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Invited Review

Ultrastructure of the parathyroid gland

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Key words: Ultrastructure, Parathyroid gland

1. Introduction

Since the first detailed description of the parathyroid glands, reported in human beings by Sandstrom in 1880, and Lever first described the ultrastructure of the parathyroid chief cells of rat in 1957, a large number of histological and ultrastructural studies have been done on the parathyroid glands of numerous animal species under normal and experimental conditions.

The biological function of the parathyroid glands is to raise serum calcium concentrations by multiple actions on the bone, kidney and gut. The parathyroid glands recognized in all vertebrate animals higher than fishes arise from the third and fourth branchial pouches. Several animals, such as the newt, lizard, gecko, mouse, rat, hamster and gerbil, have only two parathyroid glands, but most animals have four (Shoumura and Isono, 1985). In mammals, most of the parathyroid glands are closely associated with the thyroid gland, but in amphibians, reptiles and birds, the glands separate from the thyroid gland (Shoumura and Isono, 1985). In the love birds, the parathyroid glands are situated close to the carotid body (Shoumura, 1974), and in rabbits having two pairs of the parathyroid glands, two parathyroid glands (one pair) separate from the thyroid gland (Shoumura and Isono, 1985).

In some mammals, the parenchymal cells composing the parathyroid gland are classified under a light microscope into two main types of cells: chief cells and oxyphil cells (Bargmann, 1939), and examinations under an electron microscope also show chief cells as having many cell organelles and oxyphil cells filled with numerous mitochondria in the human, monkey, cow, horse, bat and turtle parathyroid glands (Trier, 1958; Lange, 1961; Roth and Munger, 1962; Holzmann and Lange, 1963; Capen et al., 1965; Nakagami, 1965; Fujimoto et al., 1967; Clark and Khairallah, 1972; Sakuma, 1974; Roth and Schiller, 1976; Shoumura and Isono, 1985). In addition, the chief cells in most animals are classified at the light microscopic level into light cells and dark cells (Bargmann, 1939; Bensly, 1947), and moreover the chief cells are also electronmicroscopically divided into a light and dark type showing different functional phases of a single cell type when osmium or glutaraldehyde fixative is used (Lever, 1957; Lange, 1961; Roth and Munger, 1962; Holzmann and Lange, 1963; Capen et al., 1965; Nakagami, 1965; Rogers, 1965; Capen and Young, 1967; Fujimoto et al., 1967; Capen and Rowland, 1968; Hara and Nagatsu, 1968; Coleman, 1969; Fetter and Capen, 1970; Iwatsutsumi, 1971; Clark and Khairallah, 1972; Narbaitz, 1972; Roth and Schiller, 1976). However, it is widely accepted today that differences in cytoplasmic density of the chief cells are due to artifacts produced in the process of tissue preparation (Stoeckel and Porte, 1966; Murakami, 1970; Furuta, 1971; Fujii and Isono, 1972; Shoumura, 1974; Fujii, 1975; Isono et al., 1976a, 1977, 1979a, b; Roth and Schiller, 1976; Takai, 1976; Setoguti, 1977; Isono and Shoumura, 1979; Emura et al., 1982, 1984b; Ishizaki et al., 1983; Krause and Cuts, 1983; Larsson et al., 1984; Iwasaki et al., 1985; Shoumura and Isono, 1985).

This review deals with two major topics: the comparative morphology of the parathyroid glands of amphibians, reptiles, birds and mammals under normal conditions used in our laboratory, and the ultrastructural changes of the parathyroid glands of rabbit and hamster in experimental conditions, especially after stimulation and suppression of the autonomic nervous system and after centrifugation (hypergravity environment).

2. Comparative morphology of the normal parathyroid glands

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a. Amphibia

The first ultrastructural studies of the parathyroid glands of urodela, the newt *Triturus pyrrhogaster* (Boié), were made by Setoguti et al. (1970a). In our studies (Setoguti et al., 1970a, b; Isono et al., 1971; 1976; Isono and Shoumura, 1973; Isono and Shoumura-Sakurai, 1973), the parenchymal cells of the parathyroid gland of the newt are divided into two main types: basal cells constantly rested on a basement membrane; suprabasal cells took a suprabasal position in the parenchyma (Fig. 1). The basal cells contained numerous cytoplasm filaments and a few cell organelles, and the suprabasal cells sparse cytoplasmic filaments and numerous cell organelles (Fig. 1). In the basal cells, the nucleus showed deep indentations, and a small number of mitochondria and poorly-developed Golgi complexes and cisternae of the granular endoplasmic reticulum were present (Fig. 1). At the basal surface pinocytotic vesicles were located, frequently arranged in a row (Fig. 1). In the suprabasal cells, mitochondria were abundantly scattered and well-developed Golgi complexes and cisternae of granular endoplasmic reticulum were widely dispersed in the cytoplasm (Fig. 1). Secretory granules of 200-400 nm in diameter, large vacuolar bodies having uncoated and coated vesicles, lysosomes and lipofuscin pigments were frequently observed in the cytoplasm (Fig. 1). In the spring, the suprabasal cells appeared to have increased activity when compared to those in the hibernating state. Though the suprabasal cells resembled the chief cells in other animals, the basal cells have not been observed in the parathyroid gland of any animals (Setoguti et al., 1970a). The basal cell might play a role as a supporting cell rather than a secreting cell (Setoguti et al., 1970a; Isono et al., 1971).

In the electron microscopic radioautograph of the parathyroid gland of the newt after injection of ^{3}H-leucine (Isono and Shoumura, 1973), most of the silver

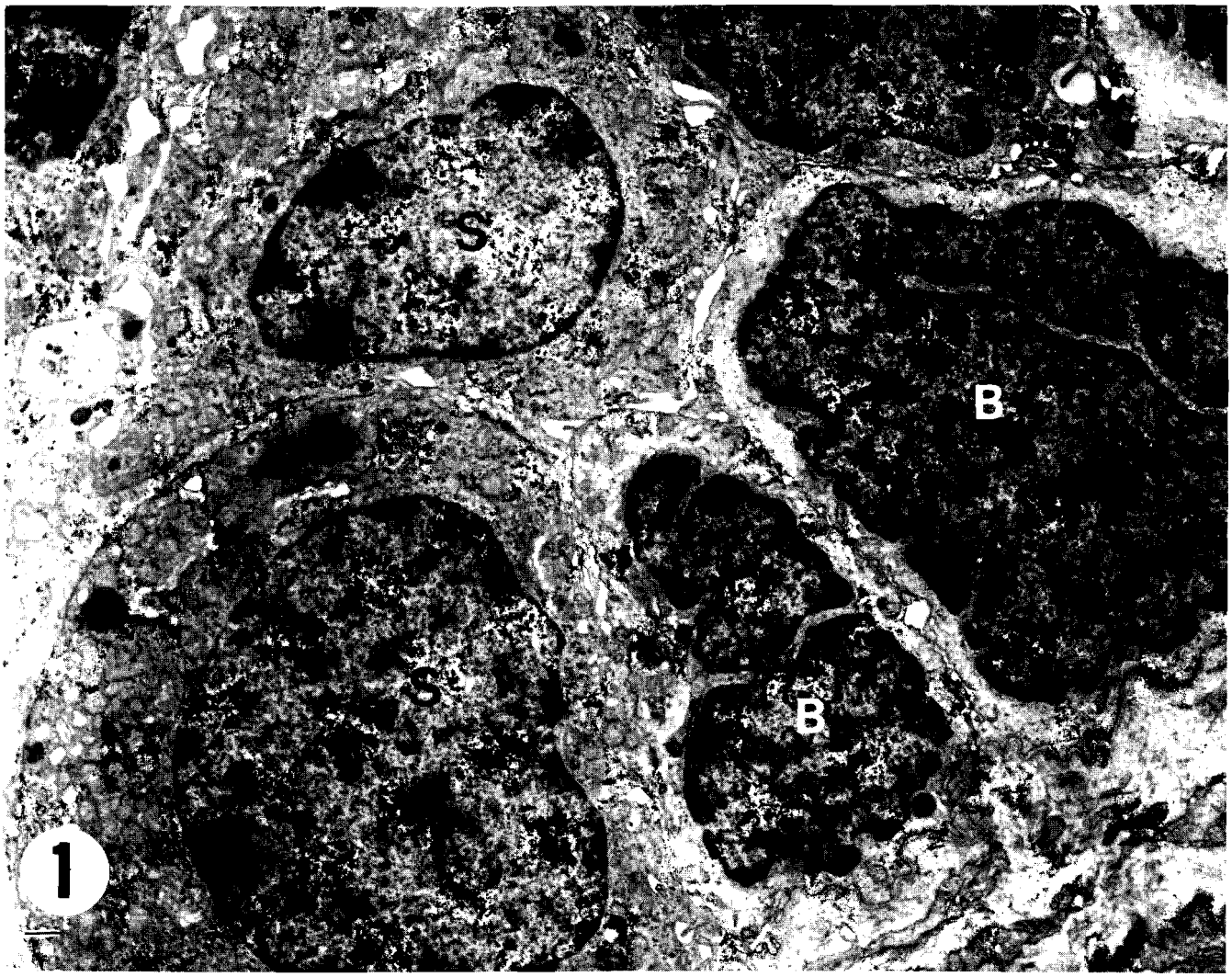


Fig. 1. Newt parathyroid gland. Basal cells (B) containing numerous cytoplasmic filaments with a few cell organelles resting on a basement membrane, and suprabasal cells (S) containing sparse cytoplasmic filaments and numerous cell organelles taking a suprabasal position in the parenchyma. Bar: 1 μm.

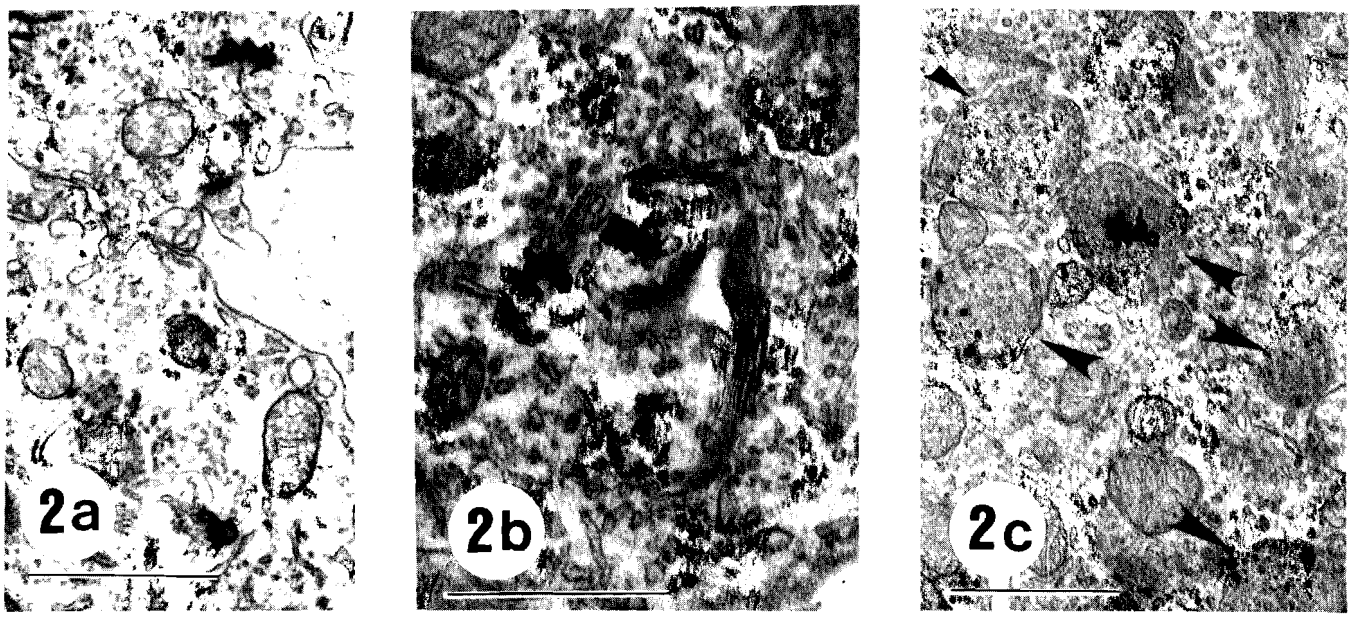


Fig. 2. In electron microscopic radioautographs of the suprabasal cells of newt after injection of ^{3}H-leucine, silver grains are seen over cisternae of the granular endoplasmic reticulum after 15 minutes (2a), over the Golgi complex after 30 minutes (2b) and over secretory granules (arrow heads) after 60 minutes from injection (2c) Bar: 1 μm.

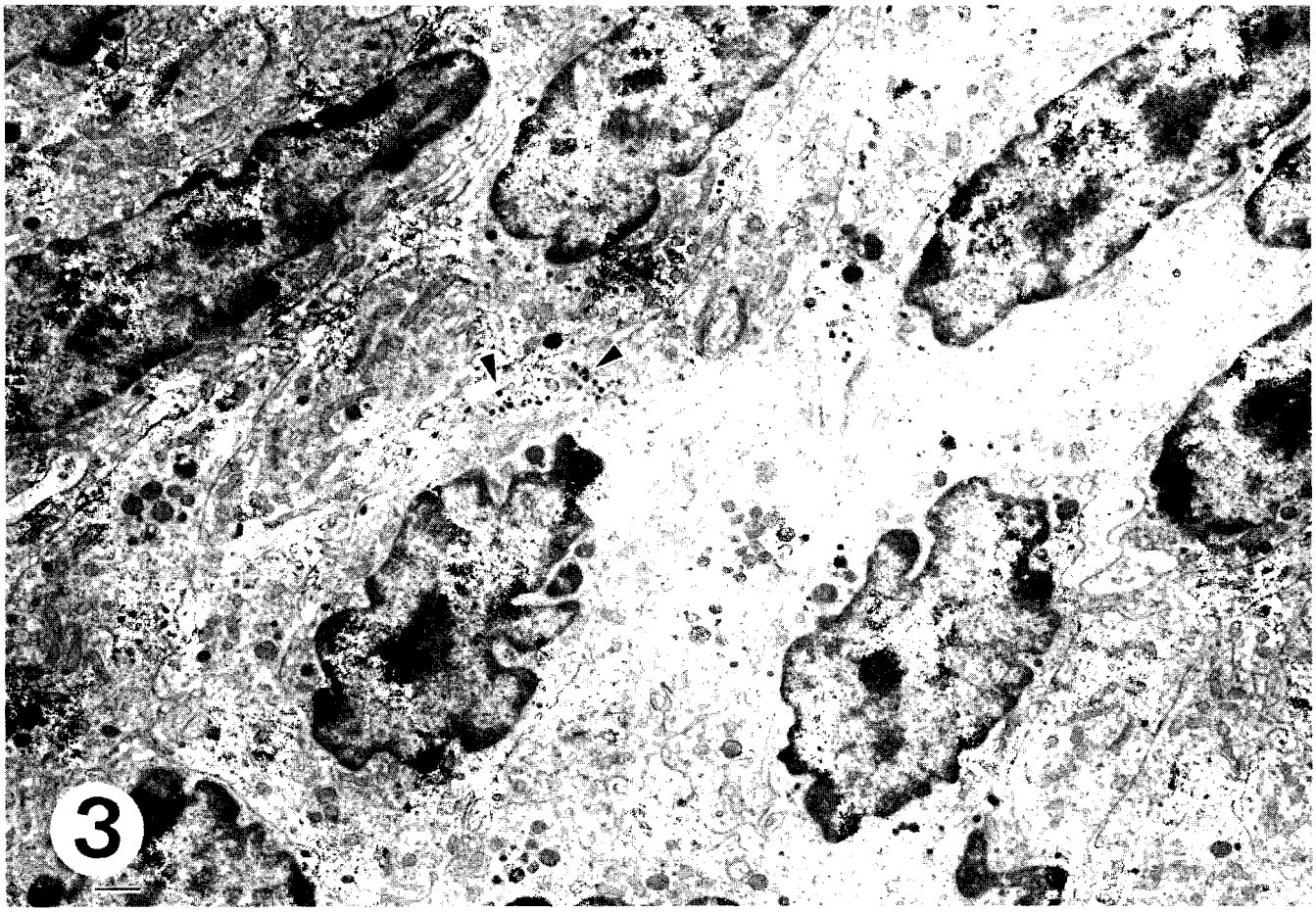


Fig. 3. Frog parathyroid gland. Large chief cells contain well-developed Golgi complexes and cisternae of the granular endoplasmic reticulum, numerous secretory granules (arrow heads) and a few lysosomes. Bar: 1 μm.

grains were seen over cisternae of the granular endoplasmic reticulum at 15 minutes (Fig. 2a), over the Golgi complexes at 30 minutes (Fig. 2b), and over secretory granules at 60 minutes (Fig. 2c). Similar results have been reported in the rat parathyroid gland (Nakagami et al., 1971). From such findings, the synthesis of secretory protein is related to ribosomes lining cisternae of the granular endoplasmic reticulum, newly synthesized secretory protein is transferred from cisternae of the granular endoplasmic reticulum to the Golgi complexes, and secretory granule is derived from the Golgi complexes.

Since Hara et al. (1959) first described the ultrastructure of the parathyroid glands of the toad *Bufo vulgaris japonicus*, several ultrastructural studies have been reported in frogs and toads (Lange and Brehm, 1963, 1965; Montsko et al., 1963; Rogers, 1965; Cortelyou and McWhinnie, 1967; Iwatsutsumi, 1971; Coleman and Phillips, 1972; Isono et al., 1976, 1978b). In our studies (Hara et al., 1959; Isono et al., 1976, 1978b), blood vessels and connective tissue were not observed in the parenchyma of the parathyroid gland (Fig. 3). The parenchymal cells consisted of small chief cells and large chief cells (Fig. 3). The small chief cells were centrally located and had a few cell organelles. The large chief cells were located in the peripheral region of the gland and contained well-developed Golgi complexes with some prosecretory granules and cisternae of the granular endoplasmic reticulum, numerous secretory granules of 200-400 nm in diameter, many vacuolar bodies, and a few lysosomes and lipid droplets (Fig. 3). There were transitional forms between the small and large chief cells. The large chief cells might be in the active phases and the small chief cells in the inactive phases of the secretory cycle.

b. Reptilia

Clark (1970) and Clark and Khairallah (1969, 1972) reported the ultrastructural findings on the reptilian parathyroid gland of the fresh-water turtles *Pseudemys scripta* and *Chrysemys picta*. The parathyroid glands of the fresh-water turtles were composed of chief cells and the oxyphil cells. Many chief cells contained large Golgi complexes with prosecretory granules, comparative numerous secretory granules of 300-400 nm in diameter, and prominent cisternae of the granular endoplasmic reticulum. The oxyphil cells had numerous mitochondria. Anderson and Capen (1976) described the ultrastructure of the parathyroid glands of the green iguanas *Iguana iguana*. In the parathyroid gland of the green iguanas, the chief cells had extensive arrays of granular endoplasmic reticulum, numerous mitochondria, many prosecretory granules associated with the Golgi complexes, small secretory granules aligned along the plasma membrane, and few secretory granules. In addition, Chin (1974) indicated seasonal ultrastructural changes in the turtle parathyroid gland.

In our study (Isono et al., 1979a), the chief cells of the parathyroid glands of the Japanese lizards *Takydromus tachydromoides* contained numerous free ribosomes and mitochondria, well-developed Golgi complexes, a few lysosomes, some multivesicular bodies, accumulation of microfilaments and relatively numerous lipid droplets (Fig. 4). The endoplasmic reticulum was mainly smooth-surfaced and cisternae of the granular endoplasmic reticulum were distributed randomly in the cytoplasm (Fig. 4). Coated vesicles were found in the Golgi region and occasional secretory granules of 150-300 nm in diameter were distributed randomly in the cytoplasm and lay close to the plasma membrane (Fig. 4). Electron-dense material similar to the contents of the secretory granules was observed in the enlarged intercellular space (Fig. 4, Inset). These findings suggest the possibility of exocytosis of the secretory granule in the parathyroid gland of the lizard.

The morphology of the parathyroid gland of gecko *Gekko japonicus* (Isono et al., 1986) resembles that of the lizard.

c. Aves

The ultrastructure of the avian parathyroid glands has been described by several authors (Nevalainen, 1969; Youshak and Capen, 1970; Gould and Hodges, 1971; Fujii and Isono, 1972; Stoeckel and Porte, 1973; Shoumura, 1974; Fujii, 1975; Chan, 1977; Isono et al., 1978a; Setoguti et al., 1981, 1982; Clark and Dunn, 1986).

The ultrastructure of the parathyroid glands in the love birds *Uroloncha striata domestica* and Australian love birds *Melopsittacus undulatus* was reported by Shoumura (1974). The chief cells contained abundant mitochondria, well-developed Golgi complexes associated with numerous prosecretory granules and cisternae of the granular endoplasmic reticulum, relatively sparse secretory granules of 100-400 nm in diameter, a few lysosomes and multivesicular bodies. Unmyelinated nerve endings including cored vesicles were present in the perivascular spaces (Fig. 5). Shoumura (1974) speculated about the possibility of exocytosis of the secretory granule and prosecretory granule, since some secretory granules and prosecretory granules were situated close to the plasma membrane and the enlarged intercellular spaces contained a finely particulate material similar to the contents of both granules in the parathyroid glands of the love birds and Australian love birds.

The ultrastructure of the parathyroid glands in the laying hen *Gallus domesticus* was described by Fujii and Isono (1972). Fujii (1975) studied age-related changes in the ultrastructure of the parathyroid glands of the domestic fowl *Gallus domesticus*. In the parathyroid glands of 8- and 10-day-old chick embryos the development of cell organelles was poor, many chief cells had plasma membranes with small folds and interdigitations, and a few secretory granules of 200-400 nm in diameter were seen in the Golgi areas. In the parathyroid glands of 14- to 20-day-old chick embryos and 1- to 15-week-old chickens, cisternae of the granular endoplasmic reticulum and the Golgi complexes associated with numerous prosecretory granules were relatively well-developed and the plasma membranes became more tortuous with

age. Fujii (1975) suggested that the parathyroid glands during the embryonal period as well as the postnatal period were already active. Many chief cells in the parathyroid glands of the hen had rich free ribosomes, abundant mitochondria, and well-developed Golgi complexes containing serpiginous profile (Fig. 6) and cisternae of the granular endoplasmic reticulum. Secretory granules increased in number with age. Some secretory granules were seen in the vicinity of or even in contact with plasma membrane (Fig. 7) and the granule contents communicated directly with the intercellular space through an opening in the fused portion of the limiting and plasma membranes (Fig. 7). Therefore, the possibility of exocytosis of the secretory granule was suggested (Fujii and Isono, 1972; Fujii, 1975). Annulate lamellae are observed in the chief cells.

The parathyroid gland of the quail *Coturnix coturnix japonica* (Isono et al., 1978) has an ultrastructure similar to that of the hen.

Setoguti et al. (1981) reported the ultrastructural studies on localization of phosphatases in the parathyroid gland of the laying hen. Activities of both alkaline phosphatase and adenosine triphosphatase were intensive on the plasma membranes between contiguous chief cells, and activities of both thiamine pyrophosphatase and inosine diphosphatase were seen in most of the Golgi cisternae, and acid phosphatase activities were mainly demonstrated in lysosomes and only occasionally encountered in the Golgi apparatus including the thick membranous cisternae, in contrast with findings in mammals (Shannon and Roth, 1971; Setoguti and Goto, 1974; Setoguti et al., 1980).

d. Mammalia

A large number of ultrastructural studies of the normal parathyroid glands have been reported in mammals and today we have a knowledge of the ultrastructural characteristics of the normal mammalian parathyroid glands. The important publications are the following: Lever (rat, 1957, 1958), Mizuochi (dog, 1958), Davis and Enders (rat, 1961), Kayser et al. (hamster, 1961), Munger and Roth (deer, 1963), Hara and Nagatsu-Ishibashi (mouse, 1964), Roth and Raisz (rat, 1964), Capen et al. (cow, 1965), Faccini and Care (sheep, 1965), Nakagami (dog, monkey, 1965), Stoeckel and Porte (mouse, 1966), Melson (rabbit, 1966), Fujimoto et al. (horse, 1967), Mazzocchi et al. (rat, 1967), Nakagami et al. (mouse, 1967), Capen and Rowland (cat, 1968a, b), Fetter and Capen (pig, 1968, 1970), Hara and Nagatsu (rat, 1968), Lupulescu et al. (dog, 1968), Melson (rabbit, 1968), Rohr and Krassig (rat, 1968), Roth et al. (rat,

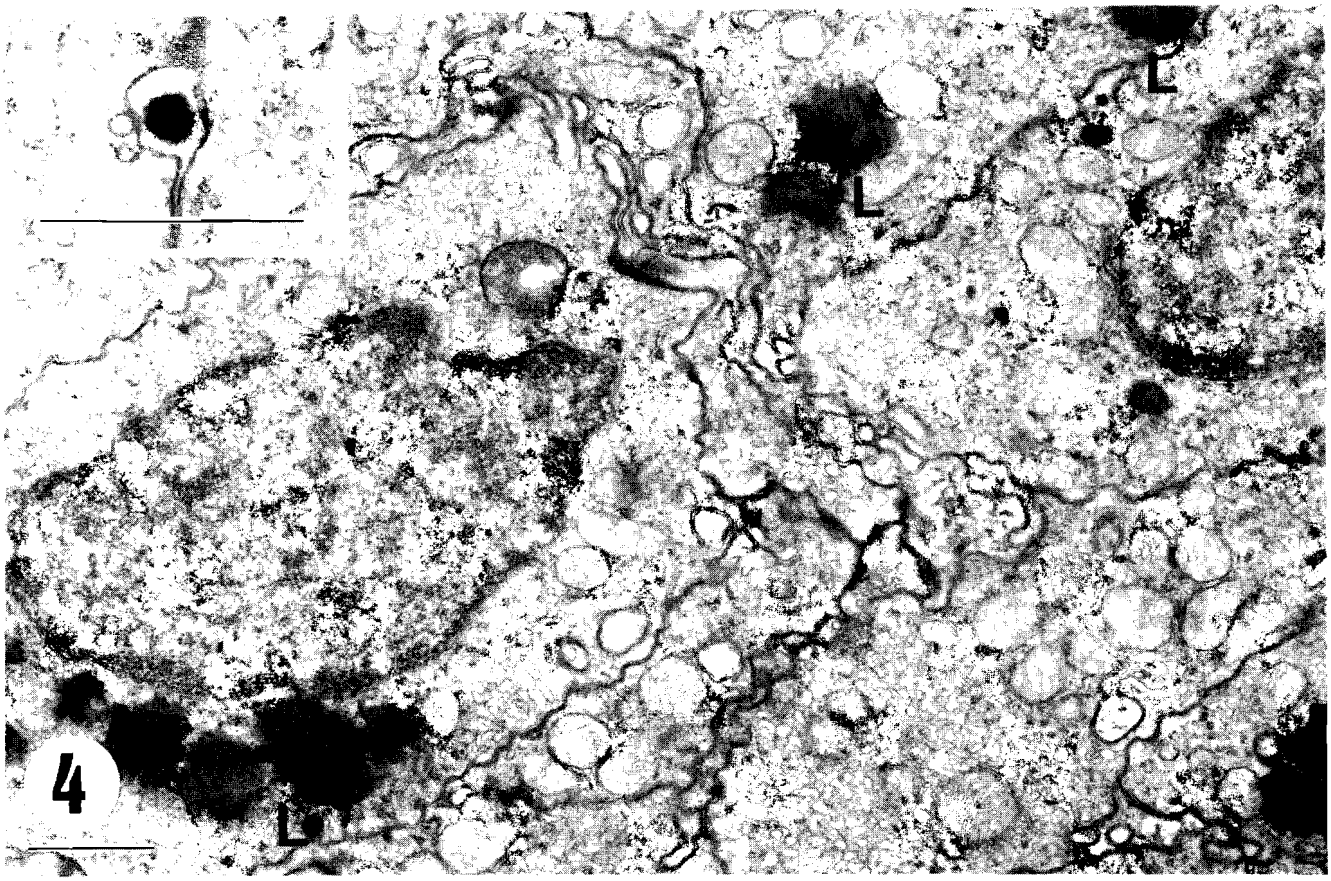


Fig. 4. Lizard parathyroid gland. The endoplasmic reticulum is mainly smooth-surfaced and relatively numerous lipid droplets (L) are present. Inset. Electron-dense material is observed in the enlarged intercellular space. Bar: 1 μm.

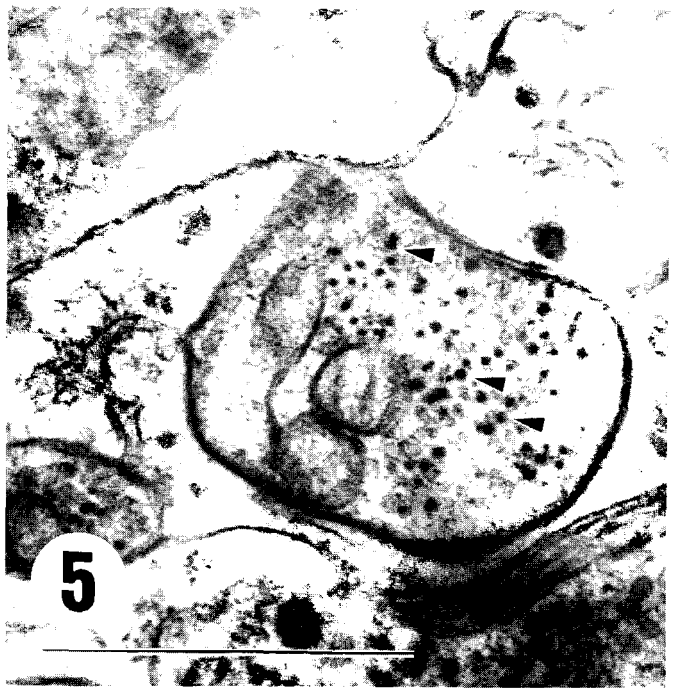


Fig. 5. Australian love bird parathyroid gland. Nerve ending including cored vesicles (arrow heads) is present in the perivascular space. Bar: 1 μm.

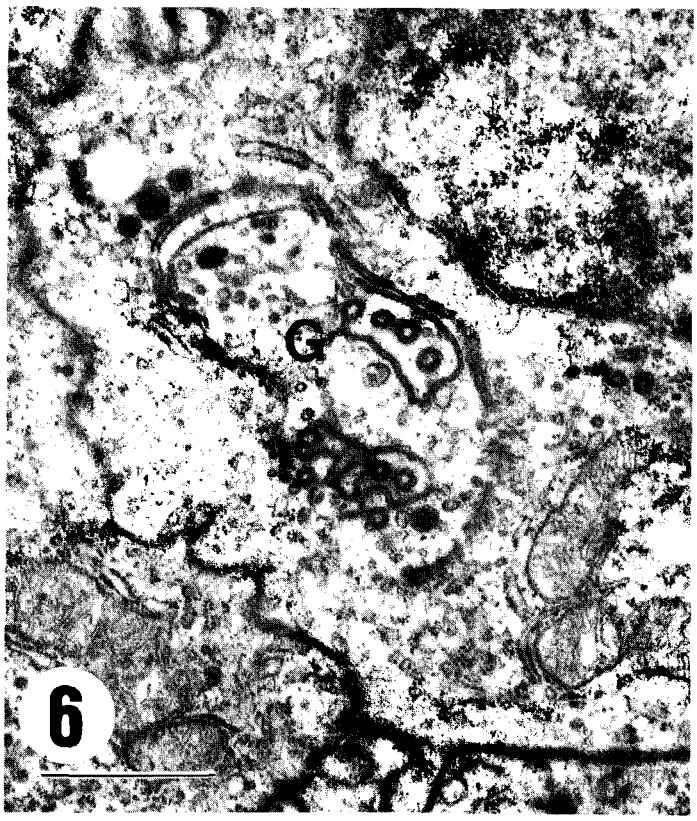


Fig. 6. Hen parathyroid gland. Well-developed Golgi complex (G) contains serpiginous profile. Bar: 1 μm.

1968), Tanaka (rabbit, 1969), Murakami (rat, 1970), Altenähr (rat, 1971), Nunez et al. (bat, 1972), Sakuma (bat, 1974), Takai (rat, 1976), Boquist (gerbil, 1977), Isono et al. (mouse, 1977, 1979b, 1980, 1981, 1983, 1985), Kapur (gerbil, 1977), Frink et al. (woodchuck, 1978), Coleman et al. (baboon, 1980), Hayashi et al. (mouse, 1980), Isono and Shoumura (rabbit, 1980), Wild (dog, 1980), Ishizaki et al. (mouse, 1983), Krause and Cutts (opossum, 1983), Emura et al. (hamster, 1982, 1984a, 1984b) and Wild and Manser (dog, 1986).

The ultrastructure of the normal human parathyroid glands has been described by Munger and Roth (1963), Weymouth and Sheridan (1966), Mazzocchi et al. (1976a), Nakagami et al. (1968), Altenähr and Seifert (1971), Altenähr (1972), Roth and Capen (1973), Capen (1975), Roth and Schiller (1976), Nilsson (1977) and Shoumura and Isono (1985).

The parathyroid glands of human beings (Munger and Roth, 1963; Mazzocchi et al., 1967a; Altenähr, 1972; Roth and Schiller, 1976; Shoumura and Isono, 1975), monkeys (Trier, 1958; Nakagami, 1965; Roth and Schiller, 1976; Shoumura and Isono, 1985), cows (Capen et al., 1965; Roth and Schiller, 1976), horses (Fujimoto et al., 1967; Roth and Schiller, 1976) and bats (Sakuma, 1974) are composed of the chief cells and the oxyphil cells.

More ultrastructural studies have been done on the parathyroid glands of the rat *Rattus norvegicus* than on those of any other species. The first ultrastructural studies on the parathyroid glands were reported by Lever (1957, 1958). Davis and Enders (1961) and Roth and Raisz (1964, 1966) reported a general description of the rat parathyroid gland and noted rare large secretory granules. Zawistowski (1966), Mazzocchi et al. (1967b), Hara and Nagatsu (1968), Stoeckel and Porte (1969, 1973), Altenähr (1970), Altenähr and Lietz (1970), Murakami (1970), and Takai (1976) postulated a secretory cycle and demonstrated rare secretory granules in the chief cells of the rat parathyroid glands. Some studies (Meneghelli and Mazzocchi, 1966; Rohr and Krässig, 1968; Dunay et al., 1969; Altenähr and Wöhler, 1971) provided evidence of secretory activity in the parathyroid glands of embryonal and fetal rat. In addition, Takai (1976) described unmyelinated nerve fibres in the perivascular space. Nakagami et al. (1971) studied the time course of the secretory cycle in the rat parathyroid gland using ^{3}H-tyrosine as a label. Label is seen in the Golgi complexes in 2 minutes, in the secretory granules in 25-30 minutes, and outside the chief cells in 45-60 minutes.

The ultrastructural studies of the parathyroid glands of the mouse *Mus musculus* were reported by Hara and Nagatsu-Ishibashi (1964), Stoeckel and Porte (1966), Nakagami (1967), Isono et al. (1977, 1979b, 1980, 1981, 1983, 1985), Hayashi et al. (1980) and Ishizaki et al. (1983). In our studies, the plasma membranes of adjacent chief cells were relatively smooth with occasional indentations and the nuclei with occasional invaginations were oval or spherical in shape. The chief cells had rich free ribosomes and abundant mitochondria. The Golgi complexes were relatively well-developed and contained numerous prosecretory granules. Cisternae of the granular

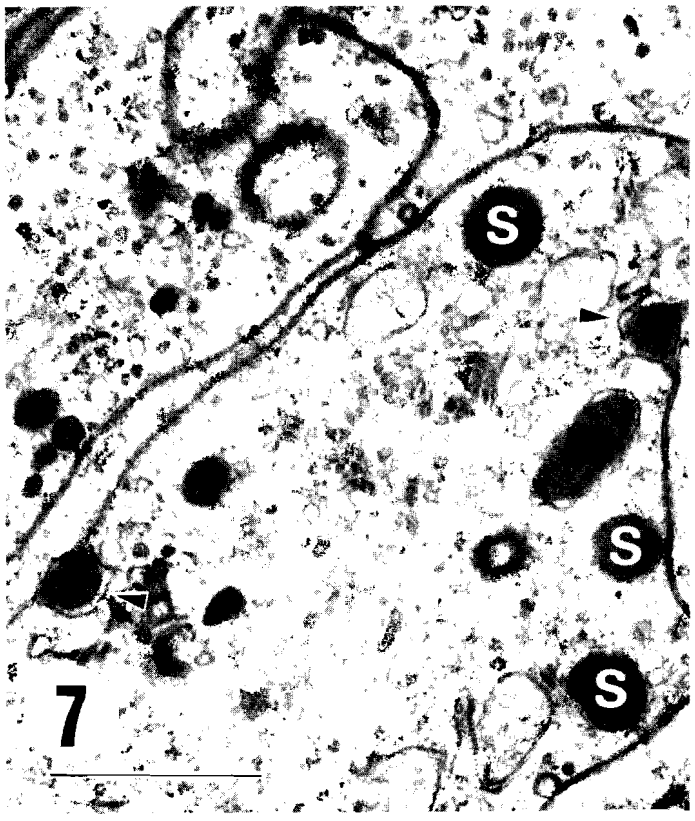
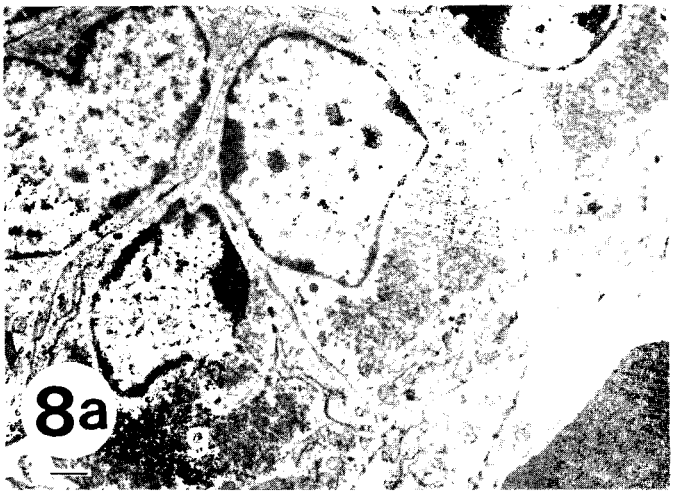


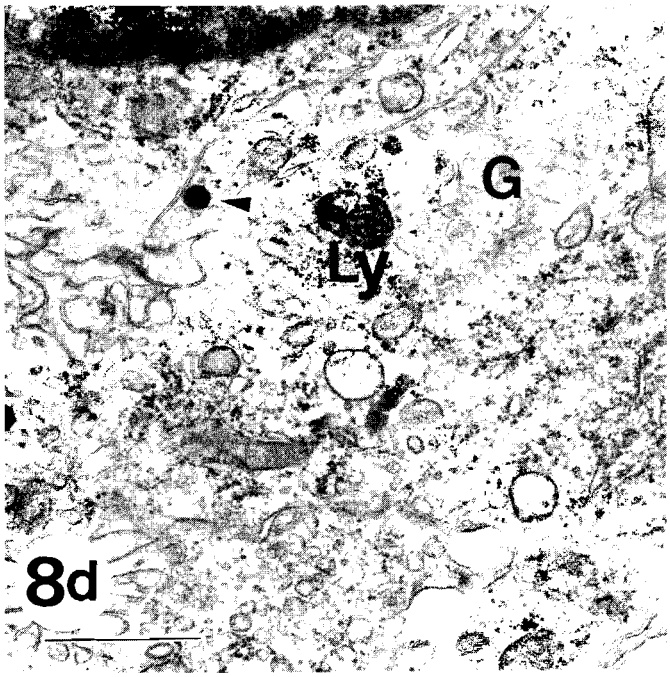
Fig. 7. Hen parathyroid gland. Secretory granules (S) are seen in the peripheral cytoplasm. The granule contents communicate with the intercellular space through an opening in the fused portion of the limiting and plasma membranes (arrow heads). Bar: 1 μm.

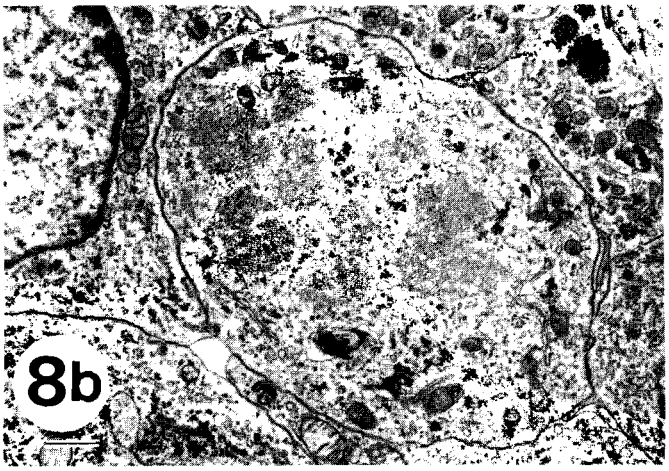
endoplasmic reticulum were randomly distributed in the cytoplasm. Many secretory granules of 150-200 nm in diameter were observed in the peripheral cytoplasm and the enlarged intercellular spaces contained a floccular or finely particulate material. Some of them were situated close to the plasma membrane. Vacuoles of 150-200 nm in diameter were sometimes seen in the peripheral cytoplasm. These findings suggest the possibility of exocytosis of the secretory granules in the mouse parathyroid gland (Isono et al., 1979b, 1980, 1981, 1983, 1985; Hayashi et al., 1980; Ishizaki et al., 1983, 1989). Such secretory granules are more numerous and smaller than those of the chief cells of the rats (Takai, 1976). Large secretory granules of 400-600 nm in diameter, multivesicular bodies, lysosomes and lipid droplets were observed in the cytoplasm. No acid phosphatase activities were demonstrated on a secretory granules nor on large secretory granules (Hayashi et al., 1980). Large secretory granules are thought to be storage granules which remain undischarged in the cells (Isono et al., 1980, 1981, 1983, 1985; Hayashi et al., 1980; Ishizaki et al., 1983, 1989). Vesicles of 50 nm in diameter lay around large secretory granules. Transitional forms between large secretory granules and multivesicular bodies were surrounded by vesicles. Cilia were noted by Stoeckel and Porte (1966), Nakagami (1967), and Isono et al. (1977). In addition, the ultrastructural observations on the postnatal development of the mouse parathyroid gland were reported (Isono et al., 1977).

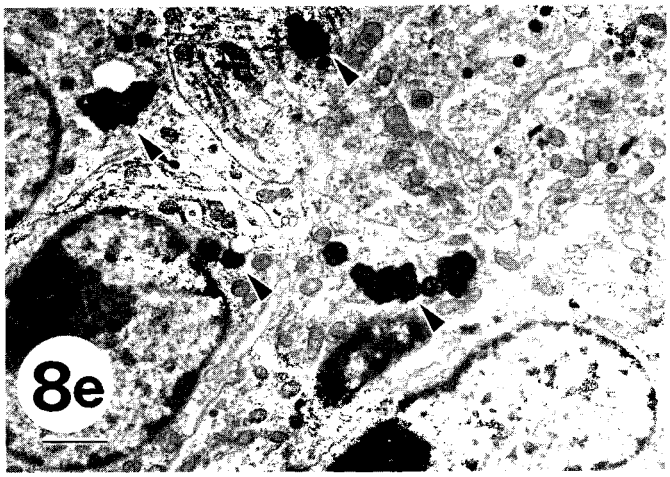
Kayser et al. (1961), Porte and Petrovic (1961), Porte et al. (1963), and Stoeckel and Porte (1969, 1973) described the ultrastructure of the parathyroid glands of hamster *Cricetus cricetulus* and Emura et al. (1982, 1984a, 1984b) golden hamsters *Mesocricetus auratus*. Kayser et al. (1981) demonstrated a seasonal change in fine structure of the hamster parathyroid glands. In the chief cells many secretory granules were observed during the winter season and aggregates of the granular endoplasmic reticulum were present during summer and winter seasons (Kayser et al., 1961).

Age-related changes in the fine structure of the parathyroid gland of the golden hamster were studied by Emura et al. (1984b). The chief cells of the parathyroid gland of 15-day-old hamster fetuses contained a small number of cell organelles, a few secretory granules of 150-300 nm in diameter, many lipid droplets and large lakes of glycogen particles (Fig. 8a), and mitoses were observed (Fig. 8b). In one-day-old hamsters the chief cells contained relatively well-developed Golgi complexes, distended cisternae of the granular endoplasmic reticulum, small lakes of glycogen particles, a few secretory granules and lipid droplets. Occasional large secretory granules of 350-650 nm in diameter, large vacuolar bodies of 350-750 nm in diameter and lysosomes, and the plasma membranes pursued tortuous course with occasional interdigitations (Fig. 8c). In 5-day-old hamsters the chief cells contained numerous large vacuolar bodies. In the hamster parathyroid glands 10, 15 and 20 days after birth, relatively well-developed Golgi complexes, numerous large vacuolar bodies, occasional large secretory granules and lipid droplets, and a few secretory granules were present. In one-month-old hamsters the prominent feature was the abundance of lipid droplets. In the parathyroid glands 3, 5 and 8 months after birth, the plasma membranes pursued a tortuous course with complex interdigitations (Fig. 8d) and floccular or finely particulate material was observed in the enlarged intercellular spaces surrounded by three or more chief cells. Mitochondria were dispersed throughout the cytoplasm, the cisternae of the granular endoplasmic reticulum were sometimes arranged in parallel arrays or randomly distributed in the cytoplasm, and the Golgi complexes were well-developed and contained a few coated vesicles and numerous prosecretory granules (Fig. 8d). Many secretory granules were observed in the peripheral cytoplasm and some granules were situated close to the plasma membrane (Fig. 8d). These findings suggest the possibility of exocytosis of the secretory granule. Large secretory granules, large vacuolar bodies, lysosomes and lipid droplets were sometimes present in the cytoplasm (Fig. 8d). Transitional forms between the large secretory granules and large vacuolar bodies were observed. Vesicles were observed near the large secretory granules, large vacuolar bodies and transitional forms. Secretory granules and lipofuscin granules increased in number with age. In the parathyroid glands 12 and 18 months after birth, the prominent feature was the abundance of lipofuscin granules (Fig. 8e). The mixed









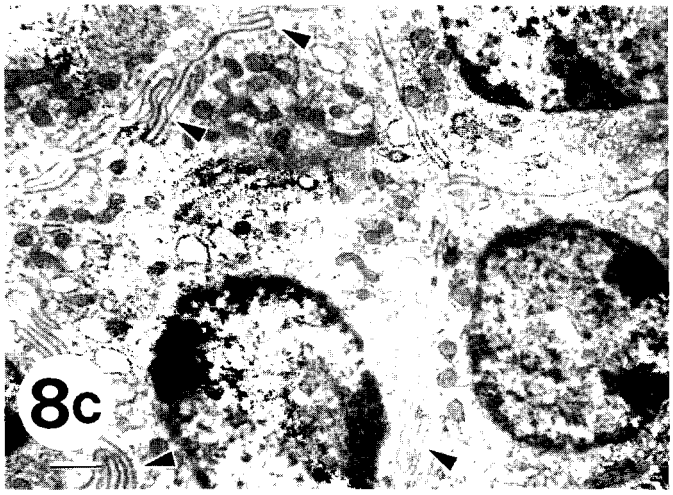


Fig. 8. Golden hamster parathyroid gland. 8a: In 15-day-old hamster fetus large lakes of glycogen particles (g) and a small number of cell organelles are observed. 8b: In 15-day-old-hamster fetus mitosis is seen. 8c: In 1-day-old hamster the chief cells contain relatively well-developed Golgi complexes and distended cisternae of the granular endoplasmic reticulum, and the plasma membranes pursue a tortuous course with interdigitations (arrow heads). 8d: In 5-month-old hamsters the chief cells contain a well-developed Golgi complex (G) and cisternae of the granular endoplasmic reticulum, secretory granule (arrow head) in the peripheral cytoplasm, large vacuolar bodies and lysosome (Ly). 8e: In 18-month-old hamsters many lipofuscin granules (arrow heads) are present. Bar: 1 μm.

fasciculi with unmyelinated and myelinated nerve fibres were present in the perivascular spaces. In adult animals, cisternae of the granular endoplasmic reticulum and the Golgi complexes were significantly increased compared with those of fetal, infant, young and senile animals. These changes suggest that in the parathyroid glands of the 15-day-old-hamster fetuses the synthesis and release of parathyroid hormone occur and that cellular activity of the parathyroid glands in adult hamsters is high when compared with that of fetal, infant, young and senile animals. Similar findings have been reported in the fetal and embryonic parathyroid glands of other animals (Nakagami et al., 1968; Altenähr and Wöhler, 1971; Narbaitz, 1972; Stoeckel and Porte, 1973; Fujii, 1975; Jordan et al., 1975; Narbaitz and Gartke, 1975; Narbaitz and Jande, 1978; Clark and Dunn, 1986; Ishizaki et al., 1989).

Immunocytochemical localization of parathyroid hormone was examined in the golden hamster parathyroid gland by using the protein A-gold technique (Shoumura et al., 1988b). Protein A-gold particles were concentrated

Fig 9. Golden hamster parathyroid gland. Protein A-gold particles are concentrated over secretory granules (arrow heads) and the Golgi vacuole (G). Bar: 1 μm.

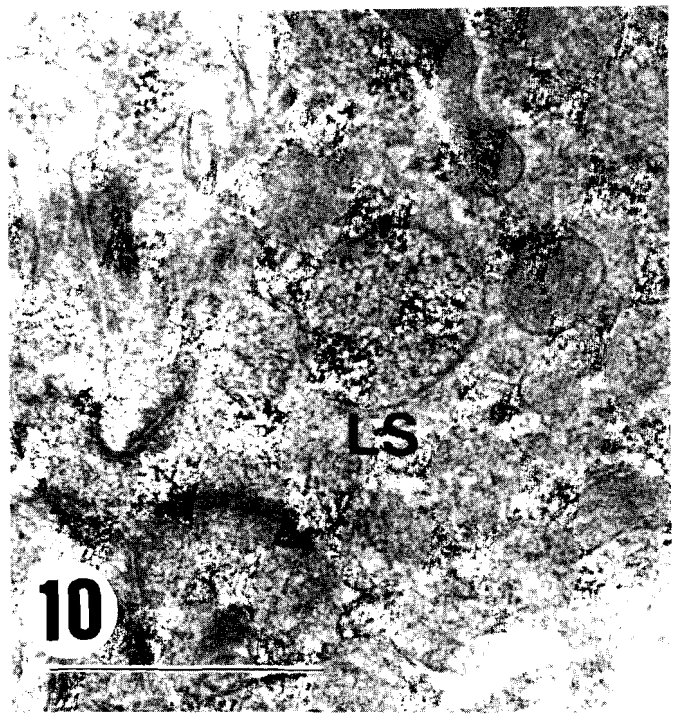


Fig. 10. Golden hamster parathyroid gland. Protein A-gold particles are observed on large secretory granule (LS). Bar: 1 nm.

over secretory granules (Fig. 9), large secretory granules (Fig. 10) and Golgi vacuoles (Fig. 9). It is thought that both granule types include parathyroid hormone. Very few particles were noted over transitional forms between large

Fig. 11. Scanning electron micrograph of vascular casts of the golden hamster parathyroid (P) and thyroid (T) glands. The network of freely anastomosing capillaries with a homogeneous distribution is observed in the parathyroid gland (P). Bar: 1 nm.

secretory granules and large vacuolar bodies. No particles were detected over large vacuolar bodies and cisternae of the granular endoplasmic reticulum. Vesicles surrounded large secretory granules, large vacuolar bodies and transitional forms. It is conceivable that some vesicles were incorporated into the large secretory granules thought to be storage granules to form certain kinds of the large vacuolar bodies and that such transformation involves lysosomal digestion of the storage granules.

Blood vascular architecture in the golden hamster parathyroid glands was revealed by scanning electron microscopy of corrosion casts (Shoumura et al., unpublished data). The hamster possesses only one pair of the parathyroid glands located at the latero-central aspect of the thyroid gland and the parathyroid glands receive a rich blood supply from the superior and inferior thyroid arteries. The network of freely anastomosing capillaries with a homogeneous distribution was observed in the parathyroid gland (Fig. 11) and direct capillary connections between the parathyroid and thyroid glands were present (Fig. 12).

The fine structure of the parathyroid gland of the rabbit *Oryctolagus cuniculus var. domesticus* was first described by Melson (1966). Some studies of the parathyroid glands have been reported in the rabbit

(Tanaka, 1969; Furuta, 1971; Isono and Shoumura, 1980). In our study (Isono and Shoumura, 1980), the plasma membranes of adjacent chief cells pursued a relatively straight course with occasional interdigitations. The intercellular spaces were narrow, and occasional enlargements contained electron-dense or floccular material. Mitochondria and free ribosomes were dispersed in the cytoplasm. Cisternae of the granular endoplasmic reticulum were distributed or occasionally arranged in parallel arrays, and lamellar bodies of concentric shape which were composed of the cisternae occurred within the cytoplasm. Most Golgi complexes were relatively well-developed and contained a few coated vesicles and occasional prosecretory granules. Many secretory granules of 150-300 nm in diameter, a few large secretory granules of 300-400 nm in diameter, some multivesicular bodies, and occasional lysosomes and large lipid droplets were observed in the cytoplasm. In addition, secretory granules were present in the peripheral cytoplasm and adjacent to the plasma membrane, and material similar to the contents of the secretory granules was observed in the enlarged intercellular spaces. These findings suggest that secretory granules are discharged into the intercellular spaces by exocytosis.

Immunocytochemical localization of parathyroid hormone was examined in the rabbit parathyroid gland by means of protein A-gold technique (Shoumura et al., 1988c). Protein A-gold particles were observed on the secretory granules and the large secretory granules, but particles were not observed on the multivesicular bodies, cisternae of the granular endoplasmic reticulum and the Golgi complexes. Both granules are thought to include parathyroid hormone and the large secretory granules are considered to be storage granules.

In order to clarify the distribution of cholesterol in the chief cells of the rabbit parathyroid gland, freeze-fracture images of the filipin-treated gland were observed (Emura et al., unpublished data). The filipin-cholesterol complexes in the plasma membrane were heterogeneously distributed and the coated pits lack the complexes (Fig. 13, Inset). Numerous complexes in the limiting membranes of the secretory granules were observed (Fig. 13). These findings suggest that the movement of the plasma membrane and the transport of the secretory granule need cholesterol. The membranes of the granular endoplasmic reticulum, of the nucleus and of mitochondria were almost free from the complexes (Fig. 13). In the Golgi complexes the trans-side is labelled with filipin (Fig. 13).

Trier (1958) was the first to describe the ultrastructure of the parathyroid gland of a primate, *Macaca mulatta*. In *Macaca mulatta*, he described the presence of the chief cells containing well-developed granular endoplasmic reticulum and prominent Golgi complexes and the oxyphil cells filled with numerous mitochondria. Subsequent studies (Nakagami, 1965; Mazzocchi, 1967) on *Macaca mulatta fascicularis* and *Erythrocebus patas* confirmed that a secretory cycle similar to that which had been reported in human beings (Munger and Roth, 1963) exists. The normal human parathyroid gland consists of two main types of chief cells: active chief cells and inactive chief cells (Roth and Munger, 1962; Munger and Roth, 1963).

In our study (Shoumura and Isono, 1985), the density of the interstitium and the number of fat cells in the normal human parathyroid glands increased with age, and the oxyphil cells were not observed in fetal and infant parathyroid glands but appeared in childhood and increased in number with age. A basement membrane separated the parenchymal cells from the perivascular space (Fig. 14). The intercellular spaces were generally narrow, but sometimes showed moderate widenings containing electron dense material and some floccular material. The plasma membranes pursued a tortuous course with complex interdigitations and neighbouring cells were interconnected by desmosomes, tight junctions and intermediate junctions. The chief cells were round, oval or irregular in shape. The nucleus had a round or oval profile and one or more nucleoli, and the nucleoplasm was finely granular and usually more electron dense along the nuclear membrane (Fig. 14). The active chief cells contained the following: rich free ribosomes; mitochondria; relatively well-developed cisternae of the granular endoplasmic reticulum; prominent Golgi complexes, associated with some prosecretory granules;

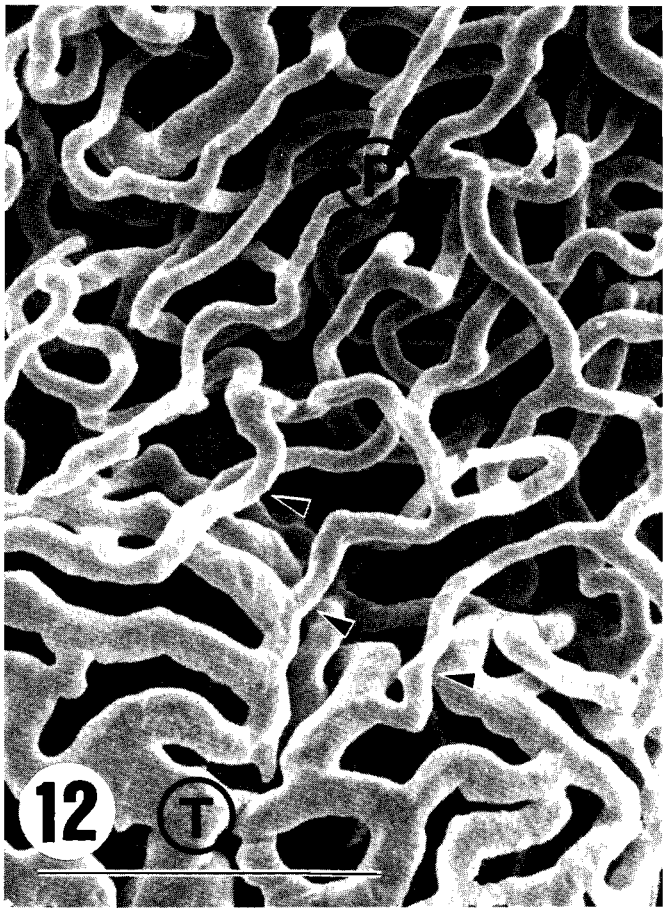


Fig. 12. Higher magnification of vascular cast in Fig. 11. Direct capillary connections (arrow heads) between the parathyroid (P) and thyroid (T) glands are present. Bar: 0.1 nm.

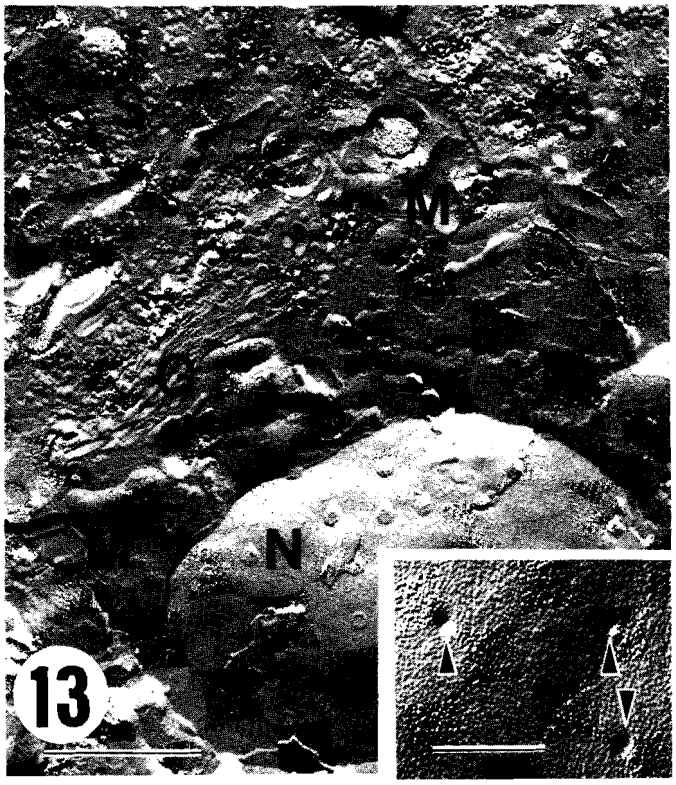
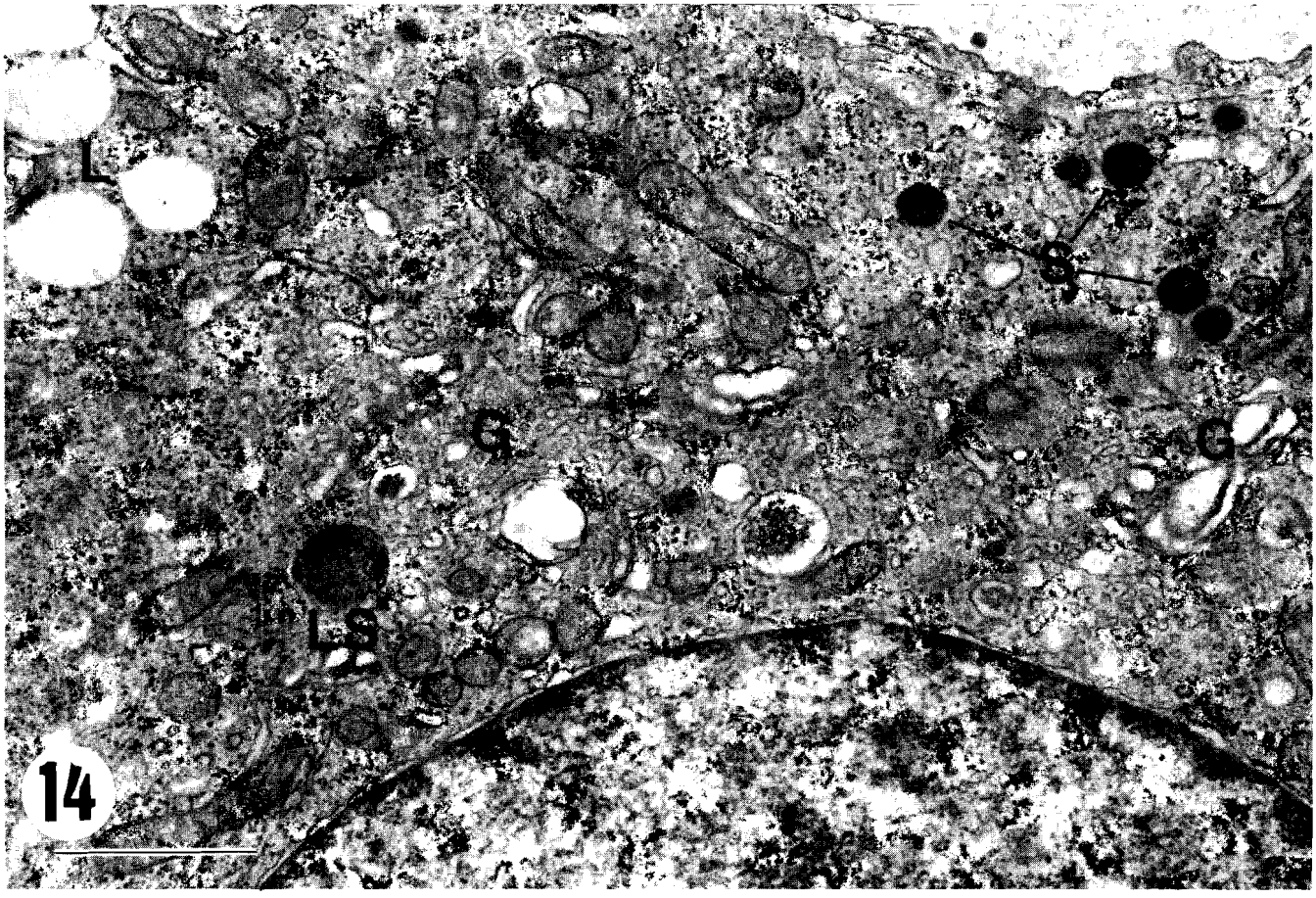


Fig. 13. Freeze-fracture image of filipin-sterol complexes in the chief cell of rabbit parathyroid gland. Numerous complexes in the limiting membranes of the secretory granules (S) are observed, and in the Golgi complex (G) the trans-side is labelled with filipin. The membranes of the granular endoplasmic reticulum, nucleus (N) and mitochondria (M) are almost free from the complexes. Inset. The complexes in the plasma membrane are heterogeneously distributed and the coated pits (arrow heads) lack the complexes. Bar: 1μm.

Fig. 14. Human parathyroid gland (30-year-old man). The active chief cell contains rich free ribosomes, mitochondria, relatively well-developed cisternae of the granular endoplasmic reticulum, prominent Golgi complexes (G), many secretory granules (S), large secretory granule (LS) and lipid droplet (L). Bar: 1 μm.



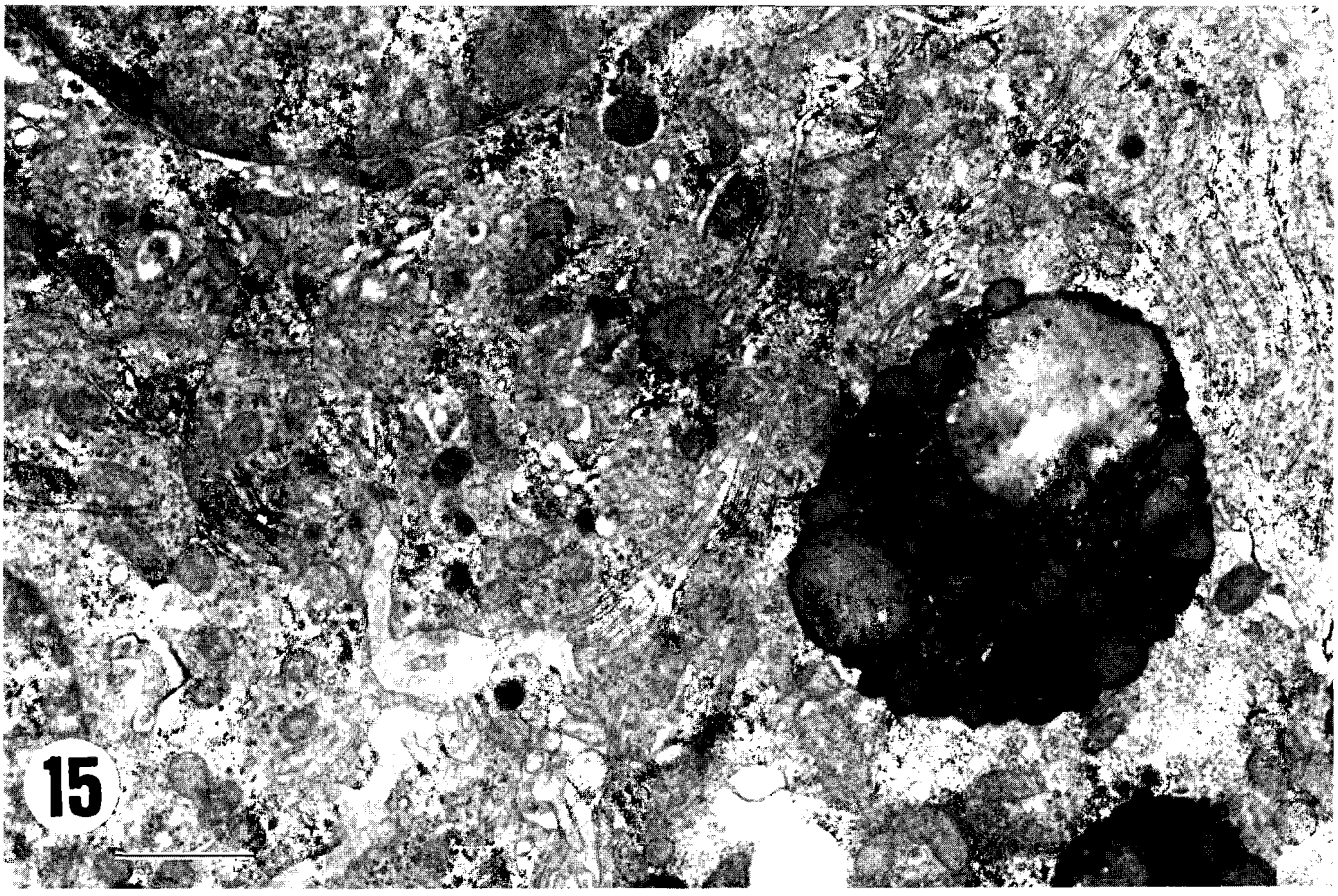


Fig. 15. Human parathyroid gland (56-year-old woman). Many lipid droplets are seen. Bar: 1 μm.

many secretory granules of 200-300 nm in diameter, located in the peripheral cytoplasm; a few large secretory granules of 400 nm in diameter; and some lipid droplets and lysosomes (Fig. 14). In addition, only a small amount of glycogen, occasional cilia and microtubules were present. In the inactive chief cells the Golgi complexes and cisternae of the granular endoplasmic reticulum were not prominent, and fewer prosecretory granules and secretory granules were visible than in the active chief cells (Fig. 15). Large amounts of glycogen, many lipid droplets and lysosomes were observed in the cytoplasm (Fig. 15). The inactive chief cells increased in number with age.

The oxyphil cells in the normal human parathyroid gland were mostly polygonal and were larger than the chief cells. The plasma membranes showed fewer interdigitations than those of the chief cells (Fig. 16). The nucleus, situated at the centre of the cell, was oval or round and nucleoli were sometimes observed. Mitochondria, which were larger than those of the chief cells, filled the whole cytoplasm (Fig. 16). Cisternae of the granular endoplasmic reticulum were very scarce and the Golgi complexes associated with few prosecretory granules were poorly developed. A few secretory granules and lysosomes were present (Fig. 16). Lipid droplets and glycogen particles were sometimes seen (Fig. 16). Many workers suggest that the oxyphil cells in the normal human parathyroid glands do not function in the synthesis and release of parathyroid hormone. Cells less rich in mitochondria than the oxyphil cells and containing more mitochondria than the chief cells are called transitional oxyphil cells (Altenähr, 1972).

The ultrastructure of the parathyroid gland of monkey is almost the same as that of human beings (Shoumura and Isono, 1985).

3. The parathyroid glands in experimental conditions

a. Autonomic innervation of the parathyroid gland and effects of the autonomic nervous system

The cells of origin of autonomic nerve fibres innervating the parathyroid gland were studied in the rabbit using the method of retrograde transport of horseradish peroxidase (HRP) (Shoumura et al., 1983). Numerous labelled neurons were observed in the caudal half of the ipsilateral superior cervical ganglion following injection of HRP into the parathyroid gland. In the medulla oblongata, labelled neurons were found in the dorsal nucleus of the vagus nerve and many of them were distributed caudally to the level of the obex.

The rabbit parathyroid glands, after vagotomy (Isono

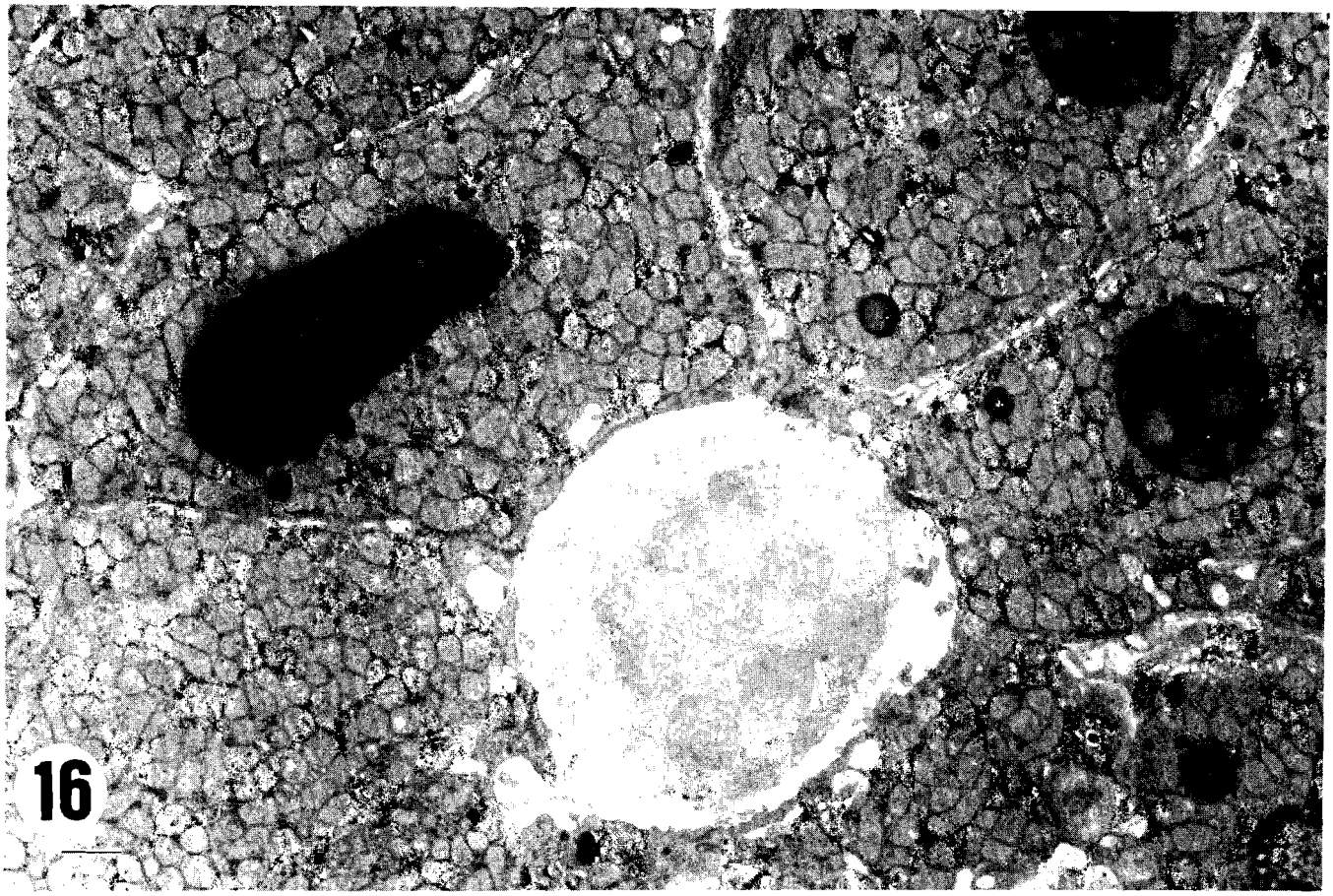


Fig. 16. Human parathyroid gland (56-year-old woman). The oxyphil cells are filled with numerous mitochondria. Bar: 1 μm.

and Shoumura, 1980) and after destruction of the dorsal nucleus of the vagus nerve (Shoumura et al., unpublished data) and the golden hamster parathyroid glands, after short-term administration of ß-adrenergic stimulator, isoproterenol (Shoumura et al., 1988d), contained well-developed Golgi complexes and cisternae of the granular endoplasmic reticulum, numerous prosecretory granules in the Golgi areas, many secretory granules in the peripheral cytoplasm (Fig. 17), and a frequent occurrence of enlarged intercellular spaces containing finely particulate material (Fig. 17) when compared with the control animals. In the rabbit parathyroid glands after stimulation of the vagus nerve (Isono et al., 1981), and the golden hamster parathyroid glands after administration of ß-adrenergic inhibitor, propranolol (Iwasaki et al., 1987), and after sympathectomy (Isono et al., unpublished data), cisternae of the granular endoplasmic reticulum, the Golgi complexes and secretory granules in the peripheral cytoplasm were significantly decreased and lipid droplets increased (Fig. 18) compared with those of the control animals. These alterations suggest that synthesis and release of parathyroid hormone are stimulated in the parathyroid gland after vagotomy, after destruction of the dorsal nucleus of the vagus nerve or after short-term administration of isoproterenol, and suppressed in the parathyroid gland after stimulation of the vagus nerve, after administration of propranolol and after sympathectomy. Mikhail (1971), Wideman (1980) and Atwal (1981) demonstrated cholinergic fibres and Ochi et al. (1970), Bennett (1971), Yeghiayan et al. (1972), Wideman (1980) and Atwal (1981) reported adrenergic fibres in the autonomic innervation of the parathyroid gland. Recent physiological or biochemical reports have suggested an important role of the autonomic nervous system in the secretion of parathyroid hormone (Morii et al., 1963; Fischer et al., 1973; Kukreja et al., 1976, 1980; Blum and Fischer, 1982). Therefore, it is considered that the vagus nerve may have an inhibitory effect and the sympathetic nerve a stimulatory one upon the functional state of the parathyroid gland (Isono and Shoumura, 1979; Shoumura and Isono, 1985).

b. Effects of hypergravity environment

The ultrastructure of the parathyroid glands of the golden hamsters exposed to 2, 5 or 10 gravity environment was studied (Shoumura et al., 1988a). In the centrifuged hamsters, many secretory granules were located in a peripheral position just beneath the plasma membrane of the chief cells, and the Golgi complexes and cisternae of the granular endoplasmic reticulum significantly increased compared with those of the control animals.

Fig. 17. Rabbit parathyroid gland after vagotomy. Enlarged intercellular space contains finely particulate material and many secretory granules are observed in the peripheral cytoplasm. Bar: 1 μm.

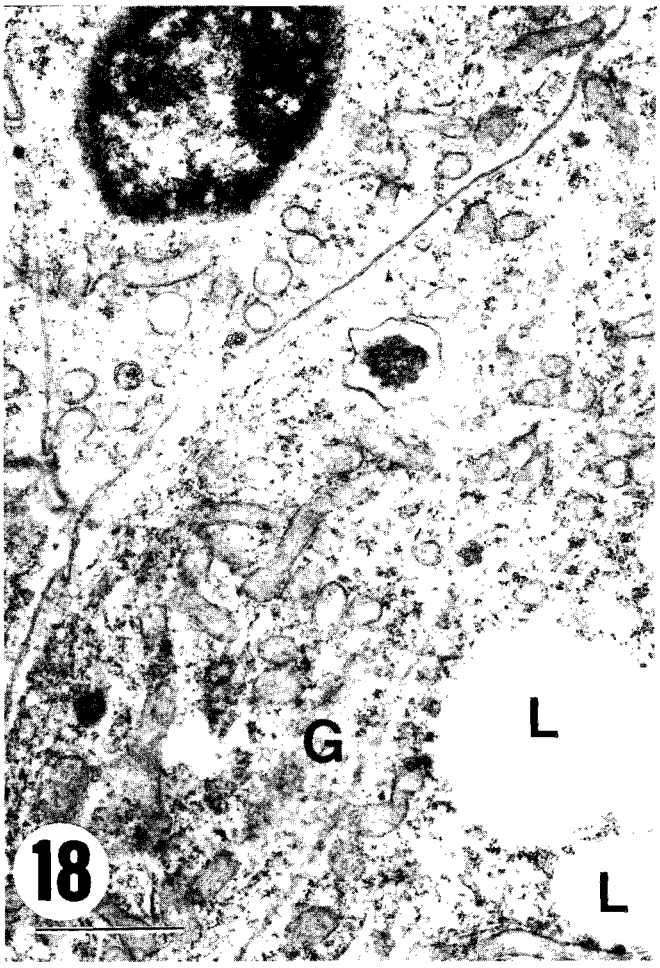


Fig. 18. Rabbit parathyroid gland after stimulation of the vagus nerve. The chief cells contain poorly-developed cisternae of the granular endoplasmic reticulum and Golgi complex (G), and numerous lipid droplets (L). Bar: 1 μm.

These findings suggest that secretory activity of the parathyroid gland is stimulated in response to a hypergravity environment (Shoumura et al., 1988a). Similar changes have been observed in the parathyroid glands of gerbils subjected to 2 gravity environment (Sannes and Hayyes, 1975).

We have examined the effects of hypergravity environment on the parathyroid gland of the isoproterenol- (Shoumura et al., 1989a), propranolol- (Shoumura et al., 1989b) or calcium-treated golden hamster (Shoumura et al., 1990). In the isoproterenol-treated hamsters exposed to a hypergravity environment, the Golgi complexes containing numerous prosecretory granules and cisternae of the granular endoplasmic reticulum were significantly increased and secretory granules were significantly decreased compared with those of the control animals (Shoumura et al., 1989a). These results suggest that the synthesis and release of parathyroid hormone may be markedly stimulated in the parathyroid glands of the isoproterenol-treated hamsters exposed to a hypergravity environment (Shoumura et al., 1989a). In the propranolol-treated hamsters subjected to a hypergravity environment, the Golgi complexes and cisternae of the granular endoplasmic reticulum were significantly increased compared with those of the propranolol-treated hamsters, but decreased compared with those of animals subjected to a hypergravity environment and were almost similar to those of the control hamsters (Shoumura et al., 1989b). These findings suggest that the parathyroid gland which is suppressed by treatment of propranolol and stimulated in response to a hypergravity environment indicates the secretory activity of the control parathyroid gland (Shoumura et al., 1989b). In addition, the morphology of the parathyroid glands of the calcium-treated hamsters subjected to a hypergravity environment resembled that of the propranolol-treated hamsters exposed to a hypergravity environment (Shoumura et al., 1990).

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