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Ultrastructural Studies of the Parotid Glands in Sialadenosis* **

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Summary. 30 parotid biopsies of patients with sialadenosis—a symmetrical, painless, non-inflammatory, recurrent parotid swelling—were studied by electron microscopy. The patients suffered from different diseases, such as diabetes mellitus, liver diseases, hypertension and other affections. Parotid biopsies from 25 patients with slight parotitis or with oral cancer were used as controls. Morphometric studies reveal that the parotid swelling is caused by an enlargement of acinar cells. In controls the average diameters of the acinar cells are 30 to 40 μ. In sialadenosis the diameters are enlarged to 50 to 70 μ, in some cases to a maximum of 100 μ.

Histologically the cytoplasm of the enlarged acinar cells shows either a granular pattern due to a numerical increase in secretory granules or a vacuolar transformation. Ultrastructurally the vacuolar transformed acinar cells also contain an increased number of granules with less electron density than the surrounding cytoplasm.

Three types of sialadenosis can be distinguished with regard to the electron density of the acinar granules: a) a dark granular type, b) a pale granular type and c) a mixed granular type. The mixed granular type probably develops from the dark granular form.

Alterations leading to the destruction of the myoepithelial cells were observed in all three types of sialadenosis with minimal changes in the dark granular type. Degenerative alterations of the autonomic nervous system are evident in all three groups with most pronounced changes in the pale granular type of sialadenosis.

The ultrastructural alterations are interpreted as a disturbance of secretion, probably primarily caused by the degeneration of the autonomic nervous system. The alteration of the autonomic nervous system is suggested to be the common pathogenetic principle in all types of human sialadenosis occurring with different basic diseases. The enlargement of the acinar cells is the result of an intracellular disturbance in the secretory process due to the preceding defect of the autonomous nerval structures.

Zusammenfassung. 30 Parotisbiopsien von Patienten mit Sialadenose (doppelseitige schmerzlose, nichtentzündliche Parotisschwellung) wurden elektronenmikroskopisch untersucht. Bei den Patienten hatten unterschiedliche Grundkrankheiten (z.B. Diabetes mellitus, Lebererkrankungen, Hypertonie u.a.) vorgelegen. Als Kontrollgruppe wurden Parotisbiopsien von 25 Patienten mit geringer Parotitis oder einem Mundhöhlencarcinom untersucht.

Die morphometrischen Untersuchungen ergaben, daß die Parotisschwellung auf einer Vergrößerung der Drüsenendstücke beruht. Die mittleren Acinusdurchmesser liegen in der Kontrollgruppe bei 30 bis 40 μ und sind bei den Sialadenosen auf 50 bis 70 μ, in einigen Fällen maximal bis auf 100 μ vergrößert. Pathohistologisch läßt sich im Cytoplasma der vergrößerten Acinuszellen entweder eine Anreicherung von Granula oder eine feinvesikuläre Aufhellung beobachten. Elektronenmikroskopisch enthalten die Acinuszellen mit vesiculärem Cytoplasma ebenfalls Granula, jedoch von geringerer elektronenoptischer Dichte als das umliegende Cytoplasma.

Nach der elektronenoptischen Dichte der Sekretgranula lassen sich drei Formen der Sialadenose unterscheiden: a) eine dunkle granuläre Form, b) eine helle granuläre Form und

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c) eine gemischte granuläre Form. Es wird angenommen, daß sich die gemischte granuläre Form aus der dunklen granulären Form entwickelt.

Alterationen der Myoepithelzellen treten bei allen drei Formen der Sialadenose auf, am geringsten bei der dunklen granulären Form. Degenerative Veränderungen des autonomen Nervensystem lassen sich bei allen drei Formen beobachten, am stärksten bei der hellen granulären Form der Sialadenose.

Die ultrastrukturellen Veränderungen sprechen für eine Sekretionsstörung, die wahrscheinlich durch eine Degeneration des autonomen Nervensystems ausgelöst wird. Die primäre Alteration des autonomen Nervensystem wird als das gemeinsame pathogenetische Prinzip aller Formen der menschlichen Sialadenose bei den verschiedenen Grundkrankheiten angesehen. Die Vergrößerung der Acinuszellen ist Ausdruck einer intracellulären Sekretionsstörung als Folge der vorausgehenden Schädigung der autonomen Innervation.

Sialadenoses are defined as non-inflammatory, painless, recurrent and symmetrical swellings, particularly of the parotid glands (Seifert, 1964, 1967). They differ from the various types of sialadenitis by clinical, radiographical, biochemical, and morphological findings. Sialadenosis of the parotid glands has been noted in various diseases, such as diabetes mellitus, chronic malnutrition, liver cirrhoses, alcoholism, and drug damages (Rauch, 1970). The sialometry of unstimulated saliva results in a diminished salivary flow or in asialia. The whole parotid gland is involved in this process, but total dryness of the mouth is rarely observed, suggesting that other salivary glands are not significantly involved (Rauch, 1959).

Many theories are discussed in the literature regarding the pathogenesis of the enlargement of the salivary glands. Two theories should be mentioned here: Jastak (1967) postulates that "because malnutrition does not stimulate the gland, zymogen granules are stored, leading to enlargement". The other theory suggests that hypertrophy is due to hyperstimulation. An excessive stimulation with "hyperactive hypertrophy" (De Plessis, 1956) is assumed in persons recovering from malnutrition, particularly when they rapidly consume large amounts of bread.

The following ultrastructural studies of 30 specimens of the parotid glands in sialadenosis were carried out in order to analyze the structural changes of the acinar and myoepithelial cells in sialadenosis. Moreover, the ultrastructure of the autonomic nervous system of the parotid glands was examined. Special attention was focused on possible damages of the nervous system which might explain the pathogenesis of the acinar enlargement.

Materials and Methods

55 biopsies of the parotid glands were studied by electron microscopy. In 30 cases there was a symmetrical, recurrent, painless, non-inflammatory swelling of the parotid glands (Table 1). The parotid tissue of 25 patients with oral cancer or slight parotitis was used as control material.

Specimens were fixed in 2.5% glutaraldehyde and 0.1 M cacodylate buffer for 2 h at room temperature. After washing in the same buffer, they were postfixed in 1.33% osmiumtetroxide and s-collidone buffer. In order to examine alterations of the autonomic nervous system, small pieces of tissue were fixed for 30 min in ice-cold 3% potassium permanganate (Richardson, 1966). These tissues were rinsed in Ringer's solution and contrasted en bloc in a 1% uranylacetate solution.

After graded dehydration in ethanol, the tissues pieces were embedded in Epon 812. Ultrathin sections were cut on a Reichert OMU²ultramicrotome and stained with lead citrate and sometimes uranylacetate. The sections were viewed in a Siemens I or a Philips EM300 electron microscope.

Table 1. Age, sex, and duration of the parotid swelling in patients with sialadenosis

Age years	Number of patients	Sex ♀	Sex ♂	Duration of the recurrent parotid swelling
10–20	3	3	—	4–18 months
21–30	5	4	1	14 days–11 years
31–40	2	2	—	$2^1/_2$ years
61–50	5	3	2	4 months–5 years
51–60	4	4	—	1–8 years
61–70	10	7	3	4 months–20 years
71–80	1	1	—	1 year

Observations

The normal ultrastructure of the acinar cells of the human parotid gland has been described in detail (Ferner and Gansler, 1961; Brunetti and Rossi, 1969; Riva *et al.*, 1969; Riva and Riva-Testa, 1973). However, to compare the cellular alterations observed in sialadenosis with the normal structure, a brief description of the cytology of parotid glands in the control group is given, with particular respect to the structures of the secretory granules and the contacts of nerve terminals to the acinar cells.

Control Group

The *acini* of the human parotid gland consist of 4 or 5 pyramidal secretory cells. The secretory cells are arranged around a central lumen. Their size and limitation depends on the functional state of the secretory cycle (Fig. 1). The opposite cell membranes build up a zonula occludens beneath the lumen, followed by a zonula adhaerens and by series of desmosomes, which are present at the cell basis. Cytoplasmic extensions folded like microvilli are found along enlarged intercellular spaces and at the basal surfaces. Between the lateral cell surfaces, there are intercellular canaliculi limited by junctional complexes and lined by microvilli. Intercellular canaliculi communicate with the central lumen.

The normal acinar cell base, as well as the region lateral to the nucleus, contains lamellar structures of granular endoplasmic reticulum. The supranuclear region contains many secretory granules, several Golgi areas associated with electron lucent vacuoles, numerous free ribosomes and elements of granular endoplasmic reticulum. Mitochondria are randomly distributed throughout the cytoplasm.

Nuclei are placed at the cell basis. Their structure seems to vary according to the pattern of their chromatin content. Acinar cells containing relatively few secretory granules have nuclei with dispersed chromatin.

These nuclei appear distended and regularly ovoid. The endoplasmic reticulum and the Golgi complexes of these secretory cells are more developed. Less endo-

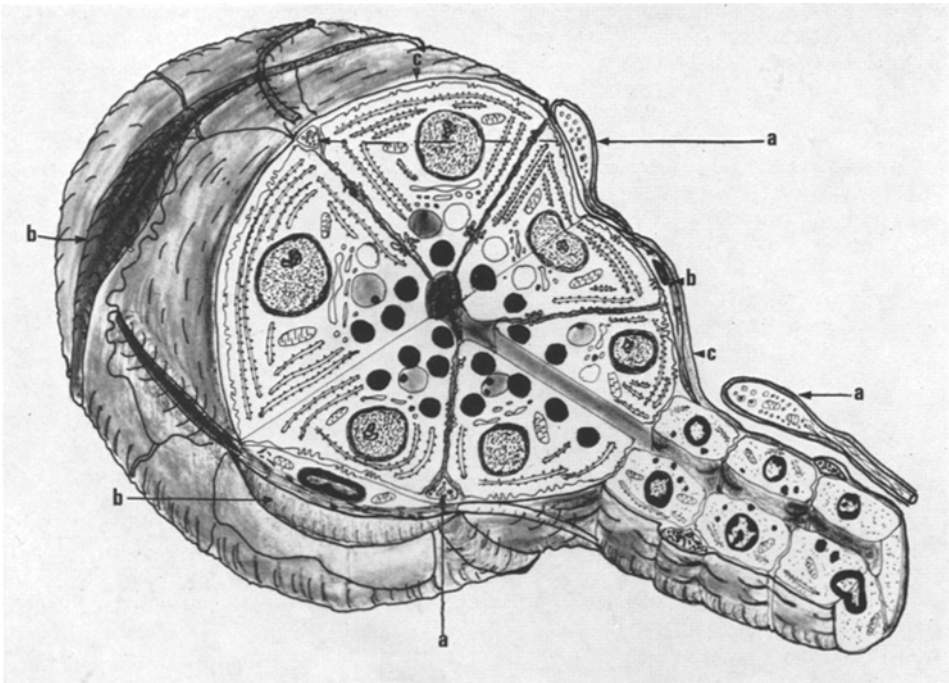

Fig. 1. Three-dimensional model of the acini and the intercalated ducts summarizing the electron microscopic findings. The acini are in the early storage phase: Condensing vacuoles, immature and mature secretory granules. Nerve terminals (*a*); myoepithelial cells (*b*); basement membrane (*c*)

plasmic reticulum, small Golgi complexes and nuclei with condensed chromatin or clustered in large blocks are seen in secretory cells with many secretory granules. The nuclei are usually smaller and irregular in outline.

Condensing vacuoles, immature and mature secretory granules are limited by a thin membrane. Condensing vacuoles are composed of a distinctly granular or filamentous substance. Occasionally, masses apparently resulting from the coalescence of condensing vacuoles, are observed. Immature secretory granules show a dense core surrounded by a lucent halo. This type of secretory granules was mainly found in parotid tissues of patients with oral or cervical tumor. Mature secretory granules are electron dense and homogeneous.

Myoepithelial cells are located between the acinar cells and their basement membrane (Fig. 1). With in the wide intercellular space of the acinar and myoepithelial cells numerous cytoplasmic membranes, folded like microvilli can be seen. The myoepithelial cells have contact to acinar cells by desmosomes.

Myoepithelial cells have an elongated shape containing the nucleus and many cytoplasmic processes with extending along the basal lamina. Their cytoplasm, rather poor in organelles, is characterized by the presence of bundles of dense filaments in the peripheral cytoplasm. Near the nucleus lipofuscin granules are often observed.

The *innervation* of acinar cells occurs by the sympathetic and parasympathetic nervous system. Bundles of nerves, generally containing up to 5 axons and surrounded by cytoplasm of a Schwann cell, were found between the parenchymal cells. Schwann cells with associated axons were not rarely found in close contact with the outer surface of an acinus, lacking a basal membrane inbetween. Sometimes, however, axons penetrate the basal membrane of the acini, and contacts were seen between axons and acinar or myoepithelial cells (Fig. 1). No specialized membranes have been detected in these sites on the axon or the parenchymal cell (Fig. 8a).

Axonal enlargement, the so-called varicosities, are places of synaptic contact. The varicosities contain dense-cored or agranular vesicles with diameters of 500 Å, in dependence of the used fixative (potassium permanganate). The two kinds of vesicles allow a distinction between the sympathetic axons with dense-cored vesicles and cholinerg axons with agranular vesicles.

Sialadenosis Group

The acinar enlargement is mainly caused by hypertrophy but rarely by hyperplasia of the acinar cells. The acini consist of 8 secretory cells in only 3 cases. The hypertrophy of the acinar cells results from a massive enrichment of secretory granules in the cytoplasm. Secretory granules fill out most of the cell cytoplasm, apparently compressing the cytoplasmic organelles and even the nucleus. The granular endoplasmic reticulum is reduced to small units and is distributed among the secretory granules and other cell organelles. The cisternae of the granular endoplasmic reticulum are dilated to a different extent. They may either be empty or contain a flocculent material of low density. Granular endoplasmic reticulum arranged in stacks of parallel lamellae at the lateral and basal cell surfaces could only be seen in few acinar cells with less secretory granules in the apical cell position. According to the ultrastructure of the secretory granules the sialadenosis can be divided into three types; a dark granular type, a pale granular type, and a mixed granular type.

Dark Granular Type. The acinar cytoplasm contains mainly homogeneous electron-dense granules, less pale vacuoles, and altered secretory granules (Fig. 2). The alterations of the mature secretory granules consist of confluence and lysis. Fused secretory granules often remained in rounded clumps, and are mainly located in the cell apex (Fig. 3a). Lysis-altered granules show central or peripheral electron, lucent defects (Fig. 3b–c) of their content. The Golgi apparatus is represented by several groups of microvesicles, packets of elongated cisternae and vacuoles with dense content. Within and around the Golgi complexes dense substances are stored. Furthermore, large vacuoles with flocculent material and membrane fragments could be observed (Fig. 4). Nuclei are round and have a fine dispersed chromatin and, occasionally, a reticulated nucleolus.

Pale Granular Type. The acinar cytoplasm contains mainly secretory granules, which are less electron-dense than the cytoplasmic matrix (Fig. 5). The granules are irregular in their outline and contain a lucent homogeneous core. Although the secretory granules are tighthy packed, no confluence could be observed (Fig. 5a). In contrast to the other typs, many free ribosomes instead of the

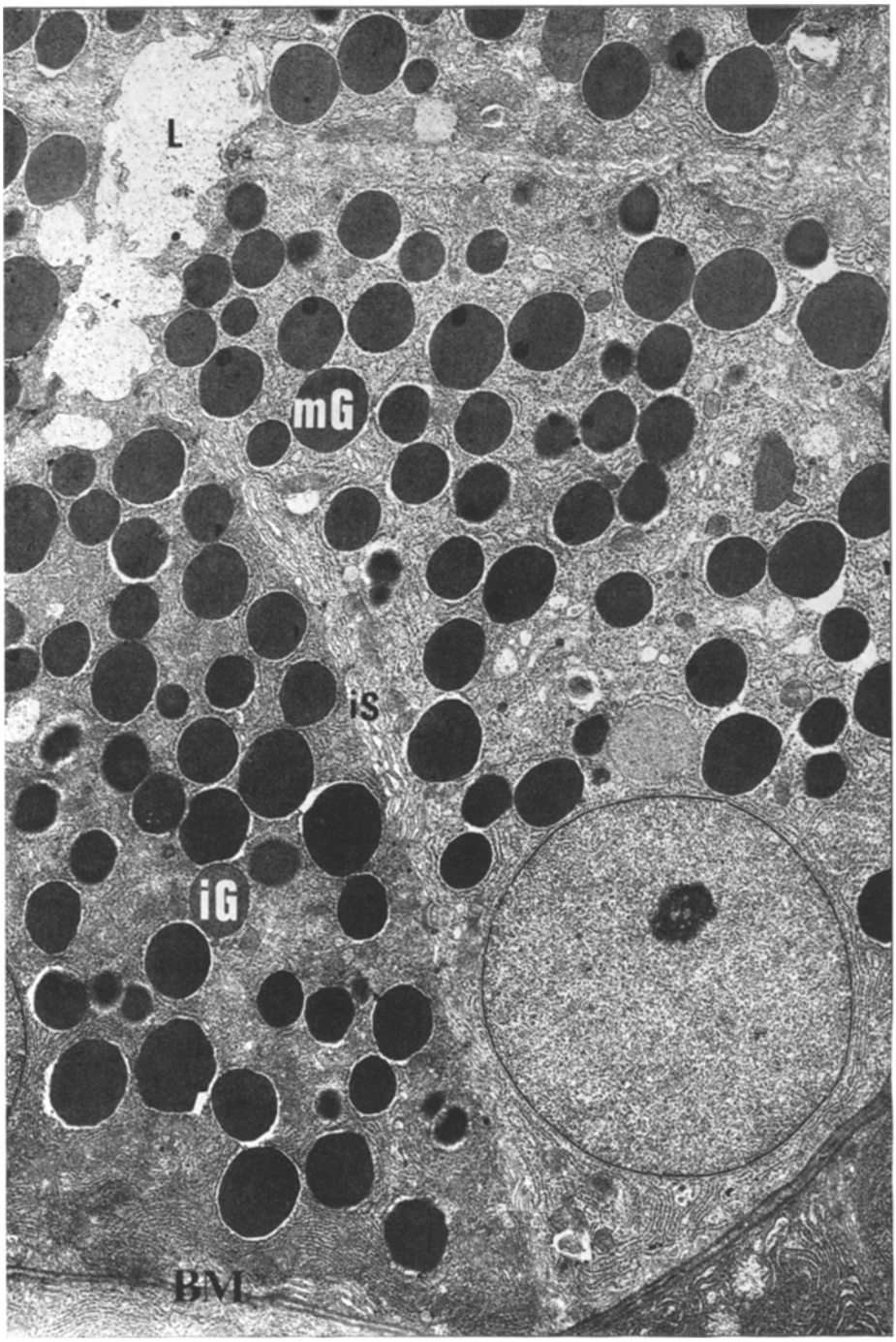

Fig. 2. Dark granular type of sialadenosis. Acinar cells with mainly mature secretory granules (*mG*), and some immature granules (*iG*). Basement membrane (*BM*), acinar lumen (*L*); intercellular space (*iS*). × 6300

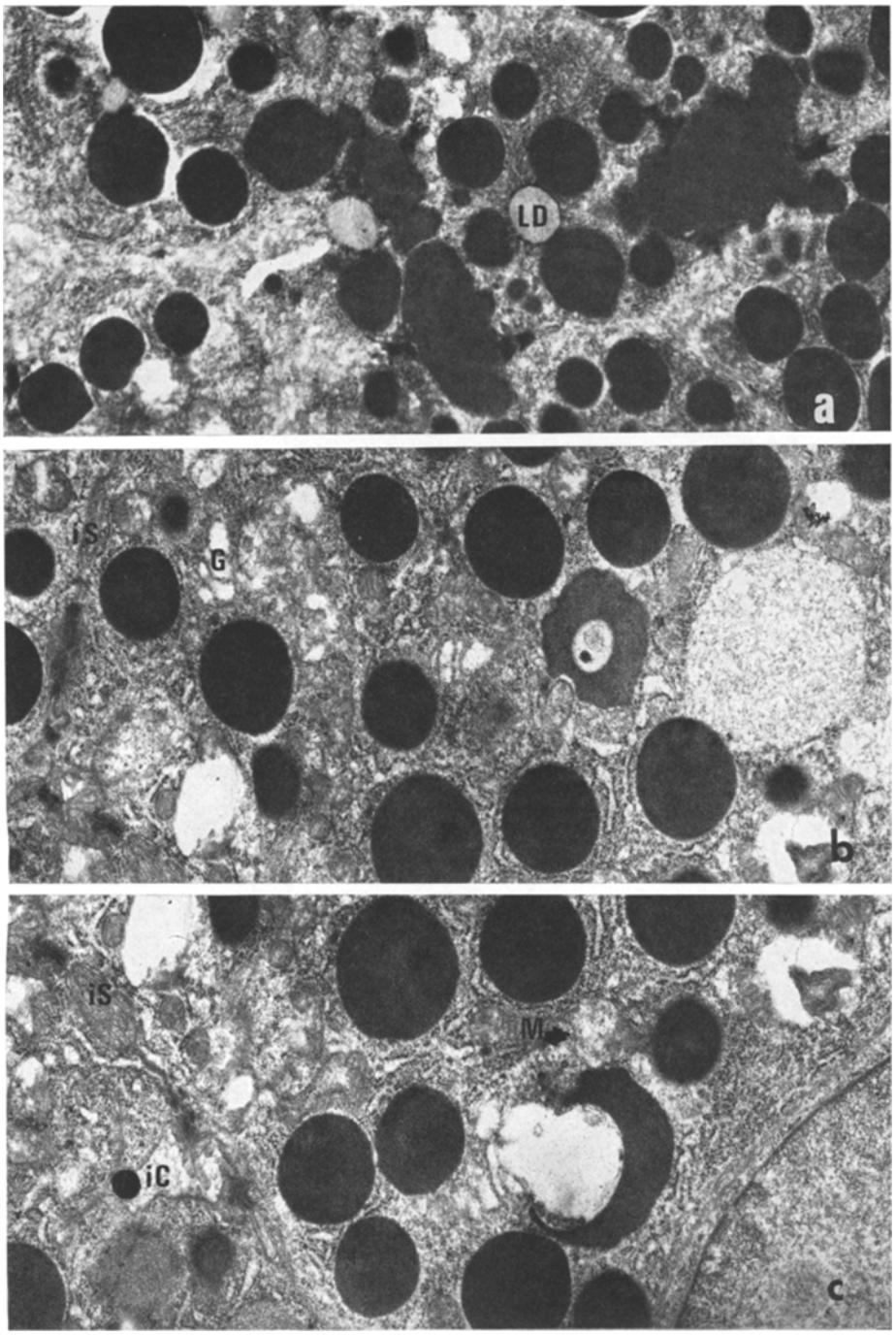

Fig. 3a—c. Dark granular type of sialadenosis. Parts of acinar cells with alterations of the secretory granules. (a) Aggregates of mature secretory granules. Lipid droplets (*LD*). × 7300. (b) Lysis of immature secretory granules. Condensing vacuoles and mature secretory granules. Golgi apparatus (*G*); intercellular space (*iS*) × 11700. (c) Lysis of mature secretory granule. Mature secretory granules; nucleus (*N*); intercellular space (*iS*); intercellular canaliculus (*iC*); mitochondrium (*M*). × 13000

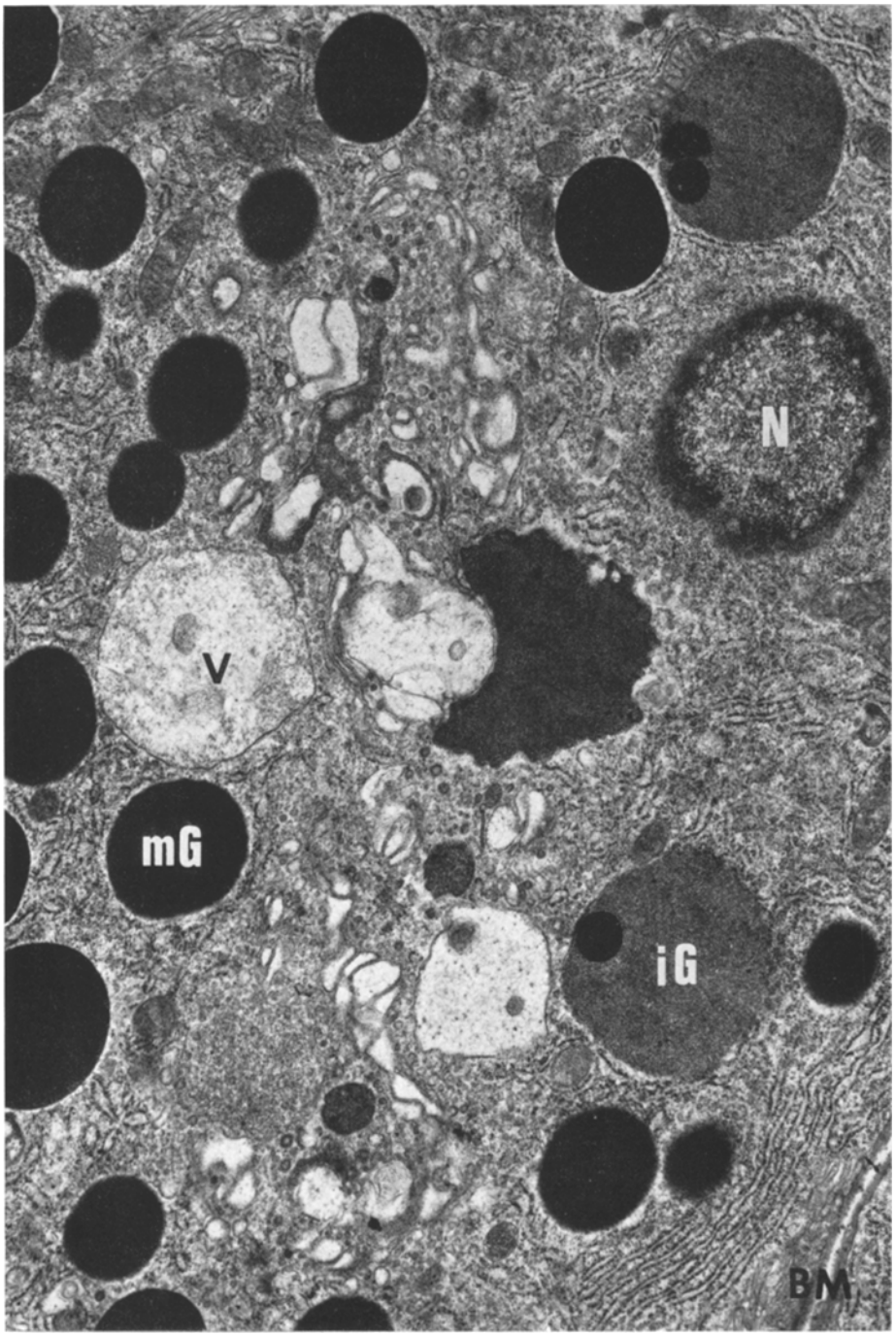

Fig. 4. Dark granular type of sialadenosis. Part of an acinar cell: Golgi apparatus with stored dense material within and around the elongated cisternae and vacuoles. Condensing vacuoles (*V*); immature secretory granules (*iG*); mature secretory granules (*mG*); nucleus (*N*); Basement membrane (*BM*). × 22900

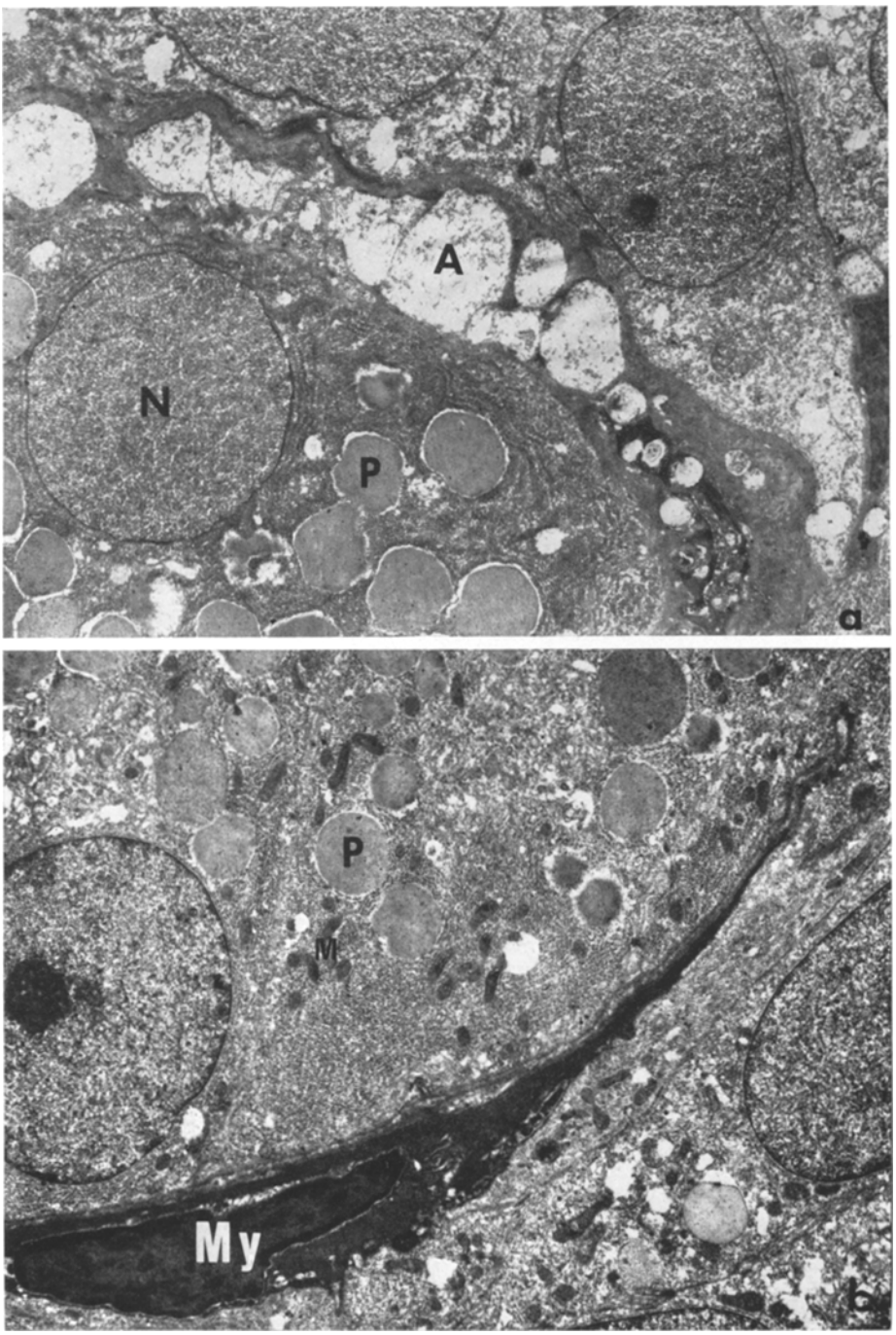

Fig. 5a and b. Pale granular type of sialadenosis. (a) Acinar cell with irregular endoplasmic reticulum. Pale secretory granules (*P*); nucleus (*N*); degenerated axons (*A*). × 5800. (b) Acinar cell with small dark mitochondria (*M*); pale secretory granules (*P*); degenerated myoepithelial cell (*My*). × 7000

parallel lamellae of endoplasmic reticulum are located around the nucleus and between the granula. The Golgi apparatus consists of small packets of empty cisternae. The small mitochondria are distributed mainly in the basal cytoplasm. The mitochondrial matrix is darker than the cytoplasmic matrix (Fig. 5b). The chromatin of the nuclei is dispersed, containing a reticulated nucleolus and occasionally one or more, rarely two dense bodies.

Mixed Granular Type. The acinar cytoplasm is filled by some small dark homogeneous granules, the main part, however, is occupied by lucent granules with a granular content (Fig. 6). Frequently, masses apparently resulting from the confluence of lucent granules are observed.

Some lucent granules show a bipartide structure, characterized by condensed body surrounded by granular material (Fig. 6). Dark and pale granules are apparently intermingled both in the basal as well as in the subluminal regions. In addition to the varying granules, some acinar cells contain additional numerous lipid droplets (Fig. 7c).

The distended Golgi apparatuses consist of disorientated smooth membrane systems with widened empty cisternae. Around the Golgi complexes there are large vacuoles with irregular outlines resulting from coalescence (Fig. 7a).

Acinar cells with degenerative lesions show pycnotic nuclei and confluent masses of flocculent material in the whole cytoplasm. Monocytes are very often in vicinity to the altered acinar cells (Fig. 7b).

The nucleus of the acinar cells is small and irregular in its outlines. It contains a compact, round nucleolus or a vacuole of the same size.

Myoepithelial cells are hardly altered in the dark granular type of sialadenosis. The myoepithelial cells of the pale granular type have a homogeneous, dark cytoplasm and dark elongated cytoplasmic processes. The perinuclear space is distended.

The nucleus is clumped (Fig. 5b). In the mixed granular type two alterations of the myoepithelial cells can be distinguished. One alteration is similar to the changes in the pale granular type. It seems that the dense filaments are hypertrophied and fill out the cytoplasm (Fig. 6). The nucleus is irregular in its outlines and shows a different chromatin density. The other cell alteration is characterized by the occurrence of large lipid droplets within the cytoplasm (Fig. 7) or by a hydropic swelling of the cytoplasm.

Innervation. Nerve terminals were found only in the dark and mixed granular type of sialadenosis. All terminals were altered, showing axon swelling. Furthermore, they contained only few dense cores or agranular vesicles, mitochondria, and occasionally lamellar bodies (Fig. 8a). In nerve bundles axon swelling predominates. In addition, ruptures of axolemma are found in increased numbers. The degenerative axon alterations are different in their electron microscopic appearance. One type of degenerative axon alteration is illustrated in Fig. 8b.

Axons are densely packed with numerous, altered dense cores, some clear vesicles, and axoplasmic organelles. The dense-cored vesicles vary in form and size from axon to axon. The other type of axon alteration is characterized by a swelling of the axoplasm, which contains only few neurotransmitter vesicles, mitochondria and, occasionally, a proliferated smooth endoplasmic reticulum (Fig. 8c), which shows an increase in vesicular and tubular elements.

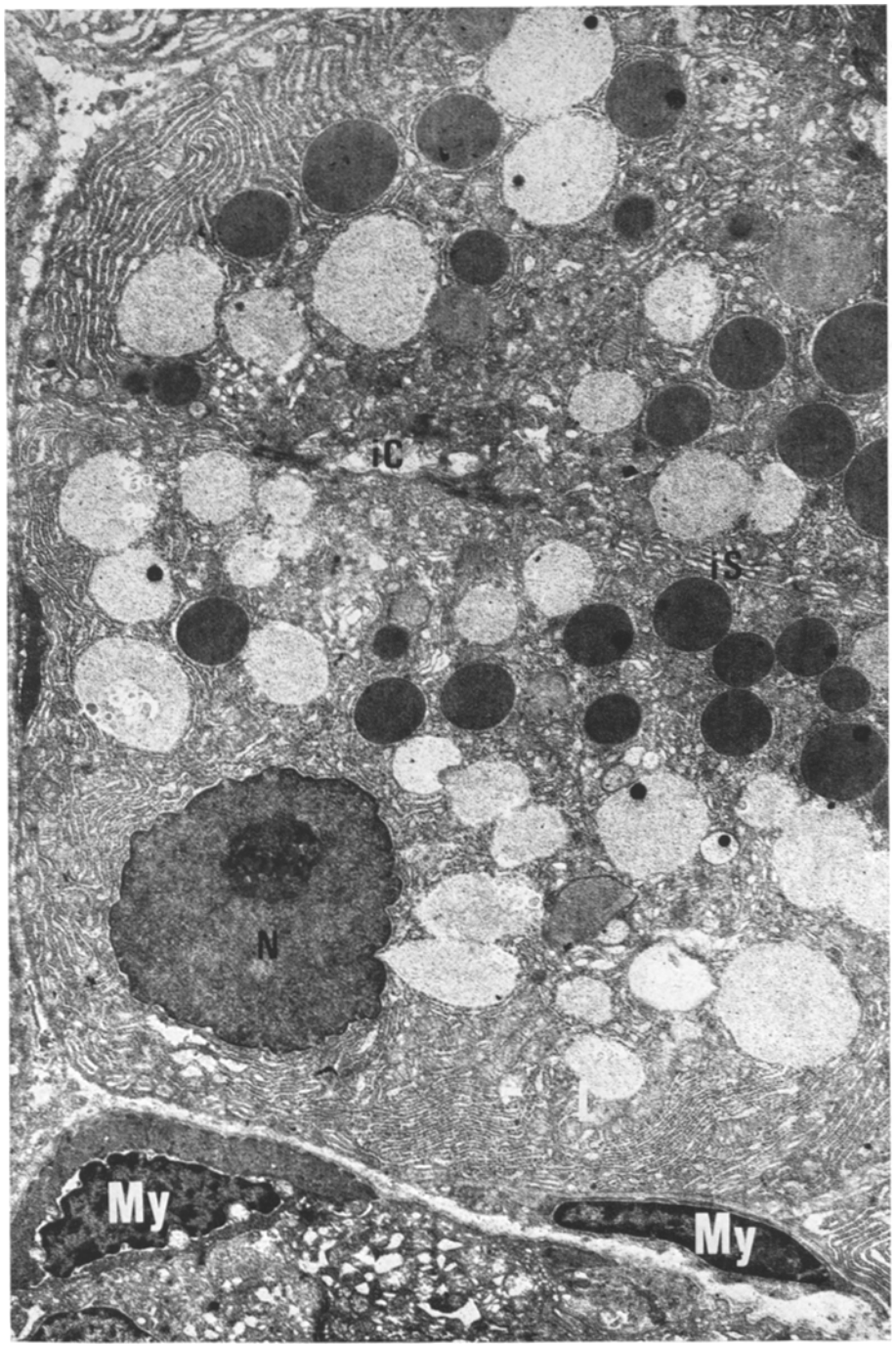

Fig. 6. Mixed granular type of sialadenosis. Acinar cells with condensing vacuoles, immature and mature secretory granules. Intercellular space (*iS*); intercellular canaliculi (*iC*); nucleus (*N*) with irregular outline. Altered myoepithelial cell (*My*). ×6500

The advanced degenerative axon alteration is found in the pale granular type of sialadenosis. Instead of axons there are frequenthy large vacuoles containing a flocculent material. Lipid droplets and pigment granules are observed in the cytoplasm of Schwann cells with degenerated axons.

The main degenerative alteration of myelinated nerves is found in the myelin sheath in the region of the nodes of Ranvier.

Discussion

Enlargement of the acinar cells accounts for the parotid swelling in sialadenosis. Morphometrical studies demonstrated that the acinar diameters are twice as large (50 to 70 μ) as those of controls. The greatest diameter was approximately 100 μ. In the controls the acinar diameters did not exceed 30 to 40 μ (average diameter of a single acinar cell 15 to 20 μ; Riva and Riva-Testa, 1973).

In sialadenosis and in the controls an equal amount of the fat tissue was found (usually less than 50%; Donath and Spillner, 1974). Until now nothing is known about the possible increase of the fat tissue in the course of sialadenosis, since only a small number of follow-up biopsies could be investigated.

The enlargement of the acinar cells is caused by a numerical increase of secretory granules. They show a different electron density. The granular pattern of the cytoplasm observed by light microscopy results from the electron density of the granules, where as the vacuolar appearance of the acinar cytoplasm is associated with the occurrence of electron lucent granules. This phenomenon accounts for the different histological patterns of sialadenosis.

The quantity of secretory granules in the acinar cytoplasm indicates a certain stage of the secretory cycle. Synthesis, storage, and secretion represent the main stages of the secretory cycle of the acinar cells. In the early phase of this cycle the acinar cytoplasm shows an increased rough endoplasmic reticulum. Later the quantity of the rough endoplasmic reticulum decreases in proportion to an increase of condensing vacuoles and immature or mature secretory granules.

The final stage of the synthetic phase is morphologically indicated by a prevalence of the secretory granules over the rough endoplasmic reticulum. The acinar diameter varies during the secretory cycle. It is smallest after the release of secretory granules and largest at the end of the storage phase. The general enlargement of the acinar cells induced by numerical increase of secretory granules evidences a disturbance of the secretion. In the dark granular type of sialadenosis the degeneration of the secretory granules indicates a disturbed secretion. Similar results were found by Hand (1972) in his experiments with starved rats. Analogous alterations of the granules were experimentally observed at the early stage of sympatholysis. In the course of sympatholysis and granular degeneration, numerous condensing vacuoles and immature or mature granules develop in addition to the degenerating mature secretory granules. In some acinar cells the condensing vacuoles flow together, forming large masses with irregular outlines (Donath, 1973). It is therefore suggested that the mixed granular type of sialadenosis has developed from the dark granular type.

The granules of the *pale granular type* of sialadenosis are homogeneous and electron-lucent. The low electron density of the pale granules is probably caused

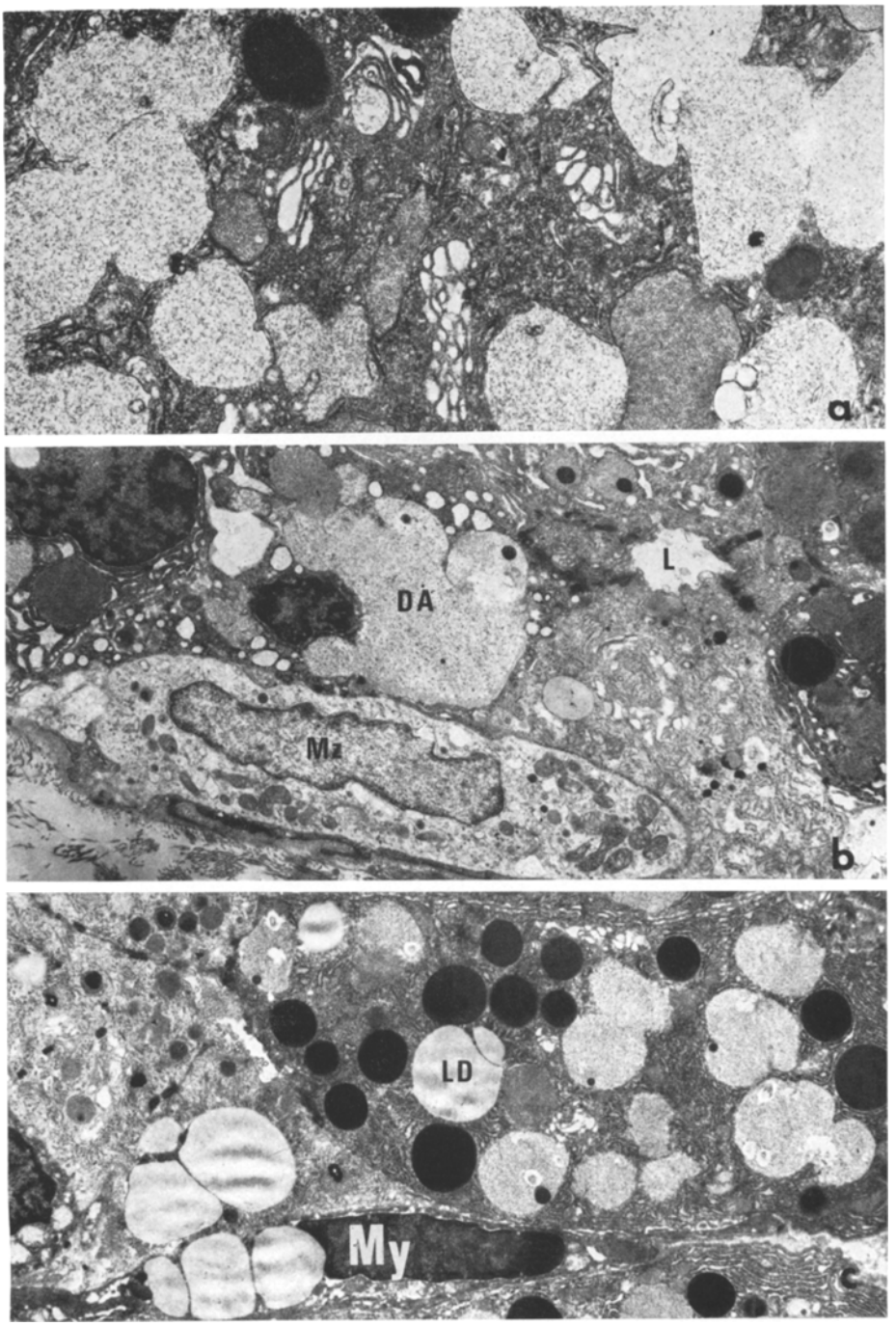

Fig. 7a—c. Mixed granular type of sialadenosis. (a) Golgi apparatus with dilated empty cisternae. Around the Golgi complexe large vacuoles with irregular outlines. × 16400. (b) Degenerated acinar cell (*DA*) with pycnotic nucleus and confluent masses of flocculent material in the cytoplasm. Monocyte (*Mc*); acinar lumen (*L*). × 5400. (c) Acinar cell with different types of granules and lipid droplets (*LD*). Myoepithelial cell (*My*) with lipid droplets in the cytoplasm. × 4800

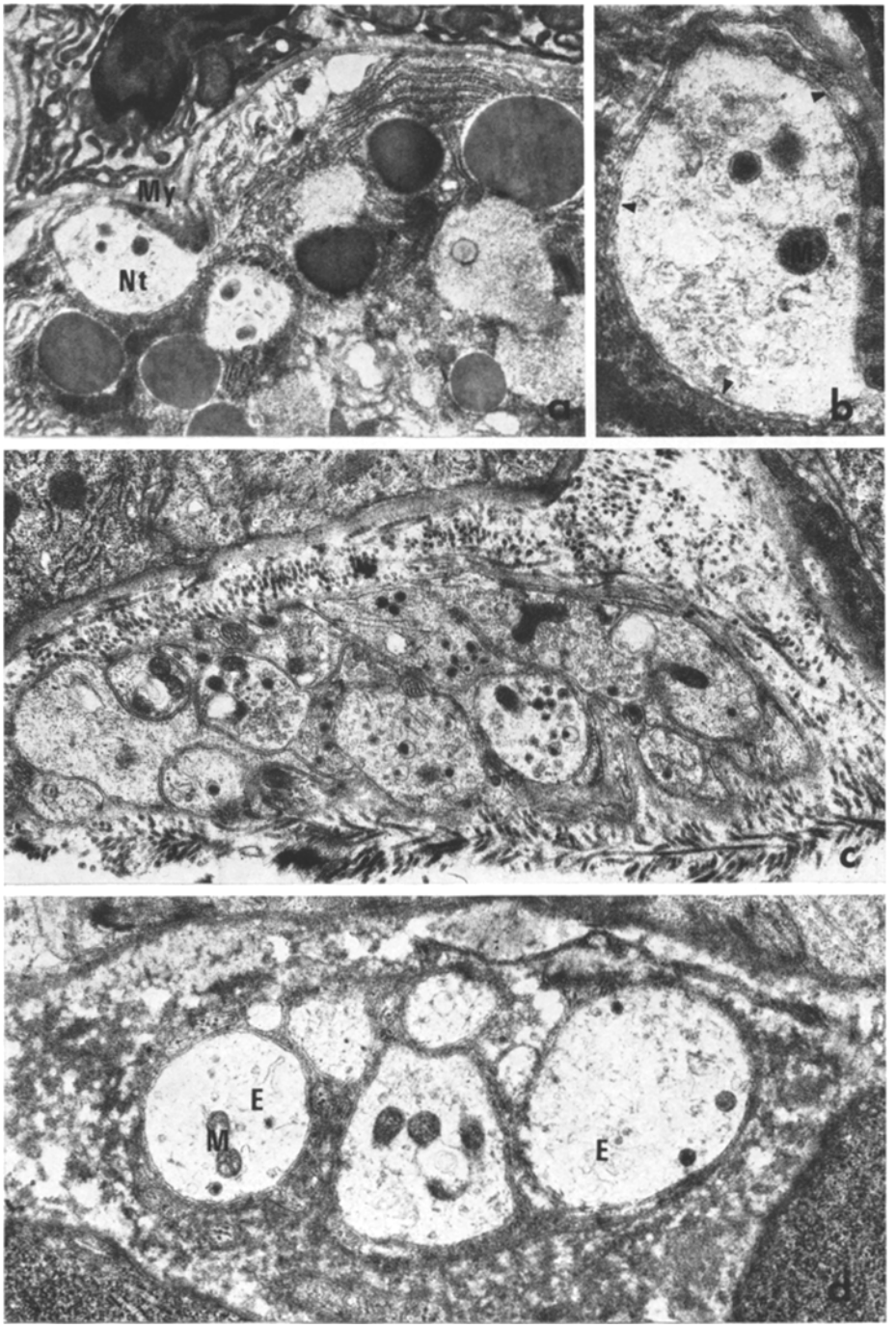

Fig. 8a—d

by a reduced protein content. This hypothesis is supported by experimental investigations. The electron density of the zymogen granules, stained with uranyl acetate, is dependent on the protein content (Lombardi *et al.*, 1971). Furthermore, a charge from high to low electron density of the secretory granules it was experimentally found by chronic administration of isoproterenol that the secretory granules change from high to low electron density (Simson, 1967). There is evidence that the pale granules result from protein deficiency. Biochemical investigations show that the protein content in parotid saliva after isoproterenol treatment shows a ninefold increase in comparison to pilocarpine treatment (Mangos *et al.*, 1973). Until now the probable low protein content of the pale granules in sialadenosis can neither be explained by clinical data nor by morphological findings.

It is suggested that probably all forms of sialadenosis are caused by degenerative changes of the autonomic nervous system, particularly involving the sympathetic nervous system.

Alterations of the myoepithelial cells provide further evidence for a lesion of the sympathetic nervous system (Donath *et al.*, 1973). In the dark granular type of sialadenosis the myoepithelial cells are hardly altered. This finding corresponds with the only light granule changes. Marked changes of the myoepithelial cells such as lipid-droplet ingestion in the cytoplasm or even degeneration were observed in the pale and mixed granular type.

It is well known that salivary secretion (quantity and quality of saliva) is controlled via the autonomic nervous system (Burgen and Emmelin, 1961). In the transfer of the nervous stimulants to the acinar cells the α- and β-receptors of the sympathetic nervous system play a decisive role. The ultrastructural demonstration of the receptors is not possible yet. The present ultrastructural results indicate that the acinar and myoepithelial cells of the human parotid glands are innervated by close synaptic contacts, as was found in rats (Hand, 1970).

In the dark and mixed granular type of sialadenosis the nerve terminals show hydropic swelling. No terminals were found in the pale granular type. Different alterations of the axons within the nerve bundles can be observed in one biopsy. The dense-cored vesicles of the axons appear to be swollen. Frequently the electron-lucent space between the dense core and the vesicular membrane is eccentrically extended. Similar changes were reported by Blümcke and Dengler (1970) following hypoxia of the rabbit iris. Degenerative axon swelling with loss of neurotubules, neurofilaments and dense-cored vesicles were observed after sympathectomy in the rat iris (Knoche and Terwort, 1973).

Fig. 8a—d. Autonomic nerves. (a) Nerve terminal (*Nt*) in close contact with an acinar and myoepithelial cell (*My*). × 8200. (b) Section of a nerve terminal limited by a membrane (←). Dense-cored vesicle, mitochondrium (*M*); neurotubules. × 24000. (c) Nerve bundles with numerous axons. The dense-cored vesicles vary in shape. The osmiophobe space between the dense core frequently displays eccentrical distension. × 14000. (d) Nerve bundles with numerous swollen axons. Few neurosecretory granules, mitochondria (*M*); proliferation of smooth endoplasmic reticulum (*E*). × 16200

The morphological alterations of the autonomic nervous system of the parotid glands (Donath *et al.*, 1974) may support the view that the enlargement of the acinar cells results from a defective secretion primarily due to a degenerative mechanism involving the autonomic nervous system. Affections of the autonomic nervous system are known in alcoholism (Bischoff, 1970) and diabetes mellitus (Watkins, 1973). Therefore we propose the following working hypothesis: protein deficiency, diabetes mellitus, and other metabolic diseases cause a defective metabolism of the autonomic nervous system, which is followed by a secondary process of degeneration. This defect of the autonomic nerves is associated with an increased release of neurotransmitter substances, producing stimulatory or inhibitory effects resulting either in sialorrhoe or in sialadenosis. This primary alteration of the autonomic nervous system may represent the common pathogenetic mechanism for all types of sialadenosis in different basic diseases.

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