in the adrenal. Thus, $0.55 \times 17 = 9.25$ per 100,000 liveborn infants will be found to have primary adrenal neuroblastomas before the age of 16 years. For our purposes, the incidence of neuroblastomas recognized after the age of 15 years is negligible. In this paper, the figure of 9.25 per 100,000 is rounded off to 1 per 10,000.

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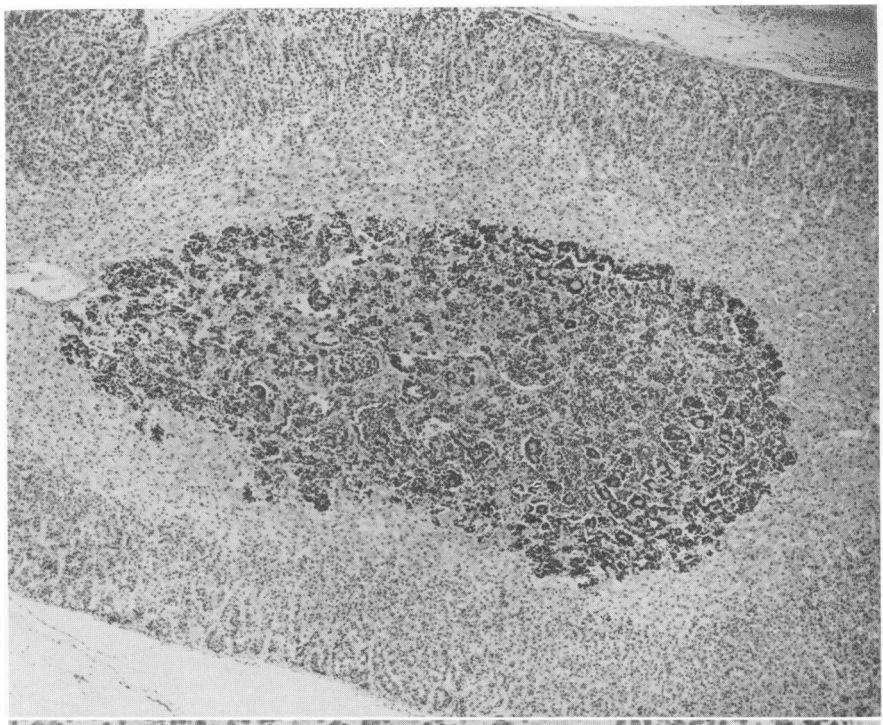
LEGENDS FOR FIGURES

Photomicrographs were prepared from sections stained with hematoxylin and eosin.

FIG. 1. Case 5. The tumor is sharply outlined, but along one edge it appears to be infiltrating the adjacent cortex. × 45.

FIG. 2. Case 5. Higher magnification of lesion shown in Figure 1. Numerous neuroblastic pseudorosettes are manifest. × 125.



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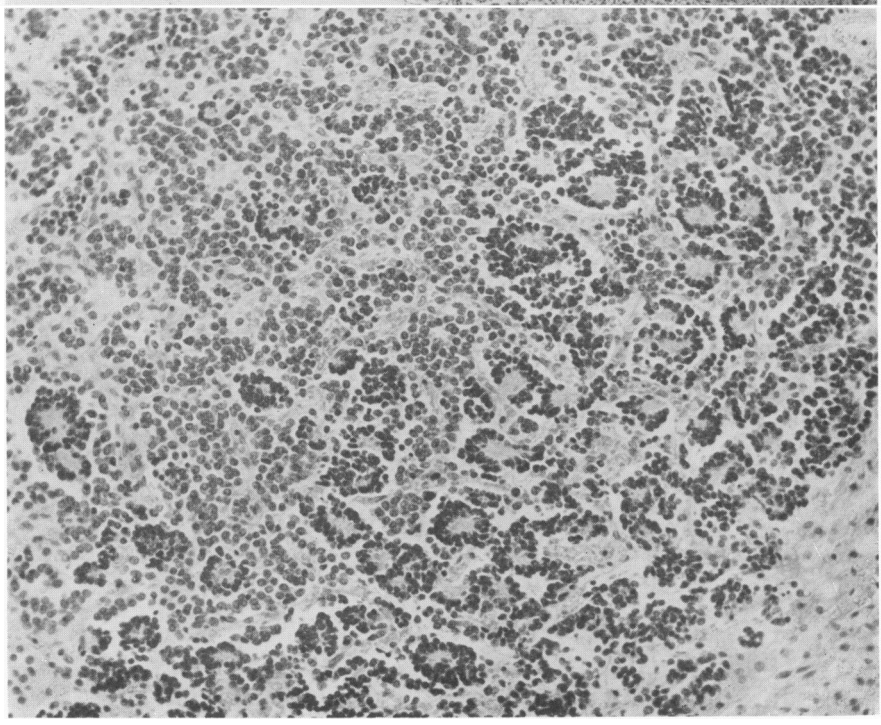

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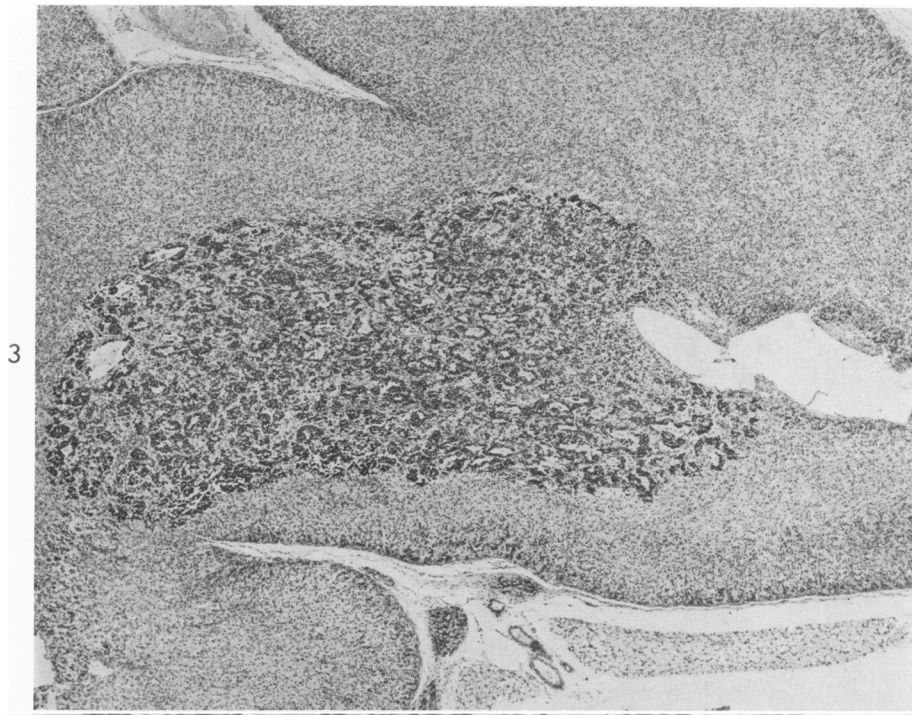


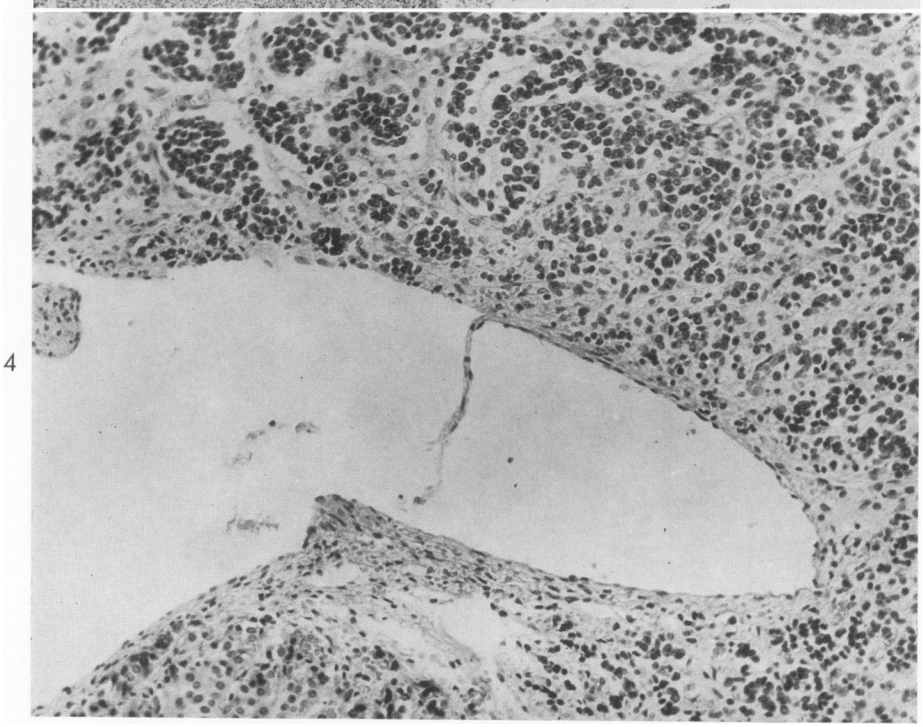
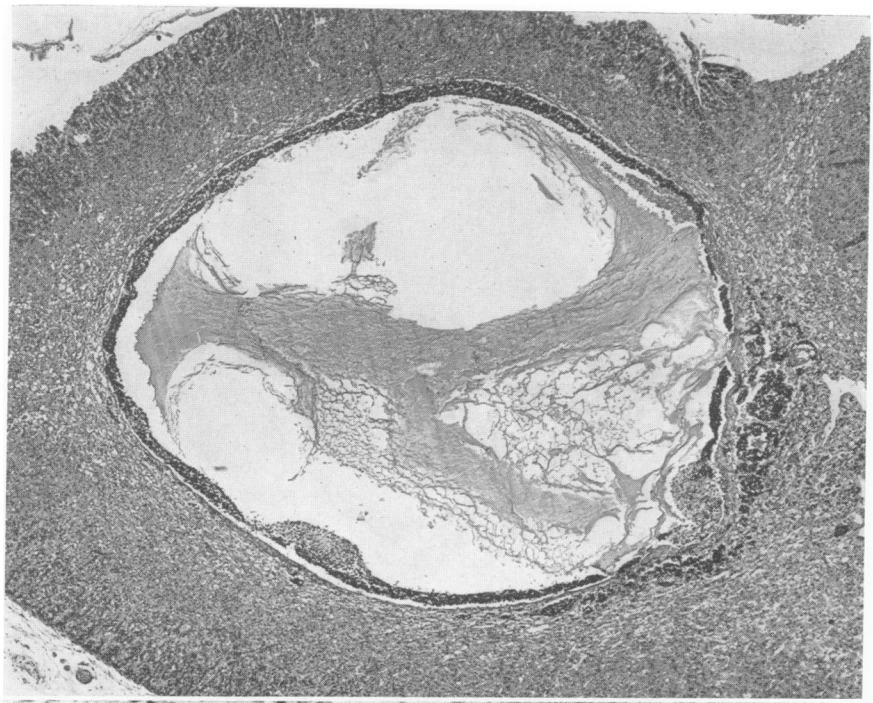


FIG. 3. Case 4. The tumor here infiltrates the adult cortex and the wall of a medullary vein. × 28.

FIG. 4. Case 4. Higher magnification of the lesion shown in Figure 3. Tumor cells lie just beneath the endothelium. The latter is in part artifactually stripped away. × 125.



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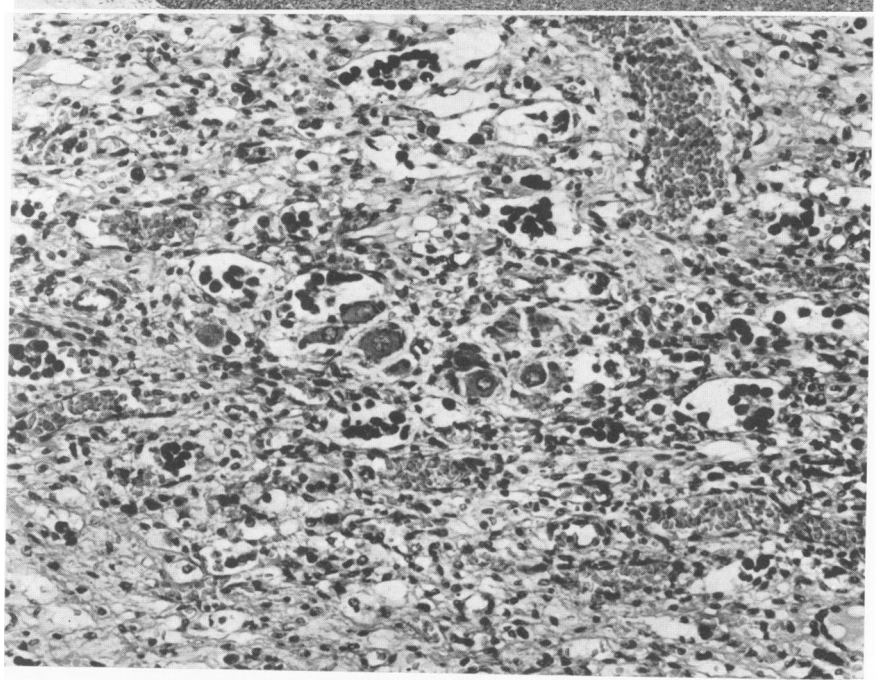

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FIG. 5. Case 2. This lesion consists of a narrow rim of tumor cells around a relatively large cystic space. × 28.

FIG. 6. Case 8. Near the center are a few mature ganglion cells surrounded by occasional immature cells. Most of the tumor in this case is necrotic. It is not certain whether the ganglion cells are differentiated tumor cells or are an inclusion of normal medullary elements. × 125.

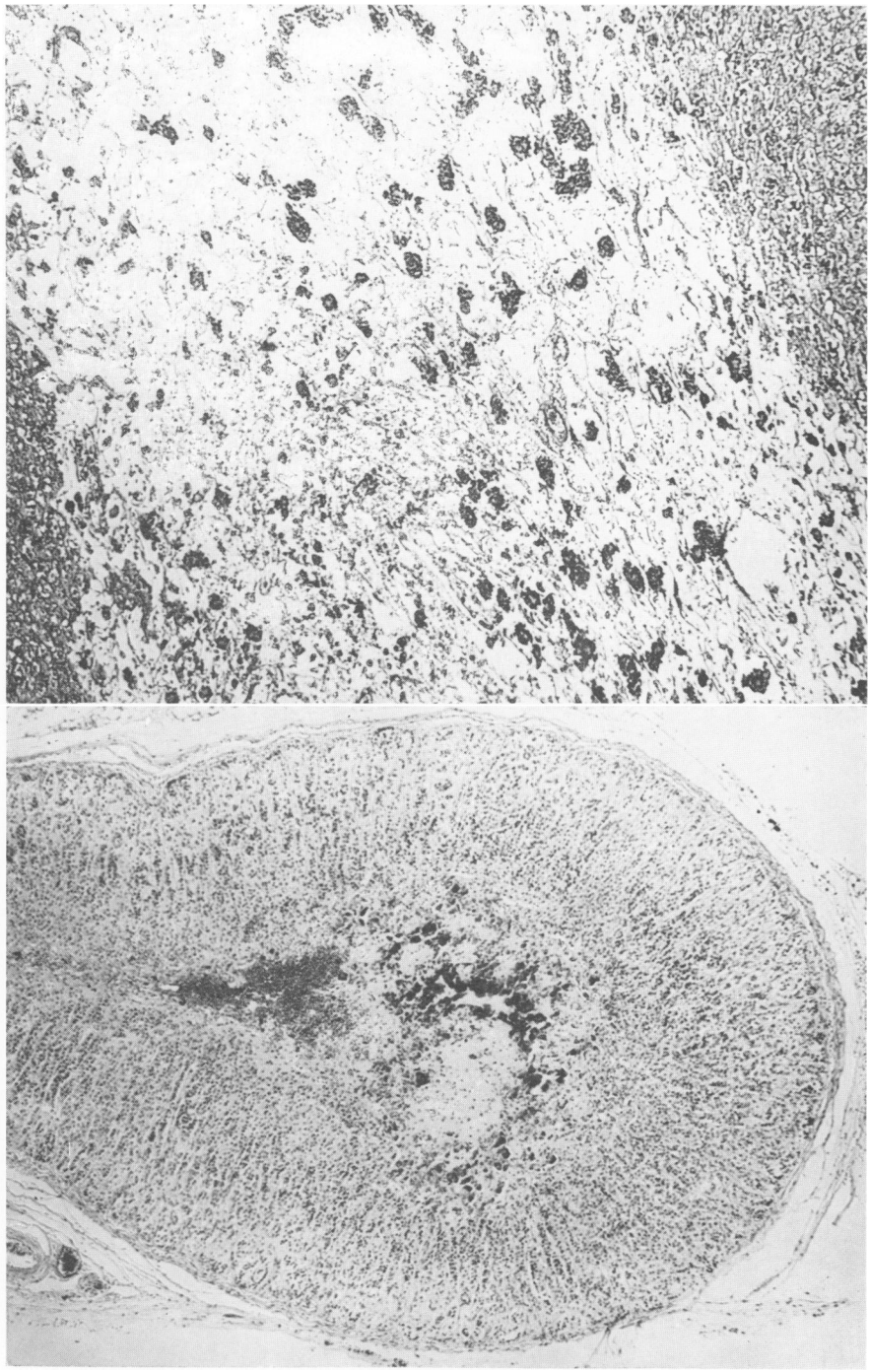

FIG. 7. Case 10. The entire tumor in this case shows extensive edema and necrosis, with only a few surviving clusters of tumor cells, some of which form pseudorosettes. × 60.

FIG. 8. LACH A-5857. A small hemorrhagic calcified focus in the adrenal of an infant aged 9 months. Such lesions may result from hemorrhage, but possibly also might mark the site of a previous *in situ* neuroblastoma. × 45.