The Natural History of Neuroblastic Cells in the Fetal Adrenal Gland

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A study was made of neuroblastic nodules of the human adrenal gland in fetal life to determine their embryonic morphology and derivation. One hundred sixty-nine glands from 92 fetuses selected from 106 consecutively submitted fetuses formed the basis of this study. All adrenal glands examined contained neuroblastic nodules. They increased in number and maximum size with increasing age, peaked at 17 to 20 weeks gestational age, and regressed in the oldest fetuses. It is concluded that such neuroblastic nodules are an integral part of the normal morphogenesis of the adrenal gland. Their presence at birth and early infancy may represent a normal variation, and they do not necessarily constitute microscopic incipient malignancy (Am J Pathol 76:225–244, 1974).

MICROSCOPIC CLUSTERS of neuroblastic cells are on occasion incidentally found in the adrenal glands of newborns and young infants. These have been termed "*in situ* neuroblastoma," and they are considered by some to be incipient malignant neuroblastomas from which clinically apparent neuroblastomas might arise.[1] Because such cell aggregates are common in young infants and newborns, a study of fetal material was conducted to investigate their derivation.

Materials and Methods

One hundred six human fetuses were obtained consecutively over a 6-month period; four were from spontaneous and 102 from saline-induced therapeutic abortions. Most of the latter were performed early in the second trimester of pregnancy, thus the material was primarily from this period. No abortions were performed for known teratogenic exposure. All pregnancies were normal, and no known serious maternal disease was present. No precipitating factors were known for the four spontaneous abortions. Only adrenal glands which were adequately preserved to permit histologic evaluation were included in the study. Of the 212 adrenals obtained, only 169 adrenals from 92 fetuses could be examined.

Gestational age was estimated from the data of Streeter[2] based on crown-rump length. To facilitate analysis, the fetuses were then classified by crown-rump length into five groups (Table 1). The fetuses ranged in age from 10 to 30 weeks' gestation, with most in the middle groups.

The fetuses were preserved whole in 10% formalin at the time of delivery.

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Table 1—Classification of Study Groups

Group	Crown-rump length (cm)	Estimated age (wk)*	Number
I	5–8	10–14	10
II	9–12	14–17	27
III	13–16	17–20	44
IV	17–20	20–23	9
V	22–26	24–30	2

* Gestational age estimated from crown-rump length from the data of Streeter.[2]

They were examined for any congenital deformities with special attention given to the cardiovascular, urogenital and musculoskeletal systems. The placentas were examined grossly. Each adrenal was weighed and sagittally sectioned at 1- to 2-mm intervals. Every section was embedded in paraffin, sectioned and stained with hematoxylin and eosin. Several selected sections were also stained with Bodian's method for axons.

All neuroblastic nodules within the adrenal glands were counted and measured. Individual cells and small groups of only a few neuroblasts were not included. Two dimensional estimates of nodule size were made at 400 times magnification using a calibrated eyepiece micrometer system. The mean length and width of each discrete nodule were measured at right angles.

Th total number of nodules, their size and location, and the number with cystic change were tabulated. Descriptive observations were made of each adrenal gland regarding the distribution pattern of neuroblasts and their relation to the capsule, cortex, central vein and extraadrenal sympathetic aggregates. Differentiation into chromaffin and ganglion cells, hemorrhage, rosette formation and other morphologic features were noted.

Results

Only one deformity was found on gross examination. A fetus aborted at 24 weeks' gestational age had a malformation of the fingers of one hand. No anomalies of the adrenals, cardiovascular or urogenital systems were found.

Adrenal Weights

There were no unusually large or small adrenal glands. Right and left adrenals were approximately the same size. Adrenal weights ranged from 0.1 mg in the youngest fetuses to 2.4 mg in the oldest (Table 2). As expected, adrenal weight increased with fetal age.

Number of Neuroblastic Nodules

At least one neuroblastic nodule was found in every gland submitted to study. The total number of nodules per gland is graphically illustrated in Text-figure 1. The values ranged from one to 35 nodules in group I (mean 9.6), one to 63 in group II (mean 14.7), one to 130 in group

Table 2—Adrenal Weights

Group	Range (mg)	Mean (mg)
I	0.1–0.4	.17
II	0.1–0.6	.39
III	0.2–1.1	.72
IV	0.7–1.6	1.00
V	0.9–2.3	1.55

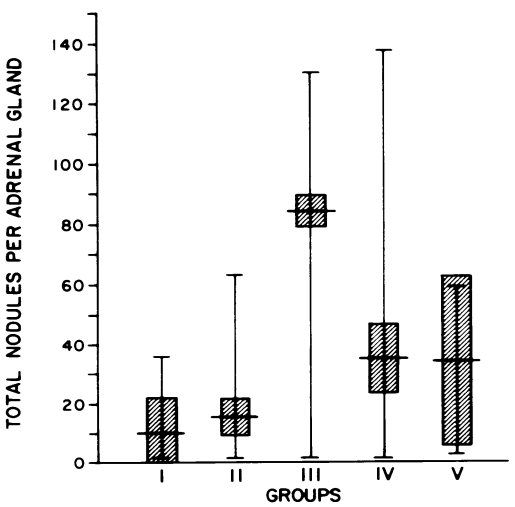
III (mean 84.0), one to 138 in group IV (mean 34.4) and three to 60 in group V (mean 34.3). The maximum number of nodules was found in the fetuses of 17 to 20 weeks (group IV), increasing gradually from the few present in the youngest fetuses and declining in the oldest.

Size of Neuroblastic Nodules

The most frequently occurring nodule size (mode) was 60 × 60 μ for all groups combined. Individual nodules ranged in size from a minimum of 20 × 20 μ in group I to a maximum of 200 × 400 μ in group II. Although the modal and minimum sizes did not vary appreciably with age, the maximum size of the nodules did vary, reaching the greatest size in the 14- to 18-week-old fetuses in groups II and III and decreasing slightly in the oldest specimens (Table 3).

Cystic Change of Neuroblastic Nodules

Cystic nodules were not found in the youngest fetuses of group I and only one was found in group II (0.2%). They were prominent in



TEXT-FIG 1—Graph showing relation of nodule number to fetal age. The range is indicated by the short horizontal bars, the mean by the long horizontal bar and two standard deviations by the hatched boxes.

Table 3—Relation of Nodule Size to Embryonic Age

Group	Maximum (μ)	Minimum (μ)	Mode (μ)
I	160 × 220	20 × 20	60 × 40
II	200 × 400	20 × 30	60 × 80
III	240 × 260	20 × 30	70 × 80
IV	220 × 240	20 × 30	60 × 80
V	90 × 110	20 × 30	60 × 40

groups III (2.9%) and IV (18.6%), and then decreased in group V (1.9%). Cystic nodules did not commonly appear until the sixteenth week of gestational age, when they were found in relatively large numbers; after this time they declined in prominence. Because of the small numbers involved, groups I and II and groups IV and V were combined for statistical computations. The G test [3] was utilized, and showed differences between the three groups to be significant at the $P = 0.0001$ level (Table 4).

Location of Neuroblastic Nodules

Superficial nodules were considered to be those in contact with the capsule of the adrenal or immediately below it. All others were classified as deep. The number of superficial nodules appeared to decline with age. Groups I and II and groups IV and V were again combined for statistical purposes. Applying the same G test, the differences were significant at $P = 0.01$ level (Table 5).

Descriptive Findings

Grossly visible medullary hemorrhages were seen in three glands. The hemorrhages were agonal without evidence of inflammatory response. Microscopic extravasations and focal hemorrhages in the proximity of the central veins were found in 13 other adrenals.

Table 4—Cystic Change of Neuroblastic Nodules

	Cystic		Solid		
Group	No.	Percent	No.	Percent	Total No.
I	0	0.0	191	100.0	191
II	1	0.2	690	99.8	691
III	260	12.9	1750	87.1	2010
IV	96	18.6	420	81.4	516
V	2	1.9	101	98.1	103

P = 0.0001
G test from Sokal and Rohlf.[3]

Table 5—Location of Neuroblastic Nodules in Adrenal

	Superficial		Deep		
Group	No.	%	No.	%	Total No.
I	11	5.8	180	94.2	191
II	19	2.8	672	97.2	691
III	50	2.5	1960	97.5	2010
IV	5	1.0	511	99.0	516
V	0	0.0	103	100.0	103

$P = 0.01$

One adrenal contained large nerve bundles and ganglion cells in the region adjacent to the central vein. One other adrenal contained a single nerve fascicle in the same area without ganglion cells. Ganglion cells were common in the developing extraadrenal sympathetic aggregates.

The migration pathway of the neuroblasts could be traced from the paravertebral sympathetic ganglia to the periadrenal sympathetic collections, through the adrenal capsule to locations deep within the gland (Figure 1). The nodules were present throughout the glomerular and fasciculoreticular zones and adjacent to the central veins. Continuity between the locations often appeared obvious (Figure 2). Deep, superficial and periadrenal neuroblastic nodules appeared to be interconnected by fine nerve fibers with the nodules scattered along their course (Figure 3). Similar delicate fibers were seen intertwined between the neuroblasts within the individual nodules. Rosettes were common in both extraadrenal and intraadrenal groups of primitive sympathetic cells. They were composed of rings of neuroblasts surrounding central zones filled with fibrillar material.

Larger neuroblastic nodules were generally oval in shape and consisted of densely packed basophilic cells (Figure 4). Small groups of several neuroblasts and occasional single cells were also found. Neither the nodules nor small groups were encapsulated. The neuroblasts were in direct contact with neighboring cortical cells and often intermingled with them (Figure 5). Neuroblastic clusters bordered directly on the endothelium of the sinusoids and central veins (Figure 6), but the nodules themselves were avascular.

The neuroblastic cells were round to oval and measured 3.5 to 6.0 μ in diameter (Figure 4). Their cytoplasm was visible only as a thin rim around the nucleus. The cells consisted mostly of nuclei which contained fine to coarse, dense, granular chromatin and prominent nucleoli.

Differentiating chromaffin cells were found in the periphery of the deeper nodules, singly or in small groups (Figure 7). They measured 15 to 20 μ in diameter and often contained brownish granules in their cytoplasm. Their nuclei were larger than the neuroblastic nuclei measuring 6 to 8 μ in diameter, with finely granular and peripherally marginated chromatin.

Cells of the fetal cortex were easily distinguished from those of neuroblastic origin. They were polyhedral in shape, measured 20 to 30 μ in diameter, and had abundant eosinophilic cytoplasm (Figure 4). Their nuclei were round or occasionally oval, measuring 7 to 11 μ in diameter. The chromatin was sparse and finely granular, and large distinct nucleoli were frequently noted. Compared to those of the fetal cortex, the cells of the glomerular cortex were smaller, more basophilic and more compact. They measured 10 to 15 μ in diameter and had paler cytoplasm. Their nuclei measured 4.5 to 7.5 μ in diameter and were otherwise similar to those of the fetal cortical cells.

Discussion

For the interpretation of the findings of this study and the discussion to follow, a review of some aspects of the embryology of the adrenal gland would be helpful.

The adrenal gland is a composite organ. The cortex develops first and is derived from the coelomic epithelium ventral to the aorta.[4] The outer layer of the adrenal cortex is the glomerular zone, and the central portion of the gland is designated the fasciculoreticular zone or fetal cortex. Beginning a few hours after birth, degenerative changes and marked hyperemia are present in the fasciculoreticular zone. By 7 to 10 days there is almost complete disorganization of the cortical elements central to a relatively wide band of basophilic cells which includes the capsule and glomerular zone. This process of involution and reorganization is essentially completed by 4 to 6 weeks. The fascicular and reticular zones of the postnatal gland develop from cells in the capsule and glomerular zone during the regenerative phase.[4]

The adrenal medulla is derived from cells of the neural crest in association with the development of the rest of the sympathetic nervous system. Neuroblastic cells migrate from the neural crest to form collections alongside the aorta, which later develop into the paravertebral sympathetic ganglia. Nerve fibers extend laterally from the last eight thoracic and first two lumbar paravertebral sympathetic ganglia.[4] Cells and fibers enter the adrenal primordium throughout

its length, passing between the cortical cells and separating them into small groups and islands. No new nerve tracts enter once the capsule is complete.[4] The primitive sympathetic cells migrate in along nerves and multiply to result in islands of neuroblasts scattered along their length.[4,5] Maturation into pheochromoblasts begins early and continues throughout the fetal and into the neonatal period.[5,6]

After postnatal degeneration of the fetal cortex, the support afforded the neuroblastic nodules by cords of cortical cells and reticulum of intervening sinusoids is lost, and the neural tissue settles against the central veins.[4] At first the nerves, chromaffin cells and neuroblasts are loosely intertwined among the remaining cortical cells and debris. By 6 weeks the medulla is fairly well organized into a compact highly vascularized structure. When the reticular zone begins to form at 12 to 18 months, cords of cortical cells again become mixed among groups of chromaffin cells, and the medulla is no longer discrete. The adult configuration of the adrenal is reached by 10 to 12 years.[4]

The neuroblasts are found within the cortex as single cells, small groups or larger tightly packed clusters. All are avascular and are surrounded by cortical cells and blood vessels.[4,5] Differentiation of neuroblasts into catecholamine-storing cells occurs in the small groups and at the periphery of the larger groups. The centrally located neuroblasts in the nodules remain undifferentiated and serve as the source for further replication.[4,5] Glucocorticoids made by the adrenal cortex reach the neuroblasts by the sinusoids or by direct contact between adjacent cells.[7] The differentiation of neuroblasts into catecholamine-storing cells and the production of phenylethenolamine-*N*-methyltransferase which converts norepinephrine into epinephrine are induced by glucocorticoids.[5,7,8]

The findings of this study are consistent with the morphogenesis of the adrenal gland as described above. The apparent migration pattern of neuroblasts, their relation to small nerves, and their subsequent replication into nodules form the basis for the observations made in this study. The period of 17 to 20 weeks' gestational age, represented by group III, appeared to be critical for the development of the sympathetic component of the adrenal glands. Neuroblastic proliferation, in terms of maximal nodule size and number, as well as cystic change, reached a peak in fetuses of this age group. Nodule size and number depend on the relative rates of replication and attrition of neuroblasts. Apparently the nodules increase to a certain maximal number, then coalesce or disappear. Fewer or perhaps no new nodules

are formed in the later stages. Although the material of this study did not go beyond 30 weeks, others have reported that in the remainder of fetal life the nodules slowly continue to mature or regress so that few remain by the time of birth.[4,6,9–11] The maximal size of individual nodules increased with increasing fetal age to peak at the same age as nodule number and to decline gradually in the oldest groups. Individual modal nodule size remained essentially unchanged at about 60 × 60 μ in all age groups, which may indicate an optimal size for these avascular, tightly packed clusters. The aggregate nodule size was considerably larger and often measured several millimeters in greatest diameter.

Cystic change within neuroblastic nodules was common and considered to be part of the normal developmental pattern. It did not appear until early in the second trimester, reached a maximum in the sixteenth week, and declined in the older fetuses. This degenerative change paralleled the progression of maximal nodule size and number.

Superficial nodes were found to decrease with age. This decline in superficial nodules could reflect either the inward migration of nodules, their attrition, or the relatively greater growth of the cortex. Even though no nodules were found in direct contact with the capsule in the oldest group, they were found throughout the gland. The nodules remain scattered in all levels of the adrenal with most of them centrally located until the postnatal degeneration of the fetal cortex following which they settle near the central veins.[4] If the fetal cortex does not degenerate, degenerates irregularly or incompletely, the fetal distribution pattern could persist after birth.

Neuroblastic nodules are a normal part of the fetal adrenal gland which may linger until birth or early infancy. Many authors have discussed these persistent microscopic clusters of embryonic cells. Some have interpreted the nodules as normal variants whereas others have considered them to be small malignancies. The term *in situ* neuroblastoma was first proposed by Beckwith and Perrin in 1963[1] to describe microscopic cell aggregates incidentally found in the adrenal glands of newborns and infants up to 3 months of age. They considered these to be tumor nodules, cytologically indistinguishable from malignant neuroblastoma with no demonstrable metastases. The authors found thirteen such examples in a retrospective study of autopsy material for an overall incidence of approximately 1 in 200 autopsies. Morphologic features included the presence of mitotic figures, infiltration of the adult cortex, peripheral invasion at the edges of the tumor, subendothelial vascular invasion, no encapsulation, and no

evidence of differentiation into ganglion cells with the possible exception of one case. Degenerative changes were considered significant and included cyst formation, calcification, edema, and hemorrhage but no frank necrosis. There was no involvement of adrenal capsule, and the lesions were usually confined to the adrenal medulla and fetal cortex, involving the adult cortex in 4 of 13 cases. They found 7 similar cases in the literature.[1,10,12–18] In their discussion of the meaning of these microscopic lesions, the authors proposed that these small lesions were true malignant neoplasms, rather than cell rests, and that some would have become clinically malignant had the host survived. Their observed incidence of 1 in 200, fifty times greater than that of clinically apparent neuroblastoma, was attributed to degeneration and regression of these lesions under normal differentiational and maturational influences. The largest lesions may well represent microscopic neuroblastomas incidentally found at autopsy, but the smallest lesions may be normal embryonic remnants. The morphologic features of apparent cortical and subendothelial vascular invasion, mitoses and cystic changes are similar to those of the normal developing adrenal, since neuroblasts are normally found scattered throughout the gland, intermingling with adjacent cortical cells and beneath the endothelium of the sinusoids and central veins. Cystic change is also a normal feature. Rare mitoses are found in the fetus. Thus, these features alone cannot define the malignancy of microscopic aggregates of neuroblasts when found in an infant, and further criteria are necessary.

Other authors have included size of the neuroblastic aggregates as a diagnostic criterion for *in situ* neuroblastoma. Shanklin and Sotelo-Avila [19] measured neuroblastic cell rests in 3 autopsied cases and found nodules ranging in size from approximately 140 × 600 to 200 × 800 μ in cross-sectional diameter. These were aggregate measurements and not measurements of individual nodules. Collectively, nodular aggregates in some of the material of the present study would be of similar size.

In 1969, Guin, Gilbert and Jones [20] did a combined retrospective and prospective study of incidental neuroblastoma. They divided the lesions they found into three groups. Their first group included the 6 youngest cases in the series. The lesions in this group were all of minute size, consisting of discrete aggregates of neuroblasts found within the medullary compartment. Several showed extension into the zona reticularis with compression of adjacent tissue. There were 2 cases in their second group, which they termed the "intermediate stage in incidental neuroblastoma." In this group the adrenals were

not grossly enlarged, but neuroblasts filled and expanded the medulla with irregular extension and compression of the cortex. Their last group included 3 cases in which the adrenals were grossly enlarged, with tumor replacing and expanding the medulla and compressing the cortex. Gross and microscopic cystic spaces, multifocal hemorrhage, necrosis, and fibrosis were found. In contrasting the incidence of *in situ* neuroblastoma found retrospectively and prospectively, the authors found approximately ten times greater incidence by systematic prospective search. This high incidence is probably valid, as many small lesions would be missed by random section. The small lesions commonly found in the youngest patients were possibly embryologic remnants. Their second group is borderline, and the largest lesions, found in the third group, appear to be true, small, intraadrenal neuroblastomas.

Several other examples of unsuspected microscopic neuroblastoma found at autopsy are reported in the literature. Wells [16] in a review of congenital neoplasms in 1940 reported four congenital neuroblastomas. One was not grossly visible and measured 2 mm in diameter. Morison [17] reported finding three microscopic lesions in approximately 1500 autopsies which he interpreted as cell rests rather than malignancies, and he stated, "Many nodules are probably not true neoplasms, but only abnormal aggregates of cells, produced occasionally during early development, which soon either acquire malignant characters, proceed to maturation, or disintegrate and disappear." [17] Russell and Rubinstein [19] reported a single case of a microscopic neuroblastoma in a stillborn premature female infant with diaphragmatic hernia and ventriculoseptal defect.

In the classic literature of embryology, neuroblastic nodules are mentioned as a common finding in the adrenals of young infants. Wiesel,[10] Zuckerkandl [9] and others [11–14] interpreted these nodules as normal variants, a part of the continued migration and multiplication of neuroblasts prior to complete maturation of the adrenal medulla.

Several case reports have appeared in the literature showing the association of *in situ* neuroblastoma with a variety of entities, including congenital heart disease,[21] adrenal cyst [22] and trisomy D.[23] Chatten and Voorhees [24] studied a family of 4 children, two of whom had malignant neuroblastoma and a third who had aganglionosis coli and microscopic neuroblastoma. The mother had increased catecholamine production. The association of congenital malformations with neuroblastic cell aggregates is probably coincidental. A large series of such cases would be necessary to determine a true relationship.

Microscopic clusters of neuroblasts found in the adrenal glands of

young infants have been called many things: cell rests, *in situ* neuroblastoma, microscopic neuroblastoma and incidental neuroblastoma. Although it is possible that these terms all describe variations of the same entity, it is valid to try to distinguish them. Morphologic features including cystic change, rosette formation, subendothelial location and lack of encapsulation are the same in the normal fetal pattern, infantile cell rests and microscopic malignancy. Cell rests and microscopic incidental neuroblastoma cannot be easily separated by size alone for the size ranges overlap. It is likely that there is a spectrum of size from the very small cell rest to the small malignant neuroblastoma. But their morphology may be similar, and size alone cannot distinguish them. To define the extremes of a possible continuum, the terms neuroblastic cell rest and incidental neuroblastoma are useful to separate these small lesions into two groups qualitatively on the basis of size.

Neuroblastic nodules are an essential part of the morphogenesis of the adrenal medulla which occasionally remain until birth and early postnatal life. When found in the newborn or young infant, they are not necessarily an indication of malignancy. It may very well be that these variations in growth can be the sites of malignant transformation, and they bear a striking morphologic similarity to neuroblastic malignancies. But they are not necessarily malignant, show no features of wide invasion or metastases, and they do not contribute to the infant's death. It is inviting to speculate that the neuroblastic remnants are *in situ* or incipient malignancies representing "stage 0" [25] in a neoplastic process. Such terminology does not leave open the possibility that these represent developmental variation. Until there is incontrovertible proof that these are neoplasms, they should not be termed incipient or *in situ* neuroblastoma.

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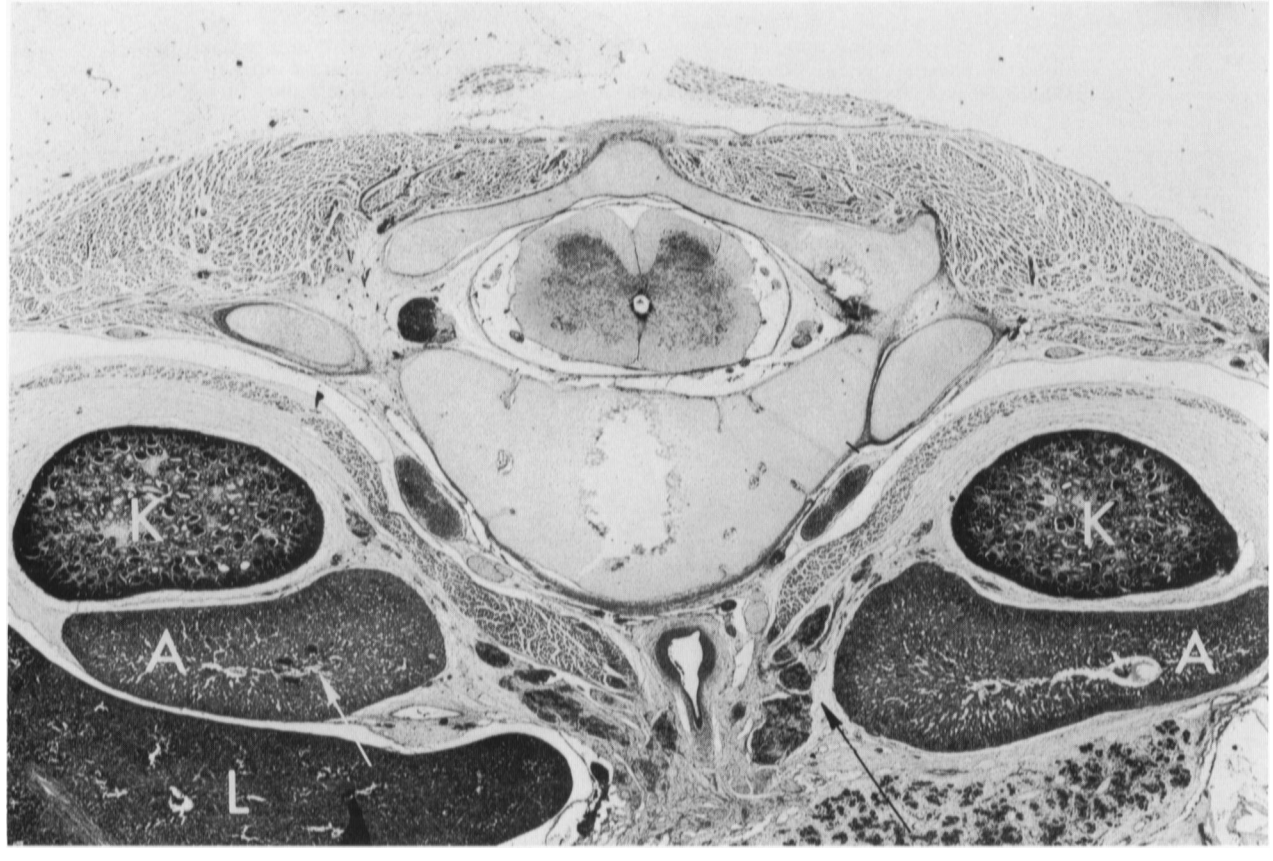

Fig 1—Tranverse section of an 11-week-old fetus at the level of the adrenal glands. Note migration pattern (*black arrow*) of neuroblastic cells from paravertebral collections to extra adrenal positions and a few nodules within the gland itself (*white arrow*). *K* = kidney, *A* = adrenal, *L* = liver (H&E, × 14).

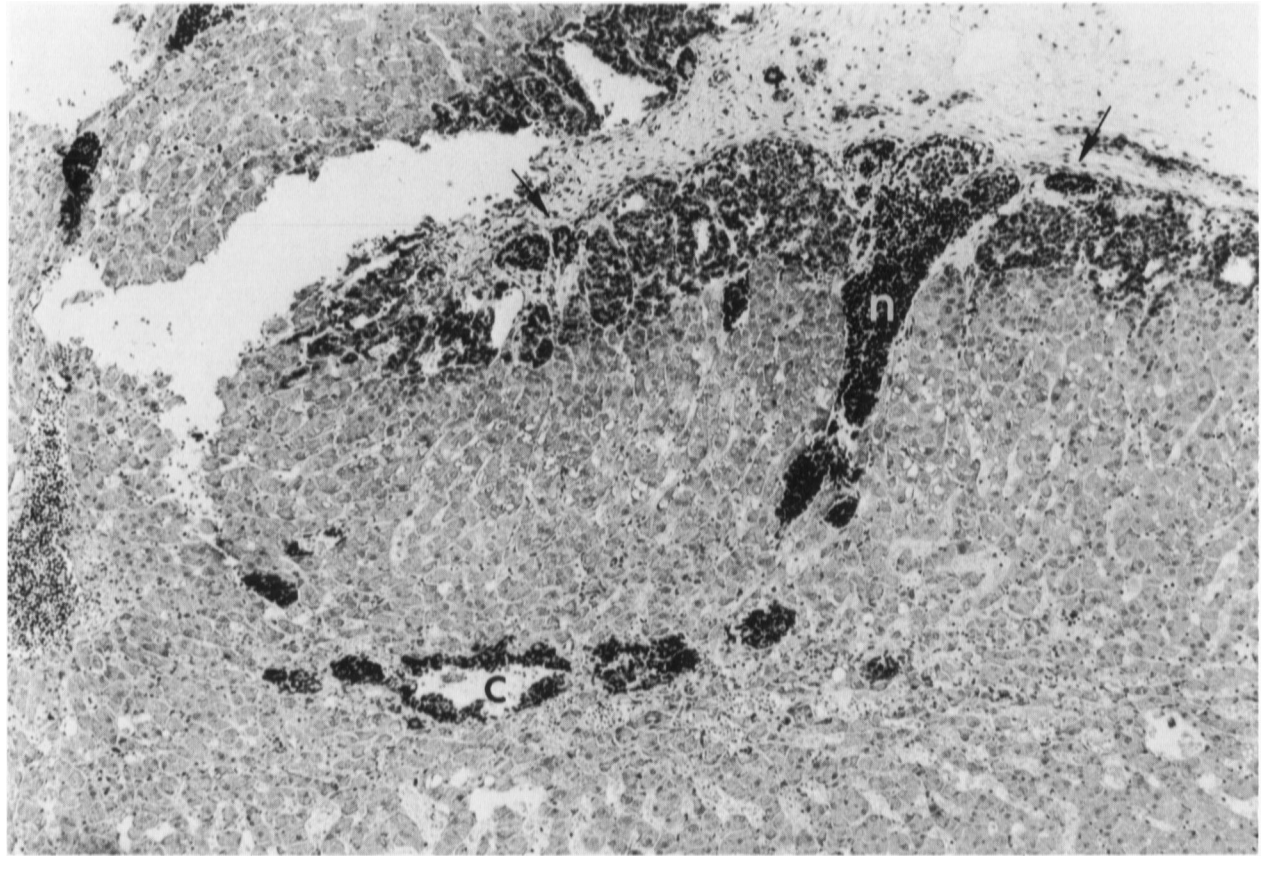

Fig 2—Adrenal gland from 19-week-old fetus showing pattern of migration of neuroblastic cells (*n*) from subscapular to deep region. *Arrows* indicate superficial neuroblastic nodules with rosette formation. Note cystic change (*c*) in a deeply located nodule (H&E, × 100).

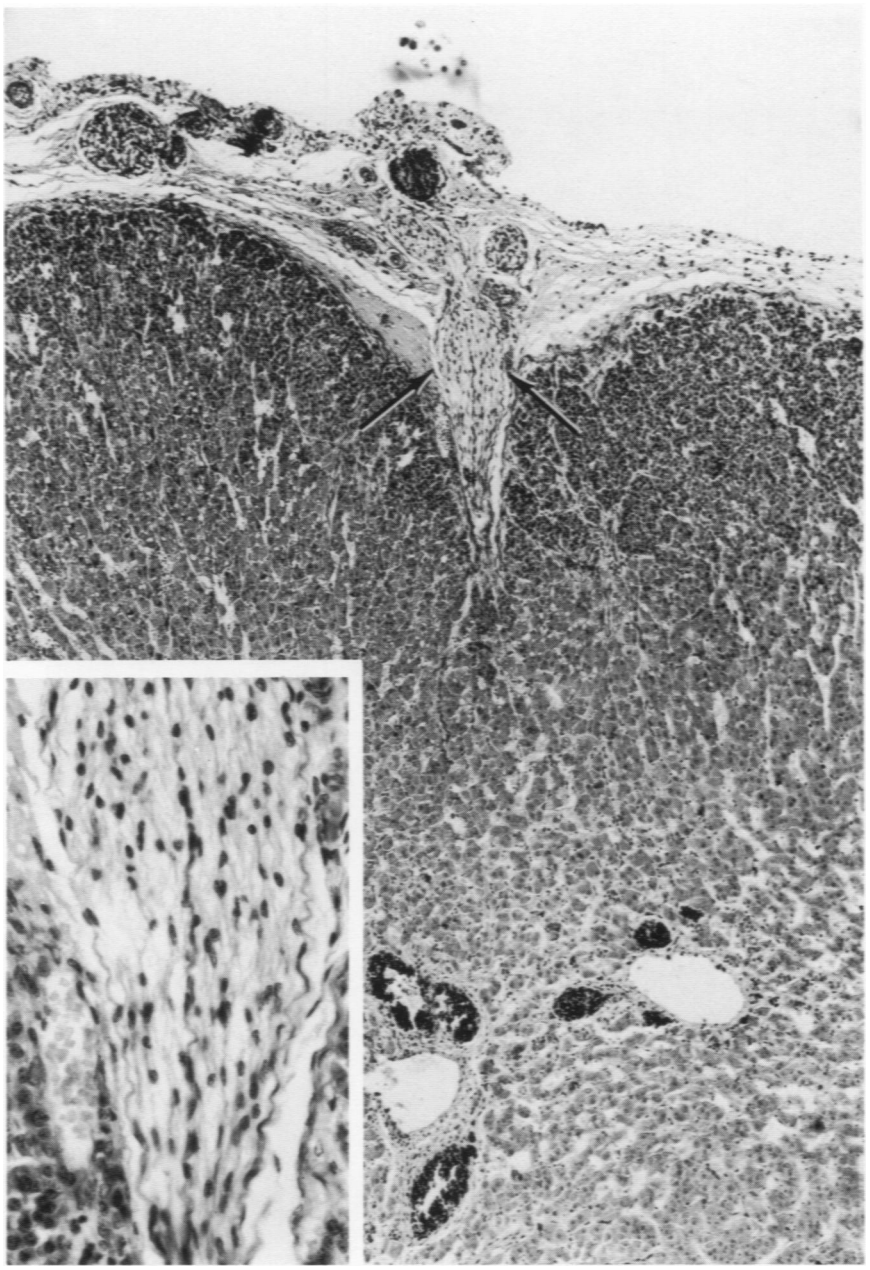

Fig 3—Fiber tract (*arrows*) entering adrenal gland, connecting extraadrenal sympathetic collections with intraadrenal nodules (H&E, × 72). **Inset**—High power detail or nerve fiber tract (H&E, × 400).

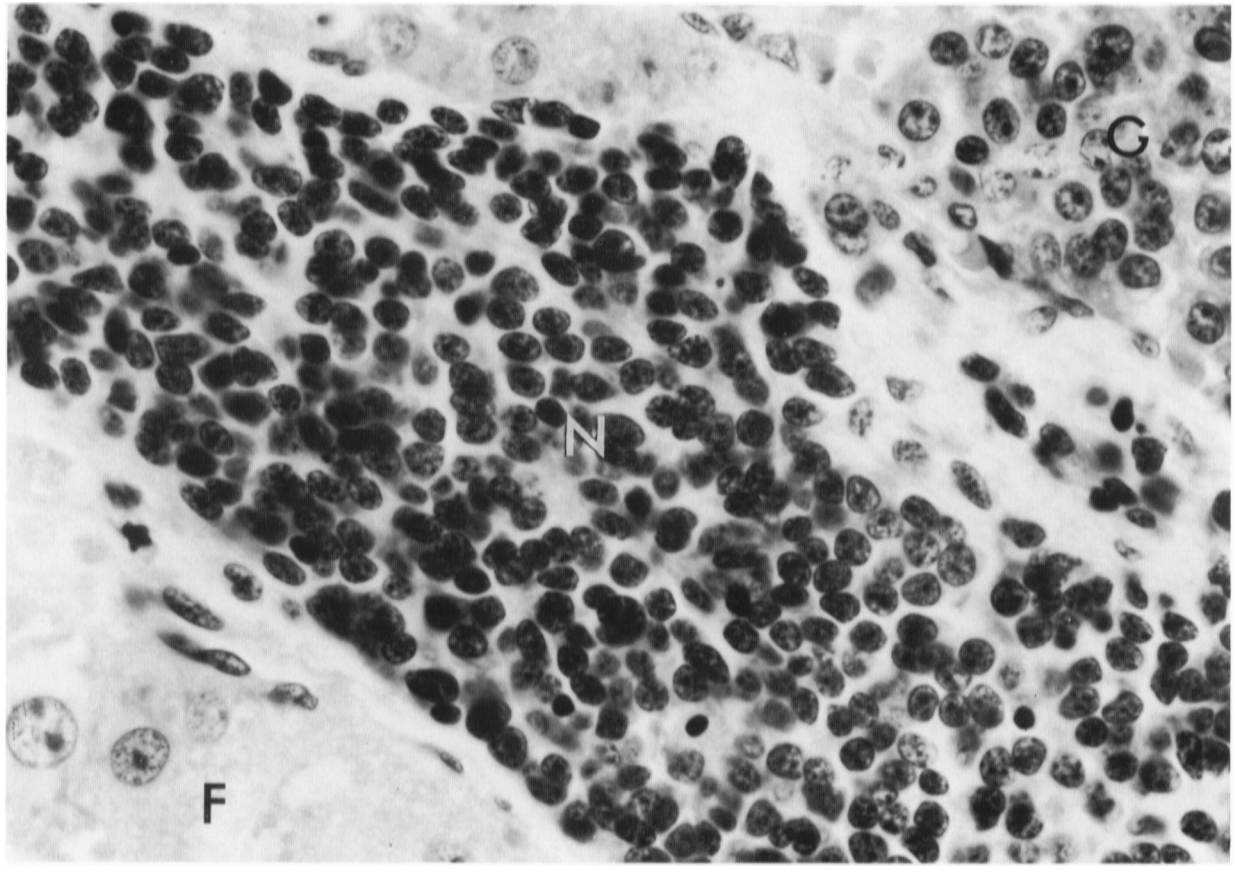

Fig 4—High power view showing cellular detail of subscapular neuroblasts (*N*), glomerular cortex (*G*, right upper corner) and fetal cortex (*F*, left lower corner) (H&E, × 920).

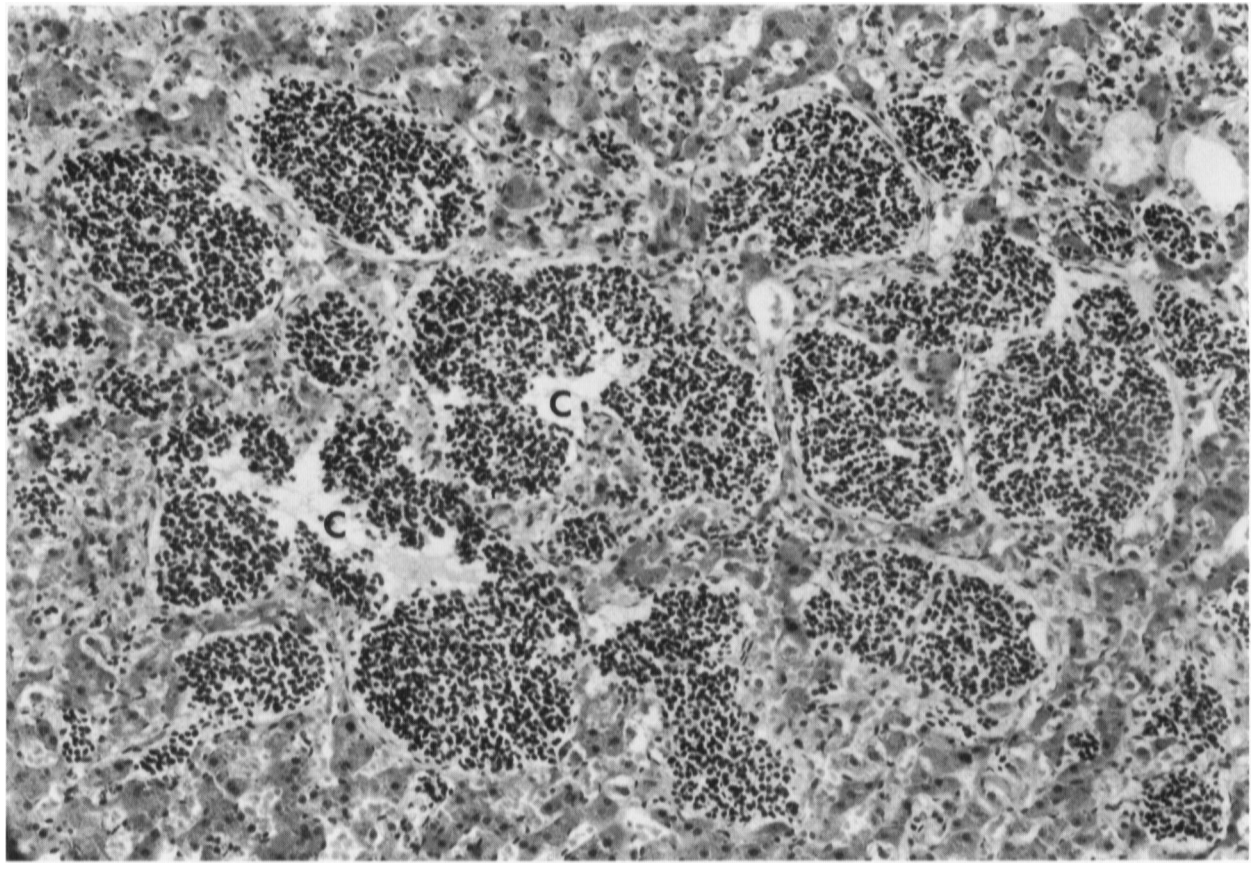

Fig 5—Example of a large group of neuroblastic nodules intermingled between cortical cells in an 18-week-old fetus. Note also the early cystic changes (*c*) (H&E, × 175).

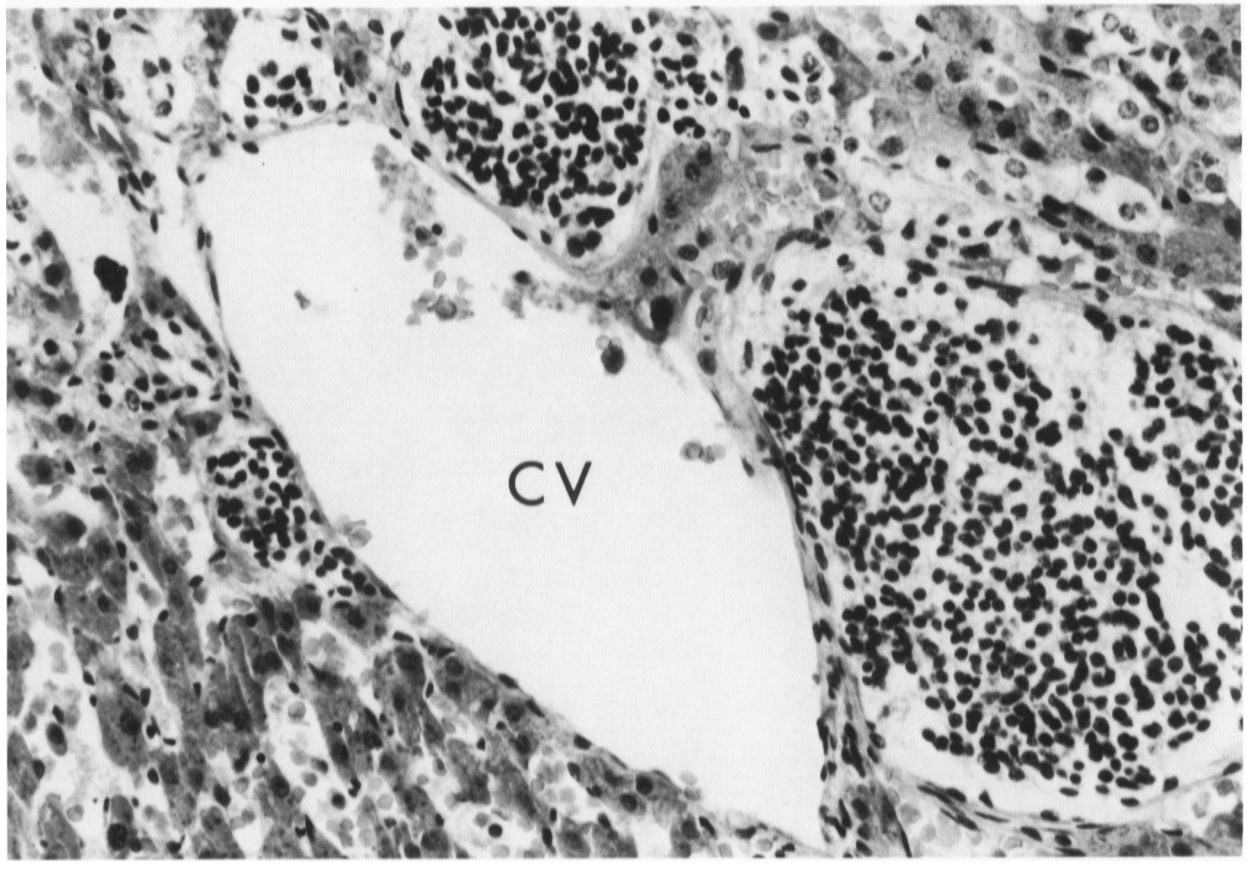

Fig 6—High power view of neuroblastic nodules immediately subjacent to endothelium of central vein (*CV*) (H&E, × 365).

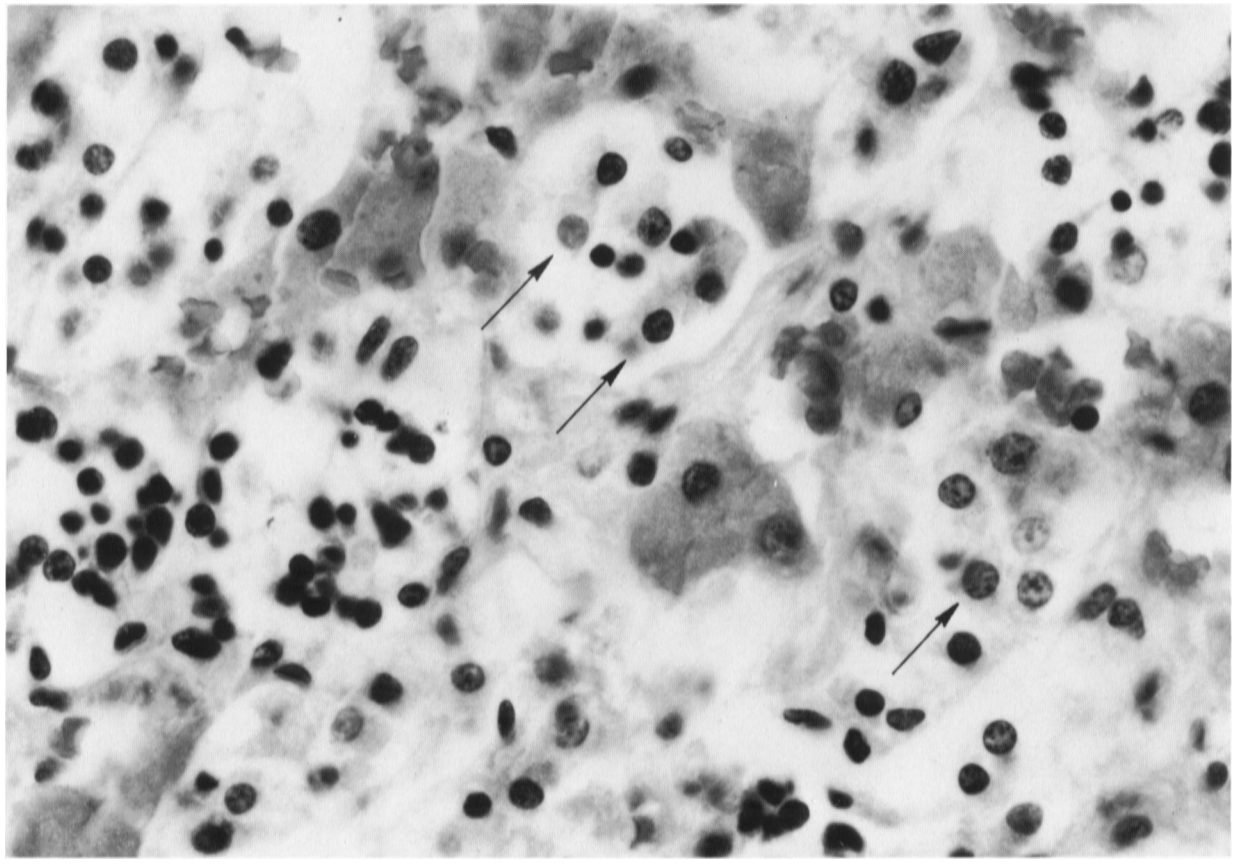

Fig 7—High power view of pheochromocytes (*arrows*) in central region of adrenal gland from a 19-week-old fetus (H&E, × 820).

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