

SUBMICROSCOPIC CHANGES OF THE SYNAPSE AFTER NERVE
SECTION IN THE ACOUSTIC GANGLION OF THE GUINEA
PIG. AN ELECTRON MICROSCOPE STUDY*. ‡

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PLATES 133 TO 136

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The occurrence of pathological changes in synaptic endings has been recognized in a number of disease conditions by early investigators (1-3). In cases of Friedreich's disease, Estable (4) showed that the degeneration of the pre-synaptic fiber is accompanied by hypertrophy, hyperargentophilia, and detachment of the neuropodia and other nerve endings, from the synaptic junctions. There is an abundant literature on the degeneration of synaptic endings after experimental section of the axon both in the peripheral and central nervous system (for references, see 5-8). The morphological changes occurring in the nerve terminals have been thoroughly studied with the light microscope in material prepared by various silver staining techniques. The alterations consist primarily of swelling and subsequent fragmentation and granulation of the endings (9, 10, 5, 11, and 12). These degenerative changes can be detected very soon after severance of the nerve fibers. In the cephalopods detectable alterations of the bouton-like nerve terminations were present 15 hours after section of the axons (9). In the central nervous system, swelling of the nerve endings has been observed as early as 24 hours after section (10, 5, 12). These changes generally precede the morphological alterations of the nerve fibers in Wallerian degeneration and are already very prominent after 48 to 72 hours. It has also been demonstrated that the changes following nerve section differ from those that take place in the postmortem degeneration of the endings (13).

In peripheral synapses regressive changes have also been studied physiologically. It has been shown that neuromuscular transmission fails before the nerve fiber has ceased to conduct (14-16). Furthermore this failure is gradual

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and not sudden as in the case of nerve conduction (8). Similar findings in sympathetic ganglia (17) have been correlated with the progressive decrease in acetylcholine content of ganglia after section of the preganglionic fiber (18).

Recent studies of the structure of the synapse with the electron microscope have focused renewed interest on the problem of the degeneration of nerve endings. In synaptic regions of the frog sympathetic ganglia and in the synaptic fields of the neuropile of the nerve cord of the earthworm De Robertis and Bennett (19, 20) have found that the pre- and postsynaptic neuronal elements are bounded by membranes 70 to 100 A thick, separated over the entire synaptic area by a distance of only 100 to 150 A. Furthermore a characteristic vesicular component, designated the *synaptic vesicles*, has been found in close relationship to the synaptic membrane on the presynaptic side of the synapse. Observation of the vesicular component was reported simultaneously by Palade (21) and Palay (22) in synapses of the central nervous system and in the neuromuscular junction. De Robertis and Franchi (23, 24) and De Robertis (25) have further emphasized the widespread occurrence of synaptic vesicles in description of synapses of the arthropods, and in the central nervous system and in the retina of mammals.

Thus it was considered to be of interest to study with the electron microscope the degenerative changes occurring in the synaptic region after nerve section, particularly with respect to the alterations of the synaptic vesicles. For this study the interneuronal synapse of the ventral ganglion of the acoustic nerve was selected. The several advantages of this material have previously been pointed out by Estable *et al.* (26). In the guinea pig the synapses of this primary nervous center can be caused to degenerate simply by destruction of the cochlea, which is located in the bulla where it is easily accessible and can be destroyed without damage to the central nervous system. The observations reported below will show that at early stages of degeneration of the nerve endings submicroscopic changes of the synaptic regions are very marked and consist mainly of the lysis and disappearance of the synaptic vesicles.

EXPERIMENTAL

Young guinea pigs ranging in weight from 120 to 250 gm. were used. Under ether anesthesia, an incision was made at one side of the neck and by proper dissection the bulla was exposed. The opening of the bulla with a trocar offers no difficulties in young animals and once the thin shell of bone is broken the cochlea can easily be destroyed.¹

Studies on the ventral acoustic ganglion were carried out 22, 44, and 48 hours after destruction of the cochlea on one side, the contralateral ganglion being used as control. Proper fixation of the ganglia requires the utmost speed in collecting the material. Under ether anesthesia the atlanto-occipital membrane is exposed and opened. The cerebellum is retracted,

¹ The surgical operations were performed by Professor Estable to whom we are very thankful.

bringing into view the floor of the fourth ventricle and the acoustic ganglia. During all this time the blood supply of the central nervous system has remained normal. The ganglia are then excised with scissors and immediately immersed in the fixative and rapidly cut into small pieces 0.5 mm. in diameter. The fixative is changed several times during the excision of tissue specimens. The best results were obtained with a modification of the buffered osmium tetroxide fixative recommended by Palade (27). The original fixative was modified as follows:

Osmium tetroxide 2 per cent.	1 part
Veronal acetate buffer according to Michaelis pH 7.4	1 part
Ringer plus 0.5 per cent CaCl ₂	1 part

In all cases the time of fixation was 4 hours.

The tissue fragments were then dehydrated, embedded in butylmethacrylate, and sectioned using an ultramicrotome modified from the design of Porter and Blum (28). The thickness of the sections was roughly estimated, while cutting, by the interference reflection colors and also, after mounting on the grids, with the aid of a Leitz metallurgical microscope. The most useful sections were of the order of 20 to 35 μ thick. The sections were observed without removal of the plastic embedding medium and the electron micrographs were taken at magnifications ranging from 3800 to 8300 diameters with subsequent photographic enlargement up to 60,000 diameters or more. The electron microscope used was an RCA model EMU 2C with a well compensated objective and with objective, condenser, and projector apertures.

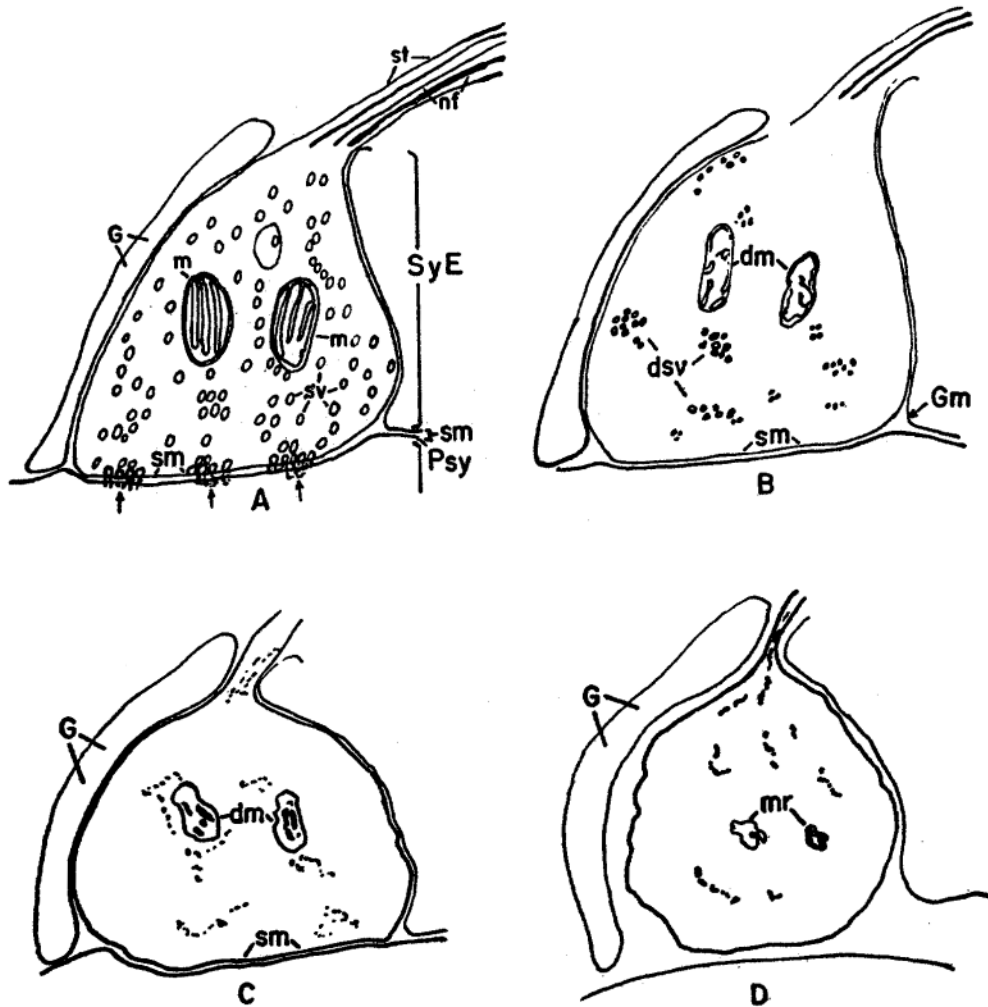
RESULTS

Submicroscopic Morphology of Normal Synapses.—

The variety of synaptic types observed microscopically with silver staining in the normal ventral acoustic ganglion of cats and dogs has been described by Estable *et al.* (26). Unfortunately in this work the sections were not thin enough to demonstrate the synaptic vesicles and other details of normal synapses which will be described here.

A representative example of a synapse with the cell body of a neuron (axosomatic synapse) is illustrated in Fig. 1 and presented diagrammatically in Text-fig. 1 A. Portions of three nerve endings are seen to make direct contact with the surface membrane of a nerve cell. At this level the cytoplasm of the pre- and postsynaptic elements are separated only by two membranes forming the so called *synaptic membrane*, and having a total thickness of about 250 A. Of the two membranes, one is considered to be postsynaptic (limiting the nerve cell body) and the other presynaptic (limiting the nerve ending). Both of them are about 60 A in thickness, and the intervening distance is about 120 to 140 A. The synaptic membrane has other characteristics which are reminiscent of details observed by De Robertis and Bennett (19, 20) in synapses of the earthworm. In Fig. 1 one can see in the synaptic membrane, regions of higher electron density alternating with regions of lower electron density. At certain points, corresponding to the regions of higher density, the synaptic vesicles often come into intimate contact with the membrane and possibly fuse with it. In other places there are suggestions of discontinuities in the membrane.

In the synaptic ending or terminus four morphological components can be



TEXT-FIG. 1. Diagram showing: *A*, some details of the submicroscopic organization of the synaptic endings in the normal acoustic ganglion. *B*, 22 hours after destruction of the cochlea. *C* and *D*, after 44 hours. The sequence *B*, *C*, *D* corresponds to the most common and progressive process of degeneration observed in the electron micrographs and described in the text (for the legends see description of figures).

recognized: the membrane, the mitochondria, the synaptic vesicles, and the cytoplasmic matrix.

The *limiting membrane of the ending* is single and at the level of the junction constitutes the presynaptic membrane already described. Beyond the synaptic junction the membrane is also single but it is in close contact with the limiting membrane of the surrounding neuroglial cell processes. The result is a double

membrane of about 250 A which is homogeneous throughout the entire surface and does not show the special relationship with the synaptic vesicles and the other characteristics described for the synaptic membrane (Fig. 1 and Text-fig. 1 A). The intimate contact of the neuroglial cells with the surface of the nerve cells and with the synaptic endings can be seen clearly in this material, but in no case is there evidence that glial processes are interposed between the nerve elements within the synaptic junction.

Mitochondria are found in almost every section of the nerve endings and vary in number from one to three or more per section. The mitochondria generally do not come into contact with the synaptic membrane. They show the typical mitochondrial internal structure with their double lamellae or or cristae (29) having a variable, but predominantly longitudinal, orientation.

The *synaptic* vesicles constitute the most characteristic component of the synaptic endings. They are uniformly distributed and present in large numbers. The description of this component for other types of synapse has already been published (19, 20, 23–25) and will not be considered further here (Figs. 1, 2, 4 and Text-fig. 1 A). It is evident however that the ending proper lacks the neuroprotofibrils that are found in the axon and dendrites and consists of a specialized expansion of the nerve terminus containing the synaptic vesicles and a few mitochondria embedded in a cytoplasmic matrix of very low density.

The *postsynaptic cytoplasm* of nerve cells contain mitochondria, and segments of the endoplasmic reticulum (30) with the dense particulate component of the cytoplasm attached to its surface (31–34) (Fig. 1). In the region immediately adjacent to the synaptic vesicles there are ill defined ghost-like outlines resembling distorted or collapsed synaptic vesicles. These images suggest the possibility of the passage of synaptic vesicles across the membrane into the postsynaptic cytoplasm. However, these structures are not as clear as those observed in the synapses of the earthworm (19, 20).

The fine structure of the normal axodendritic synapse is essentially the same and will not be described in detail. A noteworthy difference is found in the postsynaptic region where endoplasmic reticulum and associated dense particles are scanty in the dendrite and the most conspicuous components are mitochondria and long neuroprotofibrils (35) about 150 to 200 A wide and having smooth dense surface contours. Representative examples of axodendritic junctions with surrounding glial elements are illustrated in Figs. 2 and 4.

Submicroscopic Morphology of Degenerating Synapses.—

Definite submicroscopic changes in the nerve endings were observed after 22 hours of destruction of the cochlea and were still more conspicuous after 44 and 48 hours. The following account of the changes is based on the study of more than 200 electron micrographs of several specimens, but for the sake of simplicity the description will refer mainly to the few accompanying illustrations.

The degenerative changes vary in intensity in the endings in contact with

different neurons and even among neighboring endings on the same postsynaptic element, but they seem to follow a definite sequence of development. These changes involve alterations in all the components of the normal ending described above although with different timing and intensity. It is evident that the modifications of the synaptic vesicles are the most marked and the earliest to develop and these are followed by lesions of the mitochondria and of the membranes. After 22 hours there is a definite swelling of the ending with decreased electron density of the matrix (Fig. 3 and Text-fig. 1 *B*). Most of the synaptic vesicles have disappeared or appear to be in the process of dissolution. The few of them that remain are aggregated into clumps. The outlines of these vesicles are ill defined as if they were undergoing lysis (Fig. 3 and Text-fig. 1 *B*). Some mitochondria continue to have a normal appearance with their intact cristae but other mitochondria are altered, and show also a tendency to disintegrate.

In Fig. 5 from a specimen fixed after 44 hours after nerve section, several end-feet can be observed in contact with a dendrite. The nature of the degenerative changes can be appreciated best by comparing this figure with the appearance of the normal endings depicted in Figs. 2 and 4. Most of the synaptic vesicles have disappeared or are agglutinated into irregular masses in which the vesicular nature of the component is difficult to recognize. The matrix is considerably less dense and has a watery aspect. The intensity of alterations varies for the different endings. Within the dendrite neuroprotofibrils and normal mitochondria are seen.

In Fig. 6 alterations of the endings are still more intense. A few small groups of ghost-like vesicles can be found but in general the endings are swollen and largely devoid of vesicles. In one terminus there is a complete lysis of the vesicles and also some large vacuoles are present which may possibly be remnants of degenerated mitochondria (see also Text-fig. 1 *C*). On the other hand, the synaptic membrane in the case of Figs. 4 and 5 seems to be intact and the presynaptic ending continues to be attached to the postsynaptic element.

In other electron micrographs made after 44 and 48 hours the degenerative changes seem to reach a maximum with complete disappearance of the synaptic vesicles and lysis of the mitochondria (Fig. 7 and Text-fig. 1 *D*). The membrane although still present in some endings seems to be disrupted. Fig. 8 shows a ghost-like ending with complete loss of vesicles and mitochondria and an irregular limiting membrane.

DISCUSSION

In the normal ventral acoustic ganglia, the end-feet or larger synaptic endings appear as differentiated regions of the axon having a distinctive submicroscopic structure. Thus, the neuroprotofibrils commonly observed throughout the axon (35) are no longer present and the enlarged ending is filled instead

with the synaptic vesicles. The other conspicuous components of the ending, the mitochondria, are also found in other parts of the axon and in the nerve cell body neuron but in some cases they appear to be concentrated at the synaptic ending.

The presence of mitochondrion-like granules in the end-foot was described by Bartelmez (36) using the light microscope (see also references 37 and 6). In view of the present knowledge concerning their biochemical function, the presence of a concentration of mitochondria at the synapse would seem to indicate a more intense local oxidative metabolism in this region. The suggestion advanced by Bodian (6) that mitochondria could be correlated with a local secretion of acetylcholine or of cholinesterase seems rather doubtful, since it would imply a differential specialization of the mitochondria at the synapse. Furthermore, in some types of synapses mitochondria may be entirely absent (24).

From purely morphological considerations it seems more justifiable to speculate that the chemical compounds active in synaptic transmission may be related in some way to the synaptic vesicles. In fact this submicroscopic component has been found localized exclusively or in highest concentration in the synapses in all of the material studied to date (19, 20, 22-25). Furthermore, the synaptic vesicles show a close relationship to the synaptic membrane which is not displayed by mitochondria. This relationship is suggestive of a movement of vesicles to and possibly across the synaptic membrane. It is presumed that they may discharge their contents into the space immediately adjacent to the postsynaptic membrane (19, 20). In the material studied here the synaptic membrane also showed regions of higher and lower electron density and points of discontinuity which may represent transient local breakdowns of the membrane similar to those observed previously in the synaptic junctions of the earthworm (20).

The observations on degenerating nerve endings confirm the finding of earlier morphological studies with silver staining techniques which revealed morphological alterations occurring soon after section of the afferent axon (5, 9-12). Although the progress of the degeneration is variable in its course for the synapses of different cells and even for the endings on the surface of a single neuron, the most common sequence of events involves a swelling of the matrix, agglutination and lysis of the synaptic vesicles, disintegration of mitochondria, and finally detachment and breakdown of the membrane at the synaptic junction (see Text-fig. 1). Although these observations are for a synapse of the central nervous system, physiological similarities (8) would suggest that these results can be extended to peripheral synapses where similar changes are correlated with the early physiological deterioration of the synaptic transmission (14-17) and with the progressive decrease of the acetylcholine content (18).

These observations on the ultrastructure of the synapse seem thus to be consistent with the wealth of physiological, electrical, pharmacological, and pathological data which indicate that the nerve ending and the synaptic junction are highly differentiated parts of the neuron endowed with special physiological properties. The hypothesis that the synaptic vesicles may be carriers of acetylcholine or other active substances (19, 20) and that they may act as biochemical units in synaptic transmission finds a support in the recent work of Del Castillo and Katz (38). These authors observed small end plate potentials in the resting neuromuscular junction and they postulated the existence of multimolecular quanta of acetylcholine released at the synaptic membrane. A correlation between the concept of the synaptic vesicles (19) as a morphological unit and the postulated quanta of acetylcholine as a biochemical unit (38) in synaptic transmission seems to be pertinent at the present time and may prove to be a useful working hypothesis for the future.

SUMMARY

The degenerative changes of the synaptic regions after nerve section have been studied with the electron microscope in the interneuronal synapse of the ventral ganglion of the acoustic nerve of the guinea pig. Fixation with buffered osmic tetroxide was carried out 22, 44, and 48 hours after destruction of the cochlea on one side; the contralateral ganglion being used as control.

The submicroscopic organization of normal axosomatic and axodendritic synapses is described. In the synaptic ending four morphological components are recognized: the membrane, the mitochondria, the synaptic vesicles (19, 20), and the cytoplasmic matrix. The intimate contact of glial processes with the endings and with the surface of the nerve cell is described. At the level of the synaptic junction there is a direct contact of the limiting membranes of the ending and of the cell body or dendrite. Both contacting membranes constitute the synaptic one with a total thickness of about 250 Å. This membrane has regions of higher electron density where the synaptic vesicles come into intimate contact and fuse with it.

Definite degenerative submicroscopic changes in the nerve endings were observed after 22 hours of destruction of the cochlea and were much more conspicuous after 44 and 48 hours. After 22 hours there is swelling of the ending and decreased electron density of the matrix. Most synaptic vesicles have disappeared or seem to undergo a process of clumping and dissolution. Some mitochondria also show signs of degeneration. After 44 hours the synaptic vesicles have practically disappeared; mitochondria are in different stages of lysis; the membrane of the ending becomes irregular in shape, and there is shrinkage and in some cases detachment of the ending. No changes in the postsynaptic cytoplasm were observed.

These observations and particularly the rapid lysis of the synaptic vesicles are discussed in correlation with data from the literature indicating the early alteration of synaptic function and the biochemical changes occurring after section of the afferent nerve. The hypothesis that the synaptic vesicles may be carriers of acetylcholine or other active substances (19, 20) and that they may act as biochemical units in synaptic transmission is also discussed.²

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² We want to express our gratitude to Professor Don W. Fawcett for reading and correcting this manuscript.

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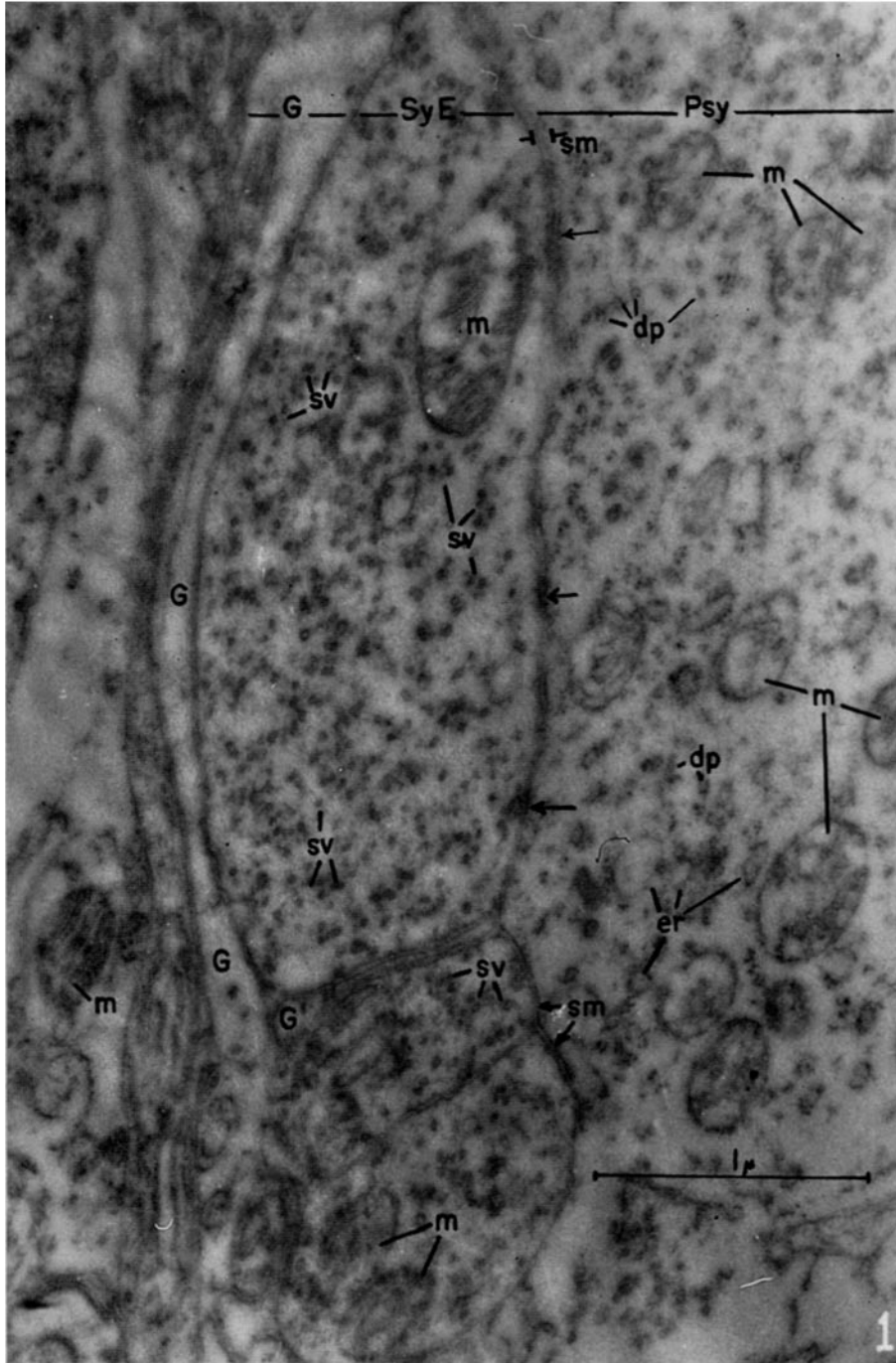
EXPLANATION OF PLATES

<p><i>A</i>, axon. <i>D</i>, dendrite. <i>DE</i>, degenerating ending. <i>dm</i>, degenerating mitochondria. <i>dp</i>, dense particles. <i>dsv</i>, degenerating synaptic vesicle. <i>er</i>, endoplasmic reticulum. <i>G</i>, glial process or cell. <i>Gm</i>, glial cell membrane.</p>	<p><i>m</i>, mitochondria. <i>mr</i>, mitochondrial remnant. <i>my</i>, myelin sheath. <i>N</i>, nucleus. <i>Psy</i>, postsynaptic cytoplasm. <i>nf</i>, neuroprotofibril. <i>sm</i>, synaptic membrane. <i>st</i>, stalk of the synaptic ending. <i>sv</i>, synaptic vesicle.</p>
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SyE, synaptic ending.

PLATE 133

FIG. 1. Electron micrograph of the synaptic region of a cell of the ventral acoustic ganglion of a normal guinea pig. On the left side three synaptic endings (*SyE*) (two small end-feet and one large) make direct contact with the postsynaptic cytoplasm of a nerve cell (*Psy*). Thin glial processes (*G*) and a submicroscopic nerve fiber are found in the vicinity of the endings. See description in the text regarding the synaptic membrane (*sm*), synaptic vesicles (*sv*), mitochondria (*m*), and other components of the ending and the postsynaptic cytoplasm. The arrows indicate regions of the synaptic membrane where the vesicles make contact and seem to go across the membrane. $\times 37,000$.

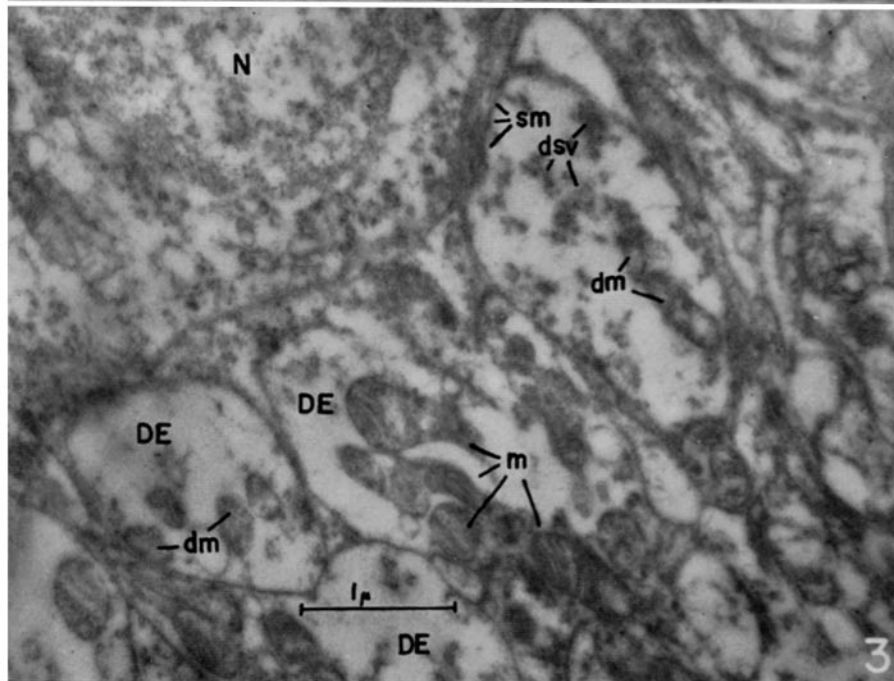
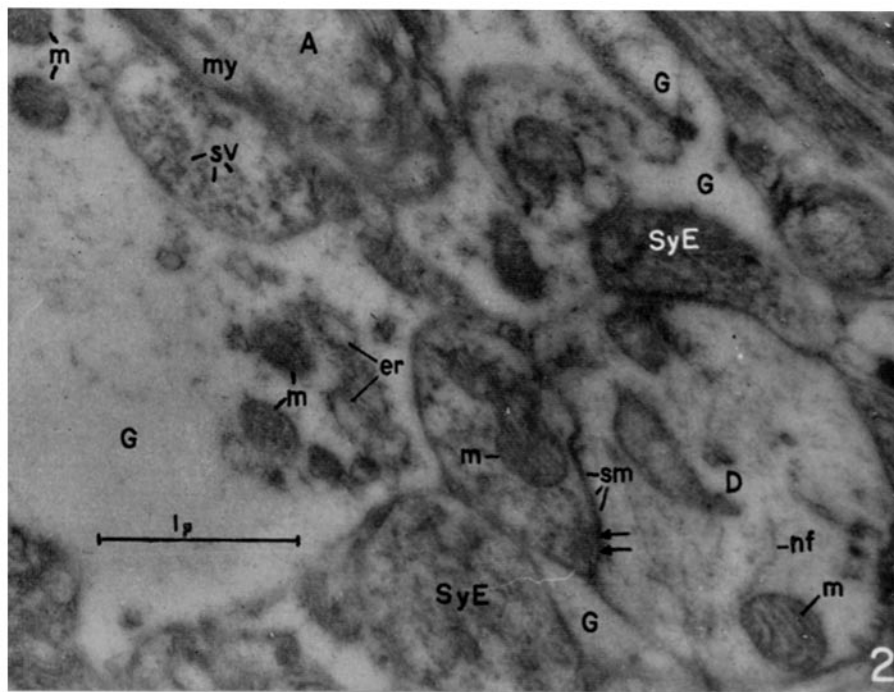


(De Robertis: Synapse after nerve section in acoustic ganglion)

PLATE 134

FIG. 2. Electron micrograph of a normal ventral acoustic ganglia of the guinea pig. Four synaptic endings (*SyE*), two of them making contact with a dendrite (*D*) are shown (axodendritic synapse). A portion of a protoplasmic glial cell with mitochondria, endoplasmic reticulum, and dense particles is present. The arrows indicate a region of the synapse in which synaptic vesicles seem to go across the membrane. $\times 27,000$.

FIG. 3. Electron micrograph of a degenerating ganglion, 22 hours after destruction of the cochlea. Note the presence of several degenerating endings (*DE*) showing swelling of the matrix, some degenerating mitochondria (*dm*), the reduction in number and size of the synaptic vesicles which are agglutinated into clumps and seem to undergo dissolution (*dsv*). Some mitochondria (*m*) and the synaptic membrane still show a normal appearance. $\times 21,000$.

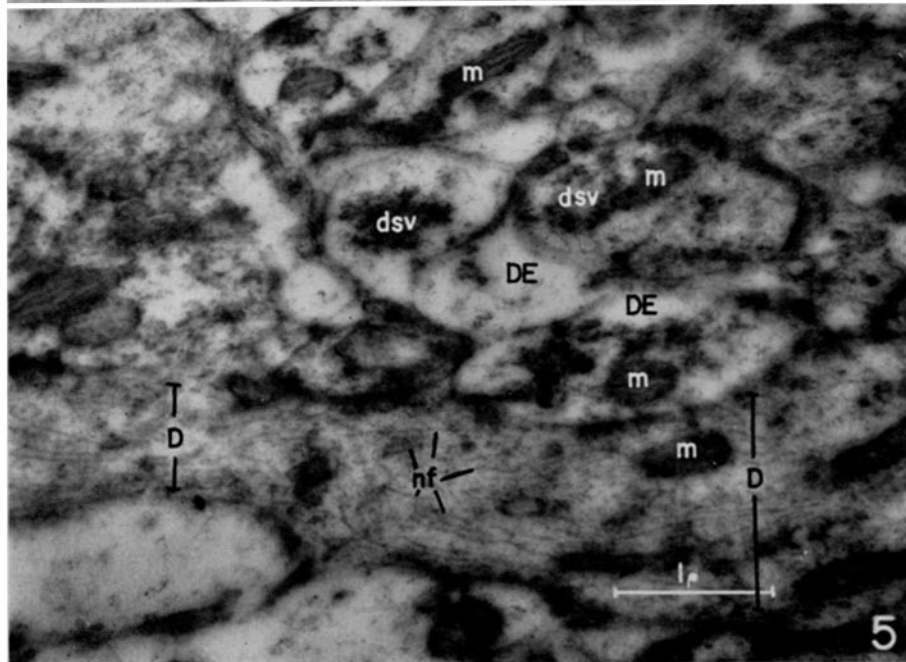
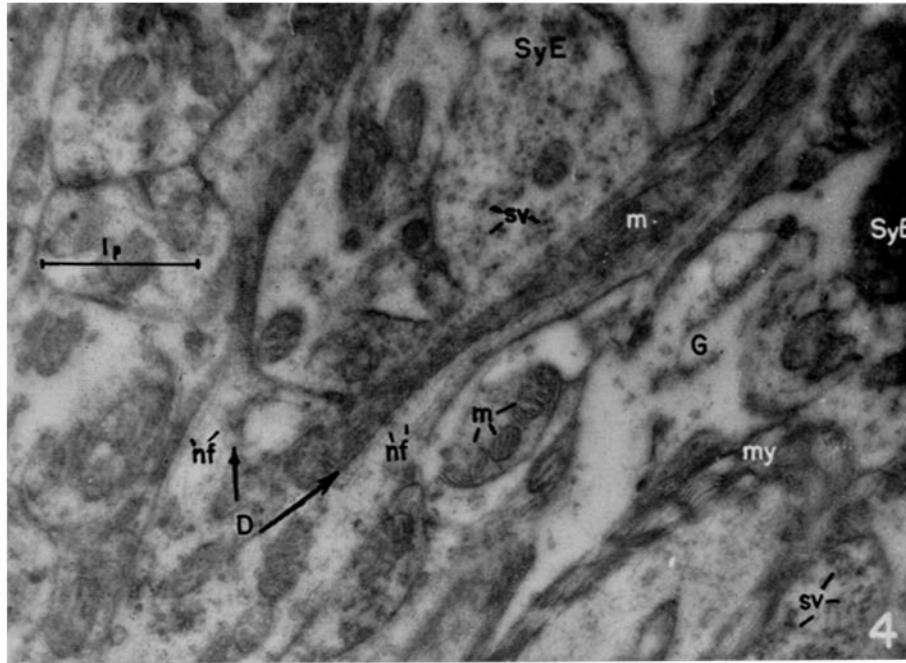


(De Robertis: Synapse after nerve section in acoustic ganglion)

PLATE 135

FIG. 4. Electron micrograph of a normal ventral acoustic ganglion showing a typical axodendritic ending (*SyE*). The dendrite possesses a very long mitochondrion, several neuroprotofibrils (*nf*), and elements of the endoplasmic reticulum with dense particles. A myelin nerve fiber, unmyelinated nerve fibers, and glial processes (*G*) are also present. $\times 21,000$.

FIG. 5. Electron micrograph of an acoustic ganglion 44 hours after destruction of the cochlea. A thick dendrite with mitochondria and well developed neuroprotofibrils (*nf*) and several degenerating endings (*DE*) are seen. See description in the text. $\times 21,000$.



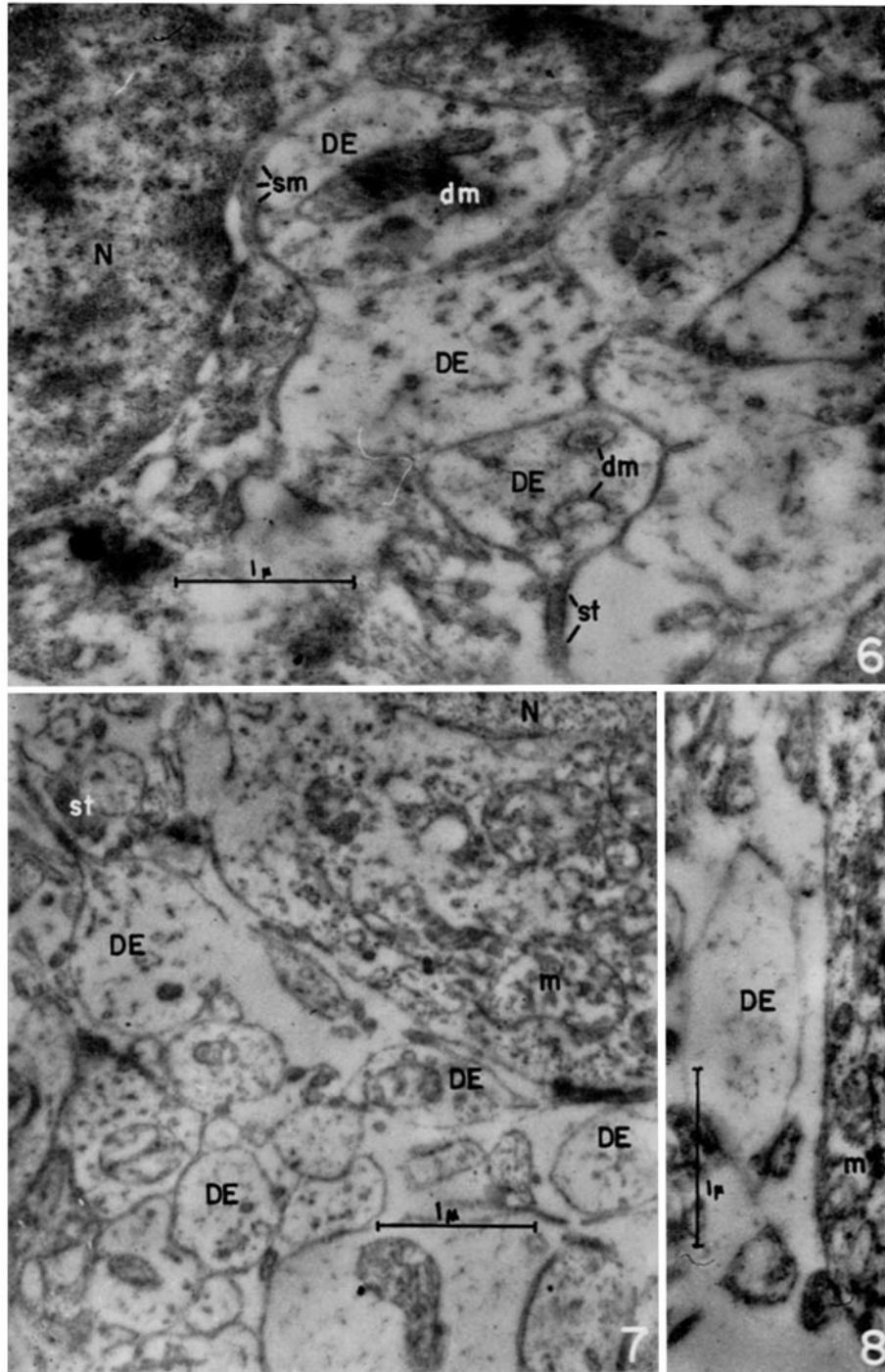
(De Robertis: Synapse after nerve section in acoustic ganglion)

PLATE 136

FIG. 6. Figs 6 to 8 are electron micrographs of degenerating synapses of the acoustic ganglion after 44 hours of destruction of the cochlea. Several degenerating endings (*DE*), one of them with the connecting stalk (*st*) are seen. Several stages of the degeneration of mitochondria are illustrated. The synaptic vesicles have practically disappeared. $\times 24,500$.

FIG. 7. Portion of a nerve cell surrounded by several severely degenerated endings. It can be seen that the membrane has a tendency to become irregular in outline probably owing to shrinkage of the ending. Mitochondria and synaptic vesicles have almost completely disappeared. $\times 21,500$.

FIG. 8. Highly advanced degeneration of a synaptic ending showing almost complete dissolution of the internal structure and an irregular limiting membrane. $\times 24,500$.



(De Robertis: Synapse after nerve section in acoustic ganglion)