

# Calcified Concretions in the Anterior Pituitary Gland of the Fetus and the Newborn: A Light and Electron Microscopic Study

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Calcified concretions including typical laminated psammoma bodies can be detected on routine hematoxylin-eosin (H&E) examination of fetal and neonatal anterior pituitary glands. This finding has seldom been reported in the literature and, to the authors' knowledge, no ultrastructural examinations of fetal or neonatal pituitary calcifications have been reported to date. In this study, histological sections of anterior pituitary glands from 200 fetuses and infants ranging in age from 15 weeks of gestation to 1 year of life revealed calcified concretions in all the cases up to 1 month of life. They decreased in incidence postnatally and were not found after 6 months of age. Most were round to ovoid, basophilic or eosinophilic, often laminated, and measured between 5 and 30  $\mu\text{m}$  in diameter. Immunohistochemical stains showed that the calcifications followed no particular pattern of distribution among the most prevalent pituitary cell types. Ultrastructural examination revealed small single or multiple intracellular calcified deposits, and larger, sometimes laminated, extracellular calcifications, suggesting an intracellular origin for the

Psammoma bodies are small calcified spherulites that occur frequently in meningiomas and papillary carcinomas of the thyroid and ovary; occasionally in gastrointestinal endocrine neoplasms and tumors of the breast, kidney, lung, and endometrium; and normal tissues, such as the meninges, choroid plexus, pineal body, and thyroid.<sup>1</sup> Among pituitary tumors, calcifications are most frequently encountered in prolactin-secreting adenomas.<sup>2,3</sup>

In fetal and neonatal pituitary glands, small irregular calcified concretions and typical laminated psammoma bodies can be detected during routine histological examination. A review of the literature disclosed only two articles reporting the light microscopic aspects of this finding.<sup>4,5</sup> Neither ultrastructural studies of the concretions nor immunohistochemical analyses correlating their location with diverse pituitary cell types have been reported to date.

To provide further information about this peculiar phenomenon, the authors herein present the histological, ultrastructural, and immunohistochemical findings from 200 fetal and neonatal pituitary glands.

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concretions with cell death occurring concomitant with their formation. This phenomenon, which to some extent resembles the formation of psammoma bodies in certain tumors, seems to represent a distinctive morphological type of developmental cell death. Apoptosis, a more common form of developmental cell death, was also found in some of the sections. Pathologists should be aware of the fact that calcified concretions represent a normal finding in the anterior pituitary gland of fetuses and young infants. Their mere presence in cases of fetal or perinatal demise with no other pertinent findings should not be attributed to intrauterine viral infections or ischemic-anoxic events. *HUM PATHOL* 27:1139-1143. Copyright © 1996 by W.B. Saunders Company

**Key words:** pituitary calcifications, psammoma bodies, apoptosis, fetal, neonatal.

**Abbreviations:** H&E, hematoxylin and eosin; GH, growth hormone; ACTH, adrenocorticotrophic hormone; PAS, periodic acid-Schiff.

## MATERIALS AND METHODS

The pituitary glands of 30 newborns, 30 infants surviving up to 1 postnatal year, and 140 fetuses were examined. The fetal age ranged from 15 to 42 weeks of gestation, and 5 glands per each week of gestation were studied. The postpartum glands were obtained from autopsy material. The fetal glands were collected from intrauterine deaths with or without established cause of death and from legal therapeutic terminations of pregnancy for fetal anomalies or maternal causes. The demographic information, maternal history, prenatal and postnatal age, clinical diagnosis, and autopsy findings were gathered from the patient's medical records.

The glands were excised within 12 hours after delivery or death, fixed in 10% formalin, embedded in paraffin, sectioned at 5  $\mu\text{m}$  and stained with hematoxylin-eosin (H&E), periodic acid-Schiff (PAS) reagent, and the von Kossa stain. One to six sections were examined in each case.

To study the relationship between the concretions and the most common pituitary cell types, further sections from 30 fetal and 15 postnatal glands were stained with the avidin-biotin-peroxidase technique for growth hormone (GH), adrenocorticotrophic hormone (ACTH), and prolactin (polyclonal; ready to use; DAKO, Santa Barbara, CA).

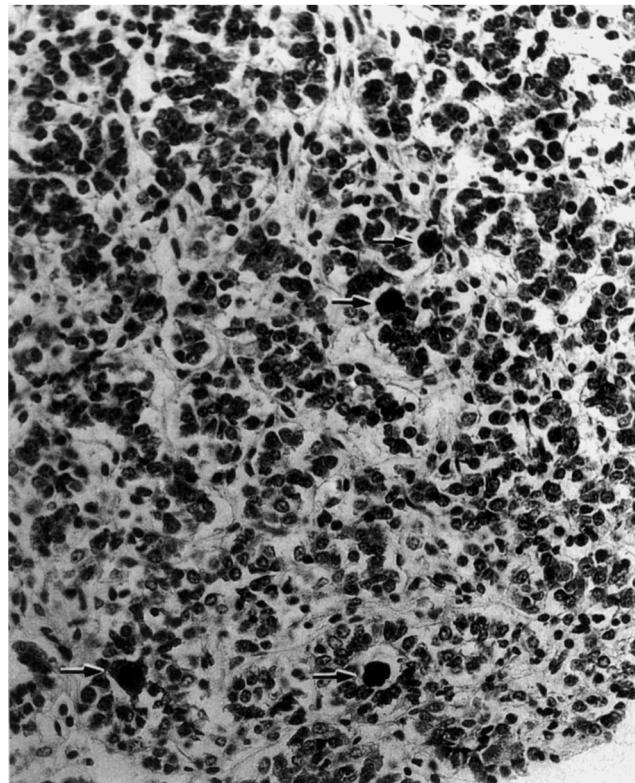
For electron microscopic study, 35 glands (25 fetal and 10 postnatal) were collected at the time of the autopsy, fixated in 3.5% cold glutaraldehyde, postfixed with 2% osmium tetroxide, and embedded in Epon. Thin sections were stained with uranyl acetate and lead citrate. Three blocks were studied in each case.

## RESULTS

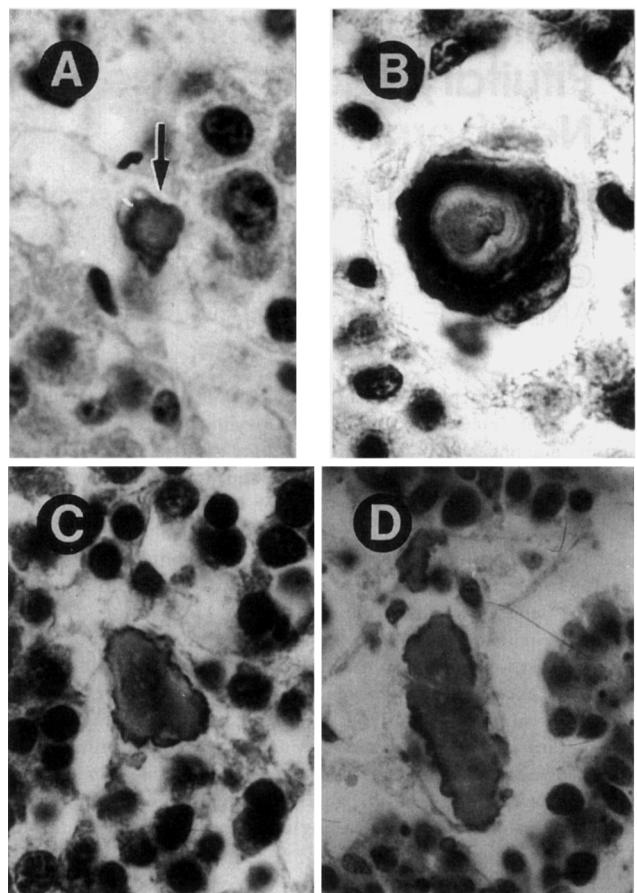
Between 2 and 30 calcified concretions were found in all the fetal and neonatal anterior pituitary glands

(Fig 1). In 85% of the cases, they were identified after examination of a single section. There was no significant correlation between quantity and fetal age. However, their occurrence decreased gradually after the 1st month of life, with no positive cases detected after 6 months. They appeared to be randomly distributed within the gland and among the different H&E cell types. Although rare calcifications were found in the pars intermedia, they were never observed in the neurohypophysis.

Four types of concretions could be distinguished (Fig 2): (1) minute (4 to 9  $\mu\text{m}$  in diameter), mostly basophilic and sometimes eosinophilic spherules; (2) prominent (10 to 40  $\mu\text{m}$ ) psammoma bodies with or without a laminated structure; (3) round, ovoid, or triangular eosinophilic concretions often showing a sharply defined basophilic periphery measuring 10 to 25  $\mu\text{m}$  at the maximum diameter; and (4) elongated, irregular basophilic, or eosinophilic forms up to 80  $\mu\text{m}$  long and sometimes accompanied by much smaller spherules in their adjacency. Not all the types were always present in a single gland. The most characteristic and easily identifiable calcifications were the round to ovoid, deeply basophilic, and sometimes concentrically laminated psammoma bodies. These structures had smooth or ragged edges and were often dislodged from their site in the section, indicating a hard consistency. The von Kossa stain was weakly reactive in the eosinophilic concretions and intensely positive in all the baso-



**FIGURE 1.** Anterior pituitary gland from a 24-week gestational age fetus showing prominent calcified concretions (arrows). (H&E stain; original magnification  $\times 200$ .)



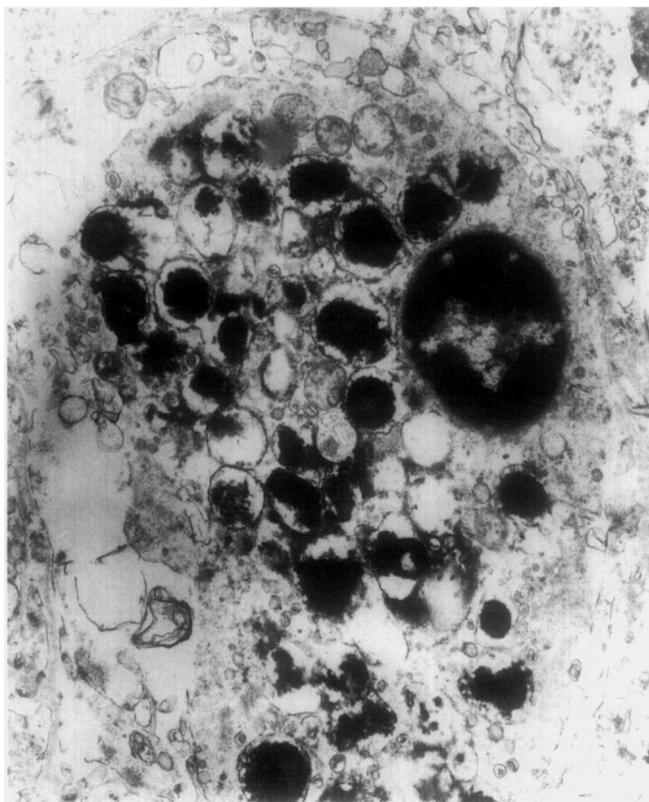
**FIGURE 2.** Various types of pituitary calcifications: (A) Small, round, basophilic microspherulite (arrow). (B) Concentrically laminated basophilic psammoma body. (C) Triangular eosinophilic concretion with a sharply defined basophilic edge. (D) Large, elongated eosinophilic concretion. Smaller fragments are seen below its upper pole. (H&E stain; A to C, original magnification  $\times 1,000$ ; D, original magnification  $\times 400$ .)

philic ones including the basophilic rim of the type III forms. When sections from the same case were compared, those stained with the von Kossa method revealed calcifications that were not evident on H&E. All types of concretions were PAS positive and resistant to diastase digestion.

Immunostaining for prolactin, GH, and ACTH failed to show any discernible pattern of distribution of the concretions among lactotrophs, somatotrophs, and corticotrophs.

Ultrastructural examination showed intracellular and extracellular calcifications. Variable numbers of small, round, granular calcified bodies were observed within the cytoplasm of the epithelial cells. Some were located within dilated, degenerating organelles and surrounded by a membrane (Fig 3); others were located within the cytoplasm, occasionally leading to the molding of organelles (Fig 4).

Extracellular calcifications were more common. Small coalescent microspherulites formed larger irregular coral-like concretions. They were composed of a sharp electron-dense periphery and a granular core



**FIGURE 3.** Electron micrograph of a fetal anterior pituitary cell showing multiple membrane-bound intracytoplasmic calcifications. (Original magnification  $\times 7,500$ .)

(Fig 5). The laminated psammoma bodies appeared as well-circumscribed circular structures. They were made of small needle-shaped crystalline structures embedded in a granular matrix and showed sharply demarcated concentric areas of variable electron density (Fig 6). The calcium deposits were usually encompassed by apparently healthy cells without any interposed material. Apoptotic cells showing pyknosis and clumping of the chromatin were also found.

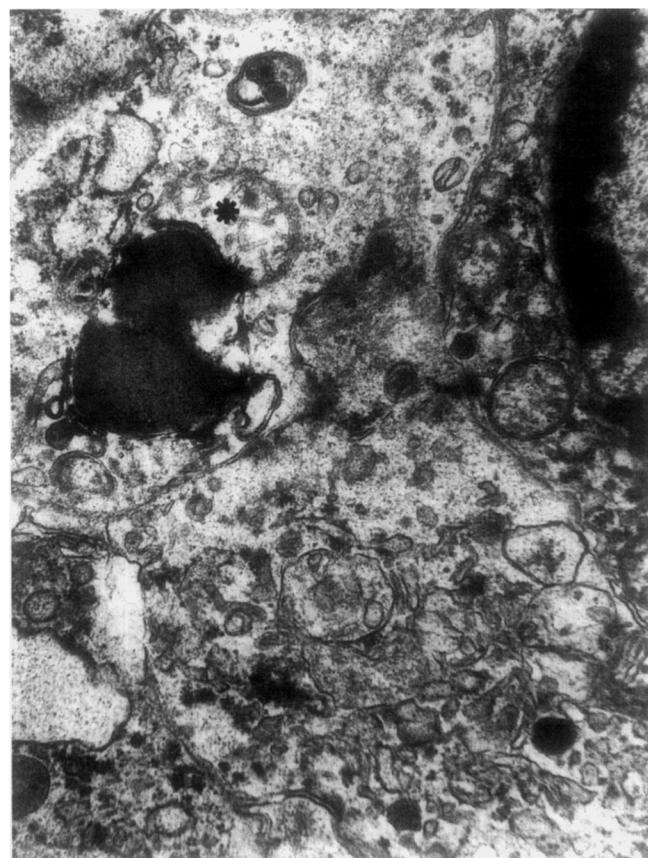
No quantitative, histological, or ultrastructural differences were noted when calcifications from male versus female, malformed versus nonmalformed, and still-born versus aborted cases were compared.

## DISCUSSION

The previous reports of Plaut and Galenson<sup>4</sup> and Barson and Symonds<sup>5</sup> together with this study have shown that calcified concretions are a normal finding in the anterior pituitary glands of fetuses and neonates, and that they tend to decrease and disappear in early infancy. In most cases, they can be identified without much difficulty. When a single section of the pituitary gland was examined, Barson and Symonds<sup>5</sup> and the present authors found calcifications in 57% and 85% of the cases, respectively. With further sections, they were identified in 100% of the fetal and neonatal cases.

In negative or doubtful cases, a von Kossa stain was helpful in detecting concretions that were overlooked on the H&E stain. Their strong PAS-diastase reactivity may be related to the presence of large amounts of glycoproteins in the matrix in which the calcification occurs.<sup>6</sup>

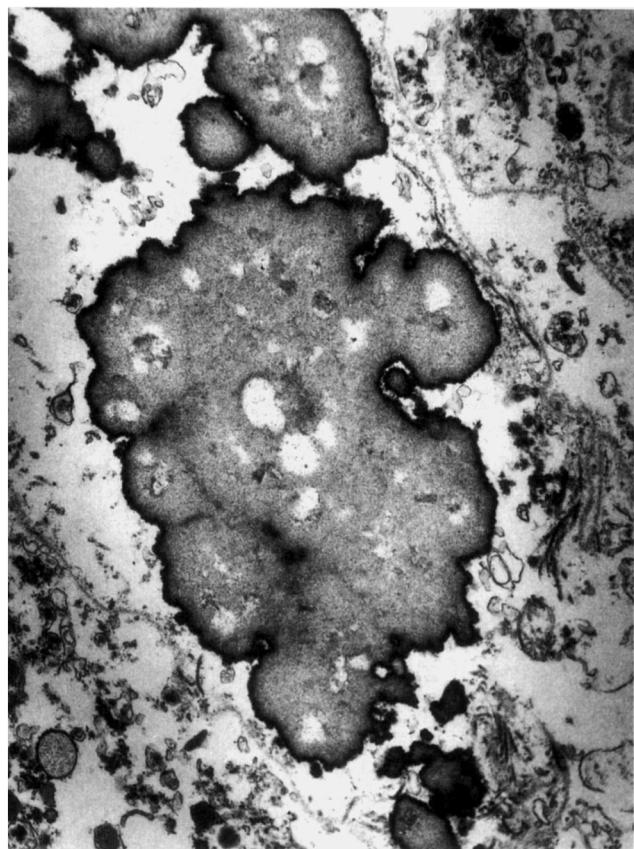
To the authors' knowledge, they are the first to study the concretions ultrastructurally. Diverse types of calcifications ranging from small intracellular deposits to well-formed laminated psammoma bodies were identified. The origin of the extracellular concretions can be attributed to degeneration and death of calcified cells, or, alternatively, to the releasing of calcifications from intact cells to the extracellular space. The authors' interpretation that cell death does occur concomitant with the formation of the concretions is supported by the ultrastructural findings. The authors suggest that foci of intracytoplasmic calcification leads to cellular damage and breakdown of the plasma membrane concomitant with growth of the calcifications. Once in the extracellular space, a dense outer line develops, and eventual growth in a layered fashion produces the laminated appearance. The calcification is dystrophic in the sense that cytoplasmic fragments from dead cells contribute to the matrix in which the calcification occurs. However, contrary to most dystrophic calcifications in



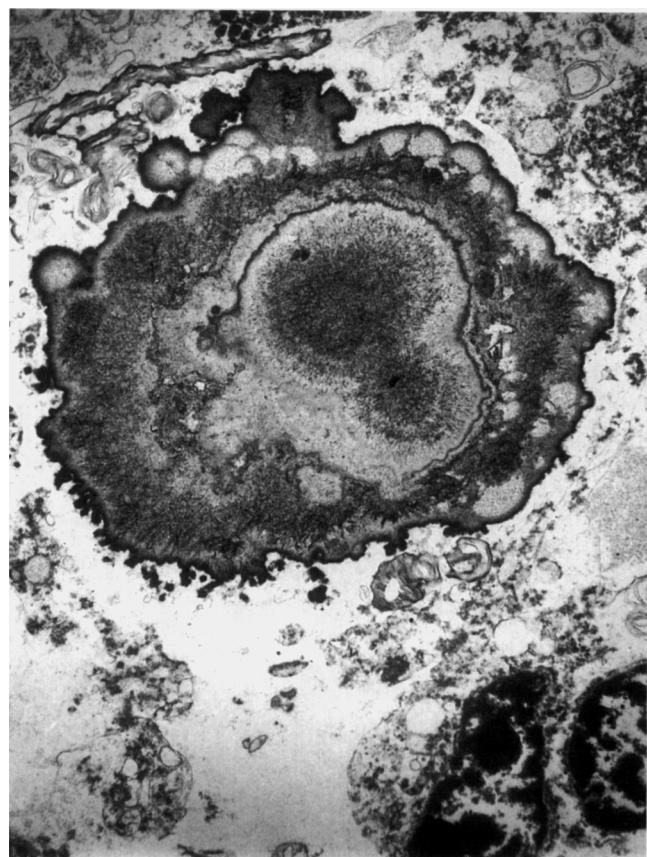
**FIGURE 4.** Electron micrograph illustrating molding of mitochondria (asterisk) by intracytoplasmic granular calcification. (Original magnification  $\times 21,000$ .)

which large areas of tissue necrosis surround the calcified deposits, in the fetal or neonatal hypophyses the concretions are immediately surrounded by apparently healthy cells. It seems that only single cells are transformed into calcified bodies. A similar pathogenesis was proposed for psammoma bodies arising in ovarian serous tumors,<sup>7</sup> pituitary adenomas,<sup>8</sup> thyroid papillary carcinomas,<sup>9</sup> and endometrial carcinomas.<sup>10</sup> The authors were unable to find descriptions of a similar process in other fetal organs. Consequently, we suggest that, in addition to apoptosis, a distinctive, perhaps unique morphological type of developmental cell death involving calcification of individual cells occurs in the human fetal and neonatal pituitary gland. Whether this represents the physiological counterpart of tumoral psammoma body formation still needs to be clarified.

Apoptosis, the most characteristic morphological type of developmental cell death, has been induced in normal and neoplastic pituitary glands of murines by bromocriptine, a dopamine-receptor agonist used therapeutically to reduce the volume of pituitary adenomas.<sup>11,12</sup> Drewett et al<sup>11</sup> induced hyperplasia of prolactin-secreting cells by estrogen implants followed by increased apoptosis after estrogen withdrawal. To the authors' knowledge, apoptosis including its relationship with fetal or maternal hormones or dopamine ago-



**FIGURE 5.** Electron micrograph of irregular coral-like concretions with a sharp electron-dense periphery and a granular core. (Original magnification  $\times 9,800$ .)



**FIGURE 6.** Electron micrograph of a laminated psammoma body showing sharply demarcated concentric areas of variable electron density. (Original magnification  $\times 9,800$ .)

nists has not been studied in the human fetal pituitary gland.

In addition to the pituitary gland, physiological intracranial calcifications can be found in the pineal gland, choroid plexus, dura mater, and arachnoid.<sup>13</sup> However, in contrast to the pituitary concretions that decrease in incidence during the first months of life, in all the other locations their incidence increases with postnatal age.<sup>13</sup> In the pineal gland, both increased concretions and decreased melatonin biosynthesis are age-related.<sup>14</sup>

Calcifications are rarely found in normal postnatal pituitary glands. Plaut and Galenson<sup>4</sup> studied 110 pituitary glands from individuals more than 1.5 years of age and found calcified bodies in only 5% of the cases. They proposed that the fetal concretions might be formed under the influence of maternal hormones because they disappear during the first postnatal months.

Among pituitary adenomas, prolactinomas are the most common to harbor calcified concretions. Rilliet et al<sup>2</sup> reported a series of 755 pituitary adenomas and found calcifications in 51 of them (6.75%). Seventy-five percent of these 51 cases were prolactinomas, 18% GH-secreting adenomas, and 7% endocrine inactive tumors. Likewise, Ho and Liu<sup>8</sup> studied a series of 27 prolactin-secreting pituitary adenomas and found calcifi-

cations in 40% of them. In fetal and neonatal pituitaries, the number of lactotrophs and prolactin secretion gradually increases. At term, their hyperplasia is comparable with that observed in maternal glands in late gestation and during lactation.<sup>14,15</sup> The constant presence of pituitary calcifications in neonatal hyperprolactinemic pituitary glands, and the relative high frequency of calcifications in prolactinomas, led Rilliet et al<sup>2</sup> to suggest a possible association between a physiological or pathological state of hyperprolactinemia with the presence of calcifications. The authors were unable to confirm this hypothesis because the immunohistochemical study failed to show any specific distribution pattern when the location of the concretions was correlated with the location of lactotrophs, somatotrophs, and corticotrophs. Further studies will be needed to determine the precise mechanism leading to the formation of the calcifications.

From the practical standpoint, the importance of the pituitary calcifications is the potential of interpreting their mere presence as the result of an intrauterine viral infection or an ischemic-anoxic event. Increased awareness of this phenomenon should help to avert this pitfall.

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